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Editorial

A Challenge: Drug Resistance

Mohsin Masud Jan
Editor

WHO's new Global Antimicrobial Surveillance System (GLASS) reported the presence of antibiotic resistance in 500,000 patients across 52 enrolled countries, both the developed and under developed ones.

The report confirms a serious and challenging situation for this resistant pattern worldwide. WHO report also confirmed a serious situation regarding the deficiency for the development of new and effective antibiotics to win this warfare for antimicrobial resistance trend.

Even some of the newly available antibiotics are just the structural modifications of already existing ones. Therefore, they are providing a temporary solution. These circumstances are posing high morbidity and mortality rate.

'The antibiotic resistance has now arose to the extent of global health emergency, which has ultimately threatened the progress in modern medicine e.g. the drug resistant tuberculosis can be attributed to the death of 250,000 people annually worldwide. Similar high mortality rate was seen with many other resistant bacterial infections as well and it is alarming that without the identification of permanent solution, even with minor surgeries, a fatal outcome can be seen.

Once, Penicillin was considered as a magic bullet to treat any sort of serious infection but now the situation has drastically changed. A reported resistance to penicillin ranges between 51 to 82 per cent for less severe infections like urinary tract infection, diarrheal illnesses, pneumonia to complicated systemic infections.

Furthermore, the lack of treatment options for multidrug resistant and extremely drug resistant tuberculosis, Acinetobacter species, Escherichia coli and Klebsiella pneumoniae are adding up to great health burdens and losses. "The miseries of patients on life saving ventilator support go on increasing by super added extremely drug resistant infections."

Moreover, availability of suitable drugs in black and on high costs adds up to worsen the situation, she said. Due to less treatment options, the resultant outcome in most cases becomes fatal and hence there is a dire need of discovery of new and safer antibiotics.

The pharmaceutical companies and researchers should come forward to identify the solution for this burning global issue and the quality of available antibiotics should be frequently checked by the national drug regulatory authorities to ensure their efficacy.

It is genuine opinion that till the availability of new options, the steps needed to combat this situation should be avoidance of frequent antibiotic usage for minor infections, early case recognition with the help of culture and sensitivity while in hospital settings, active involvement of infection control committees should be ensured to set infection control and isolation protocols for the management of such cases.

However sterilization/disinfection protocols, along with hand washing techniques, all will help checking transmission of resistant infections among the patients in hospitals.

It is required that the government should focus on training the healthcare staff for effective practice of sterilization/disinfection procedures and provision of hand disinfectants and sanitizers should be ensured with each bed in hospitals.

Also, the hospital staff associated with cleaning of washrooms should ensure usage of disinfectant to avoid spread of resistant bugs and the beddings of patients with resistant infections should be handled vigilantly. "Finally the hospital waste segregation should be done carefully for final disposal."

The malpractices of excessive use of high potency antibiotics to treat self limited infections should be checked by authorities and must be discouraged. The culture of excessive, unnecessary, high potency and multiple combinations of antibiotics should be discouraged and doctors, nursing staff, attendants and patients should work together vigilantly to combat this battle against the drug resistance.

Original Article

Treatment of Post Adolescent Female Acne with Spironolactone and Low Dose Isotretinoin

Habib ur Rehman[1], Uzma Sarwar[1], Muhammad Mansoor Majeed[2] and Muhammad Azam Bokhari[1]

ABSTRACT

Objective: To assess the synergistic efficacy and side-effects of spironolactone added to 20 mg isotretinoin/day.
Study Design: Observational study
Place and Duration of Study: This study was conducted at the Dermatology Department, Shalamar Hospital Lahore from March 2015 to December 2017.
Materials and Methods: 96 adult females between the ages of 25 and 45 years (mean age 31.6 years) were selected. All 96 women included in the study had regular menstrual history without any signs or symptoms of hyperandrogenism. They were treated with 50-100 mg spironolactone daily, in addition to 20 mg isotretinoin irrespective of age and weight of the patient for six months. Patients were clinically examined in the beginning, then every month during the treatment and on the follow up visits. Serum testosterone, DHEA-S, Serum Potassium levels were measured in the beginning and at the end of the treatment.
Results: Out of 96 patients 80 completed the study. 75 (93.75%) of patients were declared completely cured in six months. 5(6.25%) patients were not declared cured but showed satisfactory improvement. Recurrence was seen in 16(20%) patients. 17(21.25%) patients showed menstrual cycle irregularities, breast tenderness, cheilitis and xerosis. Potassium levels remained within normal limits. Serum testosterone, DHEA-S levels either decreased or remained at the same level at the end of the treatment.
Conclusion: Spironolactone given with isotretinoin was found to be more effective in adult female patients with acne than either drug alone. The drugs were well tolerated and showed good results with minimum side effects.

Key Words: Female adult onset acne, Spironolactone, Isotretinoin

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INTRODUCTION

Acne is considered as the eighth most prevalent disease around the world[1]. Adult acne is defined as acne that presents after 25 years of age. Adult acne mainly affects women and is resilient to conventional treatment in 79-82% of cases[2]. Post adolescent acne may continue past the teenage years (Persistent Acne) or develop at or after 25 years till 45 years of age even beyond (Adult Onset Acne)[3]. Acne in adult women presents with nodules, pustules, inflammatory papules or comedons. The most common part is the face but the lesion may appear on the trunk as well[4]. The most common problem faced by females because of acne vulgaris is the cosmetic issue and it may have a negative impact on a patient's quality of life.

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Adult acne in females is frequently related with nervousness, depression, and it effects the quality of life badly[5]. Acne is a disease of sebogenesis despite of the age factor[6]. Most women with acne have normal serum androgen levels. Local production of androgens or an increased sensitivity of sebaceous glands to androgens may contribute to acne in these women[7]. Assessment should include a menstrual history, premenstrual flare and examination for clinical signs of hyperandrogenism[8]. Other important history points include Age of onset, Family history, Obstetric/Gynecological history, Oral contraceptive pills[9], Obesity, Diabetes, Recent systemic illness[10]. History of drug intake, smoking and sun exposure is also important[11]. Females should be asked about the pregnancy and future plans for childbirth as it is desirable to avoid acne treatments during pregnancy[12].

Treatment: There remains a requirement for treatment options with enhanced efficacy and tolerable side effects. The general principles of the treatment are to reduce sebum secretion, comedon formation, reducing propionibacterium acne and inflammation[13]. There are high rates of treatment failure and side effects with traditional therapies[14]. Multiple courses of antibiotics failed approximately in 80% of women and around 30% of patients reverted after numerous therapeutic courses

of isotretinoin[15]. It is found that females even with normal levels of androgen have shown significant improvement when treated with antiandrogen drugs. Moreover addition of antiandrogens to isotretinoin can have a synergistic effect[16]. The American Academy of Dermatology has suggested the use of multiple agents with dissimilar mode of action in the management and treatment of acne[17]. Patients must be encouraged to complete the full course of treatment as response to treatment is slow[18].

Isotretinoin is the only therapy that impacts on all the major etiological factors implicated in acne[19]. Low-dose systemic isotretinoin (20 mg/kg/day) for the duration of about 6 months helps in resolution and reduction of acne. Low doses of isotretinoin are tolerated well with minimum side effects[20].

Spironolactone. For the last 3 decades it has been used for the management of hirsutism and acne[21]. It is not FDA approved for acne treatment but has been used off label for the treatment of adult onset acne. To get the anti-androgenic effects there are several mechanisms:

1. Competition with testosterone and DHT for androgen receptors.
2. Inhibition of local androgen synthesis.
3. Inhibition of 5α-reductase, reducing the conversion of testosterone to DHT.
4. Increasing the level of SHBG thus reducing free testosterone level[22].

The dose 50 to 200mg daily is usually given for the treatment of acne. In order to minimize the side effects associated with the higher dose, the lower doses with almost same effectiveness can be given in the management of acne[23]. Menstrual irregularities , hyperkalemia and tenderness of the breast are the most common side effects[24]. Feminization of the male fetus is the side effect of Spironolactone and it is contraindicated in pregnancy[25].

MATERIALS AND METHODS

This was an uncontrolled, open label, non-comparative, observational study, number of study participants were 96 living in Lahore and neighboring areas. The patients had mild to severe acne, ages between 25 years to 45 years were selected randomly from the outpatient of the Dermatology Department, Shalamar hospital Lahore, after obtaining ethical permission from hospital ethical committee and informed consent from participants. The study period was from March 2015 to December 2017. Global Acne Grading System(GAGS)[26] was used for assessing severity of the acne. Following criteria was used in selecting the patients:

Inclusion Criteria:

1. Patients between 25 to 45 years of age.
2. Patients with mild to severe acne.
3. Patients having normal menstrual cycle.
4. Patients giving written consent not to get pregnant during treatment or after 1 month of stopping treatment.

Exclusion Criteria:

1. Patients suffering from Diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia.
2. Patients with signs/symptoms of hyperandrogenism.
3. Patients with signs/symptoms of hyperprolactinemia.
4. Patients planning to conceive.
5. Females on contraceptives or on any other medicines which may have side effects of acne.

The patients received 25 to 100 mg spironolactone as morning dose depending on the severity and weight of the patient. 20mg Isotretinoin was given after lunch to all patients irrespective of their weight. Written consent "not to get pregnant" was signed from all the study participants. Before the start of the drug treatment the lesions were counted and patient's acne was graded before, during and at the end of the therapy. After taking consent pictures of the participant were taken. Before and after the treatment DHEAS, serum potassium and testosterone levels and blood pressure was analyzed. The duration of treatment was planned for 6 months and follow up visits were conducted every month for 6 months after completion of treatment. During the follow-up visit Blood pressures was also recorded. Regarding face cleansing same advice were given to all the research participants.

Statistical Analysis: For Data entry and Statistical analysis SPSS version 17 was used. Chi-square were used where appropriate. P value less than or equal to 0.05 was considered as significant.

RESULTS

In this study we incorporated 96 patients who followed the inclusion criteria; out of ninety-six patients 80 completed the study. Due to severe menstrual irregularities 4 of the study participants stopped the drug. Other 12 patients were excluded because they did not come for the treatment regularly and they all were those who experience of ineffective treatments previously. The ages of the patients were between 25 to 45 years (mean age was 31.6 years). Duration of the disease was variable between 2 to 10 years mean 6.5 years (Table 1). The number of participant who had undergone some kind of treatment before were 66 patients. As per severity 20(25%) patients had mild, 25(31.25%) patients had moderate and 35(43.75) patients had severe acne (Figure 1).

After 6 months of treatment clinically full improvement was observed in 75 study participants (93.75%) and were declared cured, these result are significant ($p<0.05$). The remaining 5(6.25%) patients were not cured completely but showed satisfactory response. All

not cured patients had severe acne before the start of the treatment.

Table No.1: Age and Duration of the Disease

	Minimum	Maximum	Mean
Age of the participant	25 years	45 years	31.68 ±5.27
Duration of The Disease	2 years	10 years	6.46 ± 2.24

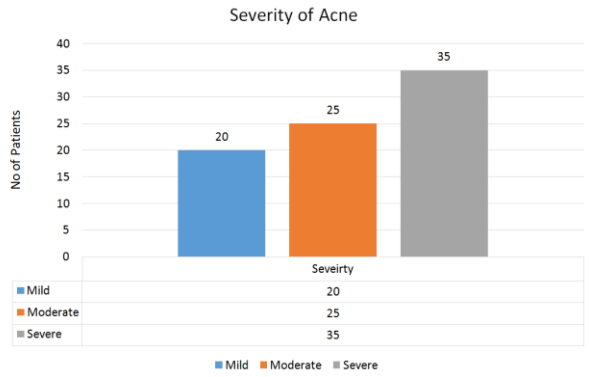

Figure No.1: No of participants with different mild, moderate and severe cases of Acne

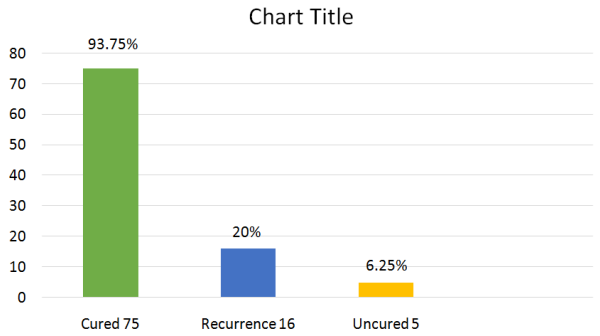

Figure No.2: Distribution of cases at the end of the treatment

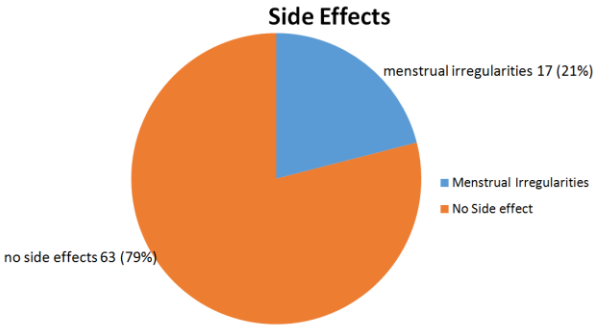

Figure No.3. Side Effects observed during treatment.

The lesions completely disappeared in those who were declared cured. Acne reoccurred in 16(20%)patients during 6-month follow-up period (Figure 2).17 patients (21.25%) experienced menstrual irregularities. Out of 17 patients, 13 (16.25%) had intermenstrual bleeding, 4 (5%) had hypermenorrhea. 63 (79%) showed no side effects (Figure 3). Additional side effects were observed in those patients already reported for menstrual irregularities, 2(2.5%) developed breast tenderness, 2(2.5%) nausea and vomiting. and 2(2.5%) developed xerosis and cheilitis. Menstrual complaints vanished within 2–3 months of treatment; all further symptoms disappeared within 15 to 45 days of the treatment. The Potassium levels were found within normal limits before and after treatment. No significant change in blood pressure was found. Serum testosterone and DHEA-S levels decreased or remained same at the end of the treatment.

DISCUSSION

In this study we analyzed the role of spironolactone along with low dose of isotretinoin for the treatment of Post Adolescent Female Acne. We found that 82.6% (n=66) of the study participants had taken the treatment before. Despite advances in the acne treatment, treatment failures are common in a significant number of adult women. Majority of the patients fail to respond to standard therapies and have a strong cyclical acne pattern, suggesting hormonal mediation[27]. In our study we found significant improvement in the patients.

Multiple researches have been conducted to find out the effect of spironolactone in the treatment of adolescent acne alone or in addition to antibiotics or isotretinoin. Yemisci et al[28] conducted a similar research and established that 85% of the participants with major improvements in acne. In a study on 139 female patients conducted in Japan with a 5 months tapering regime of oral spironolactone. Out of 139 patients, 64 completed the study and this study reported 100% response with around half of the patients showed excellent response[29]. The result of this study also favors our findings. In agreement to our results a trial was conducted, in which 27 female patients were treated with 50 to 200 mg/day spironolactone with acne for the duration of One month to one and half year and exhibited around 90% mean clinical improvement in varying degrees[30]. Our study results are in accordance with the study in which 85 female patients of acne were treated with spironolactone, 50–100 mg/day, Out of 73 patients who completed the treatment 48(66%) were completely cured or demonstrated marked improvement[31]. In a 4 year comparative retrospective study on 400 patients reported significant results with spironolactone along with topical and oral agents , moreover spironolactone with topical and oral drugs have better cure ratio than previously treated patients[32].

We have observed complete clinical improvement in 75(93.75%) of our patients. Only 5(6.25%) patients were not completely cured however we found significant decreased in the mean number of lesions after the completion of the treatment. We also found that the DHEA-S and total serum testosterone levels reduced or remained unchanged. Hughes and Cunliffe[33]

performed a study to find out the Spironolactone tolerance in females; 72% of the females with 200 mg/day of Spironolactone reported menstrual irregularities and 30% reported breast tenderness. Whereas in the present study, menstrual irregularities were present in only 17 patients (21.25%) and breast tenderness was reported only in 2 patients (2.5%). It is previously reported that 50-100 mg/day of spironolactone is linked with a considerable lower occurrence of side effects than as observed with higher doses[31]. The incidence of side-effects of low dose Spironolactone is usually mild and most females tolerate the treatment easily[34].

CONCLUSION

Our study indicates that for women with hormonal flare of acne, spironolactone can be a helpful addition. Spironolactone in low doses added to Isotretinoin is a safe and effective medication for adult females with acne. For a better and evidence-based results it is recommended that double-blind, randomized comparative studies with higher number of female patients should be conducted.

