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Editorial

Editorial

Diabetes and Vision Problems

Mohsin Masud Jan
Editor

Less than half of adults who are losing their vision to diabetes have been told by a doctor that diabetes could damage their eyesight, a new study found.

Vision loss is a common complication of diabetes, and is caused by damage that the chronic disease does to the blood vessels within the eye. The problem can be successfully treated in nearly all cases, but Johns Hopkins researchers found that many diabetics aren't taking care of their eyes, and aren't even aware that vision loss is a potential problem.

Nearly three of every five diabetics in danger of losing their sight told the Hopkins researchers they couldn't recall a doctor describing to them the link between diabetes and vision loss. The study appeared in the journal JAMA Ophthalmology. About half of people with diabetes said they hadn't seen a health-care provider in the previous year. And two in five hadn't received a full eye exam with dilated pupils, the study authors noted.

"Many of them were not getting to someone to examine them for eye problems," said study leader Dr. Neil Bressler, a professor of ophthalmology at the Johns Hopkins University School of Medicine. "That's a shame because in many of these cases you can treat this condition if you catch it in an early enough stage," added Bressler, who is also chief of the retina division at the Johns Hopkins Wilmer Eye Institute. One-third of the people said they already had suffered some vision loss related to their diabetes, according to the report.

Bressler said vision damage can be prevented or halted in 90 percent to 95 percent of cases, but only if doctors get to patients quickly enough. Drugs injected into the eye can reduce swelling and lower the risk of vision loss to less than 5 percent. Laser therapy has also been used to treat the condition, the researchers said. Dr. Robert Ratner, chief scientific and medical officer for the American Diabetes Association, called the findings "frightening" and "depressing."

For the study, researchers used survey data collected by the U.S. Centers for Disease Control and Prevention between 2005 and 2008 to review the responses of people with type 2 diabetes who had "diabetic macular edema." This condition occurs when high blood sugar levels associated with poorly controlled diabetes cause damage to the small blood vessels in the retina, the light-sensitive tissue lining the back wall of the eye.

As the vessels leak or shrink, they can cause swelling in the macula — a spot near the retina's center that is responsible for your central vision. Macular edema can ruin your ability to see detailed images and objects directly in front of you, and ultimately can lead to permanent vision loss. Many diabetics suffer from diabetic macular edema. People with diabetes have at least a 10 percent risk of developing the eye disease during their lifetimes, Bressler said. Recent reports estimate that the eye disease affects about 745,000 people with type 2 diabetes in the United States, the authors noted in background information.

The people in the survey with diabetic macular edema responded to questions about their medical care. The Johns Hopkins researchers gleaned their findings from the survey responses. "We have to really strengthen our efforts at educating people who have diabetes about the eye complications," Bressler said. "They need to get to health care providers who can provide the appropriate treatment. In the United States, we aren't doing as good a job as we probably should." Bressler, who is the editor of JAMA Ophthalmology, does not participate in deciding whether studies from Johns Hopkins are chosen for publication in the journal.

Ratner said part of the problem is that people can't afford to see a doctor for their diabetes. "I'm hopeful that as the number of uninsured individuals begins to drop, that structural problem will get better," he said. On the other hand, doctors need to do a better job when they do see patients of emphasizing the dangers of vision loss from diabetes in a clear manner.

Original Article

Frequency of Bacterial Isolates in Blood Culture among Patients with Acute Pyogenic Meningitis

Muhammad Ayaz[1], Abdul Hanan[1], Muhammad Khalid[1], Rifayatullah Afridi[2], Muhammad Haroon Shahid[1] and Shabir Hussain[1]

ABSTRACT

Objective: To determine the frequency of bacterial isolates in blood culture among patients with acute pyogenic meningitis.

Study Design: Descriptive / cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera from November, 2017 to May, 2018.

Materials and Methods: A total of 193 patients using 43.4% proportion of positive blood culture with acute bacterial meningitis, 95% confidence level and 5% margin of error, using WHO software, presenting features of pyogenic meningitis were included in the study and subjected to blood culture to record the findings.

Results: The mean age group of our sample was 32.4 $\pm$ 10.9 years of which 66.8% male patients and 33.2% female patients. Most of the patients i.e. 59.6% were in the age group up to 35.00 years. Positive blood culture was seen in 60.1% of cases with E Coli being the most frequent in 25% of patients followed by Pneumococcus in 22.4% of patients, Meningococcus in 21.6% of patients, Klebsiella in 9.5% and H. Influenza in 8.6%.

Conclusion: Acute pyogenic meningitis is a common occurrence in our population with E. Coli, Pneumococci and Meningococci being the common culprits.

Key Words: Acute Bacterial Meningitis, Blood Culture, Pneumococcus, Meningococcus, Klebsiella.

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INTRODUCTION

Meningitis is defined as inflammation of meninges which is caused by bacteria, viruses, fungi and parasites[1]. Bacterial meningitis results in worldwide morbidity and mortality, even though adequate antibiotics and vaccination strategies have been carried out[2,3].

The incidence of bacterial meningitis is approximated to be 2.6–6.0 cases per 100,000 yearly in Europe and in less developed countries it might be ten times higher [4]. The mortality rate remains high in developing countries which is 16-32%[5].Although the incidence and rates of morbidity and death related to community-acquired acute pyogenic meningitis have adequately decreased, possibly as an outcome of immunization and proper antibiotics and related therapies, the disease still has a high number. In United States, still 10% to 20% of people die of it[6].

Most common organisms causing acute pyogenic meningitis are "Streptococcus pneumonia", "Neisseria meningitidis", "Haemophilus influenza" type B, "Gram negative Bacilli" and "Staphylococcus aureus"[1,5,7]. The organisms causing community-acquired acute pyogenic meningitis slightly differ by geographic region, by age[7] and by time caused by a variety of factors[8]. Streptococcus pneumonia and Neisseria meningitidis are the prevailing pathogens in adults, causing 80–85% of all cases, with 30% mortality rate for the Pneumococcal meningitis and 10% for Meningococcal meningitis[2,9].

Meningitis might be related with notable mortality even after treatment instituted[10]. One in four adults might die with acute pyogenic meningitis and many treated retain neurological deficit. Early and appropriate antibiotics needs quick recognition of the disease causing organism. The vague clinical presentation and non-availability of laboratory facilities can delay or concealed the diagnosis[11].

Extra-meningeal infection is examined when a patient had a focal infection away from the central nervous system and the same pathogen was segregated from the primary focus or from blood culture[8]. In one study, the frequency of positive blood culture among patients having acute pyogenic meningitis was 52.6%[11].

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Another study concluded that the blood cultures were more likely to be positive (43.4% in non-elderly and 51.5% in elderly) in patients with suspected acute pyogenic meningitis[8]. Cerebrospinal fluid (CSF) culture were positive in 72.4% in non-elderly and 67.8% in elderly in patients with suspected acute pyogenic meningitis[8].

The current study is designed to find out the frequency of bacterial isolates in blood culture among patients presenting with cases of acute pyogenic meningitis. As mentioned above, the bacteriology of acute pyogenic meningitis varies from population to population with variations among age and changing patterns on time. It is also reported in literature that the bacteria found in acute pyogenic meningitis can often be identified on blood cultures, this study will produce local statistics about the magnitude of bacterial isolates in blood culture as this study is not done in the last five years in our local population. Sometimes lumbar puncture is contraindicated or difficult to obtain so blood culture is an alternative option for diagnosis in such patient as it is easy to obtain and transport as compare to CSF culture. The results will be disseminated among local health care providers to make them to know about the importance of blood culture in acute pyogenic meningitis.

MATERIALS AND METHODS

This study was conducted in the in the Department of Medicine, Qazi Hussain Ahmad Medical Complex, Nowshera from November 2nd, 2017 to May 3rd, 2018. Through a Descriptive Cross Sectional Study Design, a total of 193 patients using 43.4% proportion of positive blood culture in patients with acute bacterial meningitis[8], 95% confidence level and 5% margin of error, using WHO software, presenting features of pyogenic meningitis were included in the study and subjected to blood culture to record the findings.

Inclusion criteria: All patients presenting with ABM.

- Age ≥ 16 years.
- Both gender.

Exclusion criteria:

- Comorbid conditions due to any cause.
- History of antibiotics use in last three days.

The above mention conditions act as confounders and if not controlled will produce bias in the results.

Data Collection: The study was carried out after approval from hospitals ethical committee. An informed written consent was obtained from patients completing the inclusion criteria. From all recruited patients history, clinical examination, and routine investigations like Random blood sugar, Full Blood Count, Renal Function tests, Alanine Amino-transferase and CSF routine examination were collected.10cc of venous blood was collected under aseptic conditions on arrival of patients and was sent to laboratory in 100 ml of culture bottle to detect positive growth of any bacteria like Pneumococci, Meningococci, Escherichia Coli, Staphylococcus aureus, Hemophilus influenza and Klebsiella. CSF culture was not used in diagnostic criteria of acute pyogenic meningitis. However, CSF culture was sent as part of routine workup.

Confounders are controlled by following the Exclusion criteria. Lab tests and examination was supervised by medical specialist and pathologist.

Data Analysis: Data was recorded on Performa and statistical analysis was done by SSPS 20.0. Mean ± SD was computed for quantitative variables like age. Frequency of bacterial isolates in blood culture in acute pyogenic meningitis was stratified among age and gender to see the effect modifications. Percentage and frequencies were computed for categorical variables like gender, Positive blood culture and bacteria like "Pneumococci, Meningococci, E. Coli, staphylococcus aureus, Haemophilus influenza and Klebsiella".

RESULTS

The study was conducted on 193 patients presenting with clinical features suggestive of acute meningitis. The mean age of the sample was 32.4 ± 10.9 years. We divided the age in 4 different groups. In age group from upto 25.00 years, we had 40.4% of patients, in the group 25.01 to 35.00 years we had 19.2% patients, in age group 35.01 to 45.00 years we had 20.2% patients and in the age group 45.01 years and higher we had 20.2% of patients. (Table 1)

Table No.1:Age Wise Distribution of the Sample (n = 193)

		N	Min.	Max.	Mean	Std. Deviation
Age of the patient		193	18.50	51.50	32.4109	10.95584
Age Groups						
			Frequency	Percent		Cumulative Percent
Valid	Upto 25.00 years		78	40.4		40.4
	25.01 to 35.00 years		37	19.2		59.6
	35.01 to 45.00 years		39	20.2		79.8
	45.01 years & above		39	20.2		100.0
	Total		193	100.0		

Table No.2: Frequency Of Positive Blood Culture (n= 193)

	Frequency	Percent	Cumulative Percent
Yes	116	60.1	60.1
No	77	39.9	100.0
Total	193	100.0	

Table No.3: Type of Bacteria Among Positive Blood Culture (n = 116)

	Frequency	Percent	Cumulative Percent
Pneumococcus	26	22.4	22.4
Meningococcus	25	21.6	44.0
E. Coli	29	25.0	69.0
Staphylococcus Aureus	15	12.9	81.9
Hemophilus Influenza	10	8.6	90.5
Klebsiella	11	9.5	100.0
Total	116	100.0	

Table No.4:Age Wise Stratification Of Positive Blood Culture (n = 193)

			Positive Blood Culture		Total	P-value
			Yes	No		
Age Groups	Upto 25.00 years	Count	52	26	78	.002
		% within Age Groups	66.7%	33.3%	100.0%	
	25.01 to 35.00 years	Count	25	12	37	
		% within Age Groups	67.6%	32.4%	100.0%	
	35.01 to 45.00 years	Count	26	13	39	
		% within Age Groups	66.7%	33.3%	100.0%	
	45.01 years & above	Count	13	26	39	
		% within Age Groups	33.3%	66.7%	100.0%	
Total		Count	116	77	193	
		% within Age Groups	60.1%	39.9%	100.0%	

Out of 193 patients included in the study, there were 66.8% male patients and 33.2% female patients.

All the patients were subjected to collection of venous blood sample under aseptic technique and sent for culture examination. Out of 193 patients, 60.1% were found to have culture positive meningitis (Table 2)

The culture was further inoculated on various medial to determine the frequency of different bacteria. Out of 116 patients who were culture positive, we found that E Coli was seen in 25% of patients, Pneumococcus was seen in 22.4% of patients, Meningococcus was seen in 21.6% of patients, Klebsiella was seen in 9.5% and H. Influenza was seen in 8.6% (Table 3).

We stratified the positive blood culture with regards to age groups and observed that the difference was statistically significant with p value of 0.002. (Table 4)

We also stratified the positive blood culture with regards to different gender and observed that the difference was statistically significant with a p value of <.001 (Table 5).

We also stratified the type of bacteria found in our study with regards to age groups and observed that the difference was statistically significant with a p value of <.001. (Table 6)

We also stratified the type of bacteria found in our study with regards to gender and observed that the difference was statistically significant with a p value of <.001. (Table 7)

Table No.5: Gender Wise Stratification of Positive Blood Culture (n = 193)

			Positive Blood Culture		Total	P-value
			Yes	No		
Gender of Patient	Male	Count	90	39	129	<.001
		% within Gender of Patient	69.8%	30.2%	100.0%	
	Female	Count	26	38	64	
		% within Gender of Patient	40.6%	59.4%	100.0%	
Total		Count	116	77	193	
		% within Gender of Patient	60.1%	39.9%	100.0%	

Table No.6: Age Wise Stratification of Type of Bacteria (n = 193)

Age Groups		Type of Bacteria							Total	P-value
		Pneumococcus	Meningococcus	E. Coli	Staphylococcus Aureus	Hemophilus Influenza	Klebsiella	NA		
Upto 25.00 years	Count	0	13	3	15	10	11	26	78	<.001
	% within Age Groups	0.0%	16.7%	3.8%	19.2%	12.8%	14.1%	33.3%	100.0%	
25.01 to 35.00 years	Count	0	12	13	0	0	0	12	37	
	% within Age Groups	0.0%	32.4%	35.1%	0.0%	0.0%	0.0%	32.4%	100.0%	
35.01 to 45.00 years	Count	13	0	13	0	0	0	13	39	
	% within Age Groups	33.3%	0.0%	33.3%	0.0%	0.0%	0.0%	33.3%	100.0%	
45.01 years & above	Count	13	0	0	0	0	0	26	39	
	% within Age Groups	33.3%	0.0%	0.0%	0.0%	0.0%	0.0%	66.7%	100.0%	
Total	Count	26	25	29	15	10	11	77	193	
	% within Age Groups	13.5%	13.0%	15.0%	7.8%	5.2%	5.7%	39.9%	100.0%	

Table No.7: Gender Wise Stratification of Type of Bacteria (n = 193)

Gender		Type of Bacteria							Total	P-value
		Pneumococcus	Meningococcus	E. Coli	Staphylococcus Aureus	Hemophilus Influenza	Klebsiella	NA		
Male	Count	21	21	20	12	8	8	39	129	<.001
	% within Gender of Patient	16.3%	16.3%	15.5%	9.3%	6.2%	6.2%	30.2%	100.0 %	
Female	Count	5	4	9	3	2	3	38	64	
	% within Gender of Patient	7.8%	6.2%	14.1%	4.7%	3.1%	4.7%	59.4%	100.0 %	
Total	Count	26	25	29	15	10	11	77	193	
	% within Gender of Patient	13.5%	13.0%	15.0%	7.8%	5.2%	5.7%	39.9%	100.0 %	

DISCUSSION

Although the incidence and rates of morbidity and death related to community-acquired acute pyogenic meningitis have adequately decreased, possibly as an outcome of immunization and proper antibiotics and related therapies, the disease still has a high number. In United States, still 10% to 20% of people die of it [6].

The organisms causing community-acquired acute pyogenic meningitis slightly differ by geographic region, by age. A study conducted in United States surveillance data, from 1998 to 2007, the most prevalentagent forbacterial meningitis among adults was "Streptococcus pneumoniae"."Neisseria meningitidis" is as prevalent as "S. pneumoniae" among young adults. Listeria infections cases increases with age[6].

The epidemiologic characteristics of bacterial meningitis have varied dramatically over the past decades with the advent of the "Haemophilus influenzae" vaccine. In 1986, about half the cases of acute bacterial meningitis were due to"H. influenzae", but a decade later the incidence of "H. influenzae" meningitis had been reduced by 94%[6].

Meningitis is inflammation of the pia and arachnoid (the inner two layers of the meninges). Acute community-acquired meningitis can develop within hours to days and can be viral or bacterial. Viral meningitis usually has a good prognosis, whereas bacterial meningitis is associated with significant rates of morbidity and death, so it is critical to identify and segregate them promptly.

Meningitis may be related with significant mortality even after institution of therapy. Nearly one in four adults with acute bacterial meningitis (ABM) will die and many survivors retain neurological deficit[12]. Early initiation of appropriate antibiotics requires prompt recognition of the infecting pathogen. The non-specific clinical presentation and lack of laboratory facilities can delay or obscure diagnosis[13].

Although culture is considered to be the gold standard[14], CSF turbidity, bacteria on direct Gram stained preparation[11] and pleocytosis[11], increase in protein and decrease in sugar are preliminary indicators. However, culture for fastidious organism is difficult and time consuming and produce false negative results;[15]hence the detection of soluble antigens in CSF in suspected cases by the latex particle agglutination test is considered an important diagnostic tool which has a high sensitivity, specificity, simplicity in execution, rapidity, and interpretation[11].

In our study, we detected a variety of bacteria through blood culture of patients who were positive. In our study, the most frequent bacteria found was E Coli 25% followed by Pneumococcus in 22.4% of patients, Meningococcus was seen in 21.6% of patients, Klebsiella was seen in 9.5% and H. Influenza was seen in 8.6%. Overall, the positive blood culture was observed in 60.1% of patients.

In one study, ABM in winter and fall was reported to be 72.9% and in another only 27.1% cases in spring and summer[6,16]. These changes were probably because of geographical difference.

In our study, the maximum number of cases was in the age group of 18-51.5 years. Previous studies reported that of the patients who had bacterial meningitis, 79% were older than 15 years and 45% were older than 2 years[17]. In the present study however, 40.2% of the cases who had bacterial meningitis were above 35 years of age. This was probably because in the present study there were lesser isolations of pathogens. In addition majority of the patients inducted in our study belonged to the age group of 16-35 years (59.6%). Males were found to be affected more commonly. The overall male to female ratio was found to be 2.01:1, which was somewhat similar to other studies, with a ratio of 1.2:1[6,18] and 1.69:1[16].

Culture positive cases were 60.1%, slightly higher than those in previous reports[19,53] which denotes that culture remains the gold standard technique. E Coli 25% followed by Pneumococcus in 22.4% of patients, Meningococcus was seen in 21.6% of patients, Klebsiella was seen in 9.5% and H. Influenza was seen in 8.6%. These findings were different from those in other studies[18], probably because this study included age range

of 16-65 years unlike the other studies, which included only children.

We also stratified the type of bacteria with regards to different age groups. Here E. coli was frequently found in age range 25-45 years and Pneumococcus in the age range above 35 years, unlike in previous studies that reported Pneumococcus to be the most common isolate[19]. This was probably because the other studies included subjects with community-acquired meningitis and therefore the number of Gram-negative isolates were comparatively lower than those of the present study. In a study conducted in Nepal, ABM was found in 8.3% cases, the causative agents being "Pseudomonas areuginosa" (24.3%), coagulase negative Staphylococcus (CONS) (10.8%), and E. coli (2.7%), where they claimed to have hospital-acquired infection causing meningitis [11]. Blood cultures were positive in only 60.1% cases of bacterial meningitis, which was similar to other findings with 58.4% positivity[18].

In a study by Domingo P et al, the incidence of ABM 4.03/100,000 (Group I) and 7.40 /100,000 inhabitants/year (Group II) (RR = 1.84; 95%CI: 1.56–2.17, $P < 0.0001$). Elderly patients had co-morbid conditions more frequently ($P < 0.0001$) and more frequently lacked fever ($P = 0.0625$), neck stiffness ($P < 0.0001$) and skin rash ($P < 0.0001$), but had an altered level of consciousness more often ($P < 0.0001$). The interval admission-start of antibiotic therapy was longer for elderly patients ($P < 0.0001$). Meningococcal meningitis was less frequent in elderly patients ($P < 0.0001$), whereas listerial ($P = 0.0196$), gram-negative bacillary ($P = 0.0065$), and meningitis of unknown origin ($P = 0.0076$) were more frequent. Elderly patients had a higher number of neurologic ($P = 0.0009$) and extra-neurologic complications ($P < 0.0001$). The overall mortality ratio was higher in elderly patients ($P < 0.0001$)[8].

In a review from US, the most common organisms that cause community-acquired bacterial meningitis are "pneumococci" and "Neisseria meningitidis". The incidence of Listeria infection increases in patients over age 50 and in those with compromised cell-mediated immunity[7].

In another study from India, the organisms isolated from patients of ABM were "Escherichia coli" 25.6%, "Staphylococcus aureus" 15.4%, "Streptococcus pneumonia" 10.2%, "Klebsiella species" 10.2% and "Pseudomonas areuginosa" 10.2%[11].

In another study, streptococcus species were the most common causative micro-organism group, at 23.21% of all episodes. Its prevalence rate significantly decreased from the first 7 years of study (41.9%) to the last 10.5 years (19.2%). However, Klebsiella meningitis and Staphylococcal meningitis were more frequently noted after 1987. More than 70% of patients had at least one underlying disease or condition[20]. In another study by Weisfelt M et al[21], the frequency of positive blood culture was found in 30% with Pneumococci in 26%, Staph. Aureus in 24%, H Influenza in 8%, E Coli in 6% and Klebsiella in 4% of patients. In another study by Change WN et al, the most frequent isolate was Enterobacter species (Enterobacter cloacae, Enterobacter aerogenes), Klebsiella species (Klebsiella pneumoniae, Klebsiella oxytoca), Escherichia coli, Staphylococcus species (Staphylococcus aureus, Staphylococcus haemolyticus), "Pseudomonas areuginosa", "Acinetobacter baumannii", Enterococcus, "Serratia marcescens", "Citrobacter diversus", "Proteus mirabilis", "Streptococcus viridans" and "Neisseria meningitidis". Six of the 12 cases were found to have multi-antibiotic-resistant strains[22].

Thus to conclude, the findings in this study show a preponderance of E Coli, Pneumococci and Meningococci as the causative agent of bacterial meningitis. H. influenzae was isolated in very few cases. This could probably be due to the wide reach of Hib vaccination for H. influenzae in children even in rural and semi-urban areas. This organisms is also very delicate and die easily.

Further studies however, regarding the occurrence of other pathogens causing bacterial meningitis such as N. meningitidis, Listeria monocytogenes, and fungi such as Cryptococcus neoformans are required in the future, preferably using tests to detect antigens and even by polymerase chain reaction of the blood especially considering the fact that these organisms, which are established causes of meningitis were not isolated in the present study.

CONCLUSION

Acute pyogenic meningitis is a common occurrence in our population with E Coli, Pneumococci and Meningococci being the common culprits. Further studies regarding the occurrence of other pathogens causing bacterial meningitis such as Listeria monocytogenes, and fungi such as Cryptococcus neoformans are required in the future.

Author's Contribution:

Concept & Design of Study:	Muhammad Ayaz
Drafting:	Abdul Hanan, Muhammad Khalid
Data Analysis:	Rifayatullah Afridi, Muhammad Haroon Shahid, Shabir Hussain
Revisiting Critically:	Muhammad Ayaz, Abdul Hanan
Final Approval of version:	Muhammad Ayaz

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REFERENCES

1. Prober CG, Dyner L. Acute bacterial meningitis beyond the neonatal period. Nelson Textbook of Pediatrics, 19th ed. Philadelphia (PA): Elsevier Saunders;2011.p.2087-2096.

2. Kasanmoentalib ES, Brouwer MC, van de Beek D. Update on bacterial meningitis: epidemiology, trials and genetic association studies. Current opinion in Neurol 2013;26:282-288.
3. Heckenberg SG, et al. Adjunctive dexamethasone in adults with meningococcal meningitis. Neurol 2012;79:1563-1569.
4. Van de Beek D, et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. The Lancet Neurol 2010; 9:254-263.
5. Madhumita P, Gupta N. Clinical and bacteriological spectrum of community-acquired acute bacterial meningitis in adults at a tertiary care hospital in northern India. Int J Nutrition, Pharmacology, Neurological Diseases 2011;1:194.
6. Thigpen MC, et al. Bacterial meningitis in the United States, 1998–2007. New Engl J Med 2011;364:2016-2025.
7. Bhimraj A. Acute community-acquired bacterial meningitis in adults: an evidence-based review. Cleveland Clinic J Med 2012;393-400.
8. Domingo P, Pomar V, de Benito N, Coll P. The spectrum of acute bacterial meningitis in elderly patients. BMC infectious Dis 2013;13:108.
9. Schut ES, et al. Cerebral infarction in adults with bacterial meningitis. Neurocritical Care 2012; 16:421-427.
10. Longo DL, et al. Harrison's Principles of Internal Medicine. 18th ed. McGraw Hill Professional;2012.
11. Adhikary M, Chatterjee RN. Laboratory evaluation of cases of meningitis attending a tertiary care hospital in India: An observational study. Int J Nutr, Pharmacology, Neurological Dis 2013;3:282.
12. Jones ME, Draghi DC, Karlowsky JA, Sahm DF, Bradley JS. Prevalence of antimicrobial resistance in bacteria isolated from central nervous system specimens as reported by US hospital laboratories from 2000 to 2002. Annals Clinical Microbiol and Antimicrobials 2004;3:3.
13. Kim KS. Acute bacterial meningitis in infants and children. The Lancet infectious Dis 2010;10:32-42.
14. Dunbar SA, Eason RA, Musher DM, Clarridge JE. Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis. J Clin Microbiol 1998;36:1617-1620.
15. Mohammadi SF, Patil AB, Nadagir SD, Nandihal N, Lakshminarayana S. Diagnostic value of latex agglutination test in diagnosis of acute bacterial meningitis. Annals of Ind Academy of Neurol 2012;16: 645.
16. Farag HM, Abdel-Fattah M, Youssri A. Epidemiological, clinical and prognostic profile of acute bacterial meningitis among children in Alexandria, Egypt. Ind J Medical Microbiol 2005;23:95.
17. Bijlsma MW, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. The Lancet Infectious Dis 2016;16:339-347.
18. Pandey P, Jha B, Shrestha A. Etiology of Meningitis from Patients Suspected of Meningitis Attending Tribhuvan University Teaching Hospital, Kathmandu, Nepal. Am J Microbiol 2015;6:21.
19. Singh AK, et al. Bacteriological profile of acute bacterial meningitis at a tertiary care hospital of North India. Int J Research in Med Sci 2016;4:4387-4393.
20. Chang WN, Huang CR, Lu CH, Chien CC. Adult Klebsiella pneumoniae meningitis in Taiwan: an overview. Acta Neurol Taiwan 2012;21:87-96.
21. Weisfelt M, Van de Beek D, Spanjaard L, De Gans J. Nosocomial bacterial meningitis in adults: a prospective series of 50 cases. Journal of Hospital Infection 2007;66:71-78.
22. Chang WN, et al. Changing epidemiology of adult bacterial meningitis in southern Taiwan: a hospital-based study. Infection 2008;36:15-22.

Original Article

Anti Tuberculousis Drugs Induced Hepatitis

Prevalence of Anti Tuberculousis Drug Induced Hepatitis in Patients on Anti Tuberculous Drug in Mardan Medical Complex

Nabi Rehman[1], Sajjad Ali[1], Shah Zeb[2], Muhammad Abbas[2], Naveed Khan[2] and Rehman ud Din[2]

ABSTRACT

Objective: To determine the frequency of anti tuberculousis drugs induced hepatitis in Mardan Medical Complex.
Study Design: Descriptive / cross sectional study
Place and Duration of Study: This study was conducted at the chest OPD and TB centre of Mardan Medical Complex, Mardan from November 2018 to July 2019.
Materials and Methods: Diagnosed 309 cases of TB both pulmonary and extra pulmonary were taken. Among these only category I TB patients were selected and followed up for the development of ATT induced hepatitis.
Results: Study included a total of 309 patients in which 170 (55.01%) were male patients and 139 (44.98%) were female patients. Ages of the patients ranged between 15 and 80 years with a mean age of 34.8 years among male while 14 and 80 years with an mean age of 38.40 years among female. Out of 309 patients only 56 (18.12%) patients developed ATT induced hepatitis.
Conclusion: ATT induced hepatitis is an important and common side effect of anti tuberculous therapy and needs early recognition and treatment to avoid non compliance to ATT and treatment failure.
Key Words: Hepatitis, ATT, anti tuberculous drugs.

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INTRODUCTION

Tuberculosis is a health problem worldwide that is both preventable and curable. About one-third of world's population is infected by tuberculosis[1]. If an active case of TB is left untreated then each active case can infect 10 to 15 people in one year[1]. Pakistan is 5th amongst 22 countries with highest burden of TB[2]. The currently recommended first line treatment for Cat-1 TB is a regimen of isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and pyrazinazmind (PZA) for intial two months(intensive phase) and for next four months(continuation phase) INH and RMP[3]. Three first line drugs that are INH, RMP, and PZA are metabolized by liver and are hepatotoxic. Drug-induced hepatotoxicity associated with first-line drugs such as isoniazid, rifampin, and pyrazinamide is common, as with the use of many other therapeutic agents that causing hepatotoxicity,[4,5] this side effect of ATT drug is predictable and depend on dose of drug but for most it is idiosyncratic and dependent on parameters such as dosage, age, gender, and body mass index (BMI).[6]

The occurrence of ATT induced hepatitis is different among different countries that is the incidence is higher in the developing countries with rates ranging between 8% to 39% compared to developed countries at 3%-4%, despite similar regimens used.[7-10] As a specific example, a higher risk of 11.5% has been reported in Indian patients, compared to 4.3% in published studies from the developed countries.[1,12,13] One recent study from Singapore reported an incidence of 5.3%.[14] Higher incidence of ATT induced hepatitis in developing countries is due to risk factor like severity of the disease, nutritional status, wrong diagnosis and the effect of Hepatitis B and Hepatitis C positive serology.[15-18] One prospective cohort study from Spain has shown the incidence of anti tuberculosis drug-induced hepatotoxicity to be significantly higher in the group with risk factors (18.2%) than in the group without (5.8%).[19] In Pakistan about 19.76% of the patients developed anti tuberculosis drug induced hepatotoxicity. It usually occurs in the initial few weeks of the intensive phase of anti- tuberculosis chemotheraphy.[20]

MATERIALS AND METHODS

This was a prospective study carried out at Mardan Medical complex which is a tertiary care teaching

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hospital, from 1st November 2018 to 1st July 2019. Mardan medical complex having a chest OPD and a TB centre where diagnosed cases of tuberculoses are treated.

In our study we enrolled a total of 309 diagnosed cases of both pulmonary and extra pulmonary cases, including only category I TB patients. Approval for the study was obtained from ethical committee of the hospital. Written informed consent was taken from the patient for enrolment in study. After proper diagnosing according to the National and WHO guide lines patients were started on anti-TB drugs and followed up according to national TB treatment guidelines. The patients were also counselled to come to OPD if they developed signs and symptoms of hepato toxicity like anorexia, nausea, vomiting and yellow discolouration of the sclera and urine. Patients presenting with the above mentioned symptoms were subjected to liver functions tests (ALT, AST, ALP and serum bilirubin). Those patients fulfilling the criteria given below [23] were labelled as cases of anti-TB drug induced hepatitis. 1) ALT > 5 times normal irrespective of the signs and symptoms of hepatitis. 2) ALT >3 times normal with signs and symptoms of hepatitis. 3) Serum billirubin bilirubin to > 1.5 mg/dl.

Those patients with hepatitis while taking some other hepatotoxic drugs along with anti tuberculosis drugs were excluded from study to prevent bias because we were not known which one was the cause of hepatitis. Similarly Patients with acute hepatitis whose signs and symptoms and liver function tests did not normalize after stopping anti -tuberculosis drugs for 7 days were also excluded as they warranted further investigations for an alternative diagnosis. Also those patients who were taking second line drugs for multi drug resistant tuberculosis and those with inadequate medical records to allow complete analysis, were excluded from study.

All patients were interviewed with a questionnaire to obtain clinical data like age, sex, alcohol intake, current clinical symptoms (anorexia, nausea, vomiting and jaundice) with duration, detailed history of tuberculosis and the drug history of not only anti tuberculosis drugs but drugs for any other medical or surgical disease. All laboratory investigations were done in the Pathology Department while chest X-ray and ultrasound abdomen in the Radiology Department of Mardan medical complex. All patients with anti-tuberculosis drugs induced hepatitis were managed according to the standard guidelines. The above mentioned clinical, biochemical and historical data collection was documented on Performa and was analyzed statistically. All the information / data were kept confidential because the disease is still considered to be a social stigma. Statistical analysis was performed by using SPSS version 15.0. Frequencies / Percentages were calculated for different study variables.

RESULTS

In our study we have included a total of 309 patients in which 170 (55.01%) were male patients and 139 (44.98%) were female patients. Out of 309 patients only 61 patient developed ATT induced hepatitis but only 56 (18.12%) patients were eligible according to our inclusion criteria and remaining 5 (1.61%) patients were excluded according to our exclusion criteria. Those excluded were either active hepatitis C or hepatitis B cases, or due to non-specific pre-treatment hepatitis, and incomplete medical records. Ages of the patients ranged between 15 and 80 years with an mean age of 34.8 years among male while 14 and 80 years with an mean age of 38.40 years among female.

DISCUSSION

Tuberculosis is the disease which currently infects about 1/3rd of the world population [1] and our country Pakistan came at No 5 in the list of 22 courtiers having highest numbers of tuberculosis patients [2]. Treatment of tuberculosis patients by use of first line anti-TB drug which is a regimen of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinazmind (Z) for two months, and isoniazid (H), rifampicin for next four months. Anti tuberculous drugs are most effective against active cases of TB but due to one of the major and serious side effect which is ATT induced hepatitis patients taking anti-TB should be regularly evaluated for hepatotoxicity.

Early diagnosis of anti-TB drug hepatitis and discontinuation of anti-TB play crucial role in decreasing severity of disease and limits extend liver injury. Presentation of Drug Induced hepatotoxicity is very variable that is there may be no symptoms in some cases and others may present with sudden-onset liver failure. Therefore physicians should regularly evaluate patients taking anti tuberculosis drug for hepatotoxitiy by routine follow-up visit and doing laboratory investigation and by looking for sign and symptoms of ATT induced hepatitis. Risk factor for ATT induced hepatitis play important role in developments of anti-TB drugs induced hepatitis and may help identify those at risk. Although in this study we mainly focused only on the prevalenceof ATT induced hepatitis. However in one of my previous studies conducted in lady reading hospital Peshawar we indentified the frequency of risk factor in patient with anti-TB drug induced hepatitis. In that study we have found that frequency of risk factors in ATT induced hepatitis is significantly high.

The prevalence of anti tuberculosis induced hepatitis in this study was 18.12% which is comparable with study (19.8%) done in Karachi Pakistan [21]. The reported prevalence of ATT induced hepatitis in developing countries is higher than developed countries. In developing countries the rates of ATT induced hepatitis range between 8% to39% compared to developed

countries at 3%-4%, despite similar regimens used [7-10]. One possible reason of higher prevalence in our study may be due to presence of risk factor for ATT induced hepatitis. higher incidence of ATT induced hepatitis in developing countries is due to risk factor like age, sex, severity of the disease, nutritional status, alcoholism, wrong diagnosis and the effect of Hepatitis B and Hepatitis C positive serology [15-18].

CONCLUSION

In conclusion ATT induced hepatitis is an important side effect of anti tuberculous therapy and may lead to non compliance to ATT and treatment failure. Therefore this side effect needs vigilance, early recognition, treatment and proper counselling to improve adherence to ATT and treatment out come.

Author's Contribution:

Concept & Design of Study:	Nabi Rehman
Drafting:	Sajjad Ali, Shah Zeb
Data Analysis:	Muhammad Abbas, Naveed Khan, Rehman ud Din
Revisiting Critically:	Nabi Rehman, Sajjad Ali
Final Approval of version:	Nabi Rehman

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Global tuberculosis control report: World Health Organization:2010
2. Khan JA, Malik A, Tuberculosis in Pakistan: are we losing the battle? J Pak Med Assoc 2003; 53(8):320.
3. World health organization: treatment of tuberculosis: guidelines. 4th ed. Geneva: Word Health Organization; 2010.
4. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf 2006;5:231–249.
5. Fry RS, Khoshnood K, Vdovichenko E, Granskaya J. Barriers to completion of tuberculosis treatment among prisoners and former prisoners in St. Petersburg, Russia. Int J Tuberc Lung Dis 2005;9:1027–3.
6. Aithal PG, Day CP. The natural history of histological proved drug induced liver
7. Parthasarathy R, Sarma GR, Janardhanam B. Hepatictoxicity in South Indian patients during treatment of tuberculosiswith short -course regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1986; 67:99-108.
8. Turktas H, Unsal M, Tulek N, Oruç O. Hepatotoxicity of antituberculosis therapy (rifampicin, isoniazid and pyrazinamide) or viral hepatitis. Tubercle Lung Dis 1994; 75:58-60.
9. Combs DL, O'Brien RJ, Geiter LJ. USPHS tuberculosis short -course chemotherapy trial 21: Effectiveness, toxicity and acceptability. The report of final results. Ann Intern Med 1990;112:397-406.
10. British Thoracic Society and Tuberculosis Association. Short course chemotherapy in pulmonary tuberculosis. Lancet 1975; 305:119-24.
11. Parthasarathy R, Sarma GR, Janardhanam B, et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short -course regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1986; 67:99-108.
12. Snider DE, Long MW, Cross FS, Farer LS. Six months isoniazid and rifampicin therapy for pulmonary tuberculosis: report of a United States Public Health Service cooperative trial. Am Rev Respir Dis 1984; 129:573-9.
13. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin: a meta -analysis. Chest 1991; 99:465-71.
14. Teleman MD, Chee CB, Earnest A, et al. Hepatotoxicity of tuberculosis chemotherapy under a general program conditions in Singapore. Int J Tuberc Lung Dis 2002; 6:699-705.
15. Shakya R , Rao B.S, Bhawana S. Evaluation of risk factors for antituberculosis drug- induced hepatotoxicity in Nepalese Population. Kathmandu University J Sci, Engg and Technol 2008; 11: 1-8.
16. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: Hepatoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935–52.
17. Smink F, Hoek B, Ringer J, Altena R, Arend SM. Risk factors for acute hepatic failure during antituberculosis treatment: two cases and literature review. J Med Netherland 2006; 64: 10.
18. Fernandez VA, Sopena B, Fernandez VJ, The influence of risk factors on the severity of anti Tuberculosis drug induced hepatotoxicity. Int J Tuberc Lung Dis 2004; 8: 1499-505.
19. Fernandez-Villar A, Sopena B, Fernandez-Villar J, et al. The influence of risk factors on the severity of anti-tuberculosis drug-induced hepatotoxicity. Int J Tuberc Lung Dis 2004; 8: 1499 - 505.
20. Yew WW, leung CC. Anti-tuberculosis drugs and hepatotoxicity. Respirol 2006; 11: 699-707.
21. Khalid M, Akhtar H, Krishan LJ, Abu T, Badar-uddin A, et al. Pak J Med Sci 2007;23(1):33-38
22. Rahman N, Ali S, Khan MY, Umar M, Iqbal Z, Basit A, Ullah Z, Javaid A. Frequency of risk factors for hepatotoxicity in patients with antituberculosis drug induced hepatitis. Pak J Chest Med 2015; 21(1): 04 - 9.
23. Ungo JR, Jones D, Ashkin D, et al. Antituberculosis drug –induced hepatotoxicity. Am J Respir Crit Care Med 1998;157:1871-6.

Original Article

Efficacy of Drugs in UTI by E.Coli

Comparison of Efficacy of Intravenous Amikacin with Intravenous Cefoparazone/Sulbactum in Urinary Tract Infections Caused by Escherichia Coli Indiabetic Patients

Mohammad Nadeem[1], Mujeeb-ur-Rehman[2], Irfan Ullah[2], Adeel Basharat[1], Irfan Ullah[3] and Tahir Ghaffar[2]

ABSTRACT

Objective: To compare the efficacy of I/V Amikacin with I/V Cefoperazone/Sulbactum in urinary tract infections caused by Escherichia coli in patients having diabetes mellitus.

Study Design: Randomized clinical trial study

Place and Duration of Study: This study was conducted at the Department of Medicine, Khyber Teaching Hospital, Peshawar during November 2014 to April 2015.

Materials and Methods: It was a randomized clinical trial and the sample size was 46 patients in each group, total sample size was at least n=92.Non probability consecutive sampling was used for sample collection. Routine investigations like Full Blood Count, Ultrasound of Urinary system, Renal Function tests, 24 hours urinary proteins and creatinine clearance, Random and fasting blood Sugar and HbA1c were done on the selected patients.The patients were then divided into two groups "Group-A' for Amikacin I/V 500mg BD and 'Group-B' for Cefoperazone/Sulbactam 2 Grams I/V BD, both groups receiving treatment for 07 days. The diagnosis of UTIs was based on mentioned criteria. Urine culture was performed by collecting clean-catch midstream urine in a sterile urine bottle or sending catheter tip, if patient was catheterized and then subjecting it to growth for bacteria using kled or MacConkey agar incubated at 37C° in incubator for 24 hours in hospital laboratory. At the end of study, difference of atleast 10% in Efficacy of two groups(drugs) was considered as significant. P1=Efficacy of Amikacin (90%) andP2=Efficacy of Cefoperazone/Sulbactam(65%), Power of test(1-β)=90% and level of significance=0.05%.

Results: Our study shows that mean age in group A (I/V Amikacin) was 44 ± 2.77 years and mean age in group B (I/V Cefoperazone/Sulbactum) was 46± 3.12 years. In group A (I/V Amikacin) 32% patients were male, 68% patients were female. Whereas in group B (I/V Cefoperazone/Sulbactum) 30% patients were male, 70% patients were female. More over our study shows that I/V Amikacin was effective in 85% patients and was not effective in 15% patients whereas I/V Cefoperazone/Sulbactum was effective in 68% patients and was not effective in 32% patients

Conclusion: Our study concludes that I/V Amikacin was more effective than I/V Cefoperazone/sulbactam in urinary tract infections caused by Escherichia Coli in diabetic patients.

Key Words: Amikacin, Cefoperazone/Sulbactum, urinary tract infections, escherichia coli, diabetes mellitus.

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INTRODUCTION

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The term Urinary Tract Infection (UTI) is the infection of urinary tract by pathogenic bacteria which includes patients having cystitis, prostatitis and pyelonephritis. Urinary tract infections are amongst the most prevalent infectious diseases affecting approximately 150 million people worldwide annually.[1] Most common causative organism for the urinary tract infection is Escherichia coli, which is responsible for up to 70% of the cases both in outpatient and inpatient. Other less common gram negative bacteria include Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa, Proteus spp. Gram positive bacteria accounts for 5 – 15% of UTIs and include Enterococcus spp., Staphylococci, and Streptococci.[2]

The resistance of bacteria causing urinary tract infection (UTI) to commonly prescribed antibiotics is

increasing both in developing as well as in developed countries. Resistance has emerged even to more potent antimicrobial agents.[3] The antibiotics commonly used to treat UTIs are broad spectrum cephalosporins, floroquinolones and aminoglycosides.[4]Sulbactam is a molecule that is administered in combination with β-lactam antibiotics to overcome the effects of β-lactamase. The addition of sulbactam to cefoperazone treatment augments the activity of cefoperazone against β-lactamase-producing bacteria).[1,5]

Females are more susceptible to UTI than males and the most effective drug (effective on isolated E.coli) is Amikacin (from amino-glycosides group).[6]Highest percentages of susceptibility by E.Coli was seen for amikacin (96.6%), ciprofloxacin (95.1%), and gentamicin (92.9%).[7]So there is a strict need for developing specific guidelines for antibiotic prescriptions for UTI and directing the attention of the authorities to the development of increasing antibiotic resistance of uropathogens.Escherichia coli was found to be resistant to Amikacin in less than 10% of cases(hence 90% Efficacy) andresistance of 35% was shown by cefoperazone/sulbactam group(hence 65% Efficacy).[8]Amikacin is very cost-effective and has a good efficacy against E.coli UTIs in previous different studies. The current study is designed in this regard, to find statistics about the efficacies of Amikacin and Cefoperazone/Sulbactam for the treatment of UTIs in diabetic patients in our local population, to find the local statistics about efficacy of the two drugs so that we will be able to formulate a proper protocol for the empirical treatment of UTI in diabetic patients. Therefore a prospective randomized control trial will prove the efficacy of amikacin in treating Diabetic patients having UTI.

MATERIALS AND METHODS

This study was conducted in Department of Medicine, Khyber Teaching Hospital, Peshawar. It was Randomized Clinical Trial. Using WHO Calculator, sample size was 46 patients in each group, total sample size was at least n=92,P1=Efficacy of Amikacin and P2=Efficacy of Cefoperazone/Sulbactam, Power of test(1-β)=90% and level of significance= 0.05%. Non probability consecutive sampling technique was used. Patients included in this study were known diabetics having UTI(Urinary symptoms with >10 WBCs/HPF and E.Coli growth on urine culture) aged 20-60 years and who have already taken oral antibiotics without response atleast 48 hours before sending Urine C/S. Patients excluded were those who were hypersensitive to Amikacin Or Cefoperazone/Sulbactam, having impaired renal functions,chronic renal failure or diabetic nephropathy,pregnant females in their first trimester, terminally ill or immune-compromised patients(except having Diabetes Mellitus) like HIV, Malignancies etc.

Ethical approval was taken for this study. Routine investigations like Full Blood Count, Ultrasound of Urinary system, Renal Function tests, 24 hours urinary proteins and creatinine clearance, Random and fasting blood Sugar and HbA1c were done on the selected patients.

The patients were then divided into two groups by lottery method: "Group-A' for Amikacin I/V 500mg BD and 'Group-B' for Cefoperazone/Sulbactam 2 Grams I/V BD, both groups receiving treatment for 07 days. Detailed history and examination of patients was recorded. The diagnosis of UTIs was based on mentioned criteria. Urine culture was performed by collecting clean-catch midstream urine in a sterile urine bottle or sending catheter tip, if patient was catheterized and then subjecting it to growth for bacteria using kled or MacConkey agar incubated at 37C° in incubator for 24 hours in hospital laboratory. At the end of study, difference of atleast 10% in Efficacy of two groups(drugs) was considered as significant.

The data collected from the patients through proformas was entered and analyzed in statistical package for social sciences (SPSS) latest version. Mean ± SD was calculated for numerical variable like age and duration of diabetes mellitus. Frequencies and percentages were calculated for categorical variable like gender, efficacy and urine culture. Chi-Square test was applied to compare the efficacy of both the drugs keeping the P Value $\leq$ 0.05, was significant. Efficacy was stratified for UTIs isolates to see the effect modification of age and gender. Final results were presented as tables and graphs.

RESULTS

Our study shows that mean age in group A (I/V Amikacin) was 44 year ± 2.77 and mean age in group B (I/V Cefoperazone/Sulbactum) was 46 year ± 3.12. In group A (I/V Amikacin) 32% patients were male, 68% patients were female. Where as in group B (I/V Cefoperazone/Sulbactum) 30% patients were male, 70% patients were female.

Urine culture among two groups was analyzed as urine culture was done in all the patient of group A and group B and escherichia coli was found positive. (as shown in table no 3)

Table No. 1: Age Distribution (n=92)

AGE	GROUP A	GROUP B
20-30 years	5(12%)	4(9%)
31-40 years	14(30%)	15(32%)
41-50 years	16(35%)	16(35%)
51-60 years	11(23%)	11(24%)
Total	46(100%)	46(100%)
Mean and SD	44 year± 2.77	46 year ± 3.12

Group A:I/V Amikacin

Group B: I/V Cefoperazone/Sulbactum

Chi Square test was applied in which P value was 0.002

Efficacy among two groups was analyzed as I/V Amikacin was effective in 39(85%) patients and was not effective in 7(15%) patients. Whereas I/V Cefoperazone/ Sulbactum was effective in 31(68%) patients and was not effective in 15(32%) patients. (as shown in table no 4.

Table No. 2: Gender Distribution (n=92)

Gender	Group A	Group B
Male	15(32%)	14(30%)
Female	31(68%)	32(70%)
Total	46(100%)	46(100%)

Group A:I/V Amikacin
Group B: I/V Cefoperazone/Sulbactum
Chi Square test was applied in which P value was 0.002

Table No. 3: Urine Culture (n=92)

Urine Culture	Group A	Group B
Yes	46(100%)	46100%)
No	0(0%)	0(0%)
Total	46(100%)	46(100%)

Group A:I/V Amikacin
Group B: I/V Cefoperazone/Sulbactum
Chi Square test was applied in which P value was 0.000

Table No. 4: Efficacy (n=92)

Efficacy	Group A	Group B
Effective	39(85%)	31(68%)
Not effective	7(15%)	15(32%)
Total	46(100%)	46(100%)

Group A:I/V Amikacin
Group B: I/V Cefoperazone/Sulbactum
Chi Square test was applied in which P value was 0.004

DISCUSSION

Urinary tract infections are amongst the most prevalent infectious diseases affecting approximately 150 million people worldwide annually. UTIs occur more in young to middle age patients than in pediatric patients and affects females more commonly.[1]In pregnant women, prevalence rate of UTI is 29.57%.[11]

The most common cause of UTI in men and women with and without DM is E. coli.[4,9,10] Diabetic patients are at a higher risk of developing acute pyelonephritis, renal abscess, abnormalities of bladder scarring and pyelitis.[9] Most common causative organism for the urinary tract infection is Escherichia coli, which is responsible for up to 70% of the cases both in outpatient and inpatient.[4,9] Other less common gram negative bacteria include Klebsiella spp., Enterobacter spp., Pseudomonas aeruginosa, Proteus spp. Gram positive bacteria accounts for 5 – 15% of UTIs and include Enterococcus spp., Staphylococci, and Streptococci.[9,10]

Antimicrobial resistance among uropathogens causing community and hospital acquired urinary tract infections is increasing.[12,13]The emergence of resistance to the described antibiotics in the management of UTIs is indeed a serious public health problem in the developing countries like Pakistan, where apart from high level of poverty, ignorance and poor hygienic practices, fake and spurious drugs of questionable quality are often in circulation. Furthermore, common usage antibiotics have a high rate of resistance.[14,15]If urgent measures are not taken to arrest the situation, we may see the return of the era of search for new drugs to fight bacterial infections causing UTI.

In our study, Urinary tract infections with E. Coli were seen more in individuals 44 to 46 years of age, with a female preponderance, as in group A (I/V Amikacin) 32% patients were male, 68% patients were female whereas in group B (I/V Cefoperazone/Sulbactum) 30% patients were male, 70% patients were female. Moreover, our study shows that I/V Amikacin was effective in 85% patients and was not effective in 15% patients. Whereas I/V Cefoperazone/Sulbactum was effective in 68% patients and was not effective in 32% patients. Escherichia coli was found to be resistant to Amikacin in less than 10% of cases(hence 90% Efficacy) and resistance of 35% was shown by cefoperazone/sulbactam group(hence 65% Efficacy).

A study conducted in India shows that Amikacin sensitivity was 64.7% in E. Coli strains that were multiple drug resistant.[16]

In another study conducted by Fawwad A et al, E. coli strains were mostly susceptible to imipenem (100%) followed by ertapenem and piperacillin/tazobactam (95%), sulbactam / cefoperazone (76%), amikacin (90%) and aztereonam (62%).[17]

CONCLUSION

Our study concludes that I/V Amikacin was more effective than I/V Cefoperazone/sulbactam in urinary tract infections caused by Escherichia Coli in diabetic patients.

Author's Contribution:

Concept & Design of Study:	Mohammad Nadeem
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Data Analysis:	Adeel Basharat, Irfan Ullah, Tahir Ghaffar
Revisiting Critically:	Mohammad Nadeem, Mujeeb-ur-Rehman
Final Approval of version:	Mohammad Nadeem

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Akram M, Shahid M, Khan AU. Etiology and antibiotic resistance patterns of community-acquired urinary tract infections in JNMC Hospital Aligarh, India. Ann Clin Microbiol Antimicrob 2007; 6:4.

2. Ullah F, Malik S, Ahmed J. Antibiotic susceptibility pattern and ESBL prevalence in nosocomial Escherichia coli from urinary tract infections in Pakistan. Afr J Biotech 2009;8(16):3921–6.
3. Mandal J, Acharya NS, Buddhapriya D. Antibiotic resistance pattern among common bacterial uropathogens with a special reference to ciprofloxacin resistant Escherichia coli. Ind J Med Res 2012;136(5):842-9.
4. Humayun T, Iqbal A. The culture and sensitivity pattern of urinary tract infections in females of reproductive Age Group in Lahore. Ann Pak Inst Med Sci 2012;8(1):19-22.
5. Akova M. Sulbactam-containing beta-lactamase inhibitor combinations in Turkey. Clin Microbiol Infect 2008;14(Suppl. 1):185–8.
6. Maji SK, Maity C, Halder SK. Studies on drug sensitivity and bacterial prevalence of UTI in Tribal population of Paschimmedinipur, India. Jundishapur J Microbiol 2013;6(1):42-6.
7. Fakhriddeen AJ. Occurrence of Escherichia coli in patients with urinary tract infections in Najaf city. Kufa J Vetrn Med Sci 2011;2:2.
8. Sabharwal ER. Antibiotic susceptibility patterns of uropathogens in obstetric patients. N Am J Med Sci 2012;4(7):316–9.
9. Rother KI. "Diabetes treatment—bridging the divide". The New England J Med 2007; 356(15):1499–501.
10. Saleem M, Daniel B. Prevalence of urinary tract Infection among patients with diabetes in Bangalore city, India. Int J Emerg Sci 2011;1(2):133-42
11. Dogra V, Sharma A, Mishra B, Thakur A. Drug-resistant Gram-negative bacilli in urinary tract infection: A need for strict antibiotic prescription policy. Int J Health Allied Sci 2012;1:204-6.
12. Ahmad J, Shah A, Ali NS. Prevalence of urinary tract infection in pregnant women of Peshawar NWFP. J PG Med Inst Pesh 2011;17:2.
13. Meini M, Spitaleri P, Gigli C. Current microbiological and clinical aspects of urinary tract infections. Eur Urol 2001; 40(4):39-44
14. Arjunan M, Al-Salamah AA, Amuthan M. Prevalence and antibiotic susceptibility of uropathogens in patients from a rural environment, Tamil Nadu. Am J Infect Dis 2010;6(2):29-33.
15. Yadav K, Prakash S, Serayi RC, Shilpkar T, Shrestha S. Antimicrobial susceptibility test of pathogens isolated from urinary tract infection suspected cases. J Med Sci 2014; 2(1): 28-34.
16. Niranjan V, Malini A. Antimicrobial resistance pattern in Escherichia coli causing urinary tract infection among inpatients. Ind J Med Res 2017; 139: 945-948.
17. Salunke GV, Gidamudi SS. Antibiotic susceptibility of bacterial strains, with special reference to Escherichia coli isolated from urinary tract infections in rural Maharashtra. Asian J Pharm Clin Res 2017; 10(1): 202-5.
18. Fawwad A, Sabir R, Riaz M, Basit A. Uropathogens and the antimicrobial susceptibility patterns in patients with Type 2 Diabetes. Austin J Endocrinol Diabetes 2014;1(5): 1023.

Original Article

Antihypertensive Prescription Pattern in the Department of Nephrology Khyber Teaching Hospital Peshawar

Shandana Altaf[1], Ahmad Zeb Khan[2], Mufti Baleegh-ur-Raheem Mahmood[2], Tahira Parveen[3] and Amer Azhar[2]

ABSTRACT

Objective: To find the prescription pattern of antihypertensive drugs in the department of Nephrology Khyber Teaching Hospital Peshawar

Study Design: Observational / cross sectional study.

Place and Duration of Study: This study was conducted at the outpatient department of nephrology Khyber Teaching Hospital Peshawar from January 2018 to March 2018.

Materials and Methods: 200 patients suffering from hypertension were included in the study. We examined the frequency and proportion of various antihypertensive drugs as mono therapy, combination therapy and fixed drug combinations (FDCs).

Results: Most frequently prescribed antihypertensive drugs were CCBs (65%) followed by diuretics (54%), beta blockers (50.5%), ARBs (26%) and ACEIs (21%) respectively. 57.5% were using two drugs and most commonly used FDCs was diuretics with ACEI.

Conclusion: Calcium channel blockers are mostly prescribed while alpha blockers are the least prescribed antihypertensives drugs.

Key Words: prescription pattern, antihypertensive, calcium channel blocker

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INTRODUCTION

Hypertension is a global health issue affecting both developed and developing countries. The worldwide prevalence calculated in 2000 was 25% and is expected to increase by 30% in 2025.[1] Hypertension is one of the major risk factor for cardiovascular disease (CVD) and chronic kidney disease.[2,3,4] Hypertension also constitutes high rates of deaths worldwide.[5] Persistent antihypertensive treatment significantly reduces mortality and morbidity.[6] Reducing high blood pressure is beneficial in the prevention of CVD and CKD.[7] Lower BP target is required in high risk patients such as diabetics and renal failure patients compared to those without such co-morbidities.[8]

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Similarly, BP lowering strategy is also dealt differently in young and elderly individuals.[9] Optimal and intensive treatment options are used for achieving targeted blood pressure.[10 11]

In order to achieve this goal hypertension has to be treated with different pharmacologically available antihypertensive agents like calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEIs), ARBs, Alpha/ beta blockers and diuretics. These drugs are given as mono therapy or combination therapy.[12 13] The selection of different drugs depend on patient's age and co-morbidities like CKD, diabetes and glomerulonephritis. Drug characteristics including efficacy, side effects and financial burden due to cost of the drugs greatly influence the selection of antihypertensive drugs.[14]

MATERIALS AND METHODS

Sample data was collected from the outpatient department of nephrology Peshawar KPK from 1st January 2018 to 31st March 2018. Antihypertensive prescriptions for patients with CKD, diabetes and glomerulonephritis (GN)were included in the study. Mean age was calculated. Antihypertensive drugs were divided into 7 classes depending on their pharmacological characteristics as CCB, beta blockers, alpha blockers, diuretics, ARBs, ACEI, and centrally acting used either alone or in combination or FDCs.

RESULTS

According to table 1, among 200 patients, 109 (54.5 %) were males and 91 (45.5 %) were females showing prevalence of hypertension is 10% higher in male population compared to female population. Mean age of males and females was 57.4 ± 0.94 and 52.71 ± 0.81 years.

As shown in Table 2, 54.4 % of patients had chronic kidney disease, 26 % had diabetes and 19.5 % were suffering from glomerulonephritis. The most commonly prescribed antihypertensive group of drugs in CKD was CCB (49.5 %), beta blockers (46.5 %), diuretics (27%) followed by ARB (9.5%) and ACEI (7%) respectively. In diabetic patients most commonly used antihypertensive was ARB (13%) followed by ACEI (10%). In glomerulonephritis, diuretics use was 19.5% followed by CCB (12%) (table 3). Table no 4 shows most frequently prescribed antihypertensive was CCB (65%) followed by diuretics (54%), beta blocker (50.5%), ARBs (26%) and ACEI (21%) respectively.

Table No.1: Demographic Profile of Patients

Gender	Number (n=200)	Percentage
Male	109	54.5%
Female	91	45.5%

Table No.2: Co Morbidities of the Patients.

Co Morbidity	Male	Female	Total	%age
Chronic Kidney Disease	72	37	109	54.5%
Diabetes	33	19	52	26%
Glomerulone-phritis	20	19	39	19.5%

Table No.3: Treatment of Hypertension With Co Morbidities

Co morbidity	Calcium channel blocker	Beta blocker	Arb	Ace	Alpha blocker	Diuretics	Centrally Acting
Chronic Kidney Disease	49.5%	46.5%	9.5%	7%	1%	27%	1.5%
Diabetes	3.5%	4%	13%	10%	0%	7.5%	0%
Glomerulonephritis	12%	0%	3.5%	4%	0%	19.5%	0%

Table No.4: Frequency of Administration Of Individual Drugs

Antihypertensive group	Antihypertensive group	Number of prescriptions
Calcium Channel Blocker (65 %)	Nifedipine	109
	Amlodipine	21
Diuretics (54 %)	Furosemide	93
	Hydrochlorothiazide	23
	Spironolactone	15
	Metolazone	06
Beta Blocker (50.5%)	Carvedilol	83
	Atenolol	18
ARB (26%)	Valsartan	32
	Losartan	20
ACE (21%)	Enalapril	30
	Ramipril	12
Centrally Acting (1.5%)	Methyldopa	3
Alpha Blocker	Prazosin	2

Table No.5: Numbers of Drugs Prescribed

Number of Anti-Hypertensive Drugs	Number of Prescriptions	Percentage
One Drug	26	13%
Two Drugs	115	57.5%
Three Drugs	54	27%
Four or more Drugs	5	2.5%

Table No.6: Frequency Of Prescribing Fdc

FDC	Number of Prescriptions
Diuretics with ACE	60
Diuretics with ARB	57
ACE/ ARB/ CCB	27
Diuretics in combination	11
Three drugs FDC	7

Twenty-six patients (13%) were using one antihypertensive drug, 57.5% were on two drugs, 27% had three drugs and 5 patients (2.5%) were using four or more drugs (table 5).

Table no 6 shows frequency of fixed drug combination. Sixty prescriptions had combination of diuretics with ACEI while only seven prescriptions were of 3 drugs fixed drug combination.

DISCUSSION

Hypertension is a serious health problem and is of great concern worldwide. According to the National Health survey 18% of adult population are affected by hypertension and the prevalence is increased to 33% in adults above 45 years of age.[15] Multiple factors including genetic predisposition, sedentary life style, lack of exercise, and lack of healthy diet awareness have been identified as major causes of hypertension in Pakistani population. [16]In order to control hypertension effectively, strict compliance and correct prescription of quality antihypertensive drugs is very important. Since these drugs are prescribed for lifelong, the cost of such

drugs is also very important factor as the prices are growing faster and can affect the financial budget of a family and indirectly affecting compliance of the patient.[17]According to JNC VIII guidelines, initial drug of choice for hypertension is ACEI, ARB, thiazide diuretics and CCB.[18] The same is true for diabetics who are non-black. In blacks it is suggested to start with thiazide diuretic or CCB alone or in combination. For CKD patients it advocates ACEI / ARB alone or with other class. In our study in diabetic patients ARB (13%) followed by ACEI (10%) were most commonly used antihypertensives in line with JNC VIII guidelines. In CKD grows of patents prescription rate of CCB and beta blocker were (49.5%) and (46.5%) respectively. Only (9.5%) were using ARB and (7%) were on ACEI. This is in contrast to JNC VIII guidelines. Patients with advanced renal failure are more likely to develop hyperkalemia if there is interference with the excretion of potassium. Hyperkalemia is a life- threatening condition which can cause arrhythmia and sudden death. Kovesdy CP has reported that around 40% - 50% of patients with CKD have hyperkalemia.[19]There is no difference between ACEI and ARBs in development of hyperkalemia in CKD.[20]To continue ACEI or ARBs in patients who are at high risk of hyperkalemia such as CKD patients, their potassium levels should be closely monitored, NSAIDs should be avoided and metabolic acidosis should be promptly treated.[21] In our setup there is no proper follow up of the patients due to different reasons therefore, we usually avoid using ACEI or ARBs in CKD patients. Lee JH et al has also advocated to stop or reduce ACEI or ARBs despite their beneficial effect on renal functions.[22]In our study more than half of the patients received two drugs for the treatment of hypertension. JNC VIII hypertension guidelines also advocate combination of antihypertensive to achieve target blood pressure.[18] To improve the blood pressure control and compliance large number of patients used fixed drug combination. Most commonly used FDC was diuretics with ACEI followed by diuretics with ARBs and drugs acting on renin angiotensin system (RAS) with CCB. Only seven prescriptions included three drugs in the form of FDC. The advantage of using FDC is that the combination drugs negate the side effects of each other. Combination of ARB / ACEI with diuretics, the potassium loss produced by diuretics is taken care by potassium conservation of RAS inhibitors.

CONCLUSION

The current study shows prescribing trends and rationale for the use of antihypertensive drugs. The study will work as a baseline for further research in future. There is a need to collect data about antihypertensive therapy used in our community so as to define treatment strategy and update suitable recommendations regarding treatmentto generate guidelines for patients of different age groups and gender suffering from high blood pressure associated with co-morbidities like CKD, diabetes and glomerulonephritis.

