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Editorial

Sports and Steroids; Is It Worth It?

Mohsin Masud Jan
Editor

Now, we have all heard stories about the use, rather misuse of steroids among athletes, more prominently bodybuilders, but before delving into that, let's take a look at what exactly are these steroids? Anabolic steroids are synthetic variations of the male sex hormone testosterone. The proper term for these compounds is anabolic-androgenic steroids. "Anabolic" refers to muscle building, and "androgenic" refers to increased male sex characteristics. Some common names for anabolic steroids are Gear, Juice, Roids, and Stackers. Health care providers may often prescribe steroids to treat hormonal issues, such as delayed puberty. Steroids can also treat diseases that cause muscle loss, such as cancer and AIDS. But, today, our topic of concern is the abuse, rather than the appropriate use of steroids, we won't go deeper into that.

Some athletes and bodybuilders abuse these drugs to boost performance or improve their physical appearance. People who abuse anabolic steroids usually take them orally or inject them into the muscles. These doses may be 10 to 100 times higher than doses prescribed to treat medical conditions. Steroids are also applied to the skin as a cream, gel, or patch.

Some athletes and others who abuse steroids believe that they can avoid unwanted side effects or maximize the drugs' effects by taking them in ways that include:

- cycling—taking doses for a period of time, stopping for a time, and then restarting
- stacking—combining two or more different types of steroids
- pyramiding—slowly increasing the dose or frequency of abuse, reaching a peak amount, and then gradually tapering off

There is no scientific evidence that any of these practices reduce the harmful medical consequences of these drugs.

Why do these athletes abuse steroids in such a manner? Let's take a look at the athletic benefits of roids.

1) Increased Muscle Strength
2) Increased Body Size
3) Increased Healing Rate
4) Increased Stamina and Energy
5) Helps in losing fat

Now, Considering these benefits, who would not want to pop a few pills to achieve their goals, more so when your livelihood depends on your ability to move faster, to lift more weight, or just to simply look good without a shirt on. And it is the desire to achieve all these goals that drives athletes to use steroids, and in the long run end up abusing them.

Moving on, let us take a look at the cons related with roid use.

Short-Term Effects: Abuse of anabolic steroids may lead to mental problems, such as:

- paranoid (extreme, unreasonable) jealousy
- extreme irritability
- delusions—false beliefs or ideas
- impaired judgment

Extreme mood swings can also occur, including "roid rage"—angry feelings and behavior that may lead to violence.

Aside from mental problems, steroid use commonly causes severe acne. It also causes the body to swell, especially in the hands and feet.

Long-Term Effects

Anabolic steroid abuse may lead to serious, even permanent, health problems such as:

- kidney problems or failure
- liver damage
- enlarged heart, high blood pressure, and changes in blood cholesterol, all of which increase the risk of stroke and heart attack, even in young people

Several other effects are gender- and age-specific:

- In men:
    - shrinking testicles
    - decreased sperm count
    - baldness
    - development of breasts
    - increased risk for prostate cancer
- In women:
    - growth of facial hair or excess body hair
    - male-pattern baldness
    - changes in or stop in the menstrual cycle
    - enlarged clitoris
    - deepened voice
- In teens:
    - stunted growth (when high hormone levels from steroids signal to the body to stop bone growth too early)
    - stunted height (if teens use steroids before their growth spurt)

Some of these physical changes, such as shrinking sex organs in men, can add to mental side effects such as mood disorders.

Internationally, in countries such as the USA, there are heavy rules and regulations in place to prevent athletes from abusing steroids, and even then, every now and then, some athlete or bodybuilder dies due to the inherent risks associated with steroid abuse. But, in a country such as ours, a developing country, where there are no rules and regulations per se, let alone sports, and where most medications are available over the counter without any hassle, steroid abuse is rampant. And add to that the illiteracy, that rampant steroid abuse instantly turns a hundred times more fatal, and as we so often see on the news, some aspiring bodybuilder dies due to steroid misuse, because he had no idea what or how to use steroids let alone their inherent risks.

The mere lack of awareness of the side effects of steroids, and the burning desire to build a body like that of the greats of bodybuilding, leads several youngsters to the use of steroids, and not knowing what the side effects are or how to deal with them, many of these youngsters end up paying a heavy price for the physique they had been trying to achieve. As to this end, there needs to be an effort made by health professionals and gym owners to thwart the use of anabolic steroids. The government needs to ensure that such medications are not available to the general public without a doctor's prescription. And all sports boards, need to enforce more strict regulations when it comes to steroid use and their athletes.

Original Article

A Clinical Study of Incidence and Risk Factors Associated with Oral Premalignant Lesions

Oral Premalignant Lesions

Nazar Muhammad Afridi[1], Rana Tauqir Ullah Khan[2], Zar Khan[3] and Muhammad Usman Anjum[4]

ABSTRACT

Objective: To the determine prevalence of oral premalignant lesions as well as to identify the risk factors associated with these lesions,

Study Design: Descriptive study,

Place and duration of study: This study was conducted at the Frontier Medical and Dental College, Abbottabad from January 2016 to June 2017,

Materials and Methods: All those patients who were more than 20 years of age and whowere diagnosed cases of oral premalignant lesions were included while those patients who were already diagnosed with oral cancers were excluded from the study. Detailed history was taken specifically about risk factors such as history of smoking, use of betel quid, consumption of snuff (naswar) and alcohol, clinical examination was performed and details were recorded in a pre-structured proforma. All oral lesions were diagnosed by an experienced clinician and confirmed on histopathological examination of the biopsy samples taken from these lesions. Data was entered and analyzed using SPSS, version 21.

Results: Mean age of study participants was 40±8.4 years with 60% of them were males and 40% were females. Most of the patients, 52.5%, were between the ages of 20-40 years showing higher predilection for this age group. The most common site of involvement was buccal mucosa, 58 cases, followed by tongue, 40 cases, floor of mouth, 12 cases, and palate, 10 cases. Regarding types of oral premalignant lesions, the most common lesion diagnosed was leukoplakia, 90 cases, followed by erythroplakia, 15 cases, and oral submucous fibrosis, 12 cases. Lichen planus was quite infrequent as it was observed in only 3 cases. The most common risk factor observed was cigarette smoking, 45%, followed by betel quid, 15% and snuff (naswar), 7.5%. None of the study participants admitted to being using alcohol.

Conclusion: Oral premalignant lesions especially leukoplakia and erythroplakia are quite common. Tobacco smoking and betel quid use are strong risk factors for development of these lesions. Mass education programs should be initiated to increase awareness among masses about the risk factors associated with these diseases so as to decrease their incidence. Similarly, all oral lesions should be diagnosed early and mass lesions should be biopsied to make an accurate diagnosis as early diagnosis and treatment can prevent their progression to cancers.

Key Words: Premalignant, Oral Cavity

Citation of article: Afridi NM, Khan RTU, Khan Z, Anjum MU. A Clinical Study of Incidence and Risk Factors Associated with Oral Premalignant Lesions. Med Forum 2017;28(11):3-6.

INTRODUCTION

Oral cancers constitute a series and emerging problem globally and oropharyngeal cancers are ranked sixth amongst the most common cancers worldwide.[1] Globally the prevalence of oral cancers is estimated to be 2-4%. However, in certain areas like south Asia prevalence rates are quite high, about 45% in India and 10% in Pakistan.[2] Oral cancers are generally preceded by lesions, which are called potentially malignant disorders, which are benign in the beginning but have a potential to transform to cancers later on if not diagnosed and treated early. Therefore, such lesions are called premalignant. Most common among these oral premalignant lesions are oral leukoplakia, oral erythroplakia and oral submucous fibrosis.[3, 4]

Various different risk factors are associated with the development of oral premalignant lesions. These risk factors comprise of tobacco smoking and chewing, betel quid chewing and alcoholism with tobacco smoking being the most important of these risk factors.[3,5] Several other factors like diabetes mellitus, obesity and low fiber intake also play asignificant role in the development of such lesions.[6]

These lesions severely impair quality of life of the individual and society but also put an enormous burden on health care system. The incidence of these lesions can be reduced by primary prevention through public awareness and modification of the risk factors. Early and accurate diagnosis of these lesions markedly

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improves their outcome. Therefore, we have conducted this study to determine prevalence of oral premalignant lesions and to identify the common risk factors associated with these lesions.

MATERIALS AND METHODS

This study was conducted in Frontier Medical and Dental College, Abbottabad, from January 2016 to June 2017. All those patients who were more than 20 years of age and who were diagnosed cases of oral premalignant lesions were included in study. On the other hand, those patients who were younger than 20 years of age or who were already diagnosed cases of oral cancers were excluded from this study. After taking informed consent, detailed history was taken specifically about risk factors such as history of smoking, use of betel quid, consumption of snuff (naswar) and alcohol, clinical examination was performed and details were recorded in a pre-structured proforma. All oral lesions were diagnosed by an experienced clinician and confirmed on histopathological examination of the biopsy samples taken from these lesions. Data was entered and analyzed using SPSS, version 21.

RESULTS

There were one hundred and twenty patients in this study. Mean age of study participants was 40±8.4 years. Males constituted 60% of the study sample while females accounted for 40% with male to female ratio of 1.5:1, as shown in Figure 1.

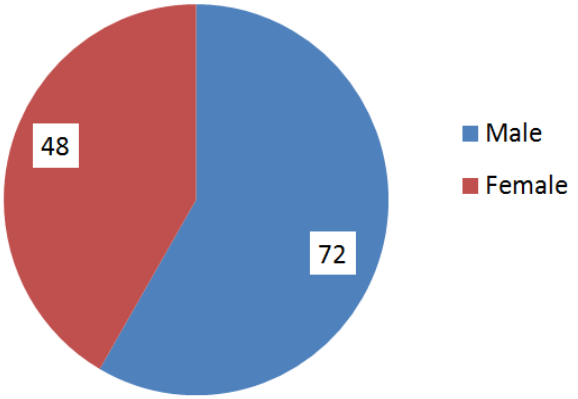

Figure No.1: Gender distribution of patients, (n=120)

Majority of the patients, 52.5%, were between the ages of 20-40 years showing higher predilection for this age group years while 43.33% belonged to 41-60 years of age, Table 1.

Table No.1: Age-wise distribution of study population, (n=120)

Age	Number	Percentage
20-40	63	52.5%
41-60	52	43.33%
61-75	05	4.17%
Total	120	100%

The most common site of involvement was buccal mucosa, 58 cases, followed by tongue, 40 cases, floor of mouth, 12 cases, and palate,10 cases, Figure 2.

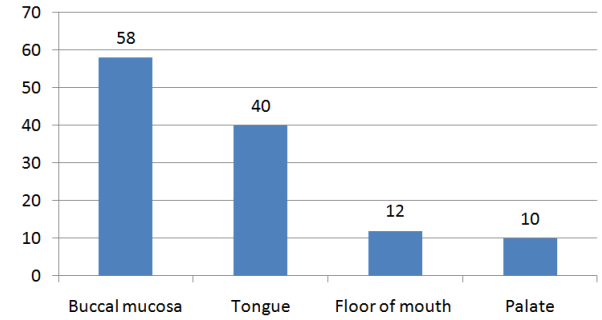

Figure No.2. Site of oral premalignant lesions, (n=120)

Regarding types of oral premalignant lesions, the most common lesion diagnosed was leukoplakia, 90 cases, followed by erythroplakia, 15 cases, and oral submucous fibrosis, 12 cases, Table 2. Lichen planus was quite infrequent as it was observed in only 3 cases.

Table No.2. Types of oral premalignant lesions, (n=120)

Type of Lesion	Number	Percentage
Leukoplakia	90	75%
Erythroplakia	15	12.5%
Oral submucous fibrosis	12	10%
Lichen planus	03	2.5%
Total	120	100%

Gender wise stratification of oral premalignant lesions is given in Figure 3. Overall, oral premalignant lesions were more common in males, 72 cases, than females, 48 cases. As per type of oral lesions, leukoplakia was considerably more common in males while rest of the lesions were common among females showing higher predilection for female gender.

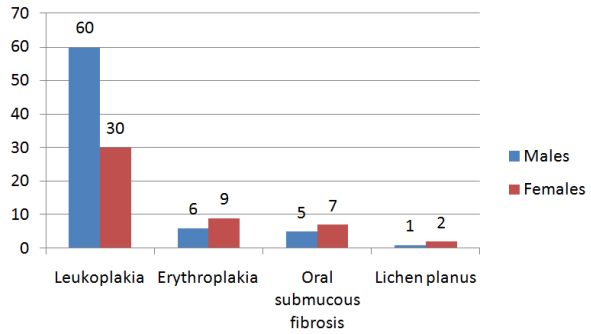

Figure No. 3.Gender-wise distribution of oral premalignant lesions, (n=120)

Table 4 delineates the commonest risk factors associated with the development of oral premalignant lesions. Only 81 patients admitted that they were using any of the substances, which constitutes risk factors for the development of these lesions, like cigarette

smoking, betel quid or naswar. The most common risk factor observed was cigarette smoking, 45%, followed by betel quid, 15% and snuff (naswar), 7.5%.None of the study participants admitted to being using alcohol.

Table No.4: Risk factors associated with oral lesions, (n=81)

Variable	Number	Percentage
Tobacco smokers	54	45%
Betel quid	18	15%
Snuff (Naswar)	09	7.5%
Alcohol	-	-
Total	81	67.5%

Table 5 shows that mostly men indulged in the habit of using these substances. Among males, cigarette smoking was the most common substance used followed by betel quid and naswar. As compared to males, females preferred betel quid and smoking as compared to any other type of addiction.

Table No.5.Stratification of risk factors based on gender, (n=81)

Gender	Male		Female		Total	
Risk factor	Number	%age	Number	%age	Numbe	%age
Tobacco smoking	50	41.67%	04	3.33%	54	45%
Betel quid	11	9.17%	07	5.83%	18	15%
Snuff (Naswar)	09	7.5%	-	-	09	7.5%
Alcohol	-	-	-	-	-	-

DISCUSSION

Premalignant lesions of oral cavity are named so because they carry significant risk of transformation into malignancy. Early detection and prompt treatment of these lesions is very important so as to avoid malignant transformation which later leads to high morbidity and mortality.[7]

Overall, oral premalignant lesions were more common in males than females in our study. This finding is substantiated by other studies. Kumar et al and Agrawal et al, both reported that the prevalence of oral premalignant lesions was significantly higher among male Indian subjects.[3, 8] Similarly, Chung et al have found that these lesions were more common among male gender in Taiwan.[9] It is believed that the reason for males being more affected by these lesions is that they are more prone to tobacco consumption and hence, at a higher risk of developing these lesions. We have found that majority of these lesions were present in patients who were between the ages of 20-40 years. Likewise, Agrawal et al have also reported that the peak incidence of benign oral lesions was between the ages of 30-39 years in their study.[8] Similarly, Pudasaini and Baral have conducted a study on the prevalence of oral cavity lesions in Nepal. Most of their study population, 47.6%, was also between the ages of 20-40 years.[10]

In our study, the most common sites of oral premalignant lesions werebuccal mucosa and tongue. Similarly, according to Modi et al, the commonest site of oral lesions was buccal mucosa and then tongue.[11] According to Pudasaini and Baral, lips followed by buccal cavity was the chief site affected by oral lesions among their Nepalese patients.[10]This varying pattern of site involvement could be attributed to the different geographical areas as well as varying pattern and modes of usage of substances e.g. tobacco, alcohol, etc. which constitute risk factors of developing these diseases.

Regarding types of oral premalignant lesions, the most common lesion diagnosed was leukoplakia followed by erythroplakiaand submucous fibrosis. Lichen planus was least common.Kumar et al have also reported that leukoplakia followed by oral submucous fibrosis were the most common oral premalignant lesions among Indian factory workers.[12]In another study which was conducted in India by Kumar et al, they have found that the commonest oral premalignant lesion among their study subjects was oral submucous fibrosis followed by leukoplakia while eryhtroplakia was least common.[3]Likewise, Gupta et al have reported that the most frequent oral premalignant lesions in their study were oral submucous fibrosis and leukoplakia while least common lesion was lichen planus.[13] This variation in the prevalence of different oral premalignant lesions wouldbe attributed to the fact that these studies were performedin different geographical areas which have different rates of tobacco and alcohol consumption as well as varying environmental, cultural, dietary and religious factors.

The commonest risk factor observed was cigarette smokingfollowed by betel quidand snuff (naswar).Male patients preferred cigarette smoking followed by betel quid and snuff while female patients preferred betel quid and tobacco smoking. As per Gupta et al, majority of their study subjects, 49.5%, used tobacco followed by pan masala ingestion.[13]Similarly, Kavarodi et al have reported that their subjects used tobacco followed by betel quid.[14]None of our study participants admitted to being using alcohol.Consuming alcohol is religiously prohibited in our society as well as it's a social taboo. Even if people consume it, they will not admit it.

CONCLUSION

Oral premalignant lesions especially leukoplakia and erythroplakiaare quite common. Tobacco smoking and betel quid use are strong risk factors for development of these lesions. Mass education programs should be initiated to increase awareness among masses about the risk factors associated with these diseases so as to decrease their incidence. Similarly, all oral lesions should be diagnosed early and mass lesions should be biopsied to make an accurate diagnosis as early diagnosis and treatment can prevent their progression to cancers.

Author's Contribution:

Concept & Design of Study:	Nazar Muhammad Afridi
Drafting:	Rana Tauqir Ullah Khan
Data Analysis:	Zar Khan, Muhammad Usman Anjum
Revisiting Critically:	Nazar Muhammad Afridi, Rana Tauqir Ullah Khan
Final Approval of version:	Nazar Muhammad Afridi

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

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Original Article

Efficacy of Lactobacillus Reuteri in Acute Watery Diarrhea

Muhammad Aqeel Khan[1], Muhammad Bilal Khattak[2], Arshia Munir[3] and Irum Naz[3]

ABSTRACT

Objective: To evaluate the efficacy of lactobacillus reuteri in acute watery diarrhea

Study Design: Randomized Clinical Trial study.

Place and Duration of Study: This study was conducted at the Department Pediatrics, KGMC / HMC Peshawar from 24th April to 23th October 2015

Materials and Methods: This RCT included 96 patients from age 6 to 55 months admitted as a case of acute watery diarrhea were enrolled in the study. After consent taken from attendants, the patients were randomly assigned to one of the study groups; either L. reuteri (5drops or 100 million cfu per day of L. reuterior) or the other group with placebo and the therapy was given for 5 days in each case. The outcome was measured in severity (frequency) and duration of the diseased.

Results: Out of 96 patients, half were subjected to L. reuteri. L.reuteri was given in a dose of 5 drops daily and patients were observed for effectiveness. The effectiveness was observed in 58 patients 24 (50%) from the placebo group and 34 (70%) from the L.reuteri group. This showed that L. reuteri was more effective than placebo in children with acute watery diarrhea with a P value of <0.05.

Conclusion: The study showed that lactobacillus reuteri group not only decreased the severity of the acute watery diarrhea but it also decreased the duration of the disease as compared to the placebo group.

Key Words: Acute watery diarrhoea, probiotics, frequency of stools

Citation of article: Khan MA, Khattak MB, Munir A, Naz I. Efficacy of Lactobacillus Reuteri in Acute Watery Diarrhea. Med Forum 2017;28(11):7-11.

INTRODUCTION

The diarrheal is mainly classified under four headings i.e. acute watery diarrhea, acute dysentery (acute bloody diarrhea), persistent and diarrhea with malnutrition[1]. Acute watery diarrhea is occurs suddenly and ranges from hours to days and defined as a increase in the water component of stools or big watery stool and /or an increase in the frequency of stool than the usual one i.e. more than 3 in 24 hours, with or without other symptoms like fever and vomiting[1,2,3] . In most of the cases acute watery diarrhea lasts for or less than a week and never equal to or more than 14 days. With more than 1.4 of the 9 million child deaths occurred due to diarrhea and almost half of this mortality burden was shared by five countries of the world including Pakistan. The incidence of acute watery diarrhea is quite common before three years of age ranges from 0.5 to 1.9 episodes per child per year[4-7].

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Oral rehydration therapies (ORT) is playing vital role in managing acute watery diarrhea with no or some dehydration[8]. Though the composition of oral rehydration solution heals the dehydration status or helps dehydration not to happen, it neither shortens the duration of the illness nor reduces the stool loss[9,10]. Probiotics including Lactic acid bacteria are non pathogenic bacteria which is important constituent of the normal flora. The probiotics have multiple beneficial effects on human beings and produce multiple beneficial effects for human beings like helping in lactose intolerance, all types of diarrhea. It also helps in healing the peptic ulcer disease, stimulates the immune system and helps in decreasing or healing allergies including atopy and lower allergic airway disorder[11]. The World Health Organization defines the probiotics as living organisms which in certain amount produce health benefit effects on the body of the host [12]. Studies have strongly favored that probiotics are extremely beneficial effects on acute watery diarrhea. The probiotics not only decreases the frequency of the diarrheal diseases but also decreases the duration of the diarrheal diseases. Probiotics along with the oral rehydration therapy it has got a vital effect on the severity and duration of the diarrheal diseases[13].

The rationale of this study was to determine the efficacy of lactobacillus reuteri in patients presenting with acute watery which is easy to introduce to all age groups and study on this very probiotics has not been done in our setup.

MATERIALS AND METHODS

This randomized controlled trial was conducted at the department of Paediatrics, KGMC / HMC, Peshawar. Non-probability consecutive sampling was used for sample selection. Using WHO calculator sample size in each group was 48 using P1 = 74% and P2 = 45% power of test is 90 % and level of confidence is 5 %. Both genders with age range between 6months to 5 years of age and duration of illness less than 7 days were included in the study. Clinical signs of some dehydration (skin pinch goes back slowly <2sec, sunken eyes and eager to drink) which was confirmed clinically. All patients who had some dehydration but could not tolerate probiotic orally. All patients with chronic diarrhea, blood in stool, using antibiotics/probiotics, in coma, shock and persistent vomiting were excluded from the study.

All patients who presented with acute diarrheal illness were admitted to pediatrics ward. The biodata, anthropometry and status of the dehydration were documented at the time of admission. All children were randomly assigned whether they will receive Lactobacilli reuteri (dose 5drops or 100million cfu per day irrespective of weight) or placebo. The therapy was started at the time of admission according to random group allocation. Detailed history and clinical examination were performed for all patients. All patients were managed using standard management protocol for diarrhea including ORT (oral rehydration therapy). Relevant laboratory investigations were performed such as stool R/E, Serum electrolytes, Full blood count.

The data was analyzed on SPSS version 20. Descriptive statistics were used to calculate Mean ± SD for numerical variables like age and duration of illness. Frequencies and percentages were calculated for categorical variables like gender, and proportion of patient having shown clinical efficacy in both the groups. Efficacy was stratified among age, gender and duration of illness to control effect modifiers. Chi-square test was used to determine the difference in the proportion of two groups keeping p–value of≤ 0.05 as significant.

RESULTS

A total of 96 cases of children presenting with acute watery diarrhea were included in the study and followed up for efficacy of treatment. Amongst 96 patients 58 (60.4%) were males and 38(39.6%) were females. The maximum number of patients (more than 60%) was in the age groups 6 to 18 months and only a small percentage in age groups more than 55months. The minimum age of our sample was 6months and the maximum age was 60months with a mean age of 20.3 months.

Effectiveness of treatment was observed in different genders .Among 58 male patients 31 patients (53%) improved with treatment, while in 38 female patients treatment was effective in 27 patients (71%) with P. Value of 0.093 as given in Table 1.

Table No.1: Effectiveness of treatment among both genders n=96

Effectiveness	Gender of the patient			P. value
	Male	Female	Total	
Effective	31	27	58	
Non effective	27	11	38	
Total	58	38	96	0.093

These patients were divided equally in placebo and h lactobacillus reuteri group. They were further subdivided into different age groups with maximum number of patients in age group 6-18months. 30 patients from the placebo and 31 from the L.reuteri group belonged to this age group given in table 02.

Table No.2: Age wise distribution into both treatment groups n=96

Age in Months	Lact. Reutri not given	Lact Reutri given	Total
6-18 months	30	31	61
19-30	08	07	15
31-42	05	02	07
43-54	05	05	10
>55	00	03	03
Total	48	48	96

While stratifying children with acute diarrhea with regards to gender groups, we found that among 58 male patients 26 (45%) were given L.reuteri and among 38 female patients 22 (58%) were subjected to L.reuteri group as shown in table 3.

Table No.3: Effectiveness of treatment among both genders n = 96

Treatment group of patient	**Gender of the patient**		
	Male	**Female**	**Total**
L. Reuteri not given	32	16	48
L. Reuteri given	26	22	48

Table No.4: Cross tabulation of effectiveness among both treatment groups

Efficacy of treatment	Treatment group of patients		Total	P.value
	L. Reuteri Not given	L. Reuteri Given		
Effective	20	31	51	
Non Effective	28	17	45	0.04
Total	48	48	96	

On the basis of operational definition efficacy was observed in 58 patients 24 (50%) from the placebo group and 34 (70%) from the L.reuteri group. This showed that L.reuteri was more effective than placebo

in children with acute watery diarrhea with a p value of <0.05 given in table 4 and 5.

Table No.5: Effectiveness of treatment among different age groups

Age group	Efficacy of treatment			P.value
	effective	Non effective	Total	
6-18	36	25	61	
19-30	8	7	15	
31-42	4	3	7	0.015
43-54	7	3	10	
>55	3	0	3	
	58	38	96	

Duration of illness was observed in both groups. Among 48 patients who were given L.Reuteri, 30 patients (62.5%) had duration of illness less than 36 hours. In the placebo group only 19 patients (39.5%) got improved in 36hours with p value of 0.041 as shown in table 6.

Table No.6: Duration of illness in both groups of patients

Groups of patients	Duration of illness		
	0-36 hours	37-72hours	Total
L.Reuteri not given	19	29	48
L.Reuteri given	30	18	48
Total	49	47	96

p Value : 0.041

DISCUSSION

Acute watery diarrhea is one of the important causes of mortality throughout the world. The mortality due to diarrheal diseases in the early days i.e. 70s was as high as 5 million childhood deaths globally each year. The invention of oral rehydration solution played an unbelievable role in reduction of deaths from dehydration secondary to acute watery diarrhea especially under five years of age [15]. Acute diarrheal diseases are the second to pneumonia in causing under five mortality globally [15,16].

The research and original work done till date about the role of various probiotics; have confirmed its efficacy in acute watery diarrhea. Not only nonpathogenic bacteria but also yeast has been found useful in this regard. Lactobacilli and bifidobacteria make major part of infants and early childhood human flora. A Cochrane review including 56 trials confirms the role of probiotics in decreasing the severity and duration of the diarrhoeas[17]. The efficacy about various probiotics has been proved through original work including lactobacilli [L.rhamnosus GG, L.reuteri(ATCC 55730), L. acidophilus, LB, Bifidobacteria, Saccharomyces boulardii, and Streptococcus thermophilus [18-21].

These findings are quite similar to the results of my study which showed that 70% of patients in L. reuteri group responded to treatment. The current study showed that children receiving L. reuteri DSM 17938; on days 2 and 3 were statistically significantly more likely to be diarrhea free and passed significantly fewer stools compared with those receiving placebo. Internationally study conducted found almost the same results; where they found that on second day of treatment only 26% of patients receiving L.reuteri had watery diarrhea compared with 81% of those receiving placebo (p=0.0005)[22]. The slightly difference of effectiveness compared to the above study may be related to the dose of L. reuteri given to these patients. Another reason for the difference may be due to the timing of administration of L. reuteri, since most of our patients usually present late in the illness. The efficacy of this probiotics is much effective when started earlier at the onset of the disease.

We found Lactobacilli reurteri DSM 17938 extremely effective and safe in the treatment of acute watery diarrhea and can be used in acute watery diarrhea irrespective of age and status of the diarrhea. Almost same results have been documented by other international studies where they found the efficacy and safety of this strain[23]. So the strain can easily be recommended by various physicians and no doubt the children included in this study i.e. six to 55 months is the most crucial age and some dehydration as was in our study case is carrying the same value. Therefore, we can argue with ease that the L.reuteri can easily be recommended in all crucial age and less severe type of diarrhea with confidence. L. reuteri is no doubt an outstanding probiotics and has been in use of food additives regularly to enhance safety of the human gut, as probiotic has been extensively studied and is widely used as food additives [24].

Two randomized controlled trials were documented in a systemic review[25]. One study included 74 cases with age range 6 to 36 months, with treatment duration of seven days and having L. reuteri group and a placebo group. There was significant reduction in the frequency and duration of acute diarrhea as compared to the placebo grou (3.3 ± 2.1 vs. 2.1 ± 1.7 days, respectively; $P < 0.03$)[26]. The second RCT was having a total number of 127 patients with age range of 3 to 60 months where patients were randomly assigned to L.retuteri or no intervention group. The group with L.reuteri had marked improvement in severity in frequency of acute diarrhea (mean difference (MD) −33.1 h, 95 % confidence interval (CI) −42.6 to −23.6) and duration of the disease period (4.3 ± 1.3 vs. 5.5 ± 1.8 days, respectively; $P < 0.001$) as compared to the control group [27].

The two RCTs of this systemic review showed that L. reuteri DSM 17938 is far better in efficacy as compared to placebo or no intrervention. Our study results closely

resemble this systemic review justifying the effect of L.reuteri resulting in reducing the duration of diarrhea and improving consistency of stool.

In another prospective, randomized and placebo-controlled study where they focus on the efficacy of of L. reuteri ATCC 55730 in children hospitalized with acute diarrhea, 50 cases, aged 6–36 months, were randomized to receive L. reuteri two times a day a dose of 10^8 CFU for the whole time period admission in the hospital or for 5 days, or a matching placebo. Rehydration therapy was the same in either group. They found that mean duration of the diarrhea was 2.3 days in L.reuteri group as compared to the placebo which was 2.9 days. On the very second day of the therapy the watery diarrhea persisted in 64% of the L. reuteri group while 84% in the placebo group, mean frequency of diarrhea (1.9 in the Lactobacillus reuteri vs. 3.4 in the placebo group. The result of this study was similar to our study which also showed a significant reduction in severity of diarrheal illness in L. reuteri treated group [28].

CONCLUSION

The study showed that lactobacillus reuteri is beneficial in the treatment of the children with acute watery diarrhea. It has dual effect i.e. it not only reduces the duration of diarrhea but also improves the consistency of stool in hospitalized patients.

Recommendations: More study and data is needed to confirm the efficacy of the Lactobacilli reuteri role in the treatment of the acute watery diarrhea in both admitted and outdoor patients. Moreover, on large scale studies are also recommended to evaluate the mechanisms of action of L. reuteri DSM 17938.

Author's Contribution:

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Original Article

Do Post Operative Drains after Emergency Laparotomy Prevent Deep Surgical Site Infection

Post Operative Drains after Laparotomy

Dileep Kumar[1], Rubina Bashir[1] and Salim Ahmed Soomro[2]

ABSTRACT

Objective: To compare the frequency of deep surgical site infection in patients undergoing emergency laparotomy with and without postoperative drains in a tertiary care hospital.

Study Design: Randomized control trial study.

Place and Duration of Study: This study was conducted at the Surgical Ward-2, JPMC, Karachi from January 2015 to January 2016.

Materials and Methods: Seven hundred and sixty two patients undergoing emergency laparotomy with age from 15-60 years, due to perforated appendix, tuberculosis, typhoid determined history, clinical examination and erect abdominal X ray were randomized into two groups i.e. with and without post-operative drains. Rate of deep surgical site infection on 3rd & 7th day was measured as outcome.

Results: The mean age of the patients was 28.92±6.246 years with 330 (43.3%) were female while rest 432 (56.7%) were male. Deep surgical site infection on 3rd day was 7.2% in patients with post-operative drains while 8.1% in patients without post-operative drains. Similarly on day 7, deep surgical site infection was 6.3% in patients with post-operative drains as compared with 8.1% in patients without post-operative drains. Differences were statistically non-significant.

Conclusion: It is concluded that there is no difference in frequency of developing deep surgical site infection on 3rd day and 7th whether you use post-operative drains after emergency laparotomy or not. So we accept the null hypothesis and conclude the use of post-operative drains is not associated with deep surgical site infection on 3rd and 7th day.

Key Words: Deep surgical site infection, Emergency laparotomy, Postoperative drains, Peritonitis.

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INTRODUCTION

Prophylactic drainage of the peritoneal cavity after gastro-intestinal (GI) surgery has been used since time immemorial, with the dictum of Lawson Tait, the 19th century British surgeon, "when in doubt, drain", well known.[1-3] Emergency laparotomy is a common procedure in our settings. To drain or not to drain has been a dilemma. Postoperative drains help the surgeon not only to detect anastomosis leakage early but also reduce postoperative adhesions. But on the other hand, drains are associated with deep surgical site infection (DSSI).[4,5] Deep surgical site infection is among common morbidities ranging from delayed healing to systemic sepsis having high impact on the economy and health care resources[6] due to increased length of stay.[7] In a Pakistani study conducted in tertiary care hospital, the overall rate of surgical site infection came out 13%[8], much higher than other developed countries like 1.9% in USA.[6]

The available evidence is lacking consensus regarding use of post operative drainage in GI procedures. In a study incidence of DSSI was significantly higher in patients who received a drain (31% vs. 9%, p = 0.001).[9] But in another study there came out statistically non-significant difference in the rate of DSSI based on the presence or absence of an intra-abdominal drain after laparotomy (17 vs 18%, P=0.88).[10] Similarly in a third study one drain placement was found as good as the two drain placement.[1] In a retrospective review to determine safety and effectiveness of routine drainage and nondrainage, no significant difference in mean time for return of bowel function (3.8 vs 4.0 days; P = .6), rate of surgical site infection (63% vs 70%; P = .39), wound dehiscence (36% vs 27%; P = .27), anastomotic leak (2.5% vs 1.5%; P = .27), enterocutaneous fistula formation (10% vs 6.1%; P = .40), intra-abdominal abscess formation (4% vs 9%; P = .18), or mean length of hospital stay (22 vs 19 days; P = .26) was observed.[11] Deep surgical site infections pose a major threat in all surgical interventions. Abdominal infections are common in our setting because of lack of implementation of standardized protocols for infection control. Gut leakage and post-operative infected

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secretions lead to deep infections and abscess formation. Placement of intra-abdominal drains has been a practice in our settings conventionally. The evidence of its benefit is contradictory as explained earlier. Current study is to explore the better practice regarding placement of drain in term of lower rate of DSSI. DSSI is a frequent cause of prolonged hospital stay in our already burdened teaching hospitals. Results of this study will help patients achieve health early and hospital managers may get reduction in bed occupancy rate.

MATERIALS AND METHODS

This randomized control trial study was carried out at Department of Surgery Ward-2, JPMC, Karachi, over a period of one year (Jan 2015 to Jan 2016). Seven hundred and sixty two patients undergoing emergency laparotomy with age from 15-60 years, due to perforated appendix, tuberculosis, typhoid determined history, clinical examination and erect abdominal X ray were randomized into two groups i.e. with intra-abdominal drains and without post-operative drains. Patients will be followed post operatively at 3rd day and 7th day for presence of deep surgical site infection by researcher himself. The data was analysed in SPSS-17. Chi square test of homogeneity will be applied to determine statistical difference in both groups regarding rate of DSSI on 3rd and 7th post-operative day. A value of $p < 0.05$ will be considered as significant.

RESULTS

There were 330 (43.3%) were female while rest 432 (56.7%) were male patients. Seven hundred and sixteen (94%) patients were below 40 years while rest of 46 (6%) patients were either 40 or above 40 years of their age with mean age of the patients were 28.92±6.246 ranging from 21 to 59 years. Five hundred and thirty eight 538 (70.6%) patients stayed in hospital less than five days while 224 (29.4%) patients stayed in hospital five and more than five days. Their hospital stay was between 2 to 9 days with mean of 5.01±1.58 days (Table 1).

Table No.1: Demographic information of the patients

Variable	No.	%
Gender		
Male	330	43.3
Female	432	56.7
Age (years)		
<40	716	94.0
≥40	46	6.0
Hospital stay (days)		
<5	538	70.6
≥5	224	29.4

Among 762 patients, 102 (13.4%) patients have deep surgical site infection on 3rd day while 55 (7.2%) patients showed up with deep surgical site infection on 7th day of operation. Deep surgical site infection on 3rd day was 7.2% with post-operative drains while 8.1% without post-operative drains. Difference was statistically non-significant. Similarly on day 7, deep surgical site infection was 6.3% in patients with post-operative drains as compared with 8.1% in patients without post-operative drains. (Table 2)

Table No.2: Comparison of surgical site infection on 3rd and 7th day

SSI	Post-operative drains	Without post-operative drains
3rd day		
Yes	55 (7.2%)	64 (8.1%)
No	707 (92.8%)	698 (91.9%)
7th day		
Yes	47 (6.3%)	64 (8.1%)
No	715 (93.7%)	698 (91.9%)

P>0.05

DISCUSSION

Deep surgical site infection (DSSI) is among common morbidities ranging from delayed healing to systemic sepsis having high impact on the economy and health care resources[6] due to increased length of stay.[7] In a Pakistani study conducted in tertiary care hospital, generally the rate of SSI was 13%[8], much higher than other developed countries like 1.9% in USA.[6] The available evidence is lacking consensus regarding use of post operative drainage in GI procedures. In a previous study incidence of DSSI was significantly higher in patients who received a drain (31% vs. 9%, p = 0.001).[3]

In our study, deep surgical site infection on 3rd day was 7.2% with post-operative drains while 8.1% without post-operative drains. The difference was statistically non-significant (Table 2). We may conclude that there is no difference in frequency of developing deep surgical site infection on 3rd day whether you use post-operative drains after emergency laparotomy or not. Similarly on day 7, deep surgical site infection was 6.3% with post-operative drains as compared with 8.1% without post-operative drains. The difference was statistically non-significant (Table 2). We may conclude that there is no difference in frequency of developing deep surgical site infection on 7th day whether you use post-operative drains after emergency laparotomy or not.

CONCLUSION

It is concluded that there is no difference in frequency of developing deep surgical site infection on 3rd day and 7th whether the use post-operative drains after

emergency laparotomy or not and the use of post-operative drains is not associated with deep surgical site infection on 3rd and 7th day.

Author's Contribution:

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Original Article

Efficacy of Sofosbuvir and Ribavirin in HCV

Treatment outcome in patients with HCV Genotype-3a Infection, Treated with 24-Weeks Dual Therapy (Sofosbuvir and Ribavirin)

Nizamuddin, Shafiq Ahmad Tariq, Sami Siraj and Waheed Iqbal

ABSTRACT

Objective: This study was mainly conducted to evaluate the efficacy of sofosbuvir and ribavirin in HCV genotype-3a infection, which is the most common genotype, infecting Pakistani community.
Study Design: Open labeled, single center, longitudinal study.
Place and Duration of Study: This study was conducted at the Institute of Basic Medical sciences (IBMS), Khyber Medical University, Peshawar from June 2016 to November 2016.
Materials and Methods: Total of 80 patients with HCV genotype-3a infection were enrolled. Patients were assigned into four groups including group-A as treatment naïve non-cirrhotic, group-B who were treatment naïve but cirrhotic, group-C as non-cirrhotic cases who were non-responder to peg-interferon and ribavirin and group-D as non-responder cirrhotic cases. Sofosbuvir plus ribavirin was given for 24-weeks. The primary end point was end of treatment (EOT-24) response with 24-weeks therapy, which is defined as HCV RNA level<40IU/ml after 24-weeks of therapy.
Results: Among 80 patients, male-female ratio was 56.25%(n=45) and 43.75%(n=35) respectively. Each group has 20 cases. Rate of EOT-24 was 90% (n=18/20) in group-A, 80%(n=16/20) in group-B, 85%(=17/20) in group-C and 75%(n=15/20) in group-D. The EOT-24 was 85%(n=34/40) in all treatment Naïve cases, while 77.5%(n=31/40) was observed in all non-responder cases. The overall response was 82.5%(n=66/80).
Conclusion: Results of this study confirm strong efficacy of dual therapy in both treatment naïve and previously non-responder cases, which may be either cirrhotic or non-cirrhotic, with chronic hepatitis-C genotype-3a infections.
Key Words: Chronic hepatitis C, Cirrhotic, dual therapy, End of Treatment response, Sofosbuvir.

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INTRODUCTION

Treatment of chronic hepatitis-C is rapidly evolving in last decade. The additions of new DAAs (Direct Acting Anti-viral) have now totally revolutionized the therapy in both cirrhotic and non-cirrhotic patients. The most important drug in DAAs is NS5B HCV RNA dependent RNA polymerase inhibitor called sofosbuvir, which is now recommended in all HCV genotypes and is considered as one of the most important weapon in the therapeutic armamentarium against hepatitis C virus.[1] Hepatitis-C is a chronic ailment, which affects human in almost every corner of the world and thus sharing a huge part in death rate of the world population. Globally, CHC is considered as emerging public health problem, which is considered the most significant single cause of liver diseases and liver transplantation.

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Hepatitis-C virus (HCV) is considered as one of the leading cause of post transfusion non-A and non-B hepatitis[2,3]. It is now documented world wide that together chronic hepatitis-C and hepatitis–B affect >75% cases of all chronic liver disease (CLD). In a survey report by WHO, the global prevalence of CHC >3%, affecting almost 170 to 200 million people worldwide[4]. Majority of these people are at highest risk to develop cirrhosis and finally hepatocellular carcinoma (HCC), which are considered as the most important complications and causes of death in patients with Hepatitis-C infection. WHO states in a report, that about 4% of HCV infection leads to HCC worldwide and this complication is usually common in those patients having, high level of detectable HCV RNA in their serum for longer period[5]. Therefore in all patients aggressive treatment is needed to completely eradicate virus from the serum, which is the only surrogate outcome in the management of CHC. This total clearance of virus from the blood or serum of these patients is termed as sustained virological response (SVR). By achieving SVR, one can decrease the risk of cirrhosis and HCC[6].

So far, 7-genotype of hepatitis-C virus (HCV) are discovered having different prevalence in different countries. Pakistani community is mostly affected by

genotype 3, especially 3a, which have got unpredictable response to different treatment regimen.