Author's Contribution:

Concept & Design of Study:	Habib ur Rehman
Drafting:	Uzma Sarwar
Data Analysis:	Muhammad Mansoor Majeed, Muhammad Azam Bokhari
Revisiting Critically:	Uzma Sarwar, Habib ur Rehman
Final Approval of version:	Habib ur Rehman

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

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Original Article

Hemostatic Abnormalities in Diabetic Patients

Subhan Uddin[1], Shahtaj Khan[2], Saadia Haroon Durrani[1] and Baber Rehman Khattak[2]

ABSTRACT

Objective: To evaluate hemostatic Abnormalities in Diabetic patients via deranged PT, APTT and D-dimer.
Study Design: Descriptive study
Place and Duration of Study: This study was conducted at the Pathology Department, Bacha Khan Medical College and MMC Teaching Hospital Mardan from September 2016 to June 2017.
Materials and Methods: In study 100 patients of Diabetes Mellitus (type-2) and 50 healthy cases as control were included. Sample was divided into Group A and Group B, each with 50 patients on the basis of glucose levels, 200-300 mg/dl and 300-400 mg/dl respectively. In all these patients Hemostatic markers were studied.
Results: In Group A, 25 patients had elevated D-dimer level. Among 20 of them D-dimer level was 250-500 ng/ml and 5 had 500-1000 ng/ml level, however 3 patients had shortened PT, mean value 12.562±0.432 seconds while APPT was normal. In Group B 27 patients had raised D-dimer level. Among 20 of them D-dimer value was 500-1000 ng/ml and 7 had 250-500 ng/ml. However 2 patients had shortened PT and 2 had prolonged APTT. Mean values of 13.562±0.232 and 43.562±0.262 seconds respectively. This study show that PT and APTT were not significantly altered, while D-dimer level was significantly elevated in both groups in comparison to control group, P<0.00326 and P<0.00322 respectively.
Conclusion The study concluded that Diabetes Mellitus is associated with significant hemostatic abnormalities and deranged hemostatic markers identify patients prone complications and helps in reducing morbidity and mortality in Diabetic patients.

Key Words Diabetes Mellitus, D-dimer, PT, APTT

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INTRODUCTION

Diabetes is the most important cause of vascular Morbidity, often associated with cardiovascular compilations, hypercholesterolemia, hypertension, obesity and increased markers of coagulation and inflammation.[1] cerebrovascular, peripheral vascular and Coronary heart disease has 80% prevalence in patient with Diabetes Mellitus.[2] Cerebrovascular disease and peripheral vascular disease is tenfold more common in Diabetic patients.[3] Increased risk of stroke has also been reported in diabetes mellitus.[4] Diabetic patients have a hyper-coagulable state, associated with high risk of thrombus formation and accelerated atherosclerosis. This is evident by increased serum level of fibrinogen, low levels of plasma proteins and increased formation of von-Willi brand factor by Endothelium.[5] Diabetes Mellitus (type 2) patients can have both micro-vascular and macro-vascular complications.[6]

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Common micro-vascular complications in these patients include neuropathy, nephropathy and retinopathy while coronary artery disease, peripheral arterial disease and strokes are macro-vascular complications.[7] Diabetes Mellitus has a hypercoagulable state and hemostatic abnormalities are commonly seen in this disease. Among diabetic patients 80% die of thrombotic complications and 70% deaths result from cardiovascular events.[8] Metabolic disturbances commonly occur in type 2. Diabetes Mellitus such as atherogenic dyslipidemia, hypertension, glucose intolerance and a pro-thrombotic state.[9] The pro-thrombotic state is caused by increased fibrinogen level, increased plasminogen activator inhibitors and many different abnormalities.[10] Diabetes Mellitus is a major public disease and involves a huge population of the world, and about 347 million individuals are affected. The aim of the study was to identify those diabetic patients who are at increased risk of hypercoagulable and pro-thrombotic states, by measuring coagulation marker like D-dimer PT and APPT which can provide immediate information regarding thromboembolic conditions and also useful to the clinician to reduce the complications of the disease.

MATERIALS AND METHODS

The study was done in the Medical unit of MMC teaching hospital Mardan and Pathology Laboratory of

Bacha Khan Mediacal College Mardan. Patients were divided into two groups, group A and group B and a control group C. In each group 50 cases were included. Group A had 50 patients of diabetes having glucose level at the range of 200-300mg/dl. Group B included patients having glucose level of 300-400 mg/dl. Group C had 50 normal healthy individual as control. Only diabetic patients both adults males and females were included in the study. The patients with Hypertension and history of DVT, pulmonary Embolism, and septicemia were excluded from the study.

Blood sample of 5 ml was collected from each patients in a tube containing sodium citrate, the plasma was then separated and this plasma was then utilized for determination of coagulation markers. Prothrombin time (PT), D-dimers and Activated partial thromboplastin time (APPT) were studied. D-dimer is a fragments of clot, it is formed due to proteolytic degradation of clot by enzyme plasmin. D-dimer fragments increases in any condition where both clot formation and subsequent fibrinolysis are increased so measurement of D-dimer identity both clot formation and its subsequent degradation. Its function is to determine the seventy of hypercoagulable state, as hypercoagulable state is more prone to thrombogenic state and this D-dimer is a reliable marker for systemic pro-thrombotic conditions or clot formation in the body. Minutex D-dimer is a latex agglutination test for semi-quantitative determination of D-dimer fragments. Minutex D-dimer contains a monoclonal antibody reacting with fibrin D-dimer fragments. In this method, 2 µl of sample is mixed with 20 µl of D-dimer reagent and agglutination is seen within 3 minutes. If agglutination is positive then serial dilution is done. Serial dilutions of test plasma are made with Buffer: for 1:2 dilution 100 µL test plasma, 100 µL Buffer solutions is added. For 1:4 dilutions, to100 µL of 1:2 diluted plasma add 100 µL Buffer solutions. For 1:8 dilution, to 100 µL 1:4 dilution plasma add 100 µL Buffer solution. Then with each dilution sample test is repeated to quantitatively measure D-dimer concentration. Normal level of D-dimer is less than 250 ng /ml in undiluted sample. When positive in undiluted sample its level is 250-500 ng/ml, if agglutination seen in 1:2 dilution its level is 500-1000 ng/ml if agglutination seen in 1:4 dilution D-dimer level is 1000-2000 ng/ml, if agglutination seen in 1:8 dilution D-dimer level is more than 2000 ng/ml. Their raised levels characterize thromboembolic condition in the body in any system and are therefore a useful hemostatic marker and help the physician to go further for other supportive investigation and treatment option. PT and APTT are also hemostatic investigation and measure the activity of both extrinsic and intrinsic pathway of coagulation cascade. Normally PT level is 10-14 seconds and APPT level is 30-40 seconds. Its increased or low level gives information to the clinician about the hemostatic states of the patients. These investigations were also performed according to standard method manually and both by coagulation analyzer for accuracy. Its prolongation signifies the coagulation factor deficiency or consumption, while its low level signifies a hypercoagulable state.

The data was statistically analyzed by Chi-Square and T-test, level of significance was set at $P<0.0005$.

RESULTS

In our study 100 patients were included, which were divided into two groups, group A and group B. Group A patients had glucose level at the range of 200-300 mg/ml and Group B patients had glucose level at the range of 300-400 mg/ml. Group C included healthy individual as a control group.

In Group A 25 out of 50 diabetic patients had raised D-dimer level, Mean D-dimer level was 250-500 ng/ml and 5 out 50 patients, D-dimer level was 500-100 ng/ml while rest of the patients had normal value. A result is shown in table 1.

In Group B 27 out 50 patients had elevated D-dimer level, 20 had D-dimer level of 500-1000 ng/ml and 7 had D-dimer level of 250-500 ng/ml. as shown in table 2.

In both the two groups D-dimer level was significantly raised as compared to control group, P value was significantly elevated in both the two groups $P<0.0032$ in Group A and $P<0.0042$ in Group B respectively. From study we concluded that D-dimer signifies coagulation activation in diabetic patients and give useful information to the clinician about the hypercoagulable state and subsequent thromboembolic condition.

Similarly in Group A, 5 out of 50 cases had shortened PT while in Group B, 3 out of 50 cases had shortened PT also 2 out of 50 patients had prolong APTT. As shown in Table 1 and Table 2. D-dimer, PT and APTT are haemostatic markers. D-dimer is the fibrin mediated proteolytic degeneration of fibrin clot and its increased level shows increased fibrin turn over, PT and APTT also haemostatic marker and its shortened and increased level also signify haemostatic abnormally in the coagulation system.

D-dimer assay were performed by agglutination method and a semi-quantitative procedure both in diluted and undiluted form according to stand operation method. PT and APTT were also performed both by manual and coagulation analyzer for accurate results. P values for D-dimer in Group A and Group B is $P<0.00326$ and $P<0.00322$ respectively.

Table No.1. Frequency of Abnormal coagulation markers in Group A Diabetes Mellitus

S.No	Test	Percentage (%)
1	D-dimer	25 out 50 (50%)
2	PT (shortened)	3 out 50 (6%)

Table No.2. Frequency of Abnormal coagulation markers in Group B Diabetes Mellitus

S. No.	Test	Percentage (%)
1	D-dimer	27 out 50 (54%)
2	PT shortened	2 out 50 (4%)
3	APTT Prolonged	2 out 50 (4%)

Table No.3. Mean Value of coagulation parameters / markers in Diabetes Mellitus in both Groups

Groups	D-dimer Level in Group A and B		PT	APTT
Group A 200 to 300 mg/dl	20 out of 50 patients	250-500 ng/ml	3 out of 50 12.562±0.432 seconds	
	5 out of 50 patients	500-1000 ng/ml		
Sugar level in Group B. 300-400 mg/dl	20 out of 50 patients	500-100 ng/ml	2 out of 50 13.65±0.23 seconds	2 out of 50 43.56±0.262 seconds
	7 out of 50 patients	250-500 ng/ml		
Control Group	5o patients	<250 ng/ml	14.562±0.246 seconds	40.325±0.262 seconds

DISCUSSION

Diabetes Mellitus Type 2 is a major public health disease and is a hypercoagulable and pro-thrombotic state, evident by many studies. Diabetes Mellitus type-2 is associated with both micro-vascular and macro-vascular complications which may result from disturbance in Hemostatic mechanism and reduced fibrinolytic activity. The entire coagulation cascade is dysfunctional in Diabetes Mellitus, which may result in a variety of complication. In this study we evaluated coagulation activation markers, D-dimer, PT and APTT. In the present study, in group A (who had glucose level at 200-300mg/dl), D-dimer level was raised in 25 out of 50 patients (50 %), Mean D-dimer level was raised to 250-500 ng/ml, in group B diabetic patients (whose glucose level were at the range of 300-400 mg/dl), D-dimer level was raised up to 500-1000 ng/ml in 27 out of 50 patients (54%) . A similar study had been conducted by Lentonja et al who reported elevated D-dimer level in their Diabetic patients.[2] Another study was conducted by Muhsin et al who reported elevated D-dimer, level in Diabetic patients Type 2.[12] The same observation had also been reported by Long Z et al that Diabetic Mellitus Type 2 is associated with elevated D-dimer level.[14]

Diabetes Mellitus has hypercoagulable state and is associated with increased risk of atherosclerosis and Hemostatic abnormalities and the development of Micro and Macro-vascular complications. The thrombogenic and atherogenic fibrinogen level and increased platelet aggregation contribute to fibrin clot formation.[15]

Premature atherosclerosis with more extensive vascular damage, platelet hyper-reactivity, increased activation of pro-thrombotic coagulation factors and depressed fibrinolysis all contribute to increased thrombosis in Diabetes.[16] Increased expression of tissue factor (TF), raised fibrinogen level are important in atherosclerosis complications.[17] Increased expressions of Tissue Factor (TF) and increased synthesis of thromboxane A2 potentiate thrombosis and increase fibrin deposition and responsible for pro-thrombotic state of Diabetic patients.[18]

In the present study in group A has 3 out of 50 patients had shortened PT while APTT were in normal range while in group B only 2 out of 50 patients had shortened PT while APPT 3 out of 5o were prolonged both of these values were not significantly changed as compare to control.

A study conducted by Sunita et al on Type 2 diabetic patients, also reported shortened PT and APPT which shows similar correlation to our study.[19] In studies conducted by Yang Zaho et al and Wolfarang Korte et al. They also reported shortened PT and APPT.[20,21]

But study performed by Abdul Rahman et al disagree with our study and they observed prolonged PT and APPT in their study of significant degree.[22] Various observation have been given by different authors regarding PT and APPT derangement in Diabetic patients. Some reported shortened and some prolonged PT and APPT the exact mechanism is not clear, but there is perturbation associated with anticoagulant system and glycemic status of diabetic patients. Hyperglycemia cause depression of the biological activity of the anticoagulant proteins such as Antithrombin-İİİ[23] and dysfunctional Antithrombin-İİİ leads to prolong PT and APPT, others reported that there is increased generation of thrombin and elevated level of both Thrombin and Prothrombin contribute to both thrombotic risk and shortened PT and APPT.[20] Diabetes Mellitus is also associated with Endothelium injury, platelet reactivity, elevated levels of coagulation factors, defects in natural anticoagulant and fibrinolytic system all these changes are caused directly or indirectly by hyperglycemia and as a whole Diabetes Mellitus is a state of hyper-coagulability and hypofibrinolysis which finally contribute to Hemostatic abnormalities and other complications.[24]

CONCLUSION

The study concluded that the Diabetic Mellitus is a hypercoagulable state and is more prone to cardiovascular, cerebrovascular, micro-vascular, macro-vascular and other thrombotic complications so these Hemostatic markers have both preventive and prognostic value to reduce Morbidity and mortality from Diabetic Mellitus.

Author's Contribution:

Concept & Design of Study:	Subhan Uddin
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Data Analysis:	Saadia Haroon Durrani, Baber Rehman Khattak
Revisiting Critically:	Subhan Uddin, Shahtaj Khan
Final Approval of version:	Subhan Uddin

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

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Original Article

Urinary Tract Infection as a Cause of Parenteral Diarrhea in Children

UTI as a Cause of Parenteral Diarrhea

Jan Muhammad Afridi[1], Sabahat Amir[1], Yasir Rehman[1] and Fazlur Rahim[2]

ABSTRACT

Objective: To determine the frequency of UTI in children presenting with diarrhea.
Study Design: Descriptive / cross sectional study
Place and Duration of Study: This study was conducted at the Department of Paediatrics, Khyber Teaching Hospital, Peshawar from July 2017 to December 2017.
Materials and Methods: 88 patients presenting with diarrhea were elected through non randomized convenient sampling. Patients were catheterized under aseptic technique for Urine sample collection before starting Antibiotics. Common clinical features were noted along with urine culture report. The cases were then managed according to standardized management criteria. Children presenting with diarrhea below 5 years age. Children above 5 years age. Children with history of Antibiotic use within 48 hrs of presentation.
Results: Out of 88 patients presenting with diarrhea 27 patients had culture proven urinary tract infection. Leading organism isolated was E.Coli (15 cases) followed by Citrobacter (8 cases) and Psudomonas (4 cases).
Conclusion: In our study we found out that E.Coli was the most common cause of diarrhea secondary to UTI comprising of 15 patients. 8 and 4 patients had Cetrobacter and Psudomonas as a causative agent respectively. Diarrhea is one of the commonest diseases in infancy and association between UTI and diarrhoea are often overlooked. Children presenting with diarrhea should be screened for underlying UTI.
Key Words: Diarrhea, Urinary tract infection

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INTRODUCTION

UTI is the most common bacterial infection in childhood[1,2]. Urinary tract infections (UTI) is a common bacterial infection in infants and young children resulting in morbidity and mortality[3]. Urinary tract infections are common in children with an estimated incidence of 1-3% in boys and 3-10% in girls. The long term consequences of UTI are renal parenchymal damage and renal scarring that can cause hypertension and progressive renal damage [3,4.]

In first year of life, UTIs are more common in boys (3.7%) than in girls (2%). This is even more pronounced in febrile infants in the first 2 mo of life, with an incidence of 5% in girls and 20.3% in uncircumcised boys, as demonstrated in oneprospective study of >1000 patients using urine specimens obtained by catheterisation[5]. Later, the incidence changes, and about 3% of prepubertal girls and 1% of prepubertal boys are diagnosed with a UTI[6,7].

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For urine collection from infants and young children, suprapubic aspiration or transurethral catheterization generally is recommended. Urethral catheterization is more likely than aspiration to obtain a sufficient sample of urine[8].