Author's Contribution:

Concept & Design of Study:	Shandana Altaf
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Data Analysis:	Tahira Parveen, Amer Azhar
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REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. The lancet 2005;365(9455):217-23.
2. O'donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the Interstroke study): a case-control study. The Lancet. 2010.
3. Huang Y, Wang S, Cai X, Mai W, Hu Y, Tang H, Xu D. Prehypertension and incidence of cardiovascular disease: a meta-analysis. BMC Medicine 2013;11(1):177.,
4. Kim MJ, Lim NK, Park HY. Relationship between prehypertensionchronic kidney disease in middle-aged people in Korea: theKorean genome and epidemiology study. BMC Public Health2012;12(1):960.
5. Redon J, Tellez-Plaza M, Orozco-Beltran D, Gil-Guillen V, PitFernandez S, NavarroPérez J, et al. Impact ofhypertension on mortalityand cardiovascular disease burden in patients with cardiovascular risk factors from a general practice setting: the ESCARVAL-riskstudy. J Hypertension 2016;34(6):1075-83.
6. Bakris GL. Hypertension in Diabetic Patients. An Overview of Interventional Studies to Preserve Renal Function. Am J Hypertension 1993;6(4S):140S-7S.
7. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: asystematic review and meta-analysis. The Lancet 2016;387(10022): 957-67.
8. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, BoehmM, Christiaens T, et al. 2013 ESH/ESC guidelines for the management of arterialhypertension: the Task Force for the

Management of Arterial Hypertension of the European Society of Hypertension (ESH) and ofthe European Society of Cardiology (ESC). Blood pressure 2013;22(4):193-278.

9. Smulyan H, Mookherjee S, Safar ME. The two faces ofhypertension: role of aortic stiffness. J Am Society Hypertension 2016;10(2):175-83.
10. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, et al, Hot Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. The Lancet 1998;351 (9118):1755-62.
11. Wright Jr JT. Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. SPRINT Research Group: A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.
12. Trialists'Collaboration BP. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ 2008;336(7653):1121-3.
13. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J kid Dis 2000;36(3):646-61.
14. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-20.
15. Saleem F, Hassali AA, Shafie AA. Hypertension in Pakistan: time to take some serious action. Br J Gen Pract 2010;60(575): 449-50.
16. Aziz KU, evolution of systemic hypertension in Pakistani population; J Coll Physicians Surg Pak 2015;25(4):286-91
17. Niëns LM, Cameron A, Van de Poel E, Ewen M, Brouwer WB, Laing R. Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world. PLoS Med 2010;7(8):e1000333.
18. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311(5):507-20.
19. Kovesdy CP. Management of hyperkalaemia in chronic kidney disease. Nature Reviews Nephrol 2014;10(11):653.
20. Espinel E, Joven J, Gil I, Suñé P, Renedo B, Fort J, et al. Risk of hyperkalemia in patients with moderate chronic kidney disease initiating angiotensin converting enzyme inhibitors or angiotensin receptor blockers: a randomized study. BMC Research Notes 2013;6(1):306.
21. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin–angiotensin–aldosterone system. New Engl J Med 2004; 351(6):585-92.
22. Lee JH, Kwon YE, Park JT, Lee MJ, Oh HJ, Han SH, et al. The effect of renin–angiotensin system blockade on renal protection in chronic kidney disease patients with hyperkalemia. Journal of the Renin-Angiotensin-Aldosterone System 2014; 15(4):491-7.

Original Article

Peripheral Neuropathy in Chronic Kidney Disease (CKD)

Neuropathy in Chronic Kidney Disease

Nadeem Ullah[1], Muhammad Burhan Pasha[3], Muhammad Mumtaz Ather[2], Muhammad Azfar Tanveer[3], Muhammad Asif Yaseen[3] and Ali Akram[3]

ABSTRACT

Objective: To study the prevalence of peripheral neuropathy and evaluate the clinical nerve dysfunction in patients with chronic kidney disease.

Study Design: Prospective study

Place and Duration of Study: This study was conducted at the Medical ward Nishtar hospital, Multan from May 2018 to May 2019.

Materials and Methods: Eighty patients of clinically and biochemically proven chronic kidney disease were selected for study. Non probability consecutive sampling was used. Patients were assessed or both sensory and motor nerve dysfunction. SPSS software was used for data analysis. Main variables of study were creatinine clearance and neuropathy of peripheral nerves.

Results: Affected patients percentage with reference to overt and subclinical neuropathy was noted as 67.5%. Overt neuropathy and subclinical neuropathy observed as 35.2% and 64.8%, respectively. Patients affected with percentage with reference to the type of peripheral neuropathy were noted 67.5%. Sensory-motor, sensory and motor was observed as 31.5%, 14.8% and 53.7%, respectively.

Conclusion: Peripheral neuropathy is highly associated with chronic kidney disease and severity and prevalence of neuropathy increases with worsening in renal failure. Early diagnosis and strict compliance required to overcome this condition.

Key Words: Chronic Kidney disease, Peripheral neuropathy, Hemodialysis, Sensory nerve, Motor nerve.

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INTRODUCTION

Chronic kidney disease is associated with peripheral neuropathy[1]. Generally, patients would not come for examination of dysfunction of peripheral nerve supply until they looked for or asked for. Now in these days' patients long term survival rate is improving because of latest advancement in medical treatment[2]. Recent improvement in CKD management with hemodialysis, peritoneal dialysis and transplant brought revolution. Lifespan of patients also improved due to latest treatment improvement[3].

It is essential to know about complications of CKD, if patients survive for long time, peripheral neuropathy is one of common complications of CKD[4]. Neuropathy in CKD is treatable. Signs and symptoms of CKD are in all cases but cases are different in nature[5]. Neuropathy is symmetrical, distal and mixed motor and sensory in nature affecting 65% CKD patients mostly lower limbs as compared to upper limb. Strict control on patient's serum creatinine with on time dialysis and medical compliance reversal and progression of neuropathy is possible[6].

Peripheral neuropathy develops in male patients is greater than female and this difference is unexplained yet[7]. Intensity of disease and chronicity are main contributing features in peripheral neuropathy[8]. Existence of peripheral neuropathy clearly suspected and described in previous literature but metabolic disturbance of CKD and its dominated state of coma was not explained with its chronicity[9,10]. Many reports were conducted on this topic but no local study is available, so in this study incidence and severity of nerve dysfunction was assumed in CKD patients to fulfill the local reference gap.

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MATERIALS AND METHODS

This prospective study was conducted at medical ward Nishtar hospital; Multan from 10th May 2018 to 10th May 219 after obtaining permission from hospital ethical board. Written consent was obtained from patients after detail information of study. Non

probability consecutive sampling was used for data collection. Clinically and biochemically diagnosed cases of CKD were included in the study patients with serum creatinine >2mg, do not on dialysis and creatinine clearance < 40ml/mt were included. Patience with other contributing factors of peripheral neuropathy like diabetes was excluded from the study.

Electrophysiological tests were performed for sensory and motor neuropathy. Median right ulnar, tibial nerve, common peronal and sural nerve supply was tested. All neurological and liver related findings were noted. SPSS version 23 was used for data analysis mean and SD was calculated for numerical values and frequencies (percentages) were calculated for qualitative data. P value less than or equal to 0.05 was taken as significant.

RESULTS

Eighty patients were included in this study, both genders. Gender distribution revealed as n=54 (67.5%) males and n=26 (32.5%) females. (Figure. I). The mean duration of CKD was 3.87±1.89 years. The distribution of CKD verses peripheral nerve dysfunction was shown in table I.

Table No.1: Distribution of peripheral nerve dysfunction in CKD patients versus duration of disease

Duration of CKD (year)	No. of patients with %	Peripheral Nerve Dysfunction
<1	n=17 (21.3%)	n=13 (76.5%)
1-3	n=28 (35%)	n=19 (67.9%)
3-5	n=20 (25%)	n=14 (70%)
>5	n=15 (18.8%)	n=9 (60%)
Total	**n=80 (100%)**	**n=55 (68.8%)**

Table No.2: Patients affected with percentage with reference to overt and subclinical neuropathy

Variable	N, (%)
Overt neuropathy	n=19 (35.2%)
Subclinical neuropathy	n=35 (64.8%)
Total	n=54 (67.5%)
Patients affected with percentage with reference to the type of peripheral neuropathy	
Sensory-motor	n=17 (31.5%)
Sensory	n=8 (14.8%)
Motor	n=29 (53.7%)
Total	n=54 (67.5%)

Affected patients with percentage with reference to overt and subclinical neuropathy was noted as n=54 (67.5%). While, overt neuropathy and subclinical neuropathy observed as n=19 (35.2%) and n=35 (64.8%), respectively. Patients affected with percentage with reference to the type of peripheral neuropathy was noted n=54 (67.5%). While, sensory-motor, sensory and motor were observed as n=17 (31.5%), n=8 (14.8%) and n=29 (53.7%), respectively. (Table. 2).

The mean creatinine clearance 14.33±4.81 ml/mt.Distribution of male and female patients affected with reference to creatinine clearance was shown in table 3.

Table No.3: Distribution of male and female patients affected with reference to creatinine clearance

Creatinine clearance ml/mt	Male	Female
<15	n=30 (75%)	n=10 (25%)
26-29	n=14 (60.9%)	n=9 (39.1%)
30-59	n=10 (58.8%)	n=7 (41.2%)

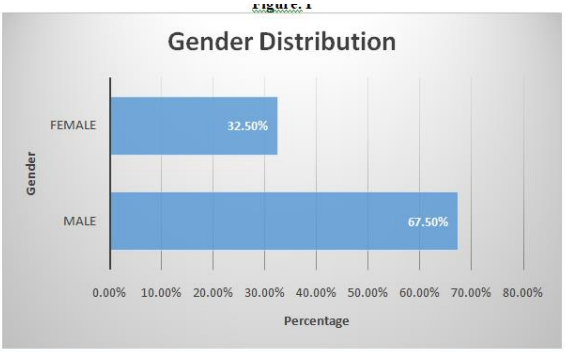

Figure No. I: Gender of patients with percentage with regard to disease.

DISCUSSION

Common and recognized complication of CKD is peripheral neuropathy. It may lead to peripheral nervous system, morbidity and mortality. Renal derangement is the contributing factor of neuropathy[11]. In a study conducted by Sultan et al[12] reported that renal derangement or CKD effect the nervous system. Peripheral neuropathy is the complication of CKD.

In a study conducted by Kumar et al[13] and concluded the involvement of CKD in disturbance of neurological system. Neuropathy is the main complication. He also reported that severity of disease has import on patient's neurological condition. Sensory neuropathy was 34% and motor neuropathy was 16% observed.

Babu et al[14] conducted a study on this topic and focused on association of CKD and peripheral neuropathy. In that study impact of age was also observed on neuropathy and its severity. Age>65 years is more prove to peripheral neuropathy in CKD.Rathankumar et al[15] completed a study in 2018 on peripheral dysfunction and CKD and conclude that distal sensory and motor neuropathy our two common types of peripheral neuropathy associated with CKD. In that study 64.8% of patients have peripheral neuropathy. Male patients with creatinine clearance having less that 15ml/mt are on greater risk.

Another study was conducted by Arnold et al[16]reported that CKD is highly associated with neurological complications which may lead to sourobidity and neutrality. May chronic neurological complications like stroke, dementia and cognitive impairment were also observed.

In a study by Bolton et al[17] observed similar findings and reported that a number of peripheral neurological disorders are associated with CKD. Cause behind this pathology is production of toxins in CKD. Renal transplantation is an option for its recovery. Another study was conducted by Nielsen et al[18]and concluded that 77% patients with CKD have peripheral neuropathy and remaining have signs of peripheral neuropathy. In that study slowing of nerve conduction was observed in patient with renal derangement since last 2 years.

Aggarwal et al[19] conducted a study on peripheral neuropathy in CKD patients and reported that sensory and motor neuropathies are associated with severity of disease or renal function; he observed symptomatic neuropathy in 51% of predialysis patients. Similar study was conducted by Krishnan et al[20] in 2005 and reported 91% peripheral neuropathy in chronic kidney disease. This association was reported irreversible that cannot be reversed with early or delayed recovery from renal derangement.

CONCLUSION

Peripheral neuropathy is highly associated with chronic kidney disease and severity and prevalence of neuropathy increases with worsening in renal failure. Early diagnosis and strict compliance required to overcome this condition.

Author's Contribution:

Concept & Design of Study:	Nadeem Ullah
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REFERENCES

1. Chillon JM, Massy ZA, Stengel B. Neurological complications in chronic kidney disease patients. Nephrol Dial Transplant 2016;31:1606–14.
2. Masson P, Webster AC, Hong M. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial Transplant 2015;30:1162–69.
3. Dad T, Weiner DE. Stroke and chronic kidney disease: epidemiology, pathogenesis, and management across kidney disease stages. Semin Nephrol 2015;35:311–22.
4. O'Lone E, Connors M, Masson P. Cognition in people with end-stage kidney disease treated with hemodialysis: a systematic review and meta-analysis. Am J Kidney Dis 2016;67:925–35.
5. Salman IM. Cardiovascular autonomic dysfunction in chronic kidney disease: a comprehensive review. Curr Hypertens Rep 2015;17:59–59.
6. Jin SH, Park YS, Park YH, Chang HJ, Kim SR. Comparison of Gait Speed and Peripheral Nerve Function Between Chronic Kidney Disease Patients with and Without Diabetes. Ann Rehabil Med 2017;41(1):72–79.
7. Kutner NG, Zhang R, Huang Y, Painter P. Gait speed and mortality, hospitalization, and functional status change among hemodialysis patients: a US renal data system special study. Am J Kidney Dis 2015;66:297–304.
8. Faiman B, Doss D, Colson K, Mangan P, King T, Tariman JD. Renal, GI, and Peripheral Nerves: Evidence-Based Recommendations for the Management of Symptoms and Care for Patients with Multiple Myeloma. Clin J Oncol Nurs 2017;21(5 Suppl):19-36.
9. Moorthi RN, Doshi S, Fried LF. Chronic kidney disease and peripheral nerve function in the Health, Aging and Body Composition Study. Nephrol Dial Transplant 2019;34(4):625–32.
10. Lange-Maia BS, Newman AB, Cauley JA. Sensorimotor peripheral nerve function and the longitudinal relationship with endurance walking in the Health, Aging and Body Composition Study. Arch Phys Med Rehabil 2016;97:45–52.
11. Campese V, Romoff M, Lavitan D, Lane K, Massry S. Mechanisms of autonomic nervous system dysfunction in Uremia. J Urol 1982;127: 405.
12. Sultan LI. Evaluation of the clinical and neurophysiologic parameters of peripheral nerve functions in uremic Egyptian patients. Egypt J Neurol Psychiatr Neurosurg 2007;44:473-87.
13. Kumar A, Prasad A, Dutta A, Roohi F. Study of nerve conduction velocity In tibial nerve of healthy male and female of different age groups. Int J Recent Sci Res 2015;6:4477-82.
14. Madhusudhana Babu M, Ravi Kiran M, Ravindra K, Srinivas V, Kandregula P, Vikram Vardhan R. Clinical manifestations and prevalence of peripheral neuropathy and nerve dysfunction in patients with chronic kidney disease. Int J Res Med Sci 2015;3:451-5.

15. Rathnakumar G, Jose JP, Anandan H. Peripheral Nerve Dysfunction in Chronic Kidney Disease. Int J Sci Stud 2018;5(10):123-25.
16. Arnold R, Pussell BA, Pianta TJ. Association between calcineurin inhibitor treatment and peripheral nerve dysfunction in renal transplant recipients. Am J Transplant 2013;13:2426–32.
17. Bolton CF, Baltzan MA, Baltzan RB. Effects of renal transplantation on uremic neuropathy. A clinical and electrophysiologic study. N Engl J Med 1971;284:1170-5.
18. Nielsen VK. The peripheral nerve function in chronic renal failure. II. Intercorrelation of clinical symptoms and signs and clinical grading of neuropathy. Acta Med Scand 1971;190:113-7.
19. Aggarwal HK, Sood S, Jain D, Kaverappa V, Yadav S. Evaluation of spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. Ren Fail 2013;35:1323-9.
20. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC, et al. Altered motor nerve excitability in end-stage kidney disease. Brain 2005;128:2164-74.

Original Article

Frequency of Peripheral Neuropathy in Chronic Liver Disease

Neuropathy in Chronic Liver Disease

Muhammad Burhan Pasha[1], Muhammad Mumtaz Ather[2], Muhammad Azfar Tanveer[1], Muhammad Asif Yaseen[1], Ali Akram[1] and Nadeem Ullah[3]

ABSTRACT

Objective: Study the magnitude of peripheral neuropathy in chronic liver disease in patients presented in tertiary care centre.

Study Design: Prospective study

Place and Duration of Study: This study was conducted at the Nishter Hospital Multan in one year duration from May 2018 to May 2019.

Materials and Methods: Ninty patients of diagnosed chronic liver disease were selected irrespective of etiology. Patients were assessed for peripheral neuropathy through electrophysiological methods. Detailed history and clinical examination was taken fromall patients. SPSS software was used for determination of data. Test of significance (t-test and chi square) were applied. P values ≤0.05 was considered as significant.

Results: Sensory nerve conduction as median nerve, ulnar nerve and sural nerve were shown in table II. The mean median nerve as amplitude and NCV was 17.25±2.68 and 41.39±2.12, respectively. The mean ulnar nerve as amplitude and NCV was 14.31±2.15 and 37.24±2.52, respectively. The mean sural verve as amplitude and NCV was 7.26±3.51 and 32.13±4.11, respectively.

Conclusion: Chronic liver disease is associated with peripheral neuropathy; grade of severity of disease increases the incidence of peripheral neuropathy. Advance age group and male gender were also observed associated with greater neuropathy.

Key Words: Peripheral neuropathy, chronic liver disease,

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INTRODUCTION

Liver cirrhosis is a major health problem in these days which may ends on several complications and mortality[1]. Cirrhosis may be characterized by hepatic fibrosis. Diagnosis of cirrhosis made on clinical, radiological and laboratory investigations[2]. Prevalence rate of cirrhosis is different in different areas and hepatitis B&C and alcohol use are the main cause of cirrhosis[3]. A list of complications is associated with cirrhosis like hepatic encephalopathy, gastric varices, variceal bleed and esophageal varices. A lot only peripheral but autonomic neuropathy is also associated with cirrhosis[4].

Dayan and William described first time peripheral neuropathy in 1967 in patients of chronic liver disease[5].

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In this study about 60% patients having sign & symptoms of demylinating peripheral nerve damage like absence of touch and sense of vibration, absence of reflexes also associated[6]. Active demylination was observed on biopsy of sural nerve. Similar damage of nerve ending was found in diabetic patients and alcohol abusers. Neuropathy of alcoholism is acute different from axonal changes of histological history[7]. Peripheral neuropathy in liver cirrhosis and its causes are not established yet.

Peripheral neuropathy develops in male patients is greater than female and this difference is unexplained yet[8,9]. Intensity of disease and chronicity are main contributing features in peripheral neuropathy[10]. Existence of peripheral neuropathy clearly suspected and described in previous literature. This study was planned to investigate the prevalence and pattern of peripheral neuropathy is diagnosed chronic liver disease at tertiary care centres of south Punjab.

MATERIALS AND METHODS

Diagnosed patients of chronic liver disease admitted in Nishter Hospital Multan were selected for study. Study was completed in one year duration from 1st May 2018 to 1st May 2019. Study was started after permission from hospital ethical board. Non probability consecutive sampling technique was used. Informed

written consent was obtained from patients after detailed information and purpose of study.

Clinical examination along with ultrasonographic and laboratory tests were performed for diagnosis of liver cirrhosis. USG evidences include splenomegaly, ascites, nodular or shrunken liver, dilation of portal vein and esophagealvarices on endoscopy. Beyond pedal edema all electrophysiological investigations were performed.

Basic liver tests routine investigation, serum B12 and clinical examination was done for all patients. Electrophysiological tests were performed for sensory and motor neuropathy. Median right ulnar, tibial nerve, common peronal and sural nerve supply was tested. All neurological and liver related findings were noted.

SPSS version was used for determination of mean and standard of numerical variables like age, nerve amplitude. Frequency and percentages were determined for categorical values like presence of neuropathy. Tests of significance (chi square and T tests)were applied. P value less than or equal to 0.05 considered as significant.

RESULTS

Ninety patients were included in this study. The motor nerve conduction results were shown in table I. The mean median nerve as DML, amplitude and NCV of the patients was 4.16±0.49, 6.42±2.31 and 46.50±0.52, respectively. The mean ulnar nerve as DML, amplitude and NCV of the patients was 3.51±0.43, 4.58±0.55 and 46.82±2.44, respectively. The mean common peroneal nerve as DML, amplitude and NCV of the patients was 5.64±1.14, 2.23±0.27 and 40.76±2.05, respectively. While, posterior tibial nerve as DML, amplitude and NCV of the patients was 5.33±2.28, 3.21±1.33 and 37.09±3.07, respectively. (Table. I).

Table No.1: Motor Nerve Conduction

Motor nerve	Parameter	Mean±S.D
Median nerve	DML	4.16±0.49
	Amplitude	6.42±2.31
	NCV	46.50±0.52
Ulnar nerve	DML	3.51±0.43
	Amplitude	4.58±0.55
	NCV	46.82±2.44
Common peroneal nerve	DML	5.64±1.14
	Amplitude	2.23±0.27
	NCV	40.76±2.05
Posterior tibial nerve	DML	5.33±2.28
	Amplitude	3.21±1.33
	NCV	37.09±3.07

Sensory nerve conduction as median nerve, ulnar nerve and sural nerve were shown in table II. The mean median nerve as amplitude and NCV was 17.25±2.68 and 41.39±2.12, respectively. The mean ulnar nerve as amplitude and NCV was 14.31±2.15 and 37.24±2.52, respectively. The mean sural verve as amplitude and NCV was 7.26±3.51 and 32.13±4.11, respectively. (Table. 2).

Table No.2: Sensory Nerve Conduction

Sensory nerve	Parameter	Mean±S.D
Median nerve	Amplitude	17.25±2.68
	NCV	41.39±2.12
Ulnar nerve	Amplitude	14.31±2.15
	NCV	37.24±2.52
Sural nerve	Amplitude	7.26±3.51
	NCV	32.13±4.11

DISCUSSION

Almost all patients of liver cirrhosis develop peripheral neuropathy irrespective of etiology either alcoholic or non alcoholic. Minor variations among both groups were found, may be due to variations in methods of evaluation of neuropathy. Other main cause of this difference was due to the severity of disease;worse disease causes more peripheral neuropathy. In some studies older age was also reported as contributing factor[11].

Kharbanda et al[12] conducted a study on this topic and reported a strong association among neuropathy and liver disease. He observed mild symptoms of neuropathy in 15% of patients but 21% patients have clinical signs of neuropathy in south Indian population. Both sensory and motor abnormalities were observed and assessed in these patients. Magnitude of neuropathy was higher in alcoholic patients as compare to non alcoholics.

Similar findings were observed by Fawiet a[l3] in his study that peripheral neuropathy is associated with liver disease and alcoholic patients have higher magnitude of neuropathy as compare to non alcoholic. In another prospective study conducted by Knill-Jones et al[14]it was found that patients of chronic liver disease with co-morbid disease like diabetes and increased level of antibodies were more prone to neuropathies.

Another study was conducted by Santoro L et al[15] on Italian population and reported higher incidence of neuropathy in untreated hepatitis C patients. He observed hepatitis C infection in 15.3% of patients, this small ratio of cirrhosis may be because of those patients who were included in study but not developed liver cirrhosis yet.

Perretti et al[16] conducted a study on cirrhotic patients and demonstrated decreased amplitude of evoked potential specifically in axonal degeneration and conduction was also slow in these patients. Demylinating sensory and motor response was also observed similar results were also observed in our study. Chaudhry et al[17] also reported similar findings about amplitude and severity of disease as described in

his study that neuropathy increased with increase in severity of disease.

Another similar study was conducted by Jain J et al[18] in 2014 and reported peripheral neuropathy in 53.6% of patients and concluded that peripheral neuropathy is very common in liver cirrhosis patients especially in chronic cases. Result of this study shows that severity of disease is highly associated with increase in peripheral neuropathy.

Hendickseet al[19] reported in his study that peripheral neuropathy is associated with chronic liver disease but there is no relationship between severity of disease and severity of peripheral neuropathy. Cause of peripheral neuropathy was also described by Dayan et al[20]that nerve damage is due to toxic metabolites caused by hepatic disturbance and decreased functioning.

Mittal M et al[21] conducted a study and reported that there neuropathy is not related to nutritional deficit and etiology but cirrhosis is contributing factors and its worse condition is more causative for peripheral neuropathy.

CONCLUSION

Chronic liver disease is associated with peripheral neuropathy; grade of severity of disease increases the incidence of peripheral neuropathy. Advance age group and male gender were also observed associated with greater neuropathy.

Author's Contribution:

Concept & Design of Study:	Muhammad Burhan Pasha
Drafting:	Muhammad Mumtaz Ather, Muhammad Azfar Tanveer
Data Analysis:	Muhammad Asif Yaseen, Ali Akram, Nadeem Ullah
Revisiting Critically:	Muhammad Burhan Pasha, Muhammad Mumtaz Ather
Final Approval of version:	Muhammad Burhan Pasha

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Ahmed S, Payeng D, Das AK. Etiological profile of cirrhosis of liver from north east India with reference to their anti-hepatitis A virus seroprevalence. Oncol, Gastroenterol and Hepatol Reports 2015;4(1):00-00.
2. Joge NP, Kumar V, Verma S, Gupta K, Misra. Vitamin B12 associated peripheral neuropathy in cirrhosis of liver: a cross sectional study, IOSR JDMS 2016;15(12):73-77.
3. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The epidemiology of cirrhosis in the United States: a population-based study, J Clin. Gastroenterol 2015; 49(8):690-6.
4. Clarkea M, Benmoussaa J, Penmetsaa AB. inaccuracies of hemoglobinA1c in liver cirrhosis: A Case Report. J Endocrinol Metab 2016;6(1):30-2.
5. Adinolfi LE, Nevola R, Lus G, et al. Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. World J Gastroenterol 2015;21(8):2269–80.
6. Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun, D. Extrahepatic manifestations of chronic hepatitis C virus infection. Therapeutic Advances in Infectious Dis, 2016;28:3–14.
7. Dalton HR, Kamar N, van Eijk JJ, Mclean BN, Cintas P, Bendall RP. Hepatitis E virus and neurological injury. Nat Rev Neurol 2016; 12(2):77-85.
8. Gill K, Ghazinian H, Manch R, Gish R. Hepatitis C virus as a systemic disease: reaching beyond the liver. HepatolInt 10(3):415–23.
9. Dedania B, Wu GY. Dermatologic extrahepatic manifestations of Hepatitis C. J Clin Transl Hepatol 2015;3:127–133.
10. Boscarino JA, Lu M, Moorman AC, et al. Predictors of poor mental and physical health status among patients with chronic hepatitis C infection: the Chronic Hepatitis Cohort Study (CHeCS) Hepatol 2015;61:802–811.
11. Bhave SA, Pandit AN, Pradhan AM, Sidhaye DG, Kantarjian A, Williams A, et al. Liver disease in India. Arch Dis Child 1982;57:922-8.
12. Kharbanda PS, Prabhakar S, Chawla YK, Das CP, Syal P. Peripheral neuropathy in liver cirrhosis. J Gastroenterol Hepatol 2003;18:922-6.
13. Fawi GH, Khalifa GA, LA D. Autonomic and peripheral neuropathies in chronic liver diseases: Clinical and neurophysiological study. Egypt J Neurol Psychiatr Neuro Surg 2005;42:87-200.
14. Knill-Jones RP, Goodwill CJ, Dayan AD, Williams R. Peripheral neuropathy in chronic liver disease: Clinical, electrodiagnostic, and nerve biopsy findings. J Neurol Neurosurg Psychiatr 1972;35:22-30.
15. Santoro L, Manganelli F, Briani C, Giannini F, Benedetti L, Vitelli E, et al. Prevalence and characteristics of peripheral neuropathy in hepatitis C virus population. J Neurol Neurosurg Psychiatr 2006;77:626-9.

16. Perretti A, Gentile S, Balbi P, Persico M, Caruso G. Peripheral neuropathy in liver cirrhosis. A clinical and electrophysiological study. Ital J Gastroenterol 1995;27:349-54.
17. Chaudhry V, Corse AM, O′Brian R, Cornblath DR, Klein AS, Thuluvath PJ. Autonomic and peripheral (sensorimotor) neuropathy in chronic liver disease: A clinical and electrophysiologic study. Hepatol 1999; 29:1698-703.
18. Jain J, Singh R, Banait S, Verma N, Waghmare S. Magnitude of peripheral neuropathy in cirrhosis of liver patients from central rural India. Ann Indian Acad Neurol 2014;17:409-15.
19. Hendrickse MT, Thuluvath PJ, Triger DR. Natural history of autonomic neuropathy in chronic liver disease. Lancet 1992;339(8807):1462-4.
20. Dayan AD, Williams R. Demyelinating peripheral neuropathy and liver disease. Lancet. 1967;2: 133-4.
21. Mittal M, Singh PV, Kurian S. Study of prevalence and pattern of peripheral neuropathy in patients with liver cirrhosis. Int J Adv Med 2017;4:1041-5.

Original Article

Role of Serum CRP, IgE, and Complement levels in Pediatric Population

Farhan Zahoor[1], Fazal ur Rehman[2], Khurram Shahnawaz[3], Kaleem Akhtar Malhi[2], Beenish Bashir Mughal[1] and Bushra Madni[4]

ABSTRACT

Objective: To evaluate the role of complement C3, C4 levels, Immunoglobulin E, eosinophil counts, platelets counts, hemoglobin levels and C-reactive protein (CRP) in children with asthma.

Study Design: This was a case control study.

Place and Duration of Study: This study was conducted at the Department of Pediatric Medicine, the Institute of Child Health, Multan and Pediatrics Department, Services Hospital, Lahore, Pakistan from September 2018 to February 2019.

Materials and Methods: A total of 160 children (80 cases and 80 controls) aged up to 16 years were included. Cases were diagnosed accompanying asthma while controls were healthy volunteers. Chi square test was adopted for comparing qualitative variables while t test was used for quantitative variables. P value less than or equal to 0.05 was taken as of statistical significance.

Results: Out of a total of 160 children, when cases and controls were compared, there was no statistical significance in terms of gender distribution ($p = 0.423$) or age ($p = 0.066$) in between cases and controls levels of CRP ($p < 0.0001$), C3 ($p < 0.0001$), Total IgE ($p < 0.0001$), hemoglobin ($p < 0.0001$) and eosinophi count ($p < 0.0001$) were significantly raised cases as compared to controls while C4 levels were noted to be significantly reduced in cases as compared to controls ($p < 0.0001$).

Conclusion: Children with asthma were found to have significantly raised C3, total IgE, eosinophil count and CRP levels but significantly reduced levels of C4 and hemoglobin and C4. These parameters could be used to mark severity as well as the prognosis of asthma in children.

Key Words: Asthma, CRP, eosinophil, hemoglobin,

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INTRODUCTION

Globally, asthma is considered as a significant cause of morbidity and mortality amongst children. More than 300 million individuals spanning all age groups are affected with asthma whereas, every year, more than 250000 deaths are attributed to asthma.[1,2] Asthma is the most frequent pulmonary disorder in children and described as chronic inflammation of airways in response to various stimuli.[3]

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Asthma's prevalence varies around the world but has been on the rise in the last couple of decades. Prevalence of asthma lies between 1 to 20 percent amongst children of different countries. It was noted that asthma's prevalence was relatively high in developed countries as compared to developing nations but in the recent years, studies from Asia, South America and Africa showed that there is a rise to asthma's prevalence in these regions.[1,4]

Asthma is noted as 3rd most frequent reason of hospitalization amongst children as more than 500000 hospitalizations are recorded every year in those children. Asthma is also a major contributor to emergency units and significant burden over healthcare facilities.[5]

Genetic as well as environmental factors play a major role contributing to asthma. Genetic connection involving families has been well documented while environmental risk factors like atopic diseases, bronchiolitis in infancy, passive smoking as well as sensitization to various allergic substances have also been noted to contribute.[6-8]

Helper-cells along with various cytokines (IL-4, IL-5) and eosinopil are thought to play a significant role in the pathogenisis of bronchial asthma.[9] Cough of non productive nature, respiratory difficulty, wheezing,

tightness of chest, headache, shortness of breath and loss of appetite are evident in asthma.[10]

Concentration of CRP are seen to enhance during inflammation, tissue damage and infection. Synthesis of CRP happens in the liver in response to pro inflammatory cytokines while it is noted to be the finest diagnostic parameter for early inflammatory processes and its treatment. In the recent years, CRP has been used to assess staging of inflammation in patients with asthma.[11]

Complement system has been presented as a major host defense entity versus pathogens and antibody mediated tissue injuries processes.[12] Levels of C3 are noted to be raised during active disease because of systemic inflammatory changes in TNF-α and IL-11.[13] IgE is involved is hypersensitivity response and provides defense to host.

Not many studies have been conducted in Pakistan evaluating role of the discussed factors in children suffering with asthma so this present study was aimed to evaluate the role of complement C3, C4 levels, Immunoglobulin E, eosinophil counts, platelets counts, hemoglobin levels and CRP in pediatric population with asthma.

MATERIALS AND METHODS

This case control, multi-centric study was done at The Department of Pediatric Medicine, The Institute of Child Health, Multan, Pakistan and Pediatric Medicine Department, Services Hospital, Lahore, Pakistan from September 2018 to February 2019. A total of 160 children i.e. 80 cases 80 controls (40 cases and 40 controls from each center), aged up to 16 years were included. Cases were diagnosed accompanying asthma on the basis of cough worsening during night and early morning for more than 6 months, and spirometry by forced expiratory volume in 1 sec (FEV1) less than or equal to 80% of predicted.[14] Controls were healthy volunteers. Children having any inflammatory disease, acute viral or any sort of bacterial infection of airway were excluded.

Informed consent was sought from parents or guardians of all the study participants. A blood sample of 5 cc was drawn from anticubital vein from all participants and sent to institutional laboratory for complete blood count, CRP, C3, C4 level and IgE.

SPSS version 21.0 was used for data analysis. Quantitative variables were presented in terms of mean and standard deviation while qualitative variables were exhibited in terms of frequency and percentages. Chi square test was adopted for comparing qualitative variables in between cases and controls while t test was used for quantitative variables. P value less than or equal to 0.05 was taken as of statistical significance.

RESULTS

Out of a total of 160 children, there were 93 (58.1%) male and 67 (41.9%) female. When cases and controls were compared, there was no statistical significance in terms of gender distribution between the groups ($p = 0.423$). Mean age of the cases was 8.25 ± 2.89 years while mean age was 9.10 ± 2.92 in controls and the difference was statistically insignificant ($p = 0.066$).

In terms of CRP, there were 38 (47.5%) cases who had their CRP above 6 mg/dl in comparison to none in controls ($p < 0.0001$). Mean C3 was noted to be 167.271 ± 41.53 mg/dl while it was 116.24 ± 14.70 mg/dl in controls ($p < 0.0001$). Mean C4 was noted to be 21.17 ± 5.63 mg/dl in cases in comparison to mean 36.57 ± 11.88 mg/dl in controls ($p < 0.0001$).

Table No.1: Gender and Age between Cases and Controls

Characteristics		Cases (n=80)	Controls (n=80)	P Value
Gender	Male	44 (55.0%)	49 (61.3%)	0.423
	Female	36 (45.0%)	31 (38.8%)	
Age (mean ± SD)		8.25 ± 2.89	9.10 ± 2.92	0.066

Table No.2: Distribution of CRP, levels of complement C3, C4, Total IgE, Hemoglobin, Eosinophil Counts and Platelet counts in between Cases and Controls

Variables		Cases (n=80)	Controls (n=80)	P Value
CRP (mg/dl)	<6	42 (52.5%)	80 (100.0%)	<0.0001
	>6	38 (47.5%)	0 (0%)	
C3 Level (mean ± SD)		167.271 ± 41.53	116.24 ± 14.70	<0.0001
C4 Level (mean ± SD)		21.17 ± 5.63	36.57 ± 11.88	<0.0001
Total IgE (mean ± SD)		397.28 ± 127.61	128.48 ± 51.95	<0.0001
Hemoglobin Level (mean ± SD)		11.24 ± 1.88	12.11 ± 1.21	0.0006
Platelet Count (mean ± SD)		314.73 ± 108.57	276.95 ± 147.24	0.0666
Eosinophil Count (mean ± SD)		3.492 ± 1.548	1.812 ± 0.645	<0.0001

Mean total IgE was noted to be 397.28 ± 127.61 IU/ml in comparison to 128.48 ± 51.95 IU/ml ($p < 0.0001$).

Mean hemoglobin was noted to be 11.24 ± 1.88 g/dl amongst cases while 12.11 ± 1.21 amongst controls (p = 0.0006). Mean platelet count was 314.73 ± 108.57 10^3 / ul amongst cases while it was 276.95 ± 147.24 10^3/ul amongst controls (p = 0.0666). Mean Eosinophil count was 3.492 ± 1.548 % in cases while 1.812 ± 0.645 % in controls (p < 0.0001)

DISCUSSION

Asthma is a global problem affecting all age groups. Amongst children, it is the most frequent chronic disease. Our study noted a comparatively higher incidence of asthma amongst boys with boys to girls ratio of 1.2:1. A study from Lahore[14] showed boys to girls ratio of 1.3:1 which is very similar to what we found. A study conducted by Yao TC et al[15] on 5351 patients highlighted that asthma was more prevalent in boys as compared to girls but opposite results were found evaluating adult age groups. These findings prove that amongst children, male gender is affected more.

As compared to controls, we noted significantly higher levels of IgE amongst children with asthma. Our findings correlate with another local study done by Bano I et al[14] where they also noted that IgE level was significantly raised in children with asthma. Razi E et al[16] also noted higher levels of IgE in asthmatic cases as compared to controls which is again consistent with our findings. Other researchers[17] have also shown that total IgE was linked with asthma in non-allergic cases as compared to non allergic ones.

Evaluating C3 and C4 levels, we noted that C3 levels were significantly higher in cases as compared to controls but on the other hand, C4 levels were significantly low as compared to controls. Our results in terms of C3 and C4 levels are very aligned with what Bano I et al[14] found. Najam FE et al[12] evaluating cases with asthma noted that C3 levels were raised as compared to controls but C4 levels were normal. The difference could be because of different sensitivity technique. Mosca T et al[18] recorded 85% of cases with asthma to have raised C3 levels while either C3 or C4 were high in 73% of asthmatic cases.

In the present study, we noted that CRP levels were significantly raised in children with asthma as compared to controls. Kilic H et al[19] aimed to not any possible relation between CRP and asthma, they noted that CRP levels were significantly raised in cases of asthma. Another local study[14] also noted significantly higher number of asthmatic children in with raised CRP as compared to controls. Findings of Lama M et al[20] were also very similar to what we found in terms of CRP in this study.

A study done by Galez D and colleagues[11] noted that C3, C4, Total IgE, platelet count as well as CRP levels were raised in children with asthma which is in accordance to our findings. The same study also noted that hemoglobin level in children were asthma were lower as compared to controls which is again very similar to our findings.

CONCLUSION

Children with asthma had significantly raised C3, total IgE, eosinophil count and CRP levels but significantly reduced levels of C4 and hemoglobin and C4. These parameters could be used to mark severity as well as the prognosis of asthma in children.

Author's Contribution:

Concept & Design of Study:	Farhan Zahoor
Drafting:	Fazal ur Rehman, Khurram Shahnawaz
Data Analysis:	Kaleem Akhtar Malhi, Beenish Bashir Mughal, Bushra Madni
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Final Approval of version:	Farhan Zahoor

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Khan AA, Tanzil S, Jamali T, Shahid A, Naeem S, Sahito A, et al. Burden of asthma among children in a developing megacity: childhood asthma study, Pakistan. J Asthma 2014;51(9):891–9.
2. Kozak LJ, Owings MF, Hall MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. Vital and health statistics. Series 13, Data from the National Health Survey 2005;(158):1-99.
3. Soferman R, Glatstein M, Sivan Y, Weisman Y. Hs CRP levels: measurement of airway inflammation in asthmatic children. Pediatr Int 2008;50(1):12-6.
4. Waqar MA, Khan M, Hasnain SM, Saleem A, Shaukat S, Sarwar F, Mahmood Y. Prevalence of allergy and asthma in school children of Islamabad, Pakistan. World Appl Sci J 2009;6:426-32.
5. Roorda RJ. Prognostic factors for the outcome of childhood asthma in adolescence. Thorax 1996;51(Suppl 1):S7-12.
6. Anderson WC, Apter AJ, Dutmer CM, Searing DA, Szefler SJ. Advances in asthma in 2016: designing individualized approaches to management. J Allergy Clin Immunol 2017;140:671–80.
7. Ito S, Noguchi E, Shibasaki M, Yamakawa-Kobayashi K, Watanabe H, Arinami T. Evidence for an association between plasma platelet activating factor acetylhydrolase deficiency and increased risk of childhood atopic asthma. J Human Genetics 2002;47(2):99-101.

8. Kato G, Takahashi K, Izuhara K, Komiya K, Kimura S, Hayashi S. Markers that can reflect asthmatic activity before and after reduction of inhaled corticosteroids: a pilot study. Biomarker insights 2013;8:97.
9. Husain AN. Lung. In: Kumar V, Abbas AK, Aster JC, editors, Robbins Basic Pathology. 8th ed. Philadelphia: Elsevier Saunders;2007,p.459-512.
10. Tillett WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Experimental Med 1930; 52(4):561-71.
11. Galez D, Dodig S, Raos M, Nogalo B. C-reactive protein in children with asthma and allergic rhinitis. Biochemiamedica 2006;16(2):163-9.
12. Najam FE, Shembesh AH, Giasuddin AS. Complement components (C3, C4) in childhood asthma. The Ind J Pediatr 2005;72(9):745-9.
13. Fattah MA, Baz ME, Sherif A, & AdelA. complement component as inflamatory markers in asthma. Ind J Pediatr 2010;77(7):771-73.
14. Bano I, Shahzad F, Ramzan M, Rathore AW, Rabia T. Serum C-Reactive Protein, Complement and Total IgE Levels in Asthmatic Children. Pak Pediatr J 2016;40(4):215-20.
15. Yao TC, Ou LS, Yeh KW, Lee WI, Chen LC, Huang JL. Associations of age, gender, and BMI with prevalence of allergic diseases in children: PATCH study. J Asthma 2011;48(5):503-10.
16. Razi E, Moosavi GA. Serum total IgE levels and total eosinophil counts: relationship with treatment response in patients with acute asthma. Jornal Brasileiro De Pneumologia 2010;36(1):23-8.
17. Beeh KM, Ksoll M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. Eur Respirat J 2000;16(4):609-14.
18. Mosca T, Menezes M, Dionigi PC, Stirbulov R, Forte WC. C3 and C4 complement system components as biomarkers in the intermittent atopic asthma diagnosis. J de Pediatria 2011;87(6):512-6.
19. Kilic H, Karalezli A, Hasanoglu HC, Erel O, Ates C. The relationship between hs-CRP and asthma control test in asthmatic patients. Allergologiaet Immune Pathologia 2012;40(6):362-7.
20. Lama M, JEE MC, Nayak C, & Chaudari TK. elevated c-reactive protein concentration in inhaled corticosteroid naive children with asthma. Int J Chem Sci 2010;4(8):2729-35

Original Article

Chronic Liver Disease and Its Associations with Hepatitis C Virus in Patients with Type 2 Diabetes Mellitus in Our Setup at DHQTH Bannu

Chronic Liver Disease with Hepatitis C Virus with Type 2 Diabetes

Raza Muhammad Khan[1], Asmatullah Khan[2], Ayub Nawaz[1], Nawab Zada Khan[3] and Yaser ud Din[1]

ABSTRACT

Objective: The objective of this study was to determine chronic liver disease and its association with hepatitis C virus in patients with type 2 diabetes mellitus in our setup at DHQTH Bannu.

Study Design: Descriptive / case series study.

Place and Duration of Study: This study was conducted at the Department of Medicine, DHQ Teaching Hospital (DHDTH) Bannu, Khyber Pakhtunkhwa from Sep 2015 to Sep 2016.

Materials and Methods: Data were collected from 53 patients already diagnosed as Type 2 diabetes mellitus for more than 10 years presented with symptoms and signs of CLD, from Sep 2015 to Sep 2016, through laboratory test, to note their cause of CLD.

Results: Out of 53 T2DM patients, 29 patients were males (54.7%) and 24 (45.3%) were females. All of these were having increase ALT >60 IU/L and increased echogenicity of liver parenchyma. Out of these, 30 patients (56.6%) (19males,11females) were having HCV +ve, 5 patients (9.4%) (3males,2 females) HbsAg +ve, and 3 patients (5.7%) (2males,1female) were B&C -ve. While in the remaining, 3 patients (5.7%) (2males,1female) were having NASH, 2 patients (3.8%)(both females) were AIH(ANA+ve) and 10 patients (18.9%) (3males,7females) were having simple Steotosis (with only increase ALT and increased echogenicity). So overall 30 patients(56.6%) with T2DM with CLD were HCV +ve.

Conclusion: In our set up, the major cause of CLD in T2DM was chronic HCV infection. Most of these patients were cirrhotic, which is an alarming situation and need proper planing by health care providers.

Key Words: T2DM, CLD, Hepatitis C virus (HCV), Cirrhosis , Bannu.

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INTRODUCTION

Type 2 diabetes mellitus is a major Health problem. Rates of diabetes are increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will to rise from 366 million in 2011 to 552 million by 2030.[1]

It is less common in non-Western countries, but as people in these countries adopt Western lifestyles, weight gain, obesity and type 2 diabetes mellitus are becoming epidemic. The top 10 countries in number of people with diabetes are currently India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy, and Bangladesh.[1]

The chronic liver disease is an under diagnosed disease in patients with type 2 diabetes. It ranges from Non Alcoholic Fatty Liver Disease (NAFLD) including Steotosis and Non Alcoholic Steoto Hepatitis (NASH), then infective hepatitis caused by HCV or HBV, and sometimes other causes including autoimmune hepatitis. Out of these, the infective causes both HCV and HBV are more important, because that can be screened and treated.

Hepatitis C and B are major world health problem. Worldwide, more than 170 million persons have hepatitis C virus (HCV) infection,[2] of whom 71 million have chronic infection.[3] In Pakistan, its prevalence is 4.8%[4]. In Khyber Pakhtunkhwa (KPK) and FATA areas which are drained to our set up, it is reported even high (up to 6.93%)[5,6].HBV is also endemic here. In Pakistan its prevalence is 2.4%[7], while in KPK and FATA, it is up to 4.49%[5].

There is a two way association between T2DM and

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HCV. Both are prevalent diseases worldwide[1,2,3] and are associated with increased morbidity and mortality.

On one hand, there is increased risk for T2D in patients with chronic HCV infection [8] esp when there is liver dysfunction [9].While insulin resistance (IR) and T2DM are more frequently reported as complications of HCV infection, HCV is also known to be associated with several autoimmune manifestations, including type 1 diabetes mellitus (T1DM)[10,11]. Therapy for chronic HCV infection, in particular interferon alpha (IFNα) can also trigger diabetes, as IFNα can induce or exacerbate autoimmune diseases such as T1DM[12]. Cirrhosis itself is "diabetogenic" with various studies describing the majority of cirrhotics as having impaired glucose tolerance[13,14,15]. T2DM was significantly higher among patients with HCV cirrhosis than in patients with cirrhosis due to other etiologies[14]. HCV infection precedes the diagnosis of T2DM in as many as 73% of cases, further suggesting HCV's pathogenic role in the development of T2DM[16,17,18]. It is estimated that up to 33% of chronic hepatitis C patients have T2DM[19]. There is significantly higher risk for T2DM in HCV patients are compared to hepatitis B virus (HBV)[8] and 2- to 10-fold increase of T2DM in chronic HCV infection compared to other liver diseases[19,20,21,22,]. It is also estimated that 20% of chronic HCV patients will develop cirrhosis and as many as ~50% of these patients will have T2DM[14,23].

On the other hand,T2DM is a predisposing factor for HCV infection[24,25,26]. Also Insulin Resistance (IR) and T2DM have a negative impact on clinical outcomes for patients with chronic HCV infection, including reduced rate of sustained virological response (SVR), progression to fibrosis and cirrhosis, and higher risk for development of hepatocellular carcinoma (HCC).

Unfortunately, no local data is available regarding chronic liver disease in T2DM patients and its association with HCV, in out set up. This is a randomized study at smaller scale which can later be applied at larger scale. Also due to many reasons such as lack of awareness, limited resources, and no cost-free screening campaign for adults, the early diagnosis and prompt treatment of viral hepatitis in not satisfactory in Khyber Pakhtunkhwa, even in high risk people, to prevent chronic liver disease and cirrhosis. HCV is a treatable disease. With the standard therapy having combination, 50–80% of people treated are cured[4]. Genotype 2&3 are common in Pakistan who show sustained response to treatment in 70-80%[27].

Keeping this in mind the following study was designed to see CLD in T2DM and its association with HCV in our community.

MATERIALS AND METHODS

This descriptive, case series study was carried out at Department of Medicine, DHQ Teaching Hospital Bannu KPK, **12** months from Sep 2015 to Sep 2016.

Sample Size: 53 patients already diagnosed as T2DM for more than 10 years, now having CLD, were analyzed for causes of CLD.

Sampling Technique: Consecutive, Non-probability Sampling.

Inclusion Criteria: All "T2DM" patients diagnosed for more than 10 years (noted from clinical record/History), of Either gender, aged above 40 and under 65 years, having CLD (increase ALT >60 IU/L plus increase echogenicity of liver parenchyma on ultrasound abdomen, present for >6months).

Exclusion Criteria: Those patients who were not filling the inclusion criteria, with a history of previous Hepatitis C infection/treatment, patients with End-stage liver disease, patients terminally ill, patients who were not willing to be included in study, and patients with dementia/mentally retarded were not included because, as they were either already infected and treated, would not benefit from future planned screening/treatment or would give recall bias. If included in the study, these would act as confounders to introduce bias in the study results.

Data Collecting Procedure: The study was conducted after approval from hospitals ethical and research committee/ board. All the patients who were T2DM and meeting the inclusion criteria, as per operational definitions, presented to the Department of Medicine, DHQ Teaching Hospital Bannu, through emergency or OPD, were included in the study. All patients were first counseled for interview. The purpose and benefits of the study were explained to all patients, and a written informed consent was obtained from all who agreed to participate in the study. A detailed medical history was taken from all the patients, regarding duration of T2DM and previous HCV infection for cause of high ALT and increase echogenicity of liver parenchyma. Then these patients (study population) were screened for HCV by ELISA (used as a diagnostic tool) and their status noted on flow sheet as data collection tool having all variables of interest.

All the patients were categorized as having Simple Fatty Liver/Steotosis, NASH, HCV related CLD, HBV related CLD, B/C negative CLD and Auto-immume Hepatitis if ANA+ve. All the information including name, age, gender, address, disease status were recorded in that pre-designed Proforma. Only a complete Proforma was subjected to analysis. Strict exclusion criteria was applied to control confounders and bias in the study results.

Statistical Analysis: Data obtained was entered into SPSS version 23 and analyzed in descriptive statistics. Mean $\pm$ SD were calculated for numerical/ quantitative variables like age. Frequencies and percentages (%) were calculated for categorical/ qualitative variables such as gender, disease status. Disease status were stratified among age and gender to see the effect modifiers. All results were presented in the form of tables, charts.

RESULTS

A total of 53 patients with T2DM were included in the study. Out of 53 T2DM patients, 29 patients were males (54.7%) and 24 (45.3%) were females, with male to female ratio of 1.21:1.0. Their age ranged between 45 and 64 years, and the mean age was 54.19±5.027 years. All of these were having increase ALT >60mg and increased echogenicity of liver parenchyma. Out of these, 30 patients (56.6%) (19 males, 11 females) were having HCV +ve, 5 patients (9.4%) (3males,2females) HbsAg +ve, and 3 patients (5.7%) (2males,1female) were B&C -ve. While in the remaining, 3 patients (5.7%) (2males,1female) were having NASH, 2 patients (3.8%)(both females) were AIH(ANA+ve) and 10 patients (18.9%) (3males, 7females) were having simple Steotosis (with only increase ALT and increased echogenicity).

So overall 30 patients(56.6%) with T2DM with CLD were HCV +ve.

Summarized Descriptive statistics of the study population are shown in tables and charts.

Table No.1:Age Distribution of Study Population (N=53):

Age group	Frequency	Percent
41-50Years	15	28.3
51-60Years	32	60.4
>60 Years	6	11.3
Total	53	100.0

Parameters	Total No of patients	Minimum (years)	Maximum (years)	Mean	Std. Deviation
Age in years	53	45.00	64.00	54.19	5.027

Table No.2: Gender distribution of study population (N=53)

Gender	Frequency	Percent	Valid Percent	Cumulative Percent	"p" value
Male	29	54.7	54.7	54.7	0.05
Female	24	45.3	45.3	100.0	
Total	53	100.0	100.0		

Table No.3; Frequency of diseases of patients (N=53)

Diseases	Frequency	Percent	Valid Percent	Cumulative Percent
Steotosis	10	18.9	18.9	18.9
NASH	3	5.7	5.7	24.5
HCV+	30	56.6	56.6	81.1
HBS+	5	9.4	9.4	90.6
B&C -ve	3	5.7	5.7	96.2
AIH (ANA+)	2	3.8	3.8	100.0
Total	53	100.0	100.0	

Table No.4: Gender wise distribution of diseases in patients (N=53) :

Gender	Disease						Total
	Steotosis	**NASH**	**HCV+**	**HBS+**	**B & C -ve**	**AIH (ANA+)**	
Male	3	2	19	3	2	0	29
Female	7	1	11	2	1	2	24
Total	**10**	**3**	**30**	**5**	**3**	**2**	**53**

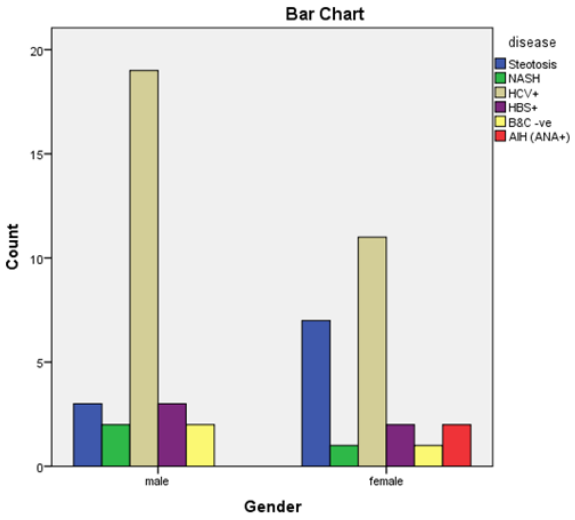

Figure No.1: Gender wise distribution of diseases in patients (N=53):

DISCUSSION

A total of 53 patients with T2DM were included in this study. Out of 53 T2DM patients, 29 patients were males (54.7%) and 24 (45.3%) were females. All of them were having increase ALT >60 IU/L and increased echogenicity of liver parenchyma on Ultasound Abdomen. When screened for viral hepatitis by Elisa, 30 patients (56.6%) (19 males,11 females) came out to be HCV +ve (also confirmed later by PCR) , and 5 patients (9.4%) (3 males,2 females) were HbsAg +ve, while the remaining only 18 patients were negative for viral hepatitis. It showed that viral hepatitis is more common here, and it is the common cause of CLD in T2DM patients having diabetes for more than 10 years, where it contributed to 66% collectively. In these patients those having HCV, majority were early cirrhosis on ultrasound abdomen, they were male, and their glycaemic control was not good. It means that diabetes with poor control has added to early and accelerated fibrosis and cirrhosis. One reason of this high prevalence of viral hepatitis in our setup is that patients are also drained from adjacent FATA area, where hepatitis B is more commonly noted.

The remaining 18 patients negative by Elisa for HBV and HCV, were further assessed for cause of increase ALT >60 IU/ml and increased echogenicity of liver

parenchyma on Ultasound Abdomen, including HBc (core) antibodies (for occult HBV), AST level and ANA , and then labeled B&C -ve, AIH, NASH or simple Fatty liver (steotosis). NASH was simply labeled on basis of increase ALT and AST levels with ALT/AST ratio <1, with no history of alcohol with no other obvious cause for increase liver enzymes, but without liver biopsy (being invasive and not available here in our setup).

This study was a preliminary randomized study in this area and on small scale which can later be applied at larger scale. It presents 53 T2DM patients who were diabetic for >10years,presented with CLD, both out patients and in-door patients, who were aged 45 and 64 years, and the mean age was 54.19±5.027 years 1-60 years. Out of these, a large portion of 35 patients(66%) were having viral hepatitis, and 30 patients HCV (56.6%), most of them were male and having early cirrhosis, though HCV can be prevented by adopting preventive measures, easily early diagnosed and promptly treated to prevent cirrhosis. This was partially because of lack of awareness/ education on part of the patients, lack of proper counseling/educating session on part of health care providers, and lack of support services and cost free screening programs for diabetic population on part of the government.

CONCLUSION

This study has demonstrated that CLD in T2DM patients was mainly because of viral hepatitis in our set up, where both the viruses have high prevalence, mainly because of HCV and they were male predominate and having early cirrhosis at presentation, all these were having poor glycaemic control.

Therefore, all those managing T2DM patients should also counsel and educate the patients, regarding preventive measures against both HCV & HBV infections, screen these patients for viral hepatitis, and if infected with HCV, then promptly treat them with standard Treatment including recent antivirals for HCV, to prevent CLD and cirrhosis. It is essential for physicians caring for HCV patients to be aware of the high risk for T2DM (and T1DM) and that they screen HCV patients for diabetes. In addition, the presence of diabetes in an HCV patient alert the clinician for the possibility of worse outcomes of HCV infection.

Recommendations: All the T2DM patients should be screened for viral hepatitis especially HCV to start prompt treatment to prevent CLD and cirrhosis, meanwhile also have a good glycaemic control to improve the treatment outcomes including End of Treatment response. Moreover all the HCV free-treatment programs, which have already been started, should incorporate free screening program.

Author's Contribution:

Concept & Design of Study:	Raza Muhammad Khan
Drafting:	Asmatullah Khan
Data Analysis:	Ayub Nawaz, Nawab Zada Khan, Yaser ud Din
Revisiting Critically:	Raza Muhammad Khan
Final Approval of version:	Raza Muhammad Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. One adult in ten will have diabetes by 2030. International Diabetes Federation. November 14, 2011.[Online]. Available from: http://www.idf. org/media-events/press-releases/2011/diabetes-atlas-5th-edition.
2. Hepatitis C: global prevalence. *Wkly Epidemiol Rec* 1997;72(46):341-4.
3. World Health Organi-zation. Hepatitis C: fact sheet. Available at http://www.who.int/media-centre/ factsheets/fs164/en/. Updated: October 2017; Accessed: January 23, 2018.
4. World Health Organization (WHO). Hepatitis C. Fact sheet. 2012 July; $N^0$164. [Online]. [Cited on 2012 Jul]. Available from: http://www.who.int/ mediacentre/factsheets/fs164/en/index.html.
5. Alam M, Behttani F. Prevalence of risk factors in Hepatitis B & C patients admitted in Eye Department of Khyber Teaching Hospital Peshawar. Opthalmol Int 2011;9(4):39-41.
6. Finance Department, Government of Khyber Pakhtunkhwa. Achievements during Year 2011-12. White Paper 2012-13;1(sectorial expenditure):11.
7. Ali SA, Donahue R, Qureshi H, Vermund SH. Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. Int J Infect Dis 2009;13(1):9-19.
8. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008;49(5):831–44.
9. Montenegro L, De MA, Misciagna G, Guerra V, Di LA. Virus C hepatitis and type 2 diabetes: a cohort study in southern Italy. Am J Gastroenterol 2013;108(7):1108–11.
10. Chen LK, Chou YC, Tsai ST, Hwang SJ, Lee SD. Hepatitis C virus infection-related type 1 diabetes mellitus. Diabet Med 2005;22(3):340–3.
11. Masuda H, Atsumi T, Fujisaku A, Shimizu C, Yoshioka N, Koike T. Acute onset of type 1 diabetes accompanied by acute hepatitis C: the potential role of proinflammatory cytokine in the pathogenesis of autoimmune diabetes. Diabetes Res Clin Pract 2007;75(3):357–61.
12. Fabris P, Floreani A, Tositti G, Vergani D, De LF, Betterle C. Type 1 diabetes mellitus in patients with chronic hepatitis C before and after interferon therapy. Aliment Pharmacol Ther 2003;18(6):

549–58.
13. Kruszynska YT, NcIntyre N. Carbohydrate metabolism. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J, editors. Oxford Textbook of Clinical Hepatology. Oxford, England: Oxford University Press;1991.p.129–34.
14. Allison ME, Wreghitt T, Palmer CR, Alexander GJ. Evidence for a link between hepatitis C virus infection and diabetes mellitus in a cirrhotic population. J Hepatol 1994;21(6):1135–9.
15. Lonardo A, Adinolfi LE, Petta S, Craxi A, Loria P. Hepatitis C and diabetes: the inevitable coincidence? Expert Rev Anti Infect Ther 2009;7(3):293–308.
16. Romero-Gomez M, Del Mar Viloria M, Andrade RJ, Salmeron J, Diago M, Fernandez-Rodriguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Gastroenterol 2005;128(3):636–41.
17. Grimbert S, Valensi P, Levy-Marchal C, Perret G, Richardet JP, Raffoux C, et al. High prevalence of diabetes mellitus in patients with chronic hepatitis C. A case-control study. Gastroenterol Clin Biol 1996;20(6–7):544–8.
18. Mehta SH, Brancati FL, Strathdee SA, Pankow JS, Netski D, Coresh J, et al. Hepatitis C virus infection and incident type 2 diabetes. Hepatol 2003;38(1):50–6.
19. Knobler H, Schihmanter R, Zifroni A, Fenakel G, Schattner A. Increased risk of type 2 diabetes in noncirrhotic patients with chronic hepatitis C virus infection. Mayo Clin Proc 2000;75(4):355–9.
20. Fraser GM, Harman I, Meller N, Niv Y, Porath A. Diabetes mellitus is associated with chronic hepatitis C but not chronic hepatitis B infection. Isr J Med Sci 1996;32(7):526–30.
21. Aytug S, Reich D, Sapiro LE, Bernstein D, Begum N. Impaired IRS-1/PI3-kinase signaling in patients with HCV: a mechanism for increased prevalence of type 2 diabetes. Hepatol 2003;38(6):1384–92.
22. el-Zayadi AR, Selim OE, Hamdy H, Dabbous H, Ahdy A, Moniem SA. Association of chronic hepatitis C infection and diabetes mellitus. Trop Gastroenterol 1998;19(4):141–4.
23. Zein NN, Abdulkarim AS, Wiesner RH, Egan KS, Persing DH. Prevalence of diabetes mellitus in patients with end-stage liver cirrhosis due to hepatitis C, alcohol, or cholestatic disease. J Hepatol 2000;32(2):209–17.
24. Simo R, Hernandez C, Genesca J, Jardi R, Mesa J. High prevalence of hepatitis C virus infection in diabetic patients. Diabetes Care 1996;19(9):998–1000.
25. Soma J, Saito T, Taguma Y, Chiba S, Sato H, Sugimura K, et al. High prevalence and adverse effect of hepatitis C virus infection in type II diabetic-related nephropathy. J Am Soc Nephrol 2000;11(4):690–9.
26. Guo X, Jin M, Yang M, Liu K. Type 2 diabetes mellitus and the risk of hepatitis C virus infection: a systematic review. Sci Rep 2013;18(3):2981.
27. Rosen HR. Clinical practice, Chronic hepatitis C infection. New Eng J Med 2011;364(25):2429–38.

Original Article

Safety of Clopidogrel in Ischemic Heart Disease Patients having Cirrhosis with Upper GI Bleed

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ABSTRACT

Objective: To evaluate the safety of clopidogrel in ischemic heart disease patients simultaneously suffering from cirrhosis with upper G bleed.

Study Design: A randomized controlled trial study.