Previously, the treatment strategy for Hepatitis-C genotype 3a infection was using Peg-interferon plus ribavirin (PEG-IFN+RBV) for 24-weeks. But this therapy has multiple adverse effects and poor outcome in term of SVR. Nowadays, highly effective oral direct acting antiviral (DAAs) like Sofosbuvir and Ribavirin can be given to these patients with few adverse effects and very good outcomes. According to AASLD and EASL guideline[7], it can be given along with ribavirin for 24 weeks to treat HCV (genotype-3a) infections in all patients with or without cirrhosis[8]. Being used extensively worldwide with very good response, clinical score improvement and minimal adverse effects, it's still needs further studies at national level in both patients (cirrhotic and non-cirrhotic), including all treatment naive and old non-responder cases for further validation of its efficacy in our Pakistani community.

MATERIALS AND METHODS

This single center, longitudinal study was conducted in the Institute of Basic Medical sciences (IBMS), Khyber Medical University Peshawar. The total duration of study was 6-months, starting from June 2016 to November 2016.The samples of this study were collected from Medical Training Institute (MTI), Hayatabad Medical Complex Peshawar. After ethical committee approval and informed consent, 80 patients having chronic hepatitis-C genotype 3a infections were enrolled in this study applying strict inclusion and exclusion criteria. Sample was collected using non-probability and purposive sampling technique, sample size for the study was calculated using WHO-online sample size calculator, on MS Excel. All these patients were divided into 4 groups, labeled as A (new non-cirrhotic cases), B (new cirrhotic cases), C (non-responders, non-cirrhotic cases) and D as (Non-responders, cirrhotic) cases. The non-responders were those cases, who have not responded to peg-interferon and ribavirin based therapy, being given previously for good 24 weeks. The demographic and clinical information like age, sex, ethnicity, treatment strategy and other complications resulting from HCV were obtained from the patients. The personal information of all patients was kept confidential.

Statistical analysis: All collected information was entered into Microsoft Excel sheet. All the percentage and frequencies of different patients group with and without cirrhosis were calculated using Microsoft Excel 2010. The rest of the data was entered using Microsoft excel 2007 and graph pad prism for construction of graphs and thus analyzed by using SPSS version7. Student's t-test is used with 95% of confidence level, and significant p-value of ≤ 0.05. Chi-square test was applied to test the association. The finding was presented in tables.

RESULTS

Out of total 80 studied patients, 56.25%(n=45) were male and 43.75%(n=35) were female, having mean age of 51±2 years.

Age distribution among 80 patients was analyzed as n=01(1.25%) patients were in age-group of 21-30 years, n=09(11.25%) patients were falling in age group of 31-40 years, n=29(36.25%) patients were falling in age group of 41-50 years, n=24(30%) patients were falling in age group of 51-60 years and n=17(21.25%) patients were above 60 years of age as shown in Table 1.

In 80 patients of all four groups, over all status of response in the form of undetectable HCV-RNA from the serum at 24-weeks was analyzed. In case of both treatment-naïve and previously non-responder cases with or without cirrhosis of all 4-group, 82.5% (n=66/80) of patients have responded to 24-weeks of therapy. In all 40-treatment naïve cases of group A and B, status of response at 24-weeks was analyzed. Among all 40-treatment naïve patients, 85% (n=34/40) of patients have responded. In all 40-non-responder cases of group C and D, status of response at 24-weeks was analyzed. Among all 40-previously non-responder cases, 77.5% (n=31/40) of patients have responded to 24-weeks of therapy, as shown in table 2.

Table No.1: Age distribution of different patient with CHC genotype 3 infection

Age	Total number of patients	Percentage
21-30 Years	01	1.25%
31-40 Years	09	11.25%
41-50 Years	29	36.25%
51-60 Years	24	30%
> 60 Years	17	21.25%
Total	80	100%

Table No.2. Response in all treatment Naïve and all non-responder cases, at 24 weeks.

Clinical status	Number of cases	Number of cases response at 24 week	%age
Treatment Naïve A+B)	40	34/40	85%
Non-responder (C+D)	40	31/40	77.5%

Table No.3: Response in all 4-groups at 24 weeks.

Groups	Number of cases	Number of cases response at 24 week	%age
Group A	20	18/20	90%
Group B	20	16/20	80%
Group C	20	17/20	85%
Group D	20	15/20	75%
Total	80	66/80	82.5%

Table No.4: Association between cirrhotic and non-cirrhotic

	Cirrhotic	Non-Cirrhotic	χ^2	p-value
Treatment Success	31	35	1.38	0.23
Treatment failure	09	05		
Total	40	40		

Table No.5: Association between treatment Naïve and Old non-responders

	Treatment Naïve	Old non-responders	Total	χ^2	p-value
Treatment Success	34	32	66	0.34	0.5
Treatment failure	06	08	14		
Total	40	40	80		

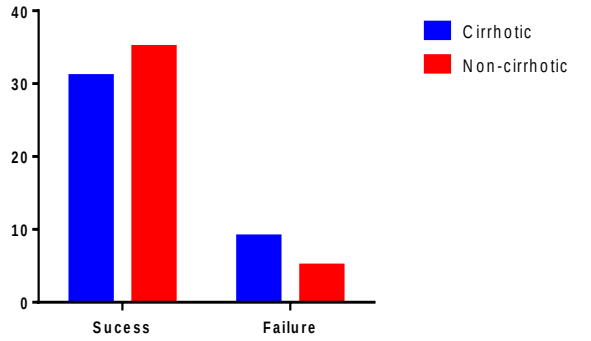

Figure No.1: Association between cirrhotic and non-cirrhotic

Figure No.2: Association between treatment Naïve and old non-responder cases

In all four groups, individual status of response in the form of undetectable HCV RNA from the serum at 24-weeks was analyzed. In all 20-treatment naïve non-cirrhotic cases of group-A, 90% (n=18/20) of patients have responded while in all 20-cases of group-B having treatment naïve cirrhotic cases, 80% (n=16/20) of patients have responded to 24-weeks of therapy. Similarly, in all 20-cases 0f group-C, having previously non-responder and non-cirrhotic cases, 85% (n=17/20) of patients have responded while in all 20-cases of group-D having previously non-responder and cirrhotic cases, 75% (n=15/20) of patients have responded to 24-weeks of therapy (Table 3).

Associations of response rate in case HCV-genotype-3a infection to dual therapy with sofosbuvir+ribavirin given for 24-weeks was further analyzed in all cirrhotic (both new and old cases) and non-cirrhotic (both new and old cases). The non-significant p-value of 0.23 shows that 24-weeks therapy is equally effective in both cirrhotic and non-cirrhotic cases as shown in figure no 1 and presented in table 4.

Associations of response rate in HCV-genotype-3a infection to the same dual therapy, given for 24-weeks was further analyzed in all treatment naïve (both having cirrhosis and those without cirrhosis) and old non-responder (both having cirrhosis and without cirrhosis). The non-significant p-value of 0.5 shows that 24-weeks therapy is equally effective in both treatment naïve and old non-responder cases as shown in figure 2 and presented in table 5.

DISCUSSION

As chronic hepatitis-C is a global problem and the paradigm shift in the treatment combination from interferon-based therapy to direct acting anti-viral therapy has totally changed the direction of research around the globe. The new DAAs have really revolutionized the treatment strategy in all HCV genotypes. One of the option in current guidelines adopted by AASLD (American Association for the Study of Liver Diseases), IDSA (Infectious Diseases Society of America)[9] and EASL (European Association for the Study of Liver)[10], for the optimal treatment of Chronic HCV genotype-3 infection is sofosbuvir with or without peg-interferon. This is also recommended along with ribavirin for 24-weeks in both cirrhotic and non-cirrhotic cases of HCV genotype-3 infection.

In our present study, 90%(n=18/20) response rate has been observed to dual therapy in case of newly diagnosed non-cirrhotic cases with HCV-genotype-3a infection, while 80%(n=16/20) response rate has been observed in case of treatment naive but cirrhotic patients with HCV-genotype-3a, being managed for 24-weeks with sofosbuvir plus ribavirin. On the other hand, 85%(n=17/20) response rate has been observed in old non-responder but non-cirrhotic cases, while 75%(n=15/20) response rate has been observed in old non-responder but cirrhotic patients with HCV genotype-3a, being treated for 24-weeks with sofosbuvir and ribavirin.

Total response observed in our study in all non-cirrhotic patients was 87.5%(n=35/40), while response observed in cirrhotic cases was 77.5%(n=31/40). The association of response rate in both non-cirrhotic and cirrhotic was further analyzed with an insignificant p-value of 0.23, which show that 24-weeks therapy is equally superior in both non-cirrhotic and cirrhotic cases and must be given judicially for 24 weeks to achieve optimal results.

Similarly, total response observed in our study in all treatment naive patients was 85%(n=34/40), while response observed in all old non-responder cases was 80%(n=32/40). The association of response rate in both treatment naïve and old non-responder was further analyzed with an insignificant p-value of 0.5, which show that 24-weeks therapy is equally superior in both treatment naïve and old non-responder cases and must be given judicially for 24-weeks to achieve good results.

Our finding are also closed to the finding of another study, conducted in Europe by Stefan Zeuzemet all, on Sofosbuvir and Ribavirin in HCV-genotypes-2 and 3 infection. Data was collected from more than 77 centers in Europe. Among 250 patients with HCV genotype-3 infections that have received 24 weeks of sofosbuvir plus ribavirin, 213(85%) patients had achieved EOT and SVR12 after the cessation of treatment[11].

Another study conducted by Michael charlton et al, on dual therapy, including sofosbuvir and ribavirin for the treatment of recurrent hepatitis-C virus infection in patients after liver transplantation. In this study, forty patients with HCV-infection were enrolled and treated. EOT and SVR12 were observed in 70%(n=28/40) patients treated with 24-weeks therapy of sofosbuvir and ribavirin. This finding show, that the recommended 24-weeks therapy is also very much effective in the treatment of HCV-infection even in patients having transplanted liver[12].

Another study conducted by Mark S. Sulkowski et al, on sofosbuvir and ribavirin containing dual therapy for the treatment of Hepatitis-C in most challenging patients with HIV-co-infection. They have enrolled patients with different genotypes and all of them were given sofosbuvir along with ribavirin for 24-weeks. EOT and SVR12 were observed in 67%(n=28/42) patients with HCV-genotype-3 infections. These finding show that good result can seen in HCV-genotype-3 and HIV co-infected patients, if they are treated with the same dual therapy of sofosbuvir and ribavirin for good 24-weeks[13].

This combination is not only associated with superior EOT and SVR rate, but also with improved quality of life and minimal adverse effects. In our study the most common adverse effects observed with this combination are insomnia, fatigue, weight loss and anxiety. This is confirmed by Younossi, ZmM. et al, in a study, showing the minimal impact of sofosbuvir and ribavirin on routine activity and health related quality of life in chronic hepatitis-C. At the same time, there was significant improvement in HRQL score in these patients with treatment and minimal adverse effects were observed[14].

Small sample size, lack of data on potential confounders, poor elaboration and investigation regarding cirrhosis, effects of the level of cirrhosis on response rate, initial immune response of hepatocyte, role of IL28B on response rate, identification of S282T variant of the NS5B protein region which is the first identified sofosbuvir resistant variant (RAV) and drug level monitoring in non-responder regarding compliance are considered as the main limitations of this study.

And finally, it is now accepted worldwide with many trials, that sofosbuvir plus ribavirin is considered as a new hope for all hepatitis-C genotype-a infection, which was once considered as the most difficult to treat sub-genotype in this group. This is the only therapy, which can be given to all patients, with normal liver or patients with an advanced cirrhotic liver. Due to ideal response rate, acceptable adverse effects profile and cost effectiveness, it is now clear that sofosbuvir should be considered the first choice in all eligible cases, infected by HCV genotype-3 and its sub-types. However, large trial is needed to address role of age, sex, and genotype 3-subgroup, initial viral load and IL28B status in the response rate of HCV genotype 3a infections to Sofosbuvir based therapy.

CONCLUSION

It is now concluded that dual therapy including sofosbuvir and weight based ribavirin can be considered as an effective treatment in both treatment Naïve patients and all previously non-responder cases with chronic hepatitis-C genotype-3a infections in Pakistani population. Further study is suggested, both at national and international level for further confirmation and specification of this regimen for HCV genotype 3a infection.

Author's Contribution:

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Revisiting Critically:	Shafiq Ahmad Tariq, Waheed Iqbal
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Incidence of Infection after Surgical Management of Open Tibial Shaft Fractures

Abdul Karim[1], Malik Asrar Ahmed[2] and Zia-ur-Rehman[1]

ABSTRACT

Objective: To study the incidence of infection after using different methods for fixation of open tibial shaft fractures.

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the Department of Orthopedic Surgery, Sheikh Khalifa Bin Zayed Al Nahyan Hospital/CMH Rawalakot Azad Kashmir from 5th January 2016 to 5th July 2016.

Materials and Methods: Study was carried out on 62 patients. Patients were included through Non-probability, purposive sampling. Detailed medical history was taken from all the patients and they were examined clinically. Gustilo and Andreson classification was applied on these open factures. All the wounds were swabbed or clinical material from them was collected and sent to laboratory for studying microbiological status. Antibiotics were administered empirically which were revised on the report of culture and sensitivity. Wounds were inspected for signs of infection after 72 hours. In cases of unproven infections, the antibiotics were stopped after three days. The patients were discharged from the hospital after three days depending upon the general condition of the patients and the wounds. All the patients were followed up on 3rd, 7th, 15th, and 30th days, then monthly for six months. The patients were evaluated for the development of infection. Data was collected on a structured questionnaire and analyzed in SPSS software version 16.

Results: The mean age of the patients were recorded as 33.25±14.89years. There were 51 (82.3%) male patients while 11 (17.7%) were female .Open type I was observed in 4 (6.5%) patients ,Type II was noted in 7 (11.3%) cases, IIIA was observed in 43 (69.35%) patients and IIIB was noted in 8(12.9%) cases. In our study, 37 (59.68%) patients were managed with external fixation (EF), while 25 (40.32%) had internal fixation (IF).The cases in which internal fixation was done , DCP was applied in 13 (52%) patients while in 12 (48%) patients ILN was done. Post-debridement wound was left open in 19 (31%) patients and it was closed in 43 (69%) patients primarily. Incidence of infection was more with EF while it was low with IF. In cases of internal fixation ,incidence of infection was more with DCP while it was low with ILN. Infection rate was lower when post-debridement wounds were left open as compared to closing them after debridement.

Conclusion: The rate of post-operative infection was higher in this study with EF as compared to IF (DCP and ILN). Closing the wound after debridement and fixation was associated with higher rate of infection as compared to leaving it open after debridement.

Key Words: Open fracture, post-operative infection, external fixation, internal fixation, open reduction and internal fixation.

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INTRODUCTION

Open fractures generally result from high energy trauma. Severity of soft tissue injury and comminution depend upon the severity of the injury.[1](Koval et al., 2006). Road traffic accidents, industrial accidents, falls and fie arm injuries are the usual causes of open fractures.[2] (Cornwell, 2003).

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Injury severity and direction of force affects the type of fracture(Close or open).[3]. (Johnson and Christie, 2008). In cases of open fractures, contamination of wound increases the risk of infection and nonunion[4].(Lima et al., 2004).

During the last two decades, there are many changes in management of open fractures. Such fractures are challenges for orthopaedic surgeons because of complications like osteomyelitis, delayed union and nonunion[5]. (Quinn and Macias, 2006).Infection is directly related with the extent of soft tissue devitalisation in open fractures[3]. (Johnson and Christie, 2008).

The most serious complication of open fracture is infection.[6](Ostermann et al., 1995). Positive effects of early administration of antibiotics have been proved by many of the studies in treating open fractures.[7] (Giannoudis et al., 2006)

As per recent advances, antibiotics should be administered for three days.[3](Johnson and Christie, 2008).Suitable antibiotic is usually decided according to bacterial culture report[8].(Solomon et al., 2005). Nosocomial infection increase the chance of infection in open fractures [9].(Seekamp et al., 2000).Infection can be primary or secondary.[10] (Walter, 1996).Permanent osteomyelitis may result from failure of contaminated bacterias eradication[9]. Seekamp et al., 2000).Bacterial multiplication is increased by dead tissue or presence of foreign material[11](Bowler et al., 2001).Outcome is dependent uponthe number of inoculated microorganisms[12].(Sen et al., 2000) The presence of specific pathogens is of primary importance[13]. (D'Souza et al., 2008)

In our study, we adopted various methods for fixation of fractures to see the results in terms of infection so that we can adopt a treatment modality that have less chances of infection.

MATERIALS AND METHODS

The study was conducted out at the Department Of Surgery/Orthopaedic Surgery Sheikh Khalifa Bin Zaid Al Nahyan Hospital (SKBZANH)/CMH Rawalakot Azad Kashmir that is teaching hospital affiliated of Poonch Medical College Rawlakot from 05th January 2016 to 05th July 2016. Many of the districts are cathment areas of SKBZANH/CMH Rawalakot. The hospital provides 24 hour emergency services and it has well equipped laboratory facilities as well.

Sample Technique: Non-probability, purposive sampling.

Inclusion criteria: All the patients between 18 to 60 years of age presenting within 06 hours of acute trauma having Open tibial shaft fractures (type I, II and III of Gustilo classification) were included in the study.

Exclusion Criteria: All the patients having old infected (neglected) fractures, with some other sites of infection in the body and patients who have received antibiotics at some other setup were excluded from the study.

Ethical Consideration: The study was carried out after formal approval by ethical committee of the hospital.

Data collection procedure: In this study, the variables included were age, type of open fracture (Gustilo classification), mode of fixation and post-operative infection. All the patients were clinically examined and their medical history was recorded. Their open fractures were classified based on Gustilo and Anderson classification. All wounds were swabbed and sent to laboratory for studying microbiological status. Request was made for Aerobic and Anaerobic cultures. Necessary stabilization of fractures was performed . Antibiotics were administered empirically. Wounds were inspected for signs of infection after 72 hours and a repeat culture was obtained and if infected, appropriate antibiotics according to sensitivity report were started. If there was no evidence of infection, the antibiotics were discontinued after third day. The patients were discharged from the hospital after three days depending upon the general condition of the patients and wound. All **the** patients were followed up on 3rd, 7th, 15th, and 30th days, then monthly for six months. The patients were evaluated for the development of infection. Data was collected on a structured questionnaire.

Data Analysis: Data was entered and analyzed in SPSS software version 16. Quantitative variables like age was presented in form of mean ± S.D. Qualitative variables like gender and infection was presented in form of frequency and percentage. Chi-square test was applied to compare the rate of infection with type of surgery performed, type of implant used and type of post-debridement wound.

RESULTS

We included total 62 patients presented during 6 months of study time in our department and who fulfilled the selection criteria with the mean age of 33.25±14.89years. The minimum and maximum age of patients was 18 and 60 years respectively.

Table No.1: Descriptive Statistics for age of patients

Age (years)	n	62
	Mean	33.25
	SD	14.89
	Minimum	18
	Maximum	60
	Range	60

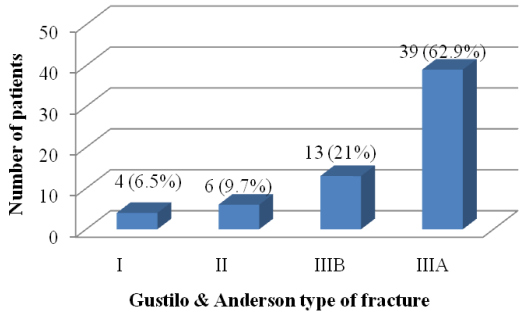

Figure No.1: Distribution of Gustillo and Anderson type of patients

Table No.2: Distribution of mode of fixation of the patients

		Frequency	Percentage
Mode of fixation	EF	37	59.7%
	IF	25	40.3%
	• DCP	• 13	• 52%
	• ILN	• 12	• 48%
	Total	62	100%

Patients were evaluated as per classification of Gustilo and Anderson. Type I was observed in 4 (6.5%) patients, Type II was noted in 6 (9.7%) cases, type IIIA was observed in 39 (62.9%) patients and type IIIB was noted in 13 (21%) cases.

In our study, 37 (59.7%) patients were managed with external fixation (EF) while remaining 25 (40.3%) were managed with internal fixation. Out of 25 cases who underwent IF,DCP fixation was done in 13 (52%) patients and 12 (48%) patient had unreamed ILN fixation.

Table No.3: Distribution of type of open fractures (Gustilo-Anderson) in relation with mode of fixation

		Mode of fixation		Total
		EF	IF	
G & A type	I	0 (0%)	4 (100%)	4 (100%)
	II	1(14.29%)	6 (85.71%)	7 (100%)
	IIIA	30 (69.77%)	13 (30.23%)	43 (100%)
	IIIB	6 (75%)	2 (25%)	8 (100%)
	Total	37(59.7%)	25 (40.3%)	62 (100%)

In this study, all 4 cases of open type I were managed by IF. Majority of open type II fractures (6 cases) underwent IF while 1 patient was managed by EF. Out of 43 cases of open type IIIA, 30 underwent EF and 13 cases were managed by IF. In 8 cases of open type IIIB fractures, 6 underwent EF while in 2 cases IF was done.

DISCUSSION

When open fractures are treated by external fixators, it can lead to pin track infection. The remedy then is the removal of these fixators and their placement at distant sites if required. Internal fixation is another option in this case[14]. (Moroni et al., 2002). Advances in the principles of fracture management has significantly decreased the infection rate during the last century[15,16,17]. (Gustilo and Anderson, 1976, Robinson and Hofman, 1989,Rojczyk and Tscherne, 1982). Infection resulting in limb loss is a great risk where there is associated major vascular injury[18].(DeBakey and Simeone, 1946, Neubauer et al., 2006)

A total of 62 patients were treated during 06 months of our study period with mean age33.25+-14.89 years of and male-to-female ratio was 4.6:1 compared with one study reporting a male to female ratio of 1.7: 1 with the mean age of 38.7yrs[19].(Madu et al., 2012)

Fractures were classified on the basis of Gustilo & Anderson classification. Percentage for Type I,Type II, Type IIIA and Type III B was 6.45%,11.29%,69.35% and 12.9% respectively.

In our study, external fixation (EF) was done in almost 60% patients while internal fixation (IF) was done in about 40% of patients. Considering internal fixators, DCP was applied in 52% patients and unreamed ILN was implanted in 48% of the patients. After debridement wounds were left open in 31% patients. Post-operative wound infection was seen in 22.6% of patients after 6 months of procedure.

After 3rddays, infection rate was almost equal with both EF and IF while after 6 months it was higher with EF as compared to IF. The infection rate was almost equal with both DCP and ILN in the former case of procedure but in later case infection rate was higher with DCP as compared to ILN. The difference between the groups was insignificant showing that chances of infection are equal with all procudures. The reason behind seems the uneven distribution of surgical procedures. In cases of internal fixation 52% cases had DCP fixation while in 48% cases unreamed ILN was used. Literature has reported 50% rate of infection with EF, 4%-9% with ILN and 45%-50% with DCP[20,21,22,23].(McGraw and Lim, 1988b, Krettek et al., 1996, Clifford et al., 1988, Schreinlechner, 1982)

Wound infections are associated with the time interval between injury and surgery or wound debridement. Effects of early debridement(within 6 hours of injury) on bone healing and wound infections is not supported by literature[24,25,26,27,28]. (DeLong et al., 1999, Harley et al., 2002, Hertel et al., 1999, Khatod et al., 2003, Kindsfater and Jonassen, 1995) In our study, 80%of patients were managed within 6 hours time of injury.

CONCLUSION

In our study the rate of post-operative infection was higher with External Fixation as compared to Internal Fixation. In cases of Internal Fixation, DCPs were associated with a higher rate of infection as compared to ILN.

Author's Contribution:

Concept & Design of Study:	Abdul Karim
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Data Analysis:	Malik Asrar Ahmed, Abdul Karim
Revisiting Critically:	Zia-ur-Rehman
Final Approval of version:	Abdul Karim

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

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Original Article

Outcome of Rubber Band Ligation in Hemorrhoids

Rubber Band Ligation in Hemorrhoids

Muhammad Saleem Shaikh, Muharram Ali, Kheo Ram Dholia

ABSTRACT

Objective: To analyze the effectiveness, safety & outcome of treatment of hemorrhoids by using Rubber band ligation.

Study Design: Prospective study.

Place and Duration of Study: This study was conducted at the Department of Surgery Unit-II, CMC Hospital Larkana, from June 2014 to July 2017.

Material and Method: All patients with 1st,2nd and 3rd degree hemorrhoids were included in our study and exclusion criteria were patients not willing to involve in study,4th degree hemorrhoids, bleeding disorders, dual pathology of anal canal and previous history of anorectal surgery. The data related to name, age and gender were recorded. Rubber Band Ligation was performed as an office procedure in Out Patient Department. The patients were asked to return OPD for follow-up after two weeks, one month, six months and 1 year. The outcome was recorded and analyzed.

Results: Two hundred twenty patients with diagnosis 1st, 2nd and 3rd degree hemorrhoids after fulfilling the inclusion criteria were enrolled with mean age of 43.5 years with SD+11.5. Majority of patients were having 2nd Degree hemorrhoids. Two third of patients having bleeding per rectum, constipation and something coming out per anus. The cure rate in our study was observed in 69%. Post procedure complications were observed in 13.1%, while recurrence rate was seen in 17.27%. Majority of the patients were having bleeding per rectum. Higher grade of hemorrhoids were observed having higher rate of complications. Statistically P-value (0.05) was significant,while P-value was not found significant when compared to gender (P=0.15).

Conclusion: Rubber Band Ligation is a simple, safe and effective modality of treatment in Out Patient Department for 1st,2nd and 3rd degree hemorrhoids, which can be performed in selected cases. The benefit of RBL has decreased the incidence of complications and does not alter the anorectal function.

Key Words: Bleeding per rectum, Rubber Band Ligation, hemorrhoidectomy, outcome.

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INTRODUCTION

Hemorrhoids (piles) are the clinical manifestation of the downward disruption of normal functional mucosa called as anal cushions[1].

Hemrrohoids are considered as one of the common abnormality of the anal canal, clinically classified into four grades[2].Overall incidence of hemorrhoidal disease worldwide is in 5% of population, affected with the complains related to this disease[3].The condition causing increased intra-abdominal pressure, like chronic cough, chronic constipation &pregnancy is considered to be one of the risk factors for developing hemorrhoids[4]. The other risk factors for hemorrhoids may be previous history of hemorrhoidal symptoms, age below 50years,anal ulcers, physical activity, consumption of spicy food and visky intake. In young females no significant risk factors associated with genital activity was found for hemorrhoidal disease[5].

Different modalities of treatment for symptomatic hemorrhoids such as dietary modification, injection sclerotherapy, cryosurgery, infrared coagulation, laser coagulation, bipolar diathermy, diod laser treatment and operative procedures are being performed worldwide. Rubber band ligation is an office procedure performed in Out Patient Department, as a nonsurgical procedure for hemorrhoids. Therefore, patients having hemorrhoids are usually advised to come in OPD for this procedure, as it is technically easy, simple and safe procedure without anesthesia[6,7,8,9]. Recently this procedure is being commonly adopted as a nonsurgical treatment modality in hemorrhoids without anesthesia therefore, no need for hospitalization. The incidence of complications of Rubber Band Ligation reported low as compared to surgical procedure[10,11].

The complications of Rubber Band Ligation occurs like pain, bleeding, infection, incontinence of faeces and flatus, as reported in various studies[12,13].

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Recently new modalities of treatment are introduced and considered superior to RBL, such as stapled hemorrhoidectomy, ligasure hemorrhoidectomy and hemorrhoidal artery ligation (HAL)[14,15]. Symptomatic hemorrhoids can be treated initially with high fiber diet and laxatives. The method of RBL was more effective for the management of 1st, 2n &3rd degree hemorrhoids[16]. The aim of our study was to analyze the effectiveness, safety, quality of life and outcome of treatment of hemorrhoids by using RBL in OPD as an office procedure.

MATERIALS AND METHODS

A prospective study, conducted at Department of Surgery Unit-II, Chandka Medical College Hospital, Larkana, from June 2014 to July 2017- a three years study.

Patients above 16 years of age with either gender were included in our study.

We enrolled the patients from surgical Out Patients Department having 1st, 2nd and 3rddegree of hemorrhoids, who came OPD for consultation and treatment. Patients with external hemorrhoids, 4th degree hemorrhoids, having bleeding disorder, dual pathology of anal canal, previous history of anorectal surgery and patients not willing to give consent for participation in our study were excluded. Separate proforma was formed including demographic features like age, gender, presenting complain such as bleeding per rectum, constipation, something coming out of anus, pruritus and pain. The procedure of RBL was explained to all patients. The data was recorded for grade and number of hemorrhoids and post procedural complications. Outcome of the Rubber Band Ligation procedure was categorized into three such as cured, Recurrence and complications occurred. The 1st category of Patients were labelled as cured when they were asymptomatic and no hemorrhoids detected on clinical examination up to 1 year. The 2nd category of recurrence was labelled for the patients who remained asymptomatic after the procedure for 1 year, later developed the same symptoms. In 3rd category, the complications were noted within one year after the procedure and recorded.

After taking proper history and clinical examination, all patients underwent Digital Rectal Examination (DRE) and proctoscopy. After taking the written& informed consent, all patients were explained about the procedure of Rubber Band Ligation and its expected complications. Kleen enema was advised a night before and patients were called in OPD in the morning. Patients were placed in left lateral position, DRE followed by proctoscopy was performed and proctoscope placed 1-2 cm above the dentate line. After all asceptic measures, RBL was performed by using sterilized instruments. All hemorrhoids were ligated in single sitting and patients were observed for one hour after procedure to evaluate post procedural complications.

When found comfortable after the procedure, they were sent home and advised high residue diet, laxative, local anal hygiene and avoid prolong standing.

They were advised to follow up in OPD after two weeks, one month, six months and at one year. At every follow up, patients were assessed with history and asked for post procedural complications, followed by clinical examination, including DRE and proctoscopy. They were advised to seek immediate medical advise if they develop any of the prior explained complication. Data analysis was performed through SPSS version 16.

RESULTS

Two hundred twenty patients with diagnosis of 1st, 2nd and 3rd degree hemorrhoids were enrolled from June 2014 to July 2017. Majority of our patients were male, 164(74.5%) while females were 56(25.5%). Mean age of the patients was 43.5 years with SD of 11.5 years. (Table 1)

Table No.1: Demographic and clinical data for patients

Results	No. of Patients	%age
Gender	43.5±11	
Male	164	(74.5%)
Female	56	(25.5%)
Grade of hemorrhoids		
Grade-1	33	(15%)
Grade-2	104	(47.3%)
Grade-3	83	(37.7%)
Number of Hemorrhoids		
Single Hemorrhoids	13	(5.9%)
Double Hemorrhoids	97	(44.1%)
Three Hemorrhoids	110	(50%)
Clinical Features		
Bleeding	19	(8.6%)
Constipation	4	(1.8%)
Something is coming out from Anus	1	(1.5%)
Bleeding, constipation & Something is coming out from Anus	138	(62.7%)
Bleeding, something is coming out from Anus & Pruritis	32	(40.5%)
Bleeding & Something is coming out from Anus	24	(10.9%)
Pruritis	2	(0.9%)

Out of 220 cases, 33 patients (15%) were having Grade-1 hemorrhoids, 104 patients (47.3%) with Grade-2, while 83patients (37.7%) had Grade-3 hemorrhoids. The number of hemorrhoids were variable, major proportion of patients had two and three

hemorrhoids. 97patients (44.1%) had two hemorrhoids and 110 patients (50%) were having three hemorrhoids, while only 13 patients (5.9%) had single hemorrhoid. Substantial number of patients had more than two symptoms at presentation like bleeding combined with constipation and something coming out per anus was reported by 138 cases (62.7%). Bleeding along with pruritis and something coming out per anus was present in 32 cases (40.5%), bleeding and something coming out in 24 patients (10.9%), while smaller proportion of patients had only bleeding 19(8.6%) and constipation 4(1.8%).

Table No.2: Post Procedure complications

Results	No. of Patients	%age
Pain	8	(3.63%)
Bleeding	13	(5.9%)
Infection	5	(2.27%)
Urinary retention	3	(1.36)
Outcome		
Uneventful recovery	153	(69%)
Complications	29	(13.1%)
Recurrence	38	(17.3%)
Total	220	(100%)

Grade of hemorrhoids with post procedure complications (P value <0.05)

Grade of hemorrhoids with gender	P=0.09
Post procedure complications with gender	P=0.15
Outcome with gender	P=0.14

The cure rate in our study was in 153 (69%), while around38 patients (17.3%) presented with recurrent disease. Majority of the patients had uneventful recovery i.e. 153 patients (69%), while 29 patients (13.1%) developed one or the other complications. (Table 2) There was no significant difference in outcome when compared to gender (p value=0.14). Post procedural bleeding was observed in 13 patients (5.9%), pain was observed in 8 patients (3.63%), while 3 patients (1.36%) developed urinary retention. Post procedural complications were more common in patients with higher grade of hemorrhoids with statistically significant p-value (p=<0.05), while these were not significant when compared to gender (p=0.15).

DISCUSSION

First line management of initial hemorrhoidal disease is a non invasive and supportive, while surgery is reserved for those who fail to improve with the supportive measures. For symptomatic hemorrhoids in Grade 1 to 3,various studies observed poor response to the non invasive measures, therefore, are advised for band ligation[17,18,19,20].Contemporary surgical practice has been evolved over the time for treatment of hemorrhoids, and rubber band ligation has emerged as a promising alternative to hemorrhoidectomy. Younger population was more affected by hemorrhoidal disease in various studies[5,7] and mean age of their patients was 48 and 47 years respectively, this is consistent with mean age of our study, that is 43 years. Rubber Band Ligation (RBL) is the most effective, safe and easy method, performed in OPD as an office procedure used for first-to-third degree hemorrhoids with minimal complications, causing fibrosis, retraction, and fixation of the hemorrhoidal cushion[21].

Recently, most update modalities of treatment which seems to be similar to RBL are introduced, such as Injection Sclerotherapy, Endoscopic ligation, cryotherapy, infrared coagulation and hemorrhoidal laser procedure, with minimal post procedural pain and bleeding.[22,23].

In our study, male population was three fold more as compared to the females which could be attributed to the psycho social regional differences which was consistent with the other studies[24].

The cure rate of successful Rubber Band Ligation ranges from 79-91.8% with no difference in cure according to the different grade of disease[25]. In our study, out of 220 patients, cure rate was observed in 153 patients (69%) which is consistent with above study.

Majority of patients after RBL develop trivial complications reported in a study in 94 patients (18.8%)[26.] while in our study, we observed one or the other complications in 38 patients (30.5%).

Bleeding was major complication in our study observed in 13 patients (5.9%) which was mild and treated symptomatically, while in other study it was observed in 31 patients (4.13%)[27]. Pain is one of the most common complication of RBL. In our study pain reported in 8 patients (3.63%), while Gupta et al observed pain in 7 patients (15.9%)[28] and in all cases patients noticed pain in first few of hours that was relieved within 12 hours. Some studies reported mild anal pain in 25% of patients for first 48 hours after banding[29,30]. Several infectious complications have been reported following RBL including pelvic sepsis, Fournier's gangrene, and liver abscess. In our study five patients (2,27%) developed anal infection that was treated by antibiotics successfully.

One of the most serious complication is pelvic sepsis reported in various studies[31,32]. Suspicion should arise in patients with pain, fever, oedema, and urinary retention. A case of Fournier's gangrene in elderly patients with diabetes was reported after RBL[33]. The development of multiple liver abscess were also reported in literature following RBL of hemorrhoids[34,35.]

The recurrence rate in our study was observed in 38 patients (17.3%) after 1 year, while in other study, 22 patients were reported (11.9%) with recurrence at 2 years after Rubber Band Ligation[25]. In recent most

studies, recurrence is >30% and is more likely with increasing prolapse[36]. Recurrences can be treated by re-banding or by surgical intervention. In recent study[37], HAL (Hemorrhoidal Artery Ligation) was compared with RBL regarding recurrence. All other parameters were same except cost. HAL was significantly more expensive. Recently a survey conducted on effectiveness of non-surgical modalities of treatment for hemorrhoids, it was concluded that RBL appears to be the most effective therapy[38]. Other new techniques are more expensive and does not necessarily prove to better outcomes compared with RBL

CONCLUSION

RBL is simple, safe, and effective modality of treatment with less complications for hemorrhoids especially in first-to-third degree, which can be performed at Out Patient Department, as an office procedure. Its beauty is day care procedure with no hospitalization and anesthesia required. This modality of treatment is recommended in all age groups and in both genders, that does not alter the anorectal function.

Author's Contribution:

Concept & Design of Study:	Muhammad Saleem Shaikh
Drafting:	Muharram Ali, Kheo Ram Dholia
Data Analysis:	Muharram Ali, Kheo Ram Dholia
Revisiting Critically:	Muhammad Saleem Shaikh, Muharram Ali
Final Approval of version:	Muhammad Saleem Shaikh

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

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Original Article

IQ Level between Night and Morning Medical Students

Intelligent Quotient (IQ) Comparison between Night Owls and Morning Larks Chronotypes in Medical Students

Urooj Bhatti[1], Rubina Ahmadani[1] and Muhammad Nadeem Chohan[2]

ABSTRACT

Objective: To compare the intelligent quotient between Night Owls and Morning Larks chronotypes in medical students of LUMHS Jamshoro Karachi.

Study Design: Descriptive / cross sectional study.

Place and Duration of Study: This study was conducted at the Department of Physiology and Pediatrics, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro from November 2015 to October 2016.

Materials and Methods: 225 MBBS students altogether including 120 males and 105 females via Simple Random Sampling from first year with age group (18-20). The student profiles were unspecified**.** Stanford Binnet Intelligence Scale was used for the IQ. To determine the chronotypes, Lark and Owl questionnaire was used which has 19 questions related to the circadian rhythm and one's best feeling time. 1st year MBBS undergraduates belonging to the group of ages (18-20) were covered. Second year to final year MBBS students, Post-graduate students, house officers and those who were suffering from any major neurological or psychological illness were excluded. All the data was interpreted, Pearson's chi square test was applied and results were drawn with the help of SPSS version 22 which is the statistical package of social sciences.

Results: Among the extremely morning types out of 31 students in total, 10 (32.5%) were found to be genius, 3(9.6%) were had very superior IQ, 12(38.7%) were found to be superior and 5(16.1%) were average as shown in Table 2. In the moderately morning type category (n=12), 5 (41.6%) were found to be genius, 2(16.6%) had very superior IQ and 2(16.6%) were average. Among neutral types (n=87), 40 (45.9%) were found to be genius, 24(27.5%) were had very superior IQ, 15(17.2%) were found to be superior and 1(1.14%) were average. Moderately evening types (n=52) were found to have 8 (15.3%) genius, 22(42.3%) were had very superior IQ and 21(40.3%) were found to be superior. Among extremely evening type (n=43), 26(60.4%) were found to be genius, 7(16.3%) were had very superior IQ, 8(18.6%) were found to be superior and 1(2.3%) were average. The evening types were seemed to have higher IQ than morning type.

Conclusion: 21st century is advancing so much in psychology that it's important to know various dimensions of our own physiology that might improve the quality of our lives. In the light of previous literature and adding to this sparse data, this study showed that the medical students are more of evening types and that Eveningness has a positive correlation with intelligence.

Key Words: Circadian rhythm; Intelligence; Students, Medical

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INTRODUCTION

In humans and mammals circadian rhythms are psychological, biochemical and physical variations that exhibit a cycle of 24 hours. Supra-chiasmatic nuclei of the hypothalamus controls these circadian cycles [1].

Sleep wake rhythm and self-awareness are influenced by Morningness and Eveningness (Diurnal precedence). People who rise early in morning are called morning larks, these like to go to bed early and achieve their maximum attentiveness in the early hours of the day. On the other side people who prefer to get up off the bed at late evening are called night owls, and these having peak alertness at night [2].

Most of the children prefer Morningness and with advancing age this shifts to Eveningness. When adolescent's reaches age 20 years, they prefer total Eveningness and they delay phase preferences. At the age of 50 years adult person prefers Morningness once again [3].

Intelligence quotient is defined as person's reasoning ability, that is measured by using problem-solving tests and this is compared to the statistical norm for their age, taken as 100 [4].For the maintenance of normal cognition and alertness, there is need of sufficient amount of sleep.

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This hypothesis is supported by brain functional radiological studies that show adequate sleep is mandatory for cognitive ability. Because it reduces glucose metabolism in cortex of brain [5]. This is the genetic difference that causes variability among both chronotypes [6].The gene that regulates circadian rhythm has been discovered in near past [7].One study proved the relation between chronotypes and cognitive function, there was higher working memory in night owl groups, even when measured during early morning[1]. Now a days Psychologist are giving more attention to see the relationship between intelligence and chronotypes.

We did this study to know the intelligence difference between these two chronotypes among medical students, as we can know the difference and can make further protocols.

MATERIALS AND METHODS

This study was done over 225 MBBS medical students at the Department of Physiology and Pediatrics, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro from November 2015 to October 2016. This was a cross sectional observational study done via random sampling technique contained both male and female medical students of age between 18-20 years.

Written consent was taken from students before collecting data and they were counseled about the importance of this study. For the determination of IQ score Stanford Binnet Intelligence Scale was used. Questionnaire was used to determine Owl and Lark. 19 questions were asked about the one's best feeling time and circadian rhythm. Only 1st year MBBS medical students age between 18 to 20 years were included in the study. 1st year Medical student, suffering from psychological or neurological disorders were excluded from the study. SPSS version 22 used for the interpretation of data and Pearson's chi square test was applied.