The signs and symptoms of UTI are nonspecific in infants and young children and also they do not usually pertain to the genitourinary tract[9]. Gastrointestinal symptoms of poor feeding, vomiting, abdominal pain and diarrhea are reported in many infants with UTI and also diarrhea can predispose infants and young children to develop UTI[10,11]. Older children with UTI may have dysuria, frequency, urgency, hesitancy, small-volume voids, or lower abdominal pain. Infants with UTI more commonly present with nonspecific symptoms such as fever, irritability, jaundice, vomiting, diarrhea or failure to thrive. Unusual odor of the urine is not helpful in predicting UTI[12]. Diarrhea may be the presenting symptom in younger children with UTI [13]. Under diagnosis of UTI results in inadequate treatment of UTI putting them at risk for renal scarring and the long term sequalae of hypertension and renal failure[3].

Diarrhea is a major health problem[14].Diarrhea is an important cause of morbidity and mortality in children from developing countries[15]. The vast majority of deaths from diarrhea are among children under-five years of age living in low- and middle- income countries[16].

The term parenteral diarrhea implies that the cause of the symptoms is outside the gastrointestinal tract. Chronic otitis media and urinary tract infections

especially in infants are some of the conditions that may present with chronic diarrhea[17].

In our country, diarrhea is one of the commonest diseases in infancy but data regarding association between UTI and diarrhoea are limited. This study was done to evaluate the incidence of UTI in infants and young children with diarrhoea.

MATERIALS AND METHODS

This study was conducted at private hospital, Khyber children hospital, Peshawar from July 2017 till December 2017. A cross-sectional descriptive study design was used and 88 patients presenting with diarrhea were elected through non randomized convenient sampling.

Patients were catheterized under aseptic technique for Urine sample collection before starting Antibiotics.

Common clinical features were noted along with urine culture report. The cases were then managed according to standardized management criteria.

Inclusion Criteria: Children presenting with diarrhea below 5 years age.

Exclusion Criteria: Children above 5 years age.

Children with history of Antibiotic use within 48 hrs of presentation

RESULTS

Out of 88 patients there were 57 (64%) male and 31 (36%) female, Male patients having UTI as a cause of diarrhea were 11(19.2%) and females were 16 (51.6%). The most common age group presenting with UTI and diarrhea was below 1 year almost 16 (59%) followed by between 1 year and 2 years 10 (37%). More than 2 year age group presenting with UTI and diarrhea was that of 1 (0.3%) . Commonest organism isolated was E.Coli 15 (55.5%) Patients followed by Citrobacter 8 (29.6%) and Pseudomonas 4 (14.8%) Patients.

Table No.1: Gender wise presentation of UTI with diarrhea.

Gender	UTI with diarrhea	Diarrhea	Total
Male	11 (19.2%)	46	57 (64%)
Female	16 (51.6%)	15	31 (36%)
Total	27 (30.6%)	61	88

Table No. 2: Age wise presentation of UTI with diarrhea.

Age Group	No of Cases	%age
<1 year	16	59%
1-2 years	10	37%
>2 years	1	0.3%

Table No.3: Organisms isolated in Culture..

Organism	No of Cases	%age
E.Coli	15	55.5%
Ceterobacter	8	29.6%
Pseudomonas	4	14.8%

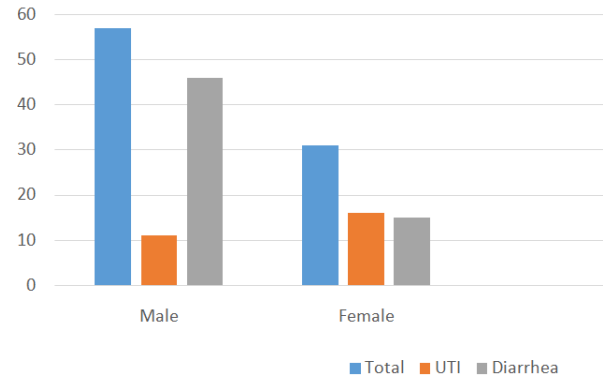

Chart **No.1: Gender wise presentation of UTI with diarrhea.**

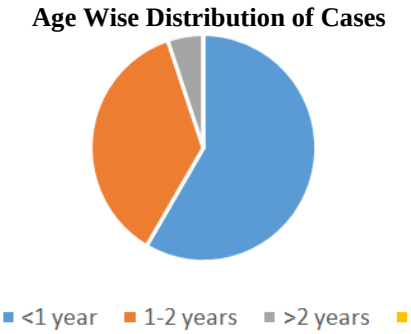

Chart No.2: Age wise presentation of UTI with diarrhea.

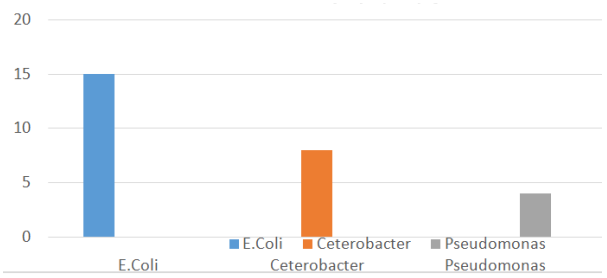

Chart No.3: Organisms isolated in Culture..

DISCUSSION

The incidence of UTI varies in early infancy and childhood, being more common in boys in first three months of life with reported male to female incidence of 5:1. In later childhood the reported male to female ratio was 1:10[18]. Diarrhea is defined as an abnormal increase in daily stool fluidity, frequency, and volume from what is considered normal for an individual. Diarrhea kills an estimated 2.5 million people each year, with about 60-70% of them being children under five years of age [19]. Children with UTI can present with diarrhoea but the definite cause for association is not known. Diarrhoea could be the result of infection of urinary tract similar to parenteral diarrhoea seen with other infections or could be the the cause of infection of

urinary tract by ascending infection. Urinary tract infection (UTI) is common in children with diarrhoea, but little is known about risk factors, aetiology and outcome of such children.

In our study total 88 patients were included. Diarrhoea with UTI (confirmed by culture) constituted 27cases (30.6%) and those without UTI constituted 61 cases (69.4%), similar findings of 25% cases of UTI associated diarrhea were reported by R. Das et al[19]. In our study E.Coli 55.5%, Ceterobacter 29.6% and Pseudomonas 14.8% were the isolated causative organisms. Escherichia coli (69%)and Klebsiella (15%) were the most commonly isolated pathogens in study by R.Das etal[19]. In our study 19.2 % males and 51.6% females had culture proven UTI, while another study by Sabahat etal[20] shows 19% male and 26% female with culture proven UTI. In our study it was found that about 59% cases of UTI were among age group of less then 1 year old and 41% cases were above 1 year age group while in a study conducted by D. Narayanapa et al[22]. Thus the most common age group with UTI presenting with diarrhea was found to be less than 1 year age which was similar to Narayanapa D, et al[21].

The overall prevalence of UTI in diarrhoea cases was 30.6% in this study while in studies done by Thakhar R et al[9], balat A et al[22], Srivaths PR et al[23], Bagga A et al[24], Jeena et al[25], Dharindharka et al[26], it ranged from 8% to 24%.

Most of the children presenting with diarrhea could not be included in study because they had history of Antibiotic use within 48 hours prior to presentation

CONCLUSION

In our study we found out that E.Coli was the most common cause of diarrhea secondary to UTI comprising of 15 patients. 8 and 4 patients had Cetrobacter and Psudomonas as a causative agent respectively. Diarrhea is one of the commonest diseases in infancy and association between UTI and diarrhoea are often overlooked. Children presenting with diarrhea should be screened for underlying UTI. Prompt treatment of UTI is mandatory to prevent long term consequences of UTI such as renal parenchymal damage and renal scarring leading to hypertension and progressive renal damage.

The present study shows that signs and symptoms of UTI in children are nonspecific and usually do not pertain to the genitourinary tract. Since diarrhea could be one of the manifestations of UTI in young children or gastroenteritis may contribute to colonisation of periurethral region and cause ascending infection, high index of suspicion is necessary and all children presenting with acute diarrhea must be screened for UTI.

Author's Contribution:

Concept & Design of Study:	Jan Muhammad Afridi
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Data Analysis:	Yasir Rehman, Fazlur Rahim
Revisiting Critically:	Jan Muhammad Afridi, Sabahat Amir
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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

Diagnosing Acute Appendicitis

Determine the Accuracy and Use of Ultrasound Guidance and Alvarado Score for Diagnosing Acute Appendicitis at Central Park Teaching Hospital Lahore

Zahid Ahmad and Muhammad Wasif Iqbal

ABSTRACT

Objective: To examine the accuracy and use of ultrasonography and Alvarado score system for diagnosing Acute Appendicitis.

Study Design: Observational / Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Surgery and Department of Radiology Central Park Teaching Hospital Lahore during from March 2016 to Dec 2016.

Materials and Methods: One hundred and thirty patients of abdominal pain having ages of 10 years to 70 years were included. All patients had diagnosis with Alvarado scoring system and ultrasound for identifying Acute Appendicitis. Patients detailed history, age, sex and histopathology and ultrasonographic results were recorded.

Results: Out of 130 patients, 95 (73.08%) patients were men and 35 (26.92%) patients were women. 15 (11.54%) patients were ages less than 20 years, 75 (57.70%) patients having ages between 20 to 39 years, 32 (24.62%) patients were aged between 40 to 59 years and 8 (6.15%) patients were ages of >59 years. Symptoms observed in all patients such as anorexia, nausea and vomiting, tenderness in right iliac fossa, rebound tenderness, elevated temperature as 71.54%, 53.85%, 100%, 95.39% and 84.62% respectively. In all 130 patients 122 (93.85%) had found acute appendicitis by using ultrasound. As per histopathology results 95 % had acute appendicitis and 5 % had chronic or normal appendicitis.

Conclusion: Alvarado Score system along with noninvasive ultrasound guidance resulted accurately and helps to reduce the rate of negative appendectomy, complications and infections with no extra cost. The combine role of Alvarado score and ultrasonography can helps to provide better treatment in acute appendicitis.

Key Words: Alvarado score system, Histopathology findings, Ultrasound results, Appendicitis

Citation of articles: Ahmad Z, Iqbal MW. Determine the Accuracy and Use of Ultrasound Guidance and Alvarado Score for Diagnosing Acute Appendicitis at Central Park Teaching Hospital Lahore. Med Forum 2018;29(5):15-18.

INTRODUCTION

Appendicitis is one of the most common disease found in all over the world. Appendicitis is defined as an inflammation in the inner lining of the vermiform appendix that proliferate to its other parts. The most common and useful treatment for appendicitis is the surgical removal of the inflamed appendix lumen.[1] Globally, appendicitis is commonly found in surgical emergencies and one of the most frequent cause of acute abdominal pain. According to the some international research, approximately 10% of all surgical operation followed by appendectomy.[2]

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Appendicitis is commonly found disease in people of all ages and have 7 to 8% prevalence with life time.[3,4] The rate of cases associated to appendectomy is 1.5 to 1.9 out of 1000 population of both gender.[5] As per high rate of appendicitis cases, more work is needed for early and accurate examination to provide better treatment and to reduce the morbidity and mortality rate. The examination of acute appendectomy is depends on patients medical related history, clinical observations and some laboratory findings like white blood cells count.[6]

Computed tomography scan, ultrasonography, and laproscopy are useful technique for diagnosing acute appendicitis accurately.[7,8] The surgical operation is mainly based on clinical examination and Lab findings. Therefore diagnostic inaccuracy may be caused and resulted 20% of prevalence of perforation and 2 to 30% rate of negative appendectomy.[9] Computerized tomography and ultrasonography with clinical examination can helps to reduce the rate of inessential abdominal surgeries.[10-12] Use of ultrasound by expertise can helps to increase the accuracy rate of diagnose acute appendicitis. Different researches regarding

appendectomy reported that 30% rate of negative appendectomy.[10] Inaccurate diagnosis can cause the complications like peritonitis and perforation in patients suffering from appendicitis.[13]

There are some other scoring systems are using in evaluation of appendectomy but Alvarado scoring system is more reliable, due to easy use as compared to other techniques.[14] Recent study was conducted to evaluate the combine role of Alvarado Score and Ultrasound guidance for diagnosing acute appendicitis so that it could be helpful for surgeons for providing better diagnosis and management.

MATERIALS AND METHODS

This cross-sectional observational study was conducted at Department of surgery and Department of Radiology Central Park Teaching Hospital Lahore during from March 2016 to Dec 2016. One hundred and thirty patients of abdominal pain having ages of 10 years to 70 years were included. All patients had diagnosis with Alvarado scoring system and ultrasound for identifying Acute Appendicitis. Patients detailed history, age, sex and histopathology and ultrasonographic results were recorded. Patients undergone laparatomy, and patients have other abdominal inflammation/infections were excluded from this study. **Alvarado score;** right lower quadrant tenderness (+2), elevated temperature (+1), rebound tenderness (+1), migration of pain to right iliac fossa(+1), anorexia (+1), nausea or vomiting (+1), leucocytosis >10,000 (+2) and leucocytosis left shift (+1) were noted. Score total; 5-6 compatible with acute appendicitis, 7-8 probable acute appendicitis and 9-10 very probable acute appendicitis were noted. Ultrasound diagnosis of acute appendicitis; aperistaltic, noncompressible, dilated appendix (>6 mm outer diameter) and inflamed periappendiceal fat and periappendiceal fluid were noted. All statistically data was analyzed by SPSS version 17. P-value <0.05 was considered as significant.

RESULTS

Out of 130 patients, 95 (73.08%) patients were men and 35 (26.92%) patients were women. 15 (11.54%) patients were ages less than 20 years, 75 (57.70%) patients having ages between 20 to 39 years, 32 (24.62%) patients were aged between 40 to 59 years and 8 (6.15%) patients were ages of >59 years (Table 1).

Symptoms observed by Alvorado score in all patients, 93 (71.54%) patients had anorexia while 37 (28.46%) patients had not found anorexia, nausea and vomiting had found in 70 (53.85%) while 60 (46.15%) patients had not found nausea, tenderness in right illiac fossa found in all patients, 124(95.39%) had rebound tenderness, elevated temperature in 110 (84.62%) patients, leukocytosis >10000/L found with white cells count had found in 60(46.15%) while 70 (53.85%) had not found. Appendicitis score was resulted such as 5,6,7,8,9,10 as 3.85%, 5.38%, 17.69%, 20.77%, 23.08%, 29.23% respectively. In all 130 patients 122 (93.85%) had found acute appendicitis by using ultrasound and as per histopathology results 95.38 % had acute appendicitis while 4.61% had chronic or normal appendicitis.

Table No/1: Demographic information of the patients

Variable	No.	%
Gender		
Male	95	73.08
Female	35	26.92
Age (years_		
< 20	15	11.54
20 -39	75	57.70
40 - 59	32	24.61
> 59	8	6.15

Table No.2: Symptoms prevalence by Alvarado Score

Symptoms/Sign	Alvarado score		
	0	1	2
Anorexia	37 (28.46%)	93 (71.54%)	-
Nausea and vomiting	60 (46.15%)	70 (53.85%)	-
Tenderness in rirght iliac	-	-	130 (100%)
Rebound tenderness	20 (15.38%)	110 (84.62%)	-
Leukocytosis>10 000/L	11 (8.46%)	6 (4.62%)	114 (87.70%)
White cells count shifting to left	70 (53.85%)	60 (46.15%)	-

Table No.3: Distribution of total scores obtained by patients

Characteristics/score	No.	%
5	5	3.85
6	7	5.38
7	23	17.69
8	27	20.77
9	30	23.08
10	38	29.23

Table No.4: Ultrasound Findings of Patients

Acute appendicitis	No.	%
Yes	122	93.85
No	8	6.15

Table No.5: Histopathology Findings of Patients

Histopathology	No.	%
Acute appendicitis	124	95.38
Normal/Chronic	6	4.62

DISCUSSION

Better clinical examination may helps to diagnose acute appendicitis accurately and lead to better treatment.[15] In present research, Out of 130 patients, 95 (73.08%) patients were men and 35 (26.92%) patients were women it shows the similarity to the some other studies conducted by soomro et al[16], Talukder et al[17] and Almulbim et al[18] in their studies, appendectomy rate in male patients population were higher than the females.