Place and Duration of Study: This study was conducted at the Department of General Medicine of Nishtar Hospital Multan from August 2018 to May, 2019.

Materials and Methods: Fifty two patients were equally divided into two groups; control group which received no antiplatelet drug and clopidogrel group in which group patients were prescribed clopidogrel at 75mg daily dose. All the patients were discharged on medication and were followed for a minimum of six months. Age, gender, underlying comorbidities including diabetes mellitus, hypertension, ischemic stroke and dyslipidemias, and incidence of upper GI bleed were compared between the two groups. Student's t test and Chi square test were applied accordingly. P ≤0.05 was considered statistically significant.

Results: Age, gender distribution and history of comorbidities including ischemic stroke, hypertension, diabetes mellitus and dyslipidemias were not significantly different between the two groups (p>0.05). Till the end of study, upper gastrointestinal bleeding was reported in 5 (19.2%) patients of the control group while it was reported in 12 (46.1%) patients of clopidogrel group and the difference in the outcome was statistically significant (p=0.039).

Conclusion: There was significantly greater occurrence of upper GI bleed among the patients taking clopidogrel during the study duration whereas less number of patients from the control group presented with upper GI bleed.

Key Words: clopidogrel, ischemic heart disease, cirrhosis, upper gastrointestinal (GI) bleed.

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INTRODUCTION

Complex changes including defects in platelet function, thrombocytopenia, decreased pro coagulant as well as anticoagulant proteins and altered fibrinolytic systems are associated with cirrhosis. All these changes result in increased bleeding tendency. Prothrombin time (PT) and Activated partial thromboplastin time (aPTT) show hypocoagulablity. However, it has been observed in clinical experience that despite significant alterations in the hemostasis of a patient with cirrhosis, the system maintains a balance by proportionate change in anti- or pro-hemostatic pathways. But this rebalanced hemostatic system of cirrhotic individuals is more friable as compared to the hemostasis in healthy individuals. Cirrhotic individuals are prone to experience thrombotic complications as well as bleeding [1-3].

It was believed that cirrhotic patients were protected against ischemic heart diseases as they were thought to be auto anticoagulated and, therefore, antithrombotic therapy was minimally given in the past. Nowadays, various thrombotic complications including arterial thrombosis, venous thrombosis and portal vein thrombosis are suspected to happen in patients with liver cirrhosis [4-6]. The incidence of these complications is suspected to rise as there has been observed a recent rise in the prevalence of liver cirrhosis and longer survival times in cirrhotic patients. Various anti-thrombotic agents used include heparins, vitamin k antagonists and antiplatelet agents. Antiplatelet agents include aspirin, clopidogrel and ticlopidine.

Use of aspirin for preventing cardiovascular events is associated with peptic ulcer disease and subsequent bleeding [7]. Patients having previous history of peptic

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ulcer disease, taking combined aspirin and clopidogrel or large doses of aspirin, taking other anticoagulant drugs, NSAIDs or steroids drugs, or having Helicobacter pylori infection are at high risk of aspirin-induced peptic ulcer bleeding [8,9]. Other anti-platelet agent is clopidogrel which prevents platelet aggregation and it does not inhibit formation of prostaglandins and functions of cyclooxygenase. Clopidogrel is known to cause less upper gastrointestinal bleed and has higher cardiovascular safety. This drug is a substitute to aspirin for avoidance of secondary cardiovascular events in the patients who either have aspirin allergy or have experience of aspirin related gastrointestinal adverse effects in the past [12]. However, the safety of clopidogrel is documented to be not enough in aspirin related peptic ulcer bleeding as t causes recurrent upper GI bleeding [10, 11]. Clopidogrel or aspirin related upper GI bleed can be well decreased by giving proton pump inhibitors [10, 12-14].

Limited studies have been carried out in the past to assess the factors leading to gastrointestinal bleeding in the patients who were using clopidogrel. Other co-existing factors such as use of other drugs and underlying comorbidities were considered to aid in increased risks of GI bleeding. We are conducting this study in a group of known cases of ischemic heart disease as well as cirrhosis, to evaluate the hazard of upper GI bleeding in the clopidogrel users as compared to patients taking no anti-platelet agents. The purpose of this study is to solely assessthe role of clopidogrel in causing upper GI bleed in ischemic heart disease patients simultaneously suffering from cirrhosis.

MATERIALS AND METHODS

It is a randomized controlled trial conducted in the Department of General Medicine of Nishtar Hospital Multan over a time period of 10 months extending from August 1st, 2018 to May 31st, 2019. Patients were selected using non-probability consecutive sampling technique after calculating sample size from the reference study [15]. We included 52 patients who were simultaneously suffering from ischemic heart disease as well as liver cirrhosis and had at least one episode of upper GI bleed. No age limit was defined. All the patients who has hematological malignancy, coagulopathy, gastrointestinal tract malignancy, gastroenteritis, or inflammatory bowel disease were not included the study.

Ethical approval was obtained from the hospital ethical review board. Informed consent was signed by all the patients before commencement of the study. All the patients were equally divided into two groups using lottery system. One group was control group and no antiplatelet drug was given to this group. Other group was the clopidogrel group. The patients of this group were prescribed clopidogrel at 75mg daily dose. Age, gender were documented before the start of the study. Complete history was taken, after which general physical examination was done. Baseline blood investigations and fasting lipid profiles were done. Any underlying comorbidity such as diabetes mellitus, hypertension, ischemic stroke and dyslipidemias was also documented. Proper treatment for cirrhosis was given. All the patients in both the groups were discharged on oral medication and were followed for a minimum of six months. During this time period, all the patients continued their prescribed medication. All the patients were advised to report immediately if there was blood in vomitus or melena. Patients were also to report if they had any type of emergency. Final outcome of this study was the incidence of upper GI bleed in both the groups.

Age, gender, underlying comorbidities including diabetes mellitus, hypertension, ischemic stroke and dyslipidemias were compared between the two groups. Student's t test was applied to compare the age. Gender and prevalence of comorbidities were compare by applying Pearson chi square test. Outcome was the incidence of upper GI bleed and it was compared between the two groups with Chi square test. $P \leq 0.05$ was considered statistically significant.

RESULTS

Mean age of the control group was 56.77 ± 8.99 years while of the clopidogrel group was 58.27 ± 8.40 years (p=0.537). Control group included 15 males and 11 females while clopidogrel group included 17 males and 9 females (p=0.569). History of ischemic stroke was present in 50% patients of the control group and 30.7% patients of clopidogrel group (p=0.158). Hypertension was positive in 38.5% patients of the control group and 46.1% patients of clopidogrel group (p=0.575).

Table No.1: Baseline and outcome characteristics of the control and clopidogrel groups

Variable	Control (n = 26)	Clopidogrel (n = 26)	p-value
Age, years (mean ± S.D)	56.77 ± 8.99	58.27 ± 8.40	0.537
Gender (male/female)	15 / 11	17 / 9	0.569
Comorbidities, N (%)			
Ischemic stroke	13 (50.0)	8 (30.7)	0.158
Hypertension	10 (38.5)	12 (46.1)	0.575
Diabetes mellitus	11 (42.3)	8 (30.7)	0.388
Dyslipidemias	7 (26.9)	11 (42.3)	0.244
Upper GI bleed, N (%)	5 (19.2)	12 (46.1)	0.039

History of diabetes mellitus was present in 42.3% patients of the control group and 30.7% patients of clopidogrel group (p=0.388). Complete lipid profile showed dyslipidemias in 26.9% patients of the control

group and 42.3% patients of clopidogrel group (p=0.244). Till the end of study, upper gastrointestinal bleeding was reported in 5 (19.2%) patients of the control group while it was reported in 12 (46.1%) patients of clopidogrel group and the difference in the outcome was statistically significant (p=0.039). Table-I

DISCUSSION

In our study, it was observed that the incidence of upper GI bleed became significantly higher with the use of clopidogrel by the ischemic heart disease patients also having cirrhosis. Clopidogrel is prescribed as an alternative to aspirin for primary as well as secondary prevention of cardiovascular events in the patients who have already experienced peptic ulcer bleeding or peptic ulcer disease with aspirin use. Significant risk factors for upper GI bleed in clopidogrel users is the concomitant use of aspirin or peptic ulcer bleed. Previous studies have shown that there are increased risks of peptic ulcer bleed in the patients who are using aspirin along with clopidogrel or have a recent history of peptic ulcer bleed. Clopidogrel is not considered to be safe to use in this high risk group of patients as it increases the chances of upper GI bleed [10, 16, 17].

Clopidogrel is known to hinder the healing process of gastric mucosa and that is why peptic ulcer bleeding reoccurs with its use in the patients with previously healed peptic ulcer disease[10,11,18]. There has been no increased in the risk of upper GI bleed in the CKD patients [19, 20]. In patients using clopidogrel, no effect of H. pylori infection or eradication has been observed on peptic ulcer bleed [10,11,16]. Ulcer prophylaxis is also another issue. PPIs have significant role in preventing peptic ulcers but no significant role of H2RAs has been observed [21]. NHI has limited the use of PPIs in the patients with peptic ulcer disease for a minimum of 4 months [22, 23].

Owing to the great risk of upper GI bleed, aspirin is absolutely contraindicated in patients of cirrhosis [24]. Although very rare at low doses, aspirin usage can precipitate hyponatremia, diuretic resistance and acute renal failure in the patients having ascites [25]. As the incidence of NAFLD is increasing, the demand for anti-platelet therapy for secondary prevention following coronary stenting has been increasing. In the light of recently available evidence, aspirin is thought to be safe in the patients who have cirrhosis but have not developed any varices yet [26]. Aspirin use has also been observed to be associated with the first variceal bleed in the patients who have already developed esophageal varices. Therefore, aspirin is contraindicated in primary as well as secondary prevention in the patients who have already developed varices.

P2Y12 receptor antagonists have recently become popular in the primary as well as secondary prevention of arterial thrombosis. These drugs act by blocking the ADP induced aggregation of the platelets. Clopidogrel in irreversible P2Y12 receptor antagonist. Drug interactions and genetic variations complicate the use of anti-platelet agents and treatment shows various reactions[27]. These agents need to be metabolically activated by the liver and pharmacokinetics cannot be predicted in the patients having cirrhosis. In Child A or B cirrhosis, there is no change in pharmacodynamics and pharmacokinetics of clopidogrel. However, cholestatic jaundice and significant liver damage are labelled as contraindications for the use of clopidogrel, on the package insert.

CONCLUSION

There was significantly greater occurrence of upper GI bleed among the patients who were given clopidogrel during the study duration whereas less number of patients from the control group presented with upper GI bleed. The patients who simultaneously suffer from ischemic heart disease and cirrhosis, should not be prescribed anti-platelet drug, clopidogrel. The frequency of upper GI bleed with clopidogrel use in the cirrhotic patients points towards the fact that these patients are already auto anti-coagulated due to loss of liver function.

Author's Contribution:

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REFERENCES

1. Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. Semin Thromb Hemost 2015;41(5):468-473.
2. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood 2010;116(6):878-85.
3. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Eng J Med 2011;365(2):147-56.
4. Tripodi A, Anstee QM, Sogaard KK, Primignani M, Valla DC. Hypercoagulability in cirrhosis: causes and consequences. J Thromb Haemost 2011;9(9):1713-23.
5. Northup PG, Sundaram V, Fallon MB, Reddy KR, Balogun RA, Sanyal AJ, et al. Coagulation in Liver

Disease Group. Hypercoagulation and thrombophilia in liver disease. J Thrombos Haemost 2008;6(1):2-9.
6. Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, et al. Coagulation in Liver Disease Study Group. Hemostasis and thrombosis in patients with liver disease: the ups and downs. J Hepatol 2010;53(2):362-71.
7. Luo JC. Gastroprotective strategy in aspirin users. J Chin Med Assoc 2009;72(7):343-45.
8. Laine L. gastrointestinal bleeding with low-dose aspirin–what's the risk?. Aliment Pharmacol Ther 2006;24(6):897-908.
9. Lanas A, Scheiman J. Low-dose aspirin and upper gastrointestinal damage: epidemiology, prevention and treatment. Curr Med Res Opin 2007;23(1):163-73.
10. Chan FK, Ching JY, Hung LC, Wong VW, Leung VK, Kung NN, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Eng J Med 2005;352(3):238-44.
11. Lai KC, Chu KM, Hui WM, Wong BC, Hung WK, Loo CK, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol 2006;4(7):860-65.
12. Huang KW, Luo JC, Leu HB, Huang CC, Hou MC, Chen TS, et al. Risk factors for upper gastrointestinal bleeding in coronary artery disease patients receiving both aspirin and clopidogrel. J Chin Med Assoc 2013;76(1):9-14.
13. Ng FH, Wong SY, Lam KF, Chu WM, Chan P, Ling YH, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterol 2010;138(1):82-88.
14. Lanas A, García-Rodríguez LA, Arroyo MT, Bujanda L, Gomollón F, Forné M, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007;102(3):507-15.
15. Lin CC, Hu HY, Luo JC, Peng YL, Hou MC, Lin HC, et al. Risk factors of gastrointestinal bleeding in clopidogrel users: a nationwide population-based study. Aliment Pharmacol Ther 2013;38(9): 1119-28.
16. Ng FH, Wong SY, Chang CM, Chen WH, Kng C, Lanas AI, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. Aliment Pharmacol Ther 2003;18(4):443-49.
17. Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. Am J Cardiol 2008;101(7):960-66.
18. Luo JC, Huo TI, Hou MC, Lin HY, Li CP, Lin HC, et al. Clopidogrel delays gastric ulcer healing in rats. Eur J Pharmacol 2012;695(1-3):112-19.
19. Luo JC, Leu HB, Huang KW, Huang CC, Hou MC, Lin HC, et al. Incidence of bleeding from gastroduodenal ulcers in patients with end-stage renal disease receiving hemodialysis. CMAJ 2011;183(18):E1345-51.
20. Luo JC, Leu HB, Hou MC, Huang KW, Lin HC, Lee FY, et al. Nonpeptic ulcer, nonvariceal gastrointestinal bleeding in hemodialysis patients. Am J Med 2013;126(3):264-e25-32.
21. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. Gastroenterol 2011;140(3):791-98.
22. Luo JC, Leu HB, Hou MC, Huang CC, Lin HC, Lee FY, Chang FY, Chan WL, Lin SJ, Chen JW. Cirrhotic patients at increased risk of peptic ulcer bleeding: a nationwide population-based cohort study. Alimentary pharmacology & therapeutics 2012;36(6):542-50.
23. Peng YL, Leu HB, Luo JC, Huang CC, Hou MC, Lin HC, et al. Diabetes is an independent risk factor for peptic ulcer bleeding: A nationwide population-based cohort study. J Gastroenterol Hepatol 2013;28(8):1295-9.
24. Miser WF. Appropriate aspirin use for primary prevention of cardiovascular disease. Am Fam Physician 2011;83(12):1380-86.
25. European Association For The Study Of The Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53(3):397-417.
26. Russo MW, Pierson J, Narang T, Montegudo A, Eskind L, Gulati S. Coronary artery stents and antiplatelet therapy in patients with cirrhosis. J Clin Gastroenterol 2012;46(4):339-44.
27. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J 2011;32(23):2922-32.
28. Cattaneo M. New P2Y12 inhibitors. Circulation 2010;121(1):171-179.

Original Article

Comparison between Operative Laparoscopy and Laparotomy in the Management of Haemodynamically Stable Patients with Ectopic Pregnancy

Sadia Zahoor, Sonia Zulfiqar, Nadia Zaman, Sadia Zulfiqar and Tahira Malik

ABSTRACT

Objective: To compare operative[1] laparoscopy vs laparotomy in the management of haemodynamically stable patients with ectopic pregnancy.

Study Design: Comparative study.

Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynaecology, Sheikh Zaid Hospital, Rahim Yar Khan from October 2017 to April 2018.

Materials and Methods: Total 72 married females of reproductive age (15-49 years) presenting in emergency/OPD of Obstetrics & Gynecology with suspected diagnosis of ectopic pregnancy till 8 weeks of gestation confirmed by transvaginal ultrasound, haemodynamically stable patients as defined in operational definitions having ß-hCG< 6000 IU/L were included in the study.

In study group A, laparoscopy was performed and in group B laparotomy was performed. Operative duration, postoperative hospital stay and wound infection was compared between the both groups.

Results: A total of 72 patients were selected for this study. Mean age of the patients was 27.56±4.23 and 25.56±4.15 years in group-A and B, respectively. In group-A, mean gestational age was 6.0±1.2 weeks and in group group-B 5.7±1.1 weeks. In laparoscopy group (A), no wound infection was noted but in laparotomy group (B), there were 4 (11.1%) patients found with wound infection. Statistically significantly difference between wound infection of both groups was noted with p value 0.040. In group A mean duration of operation was 79.89 ± 2.90 and in group B was 95.94 ± 2.55 minuets. Mean post operative hospital stay was 1.06 ± 0.23 days in group A while 3.17 ± 1.44 days in group B.

Conclusion: In conclusion, laparoscopic treatment of ectopic pregnancy yielded superior benefits over laparotomy in terms of less operative time and less postoperative hospital stay. Additionally, laparoscopy has a great role in diagnosis of clinically suspicious cases. Therefore, laparoscopy should be opted whenever possible.

Key Words: Management of ectopic pregnancy, Laparoscopy, Laparotomy

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INTRODUCTION

Ectopic pregnancy is defined as a pregnancy that is implanted outside the uterine cavity i.e. at a site that by nature is not designed anatomically and physiologically to accept the conception or to permit its growth and development.[1]

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The most common site is the tube (95%), the cervix, ovary, broad ligament or elsewhere in peritoneal cavity. There are many predisposing factors leading to ectopic pregnancy i.e. by induced abortion, pelvic inflammatory diseases, miscarriages and pelvic surgery. Previous use of intrauterine contraceptive devices (IUCD) as well as smoking also increases risk.[2-3] Age and race are not the significant risk factors.

Ectopic pregnancy was first discovered in the 11th century. The incidence of ectopic pregnancy varies between 100 and 175 per 100,000 women aged 15-44 years.[4] The Centre for Disease Control (CDC) reports that the incidence of ectopic pregnancies is 1 in 70 pregnancies while in Pakistan it varies from 1:1124 to 1:130 pregnancies.[5] The incidence rises significantly after assisted reproductive technology (ART) and varies from 2-11%.[6]

Ectopic pregnancy remains a leading cause of maternal mortality in first trimester and is responsible for about 9 percent of maternal mortalities in the United States. The

accurate diagnosis of ectopic pregnancy can now be made at an early stage by using pregnancy tests and high-resolution transvaginal ultrasound. This can lead to more options for treating ectopic pregnancy.

Surgeons use laparoscopy or laparotomy to gain access to the pelvis and can either incise the affected fallopian and remove only the pregnancy or remove the affected tube with the pregnancy.

Laparoscopy has been used in the diagnosis of ectopic pregnancy for many years, and is being used with increasing frequency in the surgical treatment of ectopic pregnancy. The advantage of operative laparoscopy for ectopic pregnancy over laparotomy is associated with shorter operation times, shorter hospital stay and less wound infection.

Study conducted in Nepal showed that incidence of wound infection was 5.0±0.1% in patients treated with laparotomy while no wound infection was observed in patients treated with laparoscopy.[7]

Study conducted in Burlington showed that operative duration was less in laparoscopy than laparotomy (77.5±26.1 vs 103.6±26.7 minutes) and postoperative hospital stay was also less in laparoscopy than laparotomy (1.34±0.8 vs 4.5±1.1 days).[8]

As no local data is available on this topic and less data is available about outcome variable like wound infection taken from different international studies there it is unclear to which procedure should adopt. So the rationale of present study is to access the outcome of laparoscopy with laparotomy that will be helpful in determining which procedure should be adopted.

Ectopic Pregnancy: A pregnancy that implanted outside the uterine cavity most commonly in fallopian tube, cervix, ovary, broad ligament or in peritoneal cavity confirmed by transvaginal ultrasound.

Haemodynamic Stable Patients: One in which following vitals were seen, blood pressure 110/70 to 130/80mmHg. Pulse 60-100 per minute, temperature 98.6°F.

Operative Duration: This was calculated in mean operative duration from start of surgery till skin suturing.

Postoperative Hospital Stay: This was calculated as mean postoperative hospital stay starting from postoperative duration till discharge

Wound Infection: Presence of any one of the followings after 8 days of surgery, purulent or serous discharge from incision line or gaped wound or pyrexia > 100.

MATERIALS AND METHODS

This randomized controlled trial was conducted at Department of Obstetrics &Gynaecology, Sheikh Zaid Hospital, Rahim Yar Khan for 6 months from October 2017 to April 2018.

Total 72 married females of reproductive age (15-49 years) presenting in emergency/OPD of Obstetrics & Gynecology with suspected diagnosis of ectopic pregnancy till 8 weeks of gestation confirmed by transvaginal ultrasound, haemodynamically stable patients as defined in operational definitions having ß-hCG< 6000 IU/L were included in the study.

The patient has a medically treatable ectopic pregnancy, the history is suggestive of minimal pelvic adhesions were excluded from the study.

Study was approved by ethical committee and written informed consent was taken from every patient. Selected patients were randomly divided into two groups A and B.

In study group A, laparoscopy was performed and in group B laparotomy was performed. Details of operative duration, postoperative hospital stay and wound infection was gathered. All this information was collected on a pre-designed proforma along with demographic profile of the patients.

Data was analyzed in SPSS version No. 16. Qualitative data (wound infection) was summarized in the form of frequencies and proportions.

Quantitative data (age of patient, gestational age, operative duration, postoperative hospital, stay) was summarized in mean±standard deviation.

Confounding variables (age of patient, parity) were controlled through stratification. Post-stratification applying chi square test for wound infection and student t test for mean operation duration and postoperative hospital stay.

Chi square test was applied to compare wound infection and student's t test was applied for mean operative duration and post-operative hospital stay between two groups. P value $p \leq 0.05$ was consider as significant.

RESULTS

A total of 72 patients were selected for this study and randomly divided into two groups A and B. In group-A mode of treatment was laparoscopy and in group-B mode of treatment was laparotomy.

Patients ranged between 15-40 years of age. Mean age of the patients was 27.56±4.23 and 25.56±4.15 years in group-A and B, respectively. In group-A, mean gestational age was 6.0±1.2 weeks and in group group-B 5.7±1.1 weeks.

In laparoscopy group (A), no wound infection was noted but in laparotomy group (B), there were 4 (11.1%) patients found with wound infection. Statistically significantly difference between wound infection of both groups was noted with p value 0.040 (Table 1)

In group A mean duration of operation was 79.89 ± 2.90 and in group B was 95.94 ± 2.55 minuets. Mean duration of operation time was significantly higher in group B as compared to group B with p value 0.001. (Table 2)

Mean post operative hospital stay was 1.06 ± 0.23 days in group A while 3.17 ± 1.44 days in group B.

difference of mean post operative hospital stay was statistically significant with p value 0.001 (Table 3)

Two age groups 15-30 years and 31-40 years were made. In age group 15-30, no patient of group A found with wound infection while 4 patients of group B found with wound infection and the difference was statistically significant with p value 0.048. In age group 31-40 years, no patients was found with wound infection.

Patients were divided into two groups according to parity i.e. para 0-3 and para 4-7. In para 0-3 group, wound infection found only in 4 (26%) patients of study group B and no wound infection was found in study group A. The difference was statistically significant with p value 0.033. In para 4-7 group, no wound infection was noted in both study groups. (Table 4)

In age group 15-30 years, mean operation time in study group A was 80.28 ± 3.02 minutes and in group B was 96.06 ± 2.60 minutes. Mean operation duration was significantly (P = 0.001) higher in study group B as compared to study group A. In age group 31-40 years, mean operation time was 78.29 ± 1.70 and 95.00 ± 2.16 minutes. Statistically significant difference between mean operation duration was noted with p value 0.001.

In para 0-3 group, mean operative time in group and B was 80.09 ±2.95 minutes and 96.30 ± 2.42 minutes and the difference was statistically significant with p value 0.001. In para 4-7 group, mean operative time in group A was 78.25 ± 2.06 minutes and in group B was 94.17 ± 2.63 minutes. The difference of mean operative time between the both groups was statistically significant with p value 0.001. (Table 5)

Table No.1: Comparison of wound infection between the both groups

Wound infection	Group-A (Laparoscopy)		Group-B (Laparotomy)	
	No.	%	No.	%
Yes	0	0	04	11.1
No	36	100	32	88.9
Total	36	100.0	36	100.0
P Value	0.040			

Table No.2: Comparison of mean duration of operation (minute)

Group	Mean	S.D
Group-A (Laparoscopy)	79.89	2.90
Group-B (Laparotomy)	95.94	2.55
P value	P < 0.001	

Table No.3: Comparison of mean postoperative hospital stay (days)

Group	Mean	S.D
Group-A (Laparoscopy)	1.06	0.23
Group-B (Laparotomy)	3.17	1.44
P value	0.001	

In age group 15-30 years, mean hospital stay in group A was 1.03 ± 0.18 days and in group B was 3.28 ± 1.48 days. Difference of hospital stay between both groups was statistically significant with p value 0.001. In age group 31-40 years, 1.14 ± 0.37 days and 2.25 ± 0.50 days respectively in study group A and B and the difference was statistically significant with p value 0.001.

Table No.4: Stratification for age and parity with regard to wound infection

Group	15-30 (Year)		31-40 (Year)	
	Wound infection		Wound infection	
	Yes	No	Yes	No
Group-A (Laparoscopy)	0	29	0	7
Group-B (Laparotomy)	4	28	0	4
P value	P=0.048		Cannot do statistical test because a column total is 0	
Group	Para 0-3		Para 4-7	
	Wound infection		Wound infection	
	Yes	No	Yes	No
Group-A (Laparoscopy)	0	32	0	4
Group-B (Laparotomy)	4	26	0	6
P value	P=0.033		Cannot do statistical test because a column total is 0	

Table No.5:Stratification of age and parity with regard to mean operation duration (minute)

Group	AGE 15-30 (Year)		AGE 31-40 (Year)	
	Operation duration		Operation duration	
	Mean	S.D	Mean	S.D
Group-A (Laparoscopy)	80.28	3.02	78.29	1.70
Group-B (Laparotomy)	96.06	2.60	95.00	2.16
P value	p<0.001		p<0.001	
Group	Para (0-3)		Para (4-7)	
	Operation duration		Operation duration	
	Mean	S.D	Mean	S.D
Group-A (Laparoscopy)	80.09	2.95	78.25	2.06
Group-B (Laparotomy)	96.30	2.42	94.17	2.63
P value	p<0.001		p<0.001	

In para 0-3 group, mean hospital stay in group A and B was 1.06 ± 0.24 days and 3.30 ± 1.53 days respectively. Difference of hospital stay between the both groups was statistically significant with p value 0.001. In para 4-7 group, mean hospital stay was 1.00 ± 0.00 days and 2.50 ± 0.54 days respectively in study group A and B

and the difference was statistically significant with p value 0.001. (Table 6)

Table No.6: Stratification of age and parity with regard to mean postoperative hospital stay (days)

Group	AGE 15-30 (Year)		AGE 31-40 (Year)	
	Hospital stay		Hospital stay	
	Mean	S.D	Mean	S.D
Group-A (Laparoscopy)	1.03	0.18	1.14	0.37
Group-B (Laparotomy)	3.28	1.48	2.25	0.50
P value	p<0.001		p<0.001	
Group	Para (0-3)		Para (4-7)	
	Hospital stay		Hospital stay	
	Mean	S.D	Mean	S.D
Group-A (Laparoscopy)	1.06	0.24	1.00	0.00
Group-B (Laparotomy)	3.30	1.53	2.50	0.54
P value	p<0.001		P=0.001	

DISCUSSION

The incidence of ectopic pregnancy has increased all over the world from 5 per 1000 pregnancies during the past three decades to almost 20 per 1000 pregnancies at present.[9-10]

An emerging technique of assisted reproductive technology, which was found to increase risk of ectopic pregnancy by 5%, is one possible reason for such a steep rise in the incidence.[10]

Delayed diagnosis of ectopic pregnancy may result in rupture and acute blood loss. Massive blood loss from ectopic mass accounted for 10-15% of overall maternal mortality in the first trimester in the past few decades.[11]

An appropriate and timely treatment of ectopic pregnancy plays an important role in reducing morbidity and mortality caused mainly by massive intraabdominal hemorrhage. Surgery which remains the mainstay of treatment can be approached either by laparotomy or laparoscopy.[12]

Yuen et al who conducted a retrospective study comparing treatment outcomes of laparoscopic surgery and laparotomy in 105 patients who had ectopic pregnancy. The authors demonstrated that laparoscopic group had lower incidence of ruptured ectopic mass during operation and lower hemoperitoneum compared to laparotomy group.[13]Actually, these more favorable factors of unruptured ectopic mass and lesser amount of hemoperitoneum may be the cause or reason (rather than the effect or result) why the surgeon made his decision to perform laparoscopy rather than laparotomy.

Present study, found a statistically significant longer operative time in laparotomy group than laparoscopic (95.94±2.55 vs 79.89±2.90 minutes, p-value < 0.001). This was consistent with previous study of Brumstedet al[12] who reported a shorter operative time in laparoscopic group. Similarly, results of Brumstedet al[8] also demonstrated that operative duration was shorter in laparoscopy than laparotomy.

In present study, postoperative hospital stay (days) was less in laparoscopy group than laparotomy (<0.001). These findings are comparable to Brumsted et al.[8] Similar results were shown in different studies and this was noted as an advantage.[8,14-15]

In current study, mean age of the patients was 27.56±4.23 and 25.56±4.15 in laparoscopy group and laparotomy, respectively, comparable to the studies carried out by Pradhan et al[16] and Wafaa P.[17]

Because laparoscopy has been shown to be superior to laparotomy, it has become the gold standard for the treatment of EP.[18] However, in women who are hemodynamically unstable, the role of laparoscopy remains controversial. But as surgeons gain increased expertise in laparoscopic surgery, even in the presence of a large hemoperitoneum, operative laparoscopy is still achievable.[13]

CONCLUSION

In conclusion, laparoscopic treatment of ectopic pregnancy yielded superior benefits over laparotomy in terms of less operative time and less postoperative hospital stay. Additionally, laparoscopy has a great role in diagnosis of clinically suspicious cases. Therefore, laparoscopy should be opted whenever possible.

More data from a prospective well controlled study are needed to confirm these favorable results of the laparoscopic treatment approach for ectopic pregnancy.

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REFERENCES

1. Shaw JL, Dey SK, Critchley HO, Horne AW. Current knowledge of the aetiology of human tubal ectopic pregnancy. Hum Reprod Update 2010;16:432-44.
2. Saleh F, Shukar-ud-din S. Tubal ectopic pregnancy after bilateral tubal ligation. J Surg Pak 2012;17: 38-9.
3. Fernandez H, Gervaise A. Ectopic pregnancies after infertility treatment: modern diagnosis and therapeutic strategy. Hum Reprod Update 2004;

10:503-13.
4. Coste J, Bouyer J, Ughetto S, Gerbaud L, Fernandez H, Pouly JL, et al. Ectopic pregnancy is again on the increase. Recent trends in the incidence of ectopic pregnancies in France (1992-2002). Hum Reprod 2004;19:2014-8.
5. Khawaja NP, Rehman R, Durrani Z. Ectopic pregnancy at gynaecology unit II Sir Ganga Ram Hospital, Lahore; study of fifty cases. Pak J Obstet Gynecol 1998;11:61-5.
6. Musarrat J, Babar A, Jakimiuk J. Bilateral ectopic pregnancy following ovulation induction JPM 2010; 24:160–2.
7. Shrestha J, Saha R. Comparison of laparoscopy and laparotomy in the surgical management of ectopic pregnancy. J Coll Physicians Surg Pak 2012; 22:760-4.
8. Brumsted J, Kessler C, Gibson C, Nakajima S, Riddick DH, Gibson M. A comparison of laparoscopy and laparotomy for the treatment of ectopic pregnancy. Obstet Gynecol 1988;71: 889-92.
9. Nama V, Manyonda I. Tubal ectopic pregnancy: diagnosis and management. Arch Gynecol Obstet 2009;279:443-53.
10. Centers for Disease Control and Prevention (CDC). Ectopic pregnancy-United States, 1990-1992. MMWR Morb Mortal Wkly Rep 1995;44:46-8.
11. Abbott A, Emmans LS, Lowenstein SR. Ectopic pregnancy: ten common pitfalls in diagnosis. Am Emerg Med 1990;8:512-22.
12. Brumsted A, Kessler C, Gibson C, Nakajima S, Riddick DH, Gibson M. A comparison of laparoscopy and laparotomy for the treatment of ectopic pregnancy. Obstet Gynecol 1988;71:889-902.
13. Yuen PM, Rogers MS, Chang A. A review of laparoscopy and laparotomy in the management of tubal pregnancy. Hong Kong Med J 1997;3:153-7.
14. Gupta B. Role of minimally invasive surgery in the treatment of ectopic pregnancy. World J of Laparoscopic Surg 2008;1:36-9.
15. Leslie L, Pun TC, Chan S. Tubal ectopic pregnancy: an evaluation of laparoscopic surgery versus laparotomy in 614 patients. Aust NZJ Obstet Gynecol 1999;39:185-7.
16. Pradhan P, Thapamagar SB, Maskey S. A profile of ectopic pregnancy at Nepal Medical College Teaching Hospital, Nepal. Med Coll J 2006; 8: 238-42.
17. Wafaa MF. Diagnosis and management of ectopic pregnancy in King Abdulaziz University Hospital: a four-year experience. JKAU Med Sci 2008; 15:15-25.
18. Lehner R, Kucera E, Jirecek S, Egarter C, Husslein P. Ectopic pregnancy. Arch Gynecol Obstet 2000; 263:87–92.

Original Article

Management of Pediatric Anterior Mandibular Fractures

Comparison of Microplate and Arch Bar with 3D Microplate in the Management of Pediatric Anterior Mandibular Fractures

Saeed Ahmad[1], Muhammad Adnan Akram[2], ArmghanIsrar Mirza[3] Kiran Nayyar[1], Irfan Ahmad Shah[1] and Usman Tariq[1]

ABSTRACT

Objective: The purpose of this study was to compare treatment outcomes using conventional titanium microplate and arch bar with 3- Dimensional titanium microplate in the management of pediatric anterior mandibular fractures.
Study Design: Comparative / Prospective study
Place and Duration of Study: This study was conducted at the department of pediatric Oral & Maxillofacial Surgery, The Children's Hospital & Institute of Child Health, Lahore in 2018.
Materials and Methods: A total number of 44pediatric patients were included in this study.Patients were randomly categorized into 2 groups. Group A comprised of patients with standard titanium microplate and arch bar while Group B patients were treated with 3-dimensional plate alone. Clinical parameters observed were, infection and assessment of intraoperative time for each plate fixation and infection.
Results: After 1st week in Group A, infection was 32%, in Group B, only two (9%) patients showed infection. On 4th week infection rate was 18% in Group A and 4.5 % in Group B. At 12 weeks there was no sin of infection in both groups. Bony union was observed clinically by pain and tenderness and bridging of fracture gap on OPG. At the end of 12th week there was complete bridging of gap in both groups. Malocclusion was 13.6% in Group A. In Group B no case of malocclusion was observed. Mean intraoperative time for Group A was 109.5 ± 9.6 minutes and that of Group B was 53.5 ± 19.9 minutes ($p<0.05$).
Conclusion: 3- Dimensional plate is a convenient and time saving alternate to conventional microplate and arch bar.
Key Words: 3D titanium miniplate , titanium miniplate, anterior Mandibular fracture

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INTRODUCTION

Globally,Trauma is the leading health problem in children[1]. Craniofacial Trauma is more common in children[2]. Among facial trauma, the mandible is the facial bone most often fractured in children[3]. Mandibular symphysis and parasymphysis fractures (Fig.1,2) are most frequent after mandibular condylar fracture[4].The presence of thick adipose tissue with added bone elasticity and tooth buds renders mandible. resistant to fracture and more frequently they are minimally displaced[5] The most predictable cause of pediatric symphysis and parasymphysis fractures is fall and road traffic accidents followed by sports related injuries, assaults and child abuse. These etiological factors depend upon age, gender, geographic circumstances, socio-economic status and cultural uniqueness of people[6].

Pediatric mandibular symphysis and parasymphysis fractures are managed on the same basic principles applied to adult fractures[7]. The main focus of mandibular fracture management is to re-establish the former normal anatomy, function and interdigitation of teeth[8]. Two treatment modalities are in practice for the management of pediatric anterior mandibular fractures that is conservative approach and open reduction and internal fixation[9]. The conservative methods included soft diet and observation, closed reduction with splints or intermaxillary fixation by arch bars [10].

More recently, 3-D titanium micro plates have been developed. 3-D microplates also follow the Champy's ideal lines of osteosynthesis for mandibular symphysis and parasymphysis. These plates are like a two-plate system with two microplates bonded together by interconnecting crossbars [11]. The screws are arranged in

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the configuration of a cube on either side of the fracture, a broad-band platform is created, increasing the resistance to twisting and bending of the long axis of the plate [12]. One of the advantages of this technique is the concomitant stabilization of the tension and compression zones and alleviating the need for additional arch bar making the 3-D microplates a time-saving alternative to conventional microplate and arch bar [13].

Currently 3-D miniplates are being used in adult patients and no published data is available in our country for use of 3-D microplates in pediatric mandibular symphysis and para-symphysis fractures. This study was conducted on pediatric anterior mandibular fractures to evaluate use of 3-D microplates without arch bar in mixed dentition stage as a convenient and time saving

The objective of this study was to compare treatment outcomes using conventional titanium microplate and arch bar with 3- Dimensional titanium microplate in the management of pediatric anterior mandibular fractures (between mental foramina).

MATERIALS AND METHODS

Forty-four patients with mandibular symphysis and para-symphysis fractures were recruited. All 44 Patients were divided into two group A andB. Group A consisted of patients treated with titanium microplate and screws with arch bar while in Group B 3-Dimensional microplate alone was used. A standard 1.6mm microplating system with 5mm monocortical screws was used for both groups.

All patients were treated under general anesthesia and nasal endotracheal intubation was passed. A standard intra oral vestibular incision was given in both groups to expose the fractured site. In Group A, an arch bar was applied to mandibular dentition after manually reducing the fractured segments. This arch bar was not only used for Temporary IMF but also used to counteract the tension band in the upper border according to Champy's principle. In Group B eyelets were used for temporary IMF. After IMF and manually reducing the fracture, internal fixation was done with titanium microplate measuring 1.6mm x 5 holes' plate and 1.6mm monocortical screws of 5mm in Group A. The plate was applied on the inferior border of the mandible and upper border was secured using arch bar. Four screws were used to secure plate 2 on each side of the fractured plate. Fixation of 3-D micro plate in Group B was done in such a way that a horizontal bar was perpendicular and vertical bar was parallel to the fracture line. The upper bar was placed in the sub apical position. Tooth buds were bypassed on the basis of radiographic assessment. 4 monocortical screws were used on corners of plate[14]. The wound was closed and tight using 3/0 resorbablepolyglactin sutures. IMF was released at the end of the surgical procedure in both groups. Duration of the procedure was noted in both groups. Patients then placed on standard 7 days' antibiotic regimen. Patients were reviewed after intervals of 1 week, 4 weeks and then after 12 weeks. Infection was noted on the basis of erythema, edema, and pus discharge[15]. Bone union was assessed both clinically and radiographically. Malocclusion as failure to achieve proper interdigitation of teeth was categorized as abnormal. Impressions were taken and models were obtained from impression to check for any occlusal discrepancy [16]. The arch bar and eyelets were removed after 4 weeks. Both Micro and 3-dimensional micro plates were removed after 3 months. OPG radiographs were carried out 1 day after treatment and after 12 weeks postoperatively to limit the exposure to radiation. Total time for each procedure was noted. Data was entered using IBM-SPSS (V-23) for analysis. Fisher's Exact test was employed to compare the outcomes; student's-test was also applied to compare the time duration. A p-value less than 0.05 was taken for statistical significance.

RESULTS

Out of 44 patients with age range was 6-12 years and mean age of 8.5 years. Male patients were 26 and female was 18. Road traffic accident (63.6%) was the most common cause of fractures followed by falls (36.4%).

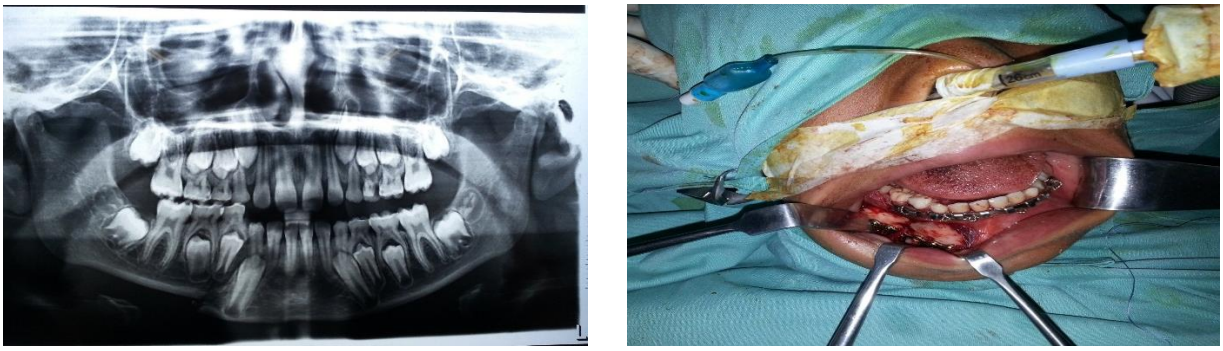


Figure No.1: Preoperative picture of 11 years old male patient with Rt. Parasymphysis. Preoperative OPG showing displaced anterior mandibular fractured segments

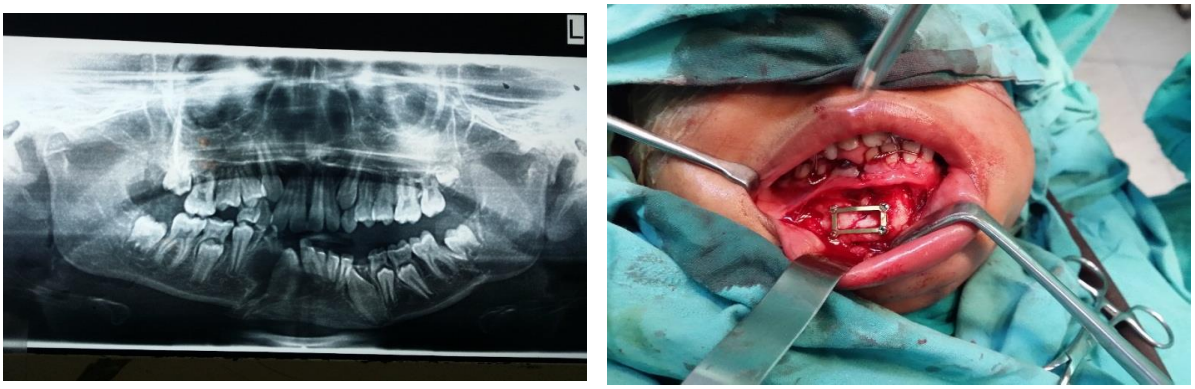
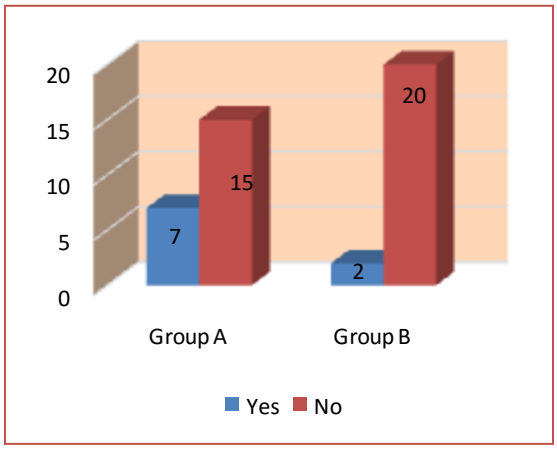
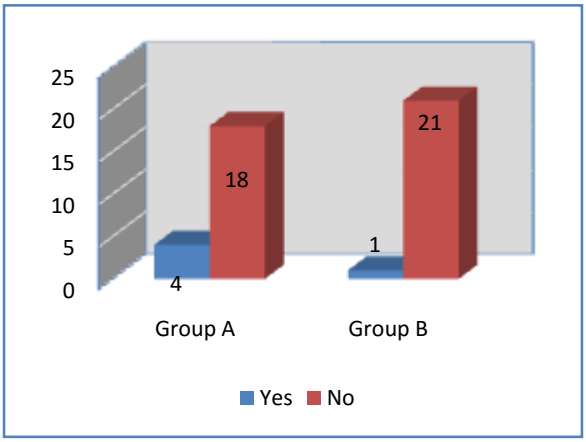


Figure No.2: Preoperative OPG of an 8 years old male patient showing fracture at Rt. Pararsymphysis



Graph No.1: Comparison of infection after first week in both groups



Graph No.2: Comparison of infection after forth week in both groups

The incidence of symphysis fractures was found as 20.5%, while for right parasymphysis as 45.5% and for left parasymphysis as 34.15%. The mean operation time for Group A was 109.5±9.6 minutes and for Group B mean operation time was 53.5±19.9 minutes which showed a statistical difference in time duration ($p<0.05$).

All the patients were followed-up for infection on 1st, 4th and 12th week postoperatively. After 1st postoperative week (Graph.1) in Group A only 7 patients showed signs of infection while in Group B 2 patients showed erythema (p-value= 0.1324). On 4th week in Group A only 4 (18%)patient showed signs (Graph.2) of infection while in Group B one patient (4.5%) showed sign of infection (p-value =0.3449). On 12th week postoperatively none of the patients in both groups had evidence of infection.

DISCUSSION

The current work equates clinical outcomes of 3-diminsional micro plate osteosynthesis with conventional micro plate osteosynthesis. The clinical outcomes were operating time and postoperative complications in terms of infection, bony union and occlusal stability. In micro plate system upper border reduction was achieved with additional mini arch bar while in 3-dimensional plate no additional arch bar was used. It was assumed that addition of vertical bars to form a geometrically stable form will provide enough stability so that the need for the additional arch bar can be omitted and thus a time saving procedure. The results obtained under defined parameters were quite encouraging.

The main etiological factor in this study was RTA (Road Traffic accident) followed by falls. The incidence of road traffic accidents is being increased because of the use of 3 wheeled auto rickshaws which are used to pick and drop children from schools. Many other studies also discussed that RTA to be the main cause of mandibular fractures[17,18].The site distribution in this study was restricted to anterior mandible only. Parasymphysis fractures was found more prevalent than symphysis. Site distribution in this study was very much confined by other studies[19,20].

Among postoperative complications infection was observed in each group on 1st, 4th and 12th weeks. On 1st postoperative week infection was shown in both groups, but results were statistically insignificant. On 4th

postoperative week both groups also reported with infection. On 12th postoperative week none of the patients showed any infection. The results were more promising in Group B. The infection rate in 4th week might be explained by the fact that oral hygiene maintenance in the presence of arch bar in pediatric patients is especially difficult where compliance is already an issue in children [21]. Various researches showed a comparable infection rate in patients treated with conventional micro plate after ist postoperative week and our results were also supported [22]. No published date is available for infection rate with the use of 3-deminsional plate in pediatric population. In this study infection rate with 3-dimensional plate was 9.1% in 1st postoperative week.

Bone union was assessed clinically and radiographically thru OPG on 1st and 12th postoperative week. The radiograph taken on 1st week was more related to general examination and obtaining a radiograph as reference. In all the patient's bony union was uneventful by the end of 12th week. All exposure was obtained from a single machine to standardize them.This finding is in line with other studies which state that incidence of nonunion is very scarce in pediatric patients [3,7].

Malocclusion was observed in 3 patients in Group A while in Group B none of the patients showed any malocclusion. The results obtained in this study thus confirm the supremacy of 3-Dimensional microplate alone over titanium microplate and arch bar in terms of stability. Malocclusion is common finding in mixed dentition phase and accepted in many other studies[2,4]. This complication in Group A may be attributed to the fact that the arch bar applied during mixed dentition phase to counter tension band in a fracture line does not provide enough anchorage to keep the fractured segments firmly in position.

The mean time duration in Group A was and Group B was found statistically different. No published data is available with reference to time comparison which makes this study unique. This study ascertains that applying arch bar with microplate is laborious and cumbersome job which can be bypassed by using 3-Dimensional plates as a time saving alternate.

CONCLUSION

Although titanium microplate with arch bar is still a standard treatment option for displaced pediatric anterior mandibular fractures, but the factors like less rate of infection, no malocclusion, freedom from the use of arch bar and the less total operation time make 3-Dimensional microplate not only a viable alternate but also a superior treatment option for managing pediatric mandibular fractures.

Author's Contribution:

Concept & Design of Study:	Saeed Ahmad
Drafting:	Muhammad Adnan Akram, ArmghanIsrar Mirza
Data Analysis:	Irfan Ahmad Shah,Usman Tariq
Revisiting Critically:	Kiran Nayyar
Final Approval of version:	Saeed Ahmad

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Ferreira PC, Barbosa J, Amarante JM, Carvalho J, Rodrigues AG, Silva ÁC. Associated injuries in pediatric patients with facial fractures in Portugal: Analysis of 1416 patients. J Cranio-Maxillo-Facial Surg 2015; 43(4):437-43.
2. Glazer M, Joshua BZ, Woldenberg Y, Bodner L. Mandibular fractures in children: analysis of 61 cases and review of the literature. Int J Pediatr Otorhinolaryngol 2011; 75(1):62-4.
3. Andrade NN, Choradia S. An institutional experience in the management of pediatric mandibular fractures: A study of 74 cases. J Cranio-Maxillo-Facial Surg 2015; 43(7):995-9.
4. Siwani R, Tombers NM, Rieck KL, Cofer SA. Comparative analysis of fracture characteristics of the developing mandible: The Mayo Clinic experience. Int J Pediatr Otorhinolaryngol 2014; 78(7):1066-70.
5. Singhal R, Singh V, Bhagol A, Agrawal A, Kumar P. Pediatric maxillofacial injuries–if a new look is required? Int J Pediatr Otorhinolaryngol 2013; 77(8):1333-6.
6. Hoppe IC, Kordahi AM, Paik AM, Lee ES, Granick MS. Age and sex-related differences in 431 pediatric facial fractures at a level 1 trauma center. J Cranio-Maxillo-Facial Surg 2014; 42(7):1408-11.
7. da Costa Nardis A, Costa SA, da Silva RA, Kaba SC. Patterns of paediatric facial fractures in a hospital of Sao Paulo, Brazil: a retrospective study of 3 years. J Cranio-Maxillo-Facial Surg 2013;41(3):226-9.
8. Jain MK, Manjunath KS, Bhagwan BK, Shah DK. Comparison of 3-dimensional and standard miniplate fixation in the management of mandibular fractures. J Oral and Maxillofacial Surg 2010; 68(7):1568-72.
9. An J, Jia P, Zhang Y, Gong X, Han X, He Y. Application of biodegradable plates for treating pediatric mandibular fractures. J Cranio-Maxillo-Facial Surg 2015;43(4):515-20.

10. Al-Moraissi EA, El-Sharkawy TM, El-Ghareeb TI, Chrcanovic BR. Three-dimensional versus standard miniplate fixation in the management of mandibular angle fractures: a systematic review and meta-analysis. Int J Oral and Maxillofacial Surg 2014; 43(6):708-16.
11. Vineeth K, Lalitha RM, Prasad K, Ranganath K, Shwetha V, Singh J. "A comparative evaluation between single noncompression titanium miniplate and three dimensional titanium miniplate in treatment of mandibular angle fracture"–A randomized prospective study. J Cranio-Maxillo-Facial Surg 2013; 41(2):103-9.
12. Höfer SH, Ha L, Ballon A, Sader R, Landes C. Treatment of mandibular angle fractures–Linea obliqua plate versus grid plate. J Cranio-Maxillo-Facial Surg 2012;40(8):807-11.
13. Bayat M, Garajei A, Ghorbani K, Motamedi MH. Treatment of mandibular angle fractures using a single bioresorbableminiplate. J Oral and Maxillofacial Surg 2010;68(7):1573-7.
14. Coletti DP, Caccamese JF. Diagnosis and management of mandibular fractures. In: Fonseca R.J, Marciani RD, editor. Oral and maxillofacial trauma. 2nd ed. Philadelphia PA: WB Saunders;2009.p.139-161.
15. Wymann NM, Hölzle A, Zachariou Z, Iizuka T. Pediatric craniofacial trauma. J Oral and Maxillofacial Surg 2008;66(1):58-64.
16. Chrcanovic BR, Abreu MH, Freire-Maia B, Souza LN. Facial fractures in children and adolescents: a retrospective study of 3 years in a hospital in Belo Horizonte, Brazil. Dental Traumatol 2010; 26(3):262-70.
17. Imahara SD, Hopper RA, Wang J, Rivara FP, Klein MB. Patterns and outcomes of pediatric facial fractures in the United States: a survey of the National Trauma Data Bank. J Am Coll Surgeons 2008;207(5):710-16.
18. Sheta MS, Shoushan MM, Hussein MM, Elaal SA. Evaluation of using microplates osteosynthesis for pediatric mandibular fractures. Tanta Dental J 2015;12(3):149-55.
19. Muñante-Cárdenas JL, Asprino L, De Moraes M, Albergaria-Barbosa JR, Moreira RW. Mandibular fractures in a group of Brazilian subjects under 18 years of age: A epidemiological analysis. Int J Pediatr Otorhinolaryngol 2010;74(11):1276-80.
20. Goth S, Sawatari Y, Peleg M. Management of pediatric mandible fractures. J Craniofacial Surg 2012;23(1):47-56.
21. Giri KY, Singh AP, Dandriyal R, Indra N, Rastogi S, Mall SK, Chowdhury S, Singh HP. Incidence and pattern of mandibular fractures in Rohilkh and region, Uttar Pradesh state, India: A retrospective study. J Oral Biol and Craniofacial Research 2015;5(3):140-5.
22. Laughlin RM, Block MS, Wilk R, Malloy RB, Kent JN. Resorbable plates for the fixation of mandibular fractures: A prospective study. J Oral Maxillofac Surg 2007;65: 89-96.

Original Article

Postoperative Wound Infection in Elective Orthopaedics Implant Surgical Cases at Public Sector Hospital

Zahoor Illahi Soomro[1], Karam Ali Shah[1], Ameer Abbass Baloch [2] and Zulfiqar Ali Soomro[3]

ABSTRACT

Objective: To determine the rate of postoperative wound infection, in clean cases with the use of ilmplant and analyse the factors responsible for surgical site infection.

Study Design: Prospective / descriptive study

Place and Duration of Study: This study was conducted at the Department of Orthopedic Surgery, Peoples University of Medical & Health Sciences (PUMHS) Nawabshah from July 2015 to June 2017.

Materials and Methods: Five hundred twenty cases were operated during two years, 26 developed infection. Patients of close fractures of long bones, immune competent, non diabetic, infection free, with age more than 10 years of either sex in which implants were used, included in this study. The cases on steroid therapy and chemotherapy were excluded from this study.

Results: Out of 520 cases operated during two years, 26 developed inflection, infection rate was 5%. The most common organism isolated was staphylococcus aureus in 18(69.2%) cases. Infected cases above 60 years of age were 18(69.2%) in 3(11.5%) patients, cause was unstable and insecure fixation, 5(19.2%) cases were infected due to the prolong operative time (more than two hours), 5(19.2%) cases had pre-operative stay in the ward (longer than two weeks).

Conclusion: In our setup the postoperative wound infection in clean Orthopaedic implant cases is much higher than International standards. Therefore, it should be controlled by early diagnosis, management and by eliminating the common factors responsible for postoperative wound infection.

Key Words: Orthopaedics Implants, Close fractures, Postoperative wound infection

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INTRODUCTION

Whena clean surgical wound becomes red, tender, swollen and drain purulent material; patient has febrile course after 3rd or 5th postoperative day, with an elevated WBC count and presence of organisms (positive cultures) in the pus, is known as postoperative wound infection. It may occurs within days, or it may not obvious until months or even years[1]. The postoperative wound infection causes significant morbidity with compromised ultimate results. There are number of factors contributing to the development of postoperative wound infections[2,3]. Pathogens may be introduced indirectlyby hematogenous route or directly into the wound via theatre atmosphere, theatre personnel, surgical instruments, surgeon, or by patient himself [4-10].

The postoperative wound infection rate has significantly decreased with introduction of antibiotics, proper sterilization methods, atraumatic surgical techniques, and improved sutures materials [11]. But inpublic sector hospitals, the incidence of postoperative wound infection is still to be high[12,13].

The purpose of this study was to analyse the factors responsible for postoperative wound infection and to reduce the rate of infection to minimum level by controlling the factors, responsible for infection either directly or indirectly.

MATERIALS AND METHODS

We conducted this prospective descriptive study at the Department of Orthopedic Surgery of Peoples University of Medical & Health Science (PUMHS) Nawabshah from July 2015 to June 2017. Patients of close fractures of long bones, immunocompetent, non diabetic, infection free with age more than 10 years of either sex in which implants were used, included in this

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study. The cases on steroid therapy, chemotherapy, diabetes mellitus, skin disease, open fractures or patients with any gross infected foci were excluded from this study.

During two years period, 520 patients of close fractures were operated in which implants were used. A proforma was filled for all patients included in the study. All the patients were operated under general anesthesia. Prophylactic antibiotic (3rd generation cephalosporin was administered 15 to 20 minutes before incision) and continued till 72 hours postoperatively. The dose was 0.5gm to 1.5gms depending upon body weight and type of surgery. The standard autoclave protocol was used for sterilization of implants. On the 3rd postoperative day the first dressing was changed and then at the time of discharge 5th to 7th postoperative day and patients called on 14th postoperative day for removal of stiches. All patients were advised to follow up in outpatients department every month for 1 to 2 years to check the signs and symptoms of late infection. The wound was examined for redness, swelling, or any discharge.

Patients, who developed postoperative fever persisting for 48 hours after surgery, were kept on close observation till their infections settled. Wound discharge cultures were taken or in case with significant collection, aspiration of fluid from collection done, alternate stitches were removed early and if needed, incision and drainage of collection was attempted. Thourough debridement was done in cases with collection and continuous irrigation suction drainage was setup postoperatively for three days.

Total number of cases operated in two years divided by the number of cases developed infection was the criteria to evaluate the rate of infection. All the information about the patients bio data, operation performed, and infection were recorded by a predesigned proforma.

Statistical Analysis:

The qualitative variables in this study were presented by their percentage frequencies and compared with chi-square test or proportion, 95% confidence interval were also completed of various proportions.

RESULTS

Five hundred twenty patients of close fractures underwent implant surgery during two years period, out of these, 494 (95%) patients were infection free, while 26 (5%) patients developed infection with 95% confidence interval of 2.8 – 8.1, Table No.1. Two hundred and ten patients operated were between 10 – 60 years of age, 8 (30.76%) cases developed infection, while 330 patients were above 60 years and in this group, 18 (69.24%) cases developed infection. There were no any significant difference in proportions of infection according to age group P – 0.24, Chi-square = 1.35. Staphylococcus aureus was the most common organism isolated from 18 (69.2%) cases with 95% confidence interval (41.3 – 88.9). The other pathogens included Pseudomonas, Klebsiella, Proteus, and E. coli isolated in 3 (11.5%) cases out of 26 infected cases with their 95% confidence interval (1.4 – 35.7%).

The methicillin resistant staphylococcus aurous (MRSA) was isolated in 1 (3.84%) case, 95% confidence interval (0.0 – 24.10). Out of 26 (19.2%) cases surgical exposure time was more than two hours, which may be one of the contributing factors. Five (19.2%) cases infected had more than 2 weeks stay in ward with their 95% confidence interval (4.4 – 45.2). Three (11.5%) cases had unstable fixation, with their 95% confidence interval (0.9 – 34.0), Table No. 2.

Five (19.23%) patients had superficial infection and were treated by antibiotics medication according to their c/s reports with their 95% confidence interval (4.4 – 45.3).

Table No. 1: Rate of Infection

Total No. of Cases	Total No. of Infected Cases	Percentage	95% confidence interval
520	26	5.0%	2.8 – 8.1

Table No. 2: Factors involved in postoperative infection

Management	Total No. of Infected Cases	Percentage	95% confidence interval
Staphylococcus aureus	18	69.2%	41.3 – 88.9
Overage above 60 years	18	69.2%	41.3 – 88.9
Prolonged surgery	5	19.2%	4.4 – 45.2
Prolong pre-operative stay	5	19.2%	4.4 – 45.2
Improper fixation	3	11.5%	0.9 – 34.0

Table No.3: Management of Infected cases

Factors	Total No. of Infected Cases	Percentage	95% confidence interval
Antibiotic therapy	5	19.2%	4.4 – 45.3
Continuously irrigation suction derange	11	42.30%	16.7 – 68.7
Through debridement of wound, removal of implant, followed by skeletal traction or external fixation	10	38.4%	15.9 – 65.2

Eleven (42.30%) patients with deep infection were treated by antibiotics therapy and continuous irrigation suction drainage till control on infection with 95% confidence (18.7 — 68.7). Ten (38.4%) infected patients were treated by removal of implants and thorough debridement followed by skeletal traction or external fixator was required for fixation with their 95% confidence interval (15.9 – 65.2), Table. No. 3.

DISCUSSION

The infection rate of 5% in clean Orthopaedic procedures was much higher than accepted standard of less than 1 -2% postoperative wound infection, although it is comparatively low as compared to another study conducted at Bahawal Victoria Hospital[14] in Bahawalpur showing 7.8% infection rate. Marston et al, in 1996, reported the infection rate of 0.25% deep, and 5% superficial in 413 total hip replacement in ideal setup[15].

Some studies conducted in Pakistan have shown an overall infection rate of 10% and 7.8% respectively[16]. The rate of postoperative wound infection has been reported to be high without prophylactic antibiotics as compared to be used with prophylactic antibiotics. It varies between 0.4% - 2.8% with prophylactic antibiotics, however one local study reported 6% infections rate[4]. Recent international studies have shown further decrease in surgical site infection rate varies between 0.23%-1.34%.[17]

One study published in 2001, conducted at Jinnah Postgraduate Medical Center, Karachi, reported (3.97%) infection rate with prophylactic antibiotics[18]. On broad cross-section studies reported incidence of infection varied from 0.2% to 10% after clean Orthopaedic operations[19]. In this study the infection rate was same as in some countries but much higher than developed countries. Advanced age and long operative time were associated with wound infection; according to Burnet et al, advanced age was important determinant of wound infection. There is some doubt in predictive value of the interval between injury and operation[20].

Another study conducted on age groups, in which patients those under 40 years of age developed 13.95% infection rate and in patients over 40 years of age developed 57.14% infection rate. This revealed increased incidence of surgical site infection with increasing age21. Staphylococcus aureus (usually coagulase positive) was the most common pathogen cultured from Orthopaedic surgical site infections, followed by Proteus vulgaris, E. coli, and Pseudomonas aeruginosa. Burke reported that more than 50% of Staphylococcus cultures were emerged from the patients. It has been suggested that the source of resistant Staphhylococcus aureus are wards, operation theater and perssonel around him. According to Lindwell study, the strains of Staphylococcus were present in the operation theatre environment during the procedure. Gram -ve bacteria like Pseudomonas aeruginosa is discovered in patients with longer hospital stay. Gram -ve pathogens causing surgical site infections outnumber Gram +ve pathogens. The surgical site infections caused by resistant microorganisms usually occurs in patients receiving prophylactic antibiotics [22].

Another predisposing factor for surgical site infection was prolong surgery. In this study, there were 5 (19.25%) infected patients out of 26 infected patients had operative procedure more than 2 hours, counted as prolonged surgical time. Longer the operative time the more probability of wound is to be infected. The procedure therefore should be performed as efficiently and safely as possible. The length of the operative procedure has been appeared to be proportional to the risk of postoperative wound infection. According to Foot Hills hospital study conducted at both 5 and 10 years, Foord and Cruse revealed surgical site infection rate doubled with every hour of the procedure. There were 1.3% wound infection rate in patients in which procedure lasting one hour or less, whereas infection rate of 4% in those patients where procedure lasting three hours or more[23]. Long preoperative stay in the hospital is another cause of surgical site infection, because of nosocomial infection and spread of pathogens from air, skin of patients, bed sheets, and beds. Five (19.2%) cases which were infected because of long preoperative stay on close fractures were reported in our study. It is commonly held that a long preoperative stay at ward is associated with wound infection, theoretically via colonisation of multiple resistant pathogens. Cruse and Foord reported to support this; there were 1.2% wound infection rate in patients hospitalised for 0 to 1 day, whereas 3.4% wound infection rate recorded in patients hospitalised for more than two weeks. Mead et al, also found a higher risk of surgical site infection in patients with long preoperative hospitalization[23].