RESULTS

In this study, there were 53% males and 47% females were. Medical students were more night owls, 19.10% (42 / 225) were extreme evening type, 12.8% (29 / 225) were the extreme morning type, 38.2% (86 / 225) were the neutral, 24% (54 / 225) and 6.2% (14 / 225) were moderately evening and moderately morning type (Table 1). Among the extremely morning types 10 (32.5%) were genius, 3(9.6%) were very superior IQ, 12(38.7%) were superior and 5(16.1%) were average (Table 2). In the moderately morning type category 5 (41.6%) were genius, 2(16.6%) had very superior IQ and 3(25.0%) were average. Among neutral types (n=87), 40 (45.9%) were genius, 24(27.5%) were very superior IQ, 15(17.2%) were superior and 4(4.59%) were average. Moderately evening types (n=52) were 8 (15.3%) genius, 22(42.3%) were very superior IQ and 21(40.3%) were superior. Among extremely evening type (n=43), 26(60.4%) were genius, 7(16.2%) were very superior IQ, 8(18.6%) were superior and 1(2.3%) were average. The X value is 76.995 and p-value is <0.000001, and this is highly significant statically, calculated by Pearson's chi square test. As compared to morning type, evening types had higher IQ.

Table No.1: Percentage of Chronotypes n=225

Extremely Morning Type (70-89)	29 (12.8%)
Moderately Morning Type (59-69)	14 (6.2%)
Neutral Type (42-58)	86 (38.2%)
Moderately Evening Type (31-41)	54 (24%)
Extremely Evening (16-30)	42 (18.6%)

Table No.2: Percentage of Intelligent Quotient of different chronotypes

Genius (over 140)	
Extremely Morning Time	10 (32.5%)
Moderately Evening Type	8 (15.3%)
Moderately Morning Type	5 (41.6%)
Extreme Evening Type	26 (60.4%)
Neutral Type	40 (45.9%)
Very Superior (120-139)	
Extremely Morning Time	3 (9.6%)
Moderately Evening Type	22 (44.3%)
Moderately Morning Type	2 (16.6%)
Extreme Evening Type	7 (16.2%)
Neutral Type	24 (27.5%)
Superior (110-119)	
Extremely Morning Time	12 (38.7%)
Moderately Evening Type	21 (40.3%)
Moderately Morning Type	3 (25%)
Extreme Evening Type	8 (18.6%)
Neutral Type	15 (17.2%)
Average (90-109)	
Extremely Morning Time	5 (16.1%)
Moderately Evening Type	1 (1.92%)
Moderately Morning Type	2 (16.6%)
Extreme Evening Type	1 (2.3%)
Neutral Type	1 (1.14%)
Dull (80-89)	
Extremely Morning Time	1 (3.2%)
Moderately Evening Type	0
Moderately Morning Type	1 (8.3%)
Extreme Evening Type	1 (2.3%)
Neutral Type	4 (4.59%)
Borderline Deficiency (70-79)	
Extremely Morning Time	0
Moderately Evening Type	0
Moderately Morning Type	0
Extreme Evening Type	1 (2, 3%)
Neutral Type	1 (1.14%)

DISCUSSION

As scientists are uncovering various mysteries of mind, so IQ levels determination and its various aspects are

gaining attention. In human psychology intelligence and nocturnality are two important factors. In this study we focused that which types has more intelligence among evening type or morning type. Our study showed that night owls had more IQ as compared to morning larks.

A similar study from United States, which was done on 420 air force recruits showed the positive correlation between intelligence and Eveningness, proving evening types to be more intelligent than Morningness [8]. In another study results did not showed any relation between chronotypes and cognition [6].

Our hypothesis shows that there might be more problems in night owl chronotypes in performing early morning jobs and institutional work. Other spectrum of night owls chronotypes shows that they require less amount of sleep and thus they require less sleep to reach their maximum neuronal activity.

It is postulated that mating intelligence has caused greater night owl intelligence[1]. According to various studies it is proved that Eveningness is seen more in university students that lead to higher cognitive abilities. As the age advances, cycle shift towards Morningness, that's why there is fall in intelligence with, advanced age [8].

Although above mentioned research are recent, but we still need more research in this field to make it more authentic and acceptable.

CONCLUSION

With the advancement in psychology and for the improvement in our life quality, we should know more about the different dimensions of our own physiology.

According to this study results we can say that Eveningness is more common in medical students, and this chronotypes has positive correlation with intelligence.

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Original Article

Intracranial Infections in Children

Frequencies of Common Intracranial Infections Leading to Coma in Children

Anila Farhat and Sohail Babar

ABSTRACT

Objective: The present study was carried out to find the frequencies of common intracranial infections like tuberculous meningitis, bacterial meningitis and viral encephalitis in children presented with coma.

Study Design: Descriptive / cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Pediatrics, Benazir Bhutoo Shaheed Hospital Abbottabad from April 2016 to July 2017.

Materials and Methods: With the approval from hospital ethical committee, 92 patients of either gender with intracranial infections presented with coma were included in the study. Details of history, clinical examination at the time of admission and clinical variables were recorded on a structured proforma. Data was entered and analyzed in SPS version 17. Mean and standard deviation were calculated for quantitative variable like age whereas for categorical variables like temperature, fits, acute onset of illness, BCG scar, neck stiffness, papilledema, corneal reflex and pupillary reaction, percentages and frequencies were calculated.

Results: In the study population, male patients predominate with a total of 68.5% patients while 31.5% patients were female. Frequencies of bacterial meningitis, viral encephalitis and tuberculous meningitis were 44.6%, 31.5% and 23.9% respectively in the patients presented with coma. The study showed that the percentage of patients presented with different clinical variables, that is, temperature more than 100°F, fits, neck stiffness, BCG scar and papilledema were 88%, 72.8%, 68.5%, 41.3%, and 37% respectively.30.4% of patients presented with coma with in 48hrs of onset of acute illness. Pupillary and corneal reflex were absent in 18.5% and 20.7% patients respectively.

Conclusion: Amongst intracranial infections in patients presented with coma, frequency of bacterial meningitis was highest followed by viral encephalitis and tuberculous meningitis.

Key Words: Intracranial infection, coma, bacterial meningitis, viral encephalitis, tuberculous meningitis

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INTRODUCTION

Coma is defined as a pathological state of deep and sustained (>1 hour) unconsciousness, distinguishable from normal sleep by the inability to be aroused. It can also be considered as a state of complete loss of arousal to any kind of stimulation and complete loss of awareness of the self and the surrounding. One of the greatest challenges a pediatrician faces is the successful management of comatosed children. Coma is one of the important pediatrics emergency.[1,2] The epidemiology of coma varies considerably with age. For instance, in the study carried out at UK by Bowker et al., the age specific incidence of coma is greatest in children under 1 year of age (160 per 100,000 children per year), whereas the incidence of coma in children from non- traumatic causes is about 30 cases per 100,000 children per year (or 6 per 100,000) general populations per year.[2]

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The cause of coma if not diagnosed timely by proper investigations, and managed accordingly, can lead to devastating consequences for child in terms of morbidity and mortality.[2]

Causes of non-traumatic coma range from common treatable to rare ones.[2] The most common cause of coma in children is intracranial infections, which include bacterial meningitis, viral encephalitis and tuberculous meningitis, followed by drug intoxication, seizures and inherited metabolic diseases.[3] Since infections of CNS are frequently encountered, high degree of suspicion is required for diagnosis.[4] CNS infections are classified on basis of etiology in to bacterial, viral, fungal and parasitic.[5,6] CNS infections cause acute encephalopathy in 65% of children presented with non-traumatic coma.[7,8] According to the study in Pakistan, 65% of the comatosed children had CNS infection in which 31% had bacterial meningitis, 18% had viral encephalitis and 12% had tuberculous meningitis[9] whereas the study in India showed 60% of the comatosed children had CNS infection in which 21% had viral encephalitis, 18% bacterial meningitis, 19% had tuberculous meningitis.[1] The importance of infective etiologies in children is in sharp contrast to adult hospital based studies where degenerative and cerebrovascular pathologies predominate. Among the

non-infectious causes, toxic-metabolic causes are the commonest.[2]

Tuberculous meningitis has 3 stages. In stage III (advance) there is severe clouding of sensorium, convulsion and coma.[10] About 97% of the patients with tuberculous meningitis present in stage II and III (coma).[11] Patients with bacterial meningitis can present with high pitch cry, irritability, vomiting, altered mental state and coma.[12] In viral encephalitis there is acute onset of neurological dysfunction that can lead to sudden deterioration of consciousness and coma.[8]

Better survival rate is observed in comatosed patients with CNS infection as compared to toxic-metabolic group so an early diagnosis of CNS infection in comatosed children is necessary by appropriate investigations.[1]

Our aim behind this study was to know relative frequencies of intracranial infections in comatosed children which will in turn be helpful in the early diagnosis and management of treatable causes of coma in our setup.

MATERIALS AND METHODS

This cross sectional study was conducted in the Department of Pediatrics, Benazir Bhutoo Shaheed Hospital Abbottabad with approval from hospital ethical committee. Full informed consent was taken from parents or attendants of the patients. Confidentiality of the data was ensured.

Inclusion criteria: This study was carried on 92 paediatric patients presented with coma with GCS <12 for more than 6 hours due to intracranial infections like tuberculous meningitis (TBM), bacterial meningitis and viral encephalitis (VE) diagnosed on the basis of history, clinical examination and relevant laboratory investigations such as lumbar puncture, CT scan and metabolic work up determined by clinical presentation. CSF cytology, biochemistry and culture were sent to hospital laboratory and reported by microbiologist and all tests were carried out in the same hospital laboratory.

Exclusion criteria: coma due to trauma, toxic-metabolic causes, post-status epilepticus, intracranial bleeding, hypertensive encephalopathy.

Details of history, examination findings and clinical variables like temperature, BCG scar, fits, acute onset of illness, neck stiffness, papilledema, corneal and pupillary reflex were recorded on structured proforma. Data was analyzed by using SPSS 17. Age, a quantitative variable, was described in terms of mean ± standard deviation. In the case of categorical variables like: gender, BCG scar, onset of illness, neck stiffness, seizures, pupillary and corneal reflexes, papilledema, GCS, and temperature; intracranial infection and its type, frequencies and percentages were calculated.

Diagnosis of bacterial meningitis was made when there was history of fever, fits, CSF culture for identification of microorganisms and/or CSF analysis showing Leucocytes > 100/mm^3 with neutrophil predominance, protein > 40 /mg, glucose < 40 mg/dl.[1]

TBM was diagnosed when there was positive family history of tuberculosis, positive mountoux test, CSF analysis showing Leukocyte count of (10 □ 500)/mm^3 with lymphocytes predominance, protein > 100 mg/dl, glucose < 40 mg/dl.[8] and/or CT/MRI showing basilar enhancement or communicating hydrocephalus with signs of cerebral edema or early tuberculoma.[20]

Diagnosis of Encephalitis was made when there was history of fever, headache and an altered mental state together with seizures and focal neurological findings with CSF analysis showing Leucocytes > 5/mm^3 with lymphocytes predominant, protein <40mg/dl, glucose < 80 mg/dl or on CT/MRI scans suggested HSV encephalitis.[1,20]

RESULTS

A total of 92 comatosed patients, who fulfilled the inclusion criteria over the study period, with evidence of intracranial infections and GCS<12 for more than 6 hours were included in the study.

Table No.1: Descriptive of comatosed patients by Gender

Gender	No. of patients		Age (Months)	
	Frequency	%age	Mean	Std. Dev.
F	29	31.5	40.69	31.738
M	63	68.5	47.91	44.959
Total	92	1100.0	45.64	41.212

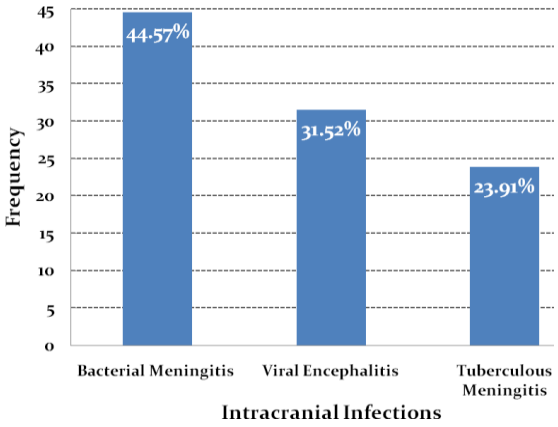

Figure 1 : Frequency of Intracranial Infections

Table 1 shows that among the total study population, male patients predominate with a total of 63 (68.5%) while 29(31.5%) were female giving male to female ratio 2.18:1. Gender wise, there was a significant difference amongst the patients. Mean age of the our patient was 45.64 ± 41.2 months with male patients having mean age of 47.91 ± 44.96 months and female patients with a mean age of 40.69 ± 31.74 months. Age wise, there was no significant difference amongst the patients.

As shown in Figure 1, the most common intracranial infection observed in comatosed patients in this study was bacterial meningitis with the frequency of 41 (44.6%) patients, followed by viral encephalitis with the frequency of 29 (31.5%) patients and tuberculous meningitis with the frequency 22 (23.9%) patients.

Among clinical variables observed in present study as tabulated in Table 2, temperature of more than 100 °F was present in 81(88%) of patient, BCG scar was present in 54 (58.7%) patients while 28 (30.4%) patients had acute onset of illness(with in 48hrs of onset of coma). Neck stiffness was observed in 63 (68.5%) patients. Fits were observed in 67 (72.8%) patients. Papilledema was detected in 34 (37%) patients. Pupillary and corneal reflex were absent in 17 (18.5%) and 19 (20.7%) of the patients respectively.

Table No.2**: Frequency of clinical variables in comatosed patients**

Variables	Frequency	Percentage(%)
Temperature (°F) > 100°F		
Absent	11	12.0
Present	81	88.0
BCG scar		
Absent	54	58.7
Present	38	41.3
Acute onset of illness		
Absent	64	69.6
Present	28	30.4
Neck stiffness		
Absent	29	31.5
Present	63	68.5
Fits		
Absent	24	26.1
Present	67	72.8
Papilledema		
Absent	58	63.0
Present	34	37.0
Pupil reactive		
Absent	17	18.5
Present	75	81.5
Corneal reflex		
Absent	19	20.7
Present	73	79.3

DISCUSSION

Coma is important clinical problem in pediatric practice. In many cases it results from primary insult to brain which if not treated timely can lead to permanent brain damage.

There are various causes of coma. Coma can result from trauma or wide variety of non-traumatic causes. Pediatric non-traumatic coma is a common presentation accounting for an estimated 10-15% of all hospital admissions. [9] Etiology of non traumatic coma is diverse ranging from common intracranial infections to rare ones however considerable regional diversity exits in these etiological factors with infectious problems suggested to be more common in developing countries. The data from developing countries is also limited where 80% of world's children live.[12] So the objective of conducting this study was to find out frequencies of common treatable intracranial infections leading to coma.

If we compare etiology of coma in children with adults we find that CNS infections are common cause of coma in children while degenerative and cerebrovascular pathologies predominate in adults.[2] Importance of infections as an aetiology of non–traumatic coma identified in this study is also supported by studies conducted in Pakistan, India, Saudi Arabia, Nigeria, England, Iran and Egypt.[1,9,13,14,15,16,17] Type of infection and their frequency seems to vary in different regions. For instance, cerebral malaria is important cause of coma in Africa and Dengue haemorrhagic fever in South East Asia.[1,18] While study conducted in Pakistan and in neighboring countries like Iran, India, Sri Lanka and Kashmir showed tuberculous meningitis, bacterial meningitis and viral encephalitis as important cause of coma in children.[1,9,17,19,20,21]

Amongst the three common causes of intracranial infections i.e. bacterial meningitis, viral encephalitis and tuberculous meningitis which were observed in present study, frequency of bacterial meningitis was highest i.e. 44%, which is consistent with the studies by Wong et al.[16], Suganthi et al.[19] Khodapanahandeh et al.[17] and Ahmed et al.[9] i.e., 47%, 42%, 36% and 31% respectively. In the present study, second most common intracranial infection was viral encephalitis in 31% of the cases; similar results were observed by Bansal et al.[1], Ahmed et al.[9], Ali et al.[14] in 30%, 18%, 17% cases respectively. In this study, tuberculous meningitis was the least common (23%), which was also observed in local study by Ahmed et al.[9], Iranian study by Khodapanahandeh et al.[17] and Kashmiri study by Ahmad et al.[20] who had 12%, 19% and 25% patients of TBM respectively. However, contradicting result was observed by Bansal et al.[1], who found tuberculous meningitis (31.6%) to be the most common CNS infection in comatosed children.

Intracranial infections are more common in the preschool age group of children having mean age of 45.64 months with predominance in male population i.e 68.5% as against 31.5% in female patients. This is in agreement with the studies of Ali et al.[14] Ibekwe et al.[15] and Ahmed et al.

Most common clinical sign observed in this study was temperature more than 100°F in 88% cases of the study population. Wong et al.[16] observed this in 55% and Ibekwe et al.[15] in 38% of cases. Wong et al.[16] and Khodapanahandeh et al.[17] observed fits as second most clinical sign in comatosed children which was also

observed in our study, i.e. 72% of the patients had fits. Fouad et al.[13] also observed fits in 65% of patients.

68.5% of our study population presented with neck stiffness while in study conducted by Bansal et al. only 29% of patients had neck stiffness. Acute onset of illness in this study was present in 28(30.4%) patients, while Ibekwe et al.[15] and Ahmed et al.[9] reported 23% and 40% patients had acute onset of illness respectively.

Papilledema indicates raised intracranial pressure and is associated with poor outcome. It was found in 40% of the cases by Bansal et al.[1] and similar result was found in this study i.e. 37%. While 18% of cases in local study by Ahmed et al.[9] had papilledema.

Pupillary reflex is good predictor of outcome; non-reactive pupil is strong predictors of fatal outcome. Bansal et al.[1], Fouad et al.[13] and Ahmed et al.[9] found 25%, 21% and 18% patients with non-reactive pupils respectively while in our study, 18.5% of the cases had non-reactive pupils.

Corneal reflex, on the other hand, shows functional interconnection in pons. In the study conducted by Bansal et al.,[1] corneal reflex was absent in 10% of the cases while in this study, 20.7% of the patients had absent corneal reflex.

CONCLUSION

It is concluded from present study that bacterial meningitis is the most common cause of non-traumatic coma in the study population followed by viral encephalitis and tuberculous meningitis. It is also concluded that intracranial infections are most common in preschool age group with male gender predominance. High grade fever is the most common clinical variable followed by fits and neck stiffness in comatose patients with underlying intracranial infections.

Author's Contribution:

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Original Article

Detection of Tubal Cause of Subfertility by Hysterosalpingography

Diagnosis of Subfertility by Hysterosalpingography

Qamarunissa[1], Shazia Rani[2] and Pushpa Malhi[1]

ABSTRACT

Objective: To determine the frequency of various tubal causes of subfertility by Hysterosalpingography in women at Isra University Hospital, Hyderabad.

Study Design: Observational / cross sectional study.

Place and Duration of Study: This study was conducted at the Obstetric and Gynecology Department, Isra University Hospital Hyderabad from 13th October 2013 to 13 October 2014.

Materials and Methods: Total 292 women were enrolled; youngest one being 15 years and maximum age was 35 years. In 55.8% cases had duration of marriage < 5 years while 38.7% women were married for 5 to 10 years and 5.5% were married for more than 10 years.

Results: The frequency of primary and secondary sub fertility was 57.5% and 42.5% respectively observed in this study. Majority of women 85.6% were nulliparous while, 13.7% were primi and 1.02% women were multipara. The tubal factor subfertility was most common in 30-35 years of age and second most common group was 25-29 years. 26.4% women had bilateral tubal pathology, 20.9 had one side tubal occlusion while uterine cavity anomaly was determined in 2.7% and peritoneal spillage was present in 49.7% cases. Majority of the subfertile women 65.1% were seen age group between 30 to 35 years, 58.9% were primary and 73.4% were secondary subfertility.

Conclusion: Hysterosalpingography remains an integral part of subfertility workup. It can be used as a first line screening investigation of tubal patency irrespective of duration of subfertility. HSG allows documentation of tubal patency, enables detection of several tubal lesions and permits assessments of fine intratubal architecture details especially when as aqueous contrast medium is used. Other than being diagnostic, it can prove to be therapeutic. Tubal factor was the most common cause of subfertility demonstrated in this study.

Key Words: Sub-Fertility, Hysterosalpingography, Tubal Cause, Uterine Causes.

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INTRODUCTION

Subfertility is the inability of a couple in reproductive age groups to conceive within twelve months of unprotected coitus. There are two types of subfertility primary and secondary, primary defined as when couples who have never conceived whereas secondary subfertility is said to couples who are unable to conceive after one year of unprotected coitus and having previous pregnancy and not using any contraceptives.[1]

Globally approximately 10-15% of the couples are subfertile.[2] The prevalence of subfertility varies within countries; the occurrence is depending on the incidence of preventable conditions that cause the subfertility.[3]

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Tubal sub-fertility is commonly seen in those with secondary sub-fertility and in populations who having higher prevalence of sexually transmitted disease. Local health care practices and policies, especially unhygienic obstetric practices, lack of antibiotic cover and unsafe abortions are also major risk factors which cause pelvic adhesions and lead to secondary sub-fertility.[4] In our setup its incidence is higher due to unsafe abortion and inadequate and inappropriate facilities .[5]

Pelvic inflammatory disease carries up to 10% risk of future tubal factor subfertility.[6]

Hysterosalpingography is the method used for screening in the routine subfertility evaluation.[7] A subfertility work up is incomplete without an hysterosylpingogram.

Hysterosylpingogram gives important information about the outlining of the uterine cavity, any it's abnormality and patency of fallopian tubes. It is also recommended for the study of the uterine cavity in the diagnosis and treatment planning of other gynaecologic problem such as intrauterine adhesions and congenital anomalies[8].

High incidence of tubal blockage in our setup due to inadequate health facilities because of our limited resources. As hysterosalpingography is gold standard,

safe, cost effective, non-invasive, easy to perform in out door patient and helpful in the detection of the causes of subfertility. On the bases of this it is recommended that hysterosalpingography should be performed first line screening investigation of tubal patency irrespective of a duration of subfertilty in third world countries like Pakistan where the facilities and expertise for laparoscopy are not routinely used.[5] The purpose of this study was to determine the frequency of various tubal causes of sub-fertility by Hysterosalpingography in women at Isra University Hospital.

MATERIALS AND METHODS

This observational / cross sectional study will be conducted amongst outdoor patients in the department of Obstetrics and Gynaecology at Isra University Hospital, Hyderabad from 13th October 2013 to 13 October 2014.

Keeping the significant of estimation at 5%, bound on the error of estimation at 5% then sample size come out 100 cases for this study. It was non probability purposive sampling.

Inclusion Criteria:

1) Primary Subfertile patients.
2) Secondary Subfertile patients
3) Women of reproductive age 15-35 age

Exclusion Criteria: -

1) Previous hysterosalpingography related to subfertility.
2) Previous diagnostic laparoscopy related to subfertility.
3) Contraindications for hysteorsalpingography or laparoscopy e.g. pelvic inflammatory disease, abnormal uterine bleeding.
4) Abnormal vaginal discharge.

Data Collection Procedure: Women with history of subfertility may be primary or secondary, meeting inclusion criteria attending Isra University Hospital will be enrolled in the study. Exclusion criteria will be strictly followed to avoid confound variables.

The initial evaluation of patients including a detail history, a complete general, physical, systemic and local pelvic examination, and then informed consent will be taken for the study as well as hysterosal pingography. It is performed in radiology department under aseptic conditions in follicular phase on the eight' day of clearance of menses. It involved in following the injection of radio opaque iodine based dye (urograffin 76%) passed through the cervix.

A radiograph is taken after injection of medium to ensure any filling defect in uterine cavity and degree of spillage in peritoneal cavity, then x-rays with documented opinion of radiologist is handed over to couple**.**

RESULTS

Total 292 women were enrolled; youngest one being 15 years and maximum age was 35 years. In 55.8% cases had duration of marriage < 5 years while 38.7% women were married for 5 to 10 years and 5.5% were married for more than 10 years.

The frequency of primary and secondary sub fertility was 57.5% and 42.5% respectively observed in this study. Majority of women 85.6% were nulliparous while, 13.7% were primi and 1.02% women were multipara.

Table No. 1: Frequency of age groups of study participants (n=292)

Age groups	Number	Percentage
15 to 19	03	1.0
20 to 24	39	13.4
25 to 29	60	20.5
30 to 35	190	65.1
Frequency of duration of marriage in groups of study participants (n = 292)		
Duration of marriage in groups	**Number**	**Percentage**
< 5 years	163	55.8%
5 to 10 years	113	38.7%
> 10 years	16	5.5%
Parity of Women (n = 292)		
Parity	**Number**	**Percentage**
0 + 0 (Nulli para)	168	57.53%
1 to 2 (Primi para)	122	41.78%
> 2 (Multipara)	02	0.68%

Table No. 2: Status of congenital abnormalities detected by hysterosalpingography (n = 08)

Congenital abnormalities	Number	Percentage
Bicornuate uterus	02	25.0%
Unicornuate uterus	02	25.0%
Diadelphus uterus	0	0
Intrauterine adhesion	02	25.0%
Filling defect	02	25.0%
Status of tubal patency detected by hysterosalpingography (n = 292)		
Patency	**Number**	**Percentage**
Two-sided tubal occlusion	77	26.4%
One sided tubal occlusion	61	20.9%
Uterine cavity anomaly	08	2.7%
Peritoneal spillage	146	50.0%

The tubal factor subfertility was most common in 30-35 years of age and second most common group was 25-29 years. 26.4% women had bilateral tubal pathology, 20.9 had one side tubal occlusion while uterine cavity anomaly was determined in 2.7% and peritoneal spillage was present in 49.7% cases. Majority of the subfertile women 65.1% were seen age group between 30 to 35 years, 58.9% were primary and 73.4% were secondary subfertility.

Table No. 3: Causes of suberfitility detected by hysterosalpingography (n = 292)

Causes of subfertility	Subfertility		Total n=292
	Primary n = 168	Secondary n = 124	
Two-sided tubal occlusion	45(26.7%)	32(25.80%)	77(26.4%)
One sided tubal occlusion	35(23.80%)	26(20.96%)	61(20.9%)
Bicornuate uterus	0	02(1.61%)	2(0.68%)
Unicornuate uterus	02(1.19%)	0	2(0.68%)
Diadelphus uterus	0	0	0
Intrauterine adhesion	0	02(1.61%)	2(0.68%)
Filling defect	1(0.59%)	1(0.80%)	2(0.68%)
Status of congenital abnormalities detected by hysterosalpingography with subfertiligy (n = 292)			
Congenital abnormalities	**Primary n= 168**	**Secondary n = 124**	**Total n=292**
Bicornuate uterus	0	02(1.61%)	02(0.68%)
Unicornuate uterus	02(1.19%)	0	02(0.68%)
Diadelphus uterus	0	0	0
Intrauterine adhesion	0	02(1.61%)	02(0.68%)
Filling defect	1(0.59%)	1(0.80%)	02(0.68%)

Table No. 4: Status of age groups with subfertiltiy (n = 292)

Age groups	Subfertility		Total
	Primary n = 168	Secondary n = 124	
15 to 19	1(0.6%)	2(1.6%)	3(1.0%)
20 to 24	26(15.5%)	13(10.5%)	39(13.4%)
25 to 29	42(25.0%)	18(14.5%)	60(20.5%)
30 to 35	99(58.9%)	91(73.4%)	190(65.1%)

Table No. 5: Status of tubal patency detected by hysterosalpingography with parity (n = 292)

Patency	Parity			Total n=292
	0 + 0 n = 168	1 + 2 n = 122	> 2 n = 2	
Two-sided tubal occlusion	45(26.7%)	32(26.22%)	0	77(26.4%)
One sided tubal occlusion	35(20.08%)	26(21.31%)	0	61(20.9%)
Uterine cavity anomaly	03(1.78%)	04 (3.27%)	1(50.0%)	8(2.7%)
Peritoneal spillage	85(50.59%)	60(49.18%)	1(50.0%)	146(50.0%)

Table No. 6: Status of congenital abnormalities detected by hysterosalpingography with age groups (n =08)

Congenital abnormalities	Age (in groups)				Total n=292
	15 to 19 n = 03	20 to 24 n = 39	25 to 29 n = 60	30 to 35 n = 190	
Bicornuate uterus	01 (33.3%)	0	0	01 (0.52%)	02 (0.68%)
Unicornuate uterus	0	01 (2.56%)	0	01 (0.52%)	02 (0.68%)
Diadelphus uterus	0	0	0	0	0
Intrauterine adhesion	0	01 (2.56%)	01 (1.66%)	0	02 (0.68%)
Filling defect	0	0	01 (1.66%)	01 (0.52%)	02 (0.68%)

DISCUSSION

Subfertility is defined as the inability of a couple to conceive after one year of unprotected intercourse.[9] In case of men, it is the inability to procreate and in case of women, it is the inability to conceive. There are different causes of subfertility which includes cervical, uterine, tubal, ovarian and peritoneal cause but initial workup of subfertility is incomplete without hysterosalpingography.[10]

Tubal cause counts for 14% cases of female subfertility,[11] but in our setup, its incidence is higher because of inappropriate health facilities.[12]

Hysterosalpingography is the method used for screening purpose and initial assessment of subfertility, it has been considered gold standard for evaluating the fallopian tubes and uterine morphology.[7]

Our aim is to find out the usefulness of hysterosal-pingography for assesment of tubal cause of subfertility and whether it can safely use as fist line investigation of tubal patency in all cases of subfertility irrespective of its duration and type.

In the present study of 292 cases, primary subfertility was higher i.e. 57.53% than secondary subfertility 42.5%. Most women i.e. 65.1% were observed in 30 to 35 years age group. These figures correlate well to the study of Poonam et al [8]conducted in Nepal, 71% had primary and secondary 10.2% subfertility, most patients belonged to age group of 26 to 30 years. In another study conducted by Kumar SCS et al[11] primary subfertility was higher i.e. 53.3% and secondary subfertility was 8.3% whereas in a local study of Rahim R et al[12] showed the same observation of subfertility.

In another study of Aflatoonian Abbas et al[13] and his colleagues conducted in Iran, they proved that primary subfertility was higher than secondary subfertility. This could be due to the hesitancy of coupes in seeking early advice, unawareness of the importance of initial treatment could be another factor contributing to such long duration of subfertility.

Tubal occlusion was in 47.2%, two-sided tubal occlusion was in 26.4% and one sided tubal occlusion was in 20.9%. The same observation was seen in the study of Bacevac J et al.[14]

Another study of Tvarijonaviciene E et al[7] conducted in Lithuania, two-sided tubal occlusion was in 15.0% and one sided was in tubal occlusion was in 21.5% while Mol BW et al[15] showed the one sided tubal occlusion in 19.0% and two-sided occlusion in 17%, these findings are similar to the present study.

Out of 292 women, congenital abnormalities were observed in 2.7% women. Of these, 25.0% women had Bicornuate, unicornuate, intrauterine adhesion and filling defect respectively whereas Poonam, et al[8] observed the comparable results to this study. In another study of Braun P et al[16] revealed 10.6% biocornuate uterus which is nearly to this study.

HSG allows documentation of tubal patency, enables detection of several tubal lesions and permits assessments of fine intratubal architecture details especially when as aqueous contrast medium is used.

The small fibroid can be missed by clinical examination and fibroid projecting in to uterine cavity may cause actual filling defect which can be detected by hysterosalpingography. Large fibroid often produced extreme distortion of uterine cavity.

When myomectomy is planned HSG has excellent value in visualization of uterine cavity and fallopian tube.

CONCLUSION

Hysterosalpingography remains an integral part of subfertility workup. It can be used as a first line screening investigation of tubal patency irrespective of duration of subfertility. HSG allows documentation of tubal patency, enables detection of several tubal lesions and permits assessments of fine intratubal architecture details especially when as aqueous contrast medium is used. Other than being diagnostic, it can prove to be therapeutic. Tubal factor was the most common cause of subfertility demonstrated in this study. Knowledge of these entities is important to avoid the practice of unnecessary and sometimes more aggressive procedures.

Author's Contribution:

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

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Original Article

Frequency of Intracranial Bleed in Infants with Vitamin-K Deficiency in 7-180 Days of Age

Ihsanul Haq, Ashfaq Ahmad, Sardar Khan and Zahir Said

ABSTRACT

Objective: To determine the frequency of intracranial bleed in infants with vitamin-K deficiency in 7-180 days of age.

Study Design: Descriptive / cross sectional study

Place and Duration of Study: This study was conducted at the Department of Pediatrics STH, Swat from 1st July 2016 to 30th June 2017.

Materials and Methods: Biodata, clinical profile and results of the investigations (coagulation profile and neuroimaging) of all theselected patients were collected on a pre designed proforma. Total of 100 patients were included who fulfilled the inclusion criteria of the study. Exclusion criteria were strictly observed to prevent confounder and bias.

Results: Out of 100 patients 65(65%) were male and 35(35%) were female. Intracranial bleed due to Vitamin-K deficiency was confirmed in 31(31%) patients. The mean age of onset of symptoms was 45.65 ± 15.35 days and male to female ratio 1.85:1 (p=0.047). 16 (51.61%) out of 31 patients with intracranial bleed were from 7-60 days of life, 10(32.25%) were from 61-120 days of life and only 5(16.12%) beyond 120 days of life.

Conclusion: Intracranial hemorrhage remains a disabling disease mostly due to unidentifiable causes, however in many cases a high index of suspicion of Vitamin K deficiency should be kept in mind which often leads to bleeding as identified in our study.

Key Words: Intracranial bleed, Vitamin-K deficiency

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INTRODUCTION

Intracranial bleed is the pathological accumulation of blood within the cranial vault. Intracranial bleed is a rare but often disabling disease leading to high rate of morbidity and mortality in this population[1], it may occur within brain parenchyma or the surrounding meningeal spaces.[2] Bleeding into the brain and related structures is a very common neonatal event and is most frequently recognized in premature infants.[3]

Intracranial hemorrhage usually presents with neurological symptoms and signs like altered level of consciousness, reluctance to feed, seizures, vomiting or fever.[4-5] It may be epidural, subdural, parenchymal or intraventricular.[6] Vascular malformation is the most frequent cause of intracranial bleed in children.[6-7] Other causes are, hematological diseases such as coagulopathies,[8] Vitamin-K deficiency or thrombocytopenia, cerebral tumors and septicemia.

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Arteriovenous malformations (AVMs) account for 14% to 46% of hemorrhagic strokes in children and nearly 50% of intraparenchymal hemorrhage. Hematologic abnormalities are reported to be the major risk factors in 10% to 30% of hemorrhagic strokes.[9]

Various pediatrics studies report different results on intracranial bleed, depending on population studied, differences in sensitivity and timing of the modality used.[1]

Imaging is the most important method for confirming or excluding the diagnosis of ICH. Ultrasound is widely used in neonatal intensive care units for brain imaging and is valuable in term neonates as a screening technique when ICH is suspected. Other modalities are CT-brain or MRI brain.[10,11,12,13]

Vitamin K is a fat soluble vitamin essential for the synthesis of functional prothrombin, factor VII, factor IX and factor X in the liver.[14,15] Because of the short half-life of these factors, and the small amounts of vitamin K that can be stored in the body, inadequate intake of vitamin K can result in deficiency in a short period of time. Infants are at higher risk for hemorrhagic disease ofthe newborn, because of a lack of vitamin K reaching the fetus across the placenta[16], the low level of vitamin K levels in breast milk[17], immature liver and low colonic bacterial synthesis.[18]

The bleeding manifestations associated with vitamin K deficiency can occur in three general time frames. Early onset vitamin K deficiency bleeding that occurs less than 24 h after birth is rare and is almost always associated with maternal medications that interfere with vitamin K metabolism. The various drugs include anticonvulsants (Phenobarbital and Phenytoin), oral anticoagulants, and anti-tuberculous drugs. Postnatal administration of vitamin K has no effect in preventing early-onset disease. Vitamin K supplementation to at risk mothers, administered prenatally may prevent this form of vitamin K deficiency bleeding.[17-19]

The classic onset of vitamin K deficiency bleeding occurs between second and seventh day after birth in breastfed infants. Causes include low vitamin K content in breast milk, which is less than 5 microgram/liter compared to 50-60micrograms/liter in formula milk, poor oral intake and sterile gut. Clinical manifestations include bleeding in to the skin or from mucosal surfaces, circumcision, or venipuncture sites. It can be prevented by vitamin K supplementation at birth.[20-21]

Late-onset vitamin K deficiency bleeding occurs one to two weeks after birth. It can, however, occur as late as 3 months postpartum. In addition to breastfeeding, risk factors includevarious disorders that reduce Vitamin K absorption like diarrhea, hepatitis, biliary atresia, cystic fibrosis (CF), celiac disease, and alpha - 1-antitrypin deficiency or absence of prophylaxis in otherwise healthy infants. Late-onset vitamin K deficiency bleeding tends to be more severe than early-onset or classic disease and has a high frequency of intracranial hemorrhage. Intracranial hemorrhage is observed in more than 50% of infants with late-onset disease.[20, 22, 23]

A recent Cochrane database systemic review concludes that intramuscular Vitamin K has been proven to prevent classical disease and oral Vitamin K has been proven to improve biochemical parameters of Vitamin K deficiency in the first week of life.[24]

In a bleeding infant, a prolonged PT without any finding considering other bleeding disorders is almost diagnostic of VKDB. Rapid correction of PT and/or cessation of bleeding after vitamin K administration confirms the diagnosis.[25]

In infants who receive no vitamin K prophylaxis, late onset VKDB has been reported to be more common in Asian countries and in warmer climates.[26]

MATERIALS AND METHODS

This descriptive cross sectional study was conducted at the Pediatrics Department (General Pediatrics, Pediatrics Intensive care unit and Neonatal Intensive Care Unit) Saidu Teaching Hospital, Saidu Sharif Swat. Total duration was 12 months that was from 1st July 2016 to 30th June 2017.

Sample size: Total of 100 patients were include in this study with confidence level of 95% and margin error 0.07%.

Methodology: The study was first approved from Ethics and Research Committee of the Hospital. All the patient who met the inclusion criteria were asked to be a part of the study, after proper counselling and consent.

Inclusion criteria:

1. Age: 7-180 days
2. Clinical suspicion of intracranial bleed, which may be any one or combination of the following
   a) Altered level of consciousness
   b) Focal neurological signs
   c) Bulging Anterior fontanelle
   d) With or without evidence of mucosal and skin bleeding
3. Prolonged PT and APTT and normalization of PT and APTT after Vitamin-K or FFPs administration.

Exclusion criteria: Patient with obvious predisposing cause of bleeding like hemophilia, thrombocytopenia, functional platelets disorders and history of trauma were excluded from study.

Total of 100 patients fulfilling the inclusion criteria were included in the study. All these patients were subjected to detailed history and clinical examination, laboratory investigations, including complete blood count, coagulation profile(PT, APTT, BT, CT and platelets count) were performed in all these patients.

Neuroimaging in the form of CT, MRI brain or U/S skull were also performed for confirmation of intracranial bleed.

Details regarding pregnancy, delivery, clinical feature and the results of theabove mentioned investigations were recorded on pre designed proforma .

The diagnosis of vitamin K deficiency was established by history and clinical examination supported by prolonged PT, APTT and prothrombin ratio with normal level of platelets count, bleeding time and fibrinogen level along with normalization of PT and APTT 24 hours after the vitamin-K or FFPs administration which were both elevated before Vitamin-K or FFPs administration.

In this study INR was used as a PR ratio which was calculated by using the following formula

PR ratio = PT (patient) / PT (control)

RESULTS

Total of 100 patients who fulfilled the inclusion criteria were enrolled in the study. Out of one hundred enrolled patients 65 were male and thirty five were female with male to female ratio of 1.85:1.

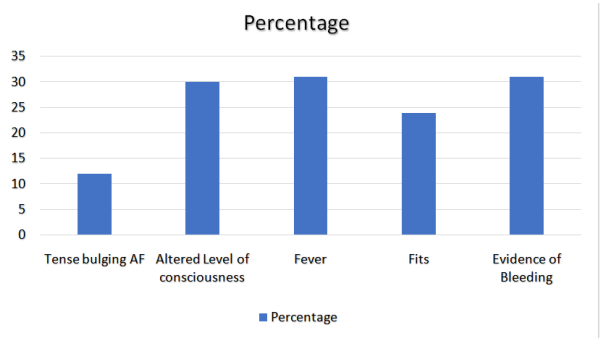
Out of 100 patients with vitamin-K deficiency 31 have been found to have intracranial bleed confirmed on neuroimaging (U/S skull, CT/MRI brain). Out of these 31 patients 20 (20%) patients were male and 11 (11%) were female.

Vitamin-K deficiency usually presents with diverse clinical signs and symptoms, the data has been stratified with clinical history and examination findings which

shows the following results presented in Table 1 and Graph 1.

Table No.1: Stratification of vitamin-k deficiency with history (n=100)

History	Vitamin-K deficiency	Frequency	%age
Term of Gestation	Full term	20	20 %
	Preterm	11	11 %
Mode of delivery	NVD	19	19 %
	C-Section	12	12 %
Vitamin-K prophylaxis at Birth	Yes	0	0 %
	No	31	31 %



Graph No.1: Frequency and percentages of clinical examination/findings in infants with intracranial bleed (n=31).

All patients with intracranial bleed belonged to age group 7- 180 days of life, the mean age of presentation was 45±2.5 days. Data is presented in Table 2.

Table No.2: Stratification of intracranial bleed with age (N=31)

Age	Frequency	Percentage
07- 60 Days	16	51%
61-120 Days	10	32.2%
121-180 Days	5	5%
Total	31	100%

As per diagnostic criteria the diagnosis of Vitamin-K deficiency was confirmed if the patient initially having deranged PT/APTT and rest of coagulation profile was normal and rapid normalization after vitamin K or FFP administration. Data stratification in the form of PT, APTT and PR ratio with pre and post treatment quantification data is presented in Table 3.