In this research, we found 15 (11.54%) patients were ages less than 20 years, this shows the similarity to the study conducted by Soomro et al[16] and some other researchers.[18,19] 75 (57.70%) patients having ages between 20 to 39 years, 32 (24.62%) patients were aged between 40 to 59 years and 8 (6.15%) patients were ages of >59 years. Symptoms observed by Alvorado score in all patients, 93 (71.54%) patients had anorexia while 37 (28.46%) patients had not found anorexia, nausea and vomiting had found in 70 (53.85%) while 60 (46.15%) patients had not found nausea, tenderness in right iliac fossa found in all patients, while if we go through the other research the results shows 91.6% patients had pain in right iliac fossa.[16] In our study we found 124 (95.39%) had rebound tenderness, elevated temperature in 110 (84.62%) patients, leukocytosis >10000/L found with white cells count had found in 60(46.15%) while 70 (53.85%) had not found, these findings show the similarity to the some other studies.[20]

In a research conducted at USA, resulted that rate of negative appendectomy with positive ultrasound was 5.5%.[20] In recent study we found 122 (93.85%) had found acute appendicitis by using ultrasound and as per histopathology results 95.38% had acute appendicitis while 4.61% had chronic or normal appendicitis.

In current research, Alvarado scoring system resulted that the diagnostic accuracy was very reliable and acceptable in high scores patients but patients with lower scores should be under observation. Appendicitis score was resulted such as 5, 6, 7, 8, 9 and 10 as 3.85%, 5.38%, 17.69%, 20.77%, 23.08%, 29.23% respectively. Patients whom had 8 to 10 scores, marked as appendicitis and undergo surgical treatment immediately.

Moreover, we should have to evaluate the significance and factors related to this disease for better treatment and to reduce the morbidity and to improve the quality of life of patients.

CONCLUSION

It is concluded that Alvarado Score system with noninvasive ultrasound guidance resulted accurately diagnosis of acute appendicitis and helps to reduce the rate of negative appendectomy, complications and infections with no extra cost. The combine role of Alvarado score and ultrasonography can helps to provide better treatment in surgical emergency , acute appendicitis.

Author's Contribution:

Concept & Design of Study:	Zahid Ahmad
Drafting:	Muhammad Wasif Iqbal
Data Analysis:	Muhammad Wasif Iqbal
Revisiting Critically:	Zahid Ahmad, Muhammad Wasif Iqbal
Final Approval of version:	Zahid Ahmad

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

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Original Article

Complications of Laparoscopic Cholecystectomy

Tanveer Sheikh[1], Khalid Azeem[1] and Maqsood Ahmad Khan[2]

ABSTRACT

Objective: To study the Complications of Laparoscopic Cholecystectomy.
Design of Study: Retrospective study.
Place and duration of Study: This study was conducted at the Islam Teaching Hospital Sialkot from January 2014 to December 2017.
Materials and Methods: 535 patients (88 men, 447 women age range 15-66 years, average age 41 years) in patients undergoing Laparoscopic Cholecystectomy. All the patients undergoing Laparoscopic Cholecystectomy were diagnosed on ultrasound examination and clinical examination of the patients. Performa was designed to note age, gender and complications in Laparoscopic Cholecystectomy. The data was analyzed for results on SPSS version 10. The informed consent of all the patients was taken and permission of ethical committee was also taken.
Results: The number of patients undergoing Lap-Cholecystectomy at age group 46-55 years was maximum in male 29 (32.95%) and in female 203 (45.41%) and minimum at age group 66 & above years in male 02 (2.27%) and in female 07 (1.56%) as shown in table no. 1. The rate of complications in patients undergoing Lap-Cholecystectomy was Intra Operative Hemorrhage 36 (6.72%), Bile Duct Injury 01 (0.18%), Suppuration at Trocar Site 17 (3.17%), Laparoscopic Re-Intervention 07 (1.30%), Bile Leakage 12 (2.24%), Conversion 21 (3.92%), Prolong Hospitalization 44 (8.22%) as shown in table no.2. It was seen that among complications in patients undergoing Lap-Cholecystectomy was Prolong Hospitalization maximum 44 (8.22%) and Bile Duct Injury 01 (0.18%) was minimum. It was also seen that the incidence of patients in Lap-Cholecystectomy were maximum in females 447 (83.55%) and minimum in male 88 (16.44%).
Conclusion: It was concluded from the study that complications of Laparoscopic cholecystectomy are yet present in spite of due care and experience of the surgeon.

Key Words: Laparoscopic Cholecystectomy, Complications, Retrospective

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INTRODUCTION

The introduction of laparoscopic cholecystectomy (LC) has caused a real "revolution" in the surgical treatment of symptomatic gallbladder diseases. The new technique is "minimally invasive"; it allows a short hospital stay, a decreased postoperative pain with an early post-operative recovery, a better cosmetic result, and, finally, a reduction of costs. All these features prompted unconditioned world-wide acceptance of the procedure by both surgeons and patients, so in the last 6 years, since Dr. Mouret's first LC in 1987, open cholecystectomy has gradually become the second choice in the surgical management of gallbladder symptomatic diseases. LC compares favorably with the conventional operation regarding morbidity and mortality, although a slightly higher incidence of biliary injury after LC has been reported[1]. The safety of LC has been therefore established in referral centers with large series of laparoscopic procedures, but not in centers that are starting their experience and are still in the "learning curve. "Compl curve." Complications after LC will probably become more and more infrequent but in certain instances they can still be devastating. The interventional radiologist and the endoscopist are often asked to help the referring surgeon in the diagnosis and treatment of such complications[2].

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MATERIALS AND METHODS

From January 2014 to December 2017, 535 patients (88 men, 447 women age range 15-66 years, average age 41 years) in patients undergoing Laparoscopic Cholecystectomy. All the patients undergoing Laparoscopic Cholecystectomy were diagnosed on ultrasound examination and clinical examination of the patients. Performa was designed to note age, gender and complications in Laparoscopic Cholecystectomy. The data was analyzed for results on SPSS version 10. The informed consent of all the patients was taken and permission of ethical committee was also taken.

RESULTS

The number of patients undergoing Lap-Cholecystectomy at age group 46-55 years was maximum in male 29 (32.95%) and in female 203 (45.41%) and minimum at age group 66 & above years in male 02 (2.27%) and in female 07 (1.56%). table 1.

Table No. 1 Age & Gender Distribution in Patients Undergoing LAP-Cholecystectomy

Sr#	Age (Years)	Male (%) N=88	Female (%) N= 447
1	15-25	01 (1.13%)	12 (2.68%)
2	26-35	13 (14.77%)	47 (10.51%)
3	36-45	25 (28.40%)	156 (34.89%)
4	46-55	29 (32.95%)	203 (45.41%)
5	56-65	18 (20.45%)	22 (4.92%)
6	66 & above	02 (2.27%)	07 (1.56%)
	Total	**88 (99.97%)**	**447 (99.97%)**

The rate of complications in patients undergoing Lap-Cholecystectomy was Intra Operative Hemorrhage 36 (6.72%), Bile Duct Injury 01 (0.18%), Suppuration at Trocar Site 17 (3.17%), Laparoscopic Re-Intervention 07 (1.30%), Bile Leakage 12 (2.24%), Conversion 21 (3.92%), Prolong Hospitalization 44 (8.22%) as shown in table 2. It was seen that among complications in patients undergoing Lap-Cholecys-tectomy was Prolong Hospitalization maximum 44 (8.22%) and Bile Duct Injury 01 (0.18%) was minimum. It was also seen that the incidence of patients in Lap-Cholecystectomy were maximum in females 447 (83.55%) and minimum in male 88 (16.44%).

Table No. 2 Complication Distribution in Patients Undergoing LAP-Cholecystectomy

Sr#	Complications	Cases	%age
1	Intra Operative Hemorrhage	36	6.72%
2	Bile Duct Injury	01	0.18%
3	Suppuration at Trocar Site	17	3.17%
4	Laparoscopic Re-Intervention	07	1.30%
5	Bile Leakage	12	2.24%
6	Conversion	21	3.92%
7	Prolong Hospitalization	44	8.22%
	Total	**138**	**25.75%**

Table No. 3 Complication Distribution in Patients Undergoing LAP-Cholecystectomy

Sr#	Complications	Cases	Percentage (%)
1	Intra Operative Hemorrhage	-Gall Bladder Bed (25) -Cystic Artery (9) -Omental Vessels (2)	4.67% 1.68% 0.37%
2	Bile Duct Injury	-Transection of CBD (00) -Partial CBD Injury (01)	0% 0.18%
3	Suppuration at Trocar Site	-Epigastric Port Site (12) -Umbilical Port Site (05)	2.24% 0.93%
4	Laparoscopic Re-Intervention	07	1.30%
5	Bile Leakage	-From Cystic Duct (04) -From CBD (01) -From Gall Bladder Bed (07)	0.74% 0.18% 1.30%
6	Conversion	-Due to difficulty in Dissection (18) -Due to CBD Injury (01) -Due to Hemorrhage (02)	3.36% 0.18% 0.37%
7	Prolong Hospitalization	44	8.22%
	Total		

DISCUSSION

The risks and complications of LC must be neither over-rated nor under-rated. Laparoscopy is not easy for the surgeon, thorough instruction as well as experience being crucial for improvement of results. Contrary to initial reports of an increased complication rate, recent data show that LC entails lower morbidity and mortality rates than open operation[3-6]. One of the most frequent situations carrying an increased operative risk is acute cholecystitis. However, the postoperative morbidity and mortality rates, as well as the excellent late results, allow us to conclude that obese patients are the principal beneficiaries of the laparoscopic technique. It avoids the wound infection, wound dehiscence and especially the incisional hernia that often complicate open cholecystectomy in the obese.

The major problems related to LC are bile duct injury, haemorrhage and subhepatic abscess. Lesions of the extrahepatic bile ducts can occur at any level as follows[7-10] post-mortem studies demonstrate their presence in 3–5% of individuals[8]. However, accessory bile ducts were only recognised in three patients immediately after detachment of the gallbladder. Postoperative bile leak and choleperitoneum were avoided by clipping these ducts. When bile leakage >500 ml/24 h persists in the early postoperative period,

endoscopic sphincterotomy or transpapillary stenting are recommended[11-14].

Woods et al[8] noted this cause in 17 of 34 cases with biliary complications. In our study we noted it in 36 patients, Bile Duct Injury 01 (0.18%), Suppuration at Trocar Site 17 (3.17%), Laparoscopic Re-Intervention 07 (1.30%), Bile Leakage 12 (2.24%), Conversion 21 (3.92%), Prolong Hospitalization 44 (8.22%) as shown in table 2. It was seen that among complications in patients undergoing Lap-Cholecystectomy was Prolong Hospitalization maximum 44 (8.22%) and Bile Duct Injury 01 (0.18%) was minimum. It was also seen that the incidence of patients in Lap-Cholecystectomy were maximum in females 447 (83.55%) and minimum in male 88 (16.44%). The most serious complication was suppuration at trocar site 17(3.17%) and bile leakage 12(2.24%). A particular mode of CBD injury that is specific to LC is clipping the 'cone' of CBD with the first clip applied to the cystic duct. To avoid this situation it is preferable to apply the clip at a little distance from the cysticocholedochal junction, because endoscopic studies show that a long cystic stump (without stones) is not a true cause of post-cholecystectomy pain[15-17].

As regards haemorrhage, even though arterial injury is usually a reason for conversion[4,5] in our study conversion was 21 (3.92%). Bile leakage and bleeding may determine subhepatic abscess formation. Huang et al[5] reported 3 such complications in a group of 350 LCs. The clinical picture was manifest 7–10 days after operations performed for acute cholecystitis. Pain in the right upper quadrant, fever, leucocytosis and ultrasonography led to the diagnosis.

CONCLUSION

It was concluded from the study that complications of Laparoscopic cholecystectomy are yet present in spite of due care and experience of the surgeon

Author's Contribution:

Concept & Design of Study:	Tanveer Sheikh
Drafting:	Khalid Azeem
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Revisiting Critically:	Khalid Azeem
Final Approval of version:	Tanveer Sheikh

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

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Original Article

Growth Hormone Therapy

Growth Hormone Therapy in Short Statured: a Study Among Children with Classic Growth Hormone Deficiency

Bader-n-Nisa, Muhammad Ashfaq, Wajid Hussain, Asifa Noor and Syed Jamal Raza

ABSTRACT

Objective: To determine the mean increase in height in response to growth hormone therapy in short statured children presenting with classic growth hormone deficiency.

Study Design: Quasi experimental study

Place and Duration of Study: This study was conducted at the pediatric endocrine OPD, National Institute of Child Health Karachi from 1st July 2013 to 31st Dec 2013.

Materials and Methods: All patients between 4-15 years of age of either gender presented with height SDS <2 plotted on CDC growth chart having peak serum growth hormone levels <10ng/ml and bone age more than 2 years behind chronological age were enrolled. Mid parental height was calculated and TCR (Target centile range) was plotted. Those patients with GH level <10ng/ml was given biosynthetic GH (Genotropin and Eutropin) in a dose of 15 IU/m^2 6 days a week s/c for 6 months. Bone age was noted at 0 and 6 months.

Results: Mean age of the patients was 9.73 ±2.66 years. There were 47 (52.2%) males and 43 (47.80%) females. Mean body surface area, bone age and chronological age of the patients was 0.76 ±0.18 m^2, 7.04 ±2.56 years and 9.73 ±2.66 years respectively. Mean post treatment increase in height from the baseline at 6 months was 8.79 ± 3.16 cm.

Conclusion: Significant increase in height in response to growth hormone therapy was noted in short statured children presenting with classic growth hormone deficiency.

Key Words: Short Statured Children, Classic Growth Hormone Deficiency, Height

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INTRODUCTION

Short stature is a common problem among children from different parts of the world. It has been a major concern of endocrinologists in developed as well in developing countries. [1] Short stature is defined as height or length more than 2SDS below the mean (<3rd percentile) for particular age and sex. The etiology of short stature is variable but the main cause include familial short stature, constitutional growth delay, growth hormone deficiency due to isolated or panhypopituitarism (classified on basis of hormonal axis involvement)[2], hypothyroidism, hypercortisolism, celiac disease, renal disease, cystic fibrosis various syndromes including classical Laron syndrome and idiopathic short stature (when all other organic and non-organic causes have been ruled out).[3] Growth hormone deficiency may be diagnosed or defined as, the presence of short stature i.e. (height SDS <2 for particular age and sex) and peak GH levels <10ng/ml following two standard provocative test (insulin induced hypoglycemia and clonidine /exercise).[4]

Since short stature is high magnitude problem globally irrespective of cause, primary or secondary. Whereas classic growth hormone deficiency, pituitary growth hormone deficiency if not treated on time can result in dwarfism. So, the establishment of definitive therapeutic response to growth hormone treatment would be beneficial for patients.

Although enormous studies have been done on this subject in neighboring and western countries but there is scarcity of data in Pakistan. Therefore, it is of paramount importance to conduct studies on this topic and to provide best available treatment to the needed patients. Furthermore, as evident from literature that early diagnosis and treatment leads to good prognosis therefore strategies could be made for prompt and early diagnosis and treatment of classic growth hormone deficiency to prevent dwarfism in our population.

MATERIALS AND METHODS

A Quasi experimental trial was conducted at pediatric endocrine OPD of National Institute of Child Health Karachi 1st July 2013 to 31st Dec 2013. All consecutive patients age between 4-15 years of either gender having height SDS <2 plotted on CDC (Centre of disease

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control) growth chart, peak serum growth hormone levels <10ng/ml, and bone age >2 years behind chronological age determined by Pyele's and Gruelich's standard were enrolled. Whereas short stature children with familial cause like short stature of parents, short stature children with constitutional cause of delay of growth and puberty, and short stature children with causes other than growth hormone deficiency (hypothyroidism, celiac disease, chronic kidney disease, Syndromic causes) were excluded.

The sample size was calculated by using WHO Sample Size Determination in Health Studies. Taking reported mean increase in height 9.8±2.9 cms[4], confidence level 95%, and margin of error 0.6 cms, the sample size came out to be 90 short statured children with growth hormone deficiency.

Short stature was defined as height or length more than 2SDS below the mean (<3rd percentile) with respect to age and sex. Growth hormone deficiency was labeled positive on the basis of presence of short stature i.e. (height SDS <2 for particular age and sex) and peak GH levels <10ng/ml following two standard provocative test (insulin induced hypoglycemia and clonidine /exercise). Growth hormone therapy was defined as recombinant (biosynthetic) growth hormone 15IU/m2 6 days in a week S/C for 6 months duration. Mean increase in height was measured at the end of 6 months by the following formula: Mean increase in height = Height at the end of 6 months− height at the baseline (cms).