The Orthopaedic implant is also an important predisposing factor to cause postoperative wound infection. Bacteria as well as human tissue cells both compete for the occupancy of the implant surface. Human tissue cells have an affinity to compete by integration and adaptation. Bacteria have an affinity to compete by adhesion and colonization. This competition is known as race of the surface[24]. The Orthopaedic implant is incorporated as in ‘inert’ biomaterial, if the human tissue cells win, otherwise resulting infection occurs, if bacteria win, therefore that infection persists until the metal is removed.

There are various factors such as quality of theatre, air contamination in theatre, sterilization, disposables, dresses, theatre personnel, and patient himself, responsible for postoperative wound infections[25].The skin flora or any infected foci of patient is the most

important source of wound infection. The transient bacteremia due to mucosal break at preoperative shaving, presence of microorganisms at incision site, and spread of microorganisms along the postoperative drain tube come up with the surgical site infections. The operation theatre personnel is also responsible to develop surgical site infection by either contact through torn theatre dresses, punctuated gloves or by air contamination by excessive talking and movements. Anaesthetists and circulating nurse are blamed to contribute in increasing theatre air contamination as they do not wear gowns, surgical suits, do lot of talking and move frequently 26,[27].

In this study all 26 cases of wound infection were managed by different methods. Five (19.1%) of patients managed by bed rest, daily dressing and proper antibiotics therapy according to pus culture and sensitivity reports. Eleven (42.3%) of patients were managed by proper parenteral antibiotics with continuous irrigation and suction drainage. Ten (38.4%) of patients were managed by extensive debridement followed by removal of metals. These patients were applied with external fixators or kept on skeletal traction till infection subsided. The type of infection, causative microorganism, culture and sensitivity reports, antibiotics characteristics, and host factors are involved in choosing the appropriate antibiotics[28].

Operation is not always necessary, but is required when an abscess is found, or when radiographic changes of chronic osteomyelitis are seen. If those are not present, a trial of antibiotics therapy according to culture and sensitivity results is appropriate. If patients doesn't respond to antibiotics within 36 to 48 hours, then an abscess is formed, therefore it should be drained accordingly. If they failed, excision of infected and necrotic material should be followed by intermittent antibiotic irrigation and suction drainage may control the infection, if possible the implant should be removed in order to achieve adequate debridement, the fracture should be held securely within external fixator or kept on skeletal traction. Prevention is the best solution and attachment to the basic principles of management of infection will lead to achievesuccess[29].

CONCLUSION

In our setup the postoperative wound infection rate in clean Orthopaedic implant cases is much higher than international standards. Therefore it should be controlled by early diagnosis, management, and by eliminating the common factors responsible for the development of postoperative wound infection given in this study.

Author's Contribution:

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Data Analysis:	Ameer Abbass Baloch, Zulfiqar Ali Soomro
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REFERENCES

1. Nair PK, Bhat VG, Vaz MS. Clinical infectious diseases. World J Clin Infect Dis 2014; 25(8): 9-15.
2. Salman M, Khan MA, Gul T, Bilal M, Kamran W. Frequency of surgical site infection in Orthopaedic implants surgery with its common bacteria and antibiotics sensitivity. Pak J Surg 2014; 30(2): 167-71.
3. Zimmerli W.Clinical presentation and treatment of Orthopaedic implant associated infection. J Int Med 2014; 276(2): 111-9.
4. Ikeanyi UO, Chukwuka CN, Chukwvanukwv TO. Risk factors for surgical site infections following clean Orthopaedic operations. Niger J Clin Pract 2013; 16(4): 443-7.
5. Baker AW, Dicks KV, Durkin MJ, Weber DJ, Lewis SS, Moehring RW, et al. Epidemiology of surgical site infection in a community hospital network. Infect Control Hosp Epidemiol 2016;37: 519-26.
6. Najjar YW, Saleh MY. Orthopaedic Surgical site infection: incidence, predisposing factors, and prevention. Int J Med Sci & Clin Invent 2017;4(2): 2651-61.
7. Al-Mayahi M, Betz M, Muller DA, Stern R, Tahintzi P, Bernard L, et al. Remission rate of implant-related infections following revision surgery after fractures. Int Orthopaedic 2013; 37: 2253-58.
8. Lebowitz D, Kressmann B, Gjoni S, Zenelaj B, Grosgurin O, Marti C, et al. Clinical features of anaerobic Orthopaedic infections. Infect Dis 2017; 49: 137-40.
9. Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty. J Bone Joint Surg Br 2013; 95: 775-82.
10. Jain RK, Shukla R, Singh P, Kumar R. Epidemiology and risk factors for surgical site infections in patients requiring Orthopaedic Surgery. Eur J Orthop Surg Tramatol 2014; 8(5): 251-4.
11. Bratzler DW, Dellinger EP, Olsen KM, PerlTM, Auwaerter PG, Maureen K, et al. Clinical practice guidelines for antimicrobial prophylaxis in Surgery. Am J Health Syst Pharm 2013;70: 195-283.
12. 12.Jamei O, Gjoni S, zenelaj B, kressmann B, Belaieff W, Hannouche D, et al. Which

orthopedic patients are infected with gram negative non-fermenting rods? J Bone Jt Infect 2017; 73-6.
13. Shah MQ, Zardari MS, Khan A, Ahmed S, Awan AS, Mohammad T. Surgical site infection in Orthopaedic implants and its common bacteria with their sensitivities to antibiotics in open reduction internal fixation. J Ayub Med Coll Abbottabad 2017; 29(1): 50-3.
14. Iqbal MZ, CheemaTA, Sabir MR. Rate of postoperative infection in clean Orthopaedic cases. J Pak Orthop Assoc 2001;13:121-4.
15. Marston RA, Cobb AG, Bantley G. Stammor compared with Charnely total hip replacement. J bone J Surg 1996; 78: 178-84.
16. Tayyab S, Hussain N, Sharaf T. Low dose cephradine prophylaxis in Caesarean section. Med Channel 1999; 5(3): 13-5.
17. Weick JA, Jackson JK, O-Brien TJ, Lurate RB, Russell JM, Dorchak JD. Efficacy of prophylactic antibiotics in arthroscopic surgery. Orthopaedics 1997; 20: 133-4.
18. Jamali AR, Mehboob G, Abdul Majid, Bhatti A, Minhas S, Akhtar R. Postoperative wound infection in Orthopaedic Surgery. J Coll Physicians Surg Pak 2001; 11: 746-9.
19. McQueen Mm, LittleJohn MA, Miles RS, Hughes SP. Antibiotic prophylaxis in proximal femoral fracture. Injury 1990; 21: 104-6.
20. Bodoky A, Neff U, Heberer M, Harder F. Antibiotic prophylaxis with two doses of cephalosporins in patients managed with internal fixation for a fracture of the hip. J Bone Joint Surg Am 1993; 75: 61-5.
21. Qureshi MA, Waheed I, Khawaja MA, Qureshi SA. Special measures in appendicectomy to reduce the incidence of wound infection. Pak J Surg 1995; 11: 39-43.
22. Uglow MG, Clarke NM. Relapse in staged surgery for the congenital talipesequinovarus. J Bone Joint Surg Br 2000; 82: 739-43.
23. Sawyer RG, pruett TL. Wound infections. SurgClin North Am 1994; 74: 519-36.
24. Christina AG, Biomaterial centered infection: microbial adhesion versus tissue integration. Science 1987; 237: 1588-95.
25. Verrier ED, Bossart KJ, Hear FW. Reduction of infection rates in abdominal incisions by delayed wound closure technique. Am J Surg 1979; 138: 22-8.
26. Gonzalez A, Suva D, Dunkel N, Nicodene JD, Lomessy A, Lauper N, et al. Are there clinical variables determining antibiotic prophylaxis susceptible versus resistant infection in open fractures? Int Orthop 2014;38: 2323-27.
27. Al-Mayahi M, Cian A, Lipsky BA, Suva D, Muller C, Landelle C, et al. Administration of antibiotic agents before Intraoperative sampling in Orthopaedic infections alters culture results. J Inf Secur 2015; 71: 518-25.
28. Nadeem RD, Akhtar M, Cheema OI, Hashim AR, Nadeem MJ, Nadeem A. Antibiotic prophylaxis in hip surgery: a comparison of two vs three doses of cefuroxime. J Pak Med Assoc 2015; 65: 136-41.
29. Mulhim FFA, Baragbah MA, Sadat-Ali M, Alomran AS, Azam MQ. Prevalence of surgical site infection in Orthopaedic Surgery: a 5 years analysis. Int Surg 2014; 99(3): 264-8.

Original Article

Accuracy of C - Reactive Protein (CRP) for the Diagnosis of Neonatal Sepsis Having Blood Culture as Gold Standard

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ABSTRACT

Objective: To assess the diagnostic accuracy of C - reactive protein (CRP) for the diagnosis of neonatal sepsis while having blood culture as gold standard.

Study Design: A descriptive / cross sectional study.

Place and Duration of Study: This study was conducted at the Department of Pediatrics, Bahawal Victoria Hospital, Bahawalpur, from December 2018 to May 2019.

Materials and Methods: A total of 160 full term neonates with suspicion of sepsis fulfilling the inclusion and exclusion criteria were included in the study. Detailed physical and clinical examination was done, and baseline investigations as per hospital criteria were asked. Sensitivity, Specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CRP in relation to blood culture were calculated.

Results: There were 107 (66.9%) male and 53 (33.1%) female, showing a male to female ratio as 2.01:1. Mean age of the study participants was 5.26 days with a standard deviation of 3.1 days. Blood culture confirmed the presence of sepsis in 77 (48.1%) cases while 82 (51.3%) neonates were found as CRP positive. Sensitivity, specificity, PPV and NPV of CRP in relation to blood cultured for neonatal sepsis were calculated as 81.8%, 77.1%, 76.8%, 82.1% respectively while accuracy of CRP was found as 79.4%.

Conclusion: CRP was found to be a precise indicator of sepsis. In neonates who are suspected for sepsis should always be tested for CRP which will help in early prediction and management of such neonates.

Key Words: neonatal sepsis, CRP, blood culture, sensitivity.

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INTRODUCTION

Neonatal sepsis is known as a clinical syndrome described by signs and symptoms related to infection in the infants aged ≤ 28 days. Neonatal sepsis exhibits itself in the shape of systemic signs linked to infection.[1,2] Infections are estimated to be the commonest cause of neonatal morbidity and mortality while neonatal sepsis is one of the major cause contributing to it.[3,4] In Pakistan, exact numbers affected with neonatal sepsis are not known but global estimates of neonatal sepsis are calculated as 2202 / 100000 live births with mortality ranging 11 to 19%.[5-7] It is also estimated that more than 40% of deaths under 5 years of age are noted in the neonatal period.[8]

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Neonatal sepsis affects all regions of the world and more than 30 million neonates are affected with it while among these, it is estimated that around 2.7 million neonates die.[8,9] In South Asia, around 25% of neonatal deaths are associated with neonatal sepsis. Those who survive from neonatal sepsis are left with increased chances of short as well as long term neurodevelopment diseases.[6,10] Mortality rate associated with neonatal sepsis increase if the condition is not diagnosed and treated properly so with non specific presentation at early stages, special attention is advised to be given by the clinicians to such neonates for good outcome.[5]

For diagnosing neonatal sepsis, blood culture and sensitivity test are considered as gold standard.[11] In Pakistan, it has been shown that pathogens like E. coli, klebsiella pneumonia, staphylococcus aureus as well as some of the group B streptococci are commonly found in cases of neonatal sepsis.[12] It is also a fact that 48 to 72 hours are consumed in blood culture and sensitivity analysis.[13] Researchers around the world are always trying different diagnostic options to diagnose a fatal condition like neonatal sepsis at the earliest. There is a need for a diagnostic test that has good sensitivity along with a reliable negative predictive value (NPV). Different laboratory parameters have been tried and tests like leukocyte count has been found showing a sensitivity of 35% and specificity as 77%, increased /

decreased neutrophil count having sensitivity as 35% and specificity as 74%, low platelet count showing sensitivity as 61% and specificity as 82% and C-reactive protein (CRP) showing sensitivity as 23% and specificity as 84%.[13] Other markers like procalcitonin, acute phase reactants as well as bacterial genomes and inflammatory cytokines are also being evaluated around the world.[6] CRP is considered to be an easy and simple investigation and aim of this study was to assess its diagnostic accuracy for the diagnosis of neonatal sepsis while having blood culture as gold standard.

MATERIALS AND METHODS

This descriptive cross sectional study was conducted at the department of Pediatrics, Bahawal Victoria Hospital, Bahawalpur, from December 2018 to May 2019. A total of 160 full term neonates with suspicion of sepsis were included in the study. Suspicion of sepsis at the time of presentation was described[5] as drowsiness, unwillingness to feed, hypothermia as less than 35 ^{0}C, fits or having difficulty while breathing, mothers of presenting neonates who were having high grade fever or those who had foul smelling discharge during delivery. All those neonates who were noted to receive oral or injectable antibiotics, whose mothers had taken any narcotic analgesic during labor or those neonates who were having congenital heart disease, were not enrolled.

Approval from Institute's ethical and research committee was acquired for this study and informed written consent was taken from all the parents / guardians. In all neonates, detailed physical and clinical examination was done, and baseline investigations as per hospital criteria were asked. All the demographical information like name, age and gender were recorded.

Under stringent aseptic technique, 10 ml of blood was drawn from all the study participants and sent to institute's central laboratory for CRP while blood culture were also asked to confirm the presence of neonatal sepsis. CRP was considered as negative with value < 5mg/dl and positive with a value above it.[5]

All the relevant information like age, gender, CRP, blood culture report and neonatal sepsis (yes/no) were noted on a predesigned proforma. SPSS version 20 was used for all kinds of data entry and analysis. Mean along with standard deviation were recorded for all quantitative variables while frequencies and percentages were calculated for qualitative variables. Sensitivity, Specificity, PPV, NPV and diagnostic accuracy of CRP were calculated in relation to blood culture.

RESULTS

Out of a total of 160 neonates, there were 107 (66.9%) were male and 53 (33.1%) female, showing a male to female ratio as 2.01:1. Mean age of the study participants was 5.26 days with a standard deviation of 3.1 days. Majority of the neonates, 78 (48.8%) were having age less than 1 week.

In all the 160 suspected sepsis cases, blood culture confirmed the presence of sepsis in 77 (48.1%) cases while others, 83 (51.9%) turned out to be negative. Amongst all neonates, 82 (51.3%) presented as CRP positive (Table No.1).

Sensitivity, specificity, PPV and NPV of CRP in relation to blood cultured confirmed sepsis were calculated as per formula given in Table number 2 as those values were found as 81.8%, 77.1%, 76.8%, 82.1% respectively while diagnostic accuracy of CRP was found as 79.4%.

Out of 77 neonates found having sepsis, E.coli (n=30, 39.0%), klebsiella pneumoniae (n=14, 18.2%) and S. auresus (n=12, 15.6%) were the commonest pathogens involved.

Table No.1:Findings of Blood Culture and CRP amongst All the Neonates

	Blood Culture	CRP
Positive	77 (48.1%)	82 (51.3%)
Negative	83 (51.9%)	78 (48.7%)
Total	196	196

Table No.2:Relation of CRP and Blood Culture amongst all the neonates

CRP	Sepsis		Total
	Positive	Negative	
Positive	63	19	82
Negative	14	64	78
Total	77	83	160
Sensitivity	(a / a + c) x 100 = 81.8%		
Specificity	(d / b + d) x 100 = 77.1%		
PPV	(a / a + b) x 100 = 76.8%		
NPV	(d / c + d) x 100 = 82.1%		
Accuracy	{(d + a) / total patients} x 100 = 79.4%		

DISCUSSION

As we know that newborn babies have Newborns have a fragile immune system that make them more susceptible to infections. It is also seen that newborn babies get worse rapidly following infections and if diagnosis and treatment is delayed, worse outcomes are commonly seen.[14] Proactive approach regarding diagnosis and treatment of neonatal sepsis has been found beneficial in researches conducted around the world so there is always a need of a diagnostic tool that can prove helpful in early diagnosis.

Neonatal sepsis commonly accompanies a presentation that is non-specific in nature so there is always a challenge indentifying neonates with and without sepsis. CRP is considered to be an easy to perform, time and cost effective test.[5] We considered CRP through qualitative method, taking cut-off level value of 5mg/dl.

In the present study, we noted the mean age amongst all the neonates as 5.26 days with a standard deviation of 3.1 days. Majority of the neonates, 78 (48.8%) were having age less than 1 week. Irshad M et al[5] found the mean age of studied neonates as 4.5 days which is quite similar to what we observed while Anwer SK and Mustafa S[15] found the mean age of studied neonates as 4 days while most of them were less than 1 week.

Majority of the neonates in our study, 107 (66.9%) were male. This is very consistent to previous findings where a predominant male prevalence has been found by earlier researchers.[5,16] X linked immune regulatory gen factor could be the contributor to this finding in male gender.[17]

In the present work, blood culture confirmed the presence of sepsis in 77 (48.1%) cases. This is pretty near to what has been found by another local study done in Peshawar[5] where 43% of neonates were found positive for sepsis while West BA et al[18] and Anwer SK et al[15] noted 43% and 42% of neonates positive for sepsis respectively which is again very close to our findings. Sriram R[17] noted 50.4% neonates with the presence of sepsis in another study which is pretty consistent to the findings of this study.

In the current study, we noted 82 (51.3%) neonates as CRP positive. Another local study with a similar design from Peshawar[5] found 48% neonates as CRP positive while Shirazi H et al[13] noted 39% neonates with CRP positive which is lower than the current finding. As neonatal sepsis commonly accompany presentation that is non-specific in nature so there is always a challenge indentifying neonates with and without neonatal sepsis.

In this study, sensitivity, specificity, PPV and NPV of CRP in relation to blood culture were calculated as 81.8%, 77.1%, 76.8%, 82.1% respectively while diagnostic accuracy of CRP was found as 79.4%. In another local study from Lady Reading Hospital from Peshawar[5] noted the sensitivity of CRP in relation to blood culture as 78 % while specificity was 74% and NPV as 81%. Our results are aligned with these findings and mean than around 3/4th of neonates who are found suspected having sepsis will be rightly diagnosed according to CRP estimation. This also mean that 1 out of every 4 neonates will have a chance of false negative results. Usually, neonates are reported to our setup with a history of antibiotics usage or mothers are administered antibiotics intrapartum, a CRP which is negative could give us a good lead to make a clinical decision to stop antibiotics usage. This can result in early discontinuation of hospitalization and could lead to cost effective treatment. West BA and coworkers[18] noted that sensitivity of CRP as 74% while specificity was found as 74.1%, PPV as 68.4% and NPV of 79.0% which is very near to what was found in the current study. Anwer SK and colleagues[15] got sensitivity, specificity, PPV and NPV of CRP in relation to positive blood culture for sepsis as 92.5%, 85.3%, 80.6% and 96.5% respectively which again shows the utility to CRP for the early prediction of sepsis in suspected neonates. Some researchers[13] reported sensitivity of CRP in diagnosis of sepsis as low as 23% which is contrary to current findings while most others[19,20] have got quite similar results in comparison to our findings. Variation in reported sensitivity of CRP in neonatal bacterial infection could be attributed to difference in diagnostic criteria labeled in the different studies and the span of infection studied.

In the present study, confirmed cases of neonatal sepsis through blood culture, E.coli (39.0%), klebsiella pneumoniae (18.2%) and S. auresus (15.6%) were found to be the commonest pathogens involved. It has been found earlier by local researchers[5,12] that E. coli is the most common pathogen involved followed by k. pneumoniae.

In the current study, diagnostic accuracy of CRP was found to be 79.4% which means that CRP can be very helpful in predicting sepsis in suspected neonates while blood culture results are awaiting. With a high NPV 82.1%, it can also help immensely in excluding neonates having sepsis that could prevent unnecessary antibiotic usage and hospital stays.

This is the 1st study conducted at our center assessing the role of CRP as a diagnostic tool for neonatal sepsis having blood culture as gold standard. Studies having larger sample size, involving multiple health institutes and local population will certainly prove helpful verifying the results of the current work.

CONCLUSION

CRP was found to be a precise indicator of sepsis. In neonates who are suspected for sepsis should always be tested for CRP which will help in early prediction and management of such neonates. CRP is an easy, quick and simple test. CRP can be highly helpful in resource constraint settings where blood culture is not always available.

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REFERENCES

1. Mersha A, Worku T, Shibiru S, Bante A, Molla A, Seifu G, et al. Neonatal sepsis and associated factors among newborns in hospitals of Wolaita Sodo Town, Southern Ethiopia. Res Rep Neonat 2019:9 1–8
2. Edwards MS, Baker CJ. Sepsis in the newborn. In: Gershon AA, Hotez PJ, Katz SL, editors. Krugman's Infectious Diseases of Children. Philadelphia PA: Mosby;2004:545.
3. Thaver D, Zaidi AK. Burden of neonatal infections in developing countries: A review of evidence from community based studies. Pediatr Infect Dis J 2009;28:3-9.
4. Afroza S. Neonatal sepsis a global problem: An overview. Mymensingh Med J 2006; 15:108-14.
5. Irshad M, Hayat M, Parvez H, Ihsan Ullah, Zia ur Rehman. Neonatal sepsis; diagnostic accuracy of C-reactive protein (CRP) in the diagnosis of neonatal sepsis. Professional Med J 2019; 26(4):608-614.
6. Fleischmann-Struzek C, Goldfarb DM, Schlattmann P, Schlapbach LJ, Reinhart K, Kissoon N. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med 2018;6(3):223–230.
7. Wu JH, Chen CY, Tsao PN, Hsieh WS, Chou HC. Neonatal sepsis: a 6-year analysis in a neonatal care unit in Taiwan. Pediatr Neonatol 2009;50(3): 88–95.
8. UNICEF, WHO, The World Bank, and The United Nations. Levels and Trends in Child Mortality. New York, NY: UNICEF; 2011.
9. GSA and WHO. World sepsis day 2017 – preventable maternal and neonatal sepsis a critical priority for WHO and Global Sepsis Alliance. Available from: https://static1.squarespace.com/static/58a7025b8419c215b30b2df3/t/59b1b9d52994caee6bc0eba7/1504819673100/Press_Release_WSD_WSC_English_Letterhead+(PDF).pdf. Accessed July 26, 2018.
10. Ferreira RC, Mello RR, Silva KS. Neonatal sepsis as a risk factor for neurodevelopmental changes in preterm infants with very low birth weight. J Pediatr (Rio J) 2014;90(3):293–299.
11. Sankar M, Agarwal R, Ashok K, Deorari V, Inod K. Sepsis in the newborn. Indian J Pediatr 2008; 75:261-6.
12. Zaidi AK, Thaver D, Ali SA, Khan TA. Pathogens associated with sepsis in the newborn and young infants in developing countries. Pediatr Infect Dis J 2009;28:10-8.
13. Shirazi H,Riaz S, Tahir R. Role of hematological profile in early diagnosis of neonatal sepsis. Ann Pak Inst Med Sci 2010; 6:152-6.
14. Bhat R, Rao AY. The performance of hematological screening parameters and CRP in early onset of neonatal infections. J Clin Diagno Res 2010;4:3331-6.
15. Anwer SK, Mustafa S. Rapid identification of neonatal sepsis. JPMA 2000:50:94.
16. Kumar R, Musoke R, Macharia WM, Revathi G. Validation of C-reactive protein in the early diagnosis of neonatal sepsis in a tertiary care hospital in Kenya. East Afr Med J 2010; 87: 255-61.
17. Sriram R. Correlation of Blood culture results with the Sepsis score and the Sepsis screen in the diagnosis of Neonatal Septicemia. Int J Biol Med Res 2011;2:360-8.
18. West BA, Peterside O, Ugwu RO, Eneh AU. Prospective evaluation of the usefulness of C-reactive protein in the diagnosis of neonatal sepsis in a sub-Saharan African region. Antimicrob Resist Infect Control 2012;1:22.
19. Ahmed Z, Ghafoor T, Waqar T. Diagnostic value of CRP and hematological parameters in neonatal sepsis. J Coll Physicians Surg Pak 2005;15:152-6.
20. Nakamura H, Uetani Y, Nagata T, Yamasaki T. Serum C-reactive protein in the early diagnosis of neonatal septicemia and bacterial meningitis. Acta Paediatr Jpn 1989; 31:567-71.

Original Article

Anthropometric Modification can be Useful for Gastro-Esophageal Reflux Disease Symptoms; which Parameter should be Targeted Most? In a Tertiary Care Hospital at Karachi

Shahid Karim, Hamid Ali, Syeda Nosheen Zehra, Afsheen Faryal, Tanveer Khalid and Ghulam Mujtaba

ABSTRACT

Objective: To find out the anthropometric modification can be useful for gastro-esophageal reflux disease symptoms; which parameter should be targeted most? in a tertiary care Hospital at Karachi.
Study Design: Cross sectional study.
Place and Duration of Study: This study was conducted at the Department of Gastroenterology, Liaquat National Hospital & Medical College, Karachi from February 2009 to March 2010
Materials and Methods. Relative sitting of patients were included in the study with no co morbid, non-smoker and non-alcoholic patients. Questionnaires were got filled from them. Logistics regression of the anthropometric measures was computed with the 95% confidence interval.
Results: Total 2191 participants were included in our study. 1130 patients (51.6%) were male and 1061 (48.4%) were females, with mean age of 33.92+12.36 years. GERD symptoms were present in 760 patients (34.7%). GERD symptoms were common in patients taking spicy meals (37.2%) and in Urdu speakers (52.5%).
Conclusion: In conclusion GERD is common in our population and there is significant inverse association of GERD with Waist hip ratio and waist height ratio.
Key Words: Anthropometric modification, Gastroesophageal reflux disease, body mass index

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the commonly known disorders in upper gastrointestinal tract[1]. GERD has been observed up to an increasing extent in Europe as well as United States of America[2, 3]. The symptoms of GERD are the considered as the most common symptoms among the gastrointestinal symptoms in the regions as mentioned earlier with the occurrence of 10-25% as indicated by the different population based studies[4]. The occurrence of Gastro esophageal reflux disease< 5% is reported for Asia[5].

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The tremendous literature from Iran indicates that same rate of prevalence of GERD which have been reported for the western countries[6,7]. DERD can be marked among the different symptoms which can be categorized into the different categories i.e. typical, atypical and esophageal symptoms. Symptoms which are having the greater specificity for GERD are known as the acid regurgitation and heartburn. When the hard symptoms are absent these can permit to conduct the presumptive diagnosis and start the empiric therapy. In the some situations, more diagnostic testing is required for the confirmation of diagnosis and as well as for the assessment of probable causes of the symptoms.

Contributing factors of GERD have been examined in the population generally as reported by the various studies but some of potential contributing factors have indicated the different results[8,9]. The data from the developing and under-developing countries have been obtained in the limited amount and few population based studies have been conducted which present the determinants of GERD[10]. This study is aimed to investigate the contributing factors of Gastro esophageal reflux disease (GERD) with the cross-sectional analysis of standard data from the Golestan

Cohort study, a potential unit of around 2290 people at Karachi, Pakistan. Data was analyzed on the basis of frequency, perceived severity of patient and the time of first occurrence of GERD symptoms.

MATERIALS AND METHODS

Potential, analytical, cross-sectional and multi-center Prospective, cross sectional analytical study was conducted from the duration of February 2009 to March 2010. The population of the study was the respondents of age of 18 years and their relatives with age above 18 years arriving at the outpatient clinic of the various section of the tertiary hospital having no history of co morbid before such as; diabetes, ischemic heart diseases, hypertension, stroke, and renal diseases. The respondents were selected randomly by the help of chart which is generated by computer, the subjects were screened and were also considered as potential for the study. The responses were taken from them with their consensus. Respondents having the history of acid peptic disease, smoking, chronic liver disease, alcohol or history of drugs such as Beta-blocker Aspirin, NSAIDS or any other drugs within the duration of last 6 months) or those respondents who were having any of the mentioned comorbids were excluded from the study. For the conduction this study, the respondents were provided with questionnaire i.e. "Ritcher Acid Scale"[11]. The questionnaire was already validated and as well as translated in local language for the study which was conducted at the department of gastroenterology (medicine) in 2005 at Agha Khan University Hospital[11].

The questionnaire survey was conducted by the team of trained volunteers they explained everything to the respondents in the case of any confusion. In the designed questionnaire respondents were inquired about GERD and screening questions were asked from them i.e. presence of retrosternal burning, burning of throat`s back, sour / bitter taste, symptoms of GERD after meal, simultaneously, they were asked about the symptoms of GERD two or more than two times in week. Two or more "Yes" for asked questions was interpreted as the presence of symptoms of GERD. On the basis of presence or absence of gastroesophageal reflux symptoms (GERD) the respondents were divided into two groups.

Questionnaire was included with the demographics i.e. gender, age, cultural background (the province of Pakistan), and qualification (illiterate, 5th, 8th, 10th, 12th, graduation). The age was categorized into three groups in order to observe the relationship of age and GERD symptoms: the groups of age were as; a <30 years, b) 31-50 years and c) > 50 years. The body mass index of the respondents was also calculated.

This study was approved to be conducted by the Ethical Board Review Committee of Agha Khan University hospital Karachi, Pakistan. All the data i.e. demographics and the clinical history were recorded by the researcher on already designed questionnaire. The responses were taken from the respondents after their consensus. Exclusion criteria was strictly followed so that the confounding variables could be avoided.

Statistical analysis: The obtained data was analyzed by using the commonly used software i.e. statistical package for social sciences (SPSS) version 22. At the very first the descriptive statistics was used for the analysis. Frequency distribution i.e. count and percentage were reported. The whole data was presented by using the mean + standard deviation. The level of statistical significance of comparison of means was investigated by using chi square and t-test and Fisher`s exact formula. 5% statistical significance i.e. p—value = 0.05 was considered.

RESULTS

Total 2297 participants were included in our study. 1167 patients (50.8%) were male and 1130 (49.2%) were females, with mean age of 34.48±12.594 years, as shown in Table-1 & Table-2.

The majority of subjects 1203 (52.4%) included in our study were Urdu speakers, 368 (16%) were Punjabi, 345 (15%) were Sindhi, 270 (11.8%) were Pathan and 111 (4.8%) were Balochi as shown in table 3.

Regarding education status in our study, majority of patient were 1105 (48.1%) were graduate, 417 (18.2%) were illiterate, 332 (14.5%) were intermediate pass and 443 (19.3%) were middle pass plus matriculation pass, as shown in Table-3.

In our study the mean BMI was 24.1386±4.02156 kg/m2, the mean Waist hip ratio was 0.90±0.15 cm, the mean Waist height ratio was 0.5170±0.07027 cm and the mean waist circumference ratio was 84.9±10.95 cm as shown in table 2.

Regarding aggravating factors history of fried meal was observed in 767 patients (33.4%), spicy meal 881 (38.4%), cold drink in 168 (7.3%) and history of chocolate was seen in 83 patients (3.6%), as shown in Table-5.

Regarding GERD symptoms, uncomfortable feeling behind breast bone moving upward were observed in 1008 (43.9%) patients, burning back of throat in 567 (24.7%), bitter taste in mouth in 607 (26.4%), symptoms after meal in 921 (40.1%), as shown in Table-4

Two are more time GERD symptoms per week were observed in 507 patients (22.1%), temporary relief with medicine was observed in 554 (24.1%), as shown in Table-4.

In our study GERD symptoms were present in 822 patients (35.8%), as shown in Table-1

GERD symptoms were more common in graduates and in Urdu speakers and patients taking spicy meals. GERD is significantly associated with Waist hip ratio (p-value 0.001) and waist height ratio (p-value 0.001).

Table No.1:Frequency Distribution of total number of study participants and gender

Total number of study participants	Frequency (n)	Percentage (%)
GERD present	822	35.8%
GERD not present	1475	64.2%
Gender: Male	1167	50.8%
Female	1130	49.2%

Table No.2: Frequency Distribution of Age, Bmi, Waist Hip Ratio, Waist Height Ratio and Waist Circumference

Variables	Min.	Max.	Mean±SD
Age years	18	74	34.48±12.594
Bmi	18	48.40	24.1386±4.02156
Waist hip ratio	0.67	3.95	0.90±0.15
Waist height ratio	0.36	1.34	0.5170±0.07027
Waist circumference ratio	56	140	84.9±10.95

Table No.3: Frequency Distribution of Ethnicity, Education Level and Occupation

Ethnicity	Frequency (n)	Percentage (%)
Punjab	368	16%
Sindh	345	15%
Kpk	270	11.8%
Urdu speaking	1203	52.4%
Balochistan	111	4.8%
Education level		
Graduate	1105	48.1%
Inter pass	332	14.5%
Middle pass + matriculation	443	19.3%
Illitrate	417	18.2%

Table No.4: Frequency Distribution of Frequency of Gerd Symptoms

Uncomfortable feeling behind the sternum	Frequency (n)	Percentage (%)
Yes	1008	43.9%
No	1289	56.1%
Burning back of throat		
Yes	567	24.7%
No	1730	75.3%
Bitter taste of mouth		
Yes	607	26.4%
No	1690	73.6%
Symptoms after meal		
Yes	921	40.1%
No	1376	59.9%
Two or more times gerd symptoms/week		
Yes	507	22.1%
No	1790	77.9%
Temperory Relief With Proton Pump Inhabitor And H2 Receptor Blocker		
Yes	554	24.1%
No	1743	75.9%

Table No.5: Frequency Distribution of Aggregating Factors

Aggregating factors		
Fried meal	frequency (n)	percentage(%)
Yes	767	33.4%
No	1530	66.6%
Spicy meal		
Yes	881	38.4%
No	1416	61.6%
Cold drink		
Yes	168	7.3%
No	2129	92.7%
Choclate		
Yes	83	3.6%
No	2214	96.4%

Table No.6: Frequency Distribution of Gerd

	Univariate analysis		Multivariate analysis	
BMI	Confidence interval(Ci)	P-value	Confidence interval(Ci)	P-value
18-23	1		1	
23-25	1.25(0.99-1.56)	0.051	1.11(0.88-1.4)	0.39
>25	1.70(1.38-2.09)	0.001	1.15(0.88-1.51)	0.32
Waist Circumference				
≤90 cm	1		1	
91-100 cm	1.24(0.97-1.60)	0.09	0.74(0.55-1.01)	0.06
≥ 101	1.90(1.41-2.54)	0.001	0.91(0.58-1.42)	0.66
Waist Hip Ratio				
≤0.90	1		1	
0.91-1.00	1.47(1.22-1.77)	0.001	1.38(1.14-1.68)	0.001
≥1.01	2.35(1.71-3.80)	0.001	2.15(1.42-3.25)	0.001
Waist Height Ratio				
≤0.50	1		1	
0.51-0.6	1.67(1.38-2.02)	0.001	1.59(1.24-2.02)	0.001
≥0.61	2.16(1.63-2.87)	0.001	2.06(1.30-3.27)	0.002

DISCUSSION

GERD disease is an unremitting disease of multi-factorial etiology in which genetic and environmental factors keep pivotal; role. It was shown in global studies that different anthropometric events were applied for GERD, that included Hip Circumference Grips, BMI, waist circumference grips and other multiple factors were concerned with GERD as like education level, society. In most but not in all studies[12] positive relation between GERD and age have been kept under consideration. The relationship between GERD symptoms and gender are mixed in present evidences. But in most of the studies this association has not been shown[13]. In our study GERD symptoms

were present in 35.8% patients as compare to 18.1% prevalence of GERD symptoms was found in the study among those respondents who were doing job. One previously conducted study indicated the relation between GERD symptoms and the socioeconomic status of the other populations[14].

It is also indicated such relation even after the adjustments for certain other causes of GERD. In our study GERD symptoms were common in graduates which is similar to one previous study showing the prevalence of the GERD symptoms was greater in the respondents having higher educational level; it was 34.1% in the graduate respondents. The association of both was highlighted as the inverse association; especially for those respondents with lower educational level; because education is often started and finished in early age before the initiation of GERD[16].

The prevalence of GERD symptoms was greater i.e. 23% in the respondents with body mass index (BMI) i.e. 23-27.4 kg/m2. Those Respondents having overweight and normal BMI, GERD was commonly found. Many previously conducted studies have indicated the relationship between GERD symptoms and higher level of BMI[17]. In this association, central deposit seemed as more important factor as compared to overall obesity[18]. The relation between the obesity and GERD is considered as the causal i.e. exposure-response which have been indicated in the various studies[17].

Increased inner abdominal pressure probably come in the explanation of relationship of GERD with body mass index (BMI) and especially central obesity[19,20]. Although, other mechanisms are also seemed to be there which contribute in this relationship i.e. lower pressure of esophageal sphincter in fat individuals[20]. Exposure of esophageal acid has been positively correlated with body mass index (BMI) in any case[20] and as well as waist circumference[21]. The clear relationship of GERD and fatness has been indicated in the western countries[22]. But in this study the relationship between obesity and GERD was not found. Inconsistent results have been concluded from the population based studies of China on the relationship between GERD and BMI[23]. The association of GERD and abdominal fatness was assessed in the study conducted by Chen et al; but no significant relationship between central obesity and reflux symptoms was found[24].

In our study GERD symptoms were seen more in males (20.5%) as compared to females (15.2%), observed more commonly (17.6%) in age group of 31-50 years. The association of high BMI and central obesity in women were reported to be associated with symptoms of GERD in the study conducted by Islami et al[15]. Whereas, in men daily symptoms were associated with the central obesity: but the significant association of BMI, waist to hip ratio was not found. The previous literature did not highlighted any difference regarding the relationship of GERD and obesity in terms of gender[20]. Variation in the results is not clear but some speculations explained the risk factors which probably be common in men by which they may minimize the apparent effect of fatness.

This study found the significant inverse association between GERD symptoms with waist hip ration and waist height ratio. More longitudinal studies on this issue are required to be conducted.

Study Strength and limitation:

Greater number of questionnaire samples was collected from the respondents which contained the detailed information of the symptoms of GERD and the other contributing factors are counted to be the strengths of this study. Lack of the data regarding the endoscopic and histological damage related with GERD was considered as the limitation of the study. Although, GERD as the clinical diagnosis in most of the instances particularly in the setting of primary care and its symptoms are considered as the common cause of discomfort level irrespective of the presence and absence of histological and endoscopic outcomes; Investigation of sources of GERD has indicated the clinical implication.

CONCLUSION

In conclusion GERD is common in our population and there is significant inverse association of GERD with Waist hip ratio and waist height ratio. GERD symptoms were common in Urdu speakers, graduates and patients who were taking spicy meals.

Author's Contribution:

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Revisiting Critically:	Shahid Karim
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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. DeVault KR, Castell DO, American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol 2005;100:190-200.
2. Friedenberg FK, Hanlon A, Vanar V, Nehemia D, Mekapati J, et al. Trends in gastroesophageal reflux disease as measured by the National Ambulatory Medical Care Survey. Dig Dis Sci 2010;55:1911–1917.
3. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Changes in prevalence, incidence and spontaneous

loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. Gut 2012;61:1390–1397.
4. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterol 2012;143: 1179–1187
5. Goh KL, Chang CS, Fock KM, Ke M, Park HJ, Lam SK. Gastro-oesophageal reflux disease in Asia. J Gastroenterol Hepatol 2000;15:230-8.
6. Fazel M, Keshteli AH, Jahangiri P, Daneshpajouhnejad P, Adibi P. Gastroesophageal Reflux Disease in Iran: SEPAHAN Systematic Review No. 2. Int J Prev Med 2012;3:S10–S17.
7. Badillo R, Francis D. Diagnosis and treatment of gastroesophageal reflux disease. World J Gastrointestinal Pharmacol Therapeutics 2014;5(3):105.
8. Pandeya N, Green AC, Whiteman DC. Prevalence and determinants of frequent gastroesophageal reflux symptoms in the Australian community. Dis Esophagus 2012;25:573–583.
9. Matsuki N, Fujita T, Watanabe N, Sugahara A, Watanabe A, et al. Lifestyle factors associated with gastroesophageal reflux disease in the Japanese population. J Gastroenterol 2013;48:340–349.
10. Somi MH, Farhang S, Nasseri-Moghadam S, Jazayeri ES, Mirinezhad SK, et al. Prevalence and risk factors of gastroesophageal reflux disease in Tabriz, Iran. Iran J Public Health 2008;37: 85–90
11. Jafri N, Jafri W, Yakoob J, Islam M, Manzoor S, Jalil A, et al. Perception of gastroesophageal reflux disease in urban population in Pakistan. J Coll Physicians Surg Pak 2005; 15: 532-4.
12. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet 2006;367: 2086–2100
13. Nusrat S, Nusrat S, Bielefeldt K. Reflux and sex: what drives testing, what drives treatment? Eur J Gastroenterol Hepatol 2012;24: 233–247.
14. Jansson C, Nordenstedt H, Johansson S, Wallander MA, Johnsen R, et al. Relation between gastroesophageal reflux symptoms and socioeconomic factors: a population-based study (the HUNT Study). Clin Gastroenterol Hepatol 2007;5: 1029–1034
15. Islami F, Nasseri-Moghaddam S, Pourshams A, Poustchi H, Semnani S, Kamangar F, et al. Determinants of Gastroesophageal Reflux Disease, Including Hookah Smoking and Opium Use–A Cross-Sectional Analysis of 50,000 Individuals. PloS one 2014 Feb 21;9(2):e89256.
16. Nocon M, Keil T, Willich SN. Prevalence and sociodemographics of reflux symptoms in Germany–results from a national survey. Aliment Pharmacol Ther 2006;23: 1601–1605
17. El Serag H. The association between obesity and GERD: a review of the epidemiological evidence. Dig Dis Sci 2008;53: 2307–2312
18. Singh S, Sharma AN, Murad MH, Buttar NS, El Serag HB, et al. Central Adiposity is Associated with Increased Risk of Esophageal Inflammation, Metaplasia, and Adenocarcinoma: a Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2013;11: 1399–1412
19. Ayazi S, Demeester SR, Hsieh CC, Zehetner J, Sharma G, et al. Thoraco-abdominal pressure gradients during the phases of respiration contribute to gastroesophageal reflux disease. Dig Dis Sci 2011;56:1718–1722
20. Derakhshan MH, Robertson EV, Fletcher J, Jones GR, Lee YY, et al. Mechanism of association between BMI and dysfunction of the gastro-oesophageal barrier in patients with normal endoscopy. Gut 2012;61: 337–343
21. Robertson EV, Derakhshan MH, Wirz AA, Lee YY, Seenan JP, et al. Central obesity in asymptomatic volunteers is associated with increased intrasphincteric acid reflux and lengthening of the cardiac mucosa. Gastroenterol 2013;145: 730–739
22. Corley DA, Kubo A, Zhao W: Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. Gut 2007;56: 756-762.
23. He J, Ma X, Zhao Y, Wang R, Yan X, Yan H, Yin P, Kang X, Fang J, Hao Y, et al: A population-based survey of the epidemiology of symptom-defined gastroesophageal reflux disease: the systematic investigation of gastrointestinal diseases in China. BMC Gastroenterol 2010;10:94-10.
24. Chen T, Lu M, Wang X, Yang Y, Zhang J, Jin L, Ye W. Prevalence and risk factors of gastro-esophageal reflux symptoms in a Chinese retiree cohort. BMC Gastroenterol 2012;12(1):161.

Original Article

Factors Influencing Perceptions of Undergraduate Students about Idealized Body Image: A Cross-Sectional Study in Peshawar

Saminullah Khan[1], Sher Bahadur[2], Atta ullah Jan[2] and Rizwan Anwar[1]

ABSTRACT

Objective: To compare the perceived factors influencing the idealized body image among medical and non-medical students in Peshawar

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the two Universities and a Medical College in Peshawar August 2018 to October 2018.

Materials and Methods: Using Convenient sampling techniques, a total of 422 of medical and non-medical students were approached to be part of the study. The students during their break time were requested to take part in the study. Data Collection was based on indigenous questionnaire, coded and entered into SPSS version 20 and analyzed for descriptive statistics.

Results: Result of the study indicated that out of 422 students 50.7% were non-medical and 49.3% were medical. Most of them were very conscious about their body image. Regarding body weight, 133(63.9%) of medical students perceived that they have normal body weight as compare to 120 (56.1%) non-medical students. However 43(20.1%) of non-medical student considered themselves as underweight as compared to 17(8.2%) of medical students which shows a significant difference (p=0.002). Student, regardless of their field of studyoften compared themselves with one or another perceived idealized person for body image. However, most (82.2% medical and 87.4% non-medical) of them were satisfied with their body image. There was no significant (p.0.05) difference regarding factors influencing the perceptions of medical and non-medical students about body image. Nearly 26% of the students were of the view that representation of females in media is a healthy trend which needs to be followed.In relationship to body weight and self-esteem, 30(14.4%) and 42(19.6%) of medical and non-medical students respectively were of the views that body weight has negatively affected their self-esteem indicating that students have similar impression regardless of their field of study (p=0.29).

Conclusion: There is no significant difference in the perceptions of medical and non-medical students regarding idealized body image and its associated influencing factors, however, in comparison to medical students, a greater proportion of non-medical students of students considered themselvesas underweight.

Key Words: Idealized body image, body weight, Perception, self-esteem, Depression

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INTRODUCTION

Body image is an important aspect of self-representation and self-evaluation throughout the life. The imagination about own body is one of multidimensional assembling of satisfaction levels regarding general appearance, shape and size.[1] It become more important when youngster perceive defect in their appearance as it also affect the behavior of the individual.[2] The satisfaction level of the individual is more linked with subjective meaning of their appearance as compared to objective reality.[3] On other hand self-perceptions about body weight acts as indicator for nutrition status, thus one can plan to maintain the ideal body weight accordingly.[4] The students are more conscious about their body image therefore their satisfaction level also varies. The medical students especially female have different perception about ideal body image.[5] A study conducted among female students in Mangalore, India where, 25(17%) were undernourished and 11(7.5%) were overweight respectively. Regarding the satisfaction 98(66.7%) of them were satisfied with their image and 30 (20.4 %) were not satisfied and wanted to reduce weight. Although they had normal BMI, but still

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42(28.6%) of students were skipping their meal.[6]Another study conducted in Saudi Arabia where 60.1% of students had shown dissatisfaction with their body image. In same area study on medical students shown that only 26.4% medical students are satisfied with their body image. Among medical students 18.6% perceived that they are too much lean.[7] In India more than 50% of the female students are dissatisfied with their body image. Most of dissatisfied female students belongs to urban area as compared to those belonged to rural area (p<0.001).[8] There was no positive association between BMI and satisfaction with body image. Media hasvital influential role to change the perception of the individual regarding body image. A study from Pakistan revealed that media has an overall negative effect on individuals' body image.[9]It is highlighted that person's perceived appearance, feelings related to their physical features and contribution to the relationships with others were the main aspects which influences a person's body image. Having negative perception about own body image among medical profession, could have negative impact on health services to the patients. This could influence the overall performance of individual especially among students and working individuals. It is also proven that cultural differences play a significant role in deciding the 'ideal' body appearance. Perception of young adolescence is mostly based on personal interpretation and it varies from person to person and this perception is influenced by variety of factors. This study aimed to know Factors influencing perceptions of undergraduate students about idealized body image.

MATERIALS AND METHODS

This was a cross-sectional study conducted among medical and non-medical students. Using convenient sampling the students from Sarhad University, Peshawar University and Khyber Medical College were requested to take part in the study. Using the W.H.O software for sample size calculation, the sample size came to be 422 assuming the confidence level (95%) anticipated population proportion[8] of (p=0.52), study power (d=95%) and 10% loss of follow-up. Data were collected on a self-administered questionnaire. After coding the variables data was entered and analyzed using SPSS version 20 and presented in terms of mean, standard deviation, frequencies and percentages.

RESULTS

A total of 422 students (mean age21.42 ± 1.68 years)out of whom 214(50.7%) were non-medical student and 208(49.3%) were medical students. Among medical students, 52(25.0%) shown extreme consciousness about your physical appearance as compare to 74 (34.6%) of non-medical students (p=0.07).

Regarding body weight, 133(63.9%) of medical students perceived that they have normal body weight as compare to 120 (56.1%) non-medical students. however 43(20.1%) of non-medical student considered themselves as underweight as compared to 17(8.2%) of medical students which has shown a significant difference (p=0.002). Among Medical students 58(27.9%) perceived that they were overweight as compare to 51(23.8%) of non-medical students. Nearly 2/5th of the students from both groups compared themselves with perceived idealized person for body image whereas 42(20.2%) and 58(27.1%) of medical and non-medical students respectively compared themselves with others. However most (82.2% medical and 87.4% non-medical) of the students were happy with their body image

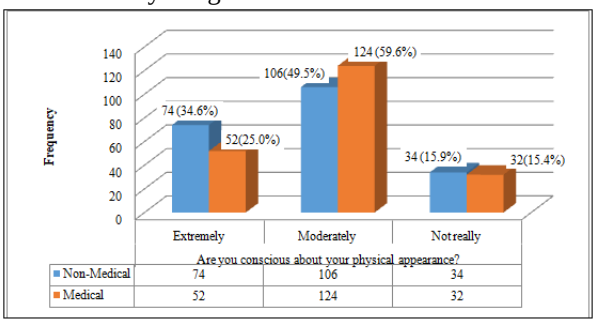

Figure No.1: Comparing the medical and non medical student's concerns about their physical appearance (p=0.07)

Table No.1: Student's intentions about their body image

Variables	Medical Students	Non-Medical Students	P-Value
Students perception about their body weight			
Normal	133(63.9%)	120 (56.1%)	0.002
Underweight	17(8.2%)	43 (20.1%)	
Overweight	58(27.9%)	51(23.8%)	
Comparing themselves with perceived idealized person for body image			
Yes	85(40.9%)	84 (39.3%)	0.40
No	123(59.1%)	130 (60.7%)	
Comparing themselves with others and "come up short"?			
Yes	42(20.2%)	58(27.1%)	0.90
No	166(79.8%)	156(72.9%)	
Status of happiness with their body looks			
Yes	171(82.2%)	187 (87.4%)	0.08
No	37(17.8%)	27(12.6%)	

Regarding the factors influencing perception about body image, 82(38.3%) of non-medical students reported that they feel insecure around the people as compared to 93(44.7%) medical students, whereas an equal number 45(21.0%) of both groups of the student reported that their perception about body image is influenced by Peer pressure. Feeling embarrassed was

the least influencing factors while other factors accounted for 65(30.4%) and 44(21.2%) among non-medical and medical respectively. When they were asked whether, they compared their body weight with others, 25(11.7%); 21(10.1%) of both non-medical and medical students did compare with frequency of65(30.4%) and 68(32.7%) said some time they compared their body image. (See figure 3)

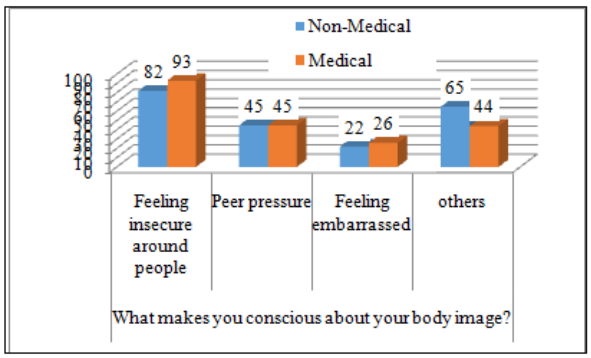

Figure No.2: Factors influencing the perceptions about body image

Table No.2: Status of Student's satisfaction to their body image and role of media in changing the perception

Variables	Responses			P-Value
	Yes	No	I don't know/ Not concerned	
Do you think media's representation of females is a healthy image to follow				
Non-Medical students	56 (26.2 %	106 (49.5%)	52 (24.3%)	0.58
Medical students	55 (26.4 %)	94 (45.2%)	59(28.4%)	
Have you ever felt depressed or upset in any way about your body?				
Non-Medical students	81 (37.9 %)	114(53.3 %)	19 (8.9%)	015
Medical students	71(34. 1%)	106(51.0 %)	31 (14.9%)	
Do you think that reduction in body weight would boost your self-confidence?				
Non-Medical students	76(35. 5%)	84 (39.3%)	54 (25.2%)	0.90
Medical students	95(45. 7%)	54 (26.0%)	59 (28.4%)	

Only 26% of each groups of the students agreed that "media's representation of females is a healthy image to be follow" however 106(49.5%) of non-medical and 94(45.2%) of medical students did not agree with this statement. Similarly 71(34.1%) and 81(37.9%) and of medical and non-medical students felt depressed or upset in any way about their body indicating that they were not satisfied with their body image. Furthermore 76 (35.5%) and 95(45.7%) of both group of the student were of the view that reduction in body weight would boost their self-confidence. There was no significant difference among the study groups (p=0.90)

Relationship of body weight and self-steam was asked from the students. The result revealed that an equal proportion 42(19.6%) of nonmedical and 30(14.4%) on Medical students were of the views that body weight has negatively affected their self-esteem, but most of them were uncertain about the effect. The perceptions of students in this regards did not vary significantly (p=0.29)

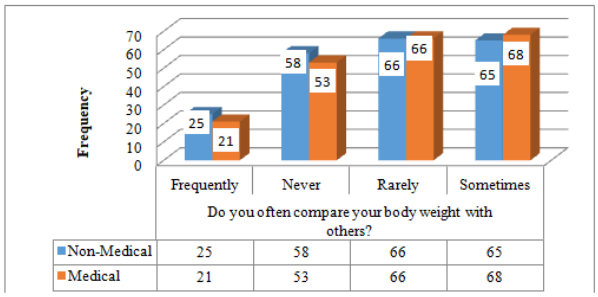

Figure No. 3: Intension of students to compare their body weight with others

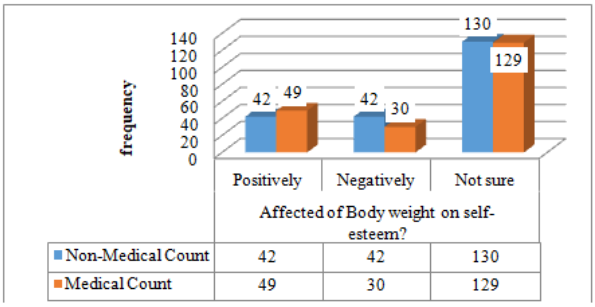

Figure No.4:Perceptions of students regarding affect of body weight on self-esteem

DISCUSSION

Students being adolescent represent a pivotal stage in the development of positive or negative body image.[2 10-12]It becomes more vital in case of medical students especially for female students, because they interact with patients of various personalities where their own self-esteem may play a vital role in communication and treatment of the patients.[13]The consequences of having negative perceptions about body image can lead to physical and psychological implications.[2 14]The present study aimed to determine the perception of undergraduate students regarding idealized body image and factors influencing the idealized body image. Results of the study indicate that out of 422 students (50.7% non-medical and 49.3% medical) a major proportions of student were very conscious about their

body image. Regarding body weight, 133(63.9%) of medical students perceived that they have normal body weight as compared to 120 (56.1%) non-medical students, However 43(20.1%) of non-medical student considered themselves as underweight as compared to 17(8.2%) of medical students which shows a significant difference (p=0.002). However, most (82.2% medical and 87.4% non-medical) of them were satisfied with their body image. The study results were in consistence with other results. A study in India shows that 51.04% of medical students were satisfied with their body image.[5] Similar study from Iran indicates that only 26.4% of medical students were satisfied with their body image, 55% of them perceived self as overweight/obese and 18.6% perceived themselves as too thin.[7]Apart from adolescent students, study on nine-grade students indicates 74.7% satisfaction rate [15], reveals that the perception about body image changes over time and individual develops more specification and determinants for idolized body image and as result their satisfaction rate declines. Females are more concerns about their body image as compare to male.[16]Result of present study indicates that students, regardless of their field compared themselves with perceived idealized person or others for body image. This finding is well explained by Yoonhyeung Choi. He reported that an individual's perception about body image is influenced by imaginary or comparison with idealized third person and this tendency is greater among female. [17]The comparison tendencies among male and female reveals that female are self-critical and male are self-hopeful. [18]There was no significant (p=0.05) difference regarding factors influencing the perceptions of medical and non-medical students about body image. Nearly 26% of the students were of the view that media's representation of females is a healthy image to be followed. A positive relationship of body image is also reported by other researchers. It is also reported that media exposure play an important role in personality development, peer pressure and development of sense of identity to make the transition into anidealized body image.[19]Results regarding relationship of body weight and self-esteem indicates that 30(14.4%) and 42(19.6%) of medical and non-medical students were of the views that body weight has negatively affected their self-esteem indicating that students have similar impression regardless of their field (p=0.29). It is apparent that there is an association of bodyweight, physical image and psychological status of every individual. Overweight and obesity are indeed inversely related to self-esteem but underweight is also connected with low self-esteem.[20]

CONCLUSION

It is concluded that the perceptions about idealized body weight among medical and non-medical student were significantly varied but they had more or less similar impression regarding factors influencing the perception of idealized body weight.

Author's Contribution:

Concept & Design of Study:	Saminullah Khan
Drafting:	Sher Bahadur
Data Analysis:	Atta ullah Jan, Rizwan Anwar
Revisiting Critically:	Saminullah Khan
Final Approval of version:	Saminullah Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Lipowska M, Lipowski M. Narcissism as a moderator of satisfaction with body image in young women with extreme underweight and obesity. PLoS One 2015;10(5):e0126724.
2. Voelker DK, Reel JJ, Greenleaf C. Weight status and body image perceptions in adolescents: current perspectives. Adolesc Health Med Ther 2015;6:149-58.
3. Silva ML, Taquette SR, Coutinho ES. Senses of body image in adolescents in elementary school. Rev Saude Publica 2014;48(3):438-44.
4. Zainuddin AA, Manickam MA, Baharudin A, Omar A, Cheong SM, Ambak R, et al. Self-perception of body weight status and weight control practices among adolescents in Malaysia. Asia Pac J Public Health 2014;26(5 Suppl): 18S-26S.
5. Goswami S, Sachdeva S, Sachdeva R. Body image satisfaction among female college students. Ind Psychiatr J 2012;21(2):168-72.
6. Priya D, Prasanna KS, Sucharitha S, Vaz NC. Body Image Perception and Attempts to Change Weight among Female Medical Students at Mangalore. Indian J Community Med 2010;35(2):316-20.
7. As-Sa'edi E, Sheerah S, Al-Ayoubi R, Al-Jehani Aa, Tajaddin W, Habeeb H. Body image dissatisfaction: Prevalence and relation to body mass index among female medical students in Taibah University, 2011. J Taibah University Med Sci 2013;8(2):126–133.
8. Sihag R, Joshi H. A study on body image satisfaction, BMI status and dietary patterns among newly entrant girl students of Punjab Institute of Medical Sciences, Jalandhar. Int J Comm Med Public Health 2017;4(7):2531-2537.
9. Khan AN, Khalid S, Khan HI, Jabeen M. Impact of today's media on university student's body image in Pakistan: a conservative, developing country's perspective. BMC Public Health 2011;11:379.
10. de Araujo TS, Barbosa Filho VC, Gubert FDA, de Almeida PC, Martins MC, Carvalho Q, et al. Factors Associated With Body Image Perception

Among Brazilian Students From Low Human Development Index Areas. J Sch Nurs 2017; 34(6):449-457.
11. Gillen MM, Lefkowitz ES. Gender and racial/ethnic differences in body image development among college students. Body Image 2011;9(1):126-30.
12. He W, Zheng Q, Ji Y, Shen C, Zhu Q, Wang W. Development of a Body Image Concern Scale using both exploratory and confirmatory factor analyses in Chinese university students. Neuropsychiatr Dis Treat 2017;13:1419-1425.
13. Naeimi AF, Haghighian HK, Gargari BP, Alizadeh M, Rouzitalab T. Eating disorders risk and its relation to self-esteem and body image in Iranian university students of medical sciences. Eat Weight Disord 2016;21(4):597-605.
14. Nayir T, Uskun E, Yurekli MV, Devran H, Celik A, Okyay RA. Does Body Image Affect Quality of Life?: A Population Based Study. PLoS One 2016;11(9):e0163290.
15. Lemes DCM, Camara SG, Alves GG, Aerts D. Body image satisfaction and subjective wellbeing among ninth-grade students attending state schools in Canoas, Brazil. Cien Saude Colet 2018; 23(12):4289-4298.
16. Kennedy MA, Templeton L, Gandhi A, Gorzalka BB. Asian body image satisfaction: ethnic and gender differences across Chinese, Indo-Asian, and European-descent students. Eat Disord 2006;12(4):321-36.
17. Choi Y, Leshner G, Choi J. Third-Person Effects of Idealized Body Image in Magazine Advertisements. American Behavioral Scientist 2008;52(2):47-164.
18. Franzoi SL, Vasquez K, Frost K, Sparapani E, Martin J, Aebly M. Exploring Body Comparison Tendencies: Women Are Self-Critical Whereas Men Are Self-Hopeful. Psychology of Women 2012;36(1):99-109.
19. Keren E, Tali Te-H. Explaining the relationship between media exposure and early adolescents' body image perceptions: The role of favorite characters. J Media Psychol 2013;25(3):129-141.
20. Olmsted MP, McFarlane T. Body Weight and Body Image. BMC Womens Health 2004;4 Suppl 1:S5.

Original Article

Spectrum of Medicolegal Cases in Physical Injury at Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan

Ejaz Ahmed Awan, Pardeep Kumar and Sultan Rajpar

ABSTRACT

Objective: The purpose behind this study was to determine the spectrum of medicolegal cases in physical injury at Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan.

Study Design: Prospective / observational study

Place and Duration of Study: This study was conducted at the at a tertiary care Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan from 2014 to 2018.

Materials and Methods: The study has been conducted through a convenience sampling technique on autopsied 259 males and females between the periods of six years to observe the frequency and location of physical injury leads to death among different age groups. Ethical consent was taken from family member and hospital before doing autopsy and use of its findings for study purpose. A structured questionnaire was used to collect the objective specific data and we used SPSS version 21 for data entry and analysis.

Results: Our study has male predominance (95.75%, N = 248) with more autopsied were performed in rural areas (66.02, N = 171).More than 77% (N = 202) autopsied persons did not had traumatic bony lesion during examination. The most commonly used weapon was hard blunt type 76.47% (N = 39/51) while comparatively less people were killed due to firearm injury (17.64%).

Conclusion: The spectrum of medicolegal cases is quite variable in people presenting at Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan in which most of them were killed due to blunt weapon.

Key Words: Autopsy findings, Clinical spectrum, Pakistan

Citation of articles: Awan EA, Kumar P, Rajpar S. Spectrum of Medicolegal Cases in Physical Injury at Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan. Med Forum 2019;30(8):69-72.

INTRODUCTION

Medicolegal cases are the most important and least documented form in the field of medical sciences that is why the actual burden and consequences from these cases are limited worldwide and very few studies are available in developing countries including Pakistan.[1,2]

The pattern of injury and causative weapon are well studied in developed countries but data is limited in Pakistan due to ethical constraints. The importance of type of weapon is defined the type of injury occurred in patient is suffered from and died. Firearm injuries cause more harm than blunt traumas.

There could be multiple reasons from which a person can be investigated for medico legal cases and these differ in developing countries from developed countries and from region to region[3-5].

The documented causes of medicolegal cases in Pakistan is still unknown but in a study published in Pakistan has shown that more than 40% of the medicolegal cases are caused by road traffic accident while blunt trauma and physical assault were less common 32% and 19%, respectively[6,7].

Available data from Pakistan is mostly from the bigger cities and comprises of urban population but there is no such study has been conducted in peripheral areas of Sindh Pakistan through which we can highlight the spectrum of medicolegal cases that is why this study has been conducted to evaluate the actual burden of medicolegal cases in Nawabshah and its surrounding so the data can be scientifically available to highlight the importance of such cases in peripheral areas of Sindh.