Table No.3: Pre and post treatment mean SD of pt/aptt/pr ratio

Pre treatment	Mean SD	Post reatment	Mean SD
PT (seconds)	25.2 ± 2.5	PT (seconds)	12 ± 2.5
APTT (seconds)	87.74 ± 5.44	APTT (seconds)	35.96 ± 4.08
PR ration	2.15 ± 0.16	PR ration	1.08 ± 0.09

DISCUSSION

Vitamin-K deficiency is common in early infancy due to certain risk factors suchas exclusive breast feeding, inadequate synthesis and absorption etc.Intracranial bleed is the frequent complication of vitamin-K deficiency as identified in our study which is 31%. Previous research works which shows different results depending on geographical variation of population studied, difference in the sensitivity, timing of the modality used and the selection of inclusion and exclusion criteria andthe use of prophylactic dose of Vitamin K etc.

In our study all patients diagnosed with Vitamin-K deficiency as per inclusion criteria were screened for complication of intracranial bleed.Amongst them 31% of patients with Vitamin K deficiency suffered from intracranial bleed. Two other studies conducted by Visser DY et al[22](march 2011), and M etal[18] respectively shows 25% and 40% frequency of intracranial bleed associated with vitamin K deficiency which are comparable to our study results.

Rana MT et al[17] and KavchiM et al[16] have shown results of 48% and 61.5% respectively in their studies, while in another research paper by Majeed et al[4]thereported frequency is only 11.4%.

In our study the male to female ratio of total patient was 1.85 to 1and inpatients with intracranial bleed male to female ratio was 1.81:1.KaraciM etal[16]and AdhikaliS et al[23] in their studies have shown comparable results of 1.6:1 and 1.66:1 respectively while Majeed R et al [4] and Rana MT et al[17] have reported higher male to female ratio of 2.18:1 and 2.12:1 respectively.

Common clinical presentation of infants with intracranial bleed identified by our study was the evidence of bleeding, deterioration of conscious status, fever and fits. The relative frequencies of the different clinical features were very much similar to those observed by Visser DY et al[22], Majeed R eta l [4],Misirliogku ED et al[27] and Klironomi I et al [8].

Mean age of presentation was 45 days which is comparable to some national and international studies results.[6, 7, 8] Prematurity and small for gestational age is not a risk factor, it is common in full term as identified in our study. The same has also been observed by Pooni PA et al[24] in their research paper.

CONCLUSION

It is concluded that Intracranial hemorrhage remains a disabling disease mostly due to unidentifiable causes, however in many cases a high index of suspicion of Vitamin K deficiency should be kept in mind which often leads to bleeding as identified in our study.

Recommendation: This study provide a proof that Vitamin K prophylaxis is mandatory in order to reduce the burden of morbidity and mortality in the form of hospitals stay, expense and outcome.

Author's Contribution:

Concept & Design of Study:	Ihsanul Haq
Drafting:	Ashfaq Ahmad, Sardar Khan
Data Analysis:	Ihsanul Haq, Ashfaq Ahmad
Revisiting Critically:	Sardar Khan, Zahir Said
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Comparison of Efficacy of Vaginal VS Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion

Nighat Kafil[1] and Farzana Rizwan Arain[2]

ABSTRACT

Objective: To compare the efficacy of misoprostol vaginally/orallyin management of first trimester missed abortion.

Study Design: Quasi experimental study.

Place and Duration of Study: This study was conducted at the Gynecology Department, Muhammad Medical College Hospital, Mirpurkhas from January 2013 - December 2014.

Materials and Methods: Eligible women satisfying inclusion/exclusion criteria were recruited after written informed consent and given 600 µg of misoprostol vaginally/orally with a maximum of 3 doses. Patients were monitored for 24 hours following complete abortion or surgical evacuation and then discharged. The primary outcome of study was defined as Success (non surgical evacuation of product of conception) or Failure (excessive bleeding with retained product of conception where surgical evacuation was performed). Associated adverse events, patient satisfaction and acceptability to treatment were also recorded and compared. The data was analysed using SPSS version 21 (IBM, Chicago, IL).

Results: Both vaginal and oral routes were highly effective, however greater proportion of patients receiving vaginal Misoprostol had success compared to those receiving oral Misoprostol (88% Vs. 71%; p-value = 0.005). Moreover, greater proportion of patients receiving vaginal Misoprostol had induction – expulsion interval within 12 hours compared to those receiving oral Misoprostol (50% vs. 39.44%; p-value = 0.041). Fewer side-effects were observed among participants receiving Vaginal Misoprostol than Oral Misoprostol. There was no significant difference in patient's satisfaction and acceptability in participants of both groups.

Conclusion: Vaginal misoprostol is more effective than oral misoprostol for first trimester missed abortion.

Keywords: First trimester, Missed abortion, Misoprostol.

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INTRODUCTION

Termination of pregnancy due to different maternal factors or on account of foetal condition is a prevalent obstetrical problem[1,2]. Missed abortion in the first trimester of pregnancy is characterized by development arrest of fetus along with ultrasound findings reporting an empty gestational sac or no cardiac activity of fetus[1,2,3]. Slightly more than 10% of clinically recognized pregnancies have reported termination of pregnancy[3]. This not only imposed significant healthcare and financial burden on cost of care but non continuing pregnancy also psychologically affects mothers. Studies have reported increased diagnosis of missed abortion on routine ultrasound screening[3,4,5].

A significant proportion of missed abortion occurs simultaneously, however some pregnancies simply stop growing without any obvious symptoms with end fate as deferment in expulsion of conceptus[6,7].

Safe induction of abortion is of immense clinical importance requiring effective and high quality medical care. Different surgical/medical methods are available for termination of pregnancy however medical methods are preferred demonstrated by lower rates of maternal morbidity/mortality[8,9]. Surgical evacuation, although quick and effective procedure when performed by a well-trained physician, carries a risk of injury, bleeding and infection, and possible complications from anesthesia[10,11]. Misoprostol is a Prostaglandin analogue widely used for termination of pregnancy, considering it efficaciousness, low cost and long shelf life (2 years) at room temperature[8,12,13]. Both oral and vaginal routes are available but oralroute is associated

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with disadvantages like decreased bioavailability, increased gastrointestinal side-effects[9,14,15].

Present study was conducted to compare the efficacy and safety of Misoprostol(i.e. 600 µg) administered intravaginally/ orally in missed abortion up to 12 weeks of gestation among patients visiting Gynecology Department of Muhammad Medical College Hospital (MMCH). Only a few studies have been conducted to compare the efficacy and safety of oral/vaginal Misoprostol in missed abortion at equal dosage (i.e. 600 µg) globally, and to the best of our knowledge first in Pakistan.

MATERIALS AND METHODS

The Quasi experimental study was conducted at Gynecology Department of Muhammad Medical College Hospital, Mirpurkhas over a period of two years from January 2013 - December 2014. Muhammad Medical College Hospital was established in 1999, located 6 km outside Mirpurkhas, Sindh. The hospital has a well-established Gynecological department with women from both rural and urban areas visiting for routine ante natal checkups, deliveries and gynecological problems.

Women with confirmed diagnosis of missed abortion on ultrasound, age duration 18-45 years, gestational age ≤ 12 weeks, closed cervix on bimanual pelvic examination and hemoglobin ≥ 9 gm/dl, place of residence within 20 km from hospital, willingness to abstain from intercourse for first two weeks after intervention given and comply with the follow-up schedule were invited to participate in this study. Women with history of inflammatory bowel disease, asthma or liver diseases, hemodynamically unstable, severe infection (assessed by presence of fever/foul smelly discharge/uterine tenderness), deranged coagulation profile (Prothrombin index ≤ 85%), ectopic pregnancy and contraindicated to prostaglandin use were excluded.

After satisfying the inclusion/exclusion criteria, baseline investigations and ultrasonographic confirmation of missed abortion, participants were recruited in this study. Participants were non-randomly allocated to treatment Group A (Vaginal Misoprostol) and treatment Group B (Oral Misoprostol). Patients in the treatment Group A received 600µg of misoprostol having soaked in normal saline solution intra-vaginally into posterior fornix, repeated six hourly up to a maximum of three doses. Prior to insertion, vaginal cleansing was performed with 10% povidone iodine, following insertion women remained fully recumbent for at least 3 hours. Patients in treatment Group B were admitted in hospital and given 600 µg of misoprostol orally with water at six hour interval, with a maximum of 3 dosesin the presence of clinician.

Data on characteristics of participants i.e. age, place of residence, parity, gestational age in weeks, previous spontaneous abortion and previous caesarian section were collected. The primary outcome of the study was defined as Success (non surgical evacuation of product of conception confirmed on ultrasound) or Failure (incomplete expulsion of products of conception or excessive bleeding with retained product of conception where surgical evacuation was performed). The other clinical outcomes assessed were number of doses, induction – expulsion intervals in hours and cervical permeability (good cervical permeability was defined as the ability to pass #8 Hegar dilator) in both treatment groups. Patients in both groups were monitored for 24 hours following complete abortion or surgical evacuation and then discharged with analgesics and prophylactic antibiotics for 5 days.

The first follow-up visit was one week after discharge. Any adverse events i.e. nausea/ vomiting, severe crampy pain, dizziness, headache, diarrhea, fever with chills, excessive bleeding, discharge per vaginum, cervical tear and uterine rupture were recorded and managed accordingly. Moreover data on patient's satisfaction, acceptability and preference to recommend to others were also collected at follow-up visit.

For this clinical study ethical approval was obtained by the institutional ethical review committee of Muhammad Medical College Hospital. Prior to enrollment in the study, written informed consent was obtained from all participants having explained the process involved, intervention given (oral or vaginal Misoprostol) and benefits/ risks of recruitment in this research. Anonymity and confidentiality of participant's data was maintained throughout the research with only investigators having access to the data.

Data was analyzed using SPSS version 21 (IBM, Chicago, IL). The qualitative variables were presented as frequency/percentage. The baseline characteristics of the study participants receiving vaginal/oral Misoprostol were compared using chi square statistics. Importantly, the clinical outcomes (success proportion, number of doses, induction – expulsion intervals in hours and cervical permeability), adverse events, patient's satisfaction and acceptability observed among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B) were also compared using chi-square statistics. For the purpose of inferential statistics p-value ≤ 0.05 was considered significant.

RESULTS

Table 1 compared the baseline characteristics of the study participants receiving vaginal or oral Misoprostol. There was no significant difference in baseline characteristics among patients non-randomly allocated to receive Group A/Group B.

Table 2 gives details of comparison of the clinical outcomes amongst Group A and Group B. Significant difference was only found in success proportion and

induction – expulsion intervals among patients non-randomly allocated inboth groups. Greater proportion of patients receiving vaginal Misoprostol had success compared to those receiving oral Misoprostol (88% Vs. 71%; p-value = 0.005).

Table No.1: Comparison of baseline characteristics of the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Baseline Characteristics	Group A (n = 100) n (%)	Group B (n = 100) n (%)	P-value
Age categories (years)			
18-20 years	15 (15)	16 (16)	0.906
21-25 years	43 (43)	47 (47)	
26-30 years	31 (31)	28 (28)	
> 31 years	11 (11)	9 (9)	
Residence			
Rural	33(33)	37 (37)	0.654
Urban	67 (67)	63 (63)	
Parity			
Primigravida	70 (70)	74 (74)	0.639
Multigravida	30 (30)	26 (26)	
Gestational age (weeks)			
< 6 weeks	8 (8)	5 (5)	0.565
6-12 weeks	92 (92)	95 (95)	
Previous spontaneous abortion			
Yes	39 (39)	41 (41)	0.887
No	61 (61)	59 (59)	
Previous caesarian section			
Yes	18 (18)	22 (22)	0.597
No	82 (82)	78 (78)	

Table No.2: Comparison of clinical outcome among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Clinical Outcomes	Group A (n = 100) n (%)	Group B (n = 100) n (%)	P-value
Success			
Yes	88 (88)	71 (71)	0.005
No	12 (12)	29 (29)	
Number of Doses			
One	10 (11.36)	2 (2.82)	0.064
Two	38 (43.18)	27 (38.03)	
Three	40 (45.45)	42 (59.15)	
Induction-Expulsion Interval (hours)			
≤ 6 hours	10 (11.36)	0 (0)	0.041
7-12 hours	34 (38.64)	28 (39.44)	
13-18 hours	41 (46.59)	36 (50.70)	
> 18 hours	3 (3.4)	3 (4.23)	
Cervical Permeability			
Permeable	12 (12)	25 (86.20)	0.439
Non-Permeable	0 (0)	4 (13.80)	

Moreover, greater proportion of patients receiving vaginal Misoprostol had induction – expulsion interval within 12 hours compared to those receiving oral Misoprostol (50% vs. 39.44%; p-value = 0.041). Importantly, none of the patients receiving oral Misoprostol had induction – expulsion interval less than or equal to 6 hours. Table 3 gives details of comparison of side effects observed among the study participants of Group A and Group B. Comparatively, the incidence of side-effects were more in patients receiving the oral Misoprostol than vaginal Misoprostol.

Table No.3: Comparison of side effects observed among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Side-Effects	Group A (n = 100) n (%)	Group B (n = 100) n (%)
Nausea/ Vomiting (Requiring anti-emetics)	61 (61)	71 (71)
Dizziness	22 (22)	27 (27)
Headache (Requiring analgesics)	19 (19)	22 (22)
Severe crampy pain (Requiring analgesics/ anti-spasmodic)	33 (33)	51 (51)
Diarrhea	14 (14)	17 (17)
Fever with chills (Requiring anti-pyretic)	5 (5)	9 (9)
Excessive bleeding	4 (4)	7 (7)
Discharge per vaginum	3 (3)	5 (5)
Cervical tear	0 (0)	0 (0)
Uterine rupture	0 (0)	0 (0)
Death	0 (0)	0 (0)

Table No.4: Comparison of patient satisfaction and acceptability to treatment observed among the study participants receiving Vaginal Misoprostol (Group A) and Oral Misoprostol (Group B)

Patient satisfaction and Acceptability	Group A (n = 100) n (%)	Group B (n = 100) n (%)	P-value
Patient satisfaction			
Satisfied	74 (74)	72 (72)	0.923
Unsatisfied	22 (22)	23 (23)	
Neither satisfied nor unsatisfied	4 (4)	5 (5)	
Acceptability			
Would choose again	77 (77)	74 (74)	0.740
Would not choose again	23 (23)	26 (26)	
Recommendations			
Would recommend to others	76 (76)	73 (73)	0.740
Would not recommend to others	24 (24)	27 (27)	

Table 4 gives details of comparison of patient's satisfaction and acceptability observed among the study participants in Group A and Group B. There was no significant difference in all criteria between the 2 groups, however, patients receiving Vaginal Misoprostol showed comparatively a slightly greater extent of patient's satisfaction, acceptability and preference to recommend to others compared to Oral

Misoprostol; however the difference was not statistically significant.

DISCUSSION

The present Quasi experimental study highlighted that vaginal misoprostol is more effective than oral misoprostol as demonstrated with increase success rate, fewer dosages with lesser side effects. Moreover, patients receiving vaginal Misoprostol demonstrated increased patient's satisfaction, acceptability, and recommendation to others.

In this study, the patients non-randomly allocated to Group A (Vaginal Misoprostol) and Group B (Oral Misoprostol) showed no significant difference in baseline characteristics (i.e. age, residence, parity, gestational age, previous spontaneous abortion and caesarian section) was observed thus implying that the two groups were comparable. Importantly, the success rate with vaginal Misoprostol was significantly higher(88%) compared to oral Misoprostol (71%).Evidence from the literature also demonstrated the greater efficacy of vaginal Misoprostol compared to the administration by oral route. A prospective, non-blinded, randomized clinical trial[16] that recruited twenty participants to compare efficacy of misoprostol given as 400 µg orally (group 1) or 800 µg vaginally (group 2) reported significantly higher success rate with vaginal misoprostol (88%) compared to administration through oral route (25%). Another, prospective randomized controlled trial was conducted to compare the efficacy and side-effects of vaginal versus oral misoprostol given in equal dose of 800 µg found no significant difference in vaginal and oral misoprostol administration (61.1% Vs. 64.4%); however significantly decreased incidence of diarrhea was identified (13.6% Vs. 65.3%, $P < 0.01$) with the use of vaginal misoprostol[17]. This is consistent with the findings of the recent study where fewer incidences of side-effects were being observed with vaginal Misoprostol compared to oral Misoprostol. Another clinical study[18]comparing misoprostol administration (oral and vaginalin equal dose of 800 µg) for treatment of missed abortion reported no significant difference (89% Vs. 92%). A randomized prospective trial[19], comparing the efficacy of misoprostol given vaginally or orally in 400 µg to a maximum of three doses six hours apart reported both routes were highly effective (vaginal=92%, oral= 74%, p=0.032).

Though, no significant difference was observed in patient's satisfaction and acceptability with the use of vaginal or oral Misoprostol; slightly higher proportion of patients were satisfied and showed greater acceptability with the vaginal use. The results of a recently published systemic review and meta-analysis that included 18 studies with 1802 participants reported that in terms of tolerability, vaginal misoprostol of 400ug was reported with fewer side effects and oral misoprostol of 600 ug was reported with more side effects[20].

CONCLUSION

Our study concluded that first trimester missed abortion can be medically managed with the use of oral or vaginal Misoprostol. They are suitable practical alternatives to conventional surgical evacuation with higher success rates. However, vaginal administration of Misoprostol should be preferred due to increased success rate, decreased side effects, increased tolerability and patients acceptance compared to oral administration.

Recommendations: Though Misoprostol both orally and vaginallyis very efficacious, commonly used in early missed abortion and termination of pregnancy, but its safety is a concern for pregnant women living in remote areas or villages receiving it in outpatient settings. Clinicians should be very cautious in prescribing it, recommended only if the patient is living nearby the hospital facility. In cases where Misoprostol is indicated for patients living in remote areas, they should be admitted first and given oral/vaginal Misoprostol as there are adverse events i.e. bleeding after its use. Considering the high prevalence of anaemia during pregnancy, the use of Misoprostol is not safe for women with health facilities inaccessible. Moreover, it should only be offered by trained clinicians in established clinical settings to provide surgical treatment in case of failed abortion or excessive bleeding.

Author's Contribution:

Concept & Design of Study:	Nighat Kafil
Drafting:	Nighat Kafil, Farzana Rizwan Arain
Data Analysis:	Farzana Rizwan Arain
Revisiting Critically:	Nighat Kafil, Farzana Rizwan Arain
Final Approval of version:	Nighat Kafil

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Original Article

Frequency of Hypothyroidism in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To determine the frequency of hypothyroidism in patients with type 2 Diabetes Mellitus.
Study Design: Descriptive / cross sectional study
Place and Duration of Study: This study was conducted at the Department of Medicine and Endocrinology, MTI HMC/KGMC Peshawar from March 2016 to September 2016
Materials and Methods: In this descriptive cross sectional study sample size was calculated according to WHO sampling technique a total of 151 using prevalence of hypothyroidism among diabetes patients are about 17%, 95% confidence level and 6% margin of error with WHO formula. Consecutive non probability sampling technique was used to collect samples for our study.
Result: In our study mean age of patients with diabetes mellitus type 2 was 55 yr with SD ± 1.26. Forty two percent patients were male and 58% patients were female. Eighty three percent patients had euthyroidism, 5% patients had hypothyroidism overt, 12 % patients had subclinical hypothyroidism.
Conclusion: The study showed that the frequency of both subclinical and clinical hypothyroidism is significant in patients with type 2 diabetes mellitus and is one of the complications or co-finding in all such patients.
Key Words: Hypothyroidism overt, subclinical hypothyroidism, type 2 Diabetes Mellitus

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INTRODUCTION

Diabetes mellitus type 2 is metabolic disorder which is manifested by hyperglycemia, resistance go Insulin and relative deficiency of insulin. Diabetes Mellitus is the commonest endocrine disorder, leading cause of death worldwide[1]. Diabetes type 2 in enormously increasing in age group 30 to 39 years; and at the same time in children and adolescent age as well [2]. The prevalence of diabetes mellitus in adult age (20 to 79 years) in 2010 was 6.4% affecting 285 million of the world population in 2010. The figure is estimated to be as high as 7.7% and will affect a world population of 439 million. For diabetics the situation is getting extremely alarming from 2010 to 1030 for developing countries where the increase is estimated to be 69% and for developed countries it will rise by 20 % by year 2030[3,4]. The commonest manifestations of Diabetes Mellitus are increase water intake, frequent and large amount of urination and weight loss.

Diabetics may also complain of increased hunger, easy fatigability and poor healing of the wounds [5]. Various symptoms of the diabetics manifest slowly and with the passage of time.

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Diabetes Mellitus type 2 patients can present with long term complications commonly and at times with short term complications. The incidence and prevalence has markedly increased from 1960 to 2013 and much higher is thought to be in coming decade[6]. Type 2 DM starts most commonly in the middle age and is strongly related to obesity. The long term complications include o prolonged hyperglycemia includes heart disease, Strokes, diabetic retinopathy which can result in blindness, nephropathy and peripheral angiopathy, endocrinnopathy and neruropathy. Least commonly acute complications like hyperosmoloar coma and ketoacidosis can also result [7-10].

Thyroid hormones play a vital role in regulation of the metabolic events including protein, carbohydrate and lipid metabolism. Hypothyroidism, like obesity is one of the pathophysiological conditions which is associated with lipid metabolism disorder and can lead to dyslipidemia. Till date pathophysiology of the thyroid functions is not clear but thyroid antibodies are considered to be causing agents[11]. Thyroid problems especially hypothyroidism is quite prevalent in diabetes mellitus and has been observed from as low as 2.2% to as high as 31% and 46% respectively. If diabetes is poorly controlled it can alter plasma triiodothyronine (T3) and in part thyroxine (T4) levels. Diabetes and hypothyroidism meet each other through various common clinical characteristics[12,13]. Both are independently associated with overweight/obesity, dyslipidemia, hypertension and depression. A combination of both diabetes and hypothyroidism puts the person at higher risk of insulin resistance and cardiovascular disease. Uncontrolled hypothyroidism

may mask the clinical features of diabetes, which becomes evident only after a euthyroid state is achieved. Subclinical hypothyroidism has been the focus of interest in the past few years. The ability to diagnose and treat unsuspected hypothyroidism in these populations may greatly enhance the quality of life. Hence, the detection of such cases is of great importance where hypothyroidism contributes to morbidity and where it is the cause for poor control of the associated conditions[14].

There is limited data both about diabetes and endocrine disorders but more so about the relationship between diabetes and hypothyroidism. Hence, we tried to explore the prevalence of hypothyroid and co-relation of the both with this study and evaluated the frequency with which hypothyroidism both overt and subclinical is associated with Type 2 Diabetes mellitus in the local adult population as it is a growing problem not only in our country but globally as well and it has been observed that patients with thyroid disorders are diagnosed quite later in their life. The prevalence of hypothyroidism has not been studied in diabetic patients in our country. This study will demonstrate patients with hypothyroidism at an early age so that timely treatment may reduce morbidity and mortality associated with the occurrence of this condition.

MATERIALS AND METHODS

This study was conducted at the Department of Medicine and Endocrinology MTI HMC Peshawar. The study was cross sectional descriptive in nature and was conducted over a time period of sex months from 5/3/2016 to 5/9/2016. All patients with diabetes mellitus type 2 were included I n the study. A Sample size was 151 using prevalence of hypothyroidism among diabetes patients is about 17%, 95% confidence level and 6% margin of error with WHO formula using consecutive non-probability sampling technique. All patients with T2DM aged 35 to 60 years and of either gender, irrespective glucose control and treatment were included in the study. Patients with Type 1 Diabetes Mellitus, with Gestational diabetes, steroid induced diabetes and patients who were on medications and/or have conditions that affect thyroid function were excluded from the study.

The study was carried out with criteria fulfilling the ethical aspects of the study. All patients seen in OPD as well admitted in hospital and meeting criteria were included in the study. The consent, purpose and aim of the study was disclosed to the patients and a prefilled documented consent was obtained. Patient's demographic data was recorded on the proforma. Detailed history was taken and relevant clinical examination was done. Strict exclusion criteria were followed in order to control confounders and bias in the study results. All patients in the study was thyroids functions tests done for thyroid status and also target organ evaluation for Diabetes Mellitus, thyroid status and demography was recorded on the approved proforma.

Data was entered and assessed by SSPS version 22. Mean + SD was used to assess numerical variables like duration of type 2 DM and age. Frequencies & Percentages were calculated for categorical data including sex, thyroid status (Euthyroidism, hypothyroidism overt and subclinical) and diabetes status. Hypothyroidism was stratified among age and duration of type 2 DM and sex to look for the effect modification. Chi-square test was applied after this wholw process of stratification with p-value ≤ 0.05. Tables were used to present the results.

RESULTS

We analyzed our data on 151 patients fulfilling the inclusion criteria. Age distribution among 151 patients was analyzed as 12(8%) cases were found below45 years, 33(22%) in the age range of 46-55 years, 106(70%) subjects documented in age range 55-60 years. We found a mean age of 55 years with SD ± 1.26. We found that out of 151 patients with type 2 DM 63(42%) patients were male and 88(58%) patients were female.

In our study we documented that the number of type 2 DM was different in different age group depending upon duration of the diabetes since onset. We found that 35(23%) patients were having diagnosed diabetes from 5-10 years, 78(52%) were having type 2 DM from 11-15 years and 38 (25%) 15-20 years. The mean period was 12 years with SD ± 2.77, as in table 1

Table No. 1: Duration of diabetes (n=151)

Duration	Frequency	Percentage
5-10 years	35	23%
11-15 years	78	52%
16-20 years	38	25%
Total	151	100%

Table No.2: Thyroid status in type 2 Diabetes Mellitus (n=151)

Thyroid Status	Frequency	Percentage
Euthyroidism	125	83%
hypothyroidism overt	8	5%
Subclinical hypothyroidism	18	12%
Total	151	100%

Mean duration of diabetes was 12 years with SD ± 2.77

In our study 109(72%) patients had already confirmed diabetes while 42(28%) patients were newly diagnosed type 2 diabetics. Thyroid status among 151 patients was analyzed as 125(83%) patients had euthyroidism, 8(5%) patients had hypothyroidism overt, 18(12%) patients had subclinical hypothyroidism as given in table 2.

Stratification of thyroid status (Euthyroidism, hypothyroidism overt and subclinical) with age,

duration of type 2 DM and sex is shown in table no 3,4 and 5.

Table No. 3: Stratification of thyroid dysfunction w.r.t age distribution (n=151)

Thyroid Status		<45 years	46-55 years	56-60 years	Total	P Value
Euthyroidism	Yes	10	28	87	125	0.9330
	No	2	5	19	26	
Total		12	33	106	151	
hypothyroidism overt	Yes	1	2	5	8	0.8479
	No	11	31	101	143	
Total		12	33	106	151	
Subclinical hypothyroidism	Yes	1	4	13	18	0.9229
	No	11	29	93	133	
Total		12	33	106	151	

Table No. 4: Stratification of thyroid dysfunction w.r.t gender stribution (n=151)

Thyroid status		Male	Female	Total	P Value
Euthyroidism	Yes	53	72	125	0.7109
	No	10	16	26	
Total		63	88	151	
hypothyroidism overt	Yes	3	5	8	0.0619
	No	60	83	143	
Toatl		63	88	151	
Subclinical hypothyroidism	Yes	8	10	18	0.8028
	No	55	78	133	
Total		63	88	151	

Table No. 5: stratification of thyroid dysfunction w.r.t duration distribution (n=151)

Thyroid Status		5-10 years	11-15 years	16-20 years	Total	P Value
Euthy-roidism	Yes	29	65	31	125	0.9727
	No	6	13	7	26	
Total		35	78	38	151	
hypothy roidism overt	Yes	2	4	2	8	0.9917
	No	33	74	36	143	
Toatl		35	78	38	151	
Subclini cal hypothy roidism	Yes	4	9	5	18	0.9635
	No	31	69	33	133	
Total		35	78	38	151	

DISCUSSION

Diabetes is becoming the most alarming medical disorder and is highly prevalent in all over the world. It is sparing only that part of the world population who are avoiding bad physical and food habits; and adopting healthy life style and food habits [15]. Our study shows that among 151 patients 8% cases were having age <45 yrs, 22% cases were in 46-55 yrs, 70% cases ranged 55-60 yrs. In our study we found that the mean age was 55 yrs with Standard Deviation (SD) ± 1.26. In our study were male and 58% cases were female. About the duration of the type 2 DM, twenty three percent had diabetes from 5-10 yrs, 52% from 11-15 years, 25% patients had diabetes from 15-20 years. We found that mean period or duration of diabetes was 12 yrs with SD ± 2.77.

In this study 72% patients had diagnosed diabetes while 28% patients had newly diagnosed diabetes. Eighty three percent of the patients had euthyroidism, 5% patients had hypothyroidism overt, 12% patients had subclinical hypothyroidism. Similar results were observed by Song F [16]. He found that the total prevalence of hypothyroidism among type 2 diabetes mellitus inpatients was 6.8 % while 77.0 % of the cases had subclinical hypothyroidism. Hypothyroidism had a direct relation with the increasing age and was also found to be occurring at higher rate in female compared to male patients i.e. 10.8 % and 3.4 % in female and male. The odds ratio and 95 % confidence interval was noted for Older age, female gender and positive thyroid peroxiadase antibody. For the advanced or older age (odds ratio, 1.74; 95 % confidence interval, 1. 05 to 2.89), for the female (odds ratio, 2.02; 95 % confidence interval, 1.05 to 3.87), and in case of positive thyroid peroxidase antibody (odds ratio, 4.99; 95 % confidence interval, 2.83 to 8.79) were attributed to the higher odds of hypothyroidism among type 2 DM indoor patients. The type 2 diabetes mellitus hospitalized with hypothyroidism had higher prevalence of CVAs (cerebrovascular accidents) diseases than those with euthyroidism after adjustment for age and gender. The prevalence of hypothyroidism among type 2 diabetes mellitus inpatients was 6.8 %, and most patients had subclinical hypothyroidism. Almost the same results were documented b a study carried out by Shaikh [17] in which a total of 120 cases were studied. In this study there were two groups a diabetic one comprising of 60 cases and a similar number of normal cases in the second group. In the diabetic group 7(11.66 %) were subclinical cases with hypothyroidism and 21(35%) cases were hypothyroid. They found that in the subclinical group male predominate female making 3 (5%) and 4(6.66%) respectively while female outnumbered the male making in the clinical hypothyroid group constituting 14(23.33%) and 7(11.66%) respectively. Jali MV et al conducted study of the same nature and he found that prevalence of thyroid dysfunction in type 2 DM was 16.2%. In his study prevalence in female was 25% and 10% in male with p value of <0.001. The prevalence in age group >55 years was high constituting 19% as compared to other groups with p value=0.036 [18].

Type 2 diabetics give the features of a hyperthyroidism like marked weight loss and increase hunger in either condition. The diabetic nephropathy has a close resemblance with the hypothyroidism because of pallor, weight gain, edema and easy fatigability in either condition [19]. Another international study documented that thyroid functions are affected in type 2 DM and the frequency in this study was 6.6 %. [20]. The abnormal level of TSH has been observed in a study conducted in

type 2 DM patients and the frequency was 31% [21]. There are studies where the frequency of hypothyroidism was as high as 35 % and clinical evidence found in 11.66% cases, which is quite high as compared to our data [22].

CONCLUSION

The study showed that the frequency of both subclinical and clinical hypothyroidism is quite significant in patients with type 2 diabetes mellitus and is one of the complications or co-finding in all such patients.

Author's Contribution:

Concept & Design of Study:	Muhammad Bilal Khattak
Drafting:	Shabnam Gul
Data Analysis:	Muhammad Aqeel Khan
Revisiting Critically:	Shabnam Gul, Muhammad Aqeel Khan
Final Approval of version:	Muhammad Bilal Khattak

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

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Original Article

Management of Complicated Intra Abdominal Sepsis

Dileep Kumar, Mariyah Anwer, Shamim Qureshi and Muhammad Naeem

ABSTRACT

Objective: To describe the clinical, microbiological, and treatment profile of complicated intra abdominal infections in developing countries

Study Design: Retrospective case series study.

Place and Duration of Study: This study was conducted at the Surgical Ward 2, JPMC, Karachi from January 2013 to January 2016.

Material and Method: A total of 190 patients admitted via emergency department with the diagnosis of secondary peritonitis were included. Data was collected from previous records. Peritonitis was diagnosed on the basis of history, clinical examination, radiological assessment and intra-operatively findings.

Results: Amongst 190 cases, Tuberculosis and typhoid were the most common pathologies (n=57:30% and n=29:15%) in small intestine followed by perforated appendix (n=29:15.3%). The small bowel was the most common site of perforation (45%) followed by the appendix (15%), duodenal perforation (22.1%), and stomach perforation (10%), peritonitis due to advance malignancy (6.8%) and diverticulitis (0.52%) respectively. Pus C/S yielded E.coli in 100% of specimen followed by Enterobacter (85%) klebsilla (70%), pseudomonas (20%) and Acetobacter (8%). These organisms were 100 % sensitive to Amikacin, 95% to meroneum and imipenem, 97% to vancomycin, 75% to cefaprazone-sulbactum and Augmentin 20%. The overall mortality rate was 36.3%,(n=69), the morbidity rate was 31.05% (n=59) and 32.6 %(n=62) of patients were discharged uneventfully.

Conclusion: The current management modality for complicated intra-abdominal infections in developing countries is a surgical challenge with a high morbidity and mortality. Early recognition, prompt source control and effective use of septic care bundle are important tools of management

Key Words: Complicated intra-abdominal infections, septic care bundle, abdominal sepsis

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INTRODUCTION

Despite our better understanding of pathophysiology and advances in surgery and antimicrobial therapy, Complicated Intraabdominal infection remains a potentially fatal affliction. It requires timely surgical intervention with appropriate antimicrobial therapy[1,2.]

CIAI accounts for 20% of overall intensive care unit admission. Thus CIAI constitute the second common cause for infectious morbidity and mortality after pneumonia[3]. There is an established role of aggressive fluid therapy for patients with septic shock or organ failure. The Surviving Sepsis Campaign guidelines for managing septic shock are well practice all over the world. Key recommendations include early use of broad-spectrum antibiotics, early goal-directed resuscitation. And surgery during first 6 hours after recognition ,involvement of critical care intensivist and surgical specialist[4,5].

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Prognosis depends on early recognition, timely targeted correction of root cause, maintained ongoing organ support.[4]

The purpose of the study is to describe the clinical, microbiological, and treatment profiles of complicated intraabdominal infections (IAIs) in a surgical unit in developing country. This aim of this study is to describe the profiling of the cohort presenting with complicated intraabdominal sepsis that have undergone emergency surgical laparotomy and to determine whether based on preoperative profile does these patient have different outcomes in terms of morbidity and mortality. PICO has used to clarify the research question. Primary objectives are to know the most common etiology of intraabdominal sepsis in the developing country and its association with post-operative outcomes. Secondary objective is to evaluate the commonly involved pathogens and their drug sensitivity traits in peritoneal sepsis. To know the level of operative and critical care provide in this cohort.

To have this in mind as a goal, it would provide us better insight of optimal management of complicated intra-abdominal infection in a developing country and help the treating clinician to take appropriate step in order to improve outcome management**.**

MATERIALS AND METHODS

This study was done at the surgical department Ward 2 of Jinnah postgraduate medical Centre Karachi. It is a retrospective study conducted from January 2013 to January 2016.

Patients more than 14 year of age with a primary diagnosis of secondary peritonitis, admitted via emergency were included. Data was collected from previous records. Peritonitis was diagnosed on the basis of history, clinical examination and radiological assessment.

Patients were resuscitated according to Surviving Sepsis Campaign guidelines[5]. After resuscitation, passing N/G and Foley Catheter, broad spectrum antibiotics were given and all patients underwent emergency surgical intervention within 3-6 hours of admission. As per protocol, intra-abdominal samples were taken for culture and sensitivity in all cases.

Post-operatively, adequate organ support was maintained; pre-operative antibiotics were continued and changed according to culture and sensitivity reports. Patients under 14 years of age and patients with the diagnosis of acute pancreatitis, acute cholecystitis and primary peritonitis were excluded from the study. Per-operative findings were noted. Statistical analysis has been done by using Microsoft Excel worksheets for the construction of graph, data bar charts, pie chart and percentages based on frequency of data and data were presented in mean, range and frequencies..

RESULTS

In this series, 190 patients with a mean age of 60 years (14-82 years) were included. Amongst them, 64.7% were male & 35.3% were females (Table 1). Most of the cases presented with distal small bowel perforations (n=86; 45% tuberculosis n=57/190,30 % & typhoid=29/190, 15%). Amongst other cases were perforated appendix (29/190,15,3%), duodenal perforation (42/190,22.1%), peritonitis due to advance malignancy (13/190,6.8%), stomach perforation (19/190,10%), and only one case(0.5%) of diverticulitis was found. During surgical intervention, intraperitoneal specimens were collected from 92.4% of the cohort and from these samples, a variety of microorganisms were collectively identified. Most of them were E.coli, Enterobacter, Klebsilla, Pseudomonas, Actinobacter, MRSA and Candida (100%, 85%, 70%, 20%, 8%, 5% and 3% respectively). (Fig-1)

Drug sensitivities were noted and Amikacin was found 100% sensitive to all organisms followed by meroneum & imipenem (95%), vancomycin (97%), cefaprazone-sulbactum: (75%) and Ampicillin/sulbactam (20%) (Fig-2) Ceftriaxone and ciprofloxacin were found to be resistant in 92%.

With regards to the severity of CIAI, 59.9% of the patients were in severe sepsis (n=62/190, 32.6%) and septic shock (n=52/190, 27.3%) at the time of their presentation. Stoma diversions were suited in 40% of cases (n=76/190) followed by primary repair or anastomosis in 85/190,61% and appendectomy in 29/190, 15.3% of patients. However, 33/190,17.3% of the cases underwent relook laparotomy due to persistent sepsis (14 cases), anastomosis leak (6 cases), imminent perforation and ileal perforation (10 cases) and appendicular stump leak in 3 cases.

The overall mortality rate was 36.3 %(n= 69/190) and morbidity rate was 31.05% (n=59/190). Rate of wound infection was very high 159/190 (83.7%) while 38/190, 16.2% patients developed respiratory complications and residual collections were developed in 21,11.1% of patients. We noticed that most common contributing factor in high mortality were old age, late presentation, high degree of sepsis and persistent organ failure. However, 62/190,32.6 % were discharged uneventfully. Mean length of stay in hospital was 11 days (14-40 days).

Table No.1: Summary of results:

Age	Mean age = 60 years (range=14-82)
Gender	Male 123/190(64.7%) Female 67/190 (35.3%)
1. Small bowel perforation i) Tuberculosis ii) Typhoid	86 (45.2%) 57 (66.2%) 29 (33.7%)
2. Perforated appendix	29 (15.3%)
3. Duodenal perforation	42 (22.1%)
4. Stomach perforation	19(10%)
5. Peritonitis due to advance malignancy	13 (6.8%)
6. Diverticulitis	1 (0.52%)
Type of procedure(n=190)	
- Stoma	76 ,41.6%
- Primary repair	
• Duodenal perforation	42,22.1%
• Stomach perforation	19,10%
• Small bowel perforation	24, 12.6%
- Appendectomy	29,15.3%
Morbidity	
1- Relook laparotomy	59/190,31.05%
• Persistent sepsis	33,17.3%
• Anastomotic leak	14
• Imminent/ileal perforation	6
• Appendix stump leak	10
2- Postoperative complication	3
• Wound infection	159,83.7%
• Residual collection	21,11.1%
• Respiratory complication/Pulmonary embolism.	38,16.2%
Mortality	69/190,36.3%
Discharge	62/190,32.6%

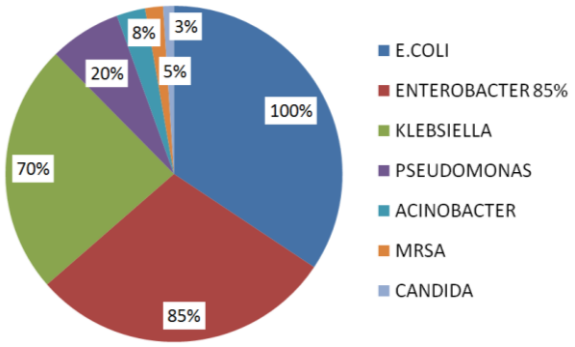

Figure No.1: Microbiology

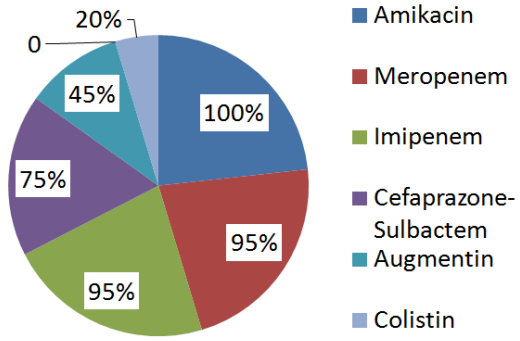

Figure No.2: Antibiotics Sensitivity

DISCUSSION

This retrospective study, performed over a period of 3 years, investigated the spectrum of findings in a group of patients with community-acquired CIAIs. We assume that this descriptive study reflects the 'real'-picture of CIAI in tertiary care hospitals in developing countries. The principal results are a high mortality rate despite adequate provision of the septic care bundle. Jhabhota at el reported that from a larger group of 504 patients, the mean age for patients having CIAI was of 36.8 years of age, while data from Sharma at el reflected an age group of 20-41 years. However, the mean age in our series was higher than the reported data (60 years) with majority of patients being male (68 45%), which is consistent with prior studies.[6,7]

Our study showed that tuberculosis and typhoid is the most common cause of secondary peritonitis in Pakistan and this finding contradicts other studies from the subcontinent where acid peptic disease and gastroduodenal perforation are the most common etiology. In 2013, Bali et al and Afridi at el in 2008, reported that perforated duodenal ulcer due to acid peptic disease was the most common cause of perforation peritonitis in 37.5% and 43.6% of the cases. However, literature published before 2000 from same demographic area is consistent with our findings[8]. Results of our study show the increasing prevalence of tuberculous and typhoid infections in the Pakistan in last one decade as compared to other developing countries in the subcontinent. At the other end of the spectrum, literature review from westernized countries documents that the causes of such perforations include : Diverticular disease, colonic malignancy, Crohn's disease, bowel ischemia, penetrating trauma and very rarely, intestinal tuberculosis[9] Noon et al reported in his series of 430 patients with gastrointestinal perforations that 210 cases were due to penetrating trauma followed by 92 cases of appendicitis.[10] Another retrospective review by Chaikof at el of 76 patients, noticed that most nontraumatic perforation in westernized world were due to malignancy and Crohns and rarely due to infectious cause.[11]

Perforations of the distal gastrointestinal tract were more common in our study which sharply contrast the other studies from developing countries from Asia(7, 8) but these results were consistent with developed countries which revealed that distal gastrointestinal tract perforations were more common[12,13]. In 2012, a large multicenter European study of 2152 patients who developed CIAI reported, 45 % cases were present with distal gastrointestinal tract perforations.[14]

In our study, E-coli was found to be more prevalent (100%) followed by Enterobacter, klebsilla, pseudomonas and candida at 85%, 70%, 20% and 3% respectively. This results matches with the CIAO Study (Complicated intra-abdominal infections

Observational study by World Society of Emergency Surgery) which underwent in 68 medical institutions worldwide during a six-month study and showed that community acquired infections are commonly caused by the non-fermenting gram-negatives E coli, Enterobacter sp, klebsilla aeruginosa and Acinetobacter and Candida sp.[15]

Most of the patients received diversions as surgical management in our study (41.6%) which is justifiable by their late presentation.[16] Sartelli et al shared his European experience in 2012 and reported that of the 100 patients with small bowel perforations, 83 underwent open small bowel resections and anastomosis (83%) the remaining 14% were treated non-surgically. This high rate of primary anastomosis were due to only 14.7% of patients were admitted in critical condition (severe sepsis/septic shock)[14] However in our study, 60% patient were in severe sepsis and septic shock.