All patients were evaluated for height (standing height measured with stadiometer), weight, upper to lower segment ratio, X-Ray of left hand/wrist for bone age, SGPT, serum creatinine, thyroid profile and celiac screening test (tTg IgA and IgG) those meeting the exclusion criteria was excluded. Growth parameters was first plotted on CDC growth charts (develop by American National Centre for Health Statistics in collaboration with the National Centre for chronic Disease Prevention and Health Promotion) and all those patients with height below < 2 SDS (3rd percentile was included in the study after satisfying inclusion criteria). Nine Centile United Kingdom charts was used to determine if the child height is below 0.4th centile. Mid parental height was calculated and TCR was plotted to identify the genetic growth potential and to exclude the familial and constitutional causes as well. After initial clinical haematological and endocrine screening, the selected patients were evaluated for growth hormone levels with the help of ITT (insulin tolerance test). Those patients with GH level <10ng/ml were given biosynthetic GH (Genotropin and Eutropin) in a dose of 15 IU/m^2 6 days a week s/c for 6 months. During treatment patients were called for follow up at 3 and 6 months. Follow up included height and weight measurements. Haematological tests including CBC, Serum creatinine, glucose, LFTs and thyroid profile (TSH, free T3 and T4). Bone age determined at 0 and 6 months, recording of side effects if any was measured at the end of 6 months.

Collected data was entered and analyzed using SPSS version 16. Frequencies and percentages were calculated for all qualitative variables like sex and educational status of the parents for which frequencies and percentages were presented. Mean ±SD was computed for numerical variables like age, weight, family monthly income, bone age, choronogical age, pre-treatment height, post treatment height and increase in height from the baseline. Effect modifiers like age, bone age, choronogical age, gender, educational status of the parents and family monthly income was addressed through stratification. Post stratification t test was applied and p value ≤0.05 was taken as significant.

RESULTS

Out of total 90 patients, majority of the patients 50 (55.6%) were presented with ≤10 years of age. The mean age of the patients was 9.73 ±2.66 years. There were 47 (52.2%) males and 43 (47.80%) females. Mean weight of the patients was 19.44 ±6.46 Kg.

Mean body surface area, bone age and chronological age of the patients was 0.76 ±0.18 m^2, 7.04 ±2.56 years and 9.73 ±2.66 years respectively. Majority of the patients 61 (67.80%) had ≤0.8m^2 body surface area while ≤7 years of bone age and ≤10 years of chronological age was found higher, i.e. 46 (51.10%) and 50 (55.60%) respectively.

Table No.1: Baseline characteristics of the patients (n=90)

Variables	Categories	n	%
Age, years	≤10	50	55.56
	>10	40	44.44
Gender	Male	47	52.22
	Female	43	47.78
Body surface area (in m2)	≤0.8	61	67.78
	>0.8	29	32.22
Bone Age	≤7	46	51.11
(in years)	>7	44	48.89
chronological Age (in years)	≤10	50	55.56
	>10	40	44.44
Family Income	≤35,000	42	46.67
(in rupees)	>35,000	48	53.33
Educational Status of Father	≤Matric	17	18.89
	≥Intermediate	73	81.11
Educational Status of Mother	≤Matric	67	74.44
	≥Intermediate	23	25.56
n: number,% Percentage			

Educational status of fathers was ≥intermediate in most of the patients 73 (81.10%) while majority of the mothers 67 (74.40%) had ≤matric educational status. Mean monthly family income was 35,566.67

±16,941.43 rupees. Majority of the patients had >35,000 rupees family income. (Table 1). Mean height SDS before growth hormone therapy was -4.22 ±1.46 while mean SDS after growth hormone therapy was -2.63 ±1.57 (p-value <0.001). Mean height before growth hormone therapy was 111.46 ±15.85 cm while mean height after growth hormone therapy was 120.25 ±15.10 cm (p-value 0.001). Mean post treatment increase in height from the baseline at 6 months was 8.79 ±3.16 cm. (Table 2)

The mean difference of increases in height from the baseline to 6 months after the treatment with respect to baseline characteristics are shown in table 2. Bone age was the only variable found significantly associated with post-treatment increase in height (p-value 0.005) whereas age (p-value 0.272), gender (p-value 0.244), body surface area (p-value 0.091), chronological age (p-value 0.272), family income (p-value 0270), educational status of father (p-value 0.940) and educational status of mother (p-value 0.770) were found to be insignificant.

Table No.2: Difference of post-treatment increases in height with respect to baseline characteristics of the children (n=90)

Variables	Categories	Post-treatment increases in height (cms) from the baseline to 6 months		
		Mean ±SD	p-value	95% CI
Age, years	≤10	9.12 ±2.98	0.272	-0.59 to 2.07
	>10	8.37 ±3.36		
Gender	Male	9.16 ±3.43	0.244	-0.54 to 2.10
	Female	8.38 ±2.82		
Body surface area (in m2)	≤0.8	9.18 ±2.39	0.091	-0.19 to 2.60
	>0.8	7.97 ±2.47		
Bone Age (in years)	≤7	9.70 ±3.23	0.005	0.58 to 3.13
	>7	7.84 ±2.81		
chronological Age (in years)	≤10	9.12 ±2.98	0.272	-0.59 to 2.07
	>10	8.37 ±3.36		
Family Income (in rupees)	≤35,000	8.39 ±1.84	0.27	-2.06 to 0.58
	>35,000	9.13 ±3.96		
Educational Status of Father	≤Matric	8.84 ±1.93	0.94	-1.64 to 1.76
	≥Intermediate	8.78 ±3.39		
Educational Status of Mother	≤Matric	8.73 ±3.13	0.77	-1.74 to 1.31
	≥Intermediate	8.95 ±3.31		

Independent t-test was applied, p-value <0.05 was taken as significant
CI: Confidence Interval, m: meter, SD: Standard Deviation

DISCUSSION

In this quasi experimental design, we have examined the increase in height after 6 months of growth hormone therapy. The findings of our study have showed significant difference in the mean height before and after the treatment. Mean post treatment increase in height from the baseline at 6 months was 8.79 ±3.16 cm. This finding matched with a study conducted in India which showed growth hormone deficiency in 16-23% cases of short stature and response to growth hormone therapy measured in terms of mean height gain was 9.8 ±2.9 cm among the patients with growth hormone deficiency in the first year of therapy.[4]

In our study, mean height SDS before growth hormone therapy -4.22 ±1.46 while mean height SDS after growth hormone therapy was -2.63 ±1.57 (p-value 0.001). In a meta-analysis, baseline pretreatment growth velocities of treatment and control groups were equivalent (pooled difference between treatment and control groups −0.05 ± 0.15 cm/y, with respective mean baseline growth rates of 4.22 ± 0.21 and 4.30 ± 0.25 cm/y. After 1 year, however, growth velocity was significantly greater in the GH-treated group than in controls; the pooled estimate for the difference in growth velocity between the 2 groups was 2.86 ± 0.37 cm/y.[6]

Short stature due to classic GH deficiency is universally accepted therapeutic indication for growth hormone treatment,[6] because dwarfism can occur due to deficiency of pituitary growth hormone.[7]

Human growth hormone prepared by recombinant DNA technique has been widely used for the treatment of GHD as well as its use in the list of FDA- approved indication in non GH deficient children has been implicated.[8]

Safety data from post marketing surveillance studies probably underestimate risks associated with higher doses of human growth hormone and changing risk factors (e.g., an increased prevalence of obesity, which carries a higher risk of diabetes) and do not inform post-treatment metabolic risks or the risk of cancer.[9-11]

A long term follow-up study from France involving persons who had growth hormone deficiency or idiopathic short stature or who were small-for gestational-age infants showed an increased standardized mortality rate of 1.33 after human growth hormone treatment, as compared with the general population in France;[12] assessment of cause-specific mortality identified increased risks of death attributable to bone cancer and circulatory system disorders among persons who received growth hormone and an increased risk of death with a dose of human growth hormone that was higher than 0.35 mg per kilogram per week. However, a similar surveillance study from Belgium, the Netherlands, and Sweden did not confirm this finding.[13] Higher-dose regimens and a longer duration of treatment increase costs and may also increase risks.[14]

CONCLUSION

Significant increase in height in response to growth hormone therapy was noted in short statured children presenting with classic growth hormone deficiency in tertiary care hospital.

Author's Contribution:

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Original Article

Determine the Diagnostic Accuracy of Color Doppler Ultrasound for Diagnosing of Endometrial Carcinoma in Post-menopausal Bleeding Women Taking Histopathology as Gold Standard

Muhammad Wasif Iqbal and Zahid Ahmad

ABSTRACT

Objective: To observe the diagnostic accuracy of color Doppler ultrasound for diagnosing endometrial carcinoma (Ca) in Post-menopausal bleeding (PMB) women.
Study Design: Cross-sectional study
Place and Duration of Study: This study was conducted at the Department of Radiology Central Park Teaching Hospital Lahore during from June 2015 to Dec 2015.
Materials and Methods: One hundred and fifteen patients aged between 45 to 70 years having abnormal vaginal bleeding (postmenopausal bleeding) were included. After taking complete consent, patients detailed history age, gender, socio-economic status and previous hospital visited record was recorded. Endometrial thickness (ET), uterine artery resistive index (UARI) and results of Doppler ultrasound (DUS) were noted. Patients marked endometrial Ca whom ET was >5mm and UARI was <0.7. Histopathology results as a gold standard were also noted. The results of Doppler ultrasound were demonstrated with histopathology record.
Results: There were 20 (17.39%) patients were ages <50 years, 62 (53.91%) having ages of 50 to 59 years, and 33 (28.70%) patients were aged of > 59 years. 70 (60.87%) were resident of urban area while 45 (39.13%) having residency of rural area. 42% were literate and 58 % were illiterate, Diagnostic results of DUS were noted as 99 (86.07%) patients having endometrial Ca while 16 (13.91%) patients found no carcinoma of endometrial. Diagnostic results of US with histopathology findings were compared to each other, results were recorded True +ve, true –ve, false +ve, false-ve respectively as 99 (86.07%), 8 (6.96%), 6 (5.22%) and 2 (1.74%). We found sensitivity 98.02%, specificity 80%, PPV (positive predictive value) 94.29% and NPV (-ve predictive value) 80%.
Conclusion: It is concluded that performing DUS for diagnosing endometrial carcinoma in patients having post-menopausal/ vaginal bleeding was very effective with better specificity, sensitivity and positive and negative predictive values. We observe no complications/problems followed by the procedure.
Key Words: Postmenopausal bleeding, Endometrial carcinoma, Doppler ultrasound, Endometrial-thickness, Uterine artery resistive index

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INTRODUCTION

Postmenopausal bleeding (PMB) or abnormal vaginal bleeding is commonly found in women. Approximately on daily basis 5% of women visit for PMB to the gynecology and department.[1] Women with post-menopausal bleeding has been described as complete ending of vaginal bleeding/periods happening at least six months or women having irregular periods cycle from at least 4 months.[2]

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Irregular or abnormal vaginal bleeding may be resulted due to many gynecological or non gynecological problems. Endometrial atrophy found to be the most frequent cause of postmenopausal bleeding[3] rather than the endometrial carcinoma, polyps, hyperplasia and leiomyomas. Many of research regarding PMB shows that Endometrial Atrophy is the most frequent cause of post-menopausal bleeding or abnormal vaginal bleeding, the findings of some other researches with Doppler ultrasound (DUS) shows that endometrial polyps and leiomyomas air the most frequent cause rather than the other causes.[4]

Up-to 75% of patients with endometrial carcinoma has found intermenstrual or postmenopausal bleeding as an early manifestation.[5] The diagnostic accuracy of this malignant disorder and better early treatment are most important for the patient's survival and quality of life.[6] Diagnostic accuracy of diagnosing carcinoma is very

helpful for suitable treatment. Woefully, tests for screening endometrial carcinoma/cancer are not accessible because endometrium is not as available as the cervix, which is effectively scanned by the pap-smear tests. Previous studies show that curettage and dilation procedure marked as the gold standard to diagnose and for the appropriate treatment endometrial disorder.

Many of studies show that color Doppler vascularity and pulsed Doppler index of endometrium is very useful to differentiate between malignant and benign endometrial pathology. Resistive index (RI) ranged from .40 to .70 have been considered to differentiate from benign to malignant endometrial, many of researcher consider 0.40 as the limit value of benign to malignant.[7] Pulsed index (PI) value is ranging from 1 to 2.00.[8]

Davidson and Dubinsky[9] consider endometrial thickness as a better evaluator of endometrial pathology than the Doppler index evaluation. This research was conducted to examine the accuracy of color Doppler ultrasound for diagnosing endometrial CRC (carcinoma) in patients with postmenopausal bleeding (PMB) taking histopathology results as a gold standard.

MATERIALS AND METHODS

This cross-sectional study was conducted at Department of Radiology Central Park Teaching Hospital Lahore during from June 2015 to Dec 2015. One hundred and fifteen patients aged between 45 to 70 years having abnormal vaginal bleeding (postmenopausal bleeding) were included. After taking complete consent, patients detailed history age, socioeconomic status and previous hospital visited record was recorded. endometrial thickness (ET), uterine artery resistive index (UARI) and results of DUS (Doppler ultrasound) were noted. Patients marked endometrial CRC whom ET was >5mm and UARI was <0.7. Histopathology results as a gold standard were also noted. The results of Doppler ultrasound (DUS) were demonstrated with histopathology record. Women having any other cause of vaginal bleeding and other gynecological problems were excluded from this study. The data was entered and analysed in SPSS-20.

RESULTS

There were 20 (17.39%) patients were ages <50 years, 62 (53.91%) having ages of 50 to 59 years, and 33 (28.70%) patients were aged of > 59 years. 70 (60.87%) were resident of urban area while 45 (39.13%) having residency of rural area. 41.72% were literate and 67 (58.28%) patients were illiterate, Diagnostic results of DUS were noted as 99 (86.07%) patients having endometrial CRC while 16 (13.91%) patients found no carcinoma of endometrial (Table 1).

Diagnostic results of US with histopathology findings were compared to each other, results were recorded True positive, true negative, false positive, false negative respectively as 99 (86.07%), 8 (6.96%), 6 (5.22%) and 2 (1.74%). We found sensitivity 98.02%, specificity 80%, (positive predictive value 94.29% and negative predictive value 80% (Table 2).

Table No.1: Demographic information of the patients

Variable	No.	%
Age (years)		
<50	20	17.39
50 – 59	62	53.91
60 -70	33	28.70
Socio-economic status		
Urban	70	60.87
Rural	45	39.13
Education		
Literate	48	41.72
Illiterate	67	58.28

Table No. 2: Comparison of endometrial Ca vs DUS

Endometrial Ca	DUS		Total
	Positive	Negative	
Positive	99 (TP)	6 (FP)	105
Negative	2 (FN)	8 (TN)	10
Total	101	14	115

$$\text{Sensitivity} = \frac{99}{99 + 2} \times 100 = 98.02\%$$

$$\text{Specificity} = \frac{8}{8 + 2} \times 100 = 80\%$$

$$\text{Positive predictive value} = \frac{99}{99 + 6} \times 100 = 94.29\%$$

$$\text{Negative predictive value} = \frac{8}{8 + 2} \times 100 = 80\%$$

DISCUSSION

Endometrial-carcinoma is commonly found malignant disease in the women genital tract.[10] As per SEER database cases of endometrial-Ca in women whom aged between 30 to 35 years is 2.3% out of 0.1 million women in all over the world[11], but in our study there is no patient of these ages it is may be due to the small number of patients, as per SEER results 6.1 out of 0.1 million endometrial Ca found in women ages $\leq$ 40 years and it increases 37 out of 0.1 million in women ages between 41 to 50 years. In PM (post-menopausal) women whom have no hormonal resistance therapy, any bleeding is considered as cancer; however the malignancy in these patients ranged from two to 10%.[12]

In the present study, 20 (17.39%) patients were ages <50 years, 62 (53.91%) having ages of 50 to 59 years, and 33 (28.70%) patients were aged of > 59 years. These results shows similarity to the other study in which maximum patients were aged between 50 to 60 years.[13] We found mostly 60.87% patients were belong to urban area while 39.13% had residency of rural area, these results were approximately similar to some other studies conducted in Pakistan.[14]

Diagnostic results by Doppler ultrasound were noted as 99 (86.07%) patients having endometrial Ca while 16 (13.91%) patients found no carcinoma of endometrial, these results were not better than the study conducted by Shazia et al.[15] It is may be due to the patients population who visited hospital for this malignancy. But in another research out of sixty five patients carcinoma was diagnosed in 54 patients.[16]

Diagnostic results of US with histopathology findings were compared to each other, results were recorded true positive, true negative, false positive, false negative respectively as 99 (86.07%), 8 (6.96%), 6 (5.22%) and 2 (1.74%). We found sensitivity 98.02%, specificity 80%, PPV (positive predictive value) 94.29% and NPV (negative predictive value) 80% with 98% accuracy rate The results of our study correlated with a research that was showing the accuracy of Doppler ultrasound for diagnosing endometrial Ca in PMB women with taking histopathology as a gold standard.[17] Sensitivity, specificity, PPV and PPN as 97.2%, 76%, 89.6% and 76.9% respectively.