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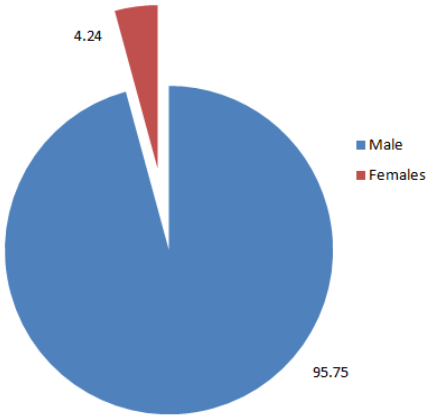
MATERIALS AND METHODS

We have conducted a longitudinal prospective study through a cross sectional sampling technique on autopsied 259 males and females between the periods of four years from 2014 to 2018 in a Tertiary Care Hospital of Nawabshah, Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan.

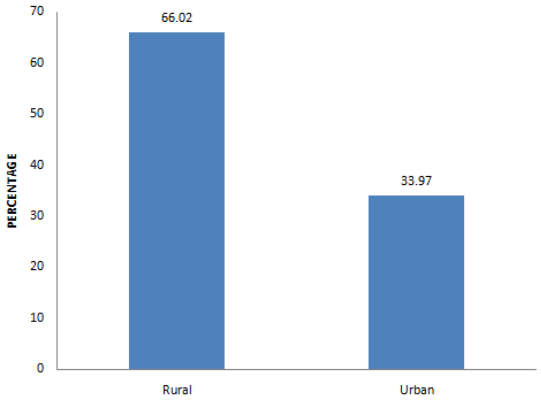
Data Collection And Analysis: Data collection for this study was started after the consent taken from ethical review committee of hospital and also the verbal consent was taken from the family member of deceased. Data was collected for baseline variables such as deceased age & area of residence and cause and pattern of death was observed as an outcome variable. For both data entry and analyses we have used SPSS version 20 and presented in the form of tables and bar charts.

RESULTS

Among all the 259 autopsies performed mostly the autopsied persons were belongs to rural areas (66.02, N = 171) and among them most of them were males (95.75%, N = 248), shown in table number 1 & 2.



Graph No. 1: Gender wise distribution of study subjects (N = 259)



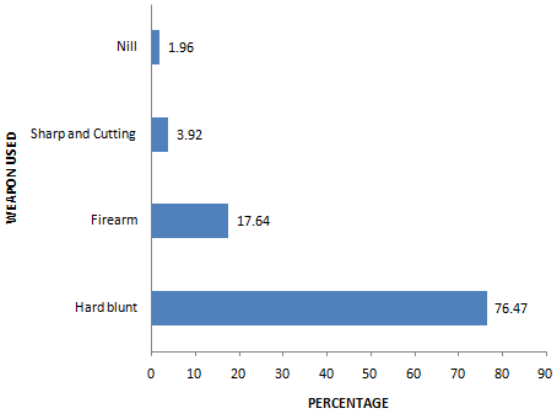
Graph No. 2: Area of Residence of Study Participants (N = 259)

The main objective behind conduction of this study was to evaluate the spectrum of medicolegal cases through which we can find the burden of causative agent and damaged caused to the body and leads them to death. Interestingly more than 77% (N = 202) autopsied persons did not had traumatic bony lesion during examination while only 69% (N = 51) had some traumatic bony lesion seen during examination, and only 2.31% (N = 6) of the autopsied body showed post-operative findings during examination.

Table number 5 shows weapon used to kill the person. The most commonly used weapon was hard blunt type 76.47% (N = 39/51) while 17.64% people were killed due to firearm.

Table No. 1: Clinical Spectrum Of Autopsied Bodies (N = 259)

Clinical Spectrum	Percentage	Number
No evidence of Traumatic Bony Lesion	77.99	202
Fracture seen in any site of a body	19.69	51
Post-operative findings	2.31	6



Graph No. 3: Type of Weapon Used (N = 51)

DISCUSSION

Any case of injury or ailment where some criminality is involved is called a Medico Legal Case (MLC). A medico legal case is where a person is injured or harmed in any way and needs medical attention for it. The injury cases suggestive of criminal offense (blunt injuries and sharp edged weapons), burn any case of injury or ailment where some criminality is involved is called a Medico Legal Case (MLC). A medico legal case is where a person is injured or harmed in any way and needs medical attention for it. The injury cases suggestive of criminal offense (blunt injuries and sharp edged weapons), burn. Such types of studies in Pakistan have not been conducted properly hence the true burden is still not known. In our study we have tried to observe and evaluate the scientific burden of such types f cases

in which the cause of injury leading to death is questionable[8,9].

In our study we have observed larger number of autopsied persons in which we have observed that most of them were males which could be due to people are more of them from rural areas and they least likely to proceed for autopsies when it comes to females. The findings of our study are similar to the findings shown in both international and national data published.[10,11]

Focusing on the main objective of our study, it has been observe that most of the autopsied persons did not had any sign of physical injury and seems to be they died from natural cause of death but people had filed case for autopsy possibly due to high crime rate at their particular area and want to rule out the cause of death. The published international and national data has in favor of our findings[12-14].

The second most common finding of our study was presence of bony lesion which lead them to death. Bony lesions are the sings of having some assault by weapon resulting in a death. The percentage of having bony lesion in our study population is rather less than the studies published internationally. This could be due to improper documentation of assaulted cases in Pakistan.[15-17].

The most common weapon used in assaulted autopsied peoples was hard blunt type which leads them to death while the prevalence of death due to firearm injury was less than 18%. This could be due to lack of availability of firearm weapons while on the other hands blunt materials are easily accessible at rural areas. International data has shown firearm injury their major cause of death in comparison to hard blunt material[18-20].

CONCLUSION

The spectrum of medicolegal cases is quite variable in people presenting at Peoples Medical College Hospital, Nawabshah, Shaheed Benazirabad, Sindh, Pakistan in which most of them were killed due to blunt weapon.

Author's Contribution:

Concept & Design of Study:	Ejaz Ahmed Awan
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Revisiting Critically:	Ejaz Ahmed Awan
Final Approval of version:	Ejaz Ahmed Awan

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Niaz K, Shujah IA. Civilian perspective of firearm injuries in Bahawalpur. J Pak Med Assoc 2013;63(1):20-4.
2. Yang Q, Zhang C, Hines K, Calder LA. Improved hospital safety performance and reduced medicolegal risk: an ecological study using 2 Canadian databases. CMAJ Open 2018;6(4):E561-E566.
3. Byrne P, Todd NV. The timing of surgery may influence causation in medicolegal cases. Br J Neurosurg 2017;31(6):749-50.
4. Muniraman H, Cascione M, Ramanathan R, Nguyen J. Medicolegal cases involving periviable births from a major United States legal database. J Matern Fetal Neonatal Med 2018;31(15):2043-9.
5. Jina R, Kotze JM. Improving the recording of clinical medicolegal findings in South Africa. S Afr Med J 2016;106(9):872-3.
6. Manzoor MA, Hassan N, Ahmed A. The applicability of the Greulich & Pyle Atlas for bone age assessment in primary school-going children of Karachi, Pakistan. Pak J Med Sci 2014;30(2):409-11.
7. Mujtaba G, Shuib L, Raj RG, Rajandram R, Shaikh K, Al-Garadi MA. Automatic ICD-10 multi-class classification of cause of death from plaintext autopsy reports through expert-driven feature selection. PLoS One 2017;12(2):e0170242.
8. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3(4):524-48.
9. Mustufa MA, Sheikh MA, Taseer IU, Raza SJ, Arshad MS, Akhter T, et al. Trajectory of cause of death among brought dead neonates in tertiary care public facilities of Pakistan: A multicenter study. World J Pediatr 2017;13(1):57-62.
10. Maixenchs M, Anselmo R, Zielinski-Gutierrez E, Odhiambo FO, Akello C, Ondire M, et al. Willingness to Know the Cause of Death and Hypothetical Acceptability of the Minimally Invasive Autopsy in Six Diverse African and Asian Settings: A Mixed Methods Socio-Behavioural Study. PLoS Med 2016;13(11):e1002172.
11. Loomba RS, Ahmed MM, Spicer DE, Backer CL, Anderson RH. Manifestations of bodily isomerism. Cardiovasc Pathol 2016;25(3):173-80.
12. Kharoshah MA, Hussain SA, Madadin M, Menezes RG. Consented Autopsy and the Middle-East. Sci Eng Ethics 2017;23(1):321-2.
13. Kyu HH, Pinho C, Wagner JA, Brown JC, Bertozzi-Villa A, Charlson FJ, et al. Global and National Burden of Diseases and Injuries Among Children and Adolescents Between 1990 and 2013: Findings From the Global Burden of Disease 2013 Study. JAMA Pediatr 2016;170(3):267-87.

14. Soofi SB, Ariff S, Khan U, Turab A, Khan GN, Habib A, et al. Diagnostic accuracy of WHO verbal autopsy tool for ascertaining causes of neonatal deaths in the urban setting of Pakistan: a hospital-based prospective study. BMC Pediatr 2015;15:144.
15. Bassat Q, Ordi J, Vila J, Ismail MR, Carrilho C, Lacerda M, et al. Development of a post-mortem procedure to reduce the uncertainty regarding causes of death in developing countries. Lancet Glob Health 2013;1(3):e125-e126.
16. Mirza FH, Hassan Q, Jajja N. An autopsy-based study of death due to road traffic accidents in metropolis of Karachi. J Pak Med Assoc 2013;63(2):156-60.
17. Mirza FH, Memon AA, Adil SE, Paryar HA. Audit of custodial deaths in Karachi--an autopsy-based study. J Pak Med Assoc 2012;62(8):752-5.
18. Nevicka E, Rozboril R, Tazky B, Zavodny I, Zdarilek M, Sidlo J. [Multiple firearm injury caused with a blank pistol]. Soud Lek 2017;62(1):8-10.
19. Myint S, Rerkamnuaychoke B, Peonim V, Riengrojpitak S, Worasuwannarak W. Fatal firearm injuries in autopsy cases at central Bangkok, Thailand: a 10-year retrospective study. J Forensic Leg Med 2014;28:5-10.
20. Singh D, Dewan I, Pandey AN, Tyagi S. Spectrum of unnatural fatalities in the Chandigarh zone of north-west India--a 25 year autopsy study from a tertiary care hospital. J Clin Forensic Med 2003;10(3):145-52.

Original Article

Functional and Radiological Outcome with Matti-Russe Grafting in Non-Union of Scaphoid

Muhammad Khalid-ur-Rehman[1], Rohail Mumtaz[2], Muhammad Usman Aslam[3] and Syed Wasif Ali Shah[4]

ABSTRACT

Objective: To evaluate the functional & radiological outcome in nonunion of scaphoid fractures – fixed with Matti-Russe grafts.

Study Design: Prospective Interventional Case Series.

Place and Duration of Study: This study was conducted at the Ameer-ud-Din Medical College, Lahore/ General Hospital, Lahore from June 2015 to June 2018.

Materials and Methods: A total of 20 patients included having age between 18-50 years with more than 4 months old fractures in scaphoid. All the fractures were treated before conservatively. The follow up was carried out at 3 and 6 months post-operatively. Both radiological evidences and functional assessment carried out and documented in Mayo's wrist score.

Results: The mean age was 31±8 years with male preponderance. Most of the patients have mean duration of injury 6±2 months. Almost half of the patients were having avascular necrosis (AVN) of the proximal pole of scaphoid. 75% of the patients resulted in good radiological healing and Mayo's Wrist Score (MWS) have value as pre op MWS 53 to post op MWS 84 which is statistically significant.

Conclusion: The results of both functional & Radiological data showed promising outcome with this technique so we conclude that Matti-Russe procedure is very effective procedure for nonunion of scaphoid but we recommend comparative study of different treatment options.

Key Words: Matti-Russe technique, Mayo's Wrist Score (MWS), Avascular Necrosis (AVN), Herbert Screws

Citation of articles: Rehman MK, Mumtaz R, Aslam MU, Shah SWA. Functional and Radiological Outcome With Matti-Russe Grafting in Non-Union of Scaphoid. Med Forum 2019;30(8):73-76.

INTRODUCTION

Scaphoid fracture is considered the most common fracture of the carpal bones. It often occurs with fall on outstretched hand with hyperextension of the wrist leading to the direct impact on scaphoid bone which can be associated with fracture of Ulna or distal radius.[1,2]

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These fractures are diagnosed with high index of suspicious as it is possible that initial x-ray will not reveal the fracture and a second set of x-rays are needed after 10 days follow up. Sometimes the decision of conservative management can lead to nonunion of the fracture with or without avascular necrosis of segment of the bone. The blood supply of this bone is very precarious which makes it prone to avascular necrosis especially in waist or proximal pole fractures. Delay in diagnosis and management can lead to osteoarthritis of the wrist or inter carpal joints.[3,4,5] Despite the invention & application of new treatment strategies nonunion is as high as 10% with or without a vascular necrosis of proximal of the pole and can result in humpback deformity of the bone itself and later osteoarthritis with poor function and quality of life of the patient.[6,7] In acute settings of less than 4 weeks old fractures of the scaphoid, closed or open reduction of the fracture with Herbert's screw fixation is the treatment of choice but in the chronic cases the management plan is modified with fixation & bone grafting. Different choices of grafts are available and used as vascularized bone graft, non-vascularized cortical bone graft, corticocancellous bone graft and only cancellous bone graft with different fixation techniques. In our study we used the Modified

Matti-Russe graft with k wire as stabilizing tool. The technique was initially presented by Heriman Matt in 1937 and later modified by Otto-Russe in 1960. Three studies[6,8,9,10] evaluated the results of Matti-Russe technique and found to have promising results in non-unions of long standing and displaced fractures.[11] So it is considered that Matti-Russe technique is established and well accepted technique in our setting which is simple and less expensive, so in our study we apply the modified Matti-Russe technique and evaluate radiological and functional satisfaction levels in the management of such fractures.

MATERIALS AND METHODS

This study was carried out in the Department of Orthopaedic Surgery at Lahore General Hospital, Lahore. The patients were admitted from the outpatient clinic between June 2015 to June 2018. We included the patients between 18-50 year of age with different modes of trauma leading to scaphoid fractures. The most of the patients were treated conservatively. The patients with open fractures, infections, previous shoulder surgery, poly trauma and patients having proven scapho-lunate dislocations were excluded from the study. The evaluation of such patients was performed clinically along with radiological investigations like X-rays & MRI of the wrist to rule out the avascular necrosis (AVN) of any of the fracture fragment. In all the patients modified Matti-Russe procedure with volar approach was carried out, the fracture fragments were identified and both proximal and distal portions of bones excavated by removing fibrous tissue from fracture site. The gap is filled with cortico-cancellous graft taken from the distal radius fracture is compressed and held with pointed reduction clamp and k-wire is inserted from dorsal to volar side percutaneously.

The reduction was confirmed in 3 dimensional views under c-arm and thumb spica cast was applied. The definition of union in scaphoid fracture is non-tender snuff box and radiological trabecular crossing of the fracture lines. The considered mean time of union is between 9-12 weeks.[3,12] So we evaluated our cases at 03 months and 06 months post operatively. The k-wires were removed at 12 weeks with also removal of spica cast. At both follow up the patients were assessed with pain recognition, return to regular employment, range of movements. The grip strength was measured by asking the patients to squeeze the index finger of the examiner (Figure 1).

RESULTS

The mean age was 31±8 years with male preponderance. Most of the patients have mean duration of injury 6±2 months. The mode of injury was distributed in sports, RTA and fall at home which was quite common in female patients. Almost half of the patients were having avascular necrosis (AVN) of the proximal pole of scaphoid which was diagnosed and confirmed on MRI. 75% of the patients resulted in good radiological healing and Mayo's Wrist score (MWS) have value as preoperative MWS 53 to postoperative MWS 84 which is statistically significant. Rest of 25% of the cases the union was delayed and only in 2 of the cases the nonunion was established at 6 months, one case was re-operated and found to have subclinical infection and debridement was performed and in 2nd case re-fixation was performed with another bone graft. We observed in one of our patient the limitation of radial deviation but rest of the movements were satisfactory.

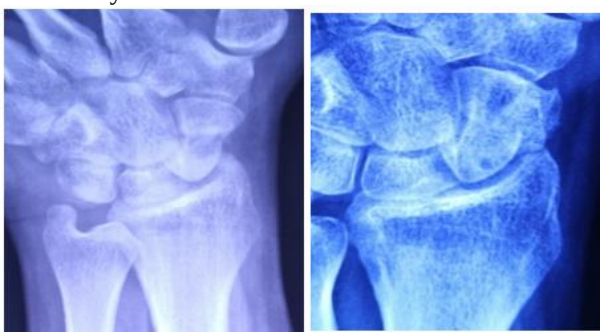

Figure No.1: A. Nonunion scaphoid **B.** Union after Matti-Russe graft

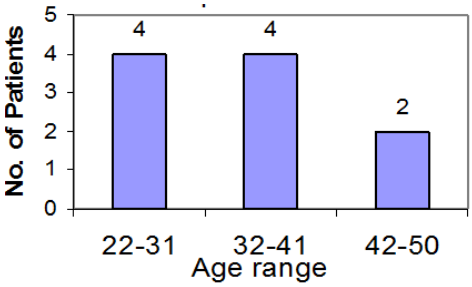

Figure No.2: Age distribution of patients.

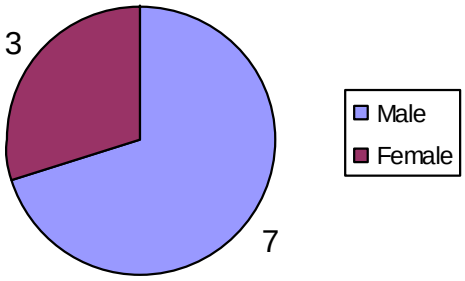

Figure No.3: Sex distribution

Table No.1: Comparison preoperative & postoperative Mayo's wrist score

Preoperative Mayo's wrist score	Postoperative Mayo's wrist score
Mean ± SD	Mean ± SD
52.90±4.90	84.20±9.05
P value <0.05	

DISCUSSION

This study was performed at Lahore General Hospital by two surgeons in all the patients of established nonunion of the scaphoid bone with or without AVN proven on MRI of the wrist. The results of our study are quite satisfactory. If we will compare our results with the studies of same nature with same procedure, our results are both clinically and statistically better. In the study of Kolodziej et al[13] in which the same procedure was performed without stabilization with K wires, the nonunion rate found 28%. In study by Bullens et al[14] good to excellent result were observed in all the parameters like ROM, hand grip strength and weight lifting with longer follow up of 3-5 years. In another study different procedures like Herbest screws fixation, Matti-Russe technique, Fisk Fermandez technique and vascularized bone graft were performed but statistically no significant difference was found in bony union & rest of the parameters but Matti-Russe procedure was found to be cost effective method[15] of treatment which also suit to our setting. Bertelli et al studied the persistence of nonunion with history of 2 years nonunion, the patients were treated by vascularized bone graft harvested from thumb with pedicle at first dorsal metacarpal artery by palmar approach. After one year the union rate of about 90% achieved which is almost the same as in our study but with this procedure the morbidity and dissection was significantly high.[16] In some of the studies the vascularized bone grafting for nonunion and avascular necrosis are considered but the graft harvested from medial femoral condyle with union rate was the same (88%).[17,18] At the cost of more morbidity, need for expertise & expensive equipment. It is also found no significant difference of the timing of the surgery on union of scaphoid fractures so it was assumed the union is independent of the age of the patient and its duration from the time of injury but carpal collapse and osteoarthritis can lead to the poor outcome in such fractures. If the patient is having nonunion with Pseud arthrosis this Matti-Russe technique had statistically significantly better outcome (81%). In those patient's supination & pronation was satisfactory but radial deviation and extension is impaired. This same finding, we observed in one of our patient but even the extension was satisfactory than the radial deviation which was clinically poor.

CONCLUSION

The results of both functional & Radiological data showed promising outcome with this technique so we conclude that Matti-Russe procedure is very effective procedure for nonunion of scaphoid but we recommend comparative study of different treatment options.

Author's Contribution:

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REFERENCES

1. Raju P, Kini SG. Fixation techniques for non-union of the scaphoid. J Orthop Surg. (Hong Kong) 2011;19:80-4.
2. Pao VS, Chang J. Scaphoid non-union: Diagnosis and treatment. Plast Reconstr Surg 2003;112:1666-77.
3. Leslie I, Dickson R. The fractured carpal scaphoid. Natural history and factors influencing outcome. J Bone Joint Surg Br 1981;63:225-30.
4. Cooney W, Dobyns JH, Linscheid RL. Fractures of the scaphoid: A rational approach to management. Clin Orthop Relat Res 1980;149:90-7.
5. Waters PM, Stewart SL. Surgical treatment of non-union and avascular necrosis of the proximal part of the scaphoid in adolescents. J Bone Joint Surg 2002;84:915-20.
6. Triantafillopoulos I, Zoubos A, Babis G, Soucacos P. Orthopaedica at Traumatologica Hellenica. J Hellenic Ass Orthop Traumatol 2005;56.
7. Herbert TJ, Fisher WE. Management of the fractured scaphoid using a new bone screw. J Bone Joint Surg Br 1984;66:114-23.
8. Stark A, Broström L, Svartengren G. Scaphoid non-union treated with the Matti-Russe technique. Long-term results. Clin Orthop Relat Res 1987;214:175.
9. Mulder J. The results of 100 cases of pseudarthrosis in the scaphoid bone treated by the Matti-Russe operation. J Hand Surg Br 1968;50:110-5.
10. Panchal A, Kubiak EN, Keshner M, Fulkerson E, Paksima N. Comparison of fixation methods for scaphoid non-unions: A biomechanical model. Bull NYU Hosp Jt Dis 2007;65:271-5.
11. Green D. The effect of avascular necrosis on Russe bone grafting for scaphoid non-union. J Hand Surg Am 1985;10:597-605.

12. Parajuli N, Shrestha D, Dhoju D, Shrestha R, Sharma V. Scaphoid fracture: Functional outcome following fixation with herbert screw. Kathmandu Univ Med J 2012;9:267-73.
13. Kodziej R, Blacha J, Bogacz A, Mazurkiewicz T. Long-term outcome of scaphoid non-union treated by the Matti-Russe operation. Ortop Traumatol Rehabil 2006;8:507-12.
14. Bullens P, Driesprong M, Lacroix H, Vegter J. Treatment of scaphoid non-union with a percutaneous corticocancellous bone graft. J Hand Surg Br 2005;30:365-8.
15. Bertelli J, Peruchi F, Rost J, Tacca C. Treatment of scaphoid non-unions by a palmar approach with vascularized bone graft harvested from the thumb. J Hand Surg Eur 2007;32:217-23.
16. Jones Jr DB, Bürger H, Bishop AT, Shin AY. Treatment of scaphoid waist non-unions with an avascular proximal pole and carpal collapse. J Bone Joint Surg Am 2008;90:2616-25.
17. Trumble T, Nyland W. Scaphoid non-unions: Pitfalls and pearls. Hand Clin 2001;17:611-24.
18. Trezies A, Davis T, Barton N. Factors influencing the outcome of bone grafting surgery for scaphoid fracture on-union. Injury 2000;31:605-7.

Original Article

Frequency of Metabolic Syndrome in Patients of Acute ST Segment Elevation Myocardial Infarction

Metabolic Syndrome in Acute ST Segment Elevation MI

Muhammad Umar Iqbal[1], Muhammad Sarwar Khalid[1], Shehzad Ahmed[1], Irfan Mumtaz[1],Mudassar Iqbal[1] and Rehana Kousar[2]

ABSTRACT

Objective: To determine the frequency of metabolic syndrome (MS) in patients with acute ST segment elevation myocardial infarction (STEMI)**.**

Study Design: Cross-Sectional study.

Place and Duration of Study: This study was conducted at the Department of Cardiology, Bahawal Victoria Hospital (BVH), Bahawalpur from March 2018 to tAugust 2018.

Materials and Methods: A total of 380 patients, in the age range of 30 –70 years with Acute STEMI were included in the study. Only the patients fulfilling the inclusion criteria were included in the study. In this study, five components of MS were assessed after the written consent of the patients using the standard state of the art techniques.

Results: Statistical analysis reveals that patients 47.36% were between 51 to 60 years of age with male to female ratio of 2:1. MS was found in 43.42% patients with 42.0% male and 46.15% female patients and incidence were increasing with passing years. The mean waist circumference was 89.12±6.43 in males and 93.23±11.65 in females, mean serum triglycerides was 146.11±27.77 in males and 148.66±28.54 in females, mean serum HDL Cholesterol was 41.17±6.32 in males and 50.94±4.55 in females, mean systolic blood pressure was 130±10 in males and 120±10 in females and mean diastolic blood pressure was 90±5 in males and 80±10 in females, mean fasting blood sugar was 114.11±15.76 in males and 108.56±20.43 in females.

Conclusion: This study concludes that there is a high frequency of metabolic syndrome (MS) in acute STEMI patients in our population with hypertension and diabetes mellitus as the major components of MS.

Key Words: Cardiovascular diseases (CVD), Myocardial Infarction (MI), Metabolic Syndrome (MS).

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INTRODUCTION

Cardiovascular diseases (CVD) are one of the prominent cause of demise in the world, especially in industrialized countries.[1]Among the cardiovascular diseases, Ischemic heart disease (IHD) is the most predominantexpression including silent ischemia (SI), acute coronary syndromes (ACS), and stable angina pectoris (SAP).[2]

IHD results due to the reduced flow of the blood in the arteries of the heart. The reduced blood flow is caused by the deposition of plaque in the arteries of the heart. The reduction of the blood flow results in reduced oxygen flow to the heart muscles. The current CVD models focus on the interventions through angiographic results which are supportive in finding CVD prognosis and progression. The literature review reveals that the threat of MI is approximately completely based on the modifiable CV risk factors like psychosocial stress, smoking, dyslipidemia, HTN, DM, and poor diet.[6-9] Most of the above mentioned factors are caused by the Metabolic Syndrome (MS).

Definition of the MS is based on obesity and any two of the following: "raised triglycerides, reduced HDL cholesterol, raised blood pressure, and raised fasting plasma glucose (FPG > 100mg/dl (5.6 mmol/L), or previously diagnosed type 2 diabetes"[10].

The mechanisms of the MS are very complex and therefore the pathophysiology of the MS is highly complex and is not completely known yet. However, the most common contributing factors are age, obesity, sedentary habits, and resistance to insulin. According to some authors, stress may also be another important contributing factor. The other important factors reported in the literature are weight, genetics,[10,11] endocrine disorders and lifestyle.[12]

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MS stimulates coronary heart disease (CHD)by raising the levels of the thrombogenicity due to increase in adipokine and plasminogen activator type 1 levels.[12-16]MS is composed of a number of modifiable disorder, therefore, controlling the modification of these disorders will help in improving the morbidity and mortality. As MS has racial and ethnic variation,[17,18] and secondly the local and the international studies were done on the same topic included both STEMI and NSTEMI and no stratification was done hence there is still no clarity. Therefore, this research was aimed to evaluate the frequency of MS in patients presenting with acute STEMI, so that a policy could be designed to raise public awareness to modify these factors and improve the mortality and morbidity of community.

MATERIALS AND METHODS

The presented study is a cross-sectional study which is conducted at the Department of Cardiology, Cardiac Complex, Bahawalpur from the 1st March 2018 to the 31st August 2018.The aim of the underlying research was to explore the frequency of MS in patients with acute STEMI. In this study sample size, comprised of total 380 cases which was determined on the basis 95% confidence level, and limiting the margin of error to the 5%. The expected prevalence of MS was taken as 60%. The used sampling technique is "Non-probability consecutive sampling". Acute STEMI was defined as**"**ST segment elevation of >1mm in limb leads and >2mm in precardial leads".

The criteria provided for the definition of the MS and/or insulin resistance syndrome (IRS) according to the international standards[3-7]is applied in this study.

The criteria for including or excluding the patients in the study are presented below:

Inclusion Criteria:

1. All patients who will be diagnosed on admission as Acute ST segment elevation Myocardial infarction (as per operational definitions).
2. Age limits for both genders are 30 to 70 years.

Exclusion Criteria:

1. Patients of chronic renal failure and cirrhosis of the liver
2. Hemodynamically unstable patient/Systolic blood pressure<90 mmHg.
3. Cushing's disease.
4. Previous history of ischemic heart disease
5. Failure to get informed consent about study
6. Pregnant females

The total number of 380 patients with acute STEMI was selected based on the mentioned criteria. The basic information which includes name, age, gender and address were recorded of every patient using the first part of the prescribed form along with a written consent of the patient to be included in the study.In the second part of the prescribed form, all the variable of the study were recorded. In the first step of measurement of the data,five components of MS were measured using the standard techniques.

Results were statistically analyzed using the state of the art statistical analysis tool "SPSS v16.0". Results are presented as mean value and deviation from the mean value i.e. standard deviation for quantitative variables whereas the qualitative variables are presented in the form of percentages. Stratifications were applied to control the impact of modifiers like age and gender. The Chi-square test is applied after the stratification to compute the impacts on the results. In this research, a p-valueis significant if ≤ 0.05.

RESULTS

Statistical analysis of the results is presented in the tables I-6. In this study, the patient's age ranges from 30 to 70 years where the mean value of age is 53.87 ± 10.42 years. The analysis shows that a 47.36% patients age ranges 51 – 60 years which is also presented in Table I. Among the 380 patients, 65.79% were male and only 34.21% were females which resulted in a ratio of

Table No.1: Age Distribution According to Gender (n=380)

Age Groups (years)	Male		Female		Total	
	No. of Patients	% age of Patients	No. of Patients	% age of Patients	No. of patients	% age of Patients
30-40	16	4.21	09	2.37	25	6.58
41-50	54	14.21	31	8.16	85	22.37
51-60	115	30.26	65	17.10	180	47.36
61-70	65	17.11	25	6.58	90	23.69
Total	250	65.79	130	34.21	380	100.0

Table No.2: Frequency of Individual Components of Metabolic Syndrome in Myocardial Infarction Patients (n=380)

Component	Male (n=250)		Female (n=130)		Total (n=380)	
	No.	%age	No.	%age	No.	%age
Central Obesity	141	56.4	75	57.69	216	56.84
Raised Triglycerides	85	34.0	50	38.46	135	35.53
Reduced HDL Cholesterol	100	40.0	55	42.31	155	40.79
Raised Blood Pressure	122	48.8	40	30.77	162	42.63
Raised Fasting Plasma Glucose	110	44.0	60	46.15	170	44.74

Table No.3: Descriptive Statistics for Different Variables

	Male (n=250)	Female (n=130)	Total (n=380)
Age (years)	53.67±10.09	55.39±10.76	53.87±10.42
Waist Circumference (cm)	89.12±6.43	93.23±11.65	91.10±8.98
Triglycerides (mg/dL)	146.11±27.77	148.66±28.54	147.30±28.10
HDL Cholesterol (mg/dL)	41.17±6.32	50.94±4.55	45.89±5.25
Blood Pressure (mmHg)	130±10/90±5	120±10/80±10	125±10/85±10
Fasting Glucose (mg/dL)	114.11±15.76	108.56±20.43	111.13±17.89

Table No.4: Frequency of Metabolic Syndrome in Different Age Groups (N=165)

Age Groups(years)	Frequency	Percentages
30-40	02	1.21%
41-50	22	13.33%
51-60	81	49.1%
61-70	60	36.36%
Total	165	100.0

Table No.5: %age of Patients with Metabolic Syndrome in Acute STEMI for Different Age Groups

Age Group (years)	No. of patients	Presence of Metabolic abnormality	
		No. of patients	%age
30-40	25	02	8.0
41-50	85	22	25.88
51-60	180	81	45.0
61-70	90	60	66.67

Table No.6: %age of Patients with Metabolic Syndrome According to Gender

Gender	No. of patients	Metabolic Syndrome			
		Present		Absent	
		No. of patients	%age	No. of Patients	%age
Male	250	105	42.0	145	58.0
Female	130	60	46.15	70	53.85
Total	380	165	43.42	215	56.58

2:1. MS was found in 165 (43.42%) patients, whereas there were no MS in 215 (56.58%) patients. Frequency of different components of MS has shown in Table 3. The mean waist circumference was 89.12±6.43 in males and 93.23±11.65 in females, mean serum triglycerides was 146.11±27.77 in males and 148.66±28.54 in females, mean serum HDL Cholesterol was 41.17±6.32 in males and 50.94±4.55 in females, mean systolic blood pressure was 130±10 in males and 120±10 in females and mean diastolic blood pressure was 90±5 in males and 80±10 in females, mean fasting blood sugar was 114.11±15.76 in males and 108.56±20.43 in females (Table 4).

Stratification on age resulted inthe highest MS in the age group of 51 – 60 years which are 49.1% followed by age group of 61 – 70 years which 36.36%. The age groups below 50 years show less MS frequency which is 13.33% in the age group of 41 – 50 years and only 1.21% in the age group of 30 – 40 years. The frequency of MS based on the stratification of the age is presented in Table 5**.** The %age of patients with MS in acute STEMI with respect to the age groups were shown in Table 6.

DISCUSSION

Diagnostic criteria of the MS have multiple directions due to non-availability of a "gold standard" diagnostic test which shows that still there is conceptual vagueness, and lack of clarity about pathophysiological processes which reflect the underlying "syndrome".

Many studies have been conducted in the literature aiming to study populations which are at high risk for CVDlike patients suffering from type 2 diabetes mellitus (DM) or hypertension. The results of these studies reveals high occurrence of MS ranging from 35 – 80%.[20,21]Similar results are reported in a cohort study in which more than 50% of patients who showed the symptoms of the CVD and underwent elective coronary angiography and showed conditions for CVD, also satisfied the criteria for MS.[22]Earlier to this study, Yasmin et al studied the frequency of MS in Pakistan however that study was based on the[23,24]NCEPATPIII criteria. With the new joint interim statement of IDF task force, it was important that the frequency of MS in IHD to be reviewed according to the current criteria. Therefore, the goal of the research was to determine the frequency of MS in patients with acute STEMI.

The mean age of patients in this study was 53.87 ± 10.42 years

which is in accordance with the research conducted by the Sandhu GA et al[22] and Ashraf T et al[25] however comparatively higher than the Danciu SC et al[8]. According to the literature acute MI is a more common disease of the male as compared to the female. In the underlying research, we also found a male high proportion as compared to the female where the observed ratio was 2:1 which is exactly in line with the previous studies[8,24,25]

In this study, MS was found in 43.42% patients, whereas there was no MS in 56.58% patients which is compatible and inline with previously researched in the similar area.[19,23-26] In this study, 50 patients (30.3%) had all components of MS alongwith abdominal obesity, and 115 (69.7%) patients had two or three components along with abdominal obesity.In a study by

Ashraf et al[25] 25.1% of patients had all components of MS along with abdominal obesity while 74.9% of patients had two or three components of MS along with abdominal obesity. Therefore, it can be acknowledged that the frequency of MS is higher in patients with acute MI.

Yasmin et al[24] reported the frequency of MS in cases of acute MI as 32% in men & 28% women whereas this study showed MS in 42.0% male and 46.15% female patients and incidence was increasing with passing years. Hassanin et al[9], Onat A et al[26,]and Wierzbicki AS et al[27] reported a similar result for Turkish and UK populations respectively.

In a meta-analysis of comprised of total 21 state of the art studies, frequency of the MS was found 23 – 46% with different levels of cardiovascular risk factors which is also in accordance the results obtained in our study.[28]

Among the individual components of MS, we have found raised fasting blood glucose to be the most common component (44.74%), followed by hypertension (42.63%). Sandhu GA et al[19] has also observed raised fasting blood glucose as the most common component in his study. This may be due to insulin resistance and hyperinsulinemia which is an important feature of this syndrome, suggesting that insulin itself is atherogenic.[19]Increased levels of triglyceride and decrease value HDL cholesterol were as solidinterpreter of vascular events as the presence of other components of MS in a potential study of patients with coronary artery disease determined by angiography.[29] In my study, these two factors were also observed as major risk factors for acute MI and were seen in 35.53% and 40.79% patients respectively. Raised serum triglycerides, increased small LDL particles and a reduced level of HDL cholesterol (HDL-C) consist of atherogenic dyslipidemia. Insulin resistance is a central patho-physiological process along with acquired factors such as excess body fat and physical inactivity.[30] Effective lifestyle change or if the required relevant pharmacological intervention can reduce the risk.

CONCLUSION

This study concludes that there is a high frequency of MS in acute STEMI patients in our population with hypertension and diabetes mellitus as the major components of MS. MS is a major threat for CVD incidence whereas the risk of evolving heart disease in the period of 5 – 10 years is twice in comparison to the persons without MS. Therefore, timely detection, deterrence, and management of the risk factors of the MS should is planned in order to reduce the CVD in the general population. Therefore, we will recommend that there should be public screening and public awareness program on national and regional levels to modify these factors and improve the mortality and morbidity of the community due to heart diseases.

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REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart Disease and Stroke Statistics--2012 Update: A Report from the American Heart Association. Circulation 2012.
2. Causes of Death 2010: National Board of Health and Welfare (Socialstyrelsen); 2011.
3. Han TS, Lean MEJ. Metabolic syndrome. Medicine 2015;43(2):80–7.
4. Ladeiras-Lopes R, Fontes-Carvalho R, Bettencourt N, Sampaio F, Gama V, Leite-Moreira A. Novel therapeutic targets of metformin: metabolic syndrome and cardiovascular disease. Expert opinion on therapeutic targets 2015;19(7):869-77..
5. Oz TK, Özbilgin N, Sungur A, Bas EG, Zengin A, Gürol T, et al. Prevalence of metabolic syndrome in young patients with ST-elevation myocardial infarction. Int J Cardiovascular Academy 2018; 4(3):53.
6. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285 (19):2486-97.
7. O'Keefe JH, Carter MD, Lavie CJ. Primary and secondary prevention of cardiovascular diseases: a practical evidence-based approach. Mayo Clin Proc 2009;84(8):741-57.
8. Lovic MB, Djordjevic DB, Tasic IS, Nedeljkovic IP. Impact of metabolic syndrome on clinical severity and long-term prognosis in patients with myocardial infarction with ST-segment elevation. Hellenic J Cardiol 2018;59(4):226-31.
9. Hassanin N, Gharib S, El Ramly MZ, Meged MA, Makram A. Metabolic syndrome and coronary artery disease in young Egyptians presenting with

acute coronary syndrome. Kasr Al Ainy Med J 2015;21(1):27.
10. Alakkas Z, Alswat KA, Otaibi MA, Althobaiti T, Alzaidi N, Khalek E-SA, et al. The prevalence and the clinical characteristics of metabolic syndrome patients admitted to the cardiac care unit. Journal of the Saudi Heart Association 2016;28(3):136–43.
11. Poulsen P, Vaag A, Kyvik K, Beck-nielsen H. Genetic versus environmental aetiology of the metabolic syndrome among male and female twins. Diabetologia 2001;44(5):537–43.
12. Katzmaryk PT, Leon AS, Wilmore JH, Skinner JS, Rao DC, Rankinen T, et al. Targeting the Metabolic Syndrome with Exercise: Evidence from the HERITAGE Family Study. Med Sci Sports Exerc 2003;35(10):1703–709.
13. Alessi MC, Juhan-Vague I. Metabolic syndrome, haemostasis and thrombosis. Thromb Haemost 2008;99(6):995-1000.
14. Perrone-Filardi P, Paolillo S, Costanzo P, Savarese G, Trimarco B, Bonow RO. The role of metabolic syndrome in heart failure. Eur Heart J 2015;36(39):2630–4.
15. Uppalakal B, Karanayil LS. Incidence of metabolic syndrome in patients admitted to medical wards with ST elevation myocardial infarction. J Clin Diagnostic Research: JCDR 2017;11(3):OC17.
16. Ahmadi A, Leipsic J, Feuchtner G, Gransar H, Kalra D, Heo R, et al. Is metabolic syndrome predictive of prevalence, extent, and risk of coronary artery disease beyond its components? Results from the multinational coronary CT angiography evaluation for clinical outcome: an international multicenter registry (CONFIRM). PloS one. 2015;10(3):e0118998.
17. Devers MC, Campbell S, Simmons D. Influence of age on the prevalence and components of the metabolic syndrome and the association with cardiovascular disease. BMJ Open Diab Res Care 2016;4(1):e000195.
18. Prussian KH, Barksdale-Brown DJ, Dieckmann J. Racial and ethnic differences in the presentation of metabolic syndrome. J Nurse Practit 2007;3(4):229-39.
19. Sandhu GA, Iqbal S, Bilal A, Rana MM, Abdullah R, Qureshi FS. The frequency of metabolic syndrome in patients presenting with acute myocardial infarction. Profess Med J Sep 2011;18(3):454-61.
20. McCracken E, Monaghan M, Sreenivasan S. Pathophysiology of the metabolic syndrome. Clinics in Dermatol 2018;36(1):14–20.
21. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
22. Solymoss BC, Bourassa MG, Campeau L, Sniderman A, Marcil M, Lésperance J, et al. Effect of increasing metabolic syndrome score on atherosclerotic risk profile and coronary artery disease angiographic severity. Am J Cardiol 2004;93:159-64.
23. Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm. Eur Heart J 2004;25:342-8.
24. Yasmin S, Mallick NH, Naveed T, Ali M. Metabolic syndrome in patients with Ischemic heart disease. J Coll Physicians Surg Pak 2008;18:605-7.
25. Ashraf T, Memon MA, Talpur MS, Panhwar Z, Rasool SI. Frequency of metabolic syndrome in patients with ischaemic heart disease. J Pak Med Assoc 2011;61(8):729-32.
26. Onat A, Ceyhan K, Ba A, Yar O, Erer B, Toprak S. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels—a prospective and cross-sectional evaluation. Atherosclerosis 2002;165:285-92.
27. Wierzbicki AS, Nishtar S, Lumb PJ, Lambert-Hammill M, Turner CN, Crook MA, et al. Metabolic syndrome and risk of coronary heart disease in a Pakistani cohort. Heart 2005;91; 1003-7.
28. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006;119:812-9.
29. Ishaq M, Beg MS, Ansari SA, Hakeem A, Ali S. CAD risk profiles at a specialized tertiary care center in Pakistan. Pak J Cardiol 2003;14:61-8.
30. Butler J, Mooyaart EAQ, DannemannN,et al. Relation of the metabolic syndrome to quantity of coronary atherosclerotic plaque. Am J Cardiol 2008;101(8):1127-30.

Original Article

Demographic, Maternal and Obstetrical Factors Associated with Infantile Colic

Fazal ur Rehman[1], Khurram Shahnawaz[2], Farhan Zahoor[3], Beenish Bashir Mughal[3], Bushra Madni[4] and Kaleem Akhtar Malhi[1]

ABSTRACT

Objective: To find out the demographic as well as maternal and obstetrical factors associated with infantile colic.
Study Design: A case control study.
Place and Duration of Study: This study was conducted at the Institute of Child Health, Multan, Pakistan and Pediatrics Department, Services Hospital, Lahore Pakistan from October 2018 to March 2019.
Materials and Methods: We enrolled 100 cases and 100 controls from outpatient facilities for this study. Cases were considered as babies of both genders who had IC as per Wessel's criteria and having age less than 3 months. Controls were babies attending clinic without colic and who were more than 3 weeks to 3 months of age. Demographic, maternal and obstetrical data was recorded and compared between cases and controls.
Results: Most of the cases with IC, 53 (53.0%) were females, aged 4 to 6 weeks 53 (53.0%) and were having mixed feeding 38 (38.0%). Mean age of the cases was recorded as 5.2 weeks in comparison to a mean of 6.2 weeks in control group ($p < 0.0001$). Mean daily sleep duration was recorded to be 9.52 hours vs 13.12 hours in control group ($p < 0.0001$). Crying at night ($p = 0.003$) was turned out to be a factor significantly associated with IC ($p > 0.05$).
Conclusion: IC is a frequent problem in younger infants. Night crying and comparatively less sleep time per day was noted babies with IC. Parents handling IC should be motivated and educated about this problem to handle their babies in a better way.
Key Words: Infantile colic, daily sleep, crying at night, younger infants.

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INTRODUCTION

Infantile colic (IC) is considered to be a frequent reason for parents visiting healthcare facilities. It is estimated that about 15 to 40% babies are affected with IC.[1] IC usually starts from 2nd or 3rd week following birth whereas self remit is spontaneous in about 3 to 4 months.[2] Definition of IC is not agreed upon but it could be labeled in terms of episodes of unexplained crying during first 3 months of life.[3] As per Wessel criteria, IC is fussy crying lasting more than 3 hours per day that spans for more than 3 days a week and for A minimum of 3 weeks.[4] IC is also described as behavioral syndrome which is depicted by paroxysmal, inconsolable, excessive crying devoid of any recognizable reason in an infant that looks healthy in the first 3 months of life.

Etiology of IC is multi-`factorial involving autonomic hyper-reactivity, deficiency of progesterone levels and events occurring within labour.[5,6] Gastrointestinal (GI) factors like GI immaturity as well as milk intolerance have also been linked with IC. In infants who present with distressed crying, less than 5% have underlying organic causes.[7]

Many treatment options are tried in babies suffering with IC but not much evidence is available in the literature about the management of IC. Treatment options like hypoallergenic formula have been shown to be beneficial.[8] Pediatricians are dealing with children suffering with IC on daily basis while parents are in a state of agony seeking solutions. This study was planned to be a multi-centric involving Institute of The Child Health Multan and Services Hospital, Lahore, Pakistan. Both these institutes are leading children healthcare facilities and our aim was to find out the demographic as well as maternal and obstetrical factors associated with IC. Findings of this study will further add to what little literature is available addressing IC in Pakistan.

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MATERIALS AND METHODS

This case control study was conducted at Department of Pediatrics, The Institute of Child Health, Multan, Pakistan and Pediatrics Department, Services Hospital, Lahore Pakistan from October 2018 to March 2019. Both study centers are tertiary care hospitals and considered to be the major referral centers in their respective cities. We enrolled 100 cases and 100 controls (50 cases and 50 controls from each center) from outpatient facilities for this study. Cases were considered children of both genders who had IC as per Wessel's criteria[4] and having age less than 3 months. Children having any other serious chronic illness or disease were excluded. Babies with other recognizable causes of colic pain including otitis media, meningitis or napkin dermatitis were also not enrolled. Controls were babies attending clinic without colic and who were aged over 3 weeks up to 3 months.

A self designed questionnaire was utilized to accumulate demographic, maternal, obstetrical and medical data from parents or guardians of all the enrolled children. Ethical clearance for this study was sought from respective institutes and informed consent was taken from parents or guardians of the enrolled babies.

SPSS verison 21.0 was used to data handling and analysis. Demographic, maternal and obstetrical factors were compared between study groups. T test was employed to compare quantitative data like age and duration of sleep while chi square test was applied to compare qualitative variables. P value less than or equal to 0.05 was considered as statically significant.

RESULTS

Most of the cases with IC, 53 (53.0%) were females, aged 4 to 6 weeks 53 (53.0%) and were having mixed feeding 38 (38.0%). Amongst cases with IC, maximum crying was noted during the whole day and night, in 32 (32.0%) and 53 (53.0%) respectively. Family history of GI disease was noted in 24 (24.0%) cases. Mode of delivery was cesarean section (CS) in most of the cases, 58 (58.0%). Gestational age for mothers was noted as 37 to 42 weeks in most, 74 (74.0%) cases. Most of the cases had birth weight between 2.5 to 4 kg, 83 (83.0%). Maternal age was noted between 20 to 35 years, in 69 (69.0%) cases. Diabetes Mellitus during pregnancy was noted in mothers of 11 (11.0%) cases.

Mean age of the cases was recorded as 5.2 weeks with a standard deviation of 0.54 weeks in comparison to a mean of 6.2 weeks with a standard deviation of 0.63 weeks in controls ($p < 0.0001$). Mean daily sleep duration was recorded to be 9.52 hours with standard deviation of 2.37 hours per day in cases as in comparison to a mean of 13.12 hours with standard deviation of 2.51 hours in comparison to controls ($p < 0.0001$).

Table No.1: Characteristics of Cases and Controls

Study variable		Cases (n=100)	Controls (n=100)	P Value
Gender	Male	47 (47.0%)	52 (52.0%)	0.479
	Female	53 (53.0%)	48 (48.0%)	
Age (weeks)	4-6	53 (53.0%)	46 (46.0%)	0.547
	7-9	23 (23.0%)	29 (29.0%)	
	>9	24 (24.0%)	25 (25.0%)	
Feeding Types	Breast Feed	24 (24.0%)	26 (26.0%)	0.053
	Bottle Feed	27 (27.0%)	14 (14.0%)	
	Mixed Feed	38 (38.0%)	47 (47.0%)	
	Lactose Free Feed	8 (8.0%)	13 (13.0%)	
	Anti-colic Feed	3 (3.0%)	0 (0%)	
Maximum Crying	Day	15 (15.0%)	35 (35.0%)	0.003
	Night	32 (32.0%)	20 (20.0%)	
	Whole Day	53 (53.0%)	45 (45.0%)	
Family History of GI Disease	Yes	24 (24.0%)	29 (29.0%)	0.423
	No	76 (76.0%)	71 (71.0%)	
Diabetes Mellitus during Pregnancy	Yes	11 (11.0%)	8 (8.0%)	0.469
	No	89 (89.0%)	92 (92.0%)	

Table No. 2: Distribution of Maternal and Obstetrical Factors With Regards to Cases and Controls

Study variable		Cases (n=100)	Controls (n=100)	P Value
Mode of Delivery	CS	58 (58.0%)	56 (56.0%)	0.775
	NVD	42 (42.0%)	44 (44.0%)	
Gestational Age (weeks)	<37	25 (25.0%)	14 (14.0%)	0.131
	37-42	74 (74.0%)	84 (84.0%)	
	>42	1 (1.0%)	2 (2.0%)	
Birth Weight (kg)	<2.5	19 (19.0%)	36 (18.0%)	0.114
	2.5-4	83 (83.0%)	77 (77.0%)	
	>4	0 (0%)	4 (4.0%)	
Maternal Age (years)	<20	20 (20.0%)	17 (17.0%)	0.734
	20-35	69 (69.0%)	74 (74.0%)	
	>35	11 (11.0%)	9 (9.0%)	

When cases were compared with controls, maximum crying at night ($p = 0.003$) was turned out to be a factor significantly associated with IC while statistically insignificant difference was noted for all other study variables in between cases and controls ($p > 0.05$).

DISCUSSION

IC is a familiar problem and could precipitate by numerous factors. Age has always been thought to be firmly linked with IC as most studies suggested that most of the infants report within 6 weeks following birth.[9,10] Our findings were in accordance to what has been found earlier[9,10] in terms of age as most of the cases, 53 (53.0%) were aged 4 to 6 months. Mean age of the cases was noted to be 5.2 weeks in the present study which is quite similar to what was found by another study[11] where mean age of the babies with IC was 5 weeks.

In the present work, majority of IC babies mothers, 69 (69.0%) had age between 20 to 35 years of age. This is pretty consistent to findings of Chalabi DA et al[10] and Chinawa JM et al[12] where they noted that most of the mothers of IC babies were between the similar age.

Our study was in accordance to previous results[13,15] where almost equal number of male and female babies got affected by IC. We noted that that most, 69 (69.0%) babies were born by CS while no significant difference was found in terms of mode of delivery between cases and controls. Our results are different to what was found in a study from Iraq[10] where they noted CS to be significantly associated with IC. The difference could possibly be because of difference in trends of adopting CS in different countries. Our results in terms of mode of delivery of babies having IC are in agreement with those of Hogdall CK et al[16] and Savino F et al.[15] Some researchers have also found smoking to be 2 folds higher in mothers of IC babies[17] but we did not plan to note smoking in IC babies mothers as smoking is not a common practice in our area.

We noted that majority of mothers of the IC cases, 74 (74.0%) had gestational age between 37 to 42 weeks. We did not notice any difference between gestational age of cases or controls. Many of the previous studies[18,19] did not enroll preterm newborns while evaluating factors for IC while some others noted that risk of IC is enhanced in preterm newborns.[20]

In the current work we did not notice any significant difference between cases and controls with regards to types of feeding. Colic has been documented as commonly in babies who are breastfed as those who are artificial fed.[10] Types of feeding has not been documented to influence incidence of IC[21,22] while some studies have reported that IC increase in babies who are breastfed.[23,24]

Night time crying was significantly more ($p = 0.0003$) in cases as compared to controls (32% vs. 20%). Night time crying has been indicated in babies with IC by many other previous studies and our results were in accordance with many other previous studies.[10,25] Clinicians should be keen to identify crying pattern while identifying IC in babies. Mean sleep duration per day was significantly less in cases as 9.52 hours as compared to a mean 13.12 hours in controls. This finding was very much anticipated and has been documented by others as well.[10] Family history of GI disease was not found to have any linkage with colic in the present study and this fact has been very well established in the previous works as well.[13,15]

CONCLUSION

IC is a frequent problem in younger infants. Night crying and comparatively less sleep time per day was noted babies with IC. Parents handling IC should be motivated and educated about this problem to handle their babies in a better way.

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Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Wade S, Kilgour T. Infantile coilc. BMJ 2001;323:437- 40.
2. Sung V. Infantile colic. Aust Prescr 2018;41(4):105–110.
3. Ghosh S, Barr RG. Colic and gas. In: Walker WA, Goulet O, Kleiman RE, et al, editors. Pediatric Gastrointestinal Disease. 4th ed. Hamilton, Ontario: BC Decker Inc; 2004. p. 210.
4. Wessel MA, Cobb JC Jackson EB, Harris GS, Detwiler AC. Paroxismal Fussing in infancy, Sometime called ''Colic''. Pediatrics 1954; 14(5): 421-35.
5. Campbell JP. Dietary treatment of infant colic: a doubleblind study. J R Coll Gen Pract 1989;39(318):11-4.
6. Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic. BMJ 1993;307(6904):600-4.
7. Roberts DM, Ostapchuk M, O'Brien JG. Infantile colic. Am Fam Phys 2004;70(4):735-40.

8. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk TM, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review. BMJ 1998;316(7144):1563-9.
9. Clifford TJ, Campbell MK, Speechley KN, Gorodzinsky F. Infant colic: evidence of the absence of an association with source of early infant nutrition. Arch Pediatr Adolesc Med 2002;156(11):1123-8.
10. Chalabi DA, Omer K, Al-Taweel N. Risk factors for infantile colic: a case control study. J Arab Board Health Spec 2016;17(2):2-8.
11. Landgren K, Kvorning N, Hallström I. Feeding, stooling and sleeping patterns in infants with colic: a randomized controlled trial of minimal acupuncture. BMC Complement Altern Med 2011;11:93.
12. Chinawa JM, Ubesie AC, Adimora GN, Obu HA, Eke CB. Mothers perception and management of abdominal colic in infants in Enugu, Nigeria. Niger J Clin Pract 2013;16(2):69-73.
13. Kheir AE. Infantile colic, facts and fiction. Ital J Pediatr 2012;38:34.
14. Talachian E, Bidari A, Rezaie MH. Incidence and risk factors for infantile colic in Iranian infants. World J Gastroenterol 2008;14(29):4662-6.
15. Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: A prospective randomized study. Pediatrics 2007;119(1):124-30.
16. Høgdall CK, Vestermark V, Birch M, Plenov G, Toftager-Larsen K. The significance of pregnancy, delivery and postpartum factors for the development of infantile colic. J Perinat Med 1991;19(4):251-7.
17. Reijneveld SA, Brugman E, Hirasing RA. Infantile colic: maternal smoking as potential risk factor. Arch Dis Child 2000;83(4):302-3.
18. Barr RG, Rotman A, Yaremko J, Leduc D, Francoeur TE. The crying of infants with colic: a controlled empirical description. Pediatrics 1992;90(1):14-21.
19. Søndergaard C, Skajaa E, Henriksen TB. Fetal growth and infantile colic. Arch Dis Child Fetal Neonatal Ed 2000;83(1):F44-7.
20. Milidou I, Søndergaard C, Jensen MS, Olsen J, Henriksen TB. Gestational age, small for gestational age, and infantile colic. Paediatr Perinat Epidemiol 2014;28(2):138-45.
21. Rautava P, Helenius H, Lehtonen L. Psychosocial predisposing factors for infantile colic BMJ 1993;307(6904):600-4.
22. Hide DW, Guyer BM. Prevalence of infant colic. Arch Dis Child 1982;57(7):59-560.
23. Crowcroft NS, Strachan DP. The social origins of infantile colic: questionnaire study covering 76,747 infants. BMJ 1997;314(7090):1325-8.
24. Rubin SP, Prendergast M. Infantile colic: incidence and treatment in a Norfolk community. Child Care Health Dev 1984 Jul-Aug;10(4):219-26.
25. James-Roberts IS, Conroy S, Wilsher K. Bases for maternal perceptions of infant crying and colic behaviour. Arch Dis Child 1996;75(5):375-84.

Original Article

Treatment Outcomes of Severe Acute Malnutrition

Examine the Treatment Outcomes of Severe Acute Malnutrition in Pediatric Population by Using Formula F100 Therapeutic Feed

Saima Rayaz[1], Mohammad Iqbal[2], Muhammad Hussain[1] and Attaullah Bizenjo[2]

ABSTRACT

Objective: To examine the prevalence and treatment outcomes of severe acute malnutrition in children.
Study Design: Prospective study
Place and Duration of Study: This study was conducted at the Department of Pediatric Medicine Unit-3, Civil Sandeman Provincial Hospital Quetta from January 2019 to June 2019.
Materials and Methods: A total of 150 patients of both genders presented with severe acute malnutrition were included in this study. Patient's ages were ranging from 2 months to 48 months. Patients demographic including age, sex, malnutrition type and residence were recorded after taking informed consent from patient's parents/guardians. Presentations on admission were recorded. F75 and F100 therapeutic feed were given to all the patients (WHO Guideline for malnutrition). Outcomes were recorded.
Results: There were 80 (53.33%) male patients while 70 (46.67%) were females. Sixty eight (45.33%) patients were ages less than 10 months and 82 (54.67% were ages above 10 months. From all the patients 134 (89.33%) patients were marasmus and 16 (10.67%) patients were khwashikor. Mean weight gain by using F100 was 7.26±3.45 gm/kg/day. 92% patients were recovered and 8% died during treatment. The most common presentation was diarrhea.
Conclusion: The use of F75 and F100 therapeutic feed for the treatment of severe acute malnutrition were very effective with low rate of mortality.
Key Words: Severe acute malnutrition (SAM), Pediatric population, F75, F100 Feed, Treatment, Outcomes

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INTRODUCTION

Acute malnutrition is one of the common disorders found all over the world. It occurs due to different infections and caused nutritional insufficiency.[1] This malignant disorders contains moderate acute and severe acute malnutrition.[1,2] It directly effects children height and weight and this nutritional defects causes high rate of morbidity and mortality. Acute malnutrition is defined as SAM when WHZ < −3, MUAC <115 mm, and/or edema [2]. In developing countries the prevalence rate of severe acute malnutrition accounted 3% and this rate is accounted 2% in children in developing countries.[3]

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In southern countries the incidence rate of severe acute malnutrition in children ages with 0 to 5 years is 1.9%.[4] In Pakistan the prevalence of severe acute malnutrition in children reported 15% as wasted and 34 percent are low weight and 43% children reported stunted according to the survey conducted to examine the prevalence of SAM in 2011.[5] Children with severe acute malnutrition causes physical and metabolic changes that can lead to severe disabilities and effect mental development so the better and affective treatment is much important to reduce the morbidity and mortality. For the treatment prospect WHO published a guideline for the treatment of severe acute malnutrition in children with ages less than 5 years. This treatment guideline contains F100 feeding therapeutic formulas that contain proteins, carbohydrates and sodium in specific proportion according to the needs of malnourished children. This treatment guideline is very effective and easy to apply with significant outcomes.[6] The mortality rate is ranging 5% to 40% and due to severe acute malnutrition the fatality rate is accounted approx 30%. WHO guideline for the treatment of SAM resulted 30% to 35% reduce in case fatality rate.[7,8] Severe acute malnutrition is one of the most common pediatric disorders in developing countries and it accounted 5%

to 50% of mortality among children with ages less than 5 years. Walking difficulties, developmental complications and many other severe disorders occurs due to severe acute malnutrition. Prompt and better treatment is very helpful and effective to reduce the rate of infectious diseases.[9,10]

MATERIALS AND METHODS

This prospective/observational study was conducted at Department of Pediatric Medicine Unit-3, Civil Sandeman Provincial Hospital Quetta from 1st January 2019 to 30th June 2019. Total 150 patients of both genders presented with severe acute malnutrition were included in this study. Patient's ages were ranging from 2 months to 48 months. Patients demographic including age, sex, malnutrition type and residence were recorded after taking informed consent from patient's parents/guardians. Children with surgical interventions, patient having other severe disorders and those parent/guardians who were not attended the complete treatment process were excluded from the study. All the patients had received F75 and F100 therapeutic feed. At first day 130ml/kg/day was given 2 hourly. Duration of feed was gradually increased to3-4 hourly. F100 was added in transition phase for 2days in same amount. During hospital stay weight gain was recorded and on discharge mean weight gain was examined. Treatment outcomes were recorded such as mortality and recovered. All the data was analyzed by SPSS 21. Mean SD was obtained for analysis. Percentages and frequency were recorded.

RESULTS

There were 80 (53.33%) male patients while 70 (46.67%) were females. Sixty eight (45.33%) patients were ages less than 10 months and 82 (54.67% were ages above 10 months. 100 (66.67%) patients had rural residency while 50 (33.33%) patients had urban residency. From all the patients 134 (89.33%) patients were marasmus and 16 (10.67%) patients were khwashikor (Table 1).

Table No. 1: Demographic information of the patients

Variable	No.	%
Gender		
Male	80	53.33
Female	70	46.67
Age (months)		
<10	68	45.33
>10	82	54.67
Residence		
Rural	100	66.67
Urban	50	33.33
Type of SAM		
Marasmus	134	89.33
Khwashikor	16	10.67

Table No.2: Clinical presentations at the time of admission

Presentation	No.	%
Diarrhea	75	50.0
Phneumonia	35	23.3
Hypoglycemia	20	13.33
UTI	12	8.0
Otitis Media	8	5.33

Table 3: Treatment outcomes of severe acute malnutrition by using F100 feeding formula (WHO Guideline)

Outcome	No.	%
Recovered	138	92.0
Died	12	8.0

Presentations at admission were recorded as diarrhea, pneumonia, hypoglycemia, urinary tract infection and otitis media in 75 (50%), 35 (23.3%), 20 (13.33%), 12 (8%) and 8 (5.33%) patients respectively (Table 2). According to the treatment outcomes we recorded mean weight gain was by using F100 was 7.26±3.45 gm/kg/day. 92% patients were recovered/discharge and 8% died during treatment (Table 3).

DISCUSSION

Severe acute malnutrition is one of the most common pediatric disorders in developing countries and it accounted 5 to 50% of mortality among children with ages less than 5 years.[11,12] Many of treatment modalities were used for severe acute malnutrition with significantly better results but WHO guidelines for the treatment of SAM (F100 feed) showed better results with respect to weight gain and quick recovery.[13] The recent study was conducted aimed to examine the outcomes of F100 feeding formula for the treatment of severe acute malnutrition. In present study 150 patients were presented with severe acute malnutrition were included in which 53.33% patients were males while 46.67% were females. These results showed similarity to many other studies in which male patient's population was high as compared to females. 50% to 60%.[14,15] In our study majority of patients were ages above 10 months 54.67%. A study conducted by Sadia et al[16] regarding treatment outcomes of severe malnutrition in children reported maximum patients were ages above 6 months.

In this study we found that 100 (66.67%) patients had rural residency while 50 (33.33%) patients had urban residency. From all the patients 134 (89.33%) patients were marasmus and 16 (10.67%) patients were khwashikor. These results were comparable to some previous studies in which majority of patients belong to rural areas.[17] In our study we found diarrhea was the most common presentation at admission and accounted 50% of patients followed by phneumonia 23.3%, hypoglycemia 13.33%. Sadia et al[16] reported diarrhea

was the most common presentation in children presented with acute severe malnutrition. Many of other studies showed similarity in which diarrhea and hypoglycemia were the most common presentation found in children.[18,19]

In present study we found mean weight gain was 7.26±3.45 gm/kg/day. Many of previous studies were reported average weight gain was 4 to 12g/kg/day as treatment outcomes.[20,21] The mortality rate was 8% in our study and 92% patients were recovered and discharge. These results were similar o several studies in which recovered rate was 85 to 95% and mortality rate lies 5 to 30% by using F100 therapeutic feed for the treatment of severe acute malnutrition.[22,23]

DISCUSSION

Severe acute malnutrition is one of the most common pediatric disorders in developing countries and it accounted 5 to 50% of mortality among children with ages less than 5 years.[11,12] Many of treatment modalities were used for severe acute malnutrition with significantly better results but WHO guidelines for the treatment of SAM (F100 feed) showed better results with respect to weight gain and quick recovery.[13] The recent study was conducted aimed to examine the outcomes of F100 feeding formula for the treatment of severe acute malnutrition. In present study 150 patients were presented with severe acute malnutrition were included in which 53.33% patients were males while 46.67% were females. These results showed similarity to many other studies in which male patient's population was high as compared to females. 50% to 60%.[14,15] In our study majority of patients were ages above 10 months 54.67%. A study conducted by Sadia et al[16] regarding treatment outcomes of severe malnutrition in children reported maximum patients were ages above 6 months.