We reported that major cause of postoperative morbidity were wound infections (83.7%), respiratory complications (16.2%) e.g., atelectasis, pneumonia, pleural effusion or ARDS, septicemia (64%) and post op collection (11.1%) which are preventable and should be detected early and aggressively treated. An unacceptably high incidence of wound infection (83.7%) and septicemia in the present series was multifactorial due to delayed presentation, gross contamination of peritoneal cavity, septicemia and nutritionally debilitation as most of them had tuberculosis. These results are higher than other

reported data. Yadav et al in his prospective review of 77 patients with CIAI showed a wound infection rate of 17.8%, followed by respiratory complications and anastomotic leaks in 7.8 and 3.9% respectively.[17] Rate of relook laparotomies in our data set were 18% in comparison to 11.7% reported in CIAOW Study[15]. A high rate in our study is attributed to late presentation and gross fecal contamination at time of intervention.

Our mortality of 36.3% is higher than the published literature from developed countries. In 2010, UK reported a 30-day hospital mortality rate of 14·9% However, USA and Denmark showed a similarly mortality rate of 14% and 19.5 % respectively. This high mortality rate could be justifiable by the large number of patients that were in septic shock at the time of their presentation. In the UK there is increasing recognition that outcomes after emergency surgery are poor and would benefit from standardization of care.[4] It is important to consider that morbidity and mortality rates have no direct association with the surgical technique, but more importantly depends on the general status of the patient, the virulence of the pathogens, and the duration and character of disease evolution preceding surgical treatment.

There is increasing resistance of community-acquired strains of gram negative organisms to selected antibiotics in many countries of the world. Specific antibiotic agent should be avoided if resistance to that agent is greater than 10% to 20% for a common intra-abdominal pathogen in the community.[18] However the rationale of empirical antibiotic therapy in CIAI is to cover the less common organism, which could be predictors of treatment of treatment failure. In order to decrease multidrug resistance, antibiotic treatment modalities need a regular update according to the hospital specific surveillance data. The use of preemptive antifungal therapy with fluconazole in high-risk patients may decrease the incidence of Candida peritonitis[19].

This paper presents the experience of clinical presentation and management of secondary peritonitis due to hollow viscous perforation in tertiary care setting, where delayed in late referral is the key factor. Which could be explained by poor primary health care referral system in our country. There are few limitations of this study as the data was collected retrospectively and based on single center. Sample size was modest. We could not provide data regarding long term complications followed by CIAI, patient's co-morbidities and it association with morbidity and mortality. None of the operative intervention was carried out by laparoscope due to lack of resources. Strength of this study include that we have discussed multiple outcomes which were lacking in other studies from subcontinent, our study findings are highlighting the increased prevalence of infectious causes in Pakistan. This data has provided strong evidence to health care authorities in our country for the establishment of developed Primary health care system and guide them to develop an accelerated pathway for early recognition of CIAI.

CONCLUSION

The study shows that management of intra-abdominal sepsis is still a surgical challenge with significant burden on the health care system. We recommend that Early recognition, prompt & proper resuscitation, adequate source control, application of septic bundle of care are important tools of management, along with an improvement of primary health care system in the developing countries may produce favorable outcomes.

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

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Original Article

Hep B, C & HIV in Cataract Surgery

Prevalence of Hepatitis B, Hepatitis C and HIV in Cataract Surgery Patients at DHQ Teaching Hospital Sargodha

Nasrullah Khan, Tamoor Iqbal and Wajid Ali Kanju

ABSTRACT

Purpose: To investigate prevalence of hepatitis B, hepatitis C and HIV in patients admitted for cataract surgery in DHQ teaching hospital Sargodha.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Department of Eye, DHQ Teaching Hospital Sargodha from 1 January 2017 to 30 June, 2017.

Materials and Methods: After taking the informed consent patients were tested in the DHQ hospital Sargodha laboratory for Hepatitis B surface antigen (HBsAg), Anti-HCV and HIV. Those with the positive results were used to determine the prevalence of Hepatitis B, Hepatitis C and HIV.

Results: 767 patients were admitted for cataract in the period of six months (January 2017 - June 2017) in DHQ Teaching Hospital Sargodha. Mean age was 61 years. Number of male patients was 417 (54.37%) and of female patients was 350 (45.63%). Total patients who were Hepatitis B positive were 15 (1.95%), Hepatitis C positive were 84 (10.95%) and HIV positive were 2 (0.26%).

Conclusion: Prevalence of Hepatitis B and C is higher among the patients presenting in DHQ teaching hospital Sargodha as compared to the average prevalence in Pakistan as well as globally. Furthermore 2 patients with HIV positivity were also found.

Key Words: Hepatitis B, Hepatitis C, HIV, Prevalence

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INTRODUCTION

Hepatitis B, Hepatitis C and HIV are viral communicable diseases that are affecting general population globally. Hepatitis is inflammation of liver. It has multiple variants that manifest in different ways. Hepatitis B and C, however, are leading causes of liver cirrhosis and hepatocellular carcinoma[1]. Hepatitis B is a DNA virus. Pakistan is highly endemic with HBV[2].About 2 billion people are infected with HBV worldwide[3,4,5] and about 9 million people are infected in Pakistan[6] with its infection rate steadily rising[7]. Hepatitis C is a RNA virus that affects around 3% of global population or 120-170 million people according to WHO data[8]. HIV is a RNA virus that causes AIDS. In Pakistan about 0.1% of population with 1% in high risk population is affected by it according to the estimations of joint effort team of WHO and UNAIDs.

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These virulent agents are transmitted by contaminated needles, contaminated blood products, sexual intercourse, vertically and infected surgical instruments[9]. Factors that result in spread and increasing incidence of these diseases include lack of knowledge, lack of screening facilities, intentionally avoiding preoperative screening of patients in hospitals[10]. This puts health care workers at serious health risk.

MATERIALS AND METHODS

This study is a cross-sectional study that was done at DHQ teaching hospital Sargodha. It is a tertiary care hospital with a well-equipped ophthalmology department. About 2000-2500 eye surgeries are performed here annually. Cataract surgery is one of the common surgery performed here in this establishment. In this only the patients that were admitted for cataract surgery during this period of six months were included. All of the patients were screened for Hepatitis B, Hepatitis C and HIV after informed consent and all the data was recorded in the indoor unit register of all the consultants. All the infected patients were operated with labelled surgical sets. Surgeons as well as O.T staff took all the protective measures and later patients were referred to medical specialists for further evaluation and treatment. It was also

ensured to inform the health care department regarding the HIV cases.

RESULTS

Total of 767 patients were included in this study during the defined span of six months. Out of these 417 patients were male (54.37%) and 350 patients were female (45.63%). There was an observable difference in the difference of prevalence Hepatitis B, Hepatits C and HIV between Male and Female patients.

Total of 15 (1.95%) patients were Hepatitis B positive with 14 (93.33%) male and 1 (6.64%) female patients. As with Hepatitis C, 84 (10.95%) patients were infected with 57 (67.86%) male while 27 (32.14%) female patients. In case of HIV only 2 (0.26%) patients were infected and both were females. Total of 101 (13.17%) patients were infected with either Hepatitis B, Hepatitis C or HIV while remaining 666 (86.83%) of patients were uninfected. Following table 1 summarizes these results.

Table No.1: Gender Distribution of Hepatitis B, C and HIV

Gender	Total	Uninfected	Infected	B+	C+	HIV
Male	417	346 (82.97%)	71(17.03%)	14 (93.33%)	57 (67.86%)	0
Female	350	320 (91.43%)	30 (8.57%)	1 (6.64%)	27 (32.14%)	2 (0.26%)

Similar results are exhibited by bar chart showing distribution of infected patients suffering from Hepatitis B, Hepatitis C and HIV respectively.

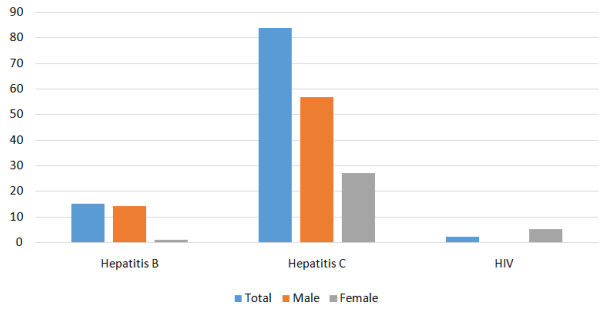

Figure No.1: Distribution of Patients according to gender

Above mentioned results were tested for association using chi-square in Minitab 18 using gender and overall patients infected with Hepatitis B, Hepatitis C and HIV. It showed a p-value of 0.002 which is below 0.05 exhibiting statistical significance as shown below.

Tabulated Statistics: gender, Worksheet columns
Rows: gender Columns: Worksheet columns

	total	infected	All
male	417 (431.22)	71 (56.78)	488
female	350 (335.78)	30 (44.22)	380
All	767	101	868

Cell Contents
Count
Expected count

Chi-Square Test

	Chi-Square	DF	P-Value
Pearson	9.201	1	0.002
Likelihood Ratio	9.521	1	0.002

Fisher's Exact Test
P-Value
0.0026929

DISCUSSION

When we compare the prevalence of Hepatitis B and C in Pakistan with the global numbers there is an evident higher prevalence rates in Pakistan. Other regions with high prevalence rates include Asia, Africa and middle east[11]. There are various risk factors that contribute to this including unsafe dental procedures, lack of vaccination, lack of screening facilities at primary and secondary health care centers, male gender, age more than 16, family history of liver disease etc[12]. Other sources include barber instruments and drug abuse. As far as our study is concerned we have found a clear difference of prevalence rates between male and female gender. Men are more affected as compared to female patients in case of Hepatitis B and C while in case HIV only 2 female patients were found. This trend has also been observed in various other studies one of these include a study by Riaz S[13]. However their study only discusses Hepatitis B and C prevalence rates which were still higher among male patients. One factor that was also observed that more male patients usually seek medical attention this may also be the reason of higher prevalence rates in males as compared to females.

To lower this growing health issues and preventing the medical professionals we have to eliminate the sources of transmission especially needle pricks and surgical malpractices[14-17]. To achieve that the is a dire need to educate the community at a national level via television campaigns and door to door yearly visits.

CONCLUSION

In Pakistan, health system is barely enough to meet the health needs of a growing population. This increasing rate of infection of Hepatitis B, C and HIV further imparts a threat to the health

system failure. To avoid a health crisis effective measures have to be adopted including health education, provision of screening facilities, improving general hygiene and preventing the transmission of the infection especially in health care establishments.

Author's Contribution:

Concept & Design of Study:	Nasrullah Khan
Drafting:	Tamoor Iqbal
Data Analysis:	Wajid Ali Kanju
Revisiting Critically:	Tamoor Iqbal, Wajid Ali Kanju
Final Approval of version:	Nasrullah Khan

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Original Article

Hypertension and RV Dysfunction in Bronchiectasis

Pulmonary Hypertension and Right Ventricular Dysfunction; An insight in the Magnitude of Problem among Patients of Bronchiectasis

M. Irfan Malik[1] and Hafiza Shafia Naz[2]

ABSTRACT

Objective: To determine the frequency of pulmonary hypertension and Right Ventricular Dysfunction in diagnosed cases of bronchiectasis by Doppler Echocardiography.
Study Design: Cross sectional study
Place and Duration of Study: This study was conducted at the Department of Pulmonology, Jinnah Hospital, Lahore from September 2013 to March 2014.
Materials and Methods: After taking an informed consent, 120 patients with HRCT diagnosis of bronchiectasis were included through consecutive sampling. Pulmonary Hypertension (a mean pulmonary artery pressure > 25 mm Hg) and Right Ventricular Dysfunction (Systolic excursion of tricuspid annulus of < 2cm) was labeled using Doppler Echocardiography. Data was collected using a predesigned proforma and analyzed using SPSS version 21.
Results: It was seen that 75 patients (72.5%) were male 45 (37.5%) were female. Right ventricular dysfunction was present in 19 (15.8%) individuals while pulmonary hypertension was found in 47 individuals (39.2%).
Conclusion: It is concluded that a considerable proportion of patients suffer Right ventricular dysfunction while the frequency of pulmonary hypertension is significantly high in patients with bronchiectasis.
Key Words: Bronchiectasis, Pulmonary Hypertension,Right Ventricular Dysfunction, Echocardiography

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INTRODUCTION

First described by Rene Theophile Laënnec in 1819, bronchiectasis (BX) is now defined as permanently dilated airways due to chronic bronchial inflammation caused by inappropriate clearance of various microorganisms and recurrent or chronic infection.[1,2]. Induction of bronchiectasis requires two factors: an infectious insult and Impaired drainage, airway obstruction, or a defect in host defense. The ensuing host response causes a transmural inflammation, mucosal edema, cratering, ulceration, and neovascularization in the airways resulting in permanent abnormal dilatation and destruction of the major bronchi and bronchiole walls.[3]

There are numerous etiologies that can induce or contribute to the pathophysiologic processes that result in bronchiectasis and their frequency varies with the geographic location and referral population.

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Airway obstruction can be caused by foreign body aspiration, an intraluminal obstructing lesion such as a carcinoid tumor, or extra luminal compression from encroaching lymph nodes.[4]It is important to identify the presence of airway obstruction because surgical resection is often curative.

The classic clinical manifestations of bronchiectasis are cough and the daily production of mucopurulent and tenacious sputum lasting months to years and is occasionally associated with hemoptysis.[5,6] Dyspnea, rhinosinusitis, hemoptysis and recurrent pleurisy along with crackles and wheezing are also common findings in patients of bronchiectasis.[7]

Diagnosing BX has become significantly easier with the advent of high resolution computed tomography (HRCT), which has proved to be highly sensitive for demonstrating bronchiectatic change in the airways along with giving information on the distribution of bronchiectasis which may be important diagnostically. [8-10]

Since infection plays a major role in causing and perpetuating bronchiectasis, antibiotics are used to treat an acute exacerbation Other treatment modalities include inhaled bronchodilators, chest physiotherapy and pulmonary rehabilitation along with newer agent under trial like aerosolized antibiotic and recombinant DNase I.[11,12] Surgical intervention is often combined with an aggressive antibiotic and bronchial hygiene

regimen to reduce bacterial infection and allow better drainage. [13]

Mortality is high because of recurrent infections and cardiac complications. Common cardiac issues are pulmonary arterial hypertension (PAH), Right ventricular (RV) dysfunction and left ventricular (LV) diastolic dysfunction. Pulmonary arterial hypertension (PAH) is a progressive disease defined by chronic elevation in the pulmonary arterial pressure, often leading to right heart failure and death.[14]Diagnostic testing is indicated whenever PH is suspected using echocardiogram. When the echocardiogram does not suggest PH, right heart catheterization should be considered if the clinical suspicion for PH is high. [15] it is certainly much more prevalent than reported in developing countries.[16] Right ventricular systolic dysfunction is usually under diagnosed in bronchiectatic patients until full blown. In a small study of Saudi population right ventricular (RV) dysfunction came out about 12.8% (12/92) and pulmonary artery hypertension in 32.9% (31/94).[17] The electrocardiogram (ECG) of a patient with PH may demonstrate signs of right ventricular hypertrophy or strain but it is not sensitive for the detection of right ventricular disease. ECG changes do not correlate with disease severity or prognosis.[18] Echocardiography is performed to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function. In addition, echocardiography can evaluate right atrial size, left ventricular systolic and diastolic function, and valve function, while detecting pericardial effusions and intracardiac shunts.[19] It is also seen that PH is associated with worse survival in COPD, but does not influence the prognosis after lung transplantation.[20]

Bronchiectasis is an underdiagnosed disease in Pakistani population but not at least less prevalent. Cardiac complications symptomatically appear late but early diagnosis of cardiac dysfunctions will help apply some intervention which may halt the disease progression. Thus this study was designed to help delineate local patterns of pulmonary hypertension and cardiac complications in bronchiectasis patients which may aid to develop some consensus for screening of every bronchiectasis patient for cardiac issues early in the course of disease. A knowledge regarding disease burden of these cardiac issues may thereby also assist in formulation of local evidence based guidelines.

MATERIALS AND METHODS

This cross-sectional study was conducted in department of pulmonology in Jinnah Hospital, Lahore from January 2016 to June 2016. A total number of 120 patients aged 15 to 70 years, who were diagnosed as cases of bronchiectasis by HRCT were taken using non-probability consecutive sampling. Patients with a history of hypertension, valvular or rheumatic heart disease, ischemic heart disease, or cardiomyopathy; previous history of resection lung surgery, fibrosis, auto-immune diseases, interstitial lung disease and those on drugs for pulmonary hypertension were excluded from the study.

Patients selected were evaluated by Doppler Echocardiography for diagnosis of Right ventricular (RV) systolic dysfunction and pulmonary arterial hypertension. Pulmonary hypertension was defined by a pulmonary artery systolic pressure > 40 mm Hg measured by Doppler Echocardiography. RV systolic function was assessed by measuring the systolic excursion of the tricuspid annulus. Systolic excursion of tricuspid annulus of < 2cm was considered as right ventricular dysfunction. They were further treated according to standardized medical protocols. Data was collected on a structured proforma and SPSS version 17 was used for data analysis. Descriptive statistics were calculated for all quantitative variables like age, systolic excursion of the tricuspid annulus and Pulmonary Artery pressure as mean $\pm$ standard deviation and qualitative variables like sex, presence of RV Dysfunction and Pulmonary arterial hypertension as percentages and frequencies.

RESULTS

The results of the study showed mean age of patients 56.9 $\pm$ 5.47 with 75 patients (72.5%) were male 45 (37.5%) were female. Right ventricular dysfunction was present in 19 (15.8%) individuals while it was absent in 101 (84.2%)**.** Pulmonary hypertension according to operational definition was found in 47 individuals (39.2%) and it was not present in 73 (60.8%) individuals (Table 1).

Table No.I: frequency distribution of pulmonary hypertension and RV dysfunction (n=120)

Cardiac complication	Frequency	%
RV dysfunction	19	15.8%
Pulmonary hypertension	47	39.2%

Table No.2: stratification of age and sex with RV dysfunction

		RV dysfunction		Total	P value (using chi square)
		Yes	No		
Sex	Male	12	63	75	0.949
	Female	7	38	45	
Total		19	101	120	
Age group	Less than 50 Years	11	1	12	0.579
	51 to 60 Years	68	15	83	
	More than 60 Years	22	3	25	
Total		101	19	120	

When cross tabulation was done between the right ventricular dysfunction and gender, there came out a

non-significant difference (P value = 0.94) (Table II). Similarly, When age was cross tabulated across patients with right ventricular dysfunction, there was a non-significant difference i.e. age was not found associated with presence of right ventricular dysfunction. (p value= 0.579). (Table 2)

Pulmonary hypertension was equally distributed among both male and female (p value = 0.16). Similarly age was equally distributed for both groups with and without pulmonary hypertension after application of chisquare test with a p value of 0.807 (Table 3).

Table No.3: stratification of age and sex with PH

		PH		Total	P value (using chi square)
		Yes	No		
Sex	Male	33	42	75	0.161
	Female	14	31	45	
Total		47	73	120	
Age group	Less than 50 Years	8	4	12	0.807
	51 to 60 Years	51	32	83	
	More than 60 Years	14	11	25	
Total		73	47	120	

DISCUSSION

Right Ventricular Dysfunction and pulmonary hypertension is a serious complication of bronchiectasis. This study was carried out to determine the effect of bronchiectasis in these patients regarding the Right Ventricular Dysfunction in pulmonary hypertension. In our sampled population Right ventricular dysfunction was found in almost 16% of the individuals which is quite high as compared to previously reported study which shows that a clinician should be sensitized to take into an account of Right ventricular dysfunction. Similarly pulmonary hypertension was very much high about 40% of the sampled population. These results are slightly higher than a study conducted in Saudi population in which about 12.8% of the patients suffered from RV dysfunction while 32.9% of the patients with bronchiectasis had pulmonary hypertension.[17] This variation migh be because of the less sample size taken in the Saudi study which decreases the external validity of that study.

Another finding of this study is that the mean age of the population was 57 years showing that it's a disease of old age ranging from 42 to 70 years. Moreover it was also seen that 62% individuals were male while 37% were female. This gives an indication of the male predominance of bronchiectasis which may be because of the presence of risk factor which are more commonly found in male population. However, on stratification of data for age and gender it was seen that pulmonary hypertension and RV dysfunction was independent of both and the results were statistically insignificant. This gives an indication that any age group or gender are equally prone to development of this complication and it is related solely with the disease process.

Pulmonary hypertension and RV dysfunction are chronic, debilitating condition and it affects the vasculature of lungs along with the heart muscles. It is associated with increased mortality along with poor prognosis in these patients.[20] An early diagnosis and control of these two condition may help in improved survival and better outcome in these patients. Limitation of our study was the measurement of pulmonary artery pressure through non-invasive technique. Further studies should be encouraged in this regard so that the exact pathophysiology can be understood and evidence based management can be done to decrease the morbidity and mortality in patients with bronciestasis..

CONCLUSION

It can be concluded from this study that a significant proportion of the patient with bronchiestasis has right ventricular dysfunction while the frequency of pulmonary hypertension is even higher. The screening of these conditions done by simple test like echocardiogram can lead to remarkable results in the outcome of the disease. Thus it should be encouraged in these patients at an earlier stage to get the benefit of lead time and improve the survival in patients with not-so-unusual bronchiectasis.

Author's Contribution:

Concept & Design of Study:	M. Irfan Malik
Drafting:	Hafiza Shafia Naz
Data Analysis:	M. Irfan Malik
Revisiting Critically:	Hafiza Shafia Naz
Final Approval of version:	M. Irfan Malik

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

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Original Article

CSOM with Cholesteatoma

Chronic Supporative Otitis Media (CSOM) without Cholesteatoma: A Matter of Concern in Internally Displaced People of North Waziristan Agency, KPK

Mohammad Iqbal

ABSTRACT

Objective: The objective of the study was to evaluate the frequency and risk factors for CSOMWC in children of IDPs of North Waziristan Agency during military operation "ZARB-E-AZAB" started in July 2014.

Study Design: Observational study / cross sectional

Place and Duration of Study: This study was conducted at the ENT Department, DHQ hospital Bannu and two main clinics serving major populations of the IDPs from 3rd December 2014 to 5th May 2015.

Materials and Methods: Data was recorded during the child's visit to the hospital & respective clinic by means of a structured interview with the parents, examination of the patients by otoscopy and by taking info from preceding medical history

Results: Comparison was made between180 children having the disease to 150 controls with similar age group who reported in ENT opd & ENT clinics. The calculated six month's incidence was 180/1000 children 1 to 15 years of age. Meaningfully, increased jeopardy for CSOM was related with a history of acute and recurrent otitis media, a maternal history of COM (chronic otitis media), bigger families and more brethren. The sex, parental age and education, allergy, sinusitis and recurrent URTI were associated with chronic suppurative otitis media.

Conclusion: Tympanomastoid surgery is taken into consideration as standard management for CSOMWC, which is unresponsive to oto-topical/oral antimicrobial therapy. Acute and recurrent otitis media, a parental history of chronic otitis media, larger families and more siblings, the sex, parental age and education, allergy, sinusitis and recurrent upper respiratory tract infections are important risk factors for CSOM. In order to improve outcomes, we should modify and cope the controllable risk factors to preclude this life condition.

Key Words: CSOM, IDPs, Cholesteatoma

Citation of article: Iqbal M. Chronic Supporative Otitis Media (CSOM) without Cholesteatoma: A Matter of Concern in Internally Displaced People of North Waziristan Agency, KPK. Med Forum 2017;28(11):66-68.

INTRODUCTION

Pakistan is a developing country. Per capita income is too low. Illiteracy and poverty are the chief problem for avoiding hospitals to get treatment. Children's parents or caretakers are unaware of CSOM (chronic suppurative otitis media) and do not know its concerns. The residents of the areas like Waziristan agencies are the main victim of this health problem.

(CSOM) Chronic suppurative otitis media is well-thought-out to be the most common ear ailments [1,2] in many of the developing countries including Pakistan. It is the most communal reason of insistent mild to moderate hearing damage in children and young adults.[3]

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The etiology and pathogenesis of otitis media are multi factorial including genetic, infections, allergy, environmental, social and racial factors and Eustachian tube dysfunction.[4] Throughout the current decade, the frequency of chronic suppurative otitis media has intensely dropped due to developments in housing, hygiene and antimicrobial chemotherapy.[5] Still some factors including unawareness, poverty and traditional views are the major risk factors for not taking treatment.

CSOM includes a series of middle ear's inflammation, infection, ulceration and granulation. There is a pus-filled emancipation through a pierced tympanic membrane which persists for more than 42 days. Technical complications involve hearing loss, mastoiditis, cholesteatoma, brain abscess, facial nerve paralysis, meningitis, and sigmoid sinus thrombosis.[6]

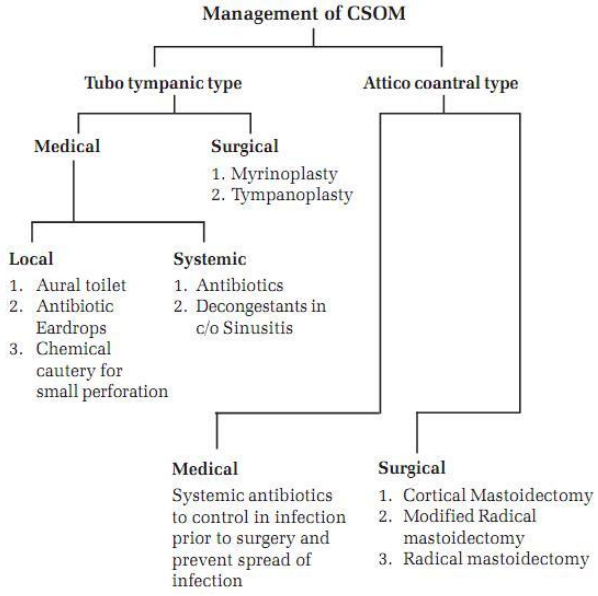
According to "World Health Organization" (WHO) approximations, 65–330 million persons are affected by CSOM globally, whose majority is in the developing countries. In UK, CSOM ratio varies between 0.9% and 0.5% of children &grown-upsrespectively. Conversely, the ratio is 12–50%[7] in developing countries as well as in the Australian Native population. CSOM and

cholesteatoma are regarded as diseases of paucity; and culture does not account for the pervasiveness of both situations.[8]

CSOM, with or without cholesteatoma accounts for up to 80% of the total hearing damage; of which, 90% cases testified in under developed republics. In children, the effects are seen on speech, language, intellectual, psychological and social development and education. Additionally, adults are probablyhurt from personal and social disgrace with decreased employment opportunities.

In July 2014, approximately 10, 00,000 IDPs came from North Waziristan agency due to military operation against anti-state forces and entered into district Bannu and its surroundings. Mostly victims arrived from an environment having poor food choices, highly disease rates, insufficiency of income, mobbing and limited healthcare facilities. Seeking health knowledge is a high precedence for relocation and this is compromised with even a mild to moderate hearing loss.[9] The general practitioner who first sees a newly arrived IDP may not have knowledge of their patient's complex and unique health issues.[10,11]

The pictorial management of CSOM is presented in the following



following risk factors contribute towards the incidence of CSOM.

- Numerous incidents of acute otitis media (AOM).
- Overcrowded living system.
- Being a member of a large family.
- Attending daycare.

Parental education studies, flaccid smoking, breast-feeding, socio-economic position and the yearly no of upper respiratory tract infections (URTIs) show questionable associations only.

Craniofacial irregularities upsurge risk: cleft lip or palate, cri du chat syndrome, choanal atresia, Down's syndrome and microcephaly, all increase the risk of CSOM.

American Academy of Otolaryngology-Head and Neck Surgery experts' panel displayed guidelines for the treatment of chronic suppurative otitis media (CSOM). The experts of the panel stressed upon the use of topical antibiotics alone as a first-line therapy for patients, without systemic infection. In case of systemic infection, oral orparenteral antibiotics are advised.

Literature review shows only a slight risk of senso-rineural hearing loss in humans having topical aminoglycosides and higher risk of vestibular toxicity.

Fluoroquinolonesdo not have potential for ototoxicity and downgrade aminoglycosides to a secondary treatment substitute. The use of aminoglycoside drops in the presence of fluoroquinolone subsequently progress hearing loss.

Patients, who develop CSOM, are generally recommended to evade swimming however, if swimming is imperative, care should be done and ears should be kept dry. Due to small evidences, consensus among experts is missing. Some advice ear plugs until perforations are extruded while others do not.

The purpose of this study was to evaluate the incidence and risk factors for chronic suppurative otitis media without cholesteatoma in children of IDPs of North Waziristan Agency during military operation "ZARB-E-AZAB" started in July 2014 and as a result of that, IDPs were migrated to Bannu district particularly.

MATERIALS AND METHODS

This is a observational / prospective cross sectional study among 1000 children aged between 1-15 years. The mean age was calculated as 14.5 years. All the children were examined otoscopically, from 3rd December 2014 to 5th May 2015 and looked for patients with a diagnosis of CSOM without cholesteatoma. Data were analyzed statistically using frequency and percentage. Follow up of management outcomes was not part of this study.

RESULTS

Table No.I: Number and gender of patients diagnosed with CSOMWC

Patients age group (years)	Gender of patients		Total n=1000	%age
	Male n=600	Female n=400		
CSOM without cholesteatoma	105	75	180	18

Out of 1000 children, 65% (n=600) were male and 35% (n=400) were female. Prevalence of CSOM without cholesteatoma was 18% (n=180) of the total patients. Male % prevalence was 58.33 (n=580) while female % prevalence was 41.66 (n=420). The results are mentioned in table 1.

DISCUSSION

No work is done on pervasiveness of CSOM without cholesteatoma in newly arrived IDPs, though unreliable evidence suggests that hearing damage is common in refugees. IDPs come to district Bannu from a region of higher concentration of the disease to an environment where occurrence is lower.

This study ratifies that the clinical prevalence of CSOM without cholesteatoma in this group of newly arrived IDPs imitates the occurrence in their area of origin and hence, is higher than in the rest of the settled areas.

The incidence of the disease without cholesteatoma will make relocation more perplexing because of the resulting deafness and subsequent difficulty with language skills, socializing, education and employment. General practitioners should be aware of this and add otoscopy and possibly hearing tests to the screening protocol for all newly arrived IDPs.

Edificationto differentiate between CSOM, AOM and OE is imperativeas the management for AOM and OE will have no influence on CSOM and might really be disadvantageous. Advocacy may be desirable to guarantee that adults with CSOM who come from a refugee background have access to evidence based ciprofloxacin treatment and hearing services.

CONCLUSION

The prevalence of CSOM can be reduced through health education through Society health programs. Socioeconomic status and health care facilities can also be a helping hand in reducing CSOM onset. However, conducting health camps is one of the most important means to search for disease and treat it accordingly. As our study had high prevalence of chronic suppurative otitis media without cholesteatoma than other studies done in school children, the authors recommend free health camps, especially for ear diseases, in different parts of KPK particularly and in the country generally.

Author's Contribution:

Concept & Design of Study:	Mohammad Iqbal
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Study on Presentations and Treatment Outcome of Plasmodium Falciparum Malaria

Treatment of Plasmodium Falciparum Malaria

Jeando Khan Daidano[1] and Akbar Hussain Yousfani[2]

ABSTRACT

Objective: To determine the presentation and treatment response to anti malarial drugs of Plasmodium Falciparum malaria.

Study Design: Descriptive / prospective study.

Place and Duration of Study: This study was conducted at the Department of Medicine, PMCH Nawabshah from January 2016 to April 2017.

Materials and Methods: 100 patients were selected for this study, statical analysis was done using SPSS 15 version. Inclusion Criteria is ICT Malaria test positive for Plasmodium Falciparum. Thick and Thin flim positive MP Plasmodium Falciparum. Exclusion Criteria is ICT Malaria test, and thick thin film negative for Plasmodium Falciparum, tuberculosis and typhoid fever.

Results: 100 patients were selected for this study, 53 were males, 47 were females. Age ranged 13-70 years. All patients presented with fever, temperature ranged 100^0F-105^0F.Anemia was present in 40 patients, 20 patients were jaundiced clinically. Altered consciousness was present in 30 patients. 18 patients had raised blood urea, bilirubin was raised in 20 patients, hemoglobin ranged 4-14 gm/dl, TLC ranged 6320-24209/mm^3, random blood sugar ranged 85-199 mg/dl, platelets ranged 40500-488245,PT was raised in 20 patients, LFT deranged in patients. All patients treated by inj. Artesunate2.5 mg/kg i/v BD for 1 day then daily . Out of 100 patients 13 died due to severity of disease.

Conclusion: Plasmodium Falciparum Malaria with complications is a major illness in our country especially patients from rural areas. Patients reach very late in hospital, Cerebral Malaria can be treated with artesunate atemether and quinine. Prevention and awareness is is necessary, mortality can be reduced.

Key Words: Malaria Plasmodium Falciparum

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INTRODUCTION

Plasmodium Falciparum Malaria is common disease in the developing world. According to WHO commonly affected country is sub-Saharan Africa .[1] Where death ratio in children under the age of five years is about 80%. Plasmodium Falciparum Malaria is transmitted by the bite of infected anopheles mosquito of genus plasmodium in human. These are plasmodium ovale, plasmodium malaria, plasmodium vivax, plasmodium falciparum and plasmodium knowlesi. More severe malaria occurs due to plasmodium falciparum and mortality is increased[2]. Clinical features include fever, malaise, headache and vomiting. Jaundice is due to liver dysfunction and hemolysis. Anemia is commonly present. Patient may present with tender hepatomegaly and spleenomegaly. Patients with Plasmodium Falciparum malaria may develop serious complications[3]. Plasmodium Falciparum malaria presented with seizures, ataxia,hemiplegia, coma and death. Neurological damage is common in cerebral malaria. 20% of children who survive after illness, develop cognitive deficits, learning and language impairments, memory impairment, psychiatric disorders, visuospatial and motor deficits.[4] In Europe malaria is common in travelers with morbidity and mortality[5]. Transmission of malaria from human to mosquito depends upon the presence of sexual stages in blood, after the cycle hundred to thousands of sporozoites in the salivary gland of mosquito and infect the host[6]. Malaria is transmitted by 60 species of anopheles mosquito[7]. Life cycle change in mosquito before it becomes infectious to other healthy individuals. The time period is required for the life cycle change increases as the temperature declines, life span of mosquito, transmission is decreased when temperature falls below 18^0C. Malaria parasite cease development when temperature is below 16^0C and malaria is reduced in temperate regions[8]. Malaria transmission increased during rain fall and humudity[9]. Temperature variation due to change in

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weather is the main factor for the geographical distribution of the disease. In the tropical regions exposure to mosquitoes is increased. Several contacts with infected mosquitoes at night, due to such inoculation rates, increased duration of parasite survival in the host, saturate local human populations rapidly and superinfection universal prevalence occur. Due to stable pattern of transmission, even vector control repeatedly failed to eradicate the parasite from tropical and sub tropical regions even control is possible[10]. Diagnostic methods, drugs and control measures has been renewed over the past decade[11]. In 2006 malaria treatment outcome was improved with use with use of artiminism based combination therapy to address resistance of plasmodium falciparum to monotherapy recommended by WHO[12]. Recovery rate with artiminism was 90% and well tolerated[13]. WHO introduced rapid diagnostic test (RPT) in all cases of malaria[14]. Severe Falcparum malaria treatment recommendation is Artesunate 2.4 mg/kg i/v 12 hours for 1 day then daily. Alternate Quinine dihydrochloride 20 mg/kg i/v over 4 hours then 10 mg /kg i/v every 8hours or Artemether 3.2 mg/kg i/m then 1.6 mg/kg/d intravenously. Drugs for prevention of Falciparum Malaria are, chloroquine, malarone, mefloquine and doxycycline.

MATERIALS AND METHODS

This descriptive and prospective study was conducted in the department of medicine at PMCH Nawabshah from January 2016 to April 2017. 100 patients were enrolled for this study, admitted in the medicine department with the diagnosis of acute Falciparum Malaria, by history general physical examination and ICT Malaria positive for Plasmodium Falciparum. Informed consent was taken from all the patients. The purpose of this study was to study the clinical features and response to anti malarial drugs.

Inclusion Criteria: Age above 12 years. ICT positive for Plasmodium Falciparum. Thick and Thin flim Positive MP Plasmodium Falciparum.

Exclusion Criteria: Afebrile. ICT and Thick and Thin film negative for Plasmodium Falciparum. Age below 12 years

RESULTS

Out of 100 patients 53 were males and 47 were females. Age range from 13 to 70 years. All the patients presented with fever, duration of fever ranged 1 day to 15 days. Fever was low grade in 10 patients, moderate in 41 patients and high grade in 49 patients. Fever range from 100^0F to 105^0F. fever was continuous in 40 patients and intermittent in 60 patients. Fever was associated with rigors and chills in 42 patients, headache 78 patients, other symptoms were abdominal pain 28 patients, vomiting 23 patients, altered consciousness was present in 32 patients, respiratory symptoms in 15 patients. On physical examination BP ranged 60-180 mmHg. All patients were positive for Falciparum Malaria on ICT and thin and thick film (microscopy) Trophozoites in in 83 cases, combined trophozoites and gametocytes in 7 cases were seen. Anemia was present in 41 patients, jaundice was positive in 21 patients Hb range 4 to 14gm/dl. Bilirubin range 0.9 to 11mg/d ,leukocyte count 6320 to 24209, platelets count 40500 to 488245, random blood sugar was between 85 to 199, blood urea 25 to 210 mg/dl, serum creatinine ranged 0.8 to 12 mg/dl, 31 patients had raised urea and 15 patients had raised creatinine level. PT prolonged in 18 patients and dehydration was positive in 23 patients. All patients were given inj Artesunate 2.4 mg/kg i/v BD for 1day then daily, few patients received antibiotic treatment for chest infection and septicemia. Fluids were given according to electrolyte disturbance and dehyderation. Out of 100 patients 13 patients died. Death was due to cerebral malaria with septicemia and renal failure.