If we go through the other study conducted by Dipi et al[17] the sensitivity of diagnosing cervix cancer by Doppler ultrasound was 57.1% and spec- was 89.7%, PPV and NPV were 66.9% and 85.4% respectively.

CONCLUSION

It is concluded that performing DUS for diagnosing endometrial carcinoma in patients having post-menopausal/ vaginal bleeding was very effective with better specificity, sensitivity and positive and negative predictive values. We observe no complications/ problems followed by the procedure.

Author's Contribution:

Concept & Design of Study:	Muhammad Wasif Iqbal
Drafting:	Zahid Ahmad
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Revisiting Critically:	Muhammad Wasif Iqbal, Zahid Ahmad
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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 Rape Among Strangers and Acquaintance

Salma Shazia[1], Hakim Khan Afridi[2] and Naveed Alam[2]

ABSTRACT

Objective: To describe the socio-demographic characteristics of female sexual assault cases among strangers and acquaintances in Peshawar District. To make the society aware about sexual crimes and provide guidelines for its prevention.

Study Design: Observational / cross sectional study

Place and Duration of Study: This study was conducted at the Department of Forensic Medicine and Toxicology of Khyber Medical College, Peshawar for a period of 2 years from January. 2010 to December 2011.

Materials and Methods: A two yearly research was done on the sexual assault cases brought by police for medico legal examination. Only female cases were selected and the observations made were recorded in proformas. The data formed of these cases was analyzed. Data analysis was done on SPSS 16.

Results: 60.6% belonged to urban area while 39.4% were the inhabitants of rural areas. 15.2% females were less than the age of 13 years, while 84.8% victims were more than 13 years that was taken as the average age of menarche. 16.73±4.78 is the mean affected age of the victim 75.8% were unmarried while 24.2% of the victims were married. 63.6% females were abducted by strangers and 36.4% of the assailants were among the acquaintances. 24.2% females left home by their own will while 75% females were taken away by unknown persons.

Conclusion: Sexual offences are the hidden crimes that leave harmful social, psychological and physical effects on the sufferers. The highest rates among all age groups are the young adults residing in urban areas. Assailants are mostly unknown to their victims.

Key Words: Rape, Stranger, Acquaintance

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INTRODUCTION

Sexual violence is a terrible and shocking crime against an individual. It is the most common but hidden form of crime. It is a atrocious crime against someone's will and body. Assailants use both psychological and physical plans to harass a person, often intimidating her privacy, well being and safety. Sexual assault results in significant mental pain, physical trauma and suffering for the victims.[1] It is a universal problem effecting all the nations in the world. It is common in every society and culture, irrespective of its sex, age and geographical boundries.[2]

Sexual assault is an enormously underreported crime. It is estimated that less than 30% of sexual assaults are reported to the police that makes collecting accurate data about sexual assault challenging(U.S. Department of Justice, 2012).

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It is the crime which is least reported. The extent of the problem globally is compared with the tip of the ice berg floating in the water.[3,4] In addition to shame and embarrassment, women do not want to tell about the incidence to anybody because of fear of being blamed and socially targeted. [5]

Sexual assault includes all sexual behaviors like comments, unwanted contacts or threats, touching, fondling, fingering or masturbation to rape or attempted rape.[6] sexual assault is defined by World Health Organization(WHO) as, "Any sexual act, attempt to obtain a sexual act, unwanted sexual advances, or acts to traffic, or otherwise directed, against a person's sexuality using force, by any person regardless of their relationship to their victim, in any setting, including but not limited to home and work." [7]

Sexual assault is one of the most destructive and demoralizing crime. Offenders are mostly among the family members, friends, acquaintances or strangers. They pressurize the victim to gain their interests by tricks, threats or by force.[8] The impact of sexual assault extends far beyond rape survivors as their family, friends, and significant others are also negatively affected. It is a violent crime committed by men against millions of women.

The word "rape" usually shows us the image of a unknown person standing alone in a dark place. We are always taught to recognize strangers and should stay

away from the unknown persons. However, the actual situation is much disturbing and different. Rape occurs with someone you know and trust instead of with a stranger. 55% of sexually assaulted women knew their attacker as said by the Canadian Centre for Justice Statistics. Acquaintance rape is a forced sexual assault committed by an individual whom you know, someone you just met, dated a few times, are in a committed relationship, a classmate, family member, a neighbor, employer, therapist, religious officials, medical doctors etc[9,10,11]. The offender can give threats to harm or actually applies physical force. Acquaintance rape is the breaking of trust among each other.

The victim offender relationship and the circumstances leading to sexual assault do not change the legal definition of rape. Moreover The legal penalty in both the cases is same. Acquaintance rape is the hidden form of the crime that is not reported. Surveys show that they mostly go unreported than stranger rapes. Less than 2% of victims of acquaintance rape had informed the police in comparison to 21% of women raped by a strangers had reported their rape to the police in an American study [10]

Most published research has been based on small samples on the victim– perpetrator relationship and consisted mainly of women who were seeking treatment for their injuries and were raped by nonromantic and nonintimate partners.

Stranger rapes mostly consist of single episode while acquaintances rapes involve multiple episodes with a single offender. It is not taken as rape so is not revealed to anybody. In general, acquaintance rapes were rated as less violent than stranger rapes.

MATERIALS AND METHODS

This study was conducted at the Department of Forensic Medicine and Toxicology of Khyber Medical College, Peshawar for a period of 2 years from January. 2010 to December 2011. A two yearly research was done on the sexual assault cases brought by police for medico legal examination. Only female cases were selected and the observations made were recorded in proformas. The data formed of these cases was analyzed. Data analysis was done on SPSS 16.

RESULTS

According to the research conducted, sexual assault is more common in urban areas. 20 (60.6%) cases are the residents of urban area and 13 (39.4%) belongs to rural areas.(fig.1) young virgin girls are more effected than older married women.(Figure 2).

The mean age estimated was 16.73 yrs ± 4.78 with the minimum age of the victim was 5 yrs, and maximum was 32 yrs, (table 2) while 75.8% are unmarried 24.2% of the victims are married. 63.6% females were abducted by strangers while 36.4% of the assailants were known to the victim. (table 2). 75% females were kidnapped forcefully and 24.2% left home by their own will. (figure 3)

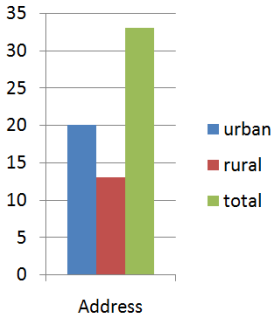

Figure No.1: Urban and rural areas details

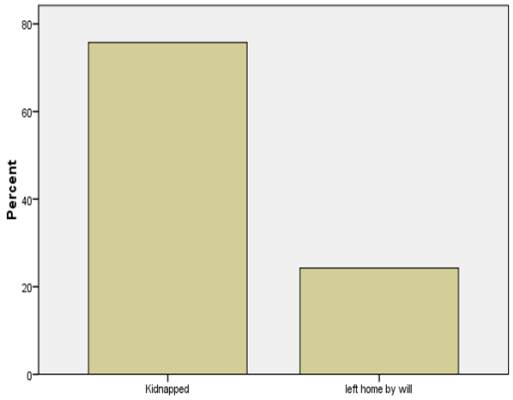

Figure No.2: Kidnapped left home by will

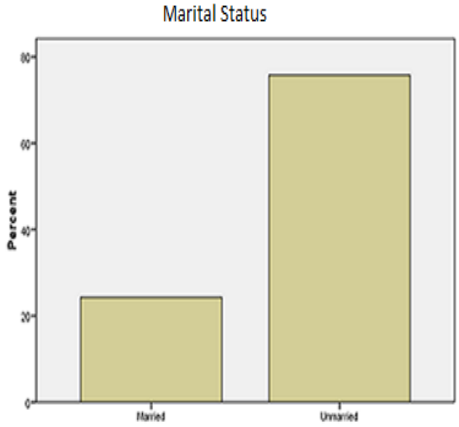

Figure No.3: Marital status

Table No.1: Details of cases

Age	N	Min.	Max.	Mean	Std. Dev.
Estimated Age	33	5	32	16.73	4.785

Table No.2: Assailant

		Frequency	Percent
Valid	Known	12	36.4
	Unknown	21	63.6
	Total	33	100.0

DISCUSSION

Sexual assault crimes are centuries old. The perpetrators of the sexual assaults were blood relations, neighbours, acquaintances, authority figure and stranger[12-15] as documented in studies.

A study conducted in 1950s distinguishes between stranger and acquaintance rape. Later on from 1958 and 1960 a study was done on American police rape files, it was found that about half of the females were raped by men who knew their victims. Diana Russell, an activist and writer, In 1978 used the phrase acquaintance rape for the first time. She found that 11% reported cases were being raped by strangers while 35% have experienced rape or attempted rape by an acquaintance in her research on 830 women in San Francisco. Later on In 1988 American feminist writer Robin Warshaw published the first major book i.e. "I Never Called It Rape", on acquaintance rape.[[16]]Most of the studies shows that in girls under 16 years of age ,the assailants are known to the victim.[[17]]

Our study showed that 75.8% are unmarried and 24.2% of the victims are married. This result is the same as with the study done in Rajshahi Medical college.[03,18, 19] Parents of the married victims had filed FIR against the husbands. 24.2% got married by their own will. The nominated assailant is the husband.

In our study 36.4% assailants were known to the victim while 63.6% were strangers. The rate of sexual assaults by an acquaintance or relative of the victim is quite high as demonstrated in different studies. [20, 21] most of the women are victims in acquaintance rape. In a national study of women and men approximately 29% of men and 45% of women reported that the assault was from an intimate partner.[22, 23] In 73.1% of cases, the victims knew their assailant in a study conducted in Lagos, Nigeria.[24] These facts are against our study. Most probably the reason behind this is that people here do not want to disclose the incident. Our society is a male dominating society. Males are always thought to be innocent until proved guilty while the women are guilty until proven innocent. Victims of acquaintance rape are traumatized with feelings of guilt that someone they know and trust could commit such an assault. These feelings of confusion, disbelief, guilt, and doubt may prevent her from reporting the crime. If a victim does decide to report the assault, she may face barriers with the police and courts. Due to these factors, very little is known about acquaintance rape.

CONCLUSION

Sexual assault is a henious under reported crime with harmful social, physical and psychological effects on its victims. Adolescents residing in urban areas continue to have the highest rates of all age groups. Assailants are mostly unknown to their victims.

Recommendations: Future research and advocacy should focus on improving the community response to rape and the prevention of sexual assault. Increased public awareness and preventive interventions are required particularly within the at-risk age group to enhance their safety.

Author's Contribution:

Concept & Design of Study:	Salma Shazia
Drafting:	Hakim Khan Afridi
Data Analysis:	Naveed Alam
Revisiting Critically:	Hakim Khan Afridi, Salma Shazia
Final Approval of version:	Salma Shazia

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

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Original Article

Effect of Response to Neoadjuvant Chemotherapy and Change in Biomarker Status Post Neoadjuvant Chemotherapy on Prognosis of Locally Advanced Breast Cancer

Naila Zahid[1], Javeria Shoaib[1], Navaira Ali[1], Rufina Soomro[2] and Naveen Faridi[3]

ABSTRACT

Objective: To explore the significance of pathological and biomarker changes in response to neoadjuvant chemotherapy in terms of disease free survival and overall survival in Pakistani population.

Study Design: Retrospective study

Place and Duration of Study: This study was conducted at the Department of Oncology, Liaquat National Hospital from January 2004 to January 2011.

Materials and Methods: A total of 104 patients with locally advanced breast carcinoma (inoperable) were included in the study retrospectively who had received neoadjuvant chemotherapy followed by surgery.

Results: Out of the 104 patients who completed chemotherapy and underwent surgery, 19 (14.4%) had complete pathological response (pCR), 47 (35.6%) had node negative residual disease (NNRD), and 38 (28.8%) had node positive residual disease (NPRD). Factors associated with better 2 year overall survival included pCR, NNRD, post-chemotherapy unchanged positive hormonal status and post chemotherapy changed from negative to positive hormonal status, prechemotherapy Ki-67 <20 % as well as Ki-67 score of >20% changed to less than 20% post chemotherapy. Factors associated with less chances of recurrence were NNRD, unchanged hormone positive and change from hormone negative to hormone positive. Prechemotherapy HER2Neu positive had higher chances of recurrence. Patients with more than 20% pre-chemotherapy Ki-67 had 8.3 times higher chances of recurrence than those with less than 20%.

Conclusion: We concluded that 2yrs overall survival in patients who received neoadjuvant chemotherapy were significantly associated with cPR, NNRD, unchanged positive hormonal status, and post chemo changed from –ve to +ve hormonal status, prechemo ki67 <20% as well as ki67 score of >20% changed to less than 20% post chemotherapy. Factors associated with less chances of recurrence were pCR, node negative residual disease, unchanged hormone +ve and change from hormone –ve to +ve disease.

Key Words: Neoadjuvant chemotherapy, Pathological complete response (PCR), Node Negative Residual Disease (NNRD), Node Positive Residual Disease (NPRD), Her2Neu Receptors, Ki-67, Estrogen Receptor, Progesterone Receptor.

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INTRODUCTION

Breast Cancer is next only to Lung Cancer as cause of cancer related deaths among women from all ethnicities.

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Locally advanced Breast Cancer (LABC) describes a subset of invasive breast cancer where initial clinical & radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes represented by Stage III T_{0-3} N_2, T_4 anyN or T_3 N_1 (AJCC) with no distant metastasis. These are the patients where an initial surgical approach is unlikely to successfully remove all these with adequate margins.

The incidence of locally advanced breast cancer is more common in third world countries with possibly more aggressive disease. This is partly attributable to deficiencies in mammographic screening and possibly lack of awareness regarding breast cancer and inadequate healthcare infrastructure.

The response of primary breast carcinoma to neoadjuvant chemotherapy co-relates with survival. Patients who achieve a complete pathological response are reported to have a significantly improved disease free and over-all survival.[1]

Several studies have reported change in biomarker status estrogen receptor (ER), progesterone receptor (PR), Human epidermal growth factor receptor 2 (Her2Neu) & Ki67 expression after neoadjuvant chemotherapy[2-5]**.** It has been reported that change in the hormone receptor status in the positive direction post neoadjuvant chemotherapy (ER -/+ or PR -/+ or both) has been associated with a statistically significant improvement in the overall survival.[6]

To explore, the significance of pathological and biomarker changes rin response to neoadjuvant chemotherapy in terms of Disease Free Survival and Overall Survival in Pakistani population, we evaluated the effect of neoadjuvant chemotherapy induced pathological and biomarker changes on survival outcome.

MATERIALS AND METHODS

This study was conducted at the Department of Oncology, Liaquat National Hospital from January 2004 to January 2011. Patients with locally advanced breast carcinoma (inoperable) were included in the study retrospectively who had received neoadjuvant chemotherapy followed by surgery. Patients who had progressed on neoadjuvant chemotherapy or had bilateral breast disease or metastatic disease were excluded from the study.

Chemotherapy regimens received included combination regimens AC followed by Taxanes & FAC regimen and Trastuzumab in case of Her2Neu positive tumors.

Hormone status (ER/PR), Her2Neu and Ki67 were performed on post chemotherapy surgical specimen on the residual disease (if any) on the available specimens by Envision method .Her2Neu positivity in specimens with 2+ (by IHC) was confirmed by FISH amplification.

Data of all patients with locally advanced breast cancer who completed their neoadjuvant chemotherapy followed by surgery was analyzed for Complete Pathological Response (CPR), Node negative Residual Disease (NNRD), Node Positive Residual Disease (NPRD), post treatment hormonal (ER/PR) Her2Neu & KI67 score, change in hormone status (change in either ER or PR or both from -/+ or +/- or unchanged), change in HER2neu from -/+ or +/- or unchanged and change in Ki67 status (from >20% to <20% or vice versa or unchanged) and was co-related with disease free survival and overall survival. Patients' 2 years follow-up was assessed retrospectively for disease recurrence and overall survival.