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CONCLUSION

The use of F100 therapeutic feed for treatment of severe acute malnutrition was very useful and effective treatment modality with very low rate of mortality. Moreover we should provide awareness to the people about this life threatening disorder so that mortality rate could decrease.

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Data Analysis:	Muhammad Hussain, Attaullah Bizenjo
Revisiting Critically:	Saima Rayaz
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REFERENCES

1. Hobbs B, Bush A. Acute malnutrition: an everyday emergency; a 10-point plan for tackling acute malnutrition in under-fives. Relief Web 2014.
2. HTP. Technical notes on management of severe acute malnutrition. 2011.
3. Sadler K. Community-based therapeutic care: treating severe acute malnutrition in sub-Saharan Africa. London: University College London; 2010.
4. Golden M, Grellety Y. Protocol for the management of severe acute malnutrition. Ethiopia: Ministry of Health 2007.
5. Central Statistical Agency (Ethiopia), ICF International. Ethiopian Demographic and Health Survey 2011. In: Central Statistical Agency, ed. Addis Ababa, Maryland: Central Statistical Agency and ICF International; 2012.
6. Black RE, Couseus S, Johnson HL, Lawa JE, Rudan I, Bassani DG, et al. Global regional and attritional causes of child mortality in 2008: a systematic analysis. Lancet 2010; 375(9730): 1969-87.
7. Khadduri R, Marsh DR, Rasmussen B, Bari A, Nazir R, Darmstadt GL. Household knowledge and practices of newborn and maternal health in Haripur district, Pak J Perinatol 2008;28(3):182-7.
8. Teferi E, Lera M, Sita S, Bogale Z, Datiko DG, Yassin MA. Treatment outcome of children with severe acute malnutrition admitted to therapeutic feeding centers in Southern Region of Ethiopia. Ethiopian J Health Dev 2010;24(3)234-8.
9. Ashworth A. Treatment of severe malnutrition. J Pediatr Gastroenterol Nutr 2001;32(5):516-8.

10. Engle PL, Fernald LC, Alderman H, Behrman J, O'Gara C, Yousafzai A, et al. Strategies for reducing inequalities and improving developmental outcomes for young children in low-income and middle-income countries. Lancet 2011;1(14):1339-53.
11. Arbab AJ, Bahawaluddin J, Ghulam RB, Abdul HS, Khurshid AA. Treatment outcome of severe acute malnutrition in children at Nutrition Stabilization Center Sukkur. Pak Pediatr J 2014; 38(1):14-8.
12. Sameen I, Moorani KN. Morbidity pattern of severe malnourished children at tertiary care Hospital. Pall Pediatr J 2014;20(3):3-8.
13. World Health Organization. Guideline: updates on the management of severe acute malnutrition in infants and children. World Health Organization; 2013.
14. Panezai A, Rafeeq M, Bajwa MA, Infections of children associated with malnutrition in Quetta. PJMHS 2011; 5(3):460-66.
15. Lazzerini M, Rubert L, Pani P. Specially formulated foods for treating children with moderate acute malnutrition in low and middle-income countries. Cochrane Database Syst Rev 2013;1(6):148-52.
16. Ejaz MS, Latif N. Stunting and micronutrient deficiencies in malnourished children. J Pak Med 2010;60(7):543-7.
17. Khan S, Ali I, Iqbal I, Ishfaq K. Treatment outcome of Severe acute Malnutrition in Children at Nutrition Stabalization Centre Multan using who Guidelines. Isra Med J 2017;9(2):59-61.
18. Nyeko R, Calbi V, Ssegujja BO, Ayot GF. Treatment outcome among children under-five years hospitalized with severe acute malnutrition in St. Mary's hospital Lacor, Northern Uganda. BMC Nutr 2016; 2(1): 19.
19. Abeje AT, Gudayu TW, Malefia YD, Befftu BB. Analysis of hospital records on treatment outcome of severe acute malnutrition: the case of gondar university tertiary hospital. Pediatr Therap 2016; 6(2): 383.
20. Chane T, Oljira L, Atomesa GE, Agedew E. Treatment outcome and associated factors among under-five children with severe acute malnutrition admitted to therapeutic feeding unit in woldia hospital, north Ethiopia. J Nutr Food Sci 2014; 4(6): 1-9.
21. Mekonnen L, Abdussemed A, Abie M, Amuamuta A. Severity of malnutrition and treatment responses in under five children in Bahir Dar Felegehiwot Referal Hospital, Northwest Ethiopia. J Food Nutr Sci 2014; 2(3): 93–8.
22. Government of Pakistan, National Nutritional Survey of Pakistan, Islamabad 2011.
23. World Health Organization Updates on the Management of Severe Acute Malnutrition in Infants and Children. Geneva: WHO 2016.

Original Article

Effectiveness of Rifaximin versus Norfloxacin in Prevention of Spontaneous Bacterial Peritonitis in Cirrhotic Patients

Aneel Kumar[1], Bashir Ahmed Shaikh[2], Zahid Ali Shaikh[2], Aftab Hussain Shah[2], Arshad Bhutto[3] and Jaipal Das[1]

ABSTRACT

Objective: This study aimed to compare the effectiveness of rifaxamin versus norfloxacin in prevention of spontaneous bacterial peritonitis in cirrhotic patients.

Study Design: Randomized Control Trial.

Place and Duration of Study: This study was conducted at the Medical Unit-II, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana from January, 2019 to June, 2019.

Materials and Methods: All patients who fulfilled the inclusion criteria and visited to the Medical unit-II, Chandka Medical College and Hospital, SMBBMU Larkana were included in the study. Informed consent was taken after explaining the procedure, risks and benefits of the study. The total of 244 patients were randomly divided into two groups i.e. (Group A Rifaxamin) and (Group B Norfloxain). Ascitic tap was done to all the patients to see the presence of SBP and blood samples weresent to the laboratory for urea, creatinine, serum sodium, serum bilirubin, serum albumin and PT. Patients were followed over the duration of 6 months and each patient was called for examination after every 3 months to assess the efficacy in term of non-reoccurrence of SBP. All the collected information was recorded on proforma and used electronically for research purpose.

Results: Mean ± SD of age was 37.74±8.75 and 38.89±8.84 years in norfloxacin and rifaximin group respectively. In group wise distribution of gender 64 (52.5%) male and 58 (47.5%) female was enrolled in norfloxacin group and 74 (60.6%) male and 48 (39.4%) female was included in rifaximin group. In comparison of both groups 103(84.4%) efficacy was noted in norfloxacin group whereas 110(90.2%) efficacy was documented in rifaximin groupand p value found to be insignificant i.e. (P=0.178).

Conclusion: As non-significant difference was found between rifaximin versus norfloxacin, so it is to be concluded that rifaximin is an appropriate alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites.

Key Words: Rifaximin, Norfloxacin, Spontaneous Bacterial Peritonitis, Efficacy.

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INTRODUCTION

Cirrhosisaccounts for approximately one million deaths every year [(1)]. It is a characterized by hepatic fibrosis to point that there is architectural distortion with formation of regenerative nodules, representing the final histological change for a variety of chronic liver diseases, clinically manifested by ascites, spontaneous bacterial peritonitis, variceal bleeding and hepatic encephalopathy[(2)].

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Pakistan has second highest estimated prevalence of cirrhosis worldwide secondary to hepatic viral infections specially HCV [(3)]. Cirrhosis is most commonly caused by Alcohol, non-alcoholic fatty liver disease, hepatitis C, hepatitis B and hepatitis D[(4)]. A number of less common causes include autoimmune hepatitis, primary biliary cholangitis, Wilson's disease, hemochromatosisand certain medications. Spontaneous bacterial peritonitis (SBP) is fatal complication of cirrhosis, approximately present in 20 to 30% of patients. However, the incidence is>40% in patients with ascitic fluid total protein <1g/dl [(5)]. American Association for the Study of Liver Diseases Practice Guideline management of adult (AASLD) defines SBP as a development of bacterial infection in the peritoneum causing peritonitis without any evidence of intra-abdominal, surgically treatable source of infection and its diagnosis is made in the presence of an elevated ascitic fluid absolute polymorphonuclear leucocytes (PMNL) count ≥250 cells/mm3. The mortality rate in patients with SBP ranges from 40-70% in adult patients

with Cirrhosis [6].The proposed mechanism for development of SBP is translocation of intestinal bacteria into the ascitic fluid. On surviving an episode of SBP, the recurrence rate is approximately 70% at 1 year [7]. High recurrences coupled with substantial mortality warrants long-term antibiotic prophylaxis to prevent SBP. Various oral antibiotics have been studied to reduce the risk of occurrence and recurrence of SBP by achieving selective intestinal decontamination [8]. The AASLD and European Association for the Study of the Liver (EASL) recommend Norfloxacin, a fluoroquinolone, as the first-line therapy for the prevention of spontaneous bacterial peritonitis [9,10].Extensive use of Norfloxacin for this purpose has increased the incidence of Quinolone-resistant and gram positive SBP[10]. Rifaximin is abroad-spectrum antibiotic and is poorly absorbed systematically, thereby reaches high levels in the gut lumen[11]. The main advantage of Rifaximin is that it is virtually unabsorbed, which minimizes the antimicrobial resistance. In addition, Rifaximin has better activity against gram-positive organism than Norfloxacin. Its role as an initial and add-on therapy for hepatic encephalopathy has been well established [12]. Studies suggest that prevention of SBP with other drugs such as Norfloxacin and trimethoprim-sulfamethoxazole reduce the rate of SBP infections in almost 68% of the patients and with Rifaximin about 89%[13]. Other studies reported the reoccurrence of SBP is significantly lower in the rifaximin group (3.88 vs. 14.13%) compared with the norfloxacin group (P=0.04) [14].

MATERIALS AND METHODS

The Randomized Control Trial study was conducted at Medical Unit-II, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana after approval of ethical review committee from January 13, 2019 to June 12, 2019. Sample size was calculated n=122 in each groupby using W.H.O sample size calculator version 2.0. Patients between age group 25-55 years ofboth genders with cirrhosis in accordance with operational definition, History of variceal bleeding, Child-Pugh score ≥ 9, Serum creatinine > 1.2 mg/dL, BUN > 25mg/dL, Serum sodium < 130mEq/L and serum albumin > 25g/dl were included in study after taking written informed consent. Their ascitic tap was done under the supervision of consultant and blood samples were sent to the laboratory for urea, creatinine, serum sodium, serum bilirubin, serum albumin and PT. The patients were randomly divided into two groups i.e. (Group A Rifaxamin) and (Group B Norfloxain) by using computer-generated sequential number placed in sealed envelopes and opened only before the commencement of the study. The study was conducted in a single-blind fashion. Patients were followed over the duration of 6 months to assess the reoccurrence of SBP. All the patients were called for examination after every 3 months. At the end of 6th month, efficacy in term of non-reoccurrence of SBP was measured. The data was entered and analyze into statistical packages for social science (SPSS Version 20). Mean ± SD was calculated for age, ChildPugh score, serum creatinine, serum sodium and serum bilirubin. Frequency and Percentage were calculated for gender. Chi-square test was applied to compare the efficacy in both groups by using two-sidedprobability value ≤ 0.05 as statistical criteria of significance. Both groups were compared by age, gender, Child-Pugh score, serum creatinine, serum sodium and serum bilirubin wise stratification by using chi-square test to see the impact of these on outcome variable considertwo-sided probability value ≤ 0.05 as statistical criteria of significance.

RESULTS

In this study 244 patients were divided randomly into two equal groupsto compare the effectiveness of rifaximin versus norfloxacin in prevention of spontaneous bacterial peritonitis in cirrhotic patients. In overall distribution of gender 138 (57%) were male and 106 (43%) were female (Figure 1).

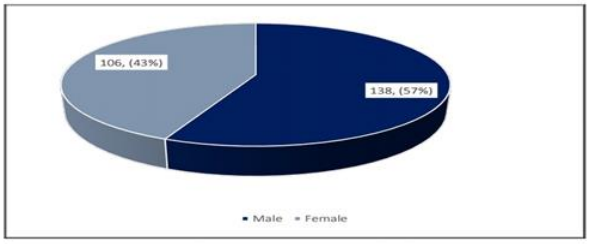

Figure No.1: Overall Distribution of Gender n=244

Table No.1: Distribution of Gender in Both Groups n=244

GROUP	MALE	FEMALE
NORFLOXACIN (n=122)	64 (52.5%)	58 (47.5%)
RIFAXIMIN (n=122)	74 (60.6%)	48 (39.3%)

Table No.2: Comparison of Efficacy in Both Group n=244

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=122)	103 (84.4%)	19 (15.6%)	0.178
RIFAXIMIN (n=122)	110 (90.2%)	12 (9.8%)	

In group wise distribution of gender 64 (52.5%) male and 58 (47.5%) female was enrolled in norfloxacin group and 74 (60.6%) male and 48 (39.4%) female was included in rifaximin group (Table 2). In comparison of both groups 103(84.4%) efficacy was noted in norfloxacin group whereas 110(90.2%) efficacy was documented in rifaximin group and p value found to be

insignificant i.e.(P=0.178) as shown in Table 2. Stratification of age, gender, serum creatinine, Pugh score, serum sodium, and serum bilirubin with respect to efficacy were done (Table 3-11).

Table No.3: Stratification 0f Age Group 25 To 40 With Respect To Efficacy n=131

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=61)	49 (37.4%)	12 (9.2%)	0.033
RIFAXIMIN (n=70)	65 (49.6%)	5 (3.8%)	

Table No.4 Stratification 0f Serum Creatinine Group 1.20 – 2.20 With Efficacy n=129

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=51)	45 (34.9%)	6 (4.7%)	0.859
RIFAXIMIN (n=78)	68 (52.7%)	10 (7.8%)	

Table No.5: Stratification 0f Serum Creatinine Group > 2.20 With Efficacy n=115

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=71)	58 (50.4%)	13 (11.3%)	0.045
RIFAXIMIN (n=44)	42 (36.5%)	2 (1.7%)	

Table No.6: Stratification of Pugh Score Of 14 – 22 With Efficacy n=161

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=86)	74 (46.0%)	12 (7.5%)	0.909
RIFAXIMIN (n=75)	65 (40.4%)	10 (6.2%)	

Table No.7: Stratification of Pugh Score > 22 With Efficacy n=83

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=36)	29 (34.9%)	7 (8.4%)	0.153
RIFAXIMIN (n=47)	45 (54.2%)	2 (2.7%)	

Table No.8: Stratification of Serum Sodium 113 – 124 With Efficacy n=136

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=72)	63 (46.3%)	9 (6.6%)	1.00
RIFAXIMIN (n=64)	56 (41.2%)	8 (5.9%)	

Table No.9: Stratification of Serum Sodium > 24 With Efficacy n=108

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=58)	40 (37.0%)	10 (9.3%)	0.050
RIFAXIMIN (n=58)	54 (50.0%)	4 (3.7%)	

Table No.10: Stratification of Serum Bilirubin 0.10 – 2.0 With Efficacy n=70

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=31)	26 (37.1%)	5 (7.1%)	0.228
RIFAXIMIN (n=39)	37 (52.9%)	2 (2.9%)	

Table No.11: Stratification of Serum Bilirubin > 0.20 With Efficacy n=174

GROUP	EFFICACY		P-VALUE
	YES	NO	
NORFLOXACIN (n=91)	77 (44.3%)	14 (8.0%)	0.524
RIFAXIMIN (n=83)	73 (42.0%)	10 (5.7%)	

DISCUSSION

Transmural bacterial translocation is believed to be a predominant factor in the development of SBP; therefore, prophylaxis is targeted at gut flora [15]. In clinical trials it has been proven that the antibiotic rifaximin has a very good safety profile due to its less absorption from the gut[16, 17]. Few adverse reactions reported were gastrointestinal like flatulence andnausea. Extensive use of norfloxacin has increased the incidence of quinolone resistant and Gram-positive SBP [16].Our study showed that the administration of rifaximin 1200 mg/day in patients with a previous episode of SBP maintained the median count of total white blood cell and neutrophils in ascitic fluid after 3 months of treatment, with no significant difference when compared with those receiving norfloxacin. This was in agreement with Kalambokis et al. [17], who reported significant reductions in white blood cell and neutrophil count in ascitic fluid of cirrhotic patients after a 4-week regimen with rifaximin 1200 mg/day, producing a decrease in SBP frequency and improvement in quality of life in cirrhotic patients with ascites. In the present study, 15.6% on rifaximin and 9.8% on norfloxacin developed SBP during the study period. Our observations are in agreement with the findings of Vlachogiannakos et al. [18], who reported a significantly reduced 5-year probability of SBP in cirrhotic patients taking rifaximin. In the meta-analysis carried out by Bernard et al. [19], comparing several treatments, the general incidence of SBP was 9% in the

norfloxacin-treated group, which was better than our findings in this study. This difference suggests the increased incidence of quinolone-resistant and Gram-positive SBP over the last two decades with extensive and long-term use of norfloxacin for the secondary prophylaxis of SBP. This increased incidence of recurrence of SBP in patients receiving norfloxacin prophylaxis should be watched closely as it suggests reconsidering of the current guidelines for the secondary prophylaxis of SBP. In the current study, the mortality rate was significantly decreased in the rifaximin group (13.74 vs. 24.43%) compared with the norfloxacingroup. Novella et al. [20] compared inpatient and continuous SBP prophylaxis with the norfloxacin group, and mortality rates were 30.2 and 23.2%, respectively, which was similar to our findings. Although there is no current consensus on whether prophylactic antibiotics provide a longterm survival benefit, prophylactic rifaximin was associated with a 30% higher rate of transplant-free survival at 9 months of follow-up in arecent study [21]. In our study, hepatic encephalopathy (HE)-related deaths were threefold higher in the norfloxacin group. A recent study showed that rifaximin at a dosage of 550 mg twice daily was highly effective in decreasing the recurrence of HE and decreasing the rate of HE-related hospitalizations over a 24-week period in a group of patients at high risk for HE [22]. In our study, 84.4% efficacy was noted in norfloxacin whereas 90.2% in rifaximin and p value found to be insignificant. In comparison, our patients who developed SBP during the study duration were significantly more likely to have had a history of previous SBP, higher baseline values for serum bilirubin, prothrombin time and Child–Pugh score. As expected, they also had significantly worse overall survival compared to patients who did not develop SBP. Despite the fact that 15.6% of patients who developed SBP in our study were on rifaximin versus 9.8% on norfloxacin, the difference, however, did not prove to be statistically significant. A few studies have investigated rifaximin versus placebo for SBP prophylaxis in cirrhotics. A cohort study by Terg R, et al. Found a transplant-free survival benefit with the use of rifaximin in cirrhotic patients with ascites and who had no prior history of SBP than those who didn't receive antibiotic prophylaxis [16].Vlachogiannakos et al. Also showed that patients who received rifaximin had a significantly lower risk of developing variceal bleeding, hepaticencephalopathy (HE), SBP and hepatorenal syndrome than matched control subjects who did not receive antibiotic prophylaxis[18]. In comparison, our results demonstrated that patients on rifaximin developed fewer episodes of Hepatic encephalopathy than patients on norfloxacin (4.7% and 9.3%, respectively).Patient succeeded to adhere to therapy slightly better with norfloxacin than rifaximin, and for a significantly longer time. Most patients reported a difficulty to adhere to the three times per day-regimen of rifaximin. The strengths of our study were scientific and systematic calculation of sample size, selection of strongest study design (RCT), and inclusion, exclusion criteria. We also perform stratification at the analysis to control for confounders and effect modifiers. The use of objective definitions for predictor and outcome variable also minimizes the source of bias in our study. There are several limitations to our study. First, since it was impossible to blind the investigator or observer to the device being applied, this study is not a double-blind trial and the potential for bias may exist; this may affect the results as a confounding factor. Also limited outcomes selected in our study affects the worth of our study.

CONCLUSION

As non-significant difference was found between rifaximin versus norfloxacin, so it is to be concluded that rifaximin is as good as norfloxacin. It seems to be an appropriate alternative for long-term primary and secondary prophylaxis of SBP in cirrhotic patients with ascites. There is a need to conduct more randomized studies using large sample size with multiple study centers in Pakistan to confirm the findings of the present study.

Author's Contribution:

Concept & Design of Study:	Aneel Kumar
Drafting:	Bashir Ahmed Shaikh, Zahid Ali Shaikh
Data Analysis:	Aftab Hussain Shah, Arshad Bhutto, Jaipal Das
Revisiting Critically:	Aneel Kumar, Bashir Ahmed Shaikh,
Final Approval of version:	Aneel Kumar

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2095-128.
2. Fernández J, Gustot T. Management of bacterial infections in cirrhosis. J Hepatol 2012;56 (Suppl 1):S1–S12.
3. 3.Shah SM, Mashia SA, Younus MF, Ghauri A, Ejaz R, Alshalabi H, Kakar IK, Umar M. Hepatic cirrhosis-disease burden. J Rawalpindi Med Coll Stud Suppl 2015;19:17-20.
4. 4.Hanouneh MA, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, et al. The role of rifaximin

in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. J Clin Gastroenterol 2012; 46:709–715
5. Biecker E. Diagnosis and therapy of ascites in liver cirrhosis. World J Gastroenterol 2011; 17:1237–1248.
6. Kalambokis GN, Mouzaki A, Rodi M, Tsianos EV. Rifaximin for the prevention of spontaneous bacterial peritonitis. World J Gastroenterol 2012; 18:1700–1702.
7. Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Longterm administration of rifaximin improves the prognosis of patients with alcohol-related decompensated cirrhosis: a case control study. J Gastroenterol Hepatol 2013; 28:450–455
8. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010; 362:1071–1081
9. 9.Koo HL, DuPont HL. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. Curr Opin Gastroenterol 2010; 26:17–25.
10. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. Gut 2012; 61:297–310
11. Narang S, Pandav N, Vyas K, Bherwani S, Buch M. Comparison of Efficacy of Rifaximin and Norfloxacin in Prevention of Spontaneous Bacterial Peritonitis. Ann Int Med Dent Res 2018;4(2):35-9
12. Kamal F1, Khan MA, Khan Z, Cholankeril G, Hammad TA, Lee WM, et al. Rifaximin for the prevention of spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2017;29(10):11091117
13. Hanouneh MA, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, et al. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. J Clin Gastroenterol 2012;46(8):709-15.
14. Elfert A, Abo Ali L, Soliman S, Ibrahim S, Abd-Elsalam S. Randomized-controlled trial of rifaximin versus norfloxacin for secondary prophylaxis of spontaneous bacterial peritonitis. Eur J Gastroenterol Hepatol 2016;28(12):1450-1454.
15. Terg R, Fassio E, Guevara M, Cartier M, Longo C, Lucero R, et al. Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study. J Hepatol 2008;48(5):774-9.
16. Biecker E. Diagnosis and therapy of ascites in liver cirrhosis. World J Gastroenterol 2011;17:1237–1248.
17. Kalambokis GN, Mouzaki A, Rodi M, Tsianos EV. Rifaximin for the prevention of spontaneous bacterial peritonitis. World J Gastroenterol 2012;18:1700–1702.
18. Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Longterm administration of rifaximin improves the prognosis of patients with alcohol-related decompensated cirrhosis: a case control study. J Gastroenterol Hepatol 2013;28:450– 455.
19. Bernard B, Grangé JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with ascites: a meta-analysis. Digestion 1998; 59 (Supp 2):54–57.
20. Novella M, Solà R, Soriano G, Andreu M, Gana J, Ortiz J, et al, Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. Hepatol 1997;25:532–536.
21. Hanouneh MA, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, et al. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. J Clin Gastroenterol 2012; 46:709–715.
22. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071–1081.

Original Article

Comparison of Outcome in Multiple Myeloma with or without Adjuvant Vitamin D Therapy

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ABSTRACT

Objective: To determine vitamin D levels in newly diagnosed cases of multiple myeloma and to determine effects of vitamin D supplementation using laboratory parameters on outcome of the disease.

Study Design: Comparative study.

Place and Duration of Study: This study was conducted at the Haematology Department of Shaikh Zayed Hospital, Lahore and INMOL Hospital, Lahore from January to June 2018.

Materials and Methods: Thirty two patients of multiple myeloma were included in the study and were divided into two equal groups A and B. Baseline laboratory parameters;vitamin D, β2 microglobulin and serum albumin levels were performed. Patients in group A were given vitamin D supplementations along with standard myeloma chemotherapy. Whereas patients in group B were without adjuvant vitamin D supplementation. Laboratory parameters in both groups were repeated and compared at 12 and 18 weeks follow-up.

Results: At baseline, mean vitamin D level in group A was 17.86 ± 14.23 ng/ml and in group B was 25.95 ± 15.89 ng/dl. At 18th week follow-up, mean vitamin D level in group A was 44.14 ± 20.99 ng/ml and in group B was23.92 ± 14.11 ng/dl, which was statistically significant (p-value 0.003).Comparison of mean β2 microglobulin and albumin levels between the two groups were found insignificant at 18th week follow-up.To determine the effect of vitamin D supplementation on outcome of multiple myeloma, hypothetical scoring was calculated and compared between the two groups which was found statistically insignificant.

Conclusion: Significant low vitamin D levels (78.12%) had been found in multiple myeloma. There was significant improvement of vitamin D levels with oral supplementations, but laboratory parameters alone has shown no significant results at short term follow-up.

Key Words: Multiple myeloma, vitamin D, β2 microglobulin

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INTRODUCTION

Multiple myeloma is a rarehaematological malignancy of the plasma cells which evolves in the bone marrow.Malignant plasma cells produce abnormal antibodies which are called 'M proteins'.[1, 2]

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Musculoskeletal pains, hypercalcemia, renal insufficiency, anemia and pathological fractures are common complications of multiple myeloma.[3]Ninety eight percent myeloma cases report over the age of forty years with peak incidencein the 7th decade of life.[4]

Vitamin D is a secosteroid that helps in absorption of calcium and phosphate in the body.Recent studies reported its rolein cell differentiation, multiplication and apoptosis.[5, 6]Multiple myeloma causes increase production of matrix metalloproteinases (MMPs) that enable cancer cells to migrate into other tissues. Vitamin D reduces MMPs production and hence the ability of cancer to spread.[7]

Vitamin D deficiency has been associated with potential risk for pathological fractures and development of various malignancies.[8, 9]Serum vitamin D levelshave shownits prognostic role in patients with breast orcolorectal carcinomas,but its role in haematological malignancieslike multiple myeloma is still unclear.[10, 11, 12]

MATERIALS AND METHODS

This cross-sectional study was conducted at. Haematology Department of Shaikh Zayed Hospital, Lahore and INMOL Hospital, Lahore

Thirty two newly diagnosed patients of multiple myeloma were taken as study population and were divided equally into two groups A and B. All the patients were staged using International staging System (ISS). Baseline laboratory parameters; vitamin D, β2 microglobulin and serum albumin levels were performed and documented on the designed proforma.

Group A: Patients from Sheikh Zayed Hospital, Lahore were given standard myeloma therapy and adjuvant vitamin D therapy.

Group B: Patients from INMOL Hospital, Lahore were given standard myeloma therapy alone (without adjuvant vitamin D therapy).

Laboratory parameters were repeated after 12 and 18 week intervals.

Inclusion Criteria:

1. New cases of multiple myeloma
2. Adults of both genders

Exclusion Criteria:

1. Patients with malabsorptive disorders (e.g. celiacdisease, cystic fibrosis, short bowl syndrome)
2. Patients on antiepileptic medicines that increases vitamin D metabolism (e.g. phenytoin and phenobarbital)

Data Analysis: Data for gender and stage of the disease were presented by using frequency and percentage. All quantitative variables (including age, vitamin D, albumin and β2 microglobulin levels) were presented by using Mean ± S.D for two groups. Comparison of above parameters between the groups was made by using Independent Sample t-test.

RESULTS

Mean age of the patients was 59.56 ± 13.02 years in Group A, while 55.50 ± 10.64 years in Group B. In Group A, there were 9 (56.25%) male and 7 (43.75%) female patients while in Group B, there were 10 (62.5%) male and 6 (37.5%) female patients.

In this study, Minimum vitamin D level found among both groups was 4.6 ng/ml and maximum was 58.91 ng/ml. In Group A, Mean vitamin D was 17.86 ± 14.23 ng/ml at baseline, 28.61 ± 11.96 ng/ml at 12 weeks and 44.14 ± 20.99 ng/ml at 18 weeks follow-up. In Group B, mean vitamin D was 25.95 ± 15.89 ng/dl at baseline, 23.74 ± 14.31 ng/dl at 12 weeks and 23.92 ± 14.11 ng/dl at 18 weeks follow-up respectively. It was found statistically significant between the both groups at 18th week(p-value 0.003). (Table-1) (Figure 1)

In Group A, mean β2 microglobulin was 14.76 ± 15.03 mg/L at baseline, 6.81 ± 6.14 mg/L at 12 weeks and 3.35 ± 0.70 mg/L at 18 weeks follow-up. In Group B, mean β2 microglobulin was 12.12 ± 12.78 mg/L at baseline, 6.36 ± 8.06 mg/L at 12 weeks and 3.13 ± 3.35mg/L at 18 weeks follow-up. At 18th week follow-up, comparison between the two groups was found statistically insignificant. (Table-1) (Figure -2)

In Group A, mean serum albumin was 3.22 ± 1.62 mg/L at baseline, 3.47 ± 0.60 mg/L at 12 weeks and 3.47 ± 0.57 mg/L at 18 weeks follow-up. In Group B, mean serum albumin was 3.33 ± 0.97 mg/L at baseline, 3.25 ± 0.71 mg/L at 12 weeks and 3.13 ± 0.67 mg/L at 18 weeks follow-up. Similarly, at 18th week follow-up comparison between the two groups was found statistically insignificant. (Table-1) (Figure-3)

In our study, we compared ISS stage of myeloma patients between group A and group B at baseline, 12 week and 18 week intervals. In group A; at baseline, 10 patients were in stage-III,3 were in stage-II and 3 were in stage-I. Whereas at 18 weeks, 3 patients left in stage-III, 7 in stage-II and 6 were in stage-I of disease.In group B, at baseline, 12 patients presented in stage-III, 3 in stage-II and 1 in stage-I. Whereas at 18 weeks, one patient was in stage-III, 11 in stage-II and 4 in stage-I of disease. (Figure-4)

Table No.1: Comparison of vitamin D, β2 microglobulin and albumin levels at baseline, 12th week and 18th week in both study groups

	Laboratory Parameters	Group A	Group B	p-value
At Baseline	Vitamin D level (ng/dl)	17.86 ± 14.23	25.95 ± 15.89	0.140
	β2 microglobulin level (mg/L)	14.76 ± 15.03	12.12 ± 12.78	0.597
	Albumin level (mg/L)	3.22 ± 1.62	3.33 ± 0.97	0.645
At 12th Week	Vitamin D level (ng/dl)	28.61 ± 11.96	23.74 ± 14.31	0.304
	β2 microglobulin level (mg/L)	6.81 ± 6.14	6.36 ± 8.06	0.860
	Albumin level (mg/L)	3.47 ± 0.60	3.25 ± 0.71	0.353
At 18th Week	Vitamin D level (ng/dl)	44.14 ± 20.99	23.92 ± 14.11	0.003*
	β2 microglobulin level (mg/L)	3.35 ± 0.70	3.13 ± 3.35	0.140
	Albumin level (mg/L)	3.47 ± 0.57	3.13 ± 0.67	0.241

*Statically significant

In order to study stage regression in our cohort and to relate it to vitamin D supplementation, a hypothetical number was assigned to each patient according to stage of the disease. Cumulate score of patients was calculated in a particular stage at baseline, 12 weeks and 18 weeks. This hypothetical scoring helped in understanding the effect of vitamin D supplementation on outcome of treatment in multiple myeloma patients. In this, stage-I patient was assigned a score of 1, stage-

II patient was assigned a score of 2 and stage-III patient was assigned a score of 3. In Group A, the cumulate score at baseline was 39, at 12 weeks was 34 and at 18 weeks was 29. In Group B, the cumulate score at baseline was 43, 30 at 12 weeks and 29 at 18 weeks. (Table-2)

When we calculate that in group A, the reduction in scoring, it was 5 point reduction at 12weeks and 10 points at 18 weeks from the baseline score of 39. In group B, reduction in scoring was 13 points at 12 weeks and 14 points at 18 weeks from baseline score of 43.Reduction in scoring from baseline, at 12 weeks and 18 weeks was compared between the both groups and was indicative of stage regression. P-value was 0.07 which was statistically insignificant. (Table-3)

Table-No.2. Three stages of Multiple Myeloma in group A and B with hypothetical scoring according to ISS stage and number of patients

Groups	Stage	At Baseline Level		At 12th week		At 18th week	
		Number of Patients	Score	Number of Patients	Score	Number of Patients	Score
Group A (With Vitamin D therapy)	I	3	3	4	4	6	6
	II	3	6	6	12	7	14
	III	10	30	6	18	3	9
	Total	16	39	16	34	16	29
Group B (Without Vitamin D therapy)	I	1	1	5	5	4	4
	II	3	6	8	16	11	22
	III	12	36	3	9	1	3
	Total	16	43	16	30	16	29

(Score= ISS stage and number of patient in a particular stage at one point of time)

Table-3. Comparison of Reduction in Hypothetical Score at Baseline, 12th week and 18th week in both groups

Groups	No. of Patients	Score at Baseline	Reduction at 12th week	Reduction at 18th week	va
Groups A (With Vitamin D)	16	39	5	10	
Group B (Without Vitamin D)	16	43	13	14	0

p value < 0.05 is significant

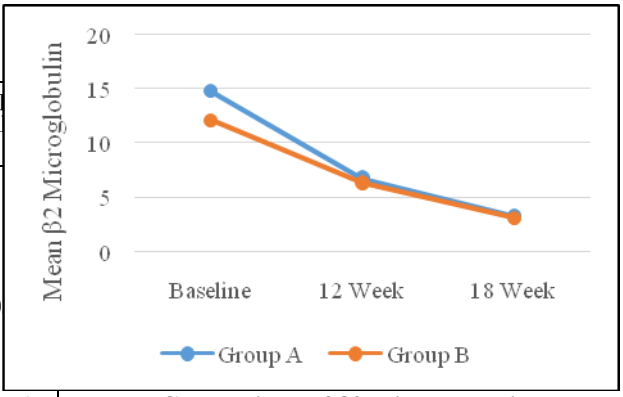

Figure No.2: Comparison of β2 microglobulin levels at baseline, 12th week and 18th week in both groups

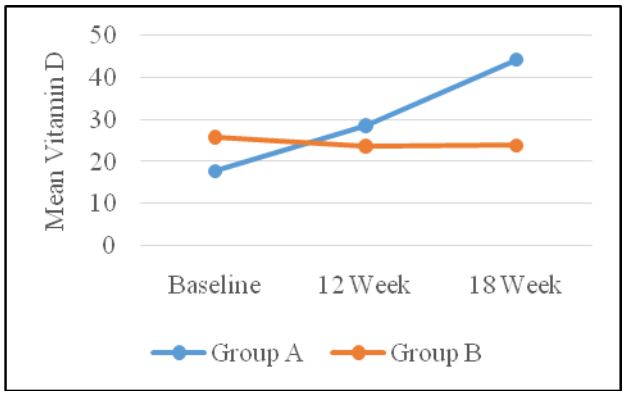

Figure No.1: Comparison of vitamin D levels at baseline, 12th weeks and 18th weeks in both groups

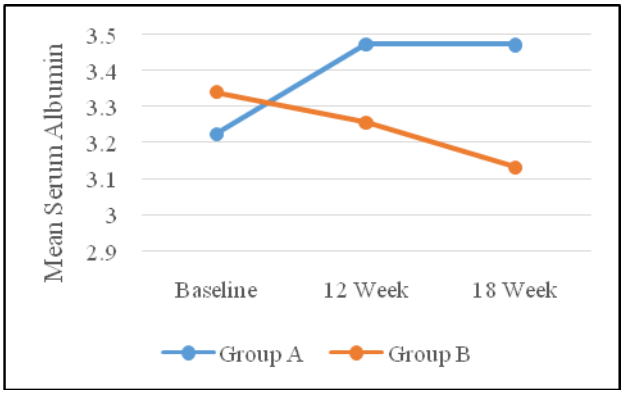

Figure No.3. Comparison of serum Albumin levels at baseline, 12th week and 18th week in both groups

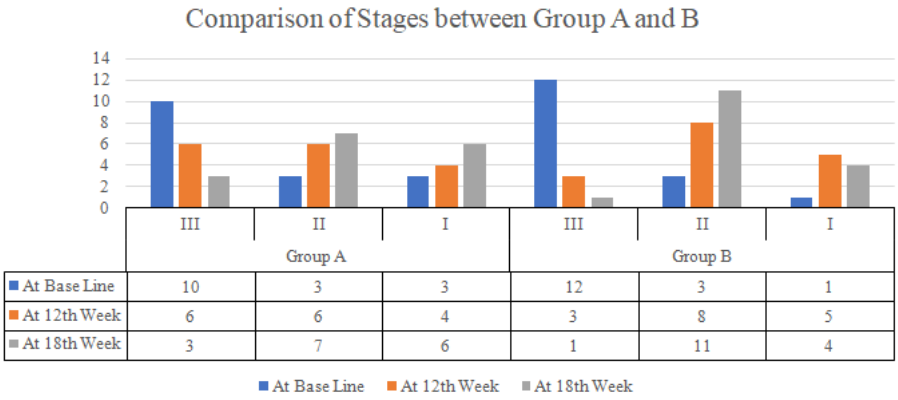

Figure No.4. Comparison of stages between group A and group B at baseline, 12th week and 18th week

DISCUSSION

Multiple myeloma is a debilitating malignancy of plasma cells that constitutes 1% of all malignancies and 10% of all haematological neoplasms.[13] Five year relative survival rate is 52.2%.[14, 15, 16]

In our study, out of total 32 patients of multiple myeloma, 22 (68.75%) had clinical stage-III, while 6 (18.75%) were in stage-II and only 4 (12.5%) were in stage-I of disease. All the patients in both the groups received chemotherapy. In an American study by Ng AC et al in 2009, only 3 (2.8%) patients had clinical stage-III, while 71 (67%) patients were in stage-II and 32 (30.2%) patients were in stage-I of disease respectively.[17] In a Turkish study by Yokus O et al in 2017, 15 (48.4%) patients had clinical stage-III, while 11 (35.5%) patients were in stage-II and only 5 (16.1%) patients were in stage-I of disease respectively.[18]

A higher number of patients in our study were in stage-III in contrast to the American study. This may be due to the fact that many patients in our population present late to specialized centers due to many socio-economic factors.

Favorable increases in mean vitamin D level from 17.86 ± 14.23 ng/ml at baseline to 44.14 ± 20.9 ng/ml at 18 week was seen in group A patients where as in group B patients, it was 25.95 ± 15.89 ng/dl at baseline to 23.92 ± 14.11 ng/dl at 18 weeks follow-up respectively. Comparison of mean vitamin D levels at 18 week follow-up among both groups was statistically significant with p value 0.003.

In German study by Lauter B et al in 2015, mean vitamin D levels among multiple myeloma patients was 14.8 ng/mL which increased to 24.0 ng/ml after vitamin D supplementation for 1 year. Results were significant with p value 0.001.[19] Comparatively good response in shorter period of time was observed in our study due to difference of dose of vitamin D supplementation. In our study, vitamin D supplementation in group A patients was given in the form of oral capsules at a dose of 5000 IU per day (35000 IU weekly).

In our study, comparison of β2 microglobulin between the two groups at 18th week follow-up was found statistically insignificant. In Australian study by Diamond T et al in 2009, β2 microglobulin level in Quartile-1 (severely deficient) was 5.5 ± 6.5 mg/L, in Quartile-2 (deficient) was 4.5 ± 4.1 mg/L, in Quartile-3 (insufficient) was 5.5 ± 4.8 mg/L and in Quartile-4 (sufficient) was 4.0 ± 3.8 mg/L respectively.[20]

β2 microglobulin is an important prognostic indicator of multiple myeloma. A patient with a level less than 4 mg/L is expected to have a median survival of 43 months, while one with a level over 4 mg/L has a median survival of only 1 year.[21] In our study, however a little rapid fall in β2 microglobulin level was observed in patients of group A but on comparison with group B at 18th weeks was found statistically insignificant. Our follow-up was maximally up to 18 weeks only which was one of the limitations of the study.

In our study, comparison of mean serum albumin between the two groups at 18th week follow-up was found statistically insignificant. In study at Mayo clinic by Ng AC et al, among 35 myeloma patients of vitamin D deficient group, serum albumin was 3.12 g/dl and among 113 patients of non-vitamin D deficient group, serum albumin was 3.39 g/dl.[17]In Australian study by Diamond T et al, mean serum albumin level in Quartile-1 (severely deficient) was 30 ± 8 mg/L, in Quartile-2 (deficient) was 36.1 ± 6 mg/L, in Quartile-3 (insufficient) was 35.9 ± 4 mg/L and in Quartile-4 (sufficient) was 35.5 ± 5 mg/L respectively.[20] Results of these studies were similar to results of our study and were found insignificant.

On relationship of vitamin D with multiple myeloma, largest published series is from the Mayo Clinic comprising of 148 newly diagnosed multiple myeloma patients for which no survival association was found, but there were associations between low vitamin D levels (< 20 ng/mL) and higher serum CRP, serum creatinine and ISS stage.[17]

Interestingly, according to our original hypothesis vitamin D therapy along with chemotherapy in multiple

myeloma showed improvement in overall outcome in patients in all three stages of disease. Deficient group showed more skeletal morbidity, pathological fractures and vertebral compressions than sufficient groups.

CONCLUSION

Although our study provided cross sectional perspective of significant improvement of vitamin D levels in multiple myeloma patients with supplementation, suggesting its potential role on natural history and clinical progression but using laboratory parameters like β2 microglobulin and serum albumin alone has shown no statistically significant results at short term follow-up. This suggests a need for larger population based studies both to confirm our findings at long term follow-up and to prospectively assess the role of vitamin D deficiency in disease progression and overall survival of multiple myeloma patients.

Author's Contribution:

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REFERENCES

1. Fairfield H, Falank C, Avery L, Reagan MR. Multiple myeloma in the marrow: pathogenesis and treatments. Ann N Y Acad Sci 2016; 1364: 32–51.
2. Díaz L, Díaz-Muñoz M, García-Gaytán AC, Méndez I. Mechanistic effects of calcitriol in cancer biology. Nutrient 2015;7:5020–5050.
3. Morais SA, DuPreez HE, Akhtar MR, Cross S, Isenberg DA. Musculoskeletal complications of haematological disease. Rheumatol 2016;55:968–981.
4. Hoffbrand AV, Moss PAH: Multiple myeloma and related disorders. Essential Haematology, 6th ed. Oxford: Wiley & Blackwell; 2011: 273.
5. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin d in reducing cancer risk and progression. Nat Rev Cancer 2014; 14: 342-57.
6. Bolland MJ, Grey A, Gamble GD, Reid IR. The effect of vitamin d supplementation on skeletal, vascular, or cancer outcomes: A trial sequential meta-analysis. Lancet Diabetes Endocrinol 2014;2: 307-320.
7. Pittayapruek P, Meephansan J, Prapapan O, Komine M, Ohtsuki M. Role of matrix metalloproteinases in photoaging and photocarcinogenesis. Int J Mol Sci 2016; 17: 868.
8. Mahmood K, Akhtar ST, Talib A,Haider I. Vitamin-D status in a Population of Healthy Adults in Pakistan. Pak J Med Sci 2009;25(4): 545-550.
9. Crew KD. Vitamin D: are we ready to supplement for breast cancer prevention and treatment?. ISRN Oncology 2013; Article ID 483687: 22.
10. Maalmi H, Ordonez-Mena JM, Schottker B, Brenner H. Serum 25-hydroxyvitamin d levels and survival in colorectal and breast cancer patients: Systematic review and meta-analysis of prospective cohort studies. Eur J Cancer 2014;50:1510-21.
11. Wang B, Jing Z, Li C, Xu S, Wang Y. Blood 25-hydroxyvitamin d levels and overall mortality in patients with colorectal cancer: A dose-response meta-analysis. Eur J Cancer 2014; 50: 2173-75.
12. Lim U, Freedman DM, Hollis BW, Horst RL, Purdue MP, Chatterjee N, et al. A prospective investigation of serum 25-hydroxyvitamin d and risk of lymphoid cancers. Int J Cancer 2009;124: 979-86.
13. Banu-Bradu A, Ionita H, Ionita I, Vernic C, Macarie C. Renal Disease In Multiple Myeloma. Timisora Medical J 2011; 61(1-2): 32-36
14. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Myeloma. National Cancer Institute. Available at http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed: February 5, 2016.
15. Collins CD. Multiple myeloma. Cancer Imaging 2010;10: 20–31.
16. Michels TC, Petersen KE. Multiple myeloma: Diagnosis and treatment. Am Fam Physician 2017; 95: 373-383.
17. Ng AC, Kumar SK, Rajkumar SV, Drake MT. Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma. Am J Haematol 2009;84:397-400.
18. Yokus O, Hilmi DM, Aydinli F, Eren R, Altindal S, et al. Vitamin D deficiency and its effects on patients with multiple myeloma. Hematol Transfus Int J 2017;5: 00112.
19. Lauter B, Schmidt-Wolf IGH. Prevalence, supplementation and impact of vitamin D deficiency in multiple myeloma patients. Cancer Investigations 2015;33:505-09
20. Diamond T, Golombick T, Manoharan A. Vitamin D status may affect the skeletal complications of multiple myeloma. Am J Hematol 2009;85:302-303.
21. Munshi NC, Longo DL, Anderson KC. Plasma Cell Disorders. In: Loscalzo J, Longo DL, Fauci AS, Dennis LK, Hauser SL, editors. Harrison's principles of internal medicine. 18th ed. McGraw-Hill Professional 2011;936–44.

Original Article

Determine the Outcome of Newborn in Post-Term Pregnancy

Ashba Anwer[1], Nazia Tufail[2] and Asma Mudassir[1]

ABSTRACT

Objective: To assess the outcome of newborn among pregnant females who deliver after prolonged pregnancy.
Study Design: Descriptive study
Place and Duration of Study: This study was conducted at the Department of Obstetrics & Gynaecology, Islam Central Hospital, Sialkot from October 2018 to March 2019.
Materials and Methods: One hundred patients with pregnancy of 42 weeks or above were included. Patients with medical disorders, intrauterine demise or pregnancy complications were excluded. Identification of parameters regarding poor neonatal outcome was done. Gestational age, parity, fetal movement, age, mode of delivery, ultrasound, admission cardiotocogram (CTG) and past prolonged pregnancy were recorded.
Results: There were 39 (39%) between 20-25 years of age. Multigravida was found in 60 (60%) and emergency caesarean section 65 (65%). Most of the babies 64% were admitted to neonatal intensive care unit (ICU). Complication of meconium aspiration syndrome was found 67 (67%). No fetal mortality was observed.
Conclusion: Pregnancy should be managed before 42 weeks of gestation and should not allow to went post-term due to high rate of neonatal mortality and morbidity.

Key Words: Neonate, Post-term pregnancy, Gestational age

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INTRODUCTION

Post-term pregnancy is defined as pregnancy more than 40 weeks of gestation (294-days) and above from last menstrual period (LMP) is defined as prolonged/post-term pregnancy.[1] There is approximately 3-12% reported frequency of post-term pregnancy.[2] However, the real incidence is probably less since most frequent reasons of prolonged pregnancy diagnosis is incorrect dating.[3] Risk factors includes genetic factors, male gender of fetus, prior post-term and primiparity for actual post-term pregnancy.[4] In the first two trimesters, obesity and consumption of fish is most recently describe factor.[5] To calculate the estimated due date (EDD) traditionally the last menstrual period (LMP) has been used, but due to use of this method, incorrectness exist in females who have irregular cycle, have first trimester bleeding or who have no recent hormone birth control methods.[6]

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Therefore, when estimate gestational age regularity and length of cycle should be taken into account other than last menstrual period date. In early pregnancy, ultrasonographic dating can improve estimated due date (EDD) reliability.[7] However, it is essential to understand error margin reported at several times in each trimester. Prolonged/post-term pregnancy is related with increased incidence of prolonged labour and vacuum assisted birth or forceps (operative delivery). Due to a large size baby, patients are at risk of vaginal birth trauma.[8] In a post-term pregnancy cesarean delivery is likely twice due to the size of baby. Wound complications and infections and postpartum hemorrhage is also increased the risk factors for patients.[9] In a post-term pregnancy there are also risk for newborn and fetus. Fetus may stop gaining weight, volume of amniotic fluid decreases and the function of placenta decreases towards the end of pregnancy. If the baby is large than birth injury may also occur. There is also risk of meconium aspiration for those babies who born after 40 weeks.[10] Prolonged pregnancy management in absence of other complications is contentious. Females should be offered induction after forty one weeks as recommended by guidelines of Royal College of Obstetricians and Gynecologists.[11] From upto 40-weeks increased antenatal monitoring should be offered to those females who decline induction, containing twice cardiotocography and single deepest amniotic pool estimation through ultrasound. Less than 8cm pool depth indicated increase risk of intrapartum to fetus.[12] If use expectant management, labour should induce at beginning of 43rd week as recommended by some sources.[13,14]

MATERIALS AND METHODS

This descriptive case series study was conducted at Department of Obstetrics & Gynecology Department of Obstetrics & Gynaecology, Islam Teaching Hospital Sialkot from 1st October 2018 to 31st March 2019.A total of 100 un-booked patients above 40-weeks duration of pregnancy were included in this study, who were sure about the date of last menstrual period or had 1st trimester ultrasound report and with regular menstrual series. The patients with medical disorders, intrauterine demise or pregnancy complications were not were excluded from the study. After obtaining informed consent data was collected and gestational age, fetal movement, past prolonged pregnancy, age, parity, CTG admissions and ultrasound findings were studied. Factors were specifically noted who affecting poor perinatal outcome like birth weight, meconium aspiration, neonatal sepsis, respiratory distress syndrome, asphyxia, birth trauma, APGAR score, jaundice, admission and stay duration in neonatal intensive care unit.The collected data was analyzed through SPSS 20.

RESULTS

Most of the patients 39 (39%) were 20-25 years old, 30 (30%) patients between the age group of 26-30years, 18 (18%) were in 31-35 years of age group and 13 (13%) were above the age of 35 years. The numbers of primigravida 40 (40%) patients and multigravida patients were 60 (60%). All patients have longitudinal lie as confirmed by the ultrasonographic findings and transverse lie not presented by any patient. 3-3.5 kg estimated fetus weight in the majority 79 (79%) while only 21 (21%) have 3.6 kg to 4 kg weight. In 90 (90%) cephalic presentation was observed and breech presentation was found in only 10 (10%). 110-150 per minute fetal heart rate was found in 82 (82%) while less than 110 per minute fetal heart rate was found in 18 (18%). The delivered babies, males babies were 65 (65%) and females 35 (35%). In 5 (5%) develop birth trauma due to instrumental delivery. The babies who shifted to neonatal intensive care unit (NICU) were 64 (64%). Within three days most of the babies 51 (51%) were discharged and between 4 to 5 days 37 (37%) babies were discharged and 12 (12%) were discharged between 6 to 7 days (Table 1). According to the patients biophysical score, 10 (10%) had 6/10 score, 50 (50%) had 8/10 and 40 (40%) patients had 10/10 score (Table 2).

According to the delivery mode, most of the patients 65% had emergency C-section followed by spontaneous, instrumental and elective C-Section 20%, 12% and 3% respectively (Table 3). Meconium aspiration syndrome was most complication which was 67 (67%). Asphyxia found in 55% neonates, 49 (49%) neonates had respiratory distress syndrome, neonatal jaundice was found in 8 (8%) and sepsis was found in 7 (7%) neonates (Table 4).

Table No.1: Demographic information of the neonatal

Variable	No.	%
Gender		
Male	65	65.0
Female	35	35.0
Birth trauma		
Yes	5	5.0
No	95	95.0
NICU admission		
Yes	64	64.0
No	36	36.0
Hospital stay (days)		
<3	51	51.0
4-5	37	37.0
6-7	12	12.0

Table No.2: Patients biophysical profile (n=100)

Biophysical Profile Score	No.	%
6/10	10	10.0
8/10	50	50.0
10/10	40	40.0

Table No.3: Frequency of delivery mode (n=100)

Delivery Mode	No.	%
Vaginal instrumental	12	12.0
Vaginal spontaneous	20	20.0
C-Section elective	3	3.0
C-Section emergency	65	65.0

Table No.4: Frequency of neonatal complications

Complication	No.	%
Sepsis	7	7.0
Neonatal jaundice	8	8.0
Respiratory distress syndrome	49	40.0
Asphyxia	55	55.0
Meconium aspiration syndrome	67	67.0

DISCUSSION

Inaccurate pregnancy dating is the most common reason to diagnose post-term pregnancy. To assess the gestational age in pregnancy last menstrual period with menstrual series is best physiological landmark. However, there are only few females which are sure about their dates and frequently causes anxiety when they came with postdate.[2] The cause of prolonged pregnancy is unknown. Mostly in obese, nulliparous the post-term pregnancy happens as well as in that females who had post-term pregnancy previously.[4-14] There is high risk of perinatal mortality & morbidity involved in post-term pregnancies which also includes oligohydramnios, sepsis neonatorum, neonatal jaundice meconium aspiration syndrome, fetal distress, fetal birth injury, macrosomia and increase rate of C-

section.[15] Determination of fetal outcome among prolonged pregnancies is the view of this conducted study. In this study, mostly patients (90%) fall under the 20-years to 30-years of age group, which is similar to another study conducted by Oakland.[16] In the study conducted by Oakland showed that 8.60% patients were below the age of thirty four years. According to these findings, in age group of 20-years to 25-years prolonged pregnancy is a common incidence. Although, nulliparous patients are more common for prolonged pregnancies, mostly patients (60%) in our study were multigravida which is similar to the study by Cucco et al.[17] In multigravida patients one of the main recognize factor of prolonged pregnancy is past history of this type of event. Patients who had past history of prolonged pregnancy are at risk of post-term pregnancy in later pregnancy.[18] In our study 40% patients had previous history of post-term pregnancy. In accordance with these findings, special care given by the obstetricians to avoid from later post-term pregnancy and patients may also take special care for prevention from post-term pregnancy.

Although abnormal fetal heart rate reported by many studies, 18% of our patients had deceleration. Prolonged pregnancy is not allied with breech presentation[19] and breech presentation itself allied with increase rate of C-section. In post-term pregnancy caesarean section rate varies quite high as reported incidence varies from 15% to 80%.[20] Nearly 1/3rd patients of our study were delivered vaginally, consequently preventing the operation risk. There was caesarean delivery in 68% patients in our study. This high rate is due to that patients were un-booked and directly presented to labour room therefore had no follow-up. Unfavorable cervical findings mostly in our patients at the time of presentation which also contribute to high caesarean section rate in our patients.

Prolonged pregnancy is the main reason to increase the fetal morbidity. Due to reduced liquor volume and poor placental reserves, asphyxia and fetal distress is more common.[21] Physiological passage of meconium which occur due to parasympathetic system maturation by forty two weeks of gestation increases the incidence of meconium aspiration.[22] Neonatal complications incidence was quite high in our study e.g. asphyxia, respiratory distress syndrome, meconium aspiration syndrome, sepsis neonatorum and jaundice which are similar incidence of these complications reported internationally.[7-8]

In the absence of other complications, prolonged pregnancy management is controversial. Among obstetricians, there is debate on expectant management of post-term patients versus elective induction of labour.[20,23] Stripping or sweeping the membranes and unprotected coitus may prevent from prolonged pregnancy.[24] To avoid from fetal morbidity close monitoring is required in any case. Careful counseling concerning the risk and benefits of each component of care should require individual patient management.[25]

CONCLUSION

Prolonged pregnancy lies high rate of fetal mortality and morbidity with severe complications for mothers. It is concluded from this study that pregnancies should not allow to go post-term as they are associated with higher neonatal mortality andmorbidity. Before 40 weeks of gestation induction of labour should be offered to females to prevent from adverse neonatal consequences.

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Revisiting Critically:	Ashba Anwer
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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. American College of Obstetriciansand Gynecologists.Practice bulletin no. 146: Management of late-term and postterm pregnancies. Obstet Gynecol 124(2pt1): 390-6.
2. Norwitz ER, Snegovskikh W, Caughey AB. Prolonged pregnancy. Clin Obstet Gynecol 2007. 50(2):547-57.
3. Bennett KA, Crane JMG, O'Shea P, Lacelle MD, Hutchens D, Copel J. Firsttrimester ultrasound screening is effective in reducing post-term induction rates: a randomized controlled trial. Am J Obstet Gynecol 2004; 190:1077–81.
4. Kistka ZA, Palomar L, Lee KA, Boslaugh SE, Wangler MF, Cole FS, et al. Radical disparity in the frequency of recurrence of preterm birth. Am J Obstet Gynecol 2007: 196:131.e1-6.
5. Olesen AW, Westergaard JG, Olsen J; Prenatal risk indicators of a prolonged pregnancy. The Danish Birth Cohort 1998-2001. Acta Obstet Gynecol Scand 2006;85(11):1338-41.
6. Gardosi J, Vanner T, Francis A. Gestational age and induction of labour for prolonged pregnancy. Br J Obstet Gynaecol 1997;104(7):792–7.
7. Savitz D, Terry JW, Dole N, Thorp JM, Siega-Riz AM, et al. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination Am J Obstet Gynecol 2002;187: 1660-6.
8. Smith GCS. Life-table analysis of the risk of perinatal death at term and post term in singleton pregnancies. Am J Obstet Gynecol 2001; 184: 489–96.

9. Olesen AW, Westergaard JG, Olsen J. Perinatal and maternal complications related to postterm delivery: a national register-based study, 1978–1993. Am J Obstet Gynecol 2003;189:222–7.
10. Hilder L, Costeloe K, Thilaganathan B. Prolonged pregnancy: evaluating gestation-specific risks of fetal and infant mortality. Br J Obstet Gynaecol 1998;105:169–73.
11. Royal College of Obstetricians and Gynecologists. Induction of labour. Evidence based clinical Guideline No. 9. London: RCOG Press, 2009.
12. Dasari P, Niveditta G, Raghavan S. The maximal vertical pocket and amniotic fluid index in predicting fetal distress in prolonged pregnancy. Int J Gynaecol Obstet 2007;96(2):89-93.
13. Treger M, Hallak M, Silberstein T, Friger M, Katz M, Mazor M. Post-term pregnancy: should induction of labor be considered before 42 weeks? J Matern Fetal Med 2002;11:50–3.
14. 14 Gelisen O, Caliskan E, Dilbaz S, Ozdas E, Dilbaz B, Ozdas E, et al. Induction of labor with three different techniques at 41 weeks of gestation or spontaneous follow-up until 42 weeks in women with definitely unfavorable cervical scores. Eur J Obstet Gynecol Reprod Biol 2005;120(2):164–9.
15. Roach VJ, Rogers MS. Pregnancy outcome beyond 41weeks gestation. Int J Gynecol Obstet 1997; 59:19–24.
16. Cleary-Goldman J, Bettes B, Robinson JN, Norwitz E, D'Alton ME, Schulkin J. Postterm pregnancy: practice patterns of contemporary obstetricians and gynecologists. Am J Perinatol 2006;23(1):15-20.
17. Aaron B, Caughey MD. Maternal and obstetric complications of pregnancy are associated with increasing gestational age at term. Am J Obstet Gynecol 2009;200:683 -5.
18. Cucco C, Osbrone MA, Cibils LA. Maternal-fetal outcomes in prolonged pregnancy. Am J Obstet Gynecol 1989; 161:916-20.
19. James C, George SS, Guanekar N, Seshadri L. Management of prolonged pregnancy: arandomized trial of induction and antepartum foetal monitoring. Nat J Ind 2001;14:270–3.
20. 20. Hannah ME. Postterm pregnancy: should all women have labour induced? A review of the literature. Fetal Maternal Med Rev 1993;5:3–17.
21. Heimstad R, Skogvoll E, Mattson L, Johansen OJ, Eik-Nes SH, Salvesen KA. Induction of labor or serial antenatal fetal monitoring in post-term pregnancy. Obstet Gynecol 2007;109:609–17.
22. 22. Caughey AB, SnegovskikhVV, Norwitz ER. Postterm pregnancy: how can we improve outcomes? Obstet Gynecol Surv 2008; 63(11): 715-24.
23. Mogen I, Stenlund H, Hodberg U. Recurrence of prolonged pregnancy. Int J Epidemiol 1999; 28(2):253-7.
24. Herabutya Y, Prasertsawat PO, Tongyai T, Isarangura Na Ayudthya N. Prolonged pregnancy: the management dilemma. Int J Gynecol Obstet 1992;37:253–8.
25. de Miranda E, van der Bom JG, BonselGJ, Bleker OP, Rosendaal FR. Membrane sweeping and prevention of post-term pregnancy in low-risk pregnancies: a randomized controlled trial. BJOG 2006;113:402–8.

Original Article

Effect of BMI on Semen Parameters in Male Infertility in Tertiary Care Hospital of Karachi

Fareena Khalil Ahmed[1], Abdul Shakoor Memon[1], Intesar Burney[1], Khalida Bano[3] and Afshan Mehboob Khan[2]

ABSTRACT

Objective: To study the effect of BMI on semen parameters in male infertile patients in tertiary care hospital of Karachi.

Study Design: Case control study

Place and Duration of Study: This study was conducted at the Department of Physiology, Basic Medical Sciences Institute (BMSI) in collaboration with Reproductive Health Sciences, (Male Infertility Clinic) at JPMC, Karachi from October 2015 to May 2016.

Materials and Methods: This study was conducted on 100 married males which are divided into two major groups, Group A (control group) and Group B (case group). Group A contains 25 subjects married fertile males and Group B contains 75 married infertile males which were further subdivided into three subgroups of 25 subject each B1= Azoospermia, B2 =Oligospermia and B3=Others. Semen Analysis was done using WHO criteria and BMI was done by dividing the subjects into three groups, 18.5-24.9 kg/m^2 (normal weight), 25-29.9 kg/m^2 (overweight) and >or= 30 kg/m^2 (obese) and by measuring the waist circumference of the subjects.

Results: The BMI examination of case and control showed a significant positive association with abnormal morphology across all the groups with the $p < 0.05$ and negative association of BMI with sperm count, pH, motility activity and normal morphology.

Conclusion: This study showed a strong positive significant association between BMI and Semen Parameters in male infertility as fertility is reduced in men with increased BMI which is the risk factors that influences the quality of semen.

Key Words: BMI, Obesity Semen Analysis, Male Infertility.

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INTRODUCTION

Over weight in men appears to be one of the most neglected issues in the diagnosis of infertility. Obesity is define as deposition of excessive amount of adipose issues which produce ill health effect and is categorized as body mass index (BMI) and the person is suffering from obesity if their BMI exceeds 30 kg/m2 (WHO,2010).[1]

Obesity is considered to be the risk factor in female infertility, but for its importance in male infertility there is no consensus found on this relation till present (Martini et al., 2010)[2] and its effects on semen parameters are less evident (Alshahrani.S et al.,2016)[3]. There are several methods to assess obesity which encompass body mass index (BMI), skin folds caliper measurements, waist circumference and waist to hip ratio (Akindele M et al., 2016)[4]. Weight is categorized by body mass index (BMI) into: underweight (18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2) and Obese (>30kg/m^2) according to international classification of Adult Weight Status (Moore .S et al., 2010)[5].