Table No.1: Descriptive Statistics:

	N	Minimum	Maximum	Mean	Std.Deviation
Age	100	13.00	70.00	40.5900	13.82071
Sex	100	1.00	2.00	1.4700	0.50161
Hemoglobin	100	4.00	14.00	9.1550	2.71425
L. count	100	6320.00	24209.00	21231.22	21227.42452
Pl.Count	100	40500	488245.00	206044.5	110532.53914
P.T	100	12.00	26.00	15.5600	4.20274
RBS	100	85.00	199.00	145.8500	31.25567
Urea	100	3.00	210.00	63.1100	55.50264
Creatinine	100	0.80	11.00	2.1270	2.70857
Biluribin	100	0.90	11.00	2.2970	2.67833
SGPT	100	29.00	187.00	55.5600	38.56683
Valid N (listwise)	100				

Table No.2: ANOVA

		Sum of squares	Df	Mean Square	F	Sig
Sex	Between Groups	10.698	45	0.238	0.903	0.635
	Within Groups	14.212	54	0.263		
	Total	24.910	99			
Hemoglobin	Between Groups	370.249	45	8.228	1.237	0.226
	Within Groups	359.099	54	6.650		
	Total	729.348	99			
L.Count	Between Groups	1.6E+010	45	364219722.2	0.697	0.892
	Within Groups	2.8E+010	54	522590076.7		
	Total	4.5E+010	99			
Pl.Count	Between Groups	6.0E+011	45	1.339E+010	1.191	0.268
	Within Groups	6.1E+011	54	1124E+010		
	Total	1.2E+012	99			
P.T	Between Groups	938.000	45	20.844	1.389	0.268
	Within Groups	810.640	54	15.012		
	Total	1748.640	99			
RBS	Between Groups	53777.476	45	1195.055	1.503	0.076
	Within Groups	42937.274	54	795.135		
	Total	96714.750	99			
Urea	Between Groups	212909.0	45	4731.312	2.775	0.000
	Within Groups	92064.740	54	1704.903		
	Total	304973.8	99			
Creatinine	Between Groups	531.961	45	4731.312	2.775	0.000
	Within Groups	194.336	54	3.599		
	Total	726.297	99			
Biluribin	Between Groups	476.360	45	10.586	2.445	0.001
	Within Groups	233.809	54	4.330		
	Total	710.169	99			
SGPT	Between Groups	98574.107	45	2190.536	2.430	0.001
	Within Groups	48678.533	54	901.454		
	Total	147252.6	99			

DISCUSSION

Cerebral Malaria is major health problem in many countries including Pakistan, patient presented with fever, chills, headache[9], anemia, bleeding from nose, delirium, coma and spleenomgaly. Plasmodium Falciparum Malaria causes major complications, hemoglobinurea, jaundice, shock, renal failure, lactic acidosis, abnormal bleeding, pulmonary edema and adult respiratory distress syndrome. Few patients develop cerebral venous or dural sinus thrombosis and cortical infarcts due to coagulation disorders. Patients presented with shock, bacterial infection[10]. Morbidity and mortality is due to irregular treatment and late treatment. Death in Plasmodium Falciparum Malaria is mainly due to respiratory failure and brain stem signs. Death commonly occur within 24 hrs of presentation in clinic or hospital[11]. The diagnosis of Plasmodium Falciparum malaria depend upon the neurological signs and asexual forms of the parasite on peripheral smear. It is necessary to exclude other causes of unconsciousness, e.g. bacterial meningitis, viral encphlitis and hypoglycemia. Malaria is fatal without treatment. In patients mortality was decreased in those patients who were on intravenous artesunate[12]. Some of the patients fully recovered few discharged with neurological deficit. central hypotonia ataxia and blindness occur and recover with time. Faciparum malaria can contribute to the development of epilepsy in later life. In some studies spinal cord lesions and peripheral neuropathy are reported in cerebral malaria, confirmed on nerve conduction studies and CSF examination[13]. In the acute phase of Plasmodium Falciparum Malaria the patients who die, many of the cerebral capillaries and venules are packed with parasitized RBC and other adjacent capillaries and venules are not obstructed. Coma and death associated with degree of packing and congestion of the cerebral micro vessels with infected and un infected RBC[14]. Retinopathy occurs in malaria in a study. Systemic pyruvate and lactate increased with severity of illness. In Plasmodium Falciparum Malaria micro vascular obstruction and impaired perfusion occurs as a pathophysiological process, mild vascular permeability

and increase vascular permeability with a disruption of endothelial intercellular junction[14]. Gross anemia occurs in young age in cerebral malaria, due to red cell removal by spleen and erythrocyte destruction at parasite shizogony. Anemia occurs rapidly and there is increased need of blood transfusion[15], thrombocy-topenia is usual and DIC is unusual. Acidosis results from accumulation of organic acids and death occur due to Plasmodium Falciparum Malaria. Acidotic breathing cause of respiratory distress is a poor prognostic sign of Cerebral Malaria. Combination of anaerobic glycolysis in tissues cause lactic acidosis, lactate production by malarial parasite and failure of real and hepatic clearance of lactate[16], hypovolumia is a contributory factor. Hypoglycemia associated with poor prognosis in Plasmodium Falciparum malaria associated with lactic acidosis, hypoglycemia is due to failure of hepatic gluconeogenesis. Due to treatment of quinine hyperinsulinaemic hypoglycemia occur[17], common in pregnancy. Quinine cause hypoglycemia due to powerful stimulation of pancreas and recurrent[17]. ARDS is complication of Cerebral Malaria. Due to anti malarial treatment pulmonary capillaries permeability is increased. In Cerebral Malaria pulmonary sequestration is increased, care in fluid management, rapid administration of large volume can be lethal[18]. Cerebral Malaria may present with oligouric renal failure, pathogenesis is unclear but inflammation and reduced microcirculatory flow. Early hem dialysis improve the condition of the patient[19]. Severe jaundice occurs in Plasmodium Falciparum Malaria more in adults than children, it is due to hemolysis, hepatic injury and cholestasis. In severe malaria liver blood flow is reduced, impaired gluconeogenesis, impaired drug metabolism, hypoglycemia and metabolic acidosis are due to hepatic dysfunction[20].

CONCLUSION

Uncomplicated Falciparum Malaria responds well to treatment, complicated Falciparum Malaria is major problem in our country especially in rural areas come late in teaching hospital, initially they receive treatment from GP or non qualified doctors. In our country mortality is common in adults and extended illness with complications. Mortality can be reduced by awareness about treatment prevention of malaria mosquito nets, spray and lotion. Poor prognosis for pregnant woman with prematurity, low birth weight baby and mortality.

Author's Contribution:

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Data Analysis:	Akbar Hussain Yousfani
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Original Article

Reliability of Greulich-Pyle Method in Comparing the Skeletal Age in Pukhtoons of District Peshawar

Age Estimation of Pakhtoons by Greulich-Pyle Method

Sadaf Ambreen, Munila Shabnum Khattak, Zahid Shah, Shabnum Aamir and Zainab Rehman

ABSTRACT

Objective: To compare the skeletal age in both genders in Pukhtoon population aged 11-16 years.
Study design: Cross sectional/ non- interventional study.
Place and Duration of Study: The study was conducted at Khyber Teaching Hospital and Forensic Department of Khyber Medical College. The duration of study was from December 2016 to May 2017.
Materials and Methods: The study sample comprised of 600 healthy subjects in the age group of 11-16 years. Dates of birth of subjects were confirmed from their birth certificates and the chronological age was calculated properly. Hand-wrist radiographs were taken and bone age determined by Greulich-Pyle method.
Results: A total of 600 subjects (male to female ratio 45.5:55.5) were evaluated for skeletal age by using Greulich-Pyle method of age determination. Chronological age was compared with skeletal age using the student "t" test in the study population comprising both genders. It was observed that females attained skeletal maturity earlier than the males.
Conclusion: It was concluded that Pukhtoon children were more advanced in bone maturation than the Europeans. Furthermore, the females show earlier bone maturation than their male counterparts.This radiographic bone assessment can be correlated to assess the age in many medical and medicolegal cases.
Key Words: Greulich-Pyle, Skeletal age, chronological age.

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INTRODUCTION

Age estimation is required in medicolegal cases and to treat many conditions related to endocrinology and paediatric dentistry [1]. Regarding certain paediatric orthopedic interventions like limb discrepancies and scoliosis,doctors have to check proper bone age. Similarly periodic bone assessment is required to treat certain hormone related diseases[2,3,4]. Osteogenesis is a complex process. Microscopic examination shows two types of bone development. The embryological bone development is known as primary or woven bone having less inorganic constituents as compared to its organic constituents. The adult form is known as secondary or lamellar bone which is more mature and organized form[5]. This pattern persists throughout the life of an individual[6].

Regarding ossification of limbbones, the ossification centersappear approximatelyat 8th week of intrauterine life.

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Primary ossification centers appear in almost all the bones at the time of birth while the secondary ossification centers develop after birth[7].

Long bones increase in length at the epiphyseal-diaphysial junction. Growth plates (epiphysealcartilage plates) are responsible for the lengthening of bones. Bones start ossifying at the end of embryonic period therefore the pregnant females are advised to take supplements containing calcium and phosphorus in order to keep their teeth and bones healthy. Children with vitamin D deficiency can manifest Rickets. Vitamin D is essential for absorption of calcium by the intestine. Calcium deficiency thus leads to disturbed ossification resulting in shortened and deformed bones[8].

Development of fetal bones is a fully programmed process being controlled by set of certain proteins. Important among them are bone morphogenic proteins (BMP5 and BMP7), growth and differentiation factor (Gdf5) and member of tumor growth factor (TGf-B)[9].Abnormalities in bone development like failure of phalanges to develop may occur due to excessive apoptosis in the absence of protein Gdf 5[10].

During skeletal development there is marked sexual dimorphism. In postnatal period, girls have advancement in skeletal maturation than boys though they have less bone mineral density. This pattern of sexual dimorphism is increased at puberty due to differential hormone secretion. Decreased bone mineral density has been observed in neonates born as a preterm

labor[11]. Neonatal bones are of critical importance because of their impact on bone development during childhood and in adult age. It has been observed that neonates born with higher birth weight acquire greater bone mineral density[12].

Skeletal framework of newly born babies closely resembles an adult but it is having 206 bones in comparison with adults whose skeleton is made up of 300 bones[13].

Radiological assessment of bones have been in practice in forensic science since 1896 for human age estimation[14].Radiographs of the specific parts of skeleton are used to assess the skeletal maturity[15].It is best done with hand-wrist radiography which is the easiest and most convenient method[16]. It is also helpful in evaluating the skeletal growth velocity, timing of pubertal growth and the proportion of the remaining growth of the bone. A significant difference has been observed in bone age of different population due to different ethnicity, socio-economic backgrounds, race and nutritional habits[17,18].

MATERIALS AND METHODS

The study comprised of 600 healthy subjects belonging to pukhtoon families in Forensic Department of Khyber Medical College (KMC) and Khyber Teaching Hospital (KTH).

The study sample was in the age group of 11-16 years and the subjects were grouped into 6 different sub Groups.

Hand-wrist radiographs were taken and gender based differences observed. Chronological age was determined from the date of birth of the subject.Bone age calculated by utilizing Greulich Pyle atlas and both genders were compared in relation to their chronological age.

RESULTS

A total number of 600 children were assessed for the skeletal age. Out of 600 children 333 were females and 267 were males. The chronological age was compared with the skeletal age in the age group of 11-16 years. Student "t" test was applied and the acquired data was analyzed. In the age group of 11 years, the mean chronological age determined was 11.35+_0.17 for males and 11.31+-0.13 for females. Meanwhile the skeletal age came out to be 12.14+_0.25 years for males and 12.27+_0.13 years for females. The difference between chronological age skeletal age was significant for males (p<_ 0.05) and females (p<_0.05) (Table 1). Same significance was observed in the subsequent age groups given in the tables below.

Table No.1: Comparison of Skeletal age with Chronological age in the age group of 11 Years.

Sex	Mean		"t" Value	Inference
	Chronological Age	Skeletal Age		
Male	11.35 ± 0.17	12.14 ± 0.25	1.99	Significant
Female	11.31 ± 0.13	12.27 ± 0.13	1.98	Significant
Combined	11.33 ± 0.15	12.20 ± 0.19	1.99	Significant

Confidence level of 95 % is statistically significant.

Table No.2: Comparison of Skeletal age with Chronological age in the age group of 13 years

Sex	Mean		"t" Value	Inference
	Chronological Age	Skeletal Age		
Male	13.29 ± 0.17	14.11 ± 0.12	1.99	Significant
Female	13.29 ± 0.15	14.27 ± 0.20	1.98	Significant
Combined	13.29 ± 0.16	14.19 ± 0.16	1.99	Significant

Confidence level of 95 % is statistically significant

Table No.3: Comparison of Skeletal age with Chronological age in the age group of 15 years.

Sex	Mean		"t" Value	Inference
	Chronological Age	Skeletal Age		
Male	15.24 ± 0.13	16.24 ± 0.10	1.99	Significant
Female	15.25 ± 0.12	16.27 ± 0.12	1.98	Significant
Combined	15.24 ± 0.12	16.25 ± 0.11	1.98	Significant

Confidence level of 95 % is statistically significant

Table No.4: Comparison of Mean Chronological age with Mean Skeletal Age.

Gender	Number	Mean Chronological Age	Mean Skeletal Age
Male	267	13.77 ± 0.15	14.64 ± 0.16
Female	333	13.79 ± 0.14	14.77 ± 0.16

DISCUSSION

As a matter of fact the somatic development is closely related to the chronological age. So if accurate age data is not available then somatic maturity indicators like the appearance of secondary sexual character, height and skeletal age can be used to assess the age[19].

The present study was conducted to assess the skeletal age by using Greulich_Pyle atlas of hand and wrist. Comparison between chronological and skeletal age was done. Moreover, gender based differences in age observed. It was noted that mean age difference between the chronological age and skeletal age come

out to be 0.87 years for males and 0.98 years for females.

This observation matches with the study done in Larkana, Pakistan by Rikashore where same increasing pattern of skeletal development was achieved in females as compared to their male counterpart[20]. In a series of studies done on white and Black races it was noticed that the blacks are ahead of the Greulich-Pyle standards[21]. Similarly the present study does not match accurately with the Greulich-Pyle digit atlas standards which is based on data derived from the study done on the children residing in Ohio,USA.

CONCLUSION

Skeletal development is more advanced in females as compared to the males as assessed by Greulich-Pyle method of bone age determination in Pukhtoons of Khyber Pukhtoonkhwa. There is marked sexual dimorphism seen in different races, therefore, it is suggested to check the applicability of Greulich-Pyle method by using a much larger sample and new standard curves should be generated specifically for each region of the country.

Author's Contribution:

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

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Original Article

WBC & Platelets Count in Malaria

Significance of White Blood Cell and Platelets Count in Malaria and their Correlation with various Morphological Forms of Plasmodia Species

Umair Ali Soomro, Shomail Saeed Siddiqui

ABSTRACT

Objective: To observe hematological variations in different types of malaria and severity of parasitemia caused by Plasmodium species.

Study Design: Cross sectional study.

Pace and Duration of Study: This study was conducted at the Department of Pathology, Isra University from January 2014 to June 2014.

Materials and Methods: The patients with clinical features suggestive of malaria and positive blood smear showing malarial parasite were included in the study. The blood for hematological parameters and thick and thin peripheral film preparation was collected in EDTA tubes. To observe the various morphological forms of plasmodium, peripheral blood films were stained with Leishman's stain. The WBC and platelet counts were determined using automated hematology analyser.

Results: Out of 96, Leukocytosis was noted in 16 (45%) and 35 (57.3%) of P. falciparum and P. vivax patients respectively. Thrombocytopenia was noted in 32 (91.4%) and 47 (77%) of P.falciparum and P.vivax patients respectively. Frequency of thrombocytopenia was more in P.falciparum patients compared to P. vivax. Ring forms and trophozoites in both P.falciparum and P.vivax were noted.

Conclusion: The present study revealed leukocytosis, leukopenia, leukocytic pigment and thrombocytopenia as the most common haematological findings among malaria patients.

Key Words: P. falciparum, P. vivax, Hematological changes, Peripheral blood smear.

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INTRODUCTION

Malaria is one of the oldest scourges of human kind. It is a vector borne protozoan disease of mankind. The anopheles mosquito is the vector and Plasmodium is the transmitted protozoa [1,2][29, 30]. Southeast Asia is over burdened with malaria with high incidence and prevalence in countries like Pakistan, Nepal, Sri Lanka, Indonesia, Bangladesh and India. According to a WHO estimate, the Pakistan lies in sub-tropical malarial zone according to incidence and prevalence. Geographical location, agricultural land, and monsoon rains contribute to malaria spread and persistence in Pakistan[3].

Malaria patients are present in the tropical countries throughout year. However, seasonal variations of malaria incidence are a rule. Malaria incidence is very high in autumn and spring [4].

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Blood abnormalities may occur in malaria due to disseminated intravascular coagulation (DIC) and thrombocytopenia[5]. Leukocyte counts may be low or normal in peripheral circulation. This occurs because of localization of white blood cells to peripheral organs like spleen and lymph nodes. Absolute reduction of leukocyte counts does never occur [6].

Severe and complicated malaria may be defined by one or more grave signs and/or symptoms like; Cerebral malaria, Hematocrit <15%, Hemoglobin <5 g/dl, Hypoglycemia (plasma glucose <40 mg/dL), Circulatory shock, Renal failure, Black water fever, Thrombocytopenia, Respiratory distress syndrome, DIC, Pulmonary edema, Jaundice and Peripheral blood smear positive for malaria [8]. Gold standard method of diagnosing malaria is through staining of thick and thin blood films and watching for malaria parasite by light microscopy [7].

It is reported that thrombocytopenia occurs in 80% of patients of malaria, infected with P. vivax or P. falciparum. Thrombocytopenia is caused by accelerated platelet destruction and underlying mechanisms remain to be elucidated [8]. The aim of the present study is to evaluate the white blood cell counts, platelete count with their correlation with different types of malaria and to visualize the species of plasmodia in malaria. Changes in these parameters may help in the

assessment of disease prognosis and prevention of its complication.

MATERIALS AND METHODS

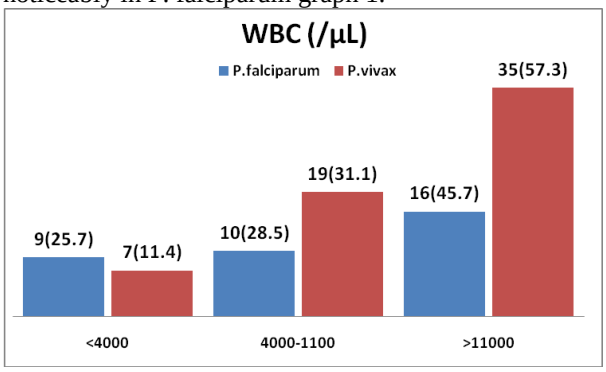
The present study was carried out at Pathology department, Isra University. The samples were collected from ER, Pediatric and general medicine ward Isra hospital Hyderabad. This cross sectional study was conducted during January 2014 to June 2014. The patients with clinical features suggestive of malaria having high grade fever and chills and positive blood smear showing malarial parasite were included in the study. The age range of the patients was between 05 to 59 years. Pregnant patients or patients who have already started anti malarial treatment and patients having typhoid, dengue and meningitis were not included in the study.

The blood for hematological parameters and thick and thin peripheral film preparation was collected in EDTA tubes. To observe the various morphological forms of plasmodium peripheral blood films were stained with Leishman's stain. The WBC and platelet counts were determined using automated hematology analyser.

Data was analyzed using SPSS version 21.0. The calculation of Mean ± SD for quantitative variables and frequency and percentages for categorical variables was done. The statistical significance between categorical groups was calculated by Chi square test. The P-value < 0.05 was considered as statistically significant.

RESULTS

A total of 96 blood samples from malaria patients were studied. Leukocytosis was noted in 16 (45.7%) and 35 (57.3%) of P. falciparum and P. vivax patients respectively. However, leucopenia was also observed noticeably in P. falciparum graph 1.



Graph No.1: White blood cell counts in P.falciparum & P.vivax patients

Thrombocytopenia was noted in 32 (91.4%) and 47 (77%) of P. falciparum and P. vivax patients respectively. Frequency of thrombocytopenia was more in P. falciparum patients compared to P. vivax as indicated by statistically significant p-value (p=0.0001) in table-1.

Table No.1: Platelet counts in study population (n=96)

Platelets (millions/µL)	P.falciparum (n=35)	P.vivax (n=61)	p-value
<0.5	22 (62.8%)	29 (47.5%)	0.0001
0.5- 1.0	8 (22.8%)	12 (19.6%)	
1.0- 1.5	2 (5.7%)	6 (9.8%)	
1.5-3.5	2 (5.7%)	9 (14.7%)	
>3.5	1(2.8%)	5 (8.1%)	

Chi square test applied.

Peripheral blood smear revealed ring forms and trophozoites in both P.falciparum and P.vivax. Typical headphone appearance of ring forms of P.falciparum is shown in figure-1. Banana shaped gametocytes of P. falciparum are shown in figure-2.

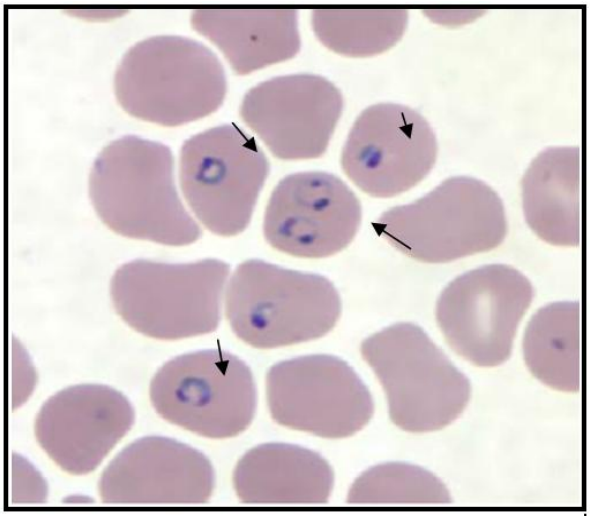


Figure No.1: Peripheral blood smear shwoing headphone appearance of P. falciparum within RBC (thin blood film)

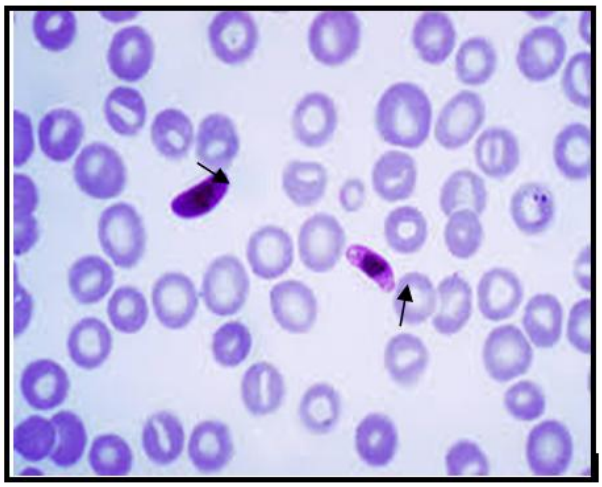


Figure No.2: Peripheral blood smear showing banana shaped gametocyte (thin blood film)

On peripheral film schizonts are also seen. Ring and trophozoites forms of P.vivax were seen and leukocyte pigments were an important finding observed in present study as shown in figure-3. The schistocytes, red blood

cell inclusions, anisocytosis and poikilocytosis with fragmented RBC were other findings observed in the present study.

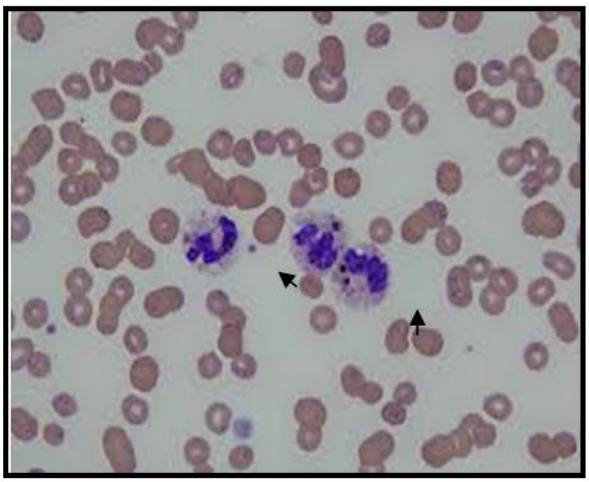


Figure No.3: Peripheral blood smear shwoing malaria pigment in polymorphs

DISCUSSION

The present study is an original research work on hematological changes in malaria conducted at Department of Pathology and Medicine, Isra University Hospital Hyderabad. Our tertiary care hospital caters thousands of patients from different areas of Sindh. Many studies have reported a wide variation of malaria frequency, clinical severity, blood changes and clinical outcome due to multiple factors, like mosquito breeding, sanitary and public health issues, natural immunity and genetic predisposition to develop complications. The malaria is taking lives of many people and these deaths are preventable if detected earlier with an effective treatment strategy.

In the present study leukocytosis was noted in 16 (45%) and 7 (11.4%) of P. falciparum and vivax patients respectively. Leucopenia was also observed noticeably in P.falciparum. Similar findings have been reported by previous studies [9-13].

Leukopenia is reported to be due to splenic sequestration of WBC, shifting to peripheral microcirculation and depletion in combating concurrent infections [9,11,13,14].

It has been reported that the leukocytosis may suggest concurrent viral infections particularly in lymphocytic leukocytosis [15]. Many recent studies also showed leukocytosis in the malaria patients. Adedapo et al (2007) has reported 9.5% frequency of leukocytosis in his study [16]. Leukocytosis has been implicated as a poor risk factor in malaria with poor outcome. A previous study had reported leukocytosis to be a poor prognostic factor in juvenile P. falciparum patients [17].

Thrombocytopenia was noted in 32 (91.4%) and 47 (77%) of P.falciparum and P.vivax patients respectively. Frequency of thrombocytopenia was more in P.falciparum patients compared to P. vivax. The findings are in agreement with previous studies [11,12,18,19]. Memon et al [20] has reported a frequency of 70% of thrombocytopenia in malaria. Malik et al [10] reported 70% of the study populations have had thrombocytopenia with a platelet count ≤150,000 per µL. Thrombocytopenia noted in present study is highly supporting the above mentioned studies.

In the study by NADEEM, *et al* [21] thrombocytopenia was observed in 83% of *P. falciparum* patients and in 70% of *P. vivax* patients, these findings are also consistent with present study. Many previous studies had reported similar results of thrombocytopenia in malaria [9,11,13]. A study from United Kingdom reported thrombocytopenia as of prognostic value in malaria patients [22].

Platelet activation is one of the recent mechanisms suggested to account for the thrombocytopenia in human malaria. It is also reported that the half life of malaria is shortened in peripheral circulation due to spleenic sequestration [23]. Loss of sialic acid, ADP dependent activation and oxidative stress are a few proposed underlying mechanisms of thrombocytopenia in malaria [9-11,24,25].

Peripheral blood smear showed ring forms and trophozoites in both P.falciparum and P.vivax. Typical headphone resembling ring forms of P.falciparum and crescent shaped (*Banana shaped)* gametocytes of P. falciparum are seen. Ring and trophozoites forms of P.vivax, schistocytes and red blood cell inclusions along with anisocytosis and poikilocytosis were noted with fragmented RBC.

Malaria pigment may serve as a peripheral indicator of parasite density and disease severity, since the pigment may be observed in monocytes and polymorphonuclear leukocytes (PMNs) under light microscopy. The presence of pigment has been strongly associated with severe disease rather than with uncomplicated cases of malaria. Pigmented neutrophils have been associated with cerebral malaria and deaths in children. Leukocyte pigments were an important finding observed in present study.

The findings of the present study suggest that creating interest of physicians will make patient management effective and mortality may then be reduced. Mortality if it occurs due to malaria in present era is shame for medical people.

CONCLUSION

The present study revealed leukocytosis, leukopenia, leukocytic pigment and thrombocytopenia as the most common haematological findings among malaria patients.

Author's Contribution:

Concept & Design of Study:	Umair Ali Soomro
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Insulin Induced Airway Hyper-Responsiveness

Attenuation of Insulin Induced Airway Hyper-Responsiveness with Anti-Inflammatory Drugs in Guinea Pig Airways

Mahjabeen Sharif[1], Bushra Tayyaba Khan[1] and Muhammad Asim Anwar[2]

ABSTRACT

Objective: Inhalational insulin was withdrawn from market because it enhances airway reactivity in human beings. So the present study was designed to observe the acute effects of insulin on airway reactivity of guinea pigs and to explore the inhibitory effects of sodium cromoglycate, beclomethasone and montelukast against insulin induced airway hyper-reactivity on isolated tracheal smooth muscle of guinea pig in vitro.

Study Design: The quasi experimental study.

Place and Duration of Study: This study was conducted at the Pharmacology Department, Army Medical College Rawalpindi from February 2012 to October 2012.

Materials and Methods: Effects of variable doses of insulin (10^{-7}- 10^{-3} M) and insulin pretreated with fixed dose of sodium cromoglycate (10^{-6} M), beclomethasone (10^{-6} M) and montelukast (10^{-5} M) were studied on isolated tracheal tissue of guinea pig by constructing cumulative dose response curves. Transducer and Four Channel Oscillograph were used to record the changes in resting tension of guinea pig airways.

Results: Beclomethasone attenuated the contractile response of insulin greater than sodium cromoglycate and montelukast.

Conclusions: Beclomethasone was more efficacious than sodium cromoglycate and montelukast in amelioration of insulin induced tracheal tissue contraction. So we infer that pretreatment of inhaled insulin with beclomethasone may be preferred over sodium cromoglycate and montelukast in reducing its airway hyper-responsiveness.

Key Words: Inhaled insulin, beclomethasone, sodium cromoglycate, montelukast, oscillograph.

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INTRODUCTION

Subcutaneous insulin is the mainstay for controlling blood glucose in diabetes.[1] Inhalational insulin had been available in market for diabetic patients who defer to take subcutaneous insulin due to needle phobia.[2] Studies have shown that use of inhalational insulin tends to normalize the blood glucose level[3] It significantly decreased HbA_{1c} and caused far less hypoglycemia and less tendency for weight gain.[4] But inhaled insulin was banned due to its high cost and increased bronchial hyper-reactivity, cough, and dyspnea.[5] The proposed mechanism of insulin airway hyper-reactivity is that insulin stimulates the release of histamine from mast cells which enhances airway hyper-responsiveness.[6,7]

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Cromoglycate sodium has been used for prevention of asthma, exerts anti-inflammatory effects in respiratory tract.[8] Recently montelukast has also been reported to possess anti-inflammatory and weak bronchodilatory properties in guinea pig and rat models of asthma. [9,10] Experimental and clinical evidences have also shown that beclomethasone prevents the allergen induced bronchial hyper-reactivity as it prevents the contractile prostaglandins and histamine release from mast cells.[11,12] Keeping in view these pharmacological effects of sodium cromoglycate, beclomethasone and montelukast, the current experimental study was designed to explore and compare the effects of these drugs to attenuate insulin induced airway hyper-reactivity in guinea pigs.

MATERIALS AND METHODS

The current study was carried out in the Department of Pharmacology Army Medical College Rawalpindi, from February 2012 to October 2012.

Twenty four guinea pigs were included in the study through non-probabilty convenient sampling and were divided into four groups. Each group has six animals. The Institutional Animal Ethics Commitee approved the study. The guinea pigs were sacrificed. The trachea was dissected out. Four to five tracheal chains were made from one trachea of guinea pig.[13,14] Tracheal strip was

connected to oxygen tube of tissue bath having krebs-Henseleit solution at 37° C and Research Grade Isometric Force Displacement Transducer Harvard Model No 72-4494 (England). Changes in the contractions of tracheal muscles were recorded on Four Channel Oscillograph Harvard Model No 50-9307.[15]

Experimental groups: In group 1, cumulative dose response curves of insulin were obtained by using the doses ranging from of 10^{-7} to 10^{-3}M.[16] When the plateau was obtained with first dose (10^{-7}M) of insulin, then the next dose (10^{-6} M) was poured without washing the previous dose. Oscillograph was used to record the changes in contractions of tracheal muscles. Maximum insulin induced contraction was obtained with 10^{-3}M dose of insulin. This group served as control group. In group 2, 10^{-6} M sodium cromoglycate was poured on the tracheal tissue.[17] After 15 minutes, the successive doses of insulin ranging from 10^{-7} to 10^{-3} M were added into the organ bath in the presence of sodium cromoglycate. Cumulative dose response curves pretreated with sodium cromoglycate were constructed. In group 3 and 4 cumulative dose response curves of insulin pretreated with fixed dose (10^{-6} M) of beclomethasone[18] and montelukast (10^{-5} M) were constructed by using the same procedure as described for group 1.[19]

Statistical Analysis: One way ANOVA followed by Post Hoc Tuckey Test using SPSS version 16 was used to find differences between amplitudes of contractions of four experimental groups. *p* value of less than 0.05 was taken significant.

RESULTS

Insulin significantly enhanced the contraction of tracheal smooth muscle (Figure 1). Changes in tracheal smooth muscle contractions were measured by taking the amplitude of contraction. Maximum response with 10^{-3} M dose of insulin was 35 ± 1.13mm. So insulin directly increased the tone of tracheal muscle. Amplitude of contractions obtained with insulin pretreated with cromoglycate sodium, beclomethasone and montelukast were 27.8 ± 1.27 mm, 22 ± 1.154 mm and 34.5 ± 1.024 mm respectively. There was statistically significant difference in constrictor response of insulin between group 1, 2 & 3, while difference between the amplitude of contraction between group 1 and 4 was insignificant (Table 1).

The percentage responses for all the four groups were also calculated. Maximum contraction of insulin treated with sodium cromoglycate and beclomethasone was attenuated by 79.42 and 62.86 percent respectively as compared with control group (Table 2). The mean percent response in the presence of montelukast remained 98.57 percent of control group (Table 2).

Although beclomethasone and cromoglycate sodium both significantly ameliorated insulin induced airway hyper-reactivity yet beclomethasone is more efficacious than sodium cromoglycate (Figure 1), while montelukast failed to counteract insulin induced smooth muscle contraction (Table 1).

Table No.1: Comparisons of means of amplitudes of contractions of isolated tracheal smooth muscle of guinea pig to insulin control (group 1), with insulin pretreated with cromoglycate sodium (group 2), beclomethasone (group 3) and montelukast (group 4)

Concentration of insulin (M)	Amplitude of contraction with insulin (n=6) (Mean ± S.E.M) (mm)	Amplitude of contraction with insulin pretreated with Sodium cromoglycate (n=6) (Mean±S.E.M)(mm)	Amplitude of contraction with insulin pretreated with beclomethasone (n=6) (Mean± S.E.M) (mm)	Amplitude of contraction with insulin pretreated with montelukast (n=6) (Mean± S.E.M) (mm)
10^{-7}	8.167 ± 0.87	2 ± 0.73	0 ± 0	7.83±0.746
10^{-6}	16.16 ± 1.01	9.83 ± 1.33	5.167 ± 0.83	16±1.045
10^{-5}	26.1 ± 1.13	17.66 ± 0.76	12.33 ± 1.08	26±1.065
10^{-4}	31.8 ± 0.832	24.16 ± 1.72	18.17 ± 1.045	30.8±1.04
10^{-3}	35 ± 1.13	27.8 ± 1.27	22 ± 1.154	34.5±1.024
p-value	0.000*	0.000*	0.000*	0.99#

P value < 0.05 = Significant (*) *P* value>0.05= insignificant (#)

Table No.2: Percent responses of isolated tracheal muscle of guinea pig to insulin (group 1), insulin pretreated with cromoglycate sodium (group 2), beclomethasone (group 3) and montelukast (group 4)

Concentration of insulin (M)	Percent response with insulin	Percent response with insulin pretreated with sodium cromoglycate	Percent response with insulin pretreated with beclomethasone	Percent response with insulin pretreated with montelukast
10^{-7}	23.34	5.71	0	22.37
10^{-6}	46.17	28.09	14.77	45.71
10^{-5}	74.58	50.46	35.23	74.29
10^{-4}	90.86	69.02	51.91	88
10^{-3}	100	79.42	62.86	98.57

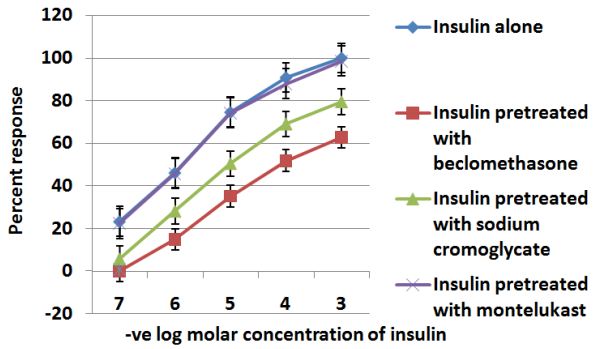

Figure No.1: Comparison of concentration response curve of group 1 with group 2, 3 and 4.

DISCUSSION

The current study was conducted to evaluate the inhibitory effects of cromoglycate sodium, beclomethasone and montelukast against insulin induced tracheal tissue contraction. Insulin reversibly enhanced the airway reactivity of guinea pigs. Our findings were consistent with a study in which isolated tracheal tissue of diabetic rat when pretreated with insulin, airway hyper-responsiveness was aggravated due to increase release of contractile prostaglandins on isolated tracheal smooth muscle of rat.[20] In group 2, cromoglycate sodium significantly reduced the insulin mediated airway smooth muscle contraction. Inhibition of mast cell degranulation and prevention of release of inflammatory mediators by cromoglycate sodium probably contribute to its beneficial effects.[21] These findings were consistent with clinical studies in which cromoglycate sodium significantly attenuated the contractile response to several kinds of allergens.[22] Beclomethasone also significantly inhibited the insulin induced tracheal smooth muscle contraction. Since insulin is a pro-inflammatory and pro-contractile hormone, potential protective effects of beclomethasone may be due to its anti-inflammatory effects and its ability to prevent the release of prostaglandins and histamine, which ameliorated airway hyper-responsiveness mediated by insulin. [23,24] In fourth group, montelukast did not significantly reduce insulin induced airway hyper-reactivity. The dose response curve of beclomethasone was compared to the curve of cromoglycate sodium and montelukast, it was concluded that beclomethasone attenuated the effects of insulin but greater than that of cromoglycate sodium and montelukast. So beclomethasone is more efficacious than cromoglycate sodium and montelukast in inhibiting the contractile response of insulin.

CONCLUSION

Insulin reversibly enhanced guinea pigs airway smooth muscle contraction. Beclomethasone was more efficacious than cromoglycate sodium and montelukast in reducing insulin induced tracheal tissue contraction. So we suggest that diabetic patients taking inhalational insulin may be pretreated with inhaled beclomethasone rather than cromoglycate sodium or montelukast to attenuate its respiratory adverse effects.

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Author's Contribution:

Concept & Design of Study:	Mahjabeen Sharif
Drafting:	Bushra Tayyaba Khan
Data Analysis:	Muhammad Asim Anwar
Revisiting Critically:	Bushra Tayyaba Khan, Muhammad Asim Anwar
Final Approval of version:	Mahjabeen Sharif

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

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Original Article

Hepatotoxicity with Low Dose Methotrexate in Rheumatoid Arthritis Patients

Muhammad Abbas, Sajjad Ali and Amir Khan

ABSTRACT

Objective: To find out the frequency of Methotrexate induced hepatotoxicity in rheumatoid arthritis patients treated for six months with low dose, 7.5 mg of Methotrexate once weekly.

Study Design: Descriptive / cross sectional study.

Place and Duration of Study: This study was conducted at the Medical Units of Mardan Medical Complex, Mardan from January 2015 to December 2016.

Materials and Methods: Study included 186 diagnosed adult patients of rheumatoid arthritis. They were treated with 7.5 mg Methotrexate per week and were followed up for 6 months with regularly monthly Liver function test (L.F.T's).

Results: Out of 186 diagnosed cases of RA, 39 (24.3%) were males and 147 (75.7%) were females. Age range was from 21years to 68 years with mean age of 38.06 years. Mean Alt was 45.34, mean billirubin was 0.93, mean Alkaline phosphatase was 23.90, mean hemoglobin was 12.63 while mean weight was 67.79 kg. Serum A.L.T was raised in 17 (9.1%) patients while it was normal in 169 (90.9%) patients. Hepatotoxicity was defined as serum A.L.T of more than two times of upper limit of reference range.

Conclusion: Hepatotoxicity is a common side effect of methotrexate therapy and regular monitoring with serum alanine transaminase of these patients is required for early recognition and treatment.

Key Words: Methoraxate. Hepatotoxicity. rheumatoid Arthritis (RA)

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INTRODUCTION

Rheumatoid arthritis is a chronic systemic autoimmune disorder characterized by a chronic polyarticular synovitis due to increase release of cytokines that may cause irreversible joint damage and may lead to deformities. Methotrexate is commonly used in weekly doses for rheumatoid arthritis, because of its effectiveness, low toxicity and cost[1]. It acts by increasing the adenosine concentration and reducing the cytokines thus decreasing the inflammation. 7-10 hrs is the plasma half life of Methotrexate, it is metabolized mainly by the liver and excreted by kidneys[2].

Hepatic folate stores are depleted by Methotrexate in doses used for rheumatoid arthritis and they can be replenished by short term administration of oral folinic acid[3]. Supplementation of oral folic acid in doses of 1 mg/day or 2.5 mg of folinic acid/week is associated with reduced incidence of hepatotoxicity[4,5]. The abnormal liver enzymes resolves within a month of decreasing the dose or stopping the drug[1].

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The raised liver enzymes above two times upper limit reference range (ULR) has been found in 13%, 3.7% of patients were forced to stop it permanently, while incidence of fibrosis after four years administration of MTX was 2.7%[6,7,8]. Hepatotoxic effects of MTX can be increased by certain risk factors such as age, duration of exposure to Methotrexate, history of NASH, diabetes mellitus, obesity, HBV or HCV infection, alcohol consumption, and hepatotoxic drugs[9,10].

In Pakistan Methotrexate is still the corner stone of therapy in patients with rheumatoid arthritis. It is very effective in arresting the disease process and preventing the joint damage but may be associated with certain undesirable side effects including hepatotoxicity, Which may disturb the quality of life by putting an extra physical and financial burden on these patients. Therefore this study is aimed at to know the exact prevalence of hepatoxicity and some important risk factors in these patients which may help in early recognition and treatment of this problem and thus further improving the management of the rheumatoid arthritis patients.

MATERIALS AND METHODS

This was a descriptive study carried out on 186 diagnosed cases of RA at the medical unit of Mardan medical complex (MMC) from January 2015 to December 2016. ACR/EULAR 2010 criteria was used for diagnosing rheumatoid arthritis[11]. The Objective of study was to find out the frequency of Methotrexate

induced hepatotoxicity in rheumatoid arthritis patients treated for six months with low dose, 7.5 mg of Methotrexate once weekly. Approval for the study was obtained from the ethical and research committee of the hospital. These patients were selected by non-probability convenient sampling method after an informed verbal consent. Adult Patients irrespective of gender were enrolled in the study. Detailed history of illness, physical examination and routine base line investigations were carried out at start of study. These patients were treated with 7.5 mg of MTX once weekly and were followed up for six months with monthly liver function test (L.F.T's). Patients with known liver disease, renal insufficiency, leucopenia, and thrombocytopenia, were excluded. As majority of rheumatoid arthritis patients were female of child bearing age and most of them were anaemic but despite of this limitation only females with mild anaemia were included and patients with moderate to severe anaemia were excluded (Hb less than 10.50 gm/l) Similarly patients with concomitant illness like DM,HTN,IHD were also excluded. However patients already taking other disease modifying anti-rheumatic drugs with normal ALT were included. Hepatotoxicity was defined as serum ALT of more than two times upper limit of reference range (ULR)[7,12,13].

RESULTS

A total of 186 rheumatoid patients comprising of 39 males(24.3%) and 147 females(75.7%), ranging from 21years to 68 years with mean age of 38.06 years participated in the study. Age of male rheumatoid patient ranges between 22 years to 68 years with a mean age of 44.07 while of female rheumatoid patient age ranges between 21 years to 65 years with a mean age of 36.47 years (Table 1).