Statistical Analysis: Descriptive statistics were used and odds ratios were calculated by applying binary logistic regression. Inferential statistics were applied to check the association between various categorical variables. Overall survival and recurrence were checked by chi-square test. Data was entered and analyzed using SPSS 17.0, Chi-square/Fisher exact test. Likelihood ratio test were applied to check association between various categorical variables, overall survival and recurrence. P-value of less than 0.05 was considered as statistically significant. Binary Logistic regression was applied to compute odds ratio.

RESULTS

From Jan 2004 to Jan 2011, we registered 1306 breast cancer patients. Out of these, 327 patients were having locally advanced breast cancer, and advised for neoadjuvant treatment. Total 132 patients received neoadjuvant chemotherapy. Complete data (residual disease status, pre chemotherapy and post chemo hormone, Her2Neu and KI67 and 2 years follow-up), was available on 104 patients which was retrospectively analyzed. The remaining 28 patients either had progressed on treatment, or lost to follow or did not undergo surgery so their data could not be analyzed. Pathological response and molecular markers were correlated with 2 year survival and the significance of change in molecular biology after neoadjuvant chemotherapy was analyzed.

Baseline Characteristics: Out of the 132 patients, none belonged to Stage I and IV of Breast Cancer. 52 patients were Stage II-B, 40 patients were III-A and 39 were III-C. Only one patient was Stage III-C. Mean Age: Mean age is 46.37 years.

Out of 104 patients who completed neoadjuvant chemotherapy and underwent surgery, 19 had pathological complete response, 47 had node negative residual disease while 38 had node positive residual disease.

84% (N-16) patient who had pCR remained recurrence free at 2 yrs which is statistically significant as compared to the patients with residual disease. Similarly patients with Node Negative Residual Disease had a statistically significant Recurrence Free Survival as compared to Node Positive Residual Disease as shown in Table I.

Patients with pCR and Node Negative Residual Disease had statistically significant better Overall Survival as compared to Node Positive Residual Disease who had Inferior Overall Survival as shown in Table 1.

Both pre and post chemotherapy Hormone & Her2Neu status were available in 64 samples, while Ki67 score both pre chemo & post chemo were available in 41 patients. Change in status is represented in table 2.

As seen in the table 5 change in hormone status, Her 2 Neu and ki 67 expression before chemo and after chemo exposure was statistically significant (p-value <0.001).

Table No.1: Relationship of recurrence with residual tumor

Recurrence: Yes[b]					
Residual Disease	Odds Ratio	95% C.I. for OR		Sig.	N
		Lower	Upper		
Complete Pathological Response	Reference				19
Node Negative Residual Disease	2.844	0.72	11.242	0.136	46
Node Positive Residual Disease	3.556	0.871	14.511	0.077[a]	35

a. Shows significant results (P-Value < 0.1); Binary Logistic Regression
b. No recurrence is a Reference category

Overall Survival : Alive[b]					
		95% C.I. for OR			
Residual Disease	Odds Ratio	Lower	Upper	Sig.	N
Complete Pathological Response	3.06	0.587	15.956	0.184	19
Node negative residual disease	2.952	0.888	9.811	0.077[a]	46
Node positive residual disease	Reference				35

a. Shows significant results (P-Value <0.1); Binary Logistic Regression
b. Expired is a reference category

Table No.2: Change in Biomarker status after neoadjuvant chemotherapy

		Unchanged				
	N	**Pos**	**Neg**	**Pos → Neg**	**Neg → Pos**	**P-value**
Hormonal Status	64	32	22	1	9	*<0.001
HER2NU	64	23	27	13	1	*<0.001
KI67	41	9	18	13	1	*<0.001

It was also been observed that pre-chemo Her2neu +ve had a higher chance of recurrence (that is among 33 patients who had recurrence, 19 patients (57.3%) were her2neu +veprechemo).(OR: 1.63).

Unchanged hormone +ve (N-32) patients were seen to have lesser chance of recurrence (31% of the patients with no recurrence) as well as better overall survival (33% of the alive patients). This was also seen among the patients who changed from prechemo hormone –ve to post chemo hormone +ve (Table 3).

Table No.3: Change in Hormone receptor and Her2Neu receptor status and it's effect on recurrence

Recurrence: Yes[b]				
	Odds Ratio	**95% C.I. for OR**		
		Lower	Upper	Sig.
Post Surgery Hormonal Status				
Unchanged –ve	Reference			
Unchanged +ve	0.833	0.264	2.631	0.756
Change from –ve to +ve	0.583	0.094	3.603	0.562
Post Surgery HER2Neu Status				
Changed from +ve to –ve	Reference			
Unchanged +ve	0.544	0.133	2.235	0.399
Unchanged –ve	0.519	0.131	2.045	0.348

a. Shows significant results (P-value < 0.1); Binary logistic regression
b. No recurrence is a reference category

Overall Survival : Alive[b]			
		95% C.I. for OR	
	Odds Ratio	**Lower**	**Upper**
Post Surgery Hormonal Status			
Unchanged –ve **Reference**			
Unchanged +ve	2.196	0.437	11.027
Change from –ve to +ve	1.647	0.155	17.47
Post Surgery HER2Neu Status			
Changed from +ve to –ve	**Reference**		
Unchanged +ve	1.727	0.212	14.048
Unchanged –ve	1	0.158	6.33

a. Shows significant results (P-value<0.1); Binary Logistic Regression
b. Expired is a reference category

Patients with more than 20% prechemo Ki67% score were seen to have an 8.3 times higher chances of recurrence than those with a prechemo ki67 score of <20%. Patients with Ki-67 score <20% Pre-Chemo as well as unchanged Post-Chemo Ki-67 score of <20%

had better Overall Survival and Relapse Free Survival whereas patients with ki-67 score changed from >20% to <20% had statistically better OS. (Table 4).

Table No.4: Change in Ki 67 and Recurrence

Recurrence				
Post Chemoki67	No	Yes	Lost to follow up	P – Value
Changed from less than 20% to more than 20%	0	0	1 (25%)	*<0.001
Changed from more than 20% to less than 20%	9 (13.4%)	4 (12.1%)	0	0.427
Unchanged Negative	16 (23.9%)	1 (3%)	1 (25%)	*0.008
Unchanged Positive	5 (7.5%)	4 (12.1%)	0	0.317
Lost to Follow	27(40.3 %)	12(36.4%)	2 (50%)	0.560
	Overall Survival			
Post Chemoki67	Expired	Alive	Lost to follow up	P – Value
Changed from less than 20% to more than 20%	0	0	1 (20%)	*<0.001
Changed from more than 20% to less than 20%	2 (12.5%)	10 (12%)	1 (20%)	*0.002
Unchanged Negative	0	17 (20.5%)	1 (20%)	*0.046
Unchanged Positive	3 (18.8%)	6(7.2%)	0	0.097
Lost to follow	8 (50%)	31 (37.3%)	2 (40%)	0.342

DISCUSSION

Neoadjuvant chemotherapy is the recommended systemic treatment approach for locally advanced breast cancer. The major aims of primary systemic therapy in these patients are to eradicate possible distant micro-metastatic disease and to increase breast conserving therapy. Neoadjuvant chemotherapy also allows in vivo assessment of tumor sensitivity to systemic treatment. Pathologic Complete Response to NAC carries prognostic significance independent of other prognostic biological markers.[7]

Change in Estrogen receptor, progesterone receptor and Her2neu receptor and Ki 67 has also been reported in several reports[8]. What is still unclear is whether there is any prognostic significance of these changes in biomarkers in response to chemotherapy. The prognostic significance of change in Ki 67 has been reported previously.

In our study we studied the effect of residual tumor in terms of size and number of positive lymph nodes on relapse free survival and overall survival. We also tried to identify any relationship between change in biomarkers in response to chemotherapy with relapse free survival and overall survival.

Patients with pathologic complete response had better 2 year recurrence free survival and overall survival which was statistically significant. Furthermore it was also seen noted that node negative residual disease also had statistically significant better recurrence free survival and overall survival as compared to node positive residual disease. Whether there was any prognostic significance of size of residual tumor could not be analyzed because of small sample size.

We also found a significant change in hormone receptor status from negative to positive, Her2neu status from positive to negative and Ki 67 score from more than 20% to less than 20%.

Pre chemotherapy hormone positive patients as well as those who changed from negative to positive had better prognosis. Prechemotherpay Her2neu positive tumors had higher relapse rate but we didn't find any prognostic significance of change in her2neu status.

Prechemotherapy Ki 67 less than 20% and change in Ki 67 score from more than 20% to less than 20% had statistically significant effect on survival but significant effect on relapse free survival couldn't be appreciated probably because of small sample size.

The limitations of this study can be treatment limitations where some Her2neu positive patients did not receive Trastuzumab which could explain the lack of prognostic significance of change in Her2neu status. Another limitation is small sample size.

CONCLUSION

2yrs overall survival in patients who received neoadjuvant chemotherapy were significantly associated with cPR, NNRD, unchanged positive hormonal status, and post chemo changed from –ve to +ve hormonal status, prechemo ki67 <20% as well as ki67 score of >20% changed to less than 20% post chemotherapy.

Factors associated with less chances of recurrence were pCR, node negative residual disease, unchanged hormone +ve and change from hormone –ve to +ve disease.

We think that these factors can guide us in planning further postoperative treatment in patients receiving neoadjuvant chemotherapy for locally advanced breast

cancer and studies should be designed to analyze treatment planning according to these factors.

Patients with a High Ki67 score & significant residual nodal disease might benefit and should be given further chemotherapy to change the outcome. Further studies/trials in this regards are needed.

Author's Contribution:

Concept & Design of Study:	Naila Zahid
Drafting:	Javeria Shoaib, Navaira Ali
Data Analysis:	Rufina Soomro, Naveen Faridi
Revisiting Critically:	Naila Zahid, Javeria Shoaib,
Final Approval of version:	Naila Zahid

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

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Original Article

Use of Supraclavicular Artery Flap in Head and Neck Reconstruction

Ijaz Hussain Shah, Muhammad Bilal Saeed, Naheed Ahmed

ABSTRACT

Objective: To evaluate the use of supraclavicular artery flap in head and neck reconstruction in terms of its reliability, clinical applications, and functional & aesthetic outcome.

Study Design: Descriptive study

Place and Duration of Study: This study was conducted at the PIBC, Nishtar Medical University, Multan.It was completed in 18 months from June 2016 to Dec 2017.

Materials and Methods: This study included 30 patients requiring soft tissue reconstruction in the head and neck region. Survival of supraclavicular artery flap, functional & aesthetic outcome, and donor site appearance were studied.

Results: All flaps survived except for a distal 10 % necrosis seen in two cases. The functional and aesthetic outcomes were excellent with an acceptable donor site appearance. The areas reconstructed included neck, chin, cheek, jawline.

Conclusion: The ideal flap to resurface head and neck defects has yet to be found. In our experience, the supraclavicular artery flap is one of the reconstructive techniques of choice for medium to large defects of the head and neck region. It is a reliable, thin and pliant fasciocutaneous flap, and expands significantly postoperatively.

Key Words: Supraclavicular artery flap, Head and neck reconstruction, Fasciocutaneous flap, thin and pliable flap, close match.

Citation of articles: Shah IH, Saeed MB, Ahmed N. Use of Supraclavicular Artery Flap in Head and Neck Reconstruction. Med Forum 2018;29(5):38-42.

INTRODUCTION

Restoration of both form and function in the head and neck region remains a challenge for the plastic and reconstructive surgeons. This challenge comes from the visibility of the head and neck during social contact. A soft tissue defect in this region can lead to loss of both structure as well as function and can render the appearance of an individual socially unacceptable.

Defects in this region arise mainly from trauma, tumours, congenital anomalies, burns[1]and infections.

The ideal flap for the head and neck reconstruction should be thin and pliable with a good colour and texture match. Moreover, the donor-site morbidity should be minimal with no resulting functional or aesthetic impairment.[2]

A number of reconstructive options are available depending on the size and complexity of the defect. These includeskin grafts,[3] local flaps,[4]pedicled fasciocutaneous,[5] and musle[6] or myocutaneous flaps,[7]tissue expansion techniques[8] and free tissue transfer.[9]

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Vacuum-assisted closure (VAC) has also been reported as a safe and useful reconstructive tool for complex defects of the head and neck region.[10] Each option has got its own merits and demerits. The skin graft has the obvious disadvantages of colour mismatch and postoperative graft contracture.[11] Tissue expansion methods[8]produce enough like tissue with good color and texture match but they require multiple operations, have high rate of complications and are more expensive. Free tissue transfer is an attractive option and when used as a super thin flap does provide excellent texture match. However the colour match is suboptimal and it also requires long operating time and is equipment and skill dependant.[2]

As a basic concept, first formulated by Gillies in 1920, the more adjacent the donor site is, the better the skin will match the recipient.[12] The head and neck region itself suffers from a lack of local tissues available for reconstruction. The areas which are adjacent to the head and neck are chest and shoulder.

The supraclavicular and shoulder areas can provide skin which fulfils most of the criteria of an 'ideal flap' for this region. The flap raised from this area, known as supraclavicular artery flap, is an extremely reliable, local, pedicledfasciocutaneous flap. It is based on the supraclavicular artery, which is a branch of the transverse cervical artery, or, less frequently, of the suprascapular artery.Its skin paddle consists of a defined region around the shoulder cap. It offers thin and pliable skin with good colour and texture match and minimal donor site morbidity. The purpose of this

study was to evaluate the role of supraclavicular artery flap in head and neck reconstruction in terms of its reliability, clinical applications, and functional and aesthetic outcome.

MATERIALS AND METHODS

It was a Descriptive study. A total number of thirty patients with lesions in head & neck region and requiring flap reconstruction were included in this study. It was convenience sampling. The collected data was analyzed by SPSS statistical package version 20. Following variables were studied:

1. Flap survival (percentage)
2. Functional restoration at one, three and six months follow-up
3. Aesthetic restoration at one, three and six months follow-up

RESULTS

A total number of 30 patients were included in this study. All of them were studied during the one and half year of this study. There were 13 (43.3%) male and 17 (56.7%) female patients, as shown in table 1. In 28 (93.3%) patients, flap survival was noted to be 100 percent. In only 2 (6.7%) patients, it was found to be 90 percent, as the distal 10% of the flap underwent necrosis as shown in Table 2.

At one month follow-up, the functional restoration was noted to be excellent in 6 (20%) patients, good in 21 (70%) patients, and satisfactory in 3 (10%) patients. None of the patients (0%) at one month follow-up was found to have a poor functional restoration.The functional restoration kept on improving with the passage of time. At three months follow-up, it became excellent in 16 (53.3%) patients, good in 12 (40%) patients and remained satisfactory in 2 (6.6%) patients. Not a single patient (0%) was found to have a poor functional restoration at this stage.At six months follow-up, still further improvement was seen in the functional restoration. It became excellent in 22 (73.3%) patients, good in 6 (20%) patients, and remained satisfactory in 2 (6.7%) patients. Again none of the patients (0%) was found to have a poor functional restoration at this stage of follow-up, as shown in table 3.