Spermatogenesis and sperm quality is vital for male fertility and any disturbances in the process of spermatogenesis leads to the infertility in male (Zhang E, et al, 2014)[6]. Male infertility is define as when a male is unable to achieve pregnancy with a fertile female (Hirsh, 2003)[7]. The reason of infertility in men is diversified in different situations. It is strongly affected by three main factors i.e. lifestyle, environmental and nutritional and the main causes of infertility are low sperm count ,Endocrine problems, Drugs, Infections and Radiations.(Treeds et al., 2011)[8] and the effect of obesity on the health are devastating and are related to future cardiovascular diseases, diabetes and cancers (XU X et al., 2016)[9] and male factor is responsible for 8-15% of couples (WHO

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2010)[1] .Infertility affects around 48.5 millions couples worldwide (Datta J, et al, 2016),[10] however, no underlying cause can be identified for primary or secondary infertility in approximately 25% of couples (Arcaniolo D et al .,2014)[11]

The relationship between semen parameters and BMI is present and it is due to the derangement in the male reproductive hormone profile and obesity is linked with poor semen quality and male infertility (Davidson L, et al, 2015)[12] and in this study we evaluated the relation between BMI and semen parameters (semen volume, sperm concentration, motility and morphology), in male infertility.

MATERIALS AND METHODS

This case control study was conducted in the Department of Physiology, Basic Medical Sciences Institute in collaboration with Reproductive health sciences (Male Infertility Clinic) at Jinnah Post Graduate Medical Centre Karachi and approval was taken from ethical committee of BMSI, JPMC Karachi for conducting the research (Ref.No.F.1-2/BMSI-E.COMT/040/JPMC)

One hundred subjects were selected from RHS A centre, Department of Obstetrics and Gynaecology, JPMC, Karachi. They are divided into two groups, Group A (control group) = Fertile married males (25 subjects) Group B (case group) = Infertile married males (75 subjects) is further subdivided into three groups

B1= Azoospermia (25 subjects)

B2=Oligospermia (25 subjects)

B3=Asthenospermia, Aspermia, Necrospermia, Oligoasthenospermia, Teratospermia (25 subjects)

Determination of Biophysical and Biochemical Parameters

Biophysical Parameters

1. Age (years)
2. Body Mass Index (BMI) (kg/m^2)
3. Waist Circumference if BMI > than 30.

Biochemical Parameters

1. Semen Analysis.

Selection Criteria

Married males aged between 18-45 years, living with their reproductively healthy wives and having unprotected sex. There is no restriction of socioeconomic status. Unmarried males and those suffering from any chronic diseases are excluded from this study.

A detailed history was taken on questionnaire with their informed consent, the examination was performed by a reproductive health expert and two types of samples (blood and Semen were collected.

Semen analysis was done according to WHO manual 2010, Analysis was done an hour after the collection of semen by a method prescribed in the WHO manual and the physical (Liquefacation, Volume, Color, Consistency, pH) and microscopic (Sperm count, Morphology and Motility) was estimated.

Normal Semen Parameters

WHO MANUAL (2010)

Semen Parameters With Lower Reference Limits

Sperm volume (ml)	1.5
Sperm concentration (10^5/ml)	15
Total sperm number (10^5/ejaculate)	39
Progressive motility (PR,%)	32
Total motility (PR+NP,%)	40
Vitality (live sperm,%)	58
Sperm morphology (NF,%)	4
pH	>/= 7.2

BMI was measured using the standard formula kg/m^2 and waist circumference was measured if BMI is greater than 30.

Category BMI range (kg/m^2)

Underweight <18.5

Normal range 18.5-24.9

Overweight 25.0-29.9

Obese $\geq$ 30

Waist Circumference if BMI > 30. (WHO, 2013).

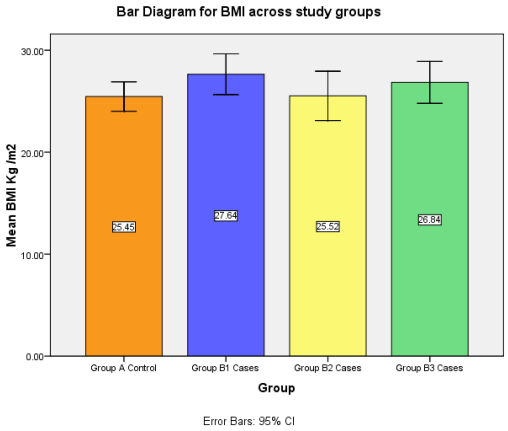
Data was stored and analyzed using SPSS 16. Counts with percentages were reported for different Variables. Mean and standard deviations were given for all quantitative variables like age in years, BMI and Sperm count. ANOVA test was applied.

RESULTS

In this case control study, we investigated subjects attending the male infertility clinic at RHS centre, JPMC.

Table 1 shows the basic information of biophysical parameters and their association across all the study groups. Table 2 shows the comparison of BMI among the groups. Table 3 shows the comparison of seminal parameters between case and control groups

Table 4 shows the correlation of BMI with the semen parameters.



Graph No.1: Error Bar Diagram

Table No.1: Physical parameters of control and case groups

Parameters	Control Group A (Fertile) n=25		Case Group B (Infertile) - n=75						P value
	Group A - n=25 Proven Father		Group B1 - n=25 Azoospermia		Group B2 - n=25 Oligospermia		Group B3 - n=25 Others		
	n	%	n	%	n	%	n	%	
Age(years)									0.60
Less or Equal to 35 Years	17	68	13	52	17	68	15	60	
More than 35 yrs	8	32	12	48	8	32	10	40	
BMI(Kg/m^2)									0.049*
Under 18.5 Under weight	-	-	1	4	4	16	-	-	
18.5-24.9 Normal	12	48	7	28	9	36	10	40	
25-29.9 Over weight	11	44	9	36	6	24	12	48	
Over 30 Obese	2	8	8	32	6	24	3	12	
Examination									<0.01*
Normal	25	100	22	88	20	80	15	60	
Have Problem	-	-	3	12	5	20	10	40	

Table No.2: Comparison of physical parameters between case and Control Groups

Parameters	Control Group A **(Fertile) n=25**	Cases Group B **(Infertile) n=75**			P value
	Group A n=25 Proven Father Mean±S.D	Group B1 n=25 Azoospermia Mean±S.D	Group B2 n=25 Oligospermia Mean±S.D	Group B3 n=25 Others Mean±S.D	
BMI(Kg/m2)	25.45±3.5	27.63±4.85	25.51±5.86	26.84±4.99	0.316
*p<0.05 was considered significant using ANOVA					

Table No.3: Comparison of Seminal Parameters between case and control groups

Parameters	Control Group A **(Fertile) n=25**	Cases Group B **(Infertile) n=75**			P value
	Group A n=25 Proven Father Mean±S.D	Group B1 n=25 Azoospermia Mean±S.D	Group B2 n=25 Oligospermia Mean±S.D	Group B3 n=25 Others Mean±S.D	
Volume(ml)	2.38±0.7	2±1.16	2.59±1.2	1.94±1.41	0.144
PH	8.1±0.36	7.8±0.46	7.79±0.33	7.97±0.43	0.018*
Motility Activity(%)	0.64±0.17	0 ±0	0.25±0.24	0.37±0.3	<0.01*
Morphology Normal(%)	0.64±0.16	0±0	0.27±0.26	0.43±0.29	<0.01*
Morphology Abnormal(%)	0.35±0.16	0±0	0.61±0.28	0.57±0.28	<0.01*
Sperm million/ml	77.92±27.02	0±0	8.2±5.52	28.78±30.84	<0.01*
*p<0.05 was considered significant using ANOVA					

Table 1 gives the basic information of the study samples; it was found that, 68% samples of control group fall in age group of less or equal to thirty five years old, 36% sample of azoospermia group were found overweight. 48% Azoospermia cases were found with age more than thirty five years old however p=0.60 gives the evidence that there was no significant association between age and study groups.

It was found that more cases of oligospermia were underweight that gives the significant association of

BMI with studied group. 40% of the samples during examination found with problem in others group while 88% samples were found normal in azoospermia group, 80% sample found with normal examination in oligospermia group, p-value <0.01 gives the significant association of studied groups with examination.

Table 2 gives the mean and standard deviation of BMI with testing of mean across studied group using one way ANOVA, it was found that, BMI across all four groups was found same on average with p value 0.316.

Table 3 showed that, PH was high in proven father on average and in other groups it was getting down, a significant change across the four groups was found with p=0.018

The mean and standard deviation of motility activity (%), morphology normal (%) and morphology abnormal, a significant p-value gives the evidence that mean values of these parameters were varying across the groups. Mean sperms in oligospermia groups was lowest, then in other, as compare to proven father, p<0.01 declared that sperms count varying significantly across the groups.

Table No.4: Correlation of BMI with Semen parameters

Spearman Rank Correlation with BMI	r	p-value
Volume (ml)	0.129	0.20
Viscocity	0.138	0.17
PH	-0.19	0.06
Colour	0.233	0.024*
Motility Activity %	-0.096	0.43
SPERM Count (million/ml)	0.043	0.71
Morphology Normal %	-0.187	0.12
Morphology Abnormal %	0.271	0.03*
*p<0.05 considered as significant		

Table 4 reports the correlation values of semen parameters with BMI, it was found that, BMI gives 23.3% significant positive association with color and 27.1% significant positive association with abnormal morphology, with p value less than 0.05, PH gives negative relation with BMI, Motility activity, and morphology Normal, however they all parameters did not give any significant association with BMI, correlation values with their significance are reported.

DISCUSSION

In this case control study we had investigated the subjects of male infertility attending the male infertility clinic at RHS a centre, JPMC. The main aim of our study was to assess the role of BMI on semen parameters and find out its association with them. Very few studies have been conducted on male infertility in Pakistan as it is the most neglected issue of the society and male are absconded to be a part of it. In our study we observed that there was a strong positive association of BMI with some semen parameters and negative association with others. Guo, et al, 2017[13] suggested that metabolites alterations in seminal plasma may be the mediator of obesity and abnormal semen quality. Anderson, et al, 2016[14] showed in their study that BMI affects the fatty acid composition of spermatozoa through regulation of fatty acid metabolism in the testis and therefore results in the abnormal semen parameters. Wen-Hao, et al, 2015[15] in their study suggested that obesity and metabolic syndrome are known to have effects on male sexual function and infertility and increasing BMI could influence the quality and quantity of semen and thereby trigger fertility status of male and this is also a result of our study. Petty J, et al, 2014[16] found from their study that decrease in total number of normal motile sperm cells occurred due to increase in BMI which suggested the combined effects of obesity on the sperm cell structure and function which causes the lower fertility in male and not the single parameter alone. Thomsen, et al, 2014[17] also find the association of BMI with the different parameters of semen and that the semen volume is reduced with the increase in BMI due to obesity and male overweight. Hajshafiha, et al, 2013[18] also proved in their study that overweight male are more likely to produce low sperm count and the production of abnormal sperms and this is also in agreement of our study. Tunc and Bakos, 2011[19] also showed that increased BMI was also associated with a fall in sperm concentration and this was also in association of our study. Hanafy, et al, 2010[20] also proved in their study that BMI had a positive correlation with abnormal sper morphology and negative correlation with sperm concentration and motility and this is in agreement with our study. Hammoud and Griffin, 2010[21] also proved that increase in BMI leads to alteration in semen parameters due to the suppression of hypothalamic pituitary-gondal axis by elevated estrogen levels. Hammoud and Gibson, 2008[22] suggested in their study that BMI was associated with low sperm concentration and lows motile perm count as it was also a result of our study.

CONCLUSION

In our study there is a strong association between BMI and different semen parameters and these parameters can be used to find out the cause of male infertility, as obesity decreases the semen quality and quantity resulting in defective spermatogenesis. Our study strongly suggests the significant positive association with color and abnormal morphology, pH gives negative association with BMI.

Author's Contribution:

Concept & Design of Study:	Fareena Khalil Ahmed
Drafting:	Afshan Mehboob Khan, Abdul Shakoor Memon

Data Analysis:	Intesar Burney, Khalida Bano
Revisiting Critically:	Fareena Khalil Ahmed
Final Approval of version:	Fareena Khalil Ahmed

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. World Health Organization, 2010. WHO Laboratory Manual for the Examination and Processing of Human Semen. World Health Organization, 2010.
2. Martini AC, Tissera A, Estofan D, Molina RI, Mangeaud A, de Cuneo MF, et al. Overweight and seminal quality: a study of 794 patients. Fertil Steril 2010;94:1739–1743.
3. Alshahrani S, Ahmed AF, Gabr AH, Abalhassan M, Ahmad G. The impact of body mass index on semen parameters in infertile men Andrologia 2016;48(10):1125-1129.
4. Akindele MO, Phillips JS, Igumbor EU. The relationship between body fat percentage and body mass index in overweight and obese individuals in an urban African setting J. Publ. Health Africa 2016;7(1):515.
5. Moore SJN, Hall S, Harper JW. Lynch Global and national socioeconomic disparities in obesity, overweight, and underweight status. J Obes 2010; 10.1155/2010/514674.
6. Zhang E, Zhang H, Zang Z, Chen J, Zhang B. Association of Body Mass Index with Semen Quality and Sexual Hormone Levels among Men in Intrauterine Insemination. Sci Res 2014;6:1861-1865.
7. Hirsh A. Male subfertility. Br Med J. 2003; 327(7416):669-672.125.
8. Teerds KJ, de Rooij DG, Keijer J. Functional relationship between obesity and male reproduction: from humans to animal models. Hum. Reprod. Update 2011;17(5):667–83.
9. Xu X, Zhou L, Miao R, Chen W, Zhou Y, Pang Q, Qu K, Liu C. Association of cancer mortality with postdiagnosis overweight and obesity using body mass index. Oncotarget 2016;7:5023–29.
10. Datta J, Palmer MJ, Tanton C, et al .Prevalence of infertility and help seeking among 15 000 women and men Hum. Reprod 2016;31(9): 2108-2118.
11. Arcaniolo DV. Favilla D. Tiscione, et al. Is there a place for nutritional supplements in the treatment of idiopathic male infertility? Arch Ital di Urol e Androl 2014;86(3):164,
12. Davidson LM, Millar K, Jones C, Fatum M, Coward K. Deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermato-genesis and male fertility Hum. Fertil 2015;18(3):184-193,
13. Guo D, Wu W, Tang Q, Qiao S, Chen Y, Chen M, et al. The impact of BMI on sperm parameters and the metabolite changes of seminal plasma concomitantly. Oncotarget 2017;8(30):48619-48634.
14. Andersen JM, Rønning PO, Herning H, Bekken SD, Haugen TB, et al. Fatty acid composition of spermatozoa is associated with BMI and with semen quality. Androl 2016;4:857–865.
15. Wen HT, Xin JZ, Lu M, Jie Q, Kai H, Lian MZ, et al. Correlation between body mass index and semen quality in male infertility patients. Turk J Med Sci 2015;45: 1300-1305.
16. Petty J, Jabara S, Prien S, Penrose L. Obesity Appears to Impact Male Fertility by Degrading Overall Semen Quality Rather than Individual Semen Parameters. Open J Obstet and Gynaecol 2014;4:917- 923.
17. Thomsen L, Humaidan P, Bungum L, Bungum M. The impact of male overweight on semen quality and outcome of assisted reproduction. Asian J Androl 2014;16:749–754.
18. Hajshafiha M, Ghareaghaji R, Salemi S, Sadegh-Asadi N, Sadeghi-Bazargani H. Association of body mass index with some fertility markers among male partners of infertile couples. Int J General Med 2013:6:447–451.
19. Tunc O, Bakos HW, Tremellen K. Impact of body mass index on seminal oxidative stress. Andrologia 2011;43:121–128.
20. Hanafy ER, Ali ME. Semen parameters and hormonal profile in obese fertile and infertile males. Fertil Steril 2010; 94(2):581-584.
21. Hammoud AO, Griffin J. Association of aromatase (TTTAn) repeats polymorphism length and the relationship between obesity and decreased sperm concentration. Hum Reprod 2010; 25(12):3146-3151.
22. Hammoud AO, Gibson M. Impact of male obesity on infertility: a critical review of the current literature. Fertil Steril 2008; 90(4):897-904.

Original Article

Prevalence of HIV Infection Among Tuberculosis Patients in Sindh, Pakistan

HIV Infection Among Tuberculosis Patients

Shafi Muhammad Khuawar[1], Arshad Hussain Laghari[2] and Akhtar Hussain Samoo[3]

ABSTRACT

Objective: To determine the occurrence of HIV infection among tuberculosis patients in Sindh, Pakistan.
Study Design: A cross sectional record analysis study.
Place and Duration of Study: This study was conducted at the department of Pulmonology and department of Biochemistry Ghulam Muhammad Mahar Medical College, Sukkur covering the period from January 2014 to October,2018.
Materials and Methods: Diagnosis of TB was performed by AFB smear and X-ray chest. For the screening of HIV, Chromatographic test was performed and for substantiation of HIV ELISA technique were used.
Results: Overall 3410 TB patients were analyzed and 13.9% HIV positive were detected. Of these 3410 patients, 39% had pulmonary Tuberculosis and 42% had extra pulmonary Tuberculosis (EPTB).
Conclusion: The commonness of HIV- Tuberculosis co-infection was 13.9%. Both male and female patients were affected.
Key Words: Prevalence, HIV, Pulmonary tuberculosis, co-infection.

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INTRODUCTION

TB is one of the leading infection cause mortality as weigh against to other infections disease of humankind particularly in rustic areas of developing countries[1]. TB is most spreading and has high mortality rate. It is reported that the rate of deaths due to TB is very high in developing countries[2]. As for as Pakistan is concern, it is not possible to present exact data of TB and TB related deaths due to the insufficiency of disease surveillance[3, 4].

South East Asia in known to have the highest TB burden in world, and about 35% of global TB incidence was reported. According to a report published in 2010 by WHO which shows that 2.0 million people are infected in India from 9.4 million TB patients worldwide[5, 6]. It was also shown in report that among 2 million 1.1 million were HIV positive. Further, it is observed that Pakistan was listed in global list of 41 countries which have highest ratio of TB with HIV infection, and Indonesia Myanmar and Thailand was top most[8]. It is also observed that people are more prone to active TB infection with HIV[9].

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The co-infection of HIV-TB with multi drug resistant TB harshly aggravates the humankind Tuberculosis circumstances[10]. Tuberculosis was most foremost grounds of loss in patients with HIV infection and HIV infection is the most effective jeopardy issue for developing active TB disease from a latent tuberculosis infection[11, 12].

It is alarming that occurrence of HIV infection with Tuberculosis in Southeast Asia was 41.2%. Where as in china is only 0.5%[13]. The occurrence of HIV infection with Tuberculosis in Kenya was 44%, 9% of TB patients were HIV positive in USA[14]. There is no such data accessible about the prevalence of co-infection of HIV-TB in Pakistan and particularly in Sind province of Pakistan. Therefore, this study was conducted to analyzed HIV-TB[15, 16].

MATERIALS AND METHODS

This cross-sectional study were design at Ghulam Muhammad Mahar Medical college (GMMMC) Teaching Hospital of Sukkur, Sindh from January 2014 to October, 2018. The patients were included in present study after gave their consent for the analysis of HIV. All patients were recruited from OPD of pulmonary diseases of GMMMC teaching hospital, Sukkur. All individual data, such as age, sex, socioeconomic surroundings, schooling Level, occupation, and history of any surgery or blood transfusion were collected. The TB has been diagnosed by using AFB Sputum smear and by FNAC/biopsy in patient expected with extra pulmonary tuberculosis (EPTB). For screening of HIV initially chromatographic technique were followed by the ELLSA and PCR. Age group were included in this study is 18-60 Year.

RESULTS

Total 3410 patients with Tuberculosis infection were investigated in present study, of the 3410 patients 2010 were males and 1400 were females. Total 13.9% of these patients were HIV positive, including 11.3% males and 2.6% females; 42% of the HIV-positive cases had pulmonary tuberculosis, whereas 58% patients had extra pulmonary tuberculosis. The most commonly affected age group was 33 - 48 years.

Table No.1: HIV Co-infection among Tuberculosis patients (n = 3410)

HIV Co-infection among TB patients (n = 3410)	
Type of TB	HIV Positive
Pulmonary TB	42 %
Extra Pulmonary TB	58 %
Total HIV Positive	13.9 %

n = Total number of TB patients

All the HIV positive cases patients presented with cough, to be had fever, loss of hunger with weight loss, accessible with dyspnea, hemoptysis,and chest pain.

Table No.2: Clinical presentation of the co-infected patients

Clinical presentation of the co-infected patients	
Symptoms	Percentage
Cough	90
Fever	78
Loss of appetite	76
Weight los	76
Dyspnea	44
Hemoptysis	14
Chest pain	10

Table No.3: Presentations of Extra Pulmonary Tuberculosis

Presentations of EPTB.	
Extra pulmonary presentation of TB	Percentage
Pleural effusion	60.7
Lymphadenopathy	25.0
Pericardial effusion	7.1
CNS TB	3.6
Bone Tb	3.6

DISCUSSION

In present study, we observed that 13.9% patients have co-infection in Sindh, Pakistan which was significantly alarming. A similar study was conducted in India in 2000 shown low prevalence than presented HIV-TB co-infection study[17]. It had shown 10.91% prevalence which is lower than this study[18]. Another study of India from 1996 to 2001 shown the prevalence in Alighar a states of India has 0.8% to 2.8% prevalence. In this study it was observed that in Sindh, Pakistan there is a higher HIV-TB co-infection in Males than Females. HIV-TB co-Infection ratio has also reported in other part of the world[19]. Apart from for a few countries in Africa, the occurrence of co-infection has been reported to be elevated among males than females. But almost all other countries, there is title dissimilarity in the sexual category proportion[20]. In many studies that gave been conducted in different parts of Hindustan have indicated considerably elevated HIV-TB co-infection in Males than in Females patients. The findings of the present study align with that pattern of India and of few countries in Africa. Moreover, in this present study, we observed that the age group which more frequently infected with HIV- TB co-infection is between 33-48 year in both males and females[21]. It is also align with other studies of world and in particularly to India. Almost all the patient was infected with HIV- TB co-infection were belonging to low socio-economic background[22]. The present study indicates that there is need to imperceptible change in society to improve the Health of people, particularly remote area of the countries. There are needs in public awareness and better treatment regimes[23, 24].

CONCLUSION

The prevalence of HIV-TB co-infection was 13.9%. Consequently, all TB patients should be assessed for HIV risk factors and counseled to undergo HIV testing. Males patients are more often infected with HIV-TB co-infection than females. Ages from 33 years to 48 years are more often infected with TB and also have co-infection with HIV. Results of this study are alarming and needs betterment in public awareness and treatment regimes.

Author's Contribution:

Concept & Design of Study:	Shafi Muhammad Khuawar
Drafting:	Arshad Hussain Laghari
Data Analysis:	Akhtar Hussain Samoo
Revisiting Critically:	Shafi Muhammad Khuawar
Final Approval of version:	Shafi Muhammad Khuawar

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. HIV Surveillance among Tuberculosis Patients in the South. East Asia Region World Health Organization Report, New Delhi; 2006.p.11-34.
2. Tb India 2011, Revised National Tb Control Programme Government of India Annual Status Report. Chapter 1: Tuberculosis Burden, 2011.
3. Pennap G, Makpa S, Ogbu 5. Sero-prevalence of HIV infection among tuberculosis patients in rural tuberculosis referral clinic in northern Nigeria. Pan Afri Med J 2010;5:22.

4. HIV testing and treatment among tuberculosis patients- Kenya, 2006-2009. Morbidity Mortality weekly Report MMWR 2010;59(46):1513-7.
5. Wang L, Liu W, Wang LU, Wang YWZ. HIV prevalence among pulmonary tuberculosis patients in Guangxl. China journal of Acquired immune Deficiency Syndrome 2010;53(Suppl 1):561.
6. Reported HIV Status of Tuberculosis Patients- united States, 1993-5005. Morbidity and Mortality Weekly Report. MMWR 2007;56(42):1103-6.
7. Thanh DH, Sy Din, Linh ND, Hoan TM, Dien HT, Thuy TB, et al. HIV Infection amont tuberculosis notification rates. The international journal of Tuberculosis and Lung Disease 2010;14(8):986-93.
8. Gleht C, Roy RB, Kneliwolf AL. The situation of HIV /M. tuberculosis co-infection in Europe. The Open Infections Disease J 2011;5(Suppl- M3): 21-35.
9. Jain SK, Aggarwal JK, Rajpal, Baveja U. Prevalence of HIV infection among tuberculosis patients in Delhi –A sentinel surveillance study. Ind J Tuberculosis 2000;47:21-6.
10. Ramachandran R, Datta M, Subramani R, Baskaran G, Paramasivan CN, Swaminathan 5. Sero prevalence of human immunodeficiency virus (HIV) infection among tuberculosis patients in Tamil Nadu. Ind J Med Res 2003;118:147-51.
11. Swaminathan, S, Ramachandran R, Baskaran G, Paramasivan CN, Ramanathan U, venkatesan P, et al. Risk of development of tuberculosis in HIV-infection patients. Int J Tuberculosis and Lung Dis 2000;4(9):839-44.
12. Mohanty KC, Basheer PM. Changing trend of HIV infection and tuberculosis in Bombay area since 1988. Ind J Tuberculosis 1995;42:117-20.
13. Tripathi S, joshi DR, Mehendale SM, Menon P, Joshi AN, Ghorpade SV, et al. Sentinel surveillance for HIV infection in tuberculosis patients in India. Ind J Tuberculosis 2002;49: 17-20.
14. Bahl R, Singh R, Singh R. Prevalence of HIV infection among patients of pulmonary tuberculosis attending chest disease hospital, Jammu (Jammu and Kashmir), Ind J Comm Med 2007:32(4) 288-9.
15. Khare KC HIV seropositivity in pulmonary tuberculosis patients in Indore, Madhya Pradesh Ind J Tuberculosis 2001; 48 (2) 153-4.
16. Ahmed Z, Bhargava R, Pandey DK, Sharma K. HIV infection seroprevalence in tuberculosis patients. Ind J Tuberculosis 2003;50:151-4.
17. Prased R. Sainin Jk, Kannaujia RK, Sarin S, Suryakant, Kulshreshth R, et al. Trend of HIV infection in patients in patients with pulmonary tuberculosis in Lucknow area. Ind J Tuberculosis 200;50;39-41.
18. Susheel B, Pal. HIV and tuberculosis, Ind J Tuberculosis 2006;53;43-6.
19. Vasuderiah V. HIV infection among tuberculosis patients. Ind J Tuberculosis 1997;44;97-8.
20. Narain JP, ying-Ru Lo. Epidemiology of HIV- TB in Asia. Ind J Medical Research 2004;120:277-89.\
21. Yanal H, Uthaivarovit W, panich V, Sawanpanyalert P, Chaimanee B, Akarasewl P, et al. Rapid Increase in HIV- related tuberculosis, Chiang Ral, Thailand, 1990-1994. AIDS 1996;10:527-31.
22. Fernandes 1, Lawande D, Mesquita AM. Prevalence of human immunodeficiency virus infection in tuberculosis 2002;49:235-6.
23. Patel AK, Thakrar SJ, Ghanchi FD. Clinical and laboratory profile of patients. Lung Ind 2011;28 (2):93-6.
24. Sharma Sk. Kadhiravan T, Banga A, Goyat T, Bhatia 1, Saha PK. Spectrum of clinical disease in a series of 135 hospitalised HIV-infection patients from North India. BMC Infections Dis 200;4:52.

Original Article

The Preventive Role of Vitamin E Against Imatinib Induced Toxicity on Liver of Albino Rats: A Histomorphometric Study

Nighat Ara, Farooq Khan, Noman Ullah Wazir, Fahad Ullah, Ambereen Hamayun and Riffat Shameem

ABSTRACT

Objective: To observe changes in the histology of hepatic tissue of Albino rats exposed to the oral administration of toxic doses of Imatinib and to assess the protective effect of vitamin E.

Study Design: Analytical experimental randomized control study.

Place and Duration of Study: This study was conducted at the Department of Anatomy, Peshawar Medical College Peshawar from February 2013 to July 2013.

Materials and Methods: This study of twenty four male albino rats was conducted at PCSIR lab complex and Peshawar Medical College, Peshawar. Rats were randomly divided into three groups, one control and two experimental groups. Experimental group I were treated with the oral administration of Imatinib for two weeks and experimental group II were treated with the oral administration of same dose of Imatinib with the concomitant administration of vitamin E. Haematoxilin and Eosin used for routine examination Masson Trichrome for hepatocellular necrosis and fibrosis.

Results: Scoring system was applied to evaluate the degree of toxic effect of Imatinib on the hepatic tissue of rats. The degree (no change, mild to moderate change and marked change) of hepatocelluler necrosis were observed. It is concluded that the most affected rats were those treated with Imatinib i.e. experimental I. Rats in experimental II, which received antioxidant in addition to Imatinib were least affected, thus conforming the protective role of vitamin E.

Conclusion: The simultaneous use of antioxidant vitamin E with Imatinib could prevent the hepatic toxicity which includes hepatocelluler necrosis.

Key Words: Imatinib, Hepatic tissue, Multifocal hepatocelluler necrosis, Vitamin E

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INTRODUCTION

Chemotherapy for cancer defines as the chemical agents use to stop the growth of cancer cell even at sites distant from the origin of primary tumor. However, since these agents do not distinguish between a cancer and a normal cell, they not only eliminate the fast growing cancer cells but also other fast growing normal cells e.g. the hair and blood cells.[1,2]

Imatinib is an anticancerous drug it was initially marketed by Novartis with the trade name of Gleevec. It is a tyrosine - kinase inhibitor that is used in the treatment of multiple cancers, most notably Philadelphia chromosomes positive (Ph+) chronic myelogenous leukemia (CML) as well as in gastrointestinal tumors.[3]

Hepatic toxicities were seen in the dogs after a two week course of Imatinib, in which mild multifocal hepatocelluler necrosis, single cell bile duct necrosis and bile duct hyperplasia. Bile duct hyperplasia remains after the recovery duration of four weeks and that was related with peribiliary fibrosis.[4]

Swelling of hepatocytes, diffuse parenchymal congestion, dilations of central vein and portal tract infiltration were also demonstrated in the patients treated with Imatinib.[5-9] Vitamin E is an important fat soluble natural nutrient . Vitamin E consists of eight forms in which alpha tochopherol is the most important natural nutrient in the human body. Vitamin E serves the body as an anti-oxidant and is also used in regulating the gene expression, cell signaling and function immuning.[10]

Antioxidants individually protect normal cells against some of the toxicities produced by the chemotherapeutic agents.[11]In animal studies, various preparations like vitamin E, vitamin C, vitamin B_6 have

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been studied, which combat or reverse the oxidative damage. Now a day, a lot of attention is being paid on the use of natural antioxidants because of their fewer side effects, and easy and cheap availability.[12]

This research project was designed to see the effects of vitamin E, if any, on the histoarchitecture of hepatic tissue of rats subjected to toxic doses of Imatinib for a period that had induced changes otherwise in the hepatocytes.

MATERIALS AND METHODS

Twenty four male albino rats were obtained from Pharmacy Department of Peshawar University. They were kept in the pharmacy department of PCSIR lab for further experiment. The rest of study was carried out in the Anatomy and Pathology department of Peshawar Medical College. Rats with any disease prior to the onset of experiment, or the ones that developed disease during the study were excluded. Eight weeks old healthy male albino rats of Sprague-Dawley strain weighing 150 to 200 gram were selected for the study. The rats were randomly divided in to three groups; one control and two experimental groups with eight rats in each group. Control group comprised of 8 rats fed on standard diet.Experimental group I comprised of 8 rats fed on standard diet, oral administration of Imatinib solution (50 mg /kg /day) 6 days a week for a period of 2 weeks. Experimental group II comprised of 8 rats fed on standard diet, oral administration of Imatinib solution (50mg/kg/day), vitamin E (500mg/kg/day) 6 days a week for a period of 2 weeks. All three groups of rats were sacrificed after completed 2 weeks to observe any morphological change in the liver due to Imatinib toxicity and possible protective role of Vitamin E.After sacrificed proper abdominal dissection was done abdominal visceras are identify and liver was remove carefully. The liver tissue was processed and then stain with the (a Haematoxalin and eosin for routine examination (b) and Masson Trichrome for demonstration of collagen fibers.

The microscopic examination of the liver sections of experimental group revealed several histological changes including, multifocal hepatocellular necrosis, dilatation and congestion of central veins and blood sinusoids were observed. These changes were ameliorated by vitamin E administration. Data analysis was conducted with statistical software SPSS.20. Significance was calculated by using Chi square test and was defined as P value <0.05.

RESULTS

The current study was conducted to observe the Imatinib induced histomorphological change in the liver of male albino rats and to find out any possible protective role of vitamin E. Animal were grouped in control, experimental group I(treated only with Imatinib for 2 weeks) and experimental group II (treated with Imatinib and vitamin E for 2 weeks).

A scoring system was applied to evaluate and standardize the degree of toxic effect of Imatinib on the hepatic tissue of experimental animal. Under this scoring system, the degree (no change, mild to moderate change and marked change) of multifocal hepatocelluler necrosis was observed. The scores given were: No change (0), mild to moderate change (1) and marked change (2).[13,14]

Multifocal hepatocelluler necrosis was found to be one of the most common findings seen in the Imatinib induced hepatic toxicities. Based on several observations, 6 animals out of 8 (75%) from experimental II group (Imatinib+Vit E treated) and 2 out of 8(25%) of experimental group I (Imatinib treated) presented with hepatocelluler necrosis of grade 1 (mild to moderate change).

While 1 animal out of 8 (12.5%) of experimental group II(Imatinib+ Vit E treated) did not reveal any hepatocelluler necrosis. The degree of severity was, marked grade 2 in 6 animal out of 8 (75%) of experimental group I (Imatinib treated)and 1 animal out of 8 (12.5%) of experimental group II(Imatinib+Vit E treated).

From the aforementioned results regarding the hepatocelluler necrosis, it is concluded that the most affected animals were those treated with Imatinib i.e. group I. The animals in experimental group II, which received antioxidant in addition to Imatinib were least effected, thus conforming the protective role of vitamin E. The Chi- square test was applied, and the P value (0.002) was highly significant.

Table No.1: Degree of multifocal hepatocellular necrosis

Degree of necrosis	Control Group	Experi-mental Group I	Experimental Group II	Total	P value
Normal	7 (87%)	-	1 (13%)	8 (33.33%)	0.005
Mild to moderate change	1 (13%)	2 (25%)	6 (75%)	9 (37.5%)	0.024
Marked change	-	6 (75 %)	1 (13%)	7 (29.16%)	0.002

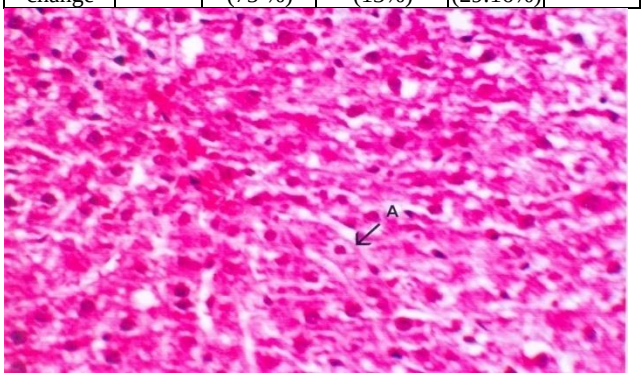

Figure No.1: Photomicrograph of 5 µm thick section of rat liver from control group showing cords of intact hepatocytes (A) H&E staining, 600 X.

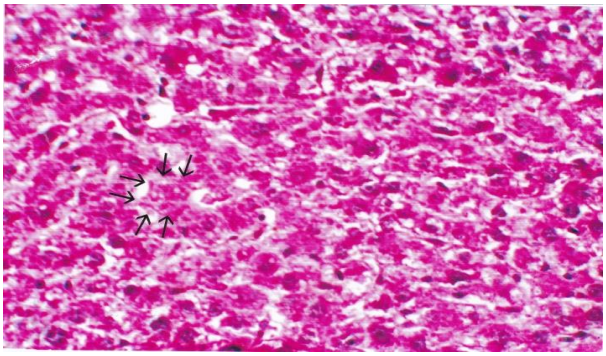

Figure No.2: Photomicrograph of 5 µm thick section of rat liver from experimental group II showing multifocal hepatocelluler necrosis of mild to moderate degree (multiple arrows) H&E stain, 300X.

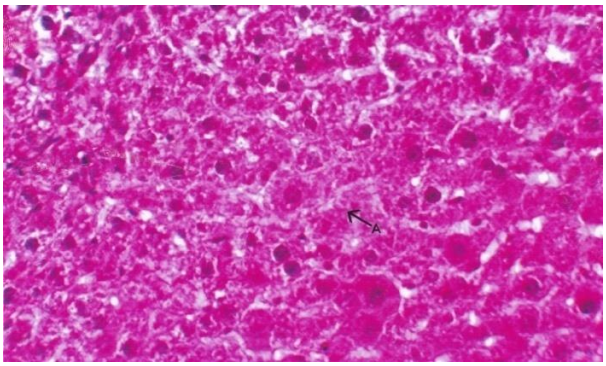

Figure No.3: Photomicrograph of 5 µm thick section of rat liver from experimental group I showing hepatocelluler necrosis of marked degree (A) H&Estain,900 X.

DISCUSSION

In developing countries like Pakistan humans are suffering from different types of cancers. It continues to represent the largest cause of mortality in the world and claims over 6 million lives every year.[15]Chemotherapy is one of the conservative treatments of this harmful disease. It is not found to be safe because of the side effects of the drugs on the healthy tissue. The liver being the first organ to be exposed to these therapeutic agents tends to be transformed and clean these agents, and while doing so, it is susceptible to the toxic effects of these agents. These drugs therefore, even introduced within the therapeutic ranges, may injure the organ.Among these chemotherapeutic agents, Imatinib mesylate is the only effective and approved systemic agent for the treatment of patient with advanced gastrointestinal tumors and chronic myeloid leukemia. To reduce the adverse effects of Imatinib during the chemotherapy co administration of antioxidant such as vitamin E have been proved to be beneficial, although very limited studies have been conducted in this regard.The present study was conducted to evaluate the toxic effects of Imatinib on hepatic tissues of albino rats and to observe the protective role of vitamin E, against Imatinib induced histological changes in the rat's hepatic tissues. For this purpose 24 male albino rats were selected. Rats were randomly divided into a control, and two experimental groups, receiving Imatinib only (group I) and Imatinib simultaneously with vitamin E (group II) respectively.

In the present study multifocal hepatocelluler necrosis was found to be one of the most common findings in the hepatic tissue of rats of both experimental groups. Based on several observations, the degree of hepatocelluler necrosis was mild to moderate in 75% of group C animals, moreover, 75% of group B animals have also shown changes though the degree of change in this group was marked hepatocelluler necrosis.

Therefore our findings are in accord with the result of a study conducted by Monovaet al[4] who recorded hepatic toxicities in animals after two weeks course of Imatinib which includes hepatocelluler necrosis.

The results of present study also corresponds to a recent case report which was presented by Tonyali et al[16] about a patient of gastrointestinal tumor who was treated with Imatinib, and developed hepatotoxicity and histological changes consist of inflammation and multifocal necrosis right after six month of treatment with Imatinib.

The results of current studies are also in agreement with a study conducted by Guilhot[17], which revealed that Imatinib treatment is toxic in the patients of chronic myeloid leukemia and causes acute liver failure and histopathological findings demonstrating cytolytic hepatitis with necrosis, and portal and lobular inflammation.

The present study is also being supported by another study conducted by a Kong et al[18], according to whom during adjuvant Imatinib treatment in a patient with Gastrointestinal tumor hepatotoxicity was observed in about 2–5% of patients receiving Imatinib. Histological changes described in some of these cases consist of inflammation, fatty degeneration and necrosis of the liver.[19]

This study is in the conformity with the study done by Talpaz et al[20], who found four out of 50 CML patients who were treated with the Imatinib, their liver biopsy revealed focal necrosis of hepatocytes and mild infiltration of hepatocytes around the necrosis.

At the same time our study is in agreement with the study done by Kedaret al.[21]They reported that alpha tocopheryl Succinate alone and with dietary micro-nutrients can be very useful as an supplement to cancer therapy by increasing tumor response and possibly decreasing some of the toxicities of cancer chemotherapy to normal cells.

Our study is also in agreement with the several clinical studies conducted by Siejaet al[22],Pace et al[23],Conklin et al[24],Branda et al[25], Bairati et al[26] and Ferreiraet al[27]who have reported that supplemental anti-oxidants with

dietary nutrients were very useful in decreasing the side effects of chemotherapy in cancerous patient.

CONCLUSION

The simultaneous use of antioxidant vitamin E could prevent the hepatic toxicity which includes multifocal hepatocelluler necrosis.

Author's Contribution:

Concept & Design of Study:	Nighat Ara
Drafting:	Farooq Khan, Noman Ullah Wazir
Data Analysis:	Fahad Ullah, Ambereen Hamayun, Riffat Shameem
Revisiting Critically:	Nighat Ara
Final Approval of version:	Nighat Ara

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer—the results of 20 years of follow-up.. N Eng J Med 1995 ;332(14):901-6.
2. De Graaf H, Willemse P, Bong S, Piersma H, Tjabbes T, Van Veelen H, et al. Dose intensity of standard adjuvant CMF with granulocyte colony-stimulating factor for premenopausal patients with node-positive breast cancer. Oncol 1996;53(4): 289-94.
3. Novartis Pharma AG. Gleevec (Imatinib mesylate) tablets prescribing information. East Hanover, NJ, Anon. Drugs of choice for cancer. Treated Guidel Med Lett 2006;1:41-52
4. Manova K, Huang EJ, Angeles M, De Leon V, Sanchez S, Pronovost SM. The Expression Pattern of the Ligand in Gonads of Mice Supports a Role for the Receptor in Oocyte Growth and in Proliferation of Spermatogonia. Dev Biol 1993;157 (1):85-99.
5. Ayoub WS, Geller SA, Tran T, Martin P, Vierling JM, Poordad FF. Imatinib induced hepatotoxicity. J Clin Gastroenterol 2005;39 (1):75-77.
6. Kikuchi S, Muroi K, Takahashi S, Kawano-Yamamoto C, Takatoku M, Miyazato A. Severe hepatitis and complete molecular response caused by imatinib mesylate: possible association of its serum concentration with clinical outcomes. Leukemia & lymphoma 2004;45 (11):2349-51.
7. Lin NU, Sarantopoulos S, Stone JR, Galinsky I, Stone RM, Deangelo DJ. Fatal hepatic necrosis following imatinib mesylate therapy. Blood 2003;102 (9):3455-56
8. Ohyashiki K, KuriyamaY, Nakajima A, Tauchi T, Ito Y, Miyazawa H. 2002. Imatinibmesylate-inducedhepatotoxicity in chronic myeloid leukemiademonstrated focal necrosis resembling acute viral hepatitis. Leukemia 2002; 16:2160-1
9. James C, Trouette H, Marit G, Cony-Makhoul P, Mahon F. Histological features of acute hepatitis after imatinib mesylate treatment. Leukemia 2003;17 (5):978-79.
10. Vitamin E- American Cancer Sociwww,Cancer. Herb, Vitamins and minerals.
11. Prasad KN, Kumar A, Kochupillai V, Cole WC. High doses of multiple antioxidant vitamins: essential ingredients in improving the efficacy of standard cancer therapy. J Oncol 1999;18 (1): 13-25.
12. Ashok A, Sajal G, Suresh S.The role of free radicals and antioxidants in reproduction. Current opinion in Obstet Gynecol 2006; 325-32
13. IshakK,Baptista A, De Groote Histological grading and staging of chronic hepatitis. J Hepatol 1995; (22): 696-99.
14. Kondell GR, Black WC, Chen TC. Formulation and application of numerical Scoring system for assessing histological activity in asymptomatic active hepatitis. Hepatol 1981;(1): 431-435.
15. Abullaev Fl, Luna RR, Roitenburd AJ. Patteren of childhood cancer mortality in Mexico. Arch Med Res 2000; 31:526-31.
16. Tonyali O, Coskun U, Yildiz R, Karakan T, Demirci U, Akyurek N, Benekli M, Buyukberber S. Imatinib mesylate-induced acute liver failure in a patient with gastrointestinal stromal tumors. J Med Oncol 2010; (27):768–73.
17. Guilhot F. Indications for imatinib mesylate therapy and clinical management. Oncologist 2004;9:271–81.
18. Kong JH, Yoo SH, Lee KE, Nam SH, Kwon JM, Lee SM, et al. Early imatinib-mesylate-induced hepatotoxicity in chronic myelogenous leukaemia. ActaHaematol 2007; (118):205-08.
19. Spataro V. Nilotinib in a patient with postnecrotic liver cirrhosis related to imatinib.J Clin Oncol 2011; (29) 50-52.
20. Talpaz M,Kantarjian HM. Imatinib mesylate: clinical results in Philadelphia chromosome-positive leukemias. Semin Oncol 2001; 5 (17): 9-18.90.
21. Kedar N. Prasad PhD, Bipin Kumar MD, Xiang-Dong Yan MD, Amy J. Hanson M & William C. α-Tocopheryl Succinate, the Most Effective Form of Vitamin E for Adjuvant Cancer Treatment.J AM Coll Nutr 2003; 2 (22):108-17
22. Sieja K. Protective role of selenium against the toxicity of multi-drug chemotherapy in patients with ovarian cancer. J Die Pharmazie 2000; 55(12):958-9.

23. Pace A, Savarese A, Picardo M. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. J Clin Oncol 2003; 21(5):927-31.
24. Conklin KA. Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. Integrative Cancer Therapies 2005;4 (2):110-30.
25. Branda RF, Naud SJ, Brooks EM, Chen Z, Muss H. Effect of vitamin E, folate, and dietary supplements on breast carcinoma chemotherapy—induced mucositis and neutropenia. J Cancer Res Ther 2004;101(5):1058-64.
26. Bairati I, Meyer F, Gelinas M. Randomized trial of antioxidant vitamins to prevent acute adverse effects of radiation therapy in head and neck cancer patients. J Clin Oncol 2005;23(24): 5805-13.
27. Ferreira PR, Fleck JF, Diehl A. Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. J Otolaryngol Head Neck Surg 2004;26(4):313-21.

Original Article

Human Papilloma Virus Related Oral Carcinomas

The Frequency of Human Papilloma Virus Related Oral Squamous Cell Carcinomas by P16 Immuno Histochemical Stain

Asmah Afzal[1], Rajia Liaqat[2], Faiza Shafqat[3], Farah Kalsoom[4], Asif Loya[1]

ABSTRACT

Objective: To determine the frequency of HPV positive oral squamous cell carcinomas by applying p16IHC stain in Pakistani population.

Study Design: Descriptive, Cross-sectional study

Place and Duration of Study: This study was conducted at the Shaukat Khanum Memorial Hospital and Research Centre for six (06) months from August 2018 to the February 2019.

Materials and Methods: In this research 140 patients with oral squamous cell carcinomas, histologically diagnosed, of all ages and either gender. Patients with treatedcases (surgery, chemotherapy, radiotherapy) were excluded. The biopsy was performed and fixed in 10% neutral bufferedformalin. Hematoxylin and eosin were used in the staining of the tissues. The Immunohistochemical (IHC) stainp16 was performed in the same batch according to the specification given by the manufacturer.

Results: Mean age in our study was 48:86 ± 9:37 years. Out of the 140 patients, 114(81:43%) were maleand 26(18:57%) were females resulting in male to female ratio of 4:4:1. HPV associated oral squamous cellcarcinomas by p16 immunocytochemistry were found in57(40:71%) patients. It was also found that therewas a significant difference (p <0:05) of HPV associated oral squamous cell carcinomas between differentage groups while no significant difference (p >0:05) of HPV associated oral squamous cell carcinomas werefound between gender and stage of tumor.

Conclusion: This study concluded that there is a high frequency of HPV associated oral squamous cellcarcinomas by p16 immunocytochemistry in our population with a positive association with younger age andmale gender.

Key Words: Squamous Cell Carcinoma, Oral, Human Papilloma Virus.

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INTRODUCTION

Oral cavity cancers are amongst the most common malignancies in Pakistan and many other countries of the world.[1,2] Among the subgroups, about 95% of cancers are squamous cell carcinomas (SCC). The non-SCC include adenocarcinoma of minor salivary glands, malignant melanomas, clear cell, and adenoid cystic carcinomas.[3]Bhurgi Y et al[4] reported an annual SSC incidence rate of 4.1 and 4.0 per 100,000/year in males and females respectively.

SCC is of epithelial origin, squamous cell, which isa major component of oral cavity. SCC originatesfrom the uncontrolled proliferation of mutated cells. Clinically, the carcinoma may present in the form of white plaques, ulcers and fungating masses. A major regional influenceof chewing tobacco, betel nut, pan, cigarette smoking and huqqa in Pakistan suggest common etiological factors in the pathogenesis of oral cancers. Other factors include alcohol use, nutritional deficiencies, syphilis, immune deficiency disorders, radiations, poor oro-dental hygiene, chronic irritation, trauma, and viruses.[5]

Among viruses, human papilloma virus (in particular type 16) has been identified in 10% to 15% of oral carcinomas and appears to be among the strongest possible risk factor.[6]Immuocytochemistry, in situ hybridization and polymerase chain reaction are commonly used techniques for virus detection in tumors. P16 IHC stain is considered as a reliable

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surrogate marker with a sensitivity of 100% and specificity of 74%[7] while in another study the sensitivity was 76% and specificity was 71%.[8]

In this research, the frequency of human papilloma virus (HPV) related oral squamous cell carcinomas (OSCC) by p16 IHCis studied for the Pakistani population.

MATERIALS AND METHODS

It is a descriptive, cross-sectional study which is conducted in the Pathology department of SKMCH & RC, Lahore, for a period of six (06) months(the 6th of August 2018 to the 5th of February 2019). The sample size of 140 cases was calculated with 8% margin of error and 95% confidence level with an expected frequency of HPV related oral squamous cell carcinoma35%. Non-probability, purposive sampling technique was used in the sampling process. For the sample selection, the following are the inclusion and exclusion criteria.

Inclusion Criteria

i. All patients with histological diagnosis of OSCC.
ii. Patients of all ages.

Exclusion Criteria

i. Unfixed and poorly preserved specimen.
ii. Treated cases (surgery, chemotherapy, radiotherapy).
iii. Site other than the oral cavity.

Data Collection Procedure

Cases of OSCC fulfilling inclusion criteria were included instudy after approval of the ethical committee of SKMCH & RC and informed consent fromthe respective patient. The biopsy was performed and fixed in 10% neutral buffered formalin. Tissuewas processed and stained with hematoxylin and eosin. The personal bias was controlledby showing all cases to one consultant with a minimum of 5 years experience. TheIHC stain p16 was performed in the same batch according to the specificationgiven by the manufacturer. Data was collected through a prescribed and approved form which contained two parts. First Part included the patient's bio-data while second part contained the study variables.

Data Analysis Procedure

The collected data is analysis through state of the art tool for data computation i.e. "SPSS version 19". The quantitative variables of the study were calculated as mean and deviation from the mean i.e. standard deviation. The qualitative variables like gender and HPV positive SCC were presented in the form of frequencies and/ or percentages. Stratification was done on three variables which are age, gender and stage to explore the impact of these variables on HPV positive SCC. Post stratification chi-square test was applied with a significant P-value at ≤ 0.05.

RESULTS

The age range in this study was from 18 to 80 years with a mean age of 48.86 ± 9.37 years. Majority of the patients 51 (36.43%) were between 36 to 50 years of age as shown in Table I. Out of the 140 patients, 114 (81.43%) were male and 26 (18.57%) were females with male to female ratio of 4.4:1. HPV associated OSCC by p16 immunocytochemistry was found in 57 (40.71%) patients, whereas there were no HPV associated oral squamous cellcarcinomas in 83 (59.29%) patients as shown in Figure I. The percentage of patients according to stage of disease have shown in Figure II which showed that majority of patients were with stage II i.e. 58 (41.43%).

When Stratification of HPV associated oral SSC with respect to age groups was done, it was found that there was significant difference ($p<0.05$) of HPV associated OSCC between different age groups as shown in Table III while the stratification of HPV associated OSCC with respect to gender and stage of carcinoma has shown in Table IV & V respectively which showed no significant difference ($p>0.05$).

Table No.1: Age distribution according to gender (n=140)

Age (years)	Male		Female		Total	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
18-35	17	14.91	01	3.85	18	12.86
36-50	44	38.60	07	26.92	51	36.43
51-65	29	25.44	11	42.31	40	28.57
66-80	24	21.05	07	26.92	31	22.14
Total	114	81.43	26	18.57	140	100.0

Mean ± SD = 48.86 ± 9.37 years

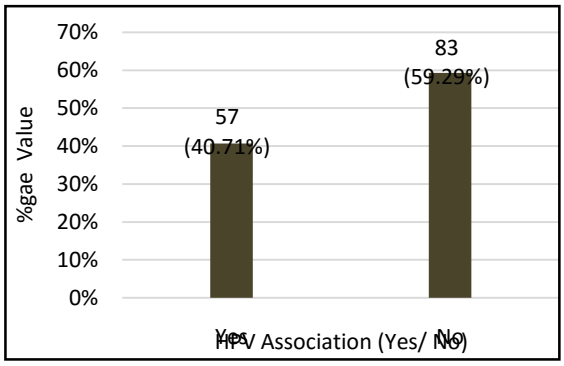

Figure No.1: %age of the Patients with HPV associated oral SSC

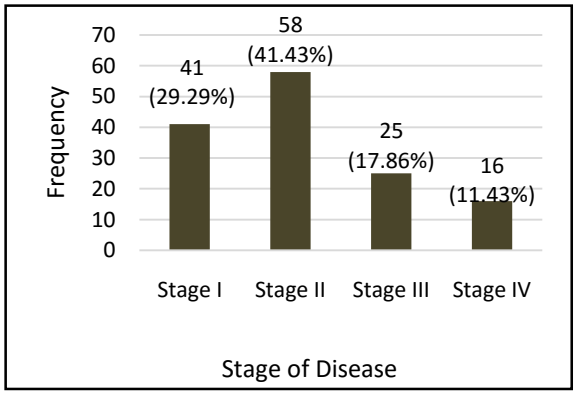

Figure No.2: %age of patients with HPV associated oral SSCAccording to the Stage

Table No.2: Stratification of HPV Associated Oral SSC with Respect to Age Groups

Age (years)	HPV associated oral SSC		p-value
	Yes	No	
18-35	10 (55.56%)	08 (44.44%)	0.009
36-50	28 (54.90%)	23 (45.10%)	
51-65	11 (27.50%)	29 (72.50%)	
66-80	08 (25.81%)	23 (74.19%)	

Table No.3: Stratification of HPV Associated Oral SSC with Respect to Gender

Gender	HPV associated oral SSC		p-value
	Yes	No	
Male	49 (42.98%)	65 (57.02%)	0.253
Female	08 (30.77%)	18 (69.23%)	

Table No.4: Stratification of HPV Associated Oral SSC with Respect to Stage of Disease

Stage of disease	HPV associated oral SSC		p-value
	Yes	No	
Stage I	17 (41.46%)	24 (58.54%)	0.743
Stage II	26 (44.83%)	32 (55.17%)	
Stage III	09 (36.0%)	16 (64.0%)	
Stage IV	05 (31.25%)	11 (68.75%)	

DISCUSSION

According to the literature, there is a strong tie between the oral HPV infection and OSSC in the cases where the subjects are addicted to the tobacco and alcohols.[9] In this context, it is possible that HPV transmission occured through the oral—genital or direct mouth-to-mouth or other means of contact.

Due to the heterogeneous nature of the OSCC, finding a relation between the HPV and OSCC is no easy task. Furthermore, it becomes more difficult due to a very small number of cases which are HPV positive. Syrjänenet al. for the first time reported in a study that some OSCC have morphological and IHC features which reveal HPV as etiological factor.[9]In this study involvement of the HPV in the pathogenesis of a subset of HNSCC was indicated.[9]According to the literature, the identification of the HPV-associated OSCC is a very difficult task which is often basaloid in histology.

In our study, HPV associated OSCC by p16 immunocytochemistry was found in 40.71% patients, whereas there was no HPV associated OSCCin rest of the 59.29% patients. As compared to our study, Agrawal GP et al[10] reported22.5% positive cases for HPV 16. However, the association between the "high risk human papillomavirus (HR HPV)" and risk of oral cancer development is reported since1983 after the detection of HPV16 OSCC. Since then HPV DNA has repeatedly been observed in head and neck cancers.[11,12]

In another study, OSCC p16 positivity of 86.66% was reported. Of 26/30 positive cases, p16 staining was positive in 70%, 90% and 100% of well-differentiated, moderately differentiated, poorly differentiated OSCC respectively.[13] Kojima A et al[14] in his study has found HPV associated OSCC by p16 immunocytochemistryin 66.66% patients.

A study conducted for Indian population shows that HPV infection is more frequent in OSCC cases which is 33.6% as compared to the 23%, 8-20% and 19% of the Japanese, American and Dutch patients.[15] This variability may be attributable to ethnicity and geography,a small number of samples analyzed, possible contamination and detection technique used.[16]

In another study, Duncan LD et al[17]utilized the p16 IHC as a substitute marker for high-risk HPV and as an alternate test to PCR. Authors of the study observed 55.6% with 0 staining, 27.2% with 1+ staining, and 8.6% with 2+ staining. **de Abreu** PM et al[18]in his study has shown a very low frequency of HPV associated oral squamous cell carcinoma (4.04%). However, in contradiction to the previous studies and our study, Young SK et al[19], and Tsuchiya H et al[20] were unable to find such association between HPV 16 and OSCC.

According to the literature, 25-75% of oropharyngeal cancers results in the HPV positive, where tonsils has the highest ratio followed by tongue and buccal mucosa.[76] The probable reason could be that HPV being an inhabitant of normal crypt epithelia and Waldeyer's ring, an antigen presenting site, may act as the reservoir for HPV.

Similar to the underlying study, Gillison ML et al[21] conducted a cross-sectional study and showedthat the frequency of oral HPV infection only in 6.9% population of the age range 14 - 69 years. The study revealed a higher frequency in male as compared to the female.

In the underlying study, distribution of HPV 16 positive/ negative cases according to the age group had shown a strong correlation with the results reported by Cruz IBF et al[22]. However, the results of this study are not in line with the results reported by the Kurose K et

al.[23]According to the gender-based distribution of the results of positive cases, close similarities are observed with the results reported by the Werness BA et al[24] where the males having predominance. Male predominance is also reported by the Cruz IBF et al[22] and Koppikar P et al.[25]

Statistical analysis of the results shows that there is no correlation between the HPV16 and histopathologic grades of differentiation which is in line with the results reported by the Schlecht NF et al[26] and Badaracco G et al[27] however, Abdelsayed RA[28] reported a strong correlation.The results indicate that the HPV association withOSCC by p16 immunocytochemistry is significant and there is positive association with young age and male gender.

CONCLUSION

This study concluded that there is a high frequency of HPV associated oral squamous cellcarcinomas by p16 immunocytochemistry in our population revealing positive association with young age and male gender. As we know from recent studies that HPV associated OSCCare more sensitive to the chemo-and-radiotherapy and accordingly require limited resection even after lymph node metastases, it is highly recommended to detect HPV positive association by p16 IHC stain as a mandatory pre-treatment assessment to segregate those who would benefit maximum from the therapy and who would not. Also, it would help in risk stratification to avoid intensification of treatment, to reduce severe acute and late treatment associated side effects, to improve the therapeutic ratio, to minimize unnecessary hospital stayand above all to aid oncologists to develop more effective and advanced treatment modalities to improve patient survival and quality of life.

Author's Contribution:

Concept & Design of Study:	Asmah Afzal, RajiaLiaqat
Drafting:	FaizaShafqat, FarahKalsoom
Data Analysis:	FaizaShafqat, FarahKalsoom
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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Rosai J. Ackerman's surgical pathology. 9th ed. St.louis: Mosby;2004.p.254-55.
2. Kedamnani D. Oral cancer. Mayo CliPrc 2007;82:878-87.
3. Nicolas B, Fabian L, Sivia A, de Blanc L, Morelatto RA. Oral squamous cell carcinoma: clinical aspects. J Oran Can 2010;51:953-78.
4. Bhurgri Y, Rahim A, Bhutto K. Incidence of carcinoma of oral cavity in Karachi: District South. J Pak Med Assoc 2010;48:321-25.
5. Rashmi M, Madhusudan A, Meenal V. Role of viruses in oral squamous cell carcinoma. Oncol Rev 2012;6:21.
6. Gaurav P, Priya S, Anishita A. Role of HPV 16 in oral epithelial dysplasia and oral squamous cell carcinoma. ISRN Pathol 2013;article id:807095.
7. Langendijk J, Psyrri A. The prognostic significance of p16 expression. Ann Oncol 2010;1093:09-21.
8. Chaturvedi AK, Engels EA, Pfeiffer RM. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29(32):4294–301.
9. Syrjanen K. Morphological and immunohisto-chemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis. Int J Oral Surg 1983;12:418-24.
10. Agrawal GP, Joshi PS, Agrawal A. Role of HPV-16 in Pathogenesis of Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma and Correlation of p16INK4A Expression in HPV-16 Positive Cases: An Immunohistochemical Study. ISRN Pathol 2013:
11. Nair S, Pillai MR. Human papillomavirus and disease mechanisms: relevance to oral and cervical cancers. Oral Dis 2005;11(6):350–59.
12. Tachezy R, Klozar J, Saláková M. HPV and other risk factors of oral cavity/oropharyngeal cancer in the Czech Republic. Oral Dis 2005;11(3):181–85.
13. Patil S, Rao RS, Amrutha N, Sanketh DS. Analysis of human papilloma virus in oral squamous cell carcinoma using p16: an immunohistochemical study. J Int Soc Prev Community Dent 2014;4(1):61–6.
14. Kojima A. Human papillomavirus type 38 infection in oral squamous cell carcinomas. Oral Oncol 2002; 38(6):591-6.
15. D'Costa J, Saranath D, Dedhia P, Sanghvi V, Mehta AR. Detection of HPV-16 genome in human oral cancers and potentially malignant lesions from India. Oral Oncol 1998;34:413–20.
16. Machado J, Reis PP, Zhang T, Simpson C, Xu W, Perez-Ordonez B, et al. Low prevalence of human papillomavirus in oral cavity carcinomas. Head Neck Oncol 2010;2:6.
17. Duncan LD, Winkler M, Carlson ER, Heidel RE, Kang E, Webb D. p16 immunohistochemistry can be used to detect human papillomavirus in oral cavity squamous cell carcinoma. J Oral Maxillofac Surg 2013;71(8):1367-75.

18. de Abreu PM, Azevedo PL, GregórioCó AC, do Valle IB, de Podestá JBV, Cordeiro-Silva MF, et al. Frequency of Human Papillomavirus infection in squamous cell carcinoma of the oral cavity and oropharynx. BMC Proceed 2014;8(Suppl 4):P67.
19. Young SK, Min KW. In situ DNA hybridization analysis of oral papillomas, leukoplakias, and carcinomas for human papillomavirus. Oral Surg Oral Med Oral Pathol 1991;71(6):726–9.
20. Tsuchiya H, Tomita Y, Shirasawa H, Tanzawa H, Sato K, Simizu B. Detection of human papillomavirus in head and neck tumors with DNA hybridization and immunohistochemical analysis. Oral Surg Oral Med Oral Pathol 1991;71(6):721–5.
21. Gillison ML, Broutian T, Pickard. Prevalence of Oral HPV Infection in the United States, 2009-2010. JAMA 2012;307:693-703.
22. Cruz IBF, Snijders PJF, Steenbergen RDM. Age-dependence of human papillomavirus DNA presence in oral squamous cell carcinomas. Eur J Cancer B 1996;32(1):55–62.
23. Kurose K, Terai M, Soedarsono N. Low prevalence of HPV infection and its natural history in normal oral mucosa among volunteers on Miyako Island, Japan. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontol 2004;98(1):91–6.
24. Werness BA, Levine AJ, Howley PM. Association of human papillomavirus types 16 and 18 E6 proteins with p53. Sci 1990;248(4951):76–79.
25. Koppikar P, De Villiers EM, Mulherkar R. Identification of human papillomaviruses in tumors of the oral cavity in an Indian community. Int J Cancer 2005;113(6):946–50.
26. Schlecht NF, Burk RD, Adrien L. Gene expression profiles in HPV-infected head and neck cancer. J Pathol 2007;213(3):283–93.
27. Badaracco G, Venuti A, Bartolazzi A, Morello R, Marzetti F, Marcante ML. Overexpression of p53 and bcl-2 proteins and the presence of HPV infection are independent events in head and neck cancer. J Oral Pathol Med 2000;29(4):173–79.
28. Abdelsayed RA. Study of human papillomavirus in oral epithelial dysplasia and epidermoid carcinoma in the absence of tobacco and alcohol use. Oral Surg Oral Med Oral Pathol 1991;71(6):730–2.