Variables included were serum billirubin, serum Alt, serum Alkaline phosphatase, hemoglobin and weight of patient. Mean values along with standard deviations of Alt, serum billirubin, Alkaline phosphatase, hemoglobin and body weight are given in Table 2.

Table No. 1 : Age and gender of patients

Gender	No of patients	% of Total Sum	Minimum age	Maximum age	Mean age	Std. Deviation
Male	39	24.3%	22.00	68.00	44.0769	12.22247
Female	147	75.7%	21.00	65.00	36.4762	8.71727
Total	186	100.0%	21.00	68.00	38.0699	10.01407

Table No. 2: Different Variables

Variables	Alanine Tranaminase	Hemoglobin	Weight Of Patient	Serum Billirubin	Alk Phosp
Mean	45.3441	12.6339	67.7903	.9310	233.9086
Std. Deviation	25.29779	.85398	20.82317	.17027	18.80504
Minimum	12.00	10.50	42.00	.20	200.00
Maximum	156.00	14.80	145.00	1.20	270.00

Table No. 3: Different parameters in hepatitis / non hepatitis groups

Different parameters in hepatitis / non hepatitis groups		No. of patients	Mean	Std. Deviation	P value
Age of patient	Hepatotoxicity	17	37.3529	9.61081	0.758
	Non Hepatitis	169	38.1420	10.07844	
Hemoglobin	Hepatotoxicity	17	11.3000	.47958	0.00
	Non Hepatitis	169	12.7680	.76356	
Weight of patient	Hepatotoxicity	17	70.8235	20.99772	0.530
	Non Hepatitis	169	67.4852	20.84384	
Serum billirubin	Hepatotoxicity	17	.9753	.12228	0.262
	Non Hepatitis	169	.9266	.17402	
Alkaline phosphatase	Hepatotoxicity	17	239.7059	15.65952	0.183
	Non Hepatitis	169	233.3254	19.03460	

Serum Alt was raised (2 times upper limit of normal) in 17 patients (9.1%) while it was within normal range in 169 patients (90.9%)

Min range of serum Alt in hepatotoxic group was 90 and max was 156 with median value of 110 having std Deviation of 23.99280.In non hepatotoxic group min range of Alt was 12 and max was 61 with median value of 40.00 having std Deviation of 10.33508.

20 patients in study were smokers in which only 2 patients showed hepatotoxicity while in remaining 18 smoker patient serum Alt was found to be within normal range. The association of smoking with hepatotoxicity was not statistically significant (p value

> 0.05).Total 39 male rheumatoid patients were included in study only 4 showed hepatotoxicity while remaining 35 comes to be under non hepatitis group. Female patients in study were 147 and 13 patients were found to be hepatotoxic and 134 rheumatoid patients were within non hepatitis group. The association of gender with hepatotoxicity was not statistically significant (p value > 0.05).

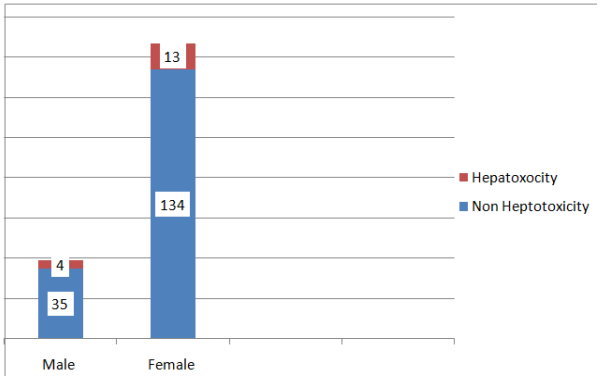

Figure No.1: Association of hepatotoxicity with gender of patient (P value : 0.785)

DISCUSSION

Among the disease modifying anti rheumatic drugs (DMARD's) Methotrexate is most commonly used and usually considered to be the first line of drug for treating rheumatoid arthtritis. Methotrexate is a well recognized cause of hepatic enzyme elevation. In our study hepatotoxicity was found in 17 patients (9.1%). A study from Rawalpindi by gilani et al has reported similar frequency of hepatotoxicity in these patients[14]. Another study conducted by R Sotoudehmanesh, B Anvari, showed hepatic enzyme elevation with methotrexate at the rate of 23.7% and this was directly related to duration of treatment.[15] In comparison with our study proportion of hepatotoxicity was lower and this difference may be explained by the greater duration of treatment with methotrexate in the study conducted by R Sotoudehmanesh, B anvari, etal. Other studies has reported that chronic low to moderate dose of MTX can cause hepatic enzyme elevation in 15 % to 50 % of cases[16,17] which is usually reversible on stopping the drug or reducing its dose[4,18]. Moreover, folate supplementation markedly diminishes liver toxicity.[4,5] Therefore, it is advisable to regularly monitor liver enzymes during MTX therapy in RA patients.

We also analyzed and compared different parameter in these patients, among these we found that serum ALT elevation was found in young as well as old patients and age was not a significant risk factor for developing hepatoxicity. In support of our results, Similar finding was noted by another local study from Pakistan.[14] Similarly no significant association was found between gender, smoking and weight with hepatotoxicity in these patients. However our study showed that hepatotoxicity was more common in anaemic patients and this association of hepatotoxicity with hemoglobin level was statiscally significant with p-value < 0.05. This means that patients who developed hepatotoxicity were also anemic. To our knowledge most female patients of child bearing age in our society are usually anemic. Moreover our study population consisted mostly of female patients. Therefore this could be either an incidental finding or may be the effect of MTX on hemoglobin level. We do not know that exact mechanism of this finding and need further work up.

The main limitation in our study was the simultaneous use of other DMARD's besides MTX to our patients which could not be controlled. Although we included only those patients who were having normal baseline liver function tests to reduce this bias. Induction of liver enzymes due to hydroxychloroquine or prednisolone are extremely rare and have been reported only in isolated cases[19,20,]. Also Sulphasalazine induced liver toxicity is relatively low (1 per 1000 cases)[21]. So contributing role of other DMARD's induced hepatotoxicity is minimum in our patients but can't be over ruled. In our study only those patients were included whose disease was limited to joints and there was no involvement of other systems. So we can assume that hepatic enzyme elevation in our patients was mainly due to methotrexate and not because of Rheumatoid disease itself. Furthermore most of our patients were female of child bearing age and they are usually anaemic and hepatic enzyme elevation in such patients was more evident as compared to patients with normal Hb level.

CONCLUSION

In conclusion treatment of rheumatoid arthritis patients with methotrexate is commonly associated with mild to moderate hepatic enzyme elevation and therefore we recommend regular monitoring of these patients with serum ALT.

Author's Contribution:

Concept & Design of Study:	Dr. Muhammad Abbas
Drafting:	Dr. Muhammad Abbas
Data Analysis:	Dr. Sajjad Ali
Revisiting Critically:	Prof. Amir Khan
Final Approval of version:	Prof . Amir Khan

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

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Original Article

Outcome of Total Knee Arthroplasty with Insall Burstein-II Prosthesis

Knee Arthroplasty with IB-II Prosthesis

Muhammad Zahid Siddiq[1], Syed Wasif Ali Shah[2] and Muhammad Nauman Akhter[1]

ABSTRACT

Objective: Evaluate the functional outcome of total knees arthroplasty with IB II prosthesis and evaluate the alignment of prosthetic components by radiological parameters and its conflation with functional outcome.
Study Design: Descriptive / case series study
Place and Duration of Study: This study was conducted at the Orthopaedic Surgery at Shaikh Zayed Hospital, Lahore from 1st September 2006 to 31st August 2009.
Subject and Methods: Sixty knees of sixty patients were replaced by using Insall Burstein II prosthesis postoperative radiographs were evaluate for alignment of knee and prosthesis components by criteria selected from knee society Roentogenographic evaluation system. Functional outcome from evaluated by rationale of knee society knee rating system.
Results: Prosthesis component was aligned in 93% and mail-alignment in 7% of the cases. There was significant improvements in function score 33.8±315.5 to 59.5±17.7 and knee score from 3±712.5 to 76.4±2.2. Postoperative functional score was found correlated with alignment significantly.
Conclusion: Total knee arthroplasty with 1-B-II prosthesis is safe durable and predictable procedure with proper surgical technique and expertise good alignment and satisfactory functional outcome can be achieved.
Key Words: Total Knee Arthroplasty, Osteoarthritis, Rheumatoid Arthritis

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INTRODUCTION

Knee pain is the common presenting complaint in the middle age and elderly patients, interfering the activities of daily living. Pain free and mobile knee joint is essential for good quality of life.[1-3]
Knee osteoarthritis is common cause of severe pain and functional limitations, affecting approximately 6% of Adult population; this percentage is increased in people who are more than fifty-five years old.[4,5]
Rheumatoid arthritis is another disabling disease affecting the knee joint along with other joints involvement. Females are effected more commonly than males, in a ratio of 2.5:1.
The primary management of the knee pain is with analgesics, change of life style, physiotherapy, intra articular steroids or hyaluronic acid injections. However after failure of this conservative management, options left for treatment includes Arthroscopic joint lavage and debridement open debridement, high tibial osteotomy for medical or lateral uni-compartmental osteoarthritis, hemi or total knee arthroplasty.
The posterior stabilized condylar knee (Insall Burstein –II) is an improvement of the total condylar design evolved in 1987. It was designed to provide posterior circuital ligament substitution by means of a central post in tibial component, which articulates against a transverse cam on the femoral component. It was designed specifically to improve range of motion, stair climbing ability and to prevent posterior subluxation.[6-9]
This prosthesis has excellent knee score and pain free range of motion up to 120 degree with stability.[10,11]
Also demonstrated excellent survivorship of the prosthesis 96% over 10 years.[12,13]
Alignment refers to the relationship of each prosthetic component to the relevant bone, as well as over all alignment of the limb. Incorrect alignment can lead to decrease functional score, abnormal wear, premature loosening and need for revision.[14,15]

MATERIALS AND METHODS

This study was conducted at the Orthopaedic Surgery at Shaikh Zayed Hospital, Lahore from 1st September 2006 to 31st August 2009. Sixty cases of total knee replacement with IB II prosthesis were selected on convenient basis. All patients were operated by single surgeon. Follow up was done at two weeks for examination of wound and after one month, three month, six month and one year for the complete examination of the patient to evaluate the functional

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status of the patient and status of knee. All patients who were lost from follow up were excluded from study.

Postoperative radiographs were evaluated for alignment of prosthetic components and overall alignment of the knee by using criteria (tibio-femoral angle on anterio-posterior view, femoral flexion and tibial angle on both anterio-posterior and lateral views) selected from Knee Society Roentgenographic evaluation and scoring system.

After the mean follow up of 1 year range from 6 month to 2 years, results were assessed by the Rationale of the knee society clinical rating system. Final rating of the results was compiled as excellent (score 85-100), good (70-84), fair (55-69) and poor (p<55).

RESULTS

During this study 60 knees of 60 patients were replaced by using Insall BursteinII prosthesis. Mean age of the patients was (60.4±6.12) years, range of 46-75 years. Male to female ratio 1:2, males were 33.7% and females 67.3%. Patients of the primary osteoarthritis were 90% and rheumatoid arthritis were 10%.

Evaluation of the preoperative radiographs revealed mean tibio-femoral angle of (6.7±3.9) degrees varus range from 0-12 degree. On the evaluation of postoperative antero-posterior radiographs the mean tibio-femoral angle was (5.0±0.53) degree range from 4-6 degrees. Mean femoral flexion angle was (96±1.88) degrees range from 94-102. Mean tibial angle (89±1.72) degrees with range from 84-92.

On lateral radiographs Mean femoral flexion angle was (10.83±1.49) degree range from 10-16 degree. Mean tibial angle (89.9±1.24) degrees with range from 85-92. No tibio-femoral mal-alignment was found. Alignment of the prosthetic component was accurate in 56 total knee arthroplasties (94%) and in 4 arthroplasties (6%), prosthetic components were not found properly aligned.

Pain in the knee joints was significantly relieved (P<0.05) and pain score was improved from mean preoperative 14.3 to 39.5 postoperatively, 80% patients had no pain or mild pain on stair climbing, 17% had mild pain on walking, 3% had continuous moderate pain in the knee postoperatively. Range of motion was also significantly improved from (Mean 85±1.7) range 75-100 degree preoperatively to (Mean 104±1.9) range 85-120 degree after total knee replacement.

Preoperative flexion contractures of the knee joint was also improved from knee (4.5±6.06) degree to (2.0±0.45) degree after total knee arthroplasty. Knee score was also significantly improved (p<0.05) from mean preoperative (36.63±12.5) to (76.4±2.2) postoperatively. Postoperative knee score was excellent in 30%, good in 47%, fair in 20%, poor in 3% of the cases.

Functional score of the patients improved significantly (p<0.05) from the mean score of (33.83±15.52) to (59.53±17.7) range 15-80 score postoperatively. Postoperative functional score was excellent in 0%, good in 40%, fair in 37%, poor in 23%.

There was no joint instability in any case. Medio-lateral laxity was less than 5 degree in 90% cases, 6-9 degree in 10% of the cases. There was no wound infection or delayed wound healing. No clinical finding of deep vein thrombosis, pulmonary embolism or fat embolism was observed in any case.

During follow up one patient was diagnosed as post-operative patellar subluxation and three patients reported moderate retro-patellar pain. The prosthetic components were found mal-aligned on the radiographs of three patients.

Patients with already replaced other knee had better function score and knee score as compared to patients having knee symptomatic (p<05). Both postoperative knee score and functional score was also correlated with preoperative knee score and functional score.

Table No.1: Correlation of alignment of prosthetic components and postoperative function score

Functional score	Mal-alignment (n=4)	Alignment (n=56)
Excellent	-	-
Good	-	24 (43%)
Fair	-	22 (39%)
Poor	4 (100%)	10 (18%)

Table No.2: Correlation of condition of other limb and postoperative function score

Functional score	Mal-alignment (n=4)	Alignment (n=56)
Excellent	-	-
Good	-	24 (43%)
Fair	-	22 (39%)
Poor	4 (100%)	10 (18%)

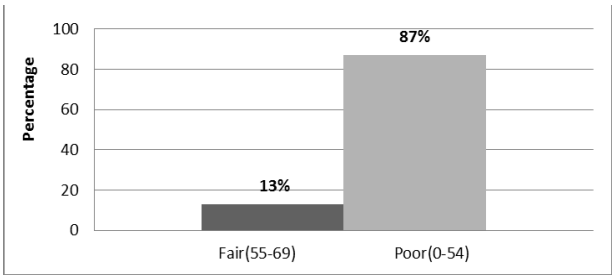

Figure No.1: Preoperative function score

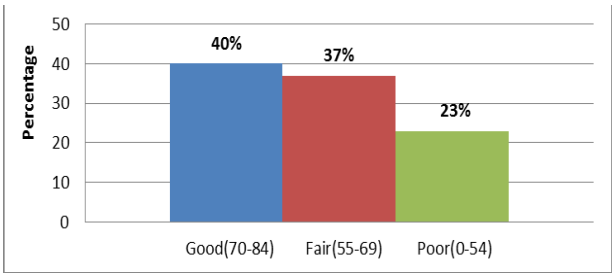

Figure No.2: Postoperative function score

Correlation of the knee score and functional score with alignment of prosthetic components was also noted significantly (Chi-square test revealed P<05). Both the patients in which prosthetic components was not aligned had poor knee score and function score.

DISCUSSION

Total knee arthroplasty is now the accepted management for the patients with severe degenerative joint disease to relieve pain, improve stability and restore function.[1]

Pain relief is the single most important determinant for long term outcome after total knee arthroplasty following by deformity.[16] Pain after knee replacement resolves quickly. Significant pain after six months of total knee replacement (TKR) may be indicative of abnormal pain.[17]

In the present study all patients had the significant improvement in the severity of pain and 97% had no pain or mild pain during walking and climbing stairs. Continuous moderate pain was recorded in only 3% of the patients.

Range of motion after knee arthroplasty is an important variable in determining clinical outcome. Motion beyond 90 degree of flexion is beneficial for many activities like walking and going up-stairs, 103 degree of flexion is required for rising out of chair.[18]

Insall et al reported on the posterior stabilized total condylar prosthesis that range of motion improved from a mean of 95 degree preoperatively to 115 degree postoperatively. There was great controversy in literature and high degree of disagreements among different authors on whether the cruciate sacrificing or a cruciate retaining knee replacement give better improvement in postoperative range of motion, as the clinical results using various designs have been essentially the same.[9,17] This controversy is been resolved with the development of posterior cruciate stabilizing prosthesis "The Insall posterior stabilized prosthesis". This design is intended to increase the motion of the knee and provide additional stability. Range of motion was increased to an average of 107 degree with this design as compared to average range of motion 90 degree in their previous series in which total condylar prosthesis was used. However, preoperative range of motion has been found to affect the amount of motion that is regained after any type of knee replacement .In our study range of motion was 105 degree.[17]

Correct positioning of the components and adequate soft tissue balancing are critical steps in successful knee arthroplasty. Optional alignment of the prosthetic component is fundamental to the knee achievement of the long term survival of total knee arthroplasty. Incorrect alignment can lead to decrease survival and patellofemoral problems. There is little margin of error.[14,15] Relation of radiological parameters of the alignment with clinical outcome of TKA is controversial.

In our study correlation of the knee score and functional score with alignment of prosthetic components was noted significantly. Alignment of the components and overall alignment of the knee mainly effect the long term survival of the total knee arthroplasties. Our study period was too short to comment on the survival of the total knee arthroplasties for which a study is required with long term follow up.

Several studies using conventional intramedullary and extra-medullary rods reported 10-20% failure to achieve ideal positioning of the components. Many studies suggested that computer assisted arthroplasties have improved alignment and have low complications rate and less surgical exposure.[19,20]

In our study alignment of the prosthesis was accurate in 93% of the cases and all the angles are consistent with these studies. The knee score increased significantly and stayed on a constant level from 2 years on, whereas function score reached a maximum at 2 years and declined subsequently. The functional score is influenced significantly by the walking distance, age, body mass index and patient category correlating moderately. The knee score is not affected by any of the factors.[21]

Insall et al reported in his study 88% excellent, 9% good or fair and 3% poor results TKA using IB-II prosthesis. Knee score increased from 50 point preoperatively to 90 points postoperatively.[9] Shah and Pervaiz also reported good to excellent scores in 90% of the patients and mal-alignment in 10% of the total knee arthroplasties with Insall Burstein IB-II prosthesis. Results of our study are consistent with these studies 77% patients had good to excellent prosthesis and 20% fair knee score. Function score was good in 40% and fair in 37%.

Patients with other knee already replaced had good functional outcome as compared to the patients with knee not replaced and symptomatic. In our study the improvement in knee score was (77% good to excellent postoperative) was much more than improvement in function score (40% good postoperative). The reason of less improvement in function score was half of the patients had other knee symptomatic which compromised the patient ability to walk and climb stairs. Other reasons were short-term follow up, poor compliance of the patients for physiotherapy and psychological apprehension to the new joint. Even then most of the patients were able to perform their daily activities with little modification because of increased pain free range of motion.

CONCLUSION

Total condylar knee arthroplasty with Insall Burstein II prosthesis is a safe, durable and predictable procedure. With proper surgical technique and expertise, it is

possible to restore the mechanical axis of knee with stability and 100 degree or more pain free range of motion. Satisfactory functional outcome can be achieved by using IB-II prosthesis.

Author's Contribution:

Concept & Design of Study:	Muhammad Zahid Siddiq
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Data Analysis:	Muhammad Nauman Akhter
Revisiting Critically:	Syed Wasif Ali Shah, Muhammad Zahid Siddiq
Final Approval of version:	Muhammad Zahid Siddiq

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

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Original Article

Effect of Diclofenac Sodium and Thiocolchicoside in Low Back Pain

Comparative Efficacy of Diclofenac Sodium Alone and in Combination with Thiocolchicoside in Patients with Low Back Pain

Nauman Akhter and Muhammad Zahid Siddiq

ABSTRACT

Objective: This study was conducted to determine that combination of a Diclofenac sodium (NSAID) and thiocolchicoside is more effective than Diclofenac Sodium alone or not.

Study Design: Observational / prospective study

Place and Duration of Study: This study was conducted at the Orthopedics Out-Patient Department, Aziz Bhatti Shaheed Hospital, Gujrat from August 2016 to August 2017.

Materials and Methods: Adult patients with acute and sub-acute low back pain was recruited for study and was randomized in group A and group B. A sample of 288 patients, 144 patients in each treatment group was collected by purposive sampling technique.

Results: Group A received Diclofenac sodium 75mg two times a day for 7 days and group B received Diclofenac sodium 75mg twice daily plus Thiocolchicoside 4mg twice daily for 7 days. On the day 0 then on the day 3 and day 7, the patients were evaluated for low back pain with a visual analogue scale (VAS) and second outcome measured was hand to floor distance. Descriptive techniques with mean, standard error of mean and graphs were used whereas for inferential statistics, repeated measure ANOVA was used to compare results of day 0, day 3 and day 7. The mean VAS and head to floor distance was equivalent at inclusion. At day 7 pain scores and hand to foot distance was decreased in both groups compared to on day 0 at inclusion. But patients group B receiving combination therapy of NSAID and Thiocolchicoside had significantly less pain and head to floor distance (disability) than group A.

Conclusion: Combination of thiocolchicoside and Diclofenac sodium was proved to be more effective than Diclofenac sodium alone for the symptomatic treatment of low back pain, and the combinations was also well tolerated.

Key Words: Diclofenac Sodium, Thiocolchicoside, Muscle Relaxant, Low Back Pain

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INTRODUCTION

Low back pain is one of the most common health problem with a prevalence of 8% to 37%.[1] This prevalence increases between age of 45-60 years. It is a common reason for absenteeism fro job also responsible of huge national health expenditure. Recent studies conducted showed that more than 60% of the population suffers from low back pain in their life till the age of 60 years.

Majority of cases low back pain is non-specific, it may originate from age related degenerative process and also due to musculo-ligamentous injuries.

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One of the features of low back pain is muscle spasm which occurs due to irritations of muscles; inter vertical disc or ligaments. Muscle spasm reduced mobility due to which daily function and physical activity disturbed very badly.[2]

The causes of low back pain can be trauma, infection, osteoporosis, strains, prolapsed disc and mechanical low back pain.[3] mostly these pains are self limiting and recover in less than a month.

Many clinical guidelines have been issued in various countries to rationalize the treatment of low back pain,[3] Consistent and common features of which are the early mobilization of the patients, gradual activation and discouragement of bed rest Recognition of psychosocial factors are also very important as the risk factors of chronicity.[4-7]

To allow the patients to return to work as soon as possible it is very important to reduce the pain and muscle spasm the main cause of disability. This can only be achieved by the use of Muscle relaxants But there are many differences and discrepancies regarding the recommendations and use of the muscle

relaxants.[8-12] According to one school of thought muscle spasm is protective mechanism so muscle relaxants should not be used according to other school of thought muscle spasm leads to ischemia which leads to pain and further spasms and this vicious circle should be broken by use of muscle relaxants. Sedation and other adverse affects are also important reason of reluctance to use of muscle relaxants commonly.[13-14]

Thiocolchicoside (TCC) is a non–curare muscle relaxant, a semi-synthetic derivative of colchicoside derived from a naturally occurring glycoside present in the plant Gloriosa superba. It has strong affinity for the inhibitory GABA A and strychnine sensitive glycine receptor and it produces very effective muscle relaxation without any subjective or objective sedation.[5,15-16]

It possess anti inflammatory and analgesic properties. In double blind placebo control trials its safety and efficacy as a monotherapy for the treatment of low back pain has been well proved, also it is devoid of any sedation unlike the most other muscle relaxants. Thus during working and in situations where attention is required it can be use safely.[7]

It is not reported that Muscle relaxants are better than the more frequently prescribed analgesics and NSAIDS for the treatment of low back pain. However many physicians routinely prescribed muscle relaxant along with NSAIDS. But there is no clear evidence that the combination of muscle relaxant with NSAIDS or analgesics which is commonly prescribed for the treatment of low back pain has any advantage over NSAIDS or Analgesics prescribed alone. That is why this study was conducted to determine that is the combination of Thiocolchicoside with Diclofenac Sodium more effective for the treatment of non specific low back pain than when Diclofenac sodium used alone or not , and how is the tolerance of this combination in our patients.

MATERIALS AND METHODS

This prospective, randomized, single center observational study was conducted from August 2016 to August 2017 on patients with low back pain of Out-Patient Department of Aziz Bhatti Shaheed Hospital, Gujrat, fulfilling inclusion criteria. A total 288 patient were selected, two groups of 144 each, one group A (D) treated with Diclofenac 75 mg two times a day for 7 days alone and other group B(D+T)treated with Diclofenac 75 mg twice daily plus Thiocolchicoside 4mg two time a day for 7 days. Patients were included in this study from 18-70 years of age, low back pain associated with muscle spasm, signs and symptoms of muscle spasm of the lumbar region and existence of low back pain equal to or greater than 5mm on VAS. Patients were excluded from the study like pregnant and nursing women, presence of any psychiatric or mental disorder, severe gastrointestinal disorders, received a muscle relaxant during preceding 10 days, symptomatic low back pain with some obvious pathology like visceral or un-common low back pain, pelvis spondylitis, spondilodiskitis, spinal tumors, paget disease, osteoprotic compress, neuropathy, surgical intervention in last 6 month, hypersensitivity to NSAID or Thiocolchicosid and diagnosed case of sever diabetes, heart failure, CLD, renal failure, AIDS, psychosis, dementia, Alcoholism. All the patients were recruited between the age of 18-70 years with low back pain with muscles spasm and low back pain greater than 5cm on visual analog score. Evaluation was done and recorded on day 0.

Treatment Protocol: Patients were placed in two groups randomly. Patients in group A were administered with Diclofenac 75mg twice daily alone for a period of 7 days. In second group B, a combination therapy of Thiocolchicoside and Diclofenac was given in a dose 4mg and 75mg respectively twice daily for 7 days. Patients were followed at out-patient department.

Outcome Measures: Patients were examined on three different follow ups; at base line, on day 3 and day 7. The pain management was measured on degree of improvement in the intensity of low back pain on three follow ups by primary outcome measure of visual analogue score (VAS), second out measure for hand to floor distance.

VAS: On VAS pain is scaled from 0-10 cm, from no pain at zero to un-bearable pain at 10cm.

Hand to Floor Distance: In this patient is assessed on mobility by asking him to bend forward and touch his hand to the ground with flexing his knees, the remaining distance between his hand and ground is measured in centimeters.

RESULTS

The percentage of patients examined in Out-patient Department of Orthopedics as: 43.8% patients were 18-30 years of age, 27.1% patients were 31-49 years, 18.8% were 50-69 and only 10.4% were above 70 years. Male patients were 47% and female patients were 53%. Complaint of sedation none. Complaint nausea vomiting abdominal discomfort few patient in both group. Diarrhea reported by 6 patients in group B.

The severity of pain was assessed by VAS, F-test value for Diclofenac (D) is 290.17 with p-value 0.000 which is less than alpha value 0.05, which means results of Diclofenac (D) were statistically significant in all days. VAS score at day zero in treatment Diclofenac is 7.31, after 3 days 4.10 and at day 7 it reduced to 1.35. This shows a significant reduction in pain from day zero to day 7 by using Diclofenac. Similar results were shown for Diclofenac + Thiocolchicoside (D+T); however,

score of VAS is least at day 7 which was much less than Diclofenac (Table 1).

The severity of pain was assessed by VAS, F-test value for Diclofenac (D) is 1335.45 with p-value 0.000 which is less than alpha value 0.05, which means results of Diclofenac (D) were statistically significant in all days. Hand to floor distance score at day zero in treatment Diclofenac is 28.79, after 3 days 18.62 and at day 7 it reduced to 12.12. This shows a significant reduction in pain from day zero to day 7 by using Diclofenac. Similar results was shown for Diclofenac + Thiocolchicoside (D+T); however, score of hand to floor distance is least at day 7 which was much less than Diclofenac

At day 7 Patients with in both groups were improved but patients receiving Thiocolchicoside and NSAID had significantly less pain ($p<0.003$) and disability (foot ankle distance ($p=0.0005$) than patients taking NSAID alone.

Table No.1: Comparison of Treatment with ANOVA for VAS

Treatment	Time	Mean SEM	F-Test (P-value)
Diclofenac (D)	Day 0	7.31±0.273	290.17 (0.000)
	Day 3	4.1±0.166	
	Day 7	1.35±0.096	
Diclofenac + Thiocolchicoside (D+T)	Day 0	7.27±0.263	292.03 (0.000)
	Day 3	3.67±0.15	
	Day 7	0.94±0.096	

Table No.2: Comparison of Treatment with ANOVA for Hand to Floor Distance

Treatment	Time	Mean SEM	F-Test (P-value)
Diclofenac (D)	Day 0	28.79±0.305	1335.45 (0.000)
	Day 3	18.62±0.260	
	Day 7	12.12±0.175	
Diclofenac + Thiocolchicoside (D+T)	Day 0	28.70±0.277	3296.36 (0.000)
	Day 3	16.93±0.116	
	Day 7	10.54±0.072	

DISCUSSION

The important goal in the treatment of patients with low back pain is to relieve the pain and accompanying muscle spasm, and enable patient to resume its routine daily activities as early as possible and allowing the patients to return to their work as soon as possible.[9,17]

Non-steroid anti inflammatory drugs are most frequently used drugs for the treatment of low back pain.[13] Among NSAIDS mostly prescribed is Diclofenac. Elsy et al showed that Diclofenac is most commonly administrated analgesics above 72% and Acetaminphen being 14% and Aceclofenac 8%.[4,14,18] There are conflicting level 3 evidence that NSAIDS are better than acetaminophen for low back pain when administered with muscle relaxant.

Muscle relaxants are commonly used in orthopaedics, mostly the drugs used are central nervous system depressants. These drugs reduce the muscle spasm but they also reduce the muscle tone as well which leads to sense of weakness and decreased mobility. Sedation is other major factor which limit their use because it reduces the working capacity of the patients. Hence due to these limiting factors the need for ideal muscle relaxant was raised which should be devoid of effects on psychomotor performance and free of sedation. thiocolchicoside produces muscle relaxation without sedation, it also has antiinflamatory and analgesic effects.[19]

The American Pain Society recommend the use of NSAIDS as first line treatment for acute pain, and in acute low back pain use of muscle relaxants along with NSAIDS have better results.[3]

In our study the decrease in severity of pain was more in group receiving combination therapy (Diclofenac sodium plus Thiocolchicoside) as compared to patients receiving Diclofenac sodium alone and the difference between two groups was significant. Our results are similar to the studies conducted by Raut et al[10] and Pareek et al[16] using acelofenac–tizanidine combination in the treatment of acute low back pain.

Desai et al[18] also shows reduction in severity of low back pain especially at rest is more in group receiving combination of Aceclofenac and Thiocolchicoside than the Aceclofenac alone, although they found differences between these two groups was not statistically significant.

Our study reported a statistically significant improvement in hand to floor distance on 7th day in both groups however the decrease in hand to floor distance was more pronounced with group B (combination therapy) as compared to group A. similar results were also reported by Lahoti et al and Kumar et al.[19,20] None of patient complaint of sedation in our study a few patients complain of diarrhea and some complaint nausea and vomiting not statistically significant.

CONCLUSION

The results of our study are very much relevant to state that combination therapy of Diclofenac sodium and Thiocolchicoside had superior efficacy than Diclofenac sodium alone for the management of nonspecific low back pain and the combination was well tolerated.

Author's Contribution:

Concept & Design of Study:	Nauman Akhter
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Data Analysis:	Nauman Akhter
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Frequency of BCG Vaccination in Patients of Tuberculous Meningitis

BCG Vaccination in Tuberculous Meningitis

Maryam Riaz and Abdul Basit

ABSTRACT

Objective; To determine frequency of BCG Vaccination in patients of tuberculous meningitis presenting at a tertiary care hospital.

Study Design: Descriptive study.

Place and Duration of Study: This study was conducted at the Department of Pediatric Medicine, Services Hospital Lahore from June 2016 to June 2017.

Materials and Methods; A total of 167 Patients were included in the study. Patients with Tuberculous meningitis (TBM) less than 5 years of age were included. Patients having acute onset of encephalopathy and those with lumbar puncture contraindicated were excluded from our study. Demographic bio data (patient name, father name, age, gender, date of admission) was taken. After that complete history regarding presenting complaints and vaccination were taken. Physical examination will be done. BCG scar ark was identified on examination. CSF examination, Chest X-ray, CT scan brain was done from single laboratory. Tuberculin test was applied and interpreted by experience pediatrician. Data was recorded on the specifically designed proforma.

Results; Of these 167 study cases, 106 (63.5%) were boys while 61 (36.5%) were girls. Mean age of our study cases was 3.31 ± 0.98 years. Mean duration of disease was noted to be 4.71 ± 1.49 weeks. History of contact with index TB patients was positive in 114 (68.3%) of our study cases, 68 (40.7%) were from rural areas and 99 (59.3%) from urban areas and majority of them i.e. 90 (53.9%) belonged to poor families with majority of mothers i.e. 129 (77.2%) were uneducated. BCG vaccination was positive in 94 (56.3 %) of our study cases.

Conclusion; Our study results support the use of BCG vaccination as it has some protective role against TB. Very high frequency of history of contact with positive index case was observed in our study. BCG vaccination was significantly associated with gender, history of contact with index case and socioeconomic status.

Key Words; BCG vaccination, tuberculous meningitis, frequency.

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INTRODUCTION

Tuberculosis (TB) is one of the leading causes of mortalities occurring due to infectious diseases all over the world although there has been dramatic advancements in the fields of diagnosis and treatment[1-3]. World Health Organization (WHO) reported approximately 10 million new patients with TB in 2010 and around2 million mortalities every year, even though it is a curable infection[4-6]. Tuberculous meningitis (TBM) in generally more prevalent in developing countries where it is more common in different population subsets and increased proportion of the human immunodeficiency virus (HIV) harbors the onset of higher numbers of new cases[7].

However in recent years tuberculosis is also commonly seen in developed countries as a result of immigrations of infected people [1] because of escalation of violence in certain regions and also due to excessive use of certain biological agents which favor TB spread.[8, 9]

Children are more vulnerable of all who are at increased risk of suffering from TBM as a result of their inability to combat the primary infection in their lungs.[1, 9] TBM is highly devastating infectious disease having approximately 30% mortality rates in case of most severe forms. Additionally other 50% of cases who survive develop neurological sequelae even after administration of appropriate intake of antibiotics.[10, 11]

BCG (Bacillus Calmette–Guérin) is a vaccine against tuberculosis that is prepared from a strain of the attenuated (virulence-reduced) live bovine tuberculosis bacillus, Mycobacterium bovis, The BCG vaccination and its protective effect appears to vary according to geography.BCG vaccination is recommended to be given intradermally by a nurse skilled in the technique after birth.[12] BCG is very efficacious against tuberculous meningitis in the pediatric age group, but its efficacy against pulmonary tuberculosis appears to be variable. BCG seems to have its greatest effect in preventing military TB or TB meningitis, so it is still extensively used even in countries where efficacy against pulmonary tuberculosis is negligible[13].

Frequency of BCG vaccination was noted in 83.4% of the Tuberculous meningitis children[14] and in another

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study it was 57.4% of tuberculous meningitis paediatric patients[15].

This study was done to monitor the efficacy of BCG vaccination in patients against tuberculous meningitis. With lack of good clinical evidence on the subject and the resulting practice variation additional data regarding this is needed. Moreover there is no such data and no clinical trials conducted on this issue is available here at in our local population.

MATERIALS AND METHODS

A total of 167 Patients were included in the study. Patients with Tuberculous meningitis (TBM) less than 5 years of age were included from department of pediatric medicine Services Hospital, Lahore. Patients having acute onset of encephalopathy and those with lumbar puncture contraindicated were excluded from our study.TMB was diagnosed as CSF showing predominant lymphocyte pleocytosis ≥50cells/umm, proteins ≥ 60mg/dl, sugar < 2/3rd of blood level plus supportive along with essential two or more present; History of fever of two weeks or more, positive family history of TB, tuberculin skin test of 10mm or more with 5 TU of PPD, superficial adenitis of tuberculosis etiology proved by histology/FNAC, positive radiological evidence of TB in chest, CT scan evidence of basal exudates and/or ventricular dilatation in CNS TB. Demographic bio data (patient name, father name, age, gender, date of admission) was taken. After that complete history regarding presenting complaints and vaccination were taken. Physical examination will be done. BCG scar ark was identified on examination. CSF examination, Chest X-ray, CT scan brain was done from single laboratory. Tuberculin test was applied and interpreted by experience pediatrician. Data was recorded on the specifically designed proforma. Data was analyzed with statistical analysis program (SPSS version 20). Mean and standard deviation was calculated for quantitative variables like age of the patients. Frequency and percentages were computed for qualitative variables like gender, history of contact with TB patients and BCG vaccination status. Confounders like age and gender were controlled by stratification. Post stratification chi-square test was applied to see their effect on outcome at 0.05 level of significance.

RESULTS

Of these 167 study cases, 106 (63.5%) were boys while 61 (36.5%) were girls. Mean age of our study cases was 3.31 ± 0.98 years ranging from 2 – 5 years. Mean age of boys was 3.23 ± 0.95 years while that of girls was 3.46 ± 1.00 years (p= 0.141). Mean duration of disease was noted to be 4.71 ± 1.49 weeks. Mean duration of illness in boys was 5.00 ± 1.62 weeks while in girls was 4.20 ± 1.09 weeks (p= 0.001).

Table No. 1: Stratification of BCG vaccination with regards to gender. (n = 167)

Gender	BCG Vaccination		P – value
	Yes (n=94)	No (n=73)	
Male (n=106)	49	57	0.001
Female (n=61)	45	16	
Total	167		

Table No. 2: Stratification of BCG vaccination with regards to age. (n = 167)

Age groups	BCG Vaccination		P – value
	Yes (n=94)	No (n=73)	
1 – 3 Years (n=99)	52	47	0.268
More than 3 Years (n=68)	42	26	
Total	167		

Table No. 3: Stratification of BCG vaccination with regards to disease duration. (n = 167)

Disease duration	BCG Vaccination		P – value
	Yes (n=94)	No (n=73)	
Less than 4 weeks (n=47)	30	17	0.231
4 – 8 weeks (n=120)	64	56	
Total	167		

Table No. 4: Stratification of BCG vaccination with regards to History of contact with TB patient.

History of contact	BCG Vaccination		P – value
	Yes (n=94)	No (n=73)	
Yes (n=114)	55	59	0.002
No (n=53)	39	14	
Total	167		

Table No. 5: Stratification of BCG vaccination with regards to residential status. (n = 167)

Residential status	BCG Vaccination		P – value
	Yes (n=94)	No (n=73)	
Rural (n=68)	37	31	0.752
Urban (n=99)	57	42	
Total	167		

History of contact with index TB patients was positive in 114 (68.3%) of our study cases, 68 (40.7%) were from rural areas and 99 (59.3%) from urban areas and majority of them i.e. 90 (53.9%) belonged to poor families with majority of mothers i.e. 129 (77.2%) were

uneducated. BCG vaccination was positive in 94 (56.3%) of our study cases.

DISCUSSION

There exists controversy regarding protective efficacy of BCG vaccination among children against tuberculous meningitis (TBM). Various factors such as child age, dietary habits, family status and positive index case in the family play potential role in its protective efficacy but there is limited data from our population on this topic. So this study was done to ascertain protective role of BCG vaccination in pediatric population with TBM[16].

Our study included a total of 167 children with tuberculous meningitis meeting inclusion/exclusion criteria of our study. Of these 167 study cases, 106 (63.5%) were boys while 61 (36.5%) were girls. Masood et al [15] reported equal distribution of male to female gender but our study results have reported male gender predominance. Nabukeera-Barungi et al [17] also reported 1:1 male to female ratio which is different from our study results.

Tuberculous meningitis has traditionally been reported to be more common in children of younger age groups[15]. Mean age of our study cases was 3.31 ± 0.98 years ranging from 2 – 5 years. Mean age of boys was 3.23 ± 0.95 years while that of girls was 3.46 ± 1.00 years (p = 0.141).Nabukeera-Barungi et al[17] reported mean age 32 months which is close to our study results. Masood et al [15]also reported that majority of the TBM patients were younger around 2 years of age which is similar to our study findings.

Mean duration of disease was noted to be 4.71 ± 1.49 weeks. Mean duration of illness in boys was 5.00 ± 1.62 weeks while in girls was 4.20 ± 1.09 weeks (p = 0.001). Our study results have indicated that majority of our study cases i.e. 120 (71.9%) presented with duration of 4 – 8 weeks of illness. Kumar et al [18] reported mean duration of disease to be 35.1 days which is close to our study results.

History of contact with index TB patients was positive in 114 (68.3%) of our study cases, 68 (40.7%) were from rural areas and 99 (59.3%) from urban areas and majority of them i.e. 90 (53.9%) belonged to poor families with majority of mothers i.e. 129 (77.2%) were uneducated. Masood et al[15] reported that 70.4 % of the children with TBM had history of contact with TB patients which is similar to our study results.

The reported efficiency of B.C.G. vaccine in prevention of primary childhood or sputum positive adult tuberculosis very widely but it is believed to offer significant protection against hematogenous forms of tuberculosis. BCG vaccination was positive in 94 (56.3%) of our study while a study conducted by Nabukeera-Barungi et al[17] reported 50% BCG vaccination in children with TBM which is close to our findings. Masood et al [15] reported 57.4 % patients with TBM had BCG vaccination. Chavalittamrong et al[19] from Thailand reported 52.1% BCG vaccination in children with TBM which is again in compliance with our study results. Similar results have been reported by Kumar et al[18].

CONCLUSION

Our study results support the use of BCG vaccination as it has some protective role against TB. Very high frequency of history of contact with positive index case was observed in our study. BCG vaccination was significantly associated with gender, history of contact with index case and socioeconomic status.