Original Article

Examine the Distant and Near Visual Outcomes after Phacoemulsification with Implantation of Accommodating versus Standard Intraocular Lenses

Muhammad Waseem[1], Abdul Ghafoor[2] and Iftikhar Ahmed[3]

ABSTRACT

Objective: To compare the visual outcomes after phacoemulsification with implantation of crystalens HD and Tek-clear as accommodating intraocular lenses versus SA60AT as standard intraocular lenses.

Study Design: Observational study

Place and Duration of Study: This study was conducted at the Department of Ophthalmology, DHQ Hospital Batkhela from July 2016 to December 2018.

Materials and Methods: A total of 36 eyes were enrolled. Patient's ages were > 35 years. Patients demographic were examined after taking informed consent. All the eyes were equally divided into three groups and implanted with three different intraocular lenses. Group A contains 12 eyes with crystalens HD, Group B contains 12 eyes with Tek-clear and Group C contain 12 eyes with SA60AT. Corrected, uncorrected and distant near visual acuity, near point of accommodation, spectacle freedom and satisfaction of patients were examined at 12 weeks postoperatively and compare the results between all groups.

Results: At follow up all the patients showed significant improvement in corrected distant visual acuity among all the groups. Uncorrected near visual acuity and distant corrected near visual acuity showed better outcomes in patients implanted with crystalens HD and Tek-clear. Near point of accommodation was closest in the crystalens HD group with p-value 0.002. Patients implanted with accommodating intraocular lenses showed better results regarding spectacle freedom and satisfaction with their near vision as compared to standard intraocular lenses.

Conclusion: The crystalens HD and Tek-clear intraocular lenses showed better outcomes regarding near vision and spectacle freedom as compared to monofocal intraocular lens.

Key Words: Cataract surgery, Accommodating, Standard Intraocular Lenses, Outcomes

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INTRODUCTION

Since the implantation of the first intraocular lens (IOL), attempts have been directed toward improvement of visual outcomes of cataract surgery. Loss of accommodation is inevitable with conventional monofocal IOLs and the first attempt to overcome this limitation was pseudophakic monovision.[1]

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Despite some reports of acceptable spectacle-free near and far visual acuity in more than half of the patients with monovision, this method may be associated with problems in stereoacuity, contrast sensitivity and dominance.[2] For lack of accommodation multifocal intraocular lenses are useful for pseudophakic cases.[3] However these intraocular lenses reported some side effects such as glare disability, decreased contrast sensitivity and halos in eyes.[4] Accommodating intraocular lenses were designed to avoid the optical side effects. Positional IOL was the 1st accommodating IOL with two types; single optic and dual optic. Single optic IOLs are based on axial (backward and forward) movement of the optic resulting from contraction and relaxation of the ciliary muscle, increasing the effective power of the IOL and thereby providing near focus.[5] Many of single optics IOLs have been developed such as Tek-Clear, Crystalens HD and Tetraflex. The plate style single optic accommodating IOL Crystalens HD is designed to be implanted within the capsular bag and is made from third generation silicone (Biosil) which unlike other IOL materials does not have internal reflectivity. Crystalens HD showed better intermediate

and near vision results with no procedural complications.[6] According to the manufacturer, the IOL has a double mechanism to improve near visual function; first, axial movement of the optic which occurs with ciliary muscle changes and second, the radius of curvature of the anterior surface (arching optic) which varies with accommodative effort. A number of studies have shown better visual and accommodative results with this lens as compared to standard monofocal IOLs.[7,8]

This study was conducted aimed to compare the visual outcomes after phacoemulsification with implantation of crystalens HD and Tek-clear as accommodating intraocular lenses versus SA60AT as standard intraocular lenses.

MATERIALS AND METHODS

This observational study was conducted at Department of Ophthalmology, DHQ Hospital Batkhela from 1st July 2016 to 31st December 2018. A total of 36 eyes of 33 patients of both genders whom were undergoing cataract extraction were enrolled in this study. Patient's ages were >35 years. Patients demographic such as age, sex, medical history were examined after taking informed consent from all the patients. Exclusion criteria included more than one diopter (D) of keratometric astigmatism,incomplete or damaged zonules,any anterior segment pathology (e.g.,chronic uveitis,rubeosis iridis,corneal dystrophy),controlled or undertreated glaucoma, retinal pathologies or history of retinal detachment,age-related macular degeneration, diabetic retinopathy, congenital cataracts,monocular status or previous ocular surgery in either eye. All the eyes were equally divided into three groups and implanted with three different intraocular lenses. Group A contains 12 eyes with crystalens HD, Group B contains 12 eyes with Tek-clear and Group C contains 12 eyes with SA60AT. Corrected, uncorrected and distant near visual acuity, near point of accommodation, spectacle freedom and satisfaction of patients were examined at 12 weeks postoperatively and compare the results between all groups. The data was analyzed using SPSS-20. Paired t-test was applied to compare the results between all groups. P-value <0.05 was considered as significant.

RESULTS

Out of 33 patients overall 24 (72.72%) patients were male (Group A 8, Group B 7, Group C 9) while rests 9 (27.28%) patients were females (Group A 3, Group B 3, Group C 3) with mean age were 57.6±10.8 years. 36 eyes of 33 patients were implanted with three different IOLs. Group A contains 12 eyes with crysatalens HD, Group B contains 12 eyes with Tek-clear and Group C contains 12 eyes with SA60AT. There was no significant difference in demographic characteristics and preoperative measurements, including sphere, cylinder, mean keratometry, axial length, uncorrected distance visual acuity (UCDVA), corrected distance visual acuity (CDVA), UCNVA and distance corrected near visual acuity (DCNVA) (Table 1).

Postoperatively all the patients showed significant improvement in corrected distant visual acuity among all the groups p-value 0.02 (Table 2). Uncorrected near and intermediate visual acuity and distant corrected near and intermediate visual acuity showed better outcomes in patients implanted with crystalens HD and Tek-clear p-value 0.002 as compared to Group C [SA60AT] (Table 3).

Table No.1: Distribution of genders in all groups

Gender	Group A	Group B	Group C
Male	8 (72.73%)	7 (70%)	9 (75%)
Female	3 (27.27%)	3 (30%)	3 (25%)

Table No.2: Mean values of postoperative refractive outcomes and distant visual acuity among all groups

Variable	Group A (12 eyes)	Group B (12 eyes)	Group C (12 eyes)
Sph (D)	0.16±2	−0.15±1.10	−0.12±0.5
Cydr (D)	−0.71±0.35	−0.98±0.40	−0.71±0.29
CDVA logMAR	0.03±0.10	0.07±0.10	0.07±0.08
UCDVA logMAR	0.17±0.11	0.25±0.12	0.27±0.12

P-value 0.02

Table No.3: At postoperative 12 weeks follow-up regarding intermediate and near acuities among all the groups

Characteristics	Group A (12 eyes)	Group B (12 eyes)	Group C (12 eyes)
UCNVA	0.13±0.15	0.19±0.16	0.35±0.10
DCNVA	0.17±0.18	0.27±0.20	0.50±0.2
UCIVA	0.16±0.15	0.23±0.14	0.40±0.12
DCIVA	0.14±0.16	0.23±0.16	0.53±0.13

P-value 0.002

Table No.4: Mean values of near point of accommodation between all the groups

Characteristics	Group A (12 eyes)	Group B (12 eyes)	Group C (12 eyes)
NPA monocular cm	32.40±5.20	54.09±3.92	95.68±7.10
NPA monocular D	2.85±0.40	1.98±0.19	1.12±0.10

P-value 0.02

Near point of accommodation was closest in the Group A (crystalens HD) group followed by Group B and C with p-value 0.002 (Table 4).

According to patient's satisfaction regarding near vision among all groups, it was 90.91% in Group A, 70% in Group B and 50% in Group C. As per spectacle freedom in Group A, B and C the rate was 72.73%,

70% and 25% respectively. According to the complications, patients implanted with crystalens HD had a high rate of posterior capsule opacification that was found in 4 (33.33%) out of 12 eyes, 1 (8.33%) in Tek-clear group and 2 (16.67%) in SA60AT group (Tables 5-6).

Table No.5: Patients satisfaction regarding near vision and no need of spectacle

Characteristics	Group A (n=11)	Group B (n=10)	Group C (n=12)
Satisfied Near Vision			
Yes	10 (90.91%)	7 (70%)	6 (50%)
No	1 (9.09%)	3 (30%)	6 (50%)
Spectacles free			
Yes	8 (72.73%)	7 (70%)	3 (25%)
No	3 (27.27%)	3 (30%)	9 (75%)

P-value <0.05

Table No.6: According to the complications among all groups

Complication	Group A (12 eyes)	Group B (12 eyes)	Group C (12 eyes)
Yes	4 (33.33%)	1 (8.33%)	2 (16.67%)
No	8 (66.67%)	91.67%	10 (83.33%)

DISCUSSION

Functional near vision is indispensable due to the necessity of several near tasks in ordinary life. Loss of reading ability can greatly reduce quality of life. Thus, providing good near vision after cataract surgery is an important goal in modern cataract surgery.[9,10] The present study compare the visual outcomes after phacoemulsification with implantation of crystalens HD and Tek-clear as accommodating intraocular lenses versus SA60AT as standard intraocular lenses. There was a significant improvement in distance vision after IOL implantation in all groups (Table 1). This is consistent with findings in previous studies on other positional accommodating IOLs as well as with cataract surgery expectations, and it confirms the safety of both accommodating IOLs used herein.[11,12] There were also no statistically significant difference between the three IOL groups in terms of postoperative CDVA (Table 1). However, night vision and glare complaints were more frequently reported in eyes implanted with accommodating IOLs than with monofocal IOLs, but the difference was not significant. These findings indicate that both accommodating IOLs had similar capacity to successfully restore distance visual function after cataract surgery. Uncorrected near acuity values were best with the Crystalens HD. We observed that 58% of eyes with Crystalens HD, 35% of eyes with Tek-Clear and none of the eyes with SA60AT Monofocal IOL had uncorrected near acuity of 20/25 (J1) or better.

DCNVA improved significantly with both accommodating IOL groups in our study. Surprisingly, UCNVA and DCNVA also improved in the monofocal IOL group. A previous study demonstrated that the monofocal IOL we used in our study has some pseudo-accommodative ability, although the mechanism was not clearly understood.[11] The difference in DCNVA between the monofocal group (J6) and accommodating IOL groups, (Crystalens [J1 to J2]; Tek-Clear [J2 to J3]) was statistically significant, and the best DCNVA occurred in eyes implanted with the Crystalens HD (Table 2). In most reports, accommodating IOLs were associated with significant improvement in near visual acuity.[8,12-16] Alió et al[7] reported significant improvement in uncorrected and corrected near visual acuity with Crystalens HD as compared to a monofocal IOL. However, accommodating IOLs did not show any superiority to monovision or multifocal IOLs in some other studies.[17,18] In one study, a dual optic accommodating IOL (Synchrony; AMO, CA, USA) showed better distant visual acuity and contrast sensitivity as compared to Crystalens HD; furthermore PCO and higher order aberrations were more common with the single optic Crystalens HD.[19,20]

Saiki et al[21] evaluated the long-term outcomes of the 1CU accommodating IOL. After 4 years, they found no significant change in CDVA, UCNVA, DCNVA, and subjective and objective accommodation amplitudes. In present study we found the outcomes according to the patient's satisfaction regarding near vision among all groups, it was 90.91% in Group A, 70% in Group B and 50% in Group C. As per spectacle freedom in Group A, B and C the rate was 72.73%, 70% and 25% respectively. All of the patients bilaterally implanted with accommodating IOLs (Crystalens or Tek-Clear) reported that they were very satisfied with their visual outcomes. Many of previous studies reported that spectacle freedom was also greater in patients with accommodating IOLs as compared to monofocal IOLs.[20,21] In our study According to the complications, patients implanted with crystalens HD had a high rate of posterior capsule opacification that was found in 4 (33.33%) out of 12 eyes, 1 (8.33%) in Tek-clear group and 2 (16.67%) in SA60AT group. These results shows similarity to some previous studies.[22] The square edge on the Crystalens IOL extends for only 240°; there is no square edge where the optic abuts the plates, while Tek-Clear and SA60AT both have 360° square edge design.

CONCLUSION

The crystalens HD and Tek-clear intraocular lenses showed better outcomes regarding near vision and spectacle freedom as compared to monofocal intraocular lens. Moreover, monofocal and accommodating IOLs in the present study restored distance visual function after cataract surgery. Both accommodating IOLs employed in this series yielded more ideal UCNVA and DCNVA than the monofocal IOL. The Crystalens HD showed better results than Tek-Clear.

Author's Contribution:

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Data Analysis:	Iftikhar Ahmed
Revisiting Critically:	Muhammad Waseem
Final Approval of version:	Muhammad Waseem

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Finkelman YM, Ng JQ, Barrett GD. Patient satisfaction and visual function after pseudophakic monovision. J Cataract Refract Surg 2009;35:998-1002.
2. Xiao J, Jiang C, Zhang M. Pseudophakic monovision is an important surgical approach to being spectacle-free. Ind J Ophthalmol 2011;59: 481-5.
3. El-Maghraby A, Marzouky A, Gazayerli E, Van der Karr M, et al. Multifocal versus monofocal intraocular lenses. Visual and refractive comparisons. J Cataract Refract Surg 1992;18:147-52.
4. Martínez Palmer A, Gómez Faiña P, España Albelda A, Comas Serrano M, Nahra Saad D, Castilla Céspedes M. Visual function with bilateral implantation of monofocal and multifocal intraocular lenses: a prospective, randomized, controlled clinical trial. J Refract Surg 2008;24:257-64.
5. Marchini G, Pedrotti E, Sartori P, Tosi R. Ultrasound biomicroscopic changes during accommodation in eyes with accommodating intraocular lenses: Pilot study and hypothesis for the mechanism of accommodation. J Cataract Refract Surg 2004;30:2476-82.
6. Doane JF, Jackson RT. Accommodative intraocular lenses: Considerations on use, function and design. Curr Opin Ophthalmol 2007;18:318-24.
7. Alió JL, Piñero DP, Plaza-Puche AB. Visual outcomes and optical performance with a monofocal intraocular lens and a new-generation single-optic accommodating intraocular lens. J Cataract Refract Surg 2010;36:1656-64.
8. Cumming JS, Colvard DM, Dell SJ, Doane J, Fine IH, Hoffman RS, et al. Clinical evaluation of the Crystalens AT-45 accommodating intraocular lens: results of the US Food and Drug Administration clin trial.J Cataract Refract Surg 2006;32:812-25.
9. Zamora-Alejo KV, Moore SP, Parker DG, Ullrich K, Esterman A, Goggin M. Objective accommodation measurement of the Crystalens HD compared to monofocal intraocular lenses. J Refract Surg 2013;29:133-9.
10. Alió JL, Plaza-Puche AB, Montalban R, Javaloy J. Visual outcomes with a single-optic accommodating intraocular lens and a low-addition-power rotational asymmetric multifocal intraocular lens. J Cataract Refract Surg 2012;38:978-85.
11. Zhao G, Zhang J, Zhou Y, Hu L, Che C, Jiang N. Visual function after monocular implantation of apodized diffractive multifocal or single-piece monofocal intraocular lens: randomized prospective comparison. J Cataract Refract Surg 2010;36:282-5.
12. Dong Z, Wang NL, Li JH. Vision, subjective accommodation and lens mobility after TetraFlex accommodative intraocular lens implantation. Chin Med J (Engl) 2010;123:2221-4.
13. Hantera MM, Hamed AM, Fekry Y, Shoheib EA. Initial experience with an accommodating intraocular lens: Controlled prospective study. J Cataract Refract Surg 2010;36:1167-72.
14. Harman FE, Maling S, Kampougeris G, Langan L, Khan I, Lee N, et al. Comparing the 1CU accommodative, multifocal, and monofocal intraocular lenses: A randomized trial. Ophthalmol 2008;115:993-1001.
15. Wang SY, Stem MS, Oren G, Shtein R, Lichter PR. Patient-centered and visual quality outcomes of premium cataract surgery: a systematic review. Eur J Ophthalmol 2017; 27(4): 387–401.
16. Jonker SMR, Bauer NJC, Makhotkina NY, Berendschot TTJM, van den Biggelaar FJHM, Nuijts RMMA. Comparison of a trifocal intraocular lens with a +3.0 D bifocal IOL: results of a prospective randomized clinical trial. J Cataract Refract Surg 2015; 41(8): 1631–40.
17. Baldassare R, Bedi R. Symfony extended depth of focus IOL: a review of reported data. Curr Ophthalmol Reports 2017; 5(3): 225–31.
18. Mill´an MS, Vega F. Extended depth of focus intraocular lens chromatic performance. Biomed Optics Express 2017; 8(9): 4294–309.
19. Reitblat O, Assia EI, Kleinmann G, Levy A, Barrett GD, Abulafia A. Accuracy of predicted refraction with multifocal intraocular lenses using two biometry measurement devices and multiple intraocular lens power calculation formulas. Clin Experimental Ophthalmol 2015; 43(4): 328–34.
20. Beiko GH. Comparison of visual results with accommodating intraocular lenses versus mini-monovision with a monofocal intraocular lens. J Cataract Refract Surg 2013;39:48-55.
21. Alió JL, Plaza-Puche AB, Montalban R, Ortega P. Near visual outcomes with single-optic and dual-optic accommodating intraocular lenses. J Cataract Refract Surg 2012; 38: 1568-75.
22. Takakura A, Iyer P, Adams JR, Pepin SM. Functional assessment of accommodating intraocular lenses versus monofocal intraocular lenses in cataract surgery: Meta-analysis. J Cataract Refract Surg 2010;36:380-88.

Original Article

Association of BMI with Blood Glucose Levels in Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To study the association of BMI with blood glucose levels (FPG) and (RPG) in type 2 diabetes mellitus.
Study Design: Cross-sectional study
Place and Duration of Study: This study was conducted at the Ayub Medical Complex, Abbottabad. It was conducted from June 2014 to Feb 2015.
Materials and Methods: The study involved 200 known type-2 diabetics, aged between 20 to 70 years. Both males and females were selected randomly. Questionnaire method was used to collect demographic and clinical data of participants. The fasting blood glucose profile was determined followed by two hours post-prandial blood glucose levels of each diabetic.
Results: Statistical analysis was done using SPSS version 21. Mean ±SD, CV% were determined for BMI, fasting plasma glucose, random plasma glucose. Frequency distribution of above control measures was determined. Pearson's correlation coefficient(r) was used to assess the association between above mentioned variables with Fasting plasma glucose and Random plasma glucose. Positive associations ($p<0.005$) were found for BMI. Non significant ($p>0.005$) association was seen in case of age; gender, for FPG. Poor glycemic levels were observed in case of our study subjects for FPG (139.3mg/dl) and RPG (207.6mg/dl).
Conclusion: Poor glycemic control was observed incase of our study subjects, predisposing them to develop complications of diabetes. These associations can be used to effectively control diabetes and to implement their role in preventing complications of diabetes.

Key Words: Diabetes mellitus, glycemic control, fasting plasma glucose, random plasma glucose.

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INTRODUCTION

Diabetes Mellitus is a group of diseases associated with high blood glucose either due to deficient production of insulin or due to inability of the body to utilize its own insulin effectively causing serious health complications and even death[1]. Diabetes mellitus is classified on the basis of etiology into following types: Type 1 diabetes, Type 2 diabetes and other specific types. Type 1 diabetes also called (IDDM) is a form of diabetes in which pancreatic β-cells are mostly destroyed due to autoimmune process[2].

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Type 2 diabetes is by far the most common and predominant type of diabetes. It is characterized by variable levels of insulin and insulin resistance, starting with optimal or high circulating insulin[3]. Many patients of type 2 diabetes exhibit β-cells dysfunction over time and ultimately need insulin for glycemic control, the relation between β-cells damage and resistance to the insulin is not established fully[4]. Diabetes mellitus type 2 previously known as Non–insulin–dependent diabetes mellitus (NIDDM) or Adult–onset diabetes involves persons who have relative (rather than absolute) insulin deficiency and it mostly remain undetected for many years because glucose level is not high enough to initiate noticeable symptoms of diabetes[5]. Diabetics are at increased risk of having macro-vascular and micro-vascular complications[6].

Type 2 diabetes involves 90% of cases globally. According to a study conducted in year 2000, about 150 million people were affected by diabetes and it is estimated to become double till 2025[7]. Diabetes has reached epidemic level in developing and newly developed countries. The minimum numbers of cases of diabetes are mostly seen in rural population where people follow healthy life patterns[8]. Presently prevalence of diabetes mellitus in Pakistan is about 12% and particularly in KPK, it is on the rise in both the sexes especially in the rural regions[9].

Increasing age, not sufficient energy intake, alcohol drinking, smoking are indirect risk factors in the pathogenesis of type 2 diabetes. In diabetics with obesity (especially visceral fat obesity) in the absence of exercise, less muscle mass, insulin resistance increases more rapidly in middle-aged and elderly diabetics[10].Unhealthy dietary habits such as more fats in diet and more intake of simple sugars as an energy source and minimum fiber intake are related to obesity and cause poor glucose tolerance. Nutrition and lifestyle intervention in type 2 diabetes[11].Following factors have been evaluated in an attempt to prevent type 2 diabetes: diet, physical activity, weight reduction and drug therapy. Smoking cessation may also be important[12]. Intensive lifestyle intervention provides the greatest benefit in prevention of diabetes. Most type 2 diabetics are obese, and obesity itself causes an increase in insulin resistance[13]. If obesity is not present by specific weight criteria then an increased percentage of body fat distribution mostly in the abdominal region is responsible. WHO recognized the BMI (18.5-24.9 kg/m²), as a normal range for all populations[14].There are significant variations in age-specific incidence regarding BMI in Pima Indians[15]. Nurse's Health study data confirmed that there is minimum risk of diabetes occurrence in persons whose body mass index was (BMI) < 21[16].As there is strong association between body weight (adiposity) and insulin resistance, weight reduction is favorable life style pattern[17].Various factors cause increase in adiposity in diabetics such as reduced glycosuria, resulting in retention of calories, changes in food intake and energy expenditure[18].The aim of the current study was to find out the association of blood glucose levels (FPG) and (RPG) with BMI and the role of above-mentioned control measures in effective control of diabetes to prevent diabetes related complications in the study population.

MATERIALS AND METHODS

A cross sectional study was done. This study was undertaken with objective to look for an effective control of diabetes in study population in order to prevent complications and to analyze the association of blood glucose levels with various demographic, clinical and nutritional parameters. The sample size consisted of 200 individuals, all of them were known type 2 diabetics. Convenient sampling technique was used.200 known diabetics satisfying the American Diabetes Association Criteria for diabetes mellitus(American Diabetes Association, 2013) were selected for the study. Previously registered two hundred known type 2diabetic patients of both sexes admitted in medical wards and those visiting the outpatient department of Ayub Medical Complex, Abbottabad, were selected for the study. Informed consent was taken and obtained from each study subject. The age of the patients was in the range of 20-80 years.Individuals with age less than 20 years, pregnant and lactating diabetic women, patients having any mental or hormonal disorder, those who did not consent to participate in the study were excluded. A questionnaire was used as a tool for collection of useful data. A specially designed bio-data form was developed which contained questions regarding demographic informationwhich included name, age, gender, weight, height, BMI.

Clinical data consisting of family history of diabetes (Yes/No), symptoms of diabetes, medical history, use of medication (Oral/Insulin/Nil) was also recorded in the same questionnaire. Record of fasting plasma glucose and random plasma glucose was also kept in same questionnaire.After taking informed consent, whole questionnaire was explained to the study subjects and data was documented in the bio-data form.The height of each participant was recorded without shoes in centimeters using a stadiometer.The weight of each participant was recorded in kilograms while wearing normal clothes and without shoes. The standard platform scale was used for recording weight with calibration to zero before each new measurement.From height and weight recorded for each participant, Body Mass Index(BMI) was calculated using standard formula kg/m^2 where kg is unit of mass & m is the unit of height.BMI=WEIGHT/(HEIGHT)². Following criteria recommended by WHO for BMI was considered as standard[19]. BMI<18.5: underweight, BMI 18.5-24.9: normal, BMI 25.0-30.0: overweight and BMI > 30.0 obese. Following criteria of FPG(80-120mg/dl) and RPG(100-140mg/dl) as recommended by ADA for the control of diabetes mellitus was considered. After an overnight fast of 8-10 hours, blood samples were collected while in a seated position.2ml of blood was collected from each participant using a disposable syringe under strict aseptic conditions. The patients were then asked to take breakfast andreport for sample collection for 2hrs postprandial blood glucose estimation as well. Blood glucose fasting was immediately measured. Plasma Glucose levels of all the study subjects were estimated by the enzymatic colorimetric method. The data was analyzed by using statistical program SPSS 21. The numeric variables were described in terms of Mean,$\pm$S.D, CV% was calculated and frequency distribution of different parameters was determined.Pearson's correlation coefficient was used to determine association between various parameters and fasting plasma glucose and random plasma glucose.

RESULTS

A total of 200 subjects were investigated. All the patients were known type 2diabetics.The mean age of study population was 41.89± 14.87. Maximum frequency was 75 and minimum frequency was 20. The co-efficient of variability CV% was 35.49% as shown in Table1.The Pearson's co-efficient for correlation

with FPG for age was (r= 0.66) as shown in table 2. The p value was 0.35 which was found to be not significant (Table3).There was no linear association between the age and FPG.(Table 2) . Pearson's coefficient of correlation of RPG for age(r= 0.089) and p value was 0.002 as shown in Table 3.

Gender is a categorical variable .It is expressed as Percentage. In our study population, there were 71%men and 29%women.The mean weight of diabetics was 69.05± 9.02. Their coefficient of variability CV % was 13.06%. The maximum frequency was 92 while the minimum frequency was 45 as shown in Table 1.

The Pearson's coefficient of correlation of FPG and RPG was(r= 0.140 &r=0.187) and (p= 0.04 and p= 0.003) respectively which was found to be statistically not significant for FPG but was found significant for RPG as shown in Table 2 and 3 respectively. The mean height was 2.69± 0.34. The maximum to minimum frequency range was 3.53 to 1.61. The coefficient of variability, CV% was 12.6% as shown in 1. The Table 2 and 3 show the Pearson's correlation coefficient of FPG and RPG respectively which was(r= 0.37 and r=0.123) respectively. The p value was (p= 0.059 and p= 0.03) respectively and was not significant. The mean BMI of the study subjects was 25.9 ± 3.7. Their maximum frequency was 38.51 and minimum frequency was 18.35. The coefficient of variability was 14.5% as shown in Table 1. Pearson's Coefficient of correlation for FPG was r= .199and positive association was found and r=.055 for RPG, significant positive association p<0.005 was present as shown in Table 2 and 3 respectively.

Table No.1: Descriptive Statistics(Demographic Variables)

	Frequency	Minimum	Maximum	CV%	Mean	Std. Error	Std Deviation	P-Value
Age(yrs)	200	20.00	75.00	35.4	41.89	1.05	14.87	0.005
Gender	200	1.00	2.00	34.8	1.29	0.03	0.454	
Weight(kg)	200	45.00	92.00	13.0	69.05	0.63	9.02	
Height(m)	200	1.61	3.53	12.6	2.69	0.02	0.340	
BMI(kg/m²)	200	18.35	38.51	14.5	26.0	0.26	3.78	0.005

The mean FPG of diabetics was 139.3 ±23.9. Their coefficient of variability CV% was 17.23%. The frequency range was from 220 to 76.00. The frequency distribution of Fasting Plasma Glucose which depicts that most of the study population had poor control of diabetes.The mean random plasma glucose of study subjects was 207.6 ± 28.5. The coefficient of variability CV% was 13.76. The frequency range was from 402 to 129.0.Most of the diabetics had raised RPG.Family history was a categorical variable, expressed as percentage. Among study subjects 68% diabetics had positive family history while 32% had no family history of diabetes. The coefficient of variability was 14.59%.The mean medication was 0.91 ± 0.49. The CV% was 54.53. Pearson's coefficient (r=-0.325)for FPG which show highly significant inverse association p<0.005 and (r=-0.319) for RPG which were found to be significant and inversely associated p<0.005.

Table:1 shows the Mean ±S.D,CV%, minimum and maximum frequency of age, weight, height and BMI. The Co-efficient of variation shows the variation in each variable. Here in this analysis the CV for age is very high as compare with other demographic variable. The most reliable variable inthis statisticsis height.

Table No.2:Pearson Correlation Co-efficient of FPG with Demographic Variables.

S. No	Variables	Pearson Correlation Co-efficient	P-Values
1	Age(years)	.066	.035
2	Gender	-.057	.042
3	Weight(kg)	.140	.049
4	Height(m)	.037	.059
5	BMI(kg/m²)	.199	.002

Table:2 shows association between demographic variables and Fasting Plasma Glucose. Statistically non-significant association was found in case of demographic parameters.P≤0.005 was considered as significant.

Table No.3: Pearson correlation coefficient of RPGwith demographic variables.

S. No	Variables	Pearson Correlation Co-efficient	P-Values
1	Age(years)	-.089	.002
2	Gender	-.054	.003
3	Weight(Kg)	0.187	.003
4	Height(m)	0.123	.003
5	BMI(Kg/m²)	.055	.003

Table:3 shows association of age,gender,weight and height with random plasma glucose. P≤0.005 was taken as significant.

DISCUSSION

Type 2 diabetes has reached epidemic proportions worldwide and in Pakistan. It carries with it an increased mortality risk, multiple co-morbidities, decreased quality of life and a significant economic burden. Much evidence suggests that many of the long-term complications of diabetes, especially the micro-vascular complications(retinopathy and nephropathy), result from many years of hyperglycemia[20].Effective glycemic control has become an important goal of diabetes care. Present study was conducted on a sample size of 200 diabetic patients in the age group ranging

between 20-80 years, both male and female subjects, selected randomly. The primary objective of the study was to study the roleof different control measures in effective control of diabetes in order to delay or prevent diabetes related out comesand to study the association of various demographic, clinical and nutritional parameters with fasting plasma glucose(FPG) and random plasma glucose(RPG).

Our study showed statistically significant positive associations for parameters, like BMI and medication were inversely associated with glucose levels. The results of our study showed poor control of diabetes FPG(139.3± 23.9) and RPG (207.6± 28)predisposing the study population to multiple complications like retinopathy, nephropathy, CVD, nephropathy and diabetic foot.The results of the present study showed no significant correlation with age (r=0.06, p>0.35) for FPG (Table 2) and significant inverse association(r=-0.08,p=0.002) for RPG(Table3) which is consistent with the study of Tasnimet al[21]who reported the negative association of age with FPG (p>0.005) andRPG(p>0.005)[21],Mean FPG(184±3.26) was observed also,reported poor glycemic control in diabetics which was consistent with our results FPG(139.3±23.9).The data was further analyzed on the basis of age groups to find the percentage frequency of age in diabetic population. The highest frequency was observed between the age groups of 20-40 years while it was lowest between 60-80 years and it was in contrast to the results of Tasnimet al[21],who found maximum frequency of poorly controlled diabetes in the age between 40-60 years and lowest between 27-40 years. Gopinath et al[22] observed (HbA1c>6.5%) suggesting poor control of diabetes in elderly >50 years but association between age and glucose was statistically not significant(p=0.382).Both studies reaffirm our findings of poor control of diabetes predisposing diabetics to various complications. The CURES study conducted to determine the prevalence and risk factors for neuropathy in South Indian diabetic subjects, age,glycatedhemoglobin were significantly associated with neuropathy.The CURES study showed that diabetes related outcomes were associated with poor glycemic control[22].

Present study has shown significant positive association(r=0.199, p < 0.005) between BMI and fasting plasma glucose (Table 2) and positive correlation(r= 0.55, p < 0.005) with random plasma glucose e(Table3) which is consistent with study of Innocent[23]etal(2012) which showed that BMI and blood glucose levels were positively correlated among 253 study subjects. The association for FPG was positively present among total participants(r=0.38,p≤0.005).Our results showed FPG(139.3±23.9) and RPG (207.6±28.5), reflecting poor control of diabetes in study population, who were found to be overweight with BMI(26.0±3.78) which was found consistent with the study of Gopinathet al[22]who observed that majority of diabetics with higher BMI(>25) had poor glycemic control but results were not found statistically significant(P=0.382).In accordance to our study Fawwadet al.[23],(2006)observed strong association (r=0.121,p<0.005) of BMI(28.3±5.2)in female subjects and (27.3±4.5)in male subjects with their fasting blood glucose(FPG≥126mg/dl) in type 2 diabetic patients suggesting poor control of diabetes in overweight diabetics. Several studies consider waist circumference or waist-to-hip ratios as a better anthropometric measure while in Japanese American population, intra-abdominal fat, is measured as predictor of diabetes mellitus[24,25,26]. According to a study, three out of every four diabetics are overweight[27] and almost half diabetics are obese[28]. Our results were found inconsistent with the results ofTasnimet al[21]who observed no association (r=-0.093, p>0.005) between BMI (27.97±0.24) and fasting plasma glucose FPG(164.0±2.92) showing overweight diabetics had poor control of diabetes, increasing the risk of CVD. Bakariet al[29]reported a non-significant association between BMI and RPG(p>0.005) among female diabetics while associated significantlyin case of male subjects(p<0.005). The findings showed a significantly higher BMI in females as compared to male population[29]. Studies have shown that lowering BMI improves the glycemic control and with increasing BMI, poor glycemic control is observed. Nurses's Health study confirmed that a BMI of 21 g/m² is most suitable for consideration because in European population there is greater risk of developing diabetes mellitus type 2 even with normal BMI but in Asian population,who have increased body fat as compared to Europeans, a lower BMI is more acceptable[30]. In case of Polynesians who have high lean body mass proportions in comparison to Europeans the higher BMI value is suitable.Habib and Aslma[31]observed higher prevalence among obese BMI(33.8±2.36) females as compared to male diabetics(FPG>126mg/dl).In another prospective study involving Caucasians and African American women conducted by Dowlings and Pisunyer[32](1993) suggested BMI had no significant relationship with random plasma glucose(p>0.005).

CONCLUSION

Our study has established the significant role of associations of BMI and medication with glycemic levels. It is clear from our discussion that effective glycemic control cannot be achieved by adopting any single control measure, diabetes related knowledge, awareness and compliance regarding management of diabetes are the first step towards better control of diabetes,in-order to achieve an effective glycemic control in diabetics,diabetics should be more active, should use proper combination of medications, be more aware of dietary changes needed to be incorporated in

their daily diet. Our study population consisted of mostly young males, who reported themselves as sedentary, most of them were on oral anti-diabeticdrugs as a result our study population showed uncontrolled diabetes mellitus predisposing themselves to various complications.

Author's Contribution:

Concept & Design of Study:	Sofia Shoukat
Drafting:	Madeeha Jadoon, Saadia Sadiq
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REFERENCES

1. American Diabetes Association-2019. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care 2019; 42(Supplement 1): S13-S28.
2. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop P, et al. Differentiation of diabetes by pathophysiology, natural history, and prognosis. Diabetes 2017;66:241–55.
3. Arslanian S, Bacha F, Grey M, Marcus MD, White NH, Zeitler P. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes Care 2018; 41: 2648–68.
4. Saisho Y. Changing the Concept of Type 2 Diabetes: Beta Cell Workload Hypothesis Revisited. Endocr Metab Immune Discord Drug Targets 2019;19(2): 121-27.
5. Farooq M. Zinc Deficiency is Associated with Poor Glycemic Control. J Coll Physicians and Surgeons Pak 2019; 29 (3): 253-57.
6. Homan EA, Reyes MV, Hickey KT, Morrow JP. Clinical Overview of Obesity and Diabetes Mellitus as Risk Factors for Atrial Fibrillation and Sudden Cardiac Death. Front Physiol 2019; 7(9):1847-50.
7. Rawshani A, Franzen S, Eliasson B, Svensson A-M, Miftaraj M, McGuire DK, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. N Engl J Med 2017; 376:1407-18.
8. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetescomplications: a review of current evidence. Diabetologia (2019); 62:3–16.
9. Seshasai SR, Kaptoge S,Thompson A, Di Angelantonio E, Gao P, Sarwar N et al. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. New Engl J Medicine 2011; 364:829–41.
10. Meo SA, Zia I, Bukhari IA. Type 2 diabetes mellitus in Pakistan: current prevalence and future forecast. J Pak Med Assoc 2016;66:1637–42.
11. Jianping Ye. Mechanisms of insulin resistance in obesity. Front Med 2013;7(1): 14–24.
12. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet 1989:17;1(8651)1356–9.
13. Paulin and Subramanian. Physical Inactivity among Diabetic Patients in Urban Tamilnadu: A Community-Based Study. J Community Med Health Edu 2019, 9:2;64913.
14. Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med 2017; 23 (7): 804-14.
15. James WPT. Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obesity Research 2001;9:228S–33S.
16. Zhao Q, Laukkanen JA, Li Q, Li G. Body mass index is associated with type 2 diabetes mellitus in Chinese elderly Clin Interv Aging 2017;12:745–52.
17. Bays HE, Chapman RH, Grandy S. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract 2007; 61(5): 737–47.
18. American Diabetes Association. Obesity Management for the Treatment of Type 2 Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019; 42(Supplement 1): S81-S89.
19. Heller S. Weight gain during insulin therapy in patients with type 2 diabetes mellitus. Diabetes Research and Clinical Practice 2004; 65(Suppl. 1):S23–S27.
20. Nuttall FQ. Body Mass Index Obesity, BMI, and Health: A Critical Review. Nutr Today. 2015; 50(3): 117–28.
21. Muc R, Saracen A, Grabska-Liberek I. Associations of Diabetic Retinopathy with Retinal Neurodegeneration on the Background of Diabetes Mellitus. Overview of Recent Medical Studies with an Assessment of the Impact on Healthcare systems. Open Med (Wars) 2018;13: 130–36.
22. Tasnim F, Abdul MC, Muhammad NK. Correlation among BMI, Fasting Plasma Glucose and HbA1c Levels in Subjects with Glycemic Anomalies Visiting Diabetic Clinics of Lahore. Pak J Zool 2009,41(3), 173-78.
23. Gopinath B,Prasad SS, Jaayarama M, and Prabhakara NK.Study of factors associated poor glycemic control in type 2 diabetics. Global J Med Publ Health 2013; 2(2): 2277-9604.
24. Fawwad A, Qasim R, Hydrie MZI., Basit A, Miyan Z, Gul A. Correlation of fasting insulin resistance indices with clinical parameters of metabolic

syndrome in type 2 diabetic subjects. Pak J Zool 2009; 41(3):173-178.
25. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willet WC. Obesity, fat distribution, and weight gain as risks factors for clinical diabetes in men. Diabetes Care 1994; 17:961-9.
26. Boyko EJ, Fujimoto WY,Leonetti DL,Newell-Morris L.Viseral adiposity and risk of type 2 diabetes:a prospective study among Japanese Americans. Diabetes Care 2000;23:465-71 .
27. Despres JP, Pouliot MC, Moorjani S, et al. Loss of abdominal fat and metabolic response to exercise training in obese women; Am J Physiol 1991; (261): E159-62.
28. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G, Gregg EW. Achievement of goals in U.S. diabetes care,1999-2010. New Eng J Med 2013;368: 1613–24.
29. Nguyen NT, Nguyen XM, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey 1999-2006. Obesity 2011;21:351–55.
30. Bakari AG. Onyemelukwe C. Sani BG. Aliyu S. Hassan SS, Aliyu TM. Relationship between casual blood sugar and body mass index in a suburban northern Nigerian population: a short communication. Nigerian J Med 2007; 16:77-8.
31. James WPT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obesity Research 2001; 9:228S–33S.
32. Habib SS, Asalma M. Risk factors, knowledge and health status in diabetic patients. Saudi Med J 2003; 24: 1219-24.
33. Dowling HJ, Pi-Sunyer FX. Race-dependent health risks of upper body obesity. Diabetes 1993; 42:537-43.

Original Article

Micro-Hardness, Degree of Conversion and Elemental Composition of Two Resin

A Comparison of Degree of Conversion, Microhardness and Surface Characterization of Two Commercially Available Composite Materials: An in Vitro Study

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ABSTRACT

Objective: To compare the micro-hardness, degree of conversion and elemental composition of two resin based composites available in the market.

Study Design: Comparative study.

Place and Duration of Study: This study was conducted at the Department of Dental Materials, Islamic International Dental College, Islamabad for 06 months from January 2018 to June 2018.

Materials and Methods: 40 disc shaped specimens of two light cured composite filling materials Filtek™Z250 XT and Filtek™Z250 were irradiated for 20s and 40s. The degree of conversion, micro-hardness, surface characterization and compositional elemental analysis wererecorded and compared.

Results: The degree of conversion (DC) of Filtek™Z250-XT was found to be greater thanFiltek™Z250 composite material yielding a higher mean degree of conversion at 20s and 40s ($p < 0.05$).It was also found that the ultrastructure and size of filler particles of the two composites varied significantly from each other resulting in a statistically significant difference in Vickers hardness micro-hardness (MH) ($p < 0.05$).

Conclusion: The DC and MH of the Filtek™Z250 composite was found to be lower than the Filtek™Z250 XT composite. Additionally, with variations in values compared to those acquired from literature it appears that the Z250 composite acquired is a counterfeit. It is recommended that clinicians should purchase original products from authorized dealers and should remain aware of other commercially available counterfeit dental products.

Key Words: Degree of conversion, micro-hardness, scanning electron microscopy, energy dispersive X-ray analyzer, composite resin, FTIR, Vickers hardness

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INTRODUCTION

Resin based composite materials gained immense popularity among dental practitioners towards the end of the twentieth century. Over the past couple of decades, with an increasing trend of minimal invasive dentistry, the use of composites both as anterior as well as posterior restorative materials has increased tremendously[1].

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Studies have shown that the longevity and quality of resin-based restorations are improving over time and they are being utilized as a substitutes for silver based amalgam restorations in posterior teeth[2].

Dental composites comprise of four main components; inorganic filler particles, an initiator-accelerator system, an organic polymer matrix and a coupling agent. In order to aid handling and improve mechanical properties, fillers are introduced to the polymeric part of the composite. The most common composites are currently being filled with silicate particles based on oxides of the elements Strontium (Sr), Zinc (Zn), Zirconium (Zr), Barium (Ba), and Aluminium (Al)[2]. It is generally believed that greater the amount of filler load both in weight and volume and higher the conversion of the monomers into such a densely packed polymeric network, better shall be the physical properties such as strength and hardness[3].

The degree of conversion (DC) is defined as the extent to which monomers react to form polymers or as the ratio of C=C double bonds that are converted into C–C single bonds[4]. Fourier Transformation Infrared (FTIR) spectroscopy is one of the most commonly used,

powerful and reliable direct methods to detect the C=C stretching vibrations before and after the curing of resin materials[5, 6]. The degree of conversion may play an imperative role in determining the ultimate success of the restoration as the extent of cure may exert not only an effect on the physical and mechanical properties of the resin system but also solubility, dimensional stability, color change, and biocompatibility. The degree of conversion in Bis-GMA-based restorative resins has been analyzed with infrared spectroscopy by a large number of researchers and has been shown to range between 50 to 80%[7].

The Vickers hardness test is effective for measuring the surface hardness of brittle materials. Gajewski et al. suggested that even though different polymers have different reaction kinetics, there exists an almost definitive link between the degree of conversion and the physical properties of composites especially hardness[8].

With the possible existence of widespread sale and utilization of dental composite resins in the Pakistani market, it has become extremely important to verify any compositional changes of suspect materials and the possible effects these variations might have on the physical and mechanical properties of these products. Clinical reports have been issued in regards to the inferior handling properties of recently available Filtek^{TM}Z250 micro-hybrid composites. In order to substantiate such a claim, this in-vitro study was undertaken to compare the degree of conversion, micro-hardness, ultrastructure and elemental analysis of Filtek^{TM} Z250 and Filtek^{TM} Z250-XT restorative composite resins. The aim of this study was therefore to identify any possible difference in the DC, MH, ultra structure and elemental composition between the Filtek^{TM}Z250 and Filtek^{TM}Z250-XT composite resin.

MATERIALS AND METHODS

This experimental study was carried out over a period of six months. The study included two main types of light-cured composite restorative materials; a micro-hybrid composite (ESPE 3M Filtek^{TM}Z250) and a Nano-composite (ESPE 3M Filtek^{TM} Z250 XT) that were randomly collected from a number of suppliers from the twin cities of Rawalpindi and Islamabad. A total of 40 disc-shaped specimens (20 specimens of Filtek^{TM}Z250 and 20 of Filtek^{TM}Z250 XT) were prepared. The specimens were prepared using a metallic mould with a central orifice of 6 mm diameter and a thickness of 2 mm.

Sample preparation and material testing were performed at IRCBM, COMSATS Lahore and at SCME NUST, Islamabad. The main difference between the two materials is related to the fillers incorporated by manufacturers, which are different in size and concentration.

These 20 specimens for each composite material were further subdivided into two groups of 10 specimens each, based on the curing time (20s and 40s). All 40 specimens (before and after curing) were submitted for Fourier transformation infrared spectroscopy(FTIR) for evaluation of the percentage of unreacted carbon to carbon double bonds (C=C) in resin-based composites. All disc-shaped specimens were then submitted for evaluation of Vickers micro-hardness using an ISO standardized hardness tester.

The samples were also submitted for surface characterization and compositional analysis for SEM and EDX.FTIR ATR mode spectra of the uncured and cured specimens of each resin composite were recorded by Fourier transformation infrared spectrometer (Nicolet 6700 FT-IT, Thermo Scientific). For ATR, samples were in direct contact with the ATR diamond crystal. All spectra were collected within the spectral range of 4000-400cm^{-1}. The spectra were measured at 8cm^{-1} resolution accumulating a total of 128 numbers of scans. After collecting spectra of the uncured specimen, the specimen was cured at 20s and 40s using LED light whose tip was in close contact to the mould while curing. The specimens were then stored dry in a sample bottle covered with aluminium foil at room temperature for a few days, after which, Vickers hardness was evaluated with a micro-hardness tester (Wolpert Micro-Hardness Tester 401/402MVD).A load of 50g was applied to the resin disks for 30 seconds, and the scores were recorded in hardness Vickers (HV). The test was performed for every restorative composite resin, and the procedure was divided into 1 indentation for each resin disk.

The surfaces were also slightly etched with a solution of 0.8%(wt./vol) H_3PO_4 for 10 seconds to obtain a clearer image during SEM observation, after which the specimens were oven dried for 1hour at 37-degree centigrade. The samples were then placed on aluminium stubs with conductive tape, sputter coated with gold for 90 seconds and observed under SEM (Vega LMU from TESCAN Brno, Czech Republic) with backscattered electron and secondary electron signals at four different magnifications (1000x, 10000x, 25000x). The compositional analysis was performed using Inca X-Act EDS detector from Oxford Instruments, Oxford UK, which was attached to SEM. Elemental composition of coated samples was determined by performing a line scan throughout the coated thickness.

All data was entered and analysed using SPSS v 23.0. Mean and standard deviation was described for quantitative data, such as micro-hardness and degree of conversion values. The MH and DC values for all samples were tabulated. All data was tested for normality. Statistical comparisons were made between the DC and MH values at 20 s and 40 s between Filtek^{TM} Z250 and Filtek^{TM} Z250-XT. Independent samples T test was used to compare normal data, while the Mann-Whitney U test was applied to compare data

not distributed normally. An arbitrary value of 0.05 was considered to be significant**.**

RESULTS

The degree of conversion of Filtek^{TM}Z250-XT was found to be significantly different from Filtek^{TM}Z250 composite resin, yielding a higher degree of conversion at 20s ($p = 0.052$) and 40s ($p = 0.001$), as shown in table 1. The curing mean values of Z250-XT were $92.90 \pm 14.85cm^{-1}$ and $112.80 \pm 18.37cm^{-1}$, while those for Filtek^{TM}Z250 were 77.60 ± 17.87cm-1 and 84.90 ± $8.72cm^{-1}$ respectively, indicating a much lower degree of conversion in comparison (Table 1).

Figure No.1: Filtek^{TM}Z250 utilized in the study

Figure No.2: Metallic Mould.

Table No.1: Analysis of Degree of Conversion for Filtek Z250 and Filtek Z250 XT

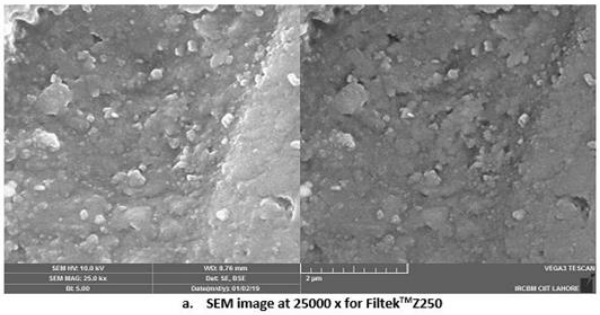
		Filtek Z250	Filtek Z250 XT	Di
Degree of Conversion	20 Minutes	77.60±17.87	92.90±14.85	15 7.3
	40 Minutes	84.90 ± 8.72	112.80±18.37	27 6.4

On analysing the difference in micro-hardness between the two groups, Filtek^{TM}Z250-XT was found to have significantly higher micro-hardness values at both 20 and 40 seconds (Table 2).The mean recorded for micro-hardness of Filtek^{TM}Z250-XT at 20s and 40s curing time was 65.58 ± 10.36KgF and 93.04 ± 14.52KgF respectively. Whereas, Filtek^{TM}Z250 presented with statistically lower micro-hardness mean values recorded at 20s and 40s curing time i.e. 13.03 ± 3.49KgF and 15.20 ± 4.91KgF respectively (Table 2).

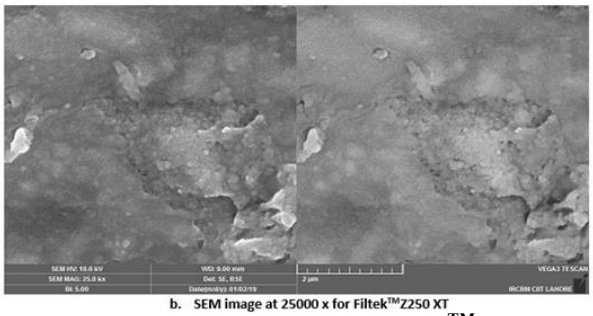
Scanning electron microscope (SEM) observation with backscattered electron and secondary electron provided an adequate contrast between the resin matrix and fillers. The shape and size of filler particles were different amongst the composites. The filler particles size and shape was more uniform and dense in Filtek^{TM}Z250-XT (nano-composite), whereas the particles size and shape in Filtek^{TM}Z250 (micro hybrid) composite were not as dense as in Filtek^{TM}Z250. Filtek^{TM}Z250 showed both micro and nano sized filler particles and the inter filler distance was greater as compared to Filtek^{TM}Z250-XT (Figure 3). Whereas, Filtek^{TM}Z250-XT contained nano sized fillers distribution with little inter-filler distance. The images were taken at 1000x, 10000x, 25000x and 50000x magnification.

Table No.2: Analysis of Microhardness for Filtek Z250 and Filtek Z250 XT

		Filtek Z250	Filtek Z250 XT	Mean Difference	P Value
Micro hardness (KgF)	20 Minutes	13.03 ± 3.49	65.58± 10.36	52.55 ± 3.46	< 0.001
	40 Minutes	15.20 ± 4.91	93.04± 14.52	77.84 ± 4.85	< 0.001



a. SEM image at 25000 x for Filtek^{TM}Z250



b. SEM image at 25000 x for Filtek^{TM}Z250 XT

Figure No. 4: SEM Images for Filtek^{TM}Z-250 and Filtek^{TM}Z-250 XT at 25000x Magnification

Electron dispersive X-ray analysis (EDX) showed the chemical compositions of the restorative composite resins including the elements with relative values expressed in weight percentage. Similar elements such as carbon(C), oxygen (O), silicon Si and zirconium(Zr) were detected; however, the concentration was different

in both composite resins. The filler contents showed interesting differences in elemental composition and concentration. Silicon(Si) and zirconium(Zr) seemed to be a common filler component. Silicon(Si) was present in a greater amount in Filtek^{TM}Z250-XT. Zirconium(Zr) filler content was higher in Filtek^{TM}Z250 (micro-hybrid) in comparison to Filtek^{TM}Z250-XT. The higher concentration of zirconium(Zr) particle in Filtek^{TM}Z250 could be due to the presence of micro size particles. However, some selected areas in Filtek^{TM}Z250 showed a lack of zirconium (Zr) content that might indicate the lower non-uniform distribution of zirconium(Zr) particles throughout the material. The EDX analysis of the Filtek^{TM}Z250-XT composite resin showed the presence of carbon (C), oxygen O, silicon(Si), zirconium(Zr) , and sodium(Na) (Figure 3).

Therefore, the results showed that the Filtek^{TM}Z250-XT composite resin presented significantly superior DC and MH values when compared to the Filtek^{TM}Z250 composite resin. The comparison revealed that most filler particles are of irregular shape with increased inter-particle distance and non-uniform distribution of filler particles in Filtek^{TM}Z250 composite resin and hence decreased filler load, which indicate low DC and MH values.

DISCUSSION

The Filtek^{TM}Z250 is being sold in the Pakistani market owing to its low price in comparison to other composites. Filtek^{TM}Z250 showed inferior properties comparative to the other tested composite. The findings suggest that even though this composite has a similar packaging and therefore not easily discernible as a counterfeit product, the compositions of the resin, filler and quality are significantly different.

Literature suggests that hardness values that exceed 50 (VHN) are ideal for composite resins. Comparing the hardness values of Filtek^{TM}Z250 obtained in this study with literature values, it was concluded that the this material currently available in the market is not ideal and the values for its VHN were below 50 (VHN)[3, 10,11].According to literature, the VHN values of commercially available authentic Filtek^{TM}Z250 are higher as compared to the Filtek^{TM}Z250 tested in this study[12]. Thus, it was concluded from this study that Filtek^{TM}Z250 utilized in this study was similar in packaging to the original Filtek^{TM}Z250 but its characterization revealed that this material was counterfeit.SEM images revealed that the counterfeit Filtek^{TM}Z250 samples have irregular particles with particle size of 0.01-3.5 µm and original Filtek^{TM}Z250-XT contains spherical shaped filler particle materials of size 20–25 nm. Comparatively, Filtek^{TM}Z250-XT yielded higher mean values for Vickers hardness and contained a higher filler load in comparison to the Filtek^{TM}Z250 composite resin. These results suggest that the hardness of the counterfeit composite resin (Filtek^{TM}Z250) could possibly have been enhanced by increasing the filler load concentration as this would result in improved packing of fillers in the polymer matrix.

Previous literature shows that the intensity of light decreases as it passes through the bulk of the restorative material, which in turn reduces the polymerization potential by reduction of the light intensity passing through[13,14]. Major factors associated with light attenuation include absorption and scattering within the material[15], and reflection from the surface of the restoration[16]. These factors are dependent on the composition of the material, predominantly the filler content, type, size and the shape of the particles[17, 18]. This study showed the micro-hybrid composite resin to have lower mean hardness values. This could be attributable to the diameter of the fillers causing light attenuation. Consequently, the composite with the lesser diameter fillers (Filtek^{TM}Z250-XT) showed the highest Vickers mean hardness values. Hardness values are also used as an indication of the depth of cure or degree of polymerization. Comparable studies showed that if hardness ratio is below 80%, it could indicate poor polymerization in the test sample. Taking the micro hardness values into consideration, it could be suggested that the Filtek^{TM}Z250 used in this study may not have been adequately polymerized. However, the values of DC obtained in this study showed the degree of polymerization within the acceptable range, suggesting adequate polymerization had taken place. These results indicate that this dental composite resin has adequate curing efficiency, which is not reflected by their hardness values.

The DC for Filtek^{TM}Z250-XT was significantly higher than Filtek^{TM}Z250 at both 20 seconds and 40 seconds. Both micro-hybrid (Filtek^{TM}Z250) and nano-hybrid composites (Filtek^{TM}Z250-XT) were used with a consistent thickness of 2mm. The findings also showed that composites cured using the LED light curing unit at 40s had a higher degree of conversion compared to those cured at 20s. Giorgi et al suggested that the irradiation time may affect the degree of conversion (DC)[19]. Literature also confirms that longer irradiation times produce a higher DC. Both composite resins in the current study reached an acceptable DC through irradiation at 20s and 40s using LED curing light. The higher degree of conversion observed in Filtek^{TM}Z250-XT and adequate DC observed in Filtek^{TM}Z250 composite resins can be explained by the presence of UDMA. UDMA based resins have proven to be more reactive than bisGMA-based resins[20]. The higher conversion level in Filtek^{TM}Z250-XT could also be related to the partial substitution of the relatively stiff, hydrogen-bonded bisGMA molecules due to longer and more flexible bisGMA molecules. For Filtek^{TM}Z250, the lower aliphatic: aromatic ratio could be an additional possible reason[21]. In this study, as both

Filtek™Z250 and Filtek™Z250-XT composite resins have the same polymeric matrix, the difference could rather be attributed to the filler particle size. Furthermore, the DC is said to be increased upon decreasing the distance of the light curing tip, using the fiber optic light guide tip and upon increasing the time of irradiation[22-24].

The distributions of filler particles seen in the SEM-images may indicate a larger inter-particle distance in Filtek™Z250 than in Filtek™Z250-XT. Energy Dispersive X-ray analyser (EDX)results indicate the presence of carbon(C), oxygen(O), silicon(Si) and zirconium(Zr) in Filtek™Z250 (micro-hybrid). The elements carbon(C), oxygen O and zirconiumZr are present in relatively higher concentrations and silicon(Si) is found in relatively lower concentrations in comparison to literature values. Contrary to literature which indicates the presence of sodium(Na) contents in Filtek™ Z250, this study presented an absence of sodium(Na) . Rogelio investigated light cure restorative composite resins which had recently been improved. The EDX results for Filtek™ Z250 indicated the presence of carbon(C), oxygen(O) , sodium(Na), silicon Si, and zirconium(Zr) in concentrations of 37.69, 33.21, 0.17, 19.77 and 9.16 respectively[25]. On the contrary, our study shows the presence of carbon(C), oxygen(O), silicon(Si) and zirconium(Zr) in concentrations of 50.41, 37.21, 12.37 and 14.28 respectively in our sample of Filtek™Z250. This could indicate why the material currently available in the market may not be up to standard as well as it does not meet the clinical demands in terms of mechanical properties. Filler morphology and inter-particle spacing which is dependent on filler load volume and size has proven to be another key factor affecting the wear resistance of composites. The shorter the distance between the particles, the better the matrix will be protected against wear and scratch. From this study it is evident thatFiltek™Z250 had a lower microhardness value owing to greater inter-filler distance in comparison to Filtek™Z250-XT.

This study compared two different composite materialswithout any prior bias, out of which one turned out to be counterfeit based after investigations. Future studies should focus on testing multiple counterfeit composites with tested products of the same filler type.

CONCLUSION

The present study suggests that Filtek™Z250-XT has superior properties, in comparison to Filtek™Z250. The Filtek™Z250 used in this study was a counterfeit product that had a packaging exactly similar to the original company-manufactured product. However, the production was not done under standardized conditions and hence the micro hardness, degree of conversion and the elemental composition were significantly compromised. It is recommended that dentists should remain aware of commercially available counterfeit dental products since these are highly likely to show poor performance in the patients.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Lang B, Jaarda M, WANG RF. Filler particle size and composite resin classification systems. J Oral Rehabilitation 1992;19(6):569-84.
2. Faltermeier A, Rosentritt M, Faltermeier R, Reicheneder C, Müßig D. Influence of filler level on the bond strength of orthodontic adhesives. The Angle Orthodontist 2007;77(3):494-8.
3. Uhl A, Sigusch BW, Jandt KD. Second generation LEDs for the polymerization of oral biomaterials. Dental Materials 2004;20(1):80-7.
4. Yoshida K, Greener E. Effects of two amine reducing agents on the degree of conversion and physical properties of an unfilled light-cured resin. Dental Materials 1993;9(4):246-51.
5. DeWald J, Ferracane J. A comparison of four modes of evaluating depth of cure of light-activated composites. J Dental Research 1987;66(3):727-30.
6. Imazato S, McCabe J, Tarumi H, Ehara A, Ebisu S. Degree of conversion of composites measured by DTA and FTIR. Dental Materials 2001;17(2):178-83.
7. Ferracane J, Mitchem J, Condon J, Todd R. Wear and marginal breakdown of composites with various degrees of cure. J Dental Research 1997;76(8):1508-16.
8. Gajewski VE, Pfeifer CS, Fróes-Salgado NR, Boaro LC, Braga RR. Monomers used in resin composites: degree of conversion, mechanical properties and water sorption/solubility. Brazilian Dental J 2012;23(5):508-14.
9. Sabatini C. Comparative study of surface microhardness of methacrylate-based composite resins polymerized with light-emitting diodes and halogen. Eur J Dentis 2013;7(3):327.
10. Catelan A, de Araújo LSN, da Silveira BCM, Kawano Y, Ambrosano GMB, Marchi GM, et al. Impact of the distance of light curing on the degree of conversion and microhardness of a composite

resin. Acta Odontologica Scandinavica 2015;73(4):298-301.
11. Neumann MG, Miranda Jr WG, Schmitt CC, Rueggeberg FA, Correa ICJJod. Molar extinction coefficients and the photon absorption efficiency of dental photoinitiators and light curing units 2005;33(6):525-32.
12. Lodhi T, Strydom. Influence of shade on curing hardness of two nanocomposites 2014;5:227-32.
13. Dunn WJ, Bush ACJTJotADA. A comparison of polymerization by light-emitting diode and halogen-based light-curing units 2002;133(3): 335-41.
14. Rueggeberg F, Craig RJJoDR. Correlation of parameters used to estimate monomer conversion in a light-cured composite 1988;67(6):932-7.
15. Yearn J. Factors affecting cure of visible light activated composites. Int Dental J 1985;35(3):218-25.
16. Watts D, Amer O, Combe EJDM. Surface hardness development in light-cured composites 1987;3(5):265-9.
17. Abuelenain DA, Neel EAA, Al-Dharrab A. Surface and mechanical properties of different dental composites. Aust J Dent 2015;2(2):1-5.
18. Galvão MR, Caldas SGFR, Bagnato VS, de Souza Rastelli AN, de Andrade MF. Evaluation of degree of conversion and hardness of dental composites photo-activated with different light guide tips. Eur J Dentis 2013;7(1):86.
19. Caldas Giorgi MC, Theobaldo J, Nunes Leite Lima DA, Marchi GM, Ambrosano GM, Baggio Aguiar FH. Influence of successive light-activation on degree of conversion and knoop hardness of the first layered composite increment. Acta Odontologica Scandinavica 2015;73(2):126-31.
20. Lovell LG, Lu H, Elliott JE, Stansbury JW, Bowman CNJDM. The effect of cure rate on the mechanical properties of dental resins 2001;17(6):504-11.
21. Emami N, Söderholm K-JM, Berglund LA. Effect of light power density variations on bulk curing properties of dental composites. J Dentis 2003;31(3):189-96.
22. Mills R, Jandt K, Ashworth SJBdj. Restorative Dentistry: Dental composite depth of cure with halogen and blue light emitting diode Technol 1999;186(8):388.
23. Obici AC, Sinhoreti MAC, Correr-Sobrinho L, Góes MFd, Consani SJJoAOS. Evaluation of mechanical properties of Z250 composite resin light-cured by different methods 2005;13(4):393-8.
24. Uhl A, Mills RW, Jandt KDJB. Photoinitiator dependent composite depth of cure and Knoop hardness with halogen and LED light curing units 2003;24(10):1787-95.
25. Par M, Marovic D, Skenderovic H, Gamulin O, Klaric E, Tarle ZJCoi. Light transmittance and polymerization kinetics of amorphous calcium phosphate composites 2017;21(4):1173-82.

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List of all contributors who do not meet the criteria for Authorship, such as a person who provided purely technical help, writing assistance or department chair who provided only general support. Financial & Material support should be acknowledged.

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