Author's Contribution:

Concept & Design of Study:	Maryam Riaz
Drafting:	Abdul Basit
Data Analysis:	Maryam Riaz
Revisiting Critically:	Abdul Basit, Maryam Riaz
Final Approval of version:	Maryam Riaz

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Original Article

Frequency of Thyroid Dysfunction in Pregnant Women Visiting Outpatient Department of a Tertiary Care Hospital of South Punjab

Thyroid Dysfunction in Pregnant

Zoya Khan, Shumaila Kiran and Muzimmal Zulfquar Bhatti

ABSTRACT

Objective: To determine the frequency of thyroid dysfunction in pregnant healthy woman.
Study Design: Cross sectional study.
Place and Duration of Study: This study was conducted at the out-patient Department of Gynecology and Obstetrics, Nishtar Hospital, Multan from May 2015 to May 2016
Materials and Methods: Four hundred fifty-one healthy pregnant women visiting out-patient department of Gynecology and Obstetrics were included in this study and serum TSH test was done in all patients enrolled in study. The patients with deranged TSH test were further assessed by free T3 and T4 levels from central lab Nishtar hospital Multan. All the data was entered and analyzed by using SPSS v-20.
Results: Our study included a total of 451 healthy pregnant ladies who met inclusion criteria of our study. Mean age of our study cases was noted to be 27.87 ± 4.76 years while majority of our study cases i.e. 289 (64.1%) belonged to age group ranging from 20 - 30 Years. Mean Parity of our study cases was 2.88 ± 0.99, our study results have shown that majority of our study cases i.e. 325 (72.1%) had parity equal or less than 3. Mean gravidity was 3.96 ± 0.95 and majority of these ladies i.e. 307 (68.1%) had parity ranging from 1 – 4. Mean gestational age of our study cases was 20.25 ± 4.30 weeks (range 13 – 26 weeks). Euthyroid was seen in 303 (67.2 %) of our study cases, of the remaining 148 (32.8%) having thyroid dysfunction, subclinical hypothyroidism was seen in 94 (20.8 %) and subclinical hyperthyroidism was seen in 54 (12.0%) of our study cases.
Conclusion: High frequency of thyroid dysfunction was noted in our study. Subclinical hypothyroid was significantly associated with increasing age, parity more than 3 and gestational age. Subclinical hyperthyroid was also significantly associated with age. Our study results suggest that all pregnant ladies should be screened for these thyroid hormones to overcome these related adverse outcomes. This will help to decrease disease morbidity and improve quality of life of our patients.

Key Words: Thyroid dysfunction, Subclinical hypothyroid, euthyroid

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INTRODUCTION

Derangement in thyroid hormone levels is a common entity, encountered by Gynecologists, among pregnant women and it may affect perinatal outcomes both in mothers and their fetus. Thyroid function regulation is significantly modified during course of pregnancy and these modifications are often caused by different factors like increase in thyroxine – binding globulin (TBG) after elevation in the levels of estrogens and human chorionic gonadotropin (hCG), loss of Iodine as a result of enhanced glomerular filtration rates (GFR) increased renal losses of iodine due to increased glomerular filtration rate and due to modified placental iodine transfer.[1] Thyroid glands can enlarge upto 10 % during pregnancy in Iodine source sufficient countries while it may enlarge to greater extent among countries where iodine source is insufficient. During pregnancy, Iodine requirement as well as thyroid hormone production may increase about 50% and pregnancy is referred to be the stress test for thyroid functioning which results in hypothyroidism among pregnant ladies having low thyroidal reserves or who have iodine insufficiency [2]. About 0.1 – 0.4 % of pregnant ladies may have hyperthyroidism while hypothyroidism may occur in 2–3% of pregnant ladies (in which around 0.5% have overt hypothyroidism and 2–2.5% exhibit subclinical hypothyroidism.[3] During pregnancy estimated 5 – 10% of the women are found positive for thyroid antibodies, so they have more risk for the development of varying degree of thyroid deficiency[4]. Maternal hypothyroidism, thyrotoxicosis and recurrent postpartum thyroiditis are most commonly encountered

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entities during pregnancy and immediately after birth [5]. Autoimmune Hashimoto's thyroiditis is believed to be major cause of hypothyroidism in pregnant women in iodine source limited regions while iodine deficiency remains commonest cause of the goiter in such areas [6] .A local study carried out in Lahore, Pakistan revealed that about 79.8% of the pregnant mothers are found to be iodine deficient, out of which 24.7% are moderately deficient in iodine which predisposes the mothers and their neonates to develop iodine deficiency thyroid disorders. As Pakistan falls in the list of Iodine deficient countries where local diets are often iodine deficient which poses potential threat to our local population in general and pregnant women in particular to develop moderate to severe iodine deficiency. This, in turn, gives rise to the development of hypothyroidism in pregnant women which leads to certain adverse maternal and fetal outcomes [7]. In one study of India, prevalence of Euthyroid was 75%, subclinical hypothyroidism to be 9%, overt hypothyroidism in 3 %, subclinical hyperthyroidism in 3.3 % and overt hyperthyroidism in 0.4% of the pregnant ladies.[8] This necessitate the need for screening for thyroid dysfunction during early pregnancy for every woman.

MATERIALS AND METHODS

Four hundred fifty-one healthy pregnant women fulfilling the inclusion and exclusion criteria visiting outpatient department of Nishtar hospital Multan were included. Pregnant ladies with age 20 to 40 years of any parity having singleton pregnancy presenting in our OPD with gestational age ranging from 13 weeks to 26 weeks, calculated from last menstrual period were enrolled. Pregnant women with known other medical disorders like thyroid, hypertension, diabetes mellitus, history of thyroid surgery or any miscarriage were excluded from our study. Informed consent was obtained from patients and ensured their confidentiality. After detailed history and examination, TSH test was done in all patients enrolled in study. The patients with deranged TSH test were further assessed by free T3 and T4 levels from central lab Nishtar hospital Multan. The reference range used in the study is based on guidelines of the American thyroid association 2011.[9]All the data was entered and analyzed by using SPSS v-20. Mean and standard deviation was calculated for all variables like age, parity and gestational age in weeks. Frequency and percentage were calculated for parity, gravidity, euthyroid, subclinical hypothyroid, subclinical hyperthyroid. Post stratification chi square test was applied and p-value≤0.05 was taken as significant.

RESULTS

Our study included a total of 451 healthy pregnant ladies who met inclusion criteria of our study. Mean age of our study cases was noted to be 27.87 ± 4.76 years while majority of our study cases i.e. 289 (64.1%) belonged to age group ranging from 20 - 30 Years. Mean Parity of our study cases was 2.88 ± 0.99, our study results have shown that majority of our study cases i.e. 325 (72.1%) had parity equal or less than 3. Mean gravidity was 3.96 ± 0.95 and majority of these ladies i.e. 307 (68.1%) had parity ranging from 1 – 4.
Mean gestational age of our study cases was 20.25 ± 4.30 weeks (range 13 – 26 weeks). Euthyroid was seen in 303 (67.2 %) of our study cases, of the remaining 148 (32.8%) having thyroid dysfunction, subclinical hypothyroidism was seen in 94 (20.8 %) and subclinical hyperthyroidism was seen in 54 (12.0%) of our study cases.

Table No. 1: Stratification of Euthyroid with regards to gestational age. (n=451)

Gestational age	Euthyroid		P – value
	Yes (n=303)	No (n=148)	
13 - 20 weeks (n=199)	161	38	0.000
21 - 26 weeks (n=252)	142	110	
Total	451		

Table No.2:Stratification of Subclinical hypothyroid with regards to gestational age. (n=451)

Gestational age	Subclinical hypothyroid		P – value
	Yes (n=94)	No (n=357)	
13 – 20weeks (n=199)	19	180	0.000
21 – 26 weeks (n=252)	75	177	
Total	451		

Table No.3:Stratification of Subclinical hyperthyroid with regards to gestational age. (n=451)

Gestational age	Subclinical hyperthyroid		P – value
	Yes (n=54)	No (n=397)	
13 – 20 weeks (n=199)	18	181	0.108
21 – 26 weeks (n=252)	36	216	
Total	451		

DISCUSSION

Thyroid dysfunction has been reported to be associated with significant adverse pregnancy outcomes particularly in first trimester as it leads to complications in fetal brain development which ultimately leads to mental retardation among these children[10-11]. Due to these adverse outcomes many researchers have reported that all pregnant ladies may be screened for thyroid hormones. Thyroid dysfunction has been reported to be associated with significant adverse pregnancy outcomes

particularly in first trimester as it leads to complications in fetal brain development which ultimately leads to mental retardation among these children[12-13]. Due to these adverse outcomes many researchers have reported that all pregnant ladies may be screened for thyroid hormones[14-16]. Our study included a total of 451 healthy pregnant ladies who met inclusion criteria of our study. Mean age of our study cases was noted to be 27.87 ± 4.76 years and 289 (64.1%) belonged to age group ranging from 20 - 30 Years. Taseer et al[17] reported 26.7 ± 4.8 years mean age of pregnant ladies visiting our institutions which is similar to our study results. Ansari et al [18] reported 26.7 ± 4.9 mean age of pregnant ladies which is similar to our study results. Haq et al [19] from Rawalpindi also reported similar range corresponding to our study results.

Mean Parity of our study cases was 2.88 ± 0.99, our study results have shown that majority of our study cases i.e. 325 (72.1%) had parity equal or less than 3. Mean gravidity was 3.96 ± 0.95, our study results have demonstrated that majority of these ladies i.e. 307 (68.1%) had parity ranging from 1 – 4. Taseer et al [17] reported similar results.

Thyroid dysfunction may results in premature deliveries, pre-eclampsia, increase in fetal mortality and low birth weight babies. Particularly in first trimester of pregnancy maternal hypothyroidism can be highly dangerous as it may lead to the mental retardation because it harms fetal brain development. Normal upper limit of TSH in pregnancy has been a subject of debate since a long time. In 2002, National Academy of Clinical Biochemistry (NACB) had laid down guidelines for the establishment of TSH reference intervals.Euthyroid was seen in 303 (67.2 %) of our study cases, subclinical hypothyroidism was seen in 94 (20.8 %) and subclinical hyperthyroidism was seen in 54 (12.0%) of our study cases. Rajput et al[9] from India reported 75 % euthyroid, 21.5 % sub – clinical hypothyroidism and sub- clinical hyperthyroidism was 3.3 %. These findings are similar to our study results. Altomare et al [20] has also reported similar results. Wang et al from China also has reported high proportions of thyroid dysfunction among pregnant ladies.

CONCLUSION

High frequency of thyroid dysfunction was noted in our study. Subclinical hypothyroid was significantly associated with increasing age, parity more than 3 and gestational age. Subclinical hyperthyroid was also significantly associated with age. Our study results suggest that all pregnant ladies should be screened for these thyroid hormones to overcome these related adverse outcomes. This will help to decrease disease morbidity and improve quality of life of our patients.

Author's Contribution:

Concept & Design of Study:	Zoya Khan
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Original Article

Comparison of Metformin with Insulin in the Management of Gestational Diabetes

Rao Muhammad Akram Khan[1], Ayesha Mukhtar[2] and Anam Khawar[2]

ABSTRACT

Objective: Purpose of this study is to determine the efficacy of metformin as opposed to insulin in management of gestational diabetes mellitus.

Study Design: Randomized control trial.

Place and Duration of study: This study was conducted at the Gynecology and Obstetrics, Lady Wellington Hospital, Lahore from May 2016 to March 2017.

Materials and Methods: Ethical approval was obtained from Hospital Ethics Committee. Sample was calculated using non probability consecutive sampling technique. Total 770 Patients were randomly divided into two equal groups, group M (metformin) and Group I (insulin). Glycemic control, mode of delivery and associated medical complication were recognized as possible maternal outcomes while congenital anomalies (if any), macrosomia, hypoglycemia, hyperbilirubinemia were the neonatal outcomes assessed by clinical and laboratory investigations. These outcomes were subjected to statistical analysis by using computer software SPSS version 23. Percentages were calculated for dichotomous variables and range, mean and standard deviation was calculated for continuous data. Chi square and t-test were applied to compare the two groups. P value less than 0.05 was considered as significant.

Results: Overall 100% (n=770) female patients were included, in this study; divided into two equal groups 50% (n=385) in each i.e. metformin (Group M) and insulin (Group I). Significant difference was found between age (p=0.000), gravidity (p=0.012), gestational age (p=0.000), BMI in early pregnancy (p=0.000), FBS at entry (p=0.000), FBS after treatment (p=0.000), HBA1c at entry (p=0.000), HBA1c after treatment (p=0.000), in groups. Association was found between Preeclampsia (p=0.000), Pre-term birth (p=0.000), Neonatal birth weight>4 (p=0.002), neonatal hypoglycemia (p=0.000), in groups.

Conclusion: This study concludes that metformin is as much effective as insulin in management of gestational diabetes mellitus. Metformin when used securely can prove effective as it does not cause any congenital anomalies or maternal or neonatal complications. But insulin still remains the gold standard for treatment of gestational diabetes mellitus.

Key Words: Diabetes Mellitus, Gestational Diabetes, Metformin, Insulin, Pregnancy

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INTRODUCTION

Glucose intolerance of any level with onset or first identified during the pregnancy can be called as gestational diabetes[1]. Overall morbidity of gestational diabetes is increasing with passing time. According to an estimate, 1 to 14% of all the pregnancies are complicated by gestational diabetes, which of course depends upon the size of the population under study, type of classification and diagnostic tests used[2]. Gestational diabetes is thought to have both short and long term outcomes which affect both mother and newly born child[3]. Out of the complications faced by the pregnant mother most common are preeclampsia, increased risk of developing diabetes mellitus type 2 after pregnancy and cesarean section. In case of neonatal morbidities, risk of neonatal loss becomes greater; there is also risk of still birth and congenital abnormalities, all because of excess glucose transfer from mother to fetus. Macrosomia is another major complication which can lead to shoulder dystocia during transvaginal birth, presenting a risk for instrumental deliveries, C-section and neonatal hypoglycemia later[4]. Intrauterine hyperglycemic environment may cause this condition to pass on to the children of the mother who is suffering from gestational diabetes[5]. That is why the aim of management of gestational diabetes is to control the glycemic levels and hence reduce the horrible post-pregnancy outcomes[6].

Possible treatments to reduce these complications can be enlisted as, exercise[7], diet modifications, insulin and

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oral hypoglycemic conditions. Up till now, insulin therapy has been considered as gold standard for treatment of gestational diabetes as diet modification with or without exercise is not enough to resolve this grave problem[8]. Although insulin is the treatment of choice but it does come with some side effects like weight gain, several injections per day and a risk of developing hypoglycemia[9]. So adjustments are made according to the BMI, lifestyle of the patient and blood glucose level. In other words, a detailed guidance is necessary regarding change in insulin dosages, so that self administration can be ensured to be safe. As expected, oral insulin therapy is much more satisfying and preferable in women with gestational diabetes, until its safe and effective.

Oral hypoglycemic drugs should also be considered especially in order to identify their effect on the final outcomes in both mothers and neonates. Metformin is first line of drug in the management of type 2 diabetes mellitus[10] and can be considered as another possible treatment option for gestational diabetes. But studies have shown a mother to fetus transfer of almost 10 to 16% in case of metformin[11] which poses a great risk to both mother and the fetus as chances of adverse effects in mothers and birth defects in newborn increases significantly. This is the reason metformin has not been used widely in gestational diabetes management.

Multiple studies have been performed in past in order to determine the efficacy and safety of metformin in management of gestational diabetes but most of these studies were cross-sectional and had smaller sample size which does not sufficiently describe the effect of metformin on maternal and neonatal outcomes. Thus, in this study our aim is to compare the efficacy of metformin with insulin therapy in gestational diabetes management, in terms of maternal and neonatal outcomes. Reference for this study was taken from a recent study performed by Hesham Borg et al[12].

MATERIALS AND METHODS

The study took place in department of Gynecology and Obstetrics, Lady Wellington Hospital, Lahore, from May 2016 to August 2017. Study design is Randomized control trial. Ethical approval was obtained from Hospital Ethics Committee. Sample was calculated using non probability consecutive sampling technique, using the reference study by Hesham Borg et al. Confidence level was taken as 95% and power of study as 80% and mean and standard deviation of outcome variable postprandial blood sugar level was used to calculate the sample size. As a result 770 patients were taken as the required sample size for our study. Total no. of 770 patients was included in the study. Inclusion criteria described by Carpenter and Coustan was used to select the patients of gestational diabetes, according to which, blood glucose level must be, fasting > 95 mg\dl, at 1hr >180mg\dl, at 2h >155mg\dl and at 3h >146mg\dl, along with hospital criteria to start insulin therapy. Those patients who were in labor, had contradiction against metformin or with fetal anomalies, preeclampsia, gestational hypertension, ruptured membranes or fetal growth restrictions were excluded from the study. Informed consent was taken from the patients before involving them into the study. Patients were randomly divided into two equal groups, group M (metformin) and Group I (insulin). Metformin was given to patients of group M as 500 mg dose\day orally in morning and increased by 500 mg per week if required. Mixed human suspension of insulin was given as 0.7 U\kg of body weight subcutaneously two times a day and was also increased as per requirement. Weekly examination of the patients was scheduled which involved, history taking, general physical examination and fasting blood sugar and postprandial blood sugar (glycemic profile).Weekly visit involved dose adjustments if required and provision of standard obstetric care. Basic facilities were provided at antenatal clinic level including ultrasound examination. Ultrasound examination was performed at first visit and then at 16 to 19 weeks (2^{nd} visit) and then monthly after 28 weeks of gestation. Glycemic control, mode of delivery and associated medical complication were recognized as possible maternal outcomes while congenital anomalies (if any), macrosomia, hypoglycemia, hyperbilirubinemia were the neonatal outcomes assessed by clinical and laboratory investigations. These outcomes were subjected to statistical analysis by using computer software SPSS version 23. Percentages were calculated for dichotomous variables and range, mean and standard deviation was calculated for continuous data. Chi square and t-test were applied to compare the two groups. P value less than 0.05 was considered as significant.

RESULTS

Overall 100% (n=770) female patients were included, in this study; divided into two equal groups 50% (n=385) in each i.e. metformin (Group M) and insulin (Group I). The mean age, gravidity, parity, gestational age, BMI in early pregnancy and BMI during treatment of the patients of group M was 24.92±2.57 years, 2.57±1.17, 1.48±0.66, 27.94±2.57 weeks, 22.08±2.98 kg/m^2 and 31.88±2.26 kg/m^2 respectively. While, the mean age, gravidity, parity, gestational age, BMI in early pregnancy and BMI during treatment of the patients of group I was 28.01±2.53 years, 2.35±1.19, 1.41±1.06, 29.92±2.27 weeks, 23.82±2.81 kg/m^2 and 32.05±1.89 kg/m^2 respectively. (Table1).

The Mean±S.D FBS at entry, FBS after treatment, 2hPPBS at entry, 2hPPBS after treatment, HBA1c at entry and HBA1c after treatment of the patients of group M was 130.06±10.34 mg/dl, 82.28±5.51 mg/dl, 175.18±7.89 mg/dl, 111.94±7.02 mg/dl, 5.73±0.54

mg/dl and 5.08±0.42 mg/dl respectively. While, the Mean±S.D FBS at entry, FBS after treatment, 2hPPBS at entry, 2hPPBS after treatment, HBA1c at entry and HBA1c after treatment of the patients of group I was 122.37±9.94 mg/dl, 76.88±7.75 mg/dl, 174.46±6.02 mg/dl, 112.34±5.02 mg/dl, 6.15±0.59 mg/dl and 5.71±0.49 mg/dl respectively.

Table No.1: Demographic Variables

Variable	Metformin n=(385) Group A	Insulin n=(385) (Group B)	Test of Sig.
Age	24.92±2.57 years	28.01±2.53 years	t=-16.80 p=0.000
Gravidity	2.57±1.17	2.35±1.19	t=2.53 p=0.012
Parity	1.48±0.66	1.41±1.06	t=1.05 p=0.293
Gestational Age	27.94±2.57 weeks	29.92±2.27 weeks	t=-11.30 p=0.000
BMI in early pregnancy	22.08±2.98 kg/m^2	23.82±2.81 kg/m^2	t=-8.323 p=0.000
BMI during treatment	31.88±2.26 kg/m^2	32.05±1.89 kg/m^2	t=-1.10 p=0.271

Table No.2: Comparison between groups with respect to pattern of blood sugar level, maternal and neonatal complications and mode of delivery

Variable	Metformin n=(385) Group A	Insulin n=(385) (Group B)	Test of Sig.
FBS at entry	130.06±10.34 mg/dl	122.37±9.94 mg/dl	t=10.53 p=0.000
FBS after treatment	82.28±5.51 mg/dl	76.88±7.75 mg/dl	t=11.15 p=0.000
2hPPBS at entry	175.18±7.89 mg/dl	174.46±6.02 mg/dl	t=1.42 p=0.157
2hPPBS after treatment	111.94±7.02 mg/dl	112.34±5.02 mg/dl	t=-0.909 p=0.364
HBA1c at entry	5.73±0.54 mg/dl	6.15±0.59 mg/dl	t=-10.04 p=0.000
HBA1c after treatment	5.08±0.42 mg/dl	5.71±0.49 mg/dl	t=-19.11 p=0.000
Gestational HTN	7.3% (n=28)	8.1% (n=31)	χ^2=0.165 p=0.684
Pre-eclampsia	4.4% (n=17)	15.6% (n=60)	χ^2=26.68 P=0.000
Pre-term birth	2.6% (n=10)	12.5% (n=48)	χ^2=26.93 P=0.000
Mode of delivery	CS 40.8% (n=157), NVD 59.2% (n=228)	CS 36.1% (n=139), NVD 63.9% (n=246)	χ^2=1.778 P=0.182
Neonatal birth weight>4	10.9% (n=42)	18.7% (n=72)	χ^2=9.27 P=0.002
Neonatal hypogly-cemia	28.3% (n=109)	52.5% (n=202)	χ^2=46.65 P=0.000
Neonatal Jaundice	51.2% (n=197)	39.7% (n=153)	χ^2=10.14 P=0.001

Gestational HTN 7.3% (n=28) and 8.1% (n=31), preeclampsia 4.4% (n=17) and 15.6% (n=60), pre-term birth 2.6% (n=10) and 12.5% (n=48), mode of delivery CS 40.8% (n=157), NVD 59.2% (n=228) and CS 36.1% (n=139), NVD 63.9% (n=246), neonatal birth weight>4 10.9% (n=42) and 18.7% (n=72), neonatal hypoglycemia 28.3% (n=109) and 52.5% (n=202), neonatal Jaundice 51.2% (n=197) and 39.7% (n=153) , were noted for the group M and I respectively. (Table 2).

Significant difference was found between age (p=0.000), gravidity (p=0.012), gestational age (p=0.000), BMI in early pregnancy (p=0.000), FBS at entry (p=0.000), FBS after treatment (p=0.000), HBA1c at entry (p=0.000), HBA1c after treatment (p=0.000), in groups. Association was found between Preeclampsia (p=0.000), Pre-term birth (p=0.000), Neonatal birth weight>4 (p=0.002), neonatal hypoglycemia (p=0.000), in groups. (Table 2).

DISCUSSION

Prevalence of gestational diabetes varies within different races and it depends upon diagnostic tests used for its diagnosis. Use of a specific diagnostic criterion and a certain ethnic background suggests that gestational diabetes incidence varies from 2 to 8% [13]. Gestational diabetes has been reported to associate with many maternal and perinatal complications including, preeclampsia, macrosomia, shoulder dystocia, hypoglycemia, cesarean section, birth injuries and respiratory distress syndrome[14,15]. Multiple studies have shown that risk of these complication rises with the rise in blood glucose level and that these complications can be prevented by proper management of hyperglycemia which is the major finding of gestational diabetes[16, 17]. Recommendations regarding diagnosis and management of gestational diabetes are derived from American College of Obstetricians and Gynecologists and American Diabetes Association in attempt to avoid these unpleasant outcomes[18,19].

Women suffering from gestational diabetes who were unable to be treated with diet modifications and exercise recommendations are traditionally treated by insulin therapy[20]. But insulin therapy carries risk of weight gain, difficulty for pregnant women as multiple injections are required daily and also there is risk of developing hypoglycemia. Therefore metformin is considered as a replacement therapy and it is also effective in gestational diabetes[21]. There are no risks of developing hypoglycemia and gaining of weight with use of metformin and metformin acts by preventing peripheral insulin resistance and diminishing gluconeogenesis in liver[22].

According to a meta-analysis, there was no risk of major congenital anomalies associated with metformin. Other studies also gave the conclusion that oral hypoglycemic agents when compared with insulin are

not much different from insulin therapy in terms of maternal or neonatal outcomes, in women with gestational diabetes[23,17].

A study by Rai et al.[24] demonstrated that although insulin showed slightly better results, even then the difference was not statistically significant (p=0.08-069). In this study it was also found that adjusted glucose levels were significantly reduced in group of patients treated with metformin as compared to those treated with insulin (p=<0.001-0.003) after treating for one week. In other words metformin was uniform in controlling glucose level in comparison to insulin. But drawback of this particular prospective study was that sample size was not large enough.

Ija's H et al.[25] demonstrated that among the patients treated with metformin 32% required additional insulin to reach the normal blood glucose level. The observations suggest that women who needed additional insulin were mostly more obese, required earlier medical treatment and had higher fasting blood sugar levels as compared to the women who only required metformin to reach normal glucose levels. These findings suggest that these women had higher insulin resistance.

CONCLUSION

This study concludes that metformin is as much effective as insulin in management of gestational diabetes mellitus. Metformin when used securely can prove effective as it does not cause any congenital anomalies or maternal or neonatal complications. But insulin still remains the gold standard for treatment of gestational diabetes mellitus.

Author's Contribution:

Concept & Design of Study:	Rao Muhammad Akram Khan
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Data Analysis:	Ayesha Mukhtar
Revisiting Critically:	Rao Muhammad Akram Khan, Anam Khawar
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Original Article

Obstructive Sleep Apnea Syndrome

Relationship of Platelet-Lymphocyte Ratio with Severity of Obstructive Sleep Apnea Syndrome

Rafia Komal Masood, Muhammad Shoaib and Sadia Falak

ABSTRACT

Objective: To assess the inflammation in obstructive sleep apnea syndrome patients by using platelet lymphocyte ratio and relationship between platelet lymphocyte ratio and severity of obstructive sleep apnea.

Study Design: Retrospective cohort study

Place and Duration of Study: This study was conducted at the Medicine department of Nishtar Hospital Multan from June 2016 to March 2017.

Materials and Methods: Total 280 patients were selected by non-probabilityconsecutive sampling. All patients underwent whole night polysomnography. Patients were divided into control group (AHI <5), mild OSAS group (AHI 5-15), moderate OSASgroup (AHI 15-30) and sever OSAS group (AHI >30) according to their AHI score. Numerical variables like age, body mass index, white cell count, platelets, hemoglobin (Hb) and platelet lymphocyte ratio were statistically analyzed by mean and standard deviation and t-test applied to assess their significance. Qualitative variables like gender and smoking status were statistically analyzed by frequency and percentage. Chi square test was applied to check the significance. P value <0.05 was regarded as significant.

Results: Platelet lymphocyte ratio was significantly raised in patients with obstructive sleep apnea syndrome. There was significant correlation between platelet lymphocyte ratio and AHI ($p<0.05$). So study showed that there was significant association between obstructive sleep apnea syndrome severity (represented by AHI) and systemic inflammation (represented by PLR). Significant differences were found between age (p=0.000), ESR (p=0.000), CRP (p=0.003), Cholesterol (p=0.000), Platelets (p=0.048), Hb (p=0.000), PLR (p=0.000) and white blood cells (p=0.000), in groups. Association was found between gender (p=0.000) and smoking status (p=0.030) in groups. So, gender and smoking were the effect modifiers.

Conclusion: New inflammatory markers are required to investigate the level of systemic inflammation in obstructive sleep apnea syndrome patients. Platelet lymphocyte ratio, an easy, quick and cheap measurable marker on routine CBC analysis, could be considered for assessing the inflammation in patients of obstructive sleep apnea syndrome.

Key Words: Obstructive sleep apnea syndrome, Platelet lymphocyte ratio, polysomnography

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is very common sleep disorder[1]. Snoring is most common symptom of obstructive sleep apnea syndrome. It affects 7% of women and 20% of men in whole population[1]. It is one of the bigger health problem of adults. Upper airway collapse during sleep results in recurring apnea, disturbed sleep, excessive daytime sleepiness and intermittent hypoxia[2].

Most occurring nocturnal symptoms of obstructive sleep apnea syndrome are snoring and observed apneas.

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Disruption of normal sleep pattern and ventilation results in many complications through various pathophysiology. Obstructive sleep apnea syndrome patients suffer impaired quality of life and decrease performance status[1]. Several factors have been considered for development of obstructive sleep apnea syndrome. Obesity is one of major risk factor for developing obstructive sleep apnea syndrome[3]. It is reported that 70% patients of obstructive sleep apnea syndrome are obese[3]. Other risk factors are alcohol consumption, smoking, chronic pain and chronic opioid therapy[4]. This disorder develops due to reduction of the expansion forces of the pharyngeal dilator muscles, as it occurs ingenioglossal muscle dysfunctionand discoordination between the respiratory effort and inspiratory activity of the muscle. It is also reported that obstructive sleep apnea syndrome is associated with vitamin D deficiency[5]. Obstructive sleep apnea syndrome is contributing factor for many diseases. It is associated with cardiovascular diseases, neurological

diseases and metabolic diseases[6]. So physicians should properly investigate and address this issue.

Many studies have shown that systemic inflammation, endothelial damage, oxidative stress, and increased coagulation factors in patients of obstructive sleep apnea syndrome are caused by many factors[7]. White blood cells and its subtypes are recognized inflammatory markers[8]. One of this is neutrophil-lymphocyte ratio (NLR). The rationale of this is because in inflammation there is decrease in lymphocytes count and increase in neutrophils count, so the ratio of these two can be used as marker of inflammation. Recent studies have shown platelet-lymphocyte ratio another inflammatory marker that can predict adverse outcome in cardio vascular diseases[9]. Because platelet count is indicator of severity of inflammation. Pro-inflammatory cytokines stimulate the megakaryocytes that result in thrombocytosis[10].

Like NLR, platelet lymphocyte ratio (PLR) is also associated with mortality of acute myocardial infarction[11]. But data is lacking about the association of inflammation in obstructive sleep apnea syndrome patients and platelet lymphocyte ratio. We want to investigate the issue in our region. So that it can help to establish the relationship between platelet lymphocyte ratio and severity of obstructive sleep apnea syndrome. It will also provide base for further research on this topic in coming days. Study done by Yeo-Jeong Song Et al. was taken as reference study[20].

MATERIALS AND METHODS

This retrospective cohort study was conducted in department of Medicine, Nishtar Hospital Multan, from June 2016 to march 2017 after approval of the study was taken from institutional ethical committee. Written permission was taken from all patients enrolled in study. Total 280 patients were selected by non-probability consecutive sampling. Patients with following disorders were excluded: 1) patients with history of any systemic disease like liver disease 2) history of secondary hypertension 3) complaint of respiratory infection and failure 4) central nervous system disorders 5) any history of malignancy 6) having critical illness with poor functional status 7)history of heart failure and acute coronary syndrome or having myocardial infarction or any revascularization procedure. Sample size of the study calculated by a reference study done by Yeo-Jeong Song Et al. For which confidence interval was taken as 95 %, power of study 80, odd ratio of platelet lymphocyte ratio was 3.37 (www.openepi.com).

All patients participated in study were enrolled from outpatient department. Patients who presented with history of fatigue, day time sleepiness, snoring and disturbed sleep were selected. Patients who had high malampati score and short neck and also having history of disturbed sleep and snoring were also selected. A detailed physical examination was conducted in each patient to investigate the features of obstructive sleep apnea syndrome, its complications and also any clues of other systemic disease. All patients with normal renal status and age between 18 to 80 were include. During first visit demographic variables like age, gender, weight, height, income, medication history and other diseases were recorded. All patients underwent polysomnography.

The system of polysomnography contains four channels of electroencephalogram and two channels of electrooculography, submental electromyography (EMG), pulse oximeter for recording oxygen saturation, thoracic and abdominal movements, electrocardiogram, tracheal sound and orinasal air flow. A complete cessation in airflow for more than 10s was taken as apnea.Air flow reduction >30% for greater than 10s with 4 % decrease in oxygen saturation of patient was defined as hypopnea.[12] Severity of obstructive sleep apnea was calculated by apnea hypopnea index. Apnea hypopnea index is number of events of apnea and hypopnea per hour during sleep. All patients were divided into four groups according to their apnea hypopnea index scores: 1) the control group with AHI <5, 2) mild OSAS group with AHI 5–15, 3) moderate OSAS group with AHI 16–30, and 4) severe OSAS group with AHI score >30.

Complete blood count was analyzed along with serum glucose, cholesterol, erythrocyte sediment rate and c reactive protein. Platelet lymphocyte ratio was calculated by dividing lymphocytes from platelets.

Data was analyzed by SPSS volume 23. Numerical variables like age, body mass index, white cell count, platelets, hemoglobin (Hb) and platelet lymphocyte ratio were statistically analyzed by mean and standard deviation and t-test applied to assess their significance. Qualitative variables like gender and smoking status were statistically analyzed by frequency and percentage. Chi square test was applied to check the significance. P value <0.05 was regarded as significant.

RESULTS

Overall, 100% (n=280) patients were enrolled in this study; divided according to OSAS status i.e. control group (n=63), mild OSAS group (n=60), moderate group (n=67) and severe OSAS group (n=90). The mean age and BMI of the control group patients was 45.22±2.57 years and 23.90±2.66 kg/m^2 respectively. There were 57.1% (n=36) males and 42.9% (n=27) females. Smoking status showed that there were 87.3% (n=55) non-smokers and 12.7% (n=8) were smokers. The mean age and BMI of the Mild OSAS group patients was 49.85±2.11 years and 24.03±2.74 kg/m^2 respectively. There were 76.7% (n=46) males and 23.3% (n=14) females. Smoking status showed that there were 90% (n=54) non-smokers and 10% (n=6) were smokers. The mean age and BMI

of the moderate OSAS group patients was 50.37±2.28 years and 27.00±3.03 kg/m^2 respectively. There were 89.6% (n=60) males and 10.4% (n=7) females. Smoking status showed that there were 74.6% (n=50) non-smokers and 25.4% (n=17) were smokers. The mean age and BMI of the severe OSAS group patients was 52.34±2.60 years and 26.54±2.66 kg/m^2 respectively. There were 82.2% (n=74) males and 17.8% (n=16) females. Smoking status showed that there were 74.4% (n=67) non-smokers and 25.6% (n=23) were smokers. (Table. 1).

Table No. 1: Demographic Variables

Variable	Control group n=(63)	Mild OSAS group n=(60)	Moderate OSAS group n=(67)	Severe OSAS group n=(90)	Test of Sig.
Age	45.22±2.57 years	49.85±2.11 years	50.37±2.28 years	52.34±2.60 years	F=3.95 p=0.000
BMI	23.90±2.66 kg/m^2	24.03±2.74 kg/m^2	27.00±3.03 kg/m^2	26.54±2.66 kg/m^2	F=1.25 p=0.175
Gender	M=57.1%, F=42.9%	M=76.7%, F=23.3%	M=89.6%, F=10.4%	M=82.2%, F=17.8%	χ^2=21.47, p=0.000
Smoking Status	Non-smoker=87.3%, Smoker=12.7%	Non-smoker=90%, Smoker=10%	Non-smoker=74.6%, Smoker=25.4%	Non-smoker=74.4%, Smoker=25.6%	χ^2=8.95 ,p=0.030

Table No. 2: Characteristics of OSAS patients

Variable	Control group n=(63)	Mild OSAS group n=(60)	Moderate OSAS group n=(67)	Severe OSAS group n=(90)	Test of Sig.
ESR, mm/hour	8.01±2.27	18.25±2.29	17.71±9.27	14.38±3.80	F=5.21, p=0.000
CRP, mg/L	0.63±0.35	1.31±0.85	0.78±0.33	1.72±1.47	F=1.92, p=0.003
Cholesterol, mg/dl	170.21±11.88	185.72±5.58	190.42±11.21	175.34±5.90	F=3.49 ,p=0.000
Platelets, 10^9/L	221.35±12.11	225.23±5.88	230.96±4.69	254.01±10.78	F=1.49 ,p=0.048
Lymphocytes, %	36.25±5.00	35.20±2.66	31.88±4.37	28.24±4.96	F=1.39, p=0.085
Hb, g/dl	12.95±1.30	15.26±2.14	13.01±2.08	14.06±1.14	F= 2.71, p=0.000
PLR	98.80±7.69	114.90±2.13	121.63±5.53	141.60±19.83	F=2.59, p=0.000
WBC, 10^6/L	6760.23±14.10	7287.03±24.08	7314.83±23.36	7720.83±27.44	F=4.81, p=0.000

The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the control patients was 8.01±2.27 mm/hr, 0.63±0.35 mg/L, 170.21±11.88 mg/dl, 221.35±12.11×10^9/L, 36.25±5.00 %, 12.95±1.30 g/dl, 98.80±7.69 and 6760.23±14.10×10^6/L respectively. The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the mild OSAS patients was 18.25±2.29 mm/hr, 1.31±0.85 mg/L, 185.72±5.58 mg/dl, 225.23±5.88 ×10^9/L, 35.20±2.66 %, 15.26±2.14 g/dl, 114.90±2.13 and 7287.03±24.08×10^6/L respectively. The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the moderate OSAS patients was 17.71±9.27 mm/hr, 0.78±0.33 mg/L, 190.42±11.21 mg/dl, 230.96±4.69 ×10^9/L, 31.88±4.37 %, 13.01±2.08 g/dl, 121.63±5.53 and 7314.83±23.36×10^6/L respectively. The mean ESR, CRP, cholesterol, platelets, lymphocytes, Hb, PLR and WBC of the severe OSAS patients was 14.38±3.80 mm/hr, 1.72±1.47 mg/L, 175.34±5.90 mg/dl, 254.01±10.78 ×10^9/L, 28.24±4.96%, 14.06±1.14 g/dl, 141.60±19.83 and 7720.83±27.44×10^6/L respectively. (Table. 2).

Significant differences were found between age (p=0.000), ESR (p=0.000), CRP (p=0.003), Cholesterol (p=0.000), Platelets (p=0.048), Hb (p=0.000), PLR (p=0.000) and white blood cells (p=0.000), in groups. Association was found between gender (p=0.000) and smoking status (p=0.030) in groups. So, gender and smoking were the effect modifiers. (Table. 1-2).

DISCUSSION

Study was concluded with two main findings. One, thatplatelet lymphocyte ratio, an inflammatory marker, was significantly raised in obstructive sleep apnea syndromepatients. Second, there was significant correlation between platelet lymphocyte ratio and AHI ($p<0.05$). So study showed a significant association between obstructive sleep apnea syndrome severity (represented by AHI) and systemic inflammation (represented by PLR).

Previous studies had shown that there is association of elevated platelet counts with poor outcome of cardiovascular (CV) diseases[13-14], and also there is association of lower lymphocytes count with higher mortality and morbidity of cardiovascular diseases[14]. So combination of these two markers have emerged as potential inflammatory marker and outcome predictor in many malignant diseases and cardio vascular diseases[15-16]. It has been also reported that platelet lymphocyte ratio is predictor of long term and in hospital mortality in patients with STEMI and non-STEMI[17-18].

Platelets can interact with many inflammatory cells like dendritic cell, neutrophils, T-lymphocytes, mono-nuclear phagocytes and can also interact with endothelial cells. The relation between these cells and platelets might initiate the inflammation. Previous studied reported that activated platelets could initiate inflammation by recruitment of white blood cells.

Obstructive sleep apnea syndrome is not simple disorder that occurs during sleep. Multiple studies had shown that obstructive sleep apnea syndrome patients have increased levels of inflammatory markers compared to matched controls and after using continuous positive airway pressure as treatment, significant decrease in these markers occur[19].

Previous study also reported results that are equivocal to our study and these results show that there is significant association between platelet lymphocyte ratio and severity of obstructive sleep apnea syndrome[20]. In this study there was also significant correlation between higher age and body mass index with higher AHI index.

Another study also supports this investigation with results that increased systemic inflammation assessed by platelet lymphocyte ratio with severity of obstructive sleep apnea syndrome[21].

In past there were conflicting reports about association of upper airway obstruction and inflammatory markers[22-23]. Korkmaz M.et al[22] reported that severity of systemic inflammation cannot be predicted by other traditional markers like C-reactive protein and ESR.

Explanation to the relationship between inflammation and severity of obstructive sleep apnea syndrome is sleep deprivation and intermittent hypoxia. Many reports had shown that obstructive sleep apnea syndrome develop inflammatory response and high level of inflammatory mediators like coagulation factor, inter cellular adhesion molecules (ICAM) and CRP[24].

Calculation of platelet lymphocyte ratio is very cheap and easy method as compared to other mediators like interleukins (IL-6, IL-1b) and TNF-alpha. Study results showed that inflammation in obstructive sleep apnea syndrome patients can be predicted by platelet lymphocyte ratio. So this inexpensive and easy procedure should be adopted by pulmonologists to assess the inflammation in patients of obstructive sleep apnea syndrome on first stage.

Limitation of the study was that sample size was very small relatively and other inflammatory markers like ESR and CRP were not compared with platelet lymphocyte ratio.

CONCLUSION

New inflammatory markers are required to investigate the level of systemic inflammation in obstructive sleep apnea syndrome patients. Platelet lymphocyte ratio, an easy, quick and cheap measurable marker on routine CBC analysis, could be considered for assessing the inflammation in obstructive sleep apnea syndrome patients.

Author's Contribution:

Concept & Design of Study:	Rafia Komal Masood
Drafting:	Sadia Falak, Muhammad Shoaib
Data Analysis:	Sadia Falak, Muhammad Shoaib
Revisiting Critically:	Rafia Komal Masood, Sadia Falak
Final Approval of version:	Rafia Komal Masood

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

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