Table No.1: Distribution of Cases by Sex

Sex	Frequency (%)
Male	13 (43.3)
Female	17 (56.7)
Total	30 (100.0)

n=30

Table No. 2. Distribution of Cases by Flap Survival

Flap Survival (%)	Frequency (%)
100	28 (93.3)
90	2 (6.7)
Total	30

n=30

Table No.3: Distribution of Cases by Functional Restoration at 1, 3 and 6 Months Follow-up

Functional Restoration	Frequency (%)		
	At 1 month follow-up	At 3 months follow-up	At 6 months follow-up
Excellent	6 (20.0)	16 (53.0)	22 (73.3)
Good	21 (70.0)	12 (40.0)	6 (20.0)
Satisfactory	3 (10.0)	2 (6.7)	2 (6.7)
Poor	0 (00.0)	0 (00.0)	0 (00.0)
Total	30 (100.0)	30 (100.0)	30 (100.0)

n=30

Table No.4: Distribution of Cases by Aesthetic Restoration at 1, 3 and 6 Months Follow-up

Aesthetic Restoration	Frequency (%)		
	At 1 month follow-up	At 3 months follow-up	At 6 months follow-up
Excellent	11 (36.7)	17 (56.7)	21 (70.0)
Good	13 (43.3)	9 (30.0)	5 (16.7)
Satisfactory	6 (20.0)	4 (13.3)	4 (13.3)
Poor	0 (00.0)	0 (00.0)	0 (00.0)
Total	30 (100.0)	30 (100.0)	30 (100.0)

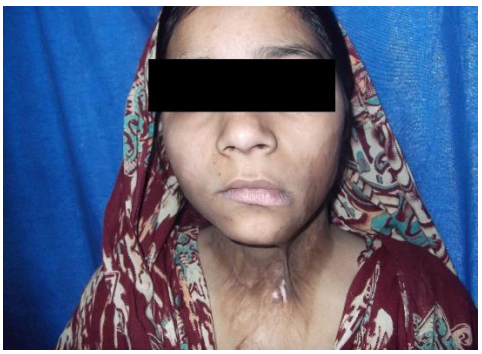

Figure No.1: Postburn neck contracture (front view)

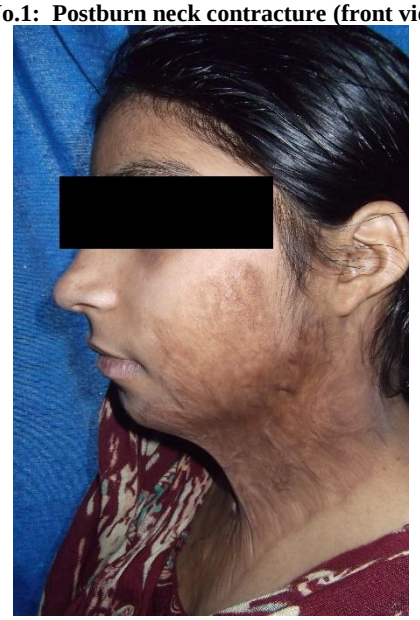

Figure No.2: Postburn neck contracture (lateral view)

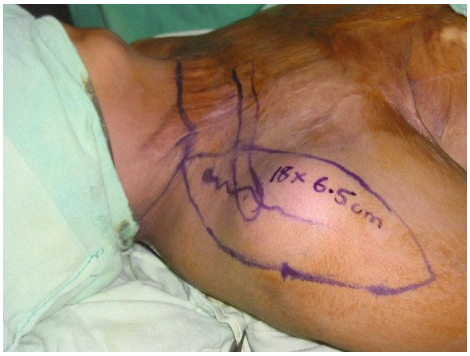

Figure No.3: Flap markings for right supraclavicular artery flap.

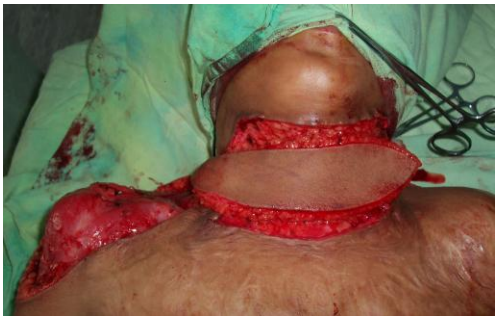

Figure No.4: Flap transferred to the defect.

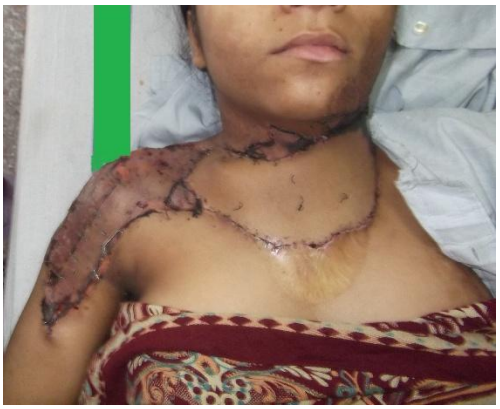

Figure No.5: Early Post operative view

At one month follow-up, the aesthetic restoration was noted to be excellent in 11 (36.7%) patients, good in 13 (43.3%) and satisfactory in 6 (20%) patients. No patient (0%) had a poor aesthetic outcome.Like the functional restoration, the aesthetic restoration was also seen to be improving with the passage of time. At 3 months, it became excellent in 17 (46.7%) patients, good in 9 (30%) patients and remained satisfactory in 4 (13.3%) patients. None of the patients (0%) had a poor aesthetic outcome at this follow-up.At 6 months follow-up, still further improvement was noted in the aesthetic restoration. It became excellent in 21 (70%) patients, good in 5 (16.7%) patients and remained satisfactory in 4 (13.3%) patients. Again none of the patients (0%) was seen to have a poor aesthetic outcome at this stage of follow up, as shown in table 4.

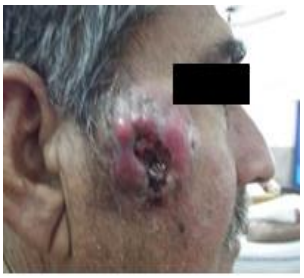

Figure No.6: Tumour of cheeck

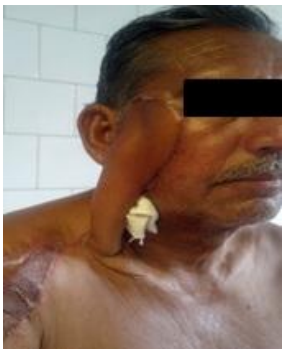

Figure No.7: Supraclavicular artery flap attached.

Figure No.8: After flap division.

DISCUSSION

Reconstructive procedures in the head and neck region have to take account of anatomic, aesthetic and functional aspects. First, normal contours have to be achieved; in the neck, the cervico-mandibular angle has to be reformed. Second, the aesthetic units have to be taken into account. Third, the functional outcome has to ensure full range of movements, both of the lower face and neck. Finally, additional scarring of the upper chest should be avoided. To achieve these goals, a thin reliable flap, harvested close to the face/neck region with good colour and texture match, and a smooth hairless skin surface is needed. Everyday clothing should conceal the donor site.

So for thin, flexible and smooth hairless resurfacing with acceptable donor site camouflage, supraclavicular artery flap which is raised from region of shoulder seems to be the best choice. It can provide skin which fulfils most of the criteria of an ideal flap for this region.

Lamberty was the first to describe a supraclavicular artery based flap in 1979.[16]Pallua modified it as an island flap to increase its versatility and to minimise dog ears and scars in the supraclavicular region.[13]

In our series of 30 patients, the most common site requiring reconstruction was the neck region (n=21). The next most common site was the cheek (n=5). The other sites reconstructed included chin (n=1), oral cavity (n=1), jawline (n=1), and hypopharnx and cervical oesopahus (n=1). Pallua and Noah,[13] and Di Benedetto et al.[14] have used this flap for almost similar type of defect locations. In addition, the latter group has reported the use of this flap for chest wall reconstruction as well.

All flaps used in our study survived. In 28 (93.3%) patients, the flap survival was complete (without any necrosis). In only 2 (6.7%) patients, tip necrosis (distal 10% loss) was seen. In one of them, the cause of this tip necrosis was found to be haematoma formation under the distal area of the flap despite the placement of a suction drain which probably blocked by clotted blood. The haematoma was drained, necrosed part was debrided and the resulting raw area was covered by advancement of the flap. In the other patient, it was probably too much tension across the distal edges of the flap which led to tip necrosis. The necrosed area was debrided and the resulting defect was closed primarily by advancing the flap. Pallua and Noah,[13] Di Benedetto et al.,[14] Rashid et al.[2] have reported almost similar results about the supraclavicular artery flap survival in their series of 28, 27, 25 and 30 patients respectively.

Each patient was followed up for a period of at least six months. Chaudhry et al.[15] have also presented their results after a follow-up of six months.

Functional and aesthetic restorations were recorded at one, three and six months follow up. With the passage of time, a progressive improvement in the range of motion in reconstructed areas like neck, cheek, chin and oral cavity was observed. At one month follow-up, the functional restoration was noted to be excellent in 6 (20%) patients, good in 21 (70%) patients, and satisfactory in 3 (10%) patients. None of the patients (0%) at one month follow-up was found to have a poor functional restoration. At three months follow-up, it became excellent in 16 (53.3%) patients, good in 12 (40 %) patients and remained satisfactory in 2 (6.6%) patients. Not a single patient (0%) was found to have a poor functional restoration at this stage. At six months follow up, 22 (73.3%) patients had excellent, 6 (20%) patients had good while 2 (6.7%) patients had satisfactory functional restoration. None of the patients (0%) had poor functional outcome. This significant improvement in function was mainly due to postoperative expansion of the flap These results are comparable to those reported by Rashid et al.[2] They used Watusi splint in all of their cases for postoperative stretching of the flap. They followed-up their patients at 3, 6 and 12 months, measured the width of the flap at each follow-up and found an average of 63% increase in width at one year.

Just like the gradual improvement seen in function, the aesthetic appearance also kept on improving with the passage of time. At one month follow-up, the aesthetic restoration was noted to be excellent in 11 (36.7%) patients, good in 13 (43.3%) and satisfactory in 6 (20%) patients. No patient (0%) had a poor aesthetic outcome. At three months follow-up, it became excellent in 17 (46.7%) patients, good in 9 (30%) patients and remained satisfactory in 4 (13.3%) patients. None of the patients (0%) had a poor aesthetic outcome at this follow-up. At six months follow-up, excellent aesthetic restoration was seen in 21 (70%) patients, good in 5 (16.7%) patients and remained satisfactory in the remaining 4 (13.3%) patients. None of the patients (0%) had a poor aesthetic outcome. These results are comparable to those reported by Di Benedetto et al.[14] and Chaudhry et al.[15]

CONCLUSION

The ideal flap to resurface head and neck defects has yet to be found. In our experience, the supraclavicular artery flap is one of the reconstructive techniques of choice for medium to large defects of the head and neck region. It is a reliable, thin and pliant fasciocutaneous flap, and expands significantly postoperatively.

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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

Eosinophilia in COPD

Frequency of Blood Eosinophilia in Patients of COPD Exacerbations

Huma Batool[1], Noor ul-Arfeen[2] and Muhammad Hussain[3]

ABSTRACT

Objective: To determine frequency of blood eosinophilia in patients with COPD exacerbation

Study Design: *Cross-sectional Study*

Place and Duration of Study: This study was conducted at the Department of Pulmonology, Services Hospital Lahore from 01-02-2017 to 31-07-2017.

Material and Methods: 150 patients fulfilling inclusion criteria for all types of COPD with acute exacerbations before treatment were included in study from outdoor and indoor of pulmonology department of Services Hospital, Lahore. Informed consent was taken. The data was collected through a predesigned proforma. Bias effect was controlled by having eosinophil count measured from single laboratory of Services hospital by digital method followed by manual verification for those having >2% eosinophilia. All the information was written in pre-designed proforma.

Results: Out of 150 cases 90 % (n=135) were males and only 10% (n=15) were females. Mean age of presentation was 60.27±9.7.42% (n=63) patients were found to be having raised peripheral blood eosinophilia while 58% (n=87) patients had normal eosinophil count.Male to female ratio was 9:1

Conclusion: Peripheral blood eosinophilia is a significant biomarker in patients with acute exacerbation of COPD for our population.

Key Words: COPD,Acute exacerbation of COPD, Peripheral blood eosinophilia, airway eosinophilia.

Citation of articles: Batool H, Arfeen N, Hussain M. Frequency of Blood Eosinophilia in Patients of COPD Exacerbations. Med Forum 2018;29(5):43-45.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[1]

Chronic obstructive pulmonary disease (COPD) has an extensive, adverse effect on both patients and the healthcare system. It is the fourth-ranked cause of death in the United States, killing more than 120,000 individuals each year.[2]

The diagnosis of COPD required pulmonary function tests (PFTs) in symptomatic patients with history of exposure to tobacco smoke, occupational dust, or occupational chemicals[3]. COPD is confirmed when a patient who has symptoms that are compatible with COPD is found to have airflow obstruction (ie, a forced expiratory volume in one second [FEV1]/forced vital capacity [FVC] ratio less than 0.70) and there is no alternative explanation for the symptoms and airflow obstruction.Any exacerbation of COPD is an acute event which is characterized by worsening of the patient's respiratory symptoms (shortness of breath, increase in sputum productionand change in sputum colour) that is beyond normal day to day variation and leads to a change in medications[4].

Current guidelines advocate use of systemic steroids in acute exacerbation of COPD but the treatment responses are heterogeneous, efficacy is marginal and treatment is not without side effects[8]. Airway eosinophilia is associated with corticosteroids responsiveness in COPD and peripheral blood eosinophil count is a sensitive and specific biomarker for airway eosinophilia during exacerbation of COPD[9.]

Empirical antibiotics and systemic steroids for 7-10 days are usually prescribed for the treatment of exacerbation according to GOLD guideline for COPD. A biomarker directed treatment strategy using the peripheral blood eosinophil count to guide corticosteroid prescription can be used to treat exacerbation of COPD. Peripheral blood eosinophils are a highly sensitive and specific marker of sputum eosinophilia during exacerbation of COPD[11] as COPD patients with eosinophilia respond better to

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corticosteroid treatment.A randomized placebo controlled trial conducted in United Kingdom by Bafadhel and colleagues included 166 subjects, out of which biomarker directed arm (86) showed 51% (44) patients to be having blood eosinophilia[12,13].

MATERIALS AND METHODS

This was a cross-sectional study that was performed in Department of Pulmonology Services Hospital Lahore from 01-02-2017 to 31-07-2017. One hundred and fifty patients (both gender) of age >20 years and with acute COPD exacerbation before treatment were included in the study. Patient with known case of hypereosinophilic disease or taking systemic steroids in last 2 weeks were excluded from the study.Informed consent was taken. The data was collected through a predesigned proforma.Bias effect was controlled by having eosinophil count measured from single laboratory of Services hospital by digital method followed by manual verification for those having >2% eosinophilia. All the information was written in pre-designed proforma.The collected information was entered in SPSS version 20.0 and analyzed. Quantitative variable of the study like age were presented as mean ± standard deviation. The qualitative variables like gender and blood eosinophilia were presented as frequency and percentages.As this was a cross sectional study, therefore no test of significance will be applied.

RESULTS

One hundred and fifty patients were enrolled with mean age of 60.27 ± 9.7 years [range 44 – 79]. Majority of the patients 51% (n=76) were between 40 -59 years of age (Table 1).Out of 150 patients, there were 135 (90%) male patients, while remaining only 15 (10%) patients were females. Male to female ratio was 9:1 (Table 2). Peripheral blood eosinophiliawas present in 42% (n=63) while 58% (n=87) were having normal peripheral blood eosinophil count (Table 3).Our results showed that 90% (n=57) patients with blood eosinophilia were males and 10% (n=6) patients were females (Table 4).

Table No.1: Distribution of cases by age

Age	Number of Cases	Percentage
40-49	28	19%
50-59	48	32%
60-70	44	29%
>70	30	20%
Total	150	100%
Mean±SD	**60.27± 9.7**	

Table No.2: Distribution of cases by sex

	Number of Cases	Percentage
Male	135	90%
Female	15	10%
Total	150	100%

Male: female 9:1

Table No.3: Distribution of Subjects According To blood eosinophilia

Eosinophilia	Frequency	Percent
Present	63	42
Absent	87	58
Total	150	100.0

Eosinophilia : Blood eosinophil count >2%

Table No.4: Gender distribution according to blood eosinophilia

Gender	Frequency	Percent
Females	06	10 %
Males	57	90 %
Total	29	100 %

Male: Female 8.5:1

DISCUSSION

COPD affects 329 million people or nearly 5% of the population. In 2011, it ranked as the fourth-leading cause of death, killing over 3 million people[14].The number of deaths is projected to increase due to higher smoking rates and an aging population in many countries.[15]Chronic obstructive pulmonary disease (COPD) has an extensive, adverse effect on both patients and the healthcare system[3].Acute exacerbations of COPD are associated with significant morbidity and mortality[6,20].

A randomized placebo controlled trial conducted in United Kingdom by Bafadhel and colleagues included 166 subjects, out of which biomarker directed arm (86) showed 51% (44) patients to be having blood eosinophilia[8].

In our study we found out 42% patients to be having peripheral blood eosinophilia. The lesser percentage as compared to Bafadhel study is possibly because of the ethnic differences among two populations. Differences in COPD by ethnicity were identified and significant differences in drug and non-drug management and hospital admissions observed[17]. Study conducted by Barbara Bain revealed that there is difference in eosinophil count in white and black population in UK[16].

Mean age at presentation in our study was 60.27 ± 9.7 which is quite similar to results of study by Mohan et al[16],having mean age of 62.1±9.8.

Moreover our study showed lesser magnitude of problem in females i.e., only 10% which is significantly closer to data by Mohan[16] i.e., 12% but lower than western population.

This indirectly coincide with lesser percentage of smoking in our female population as compared to west as revealed by study by Nasir K i.e., 25.4% smokers were males while only 3.5% of females smoked[17,19]. By contrast in 2008, 21.1 million (18.3%) women smoked in United States compared to 23.1% men[18].

Our study is first of its kind in Pakistan to target the judicious use of systemic steroids with the help of simple and easily accessible eosinophil count that may

help to avoid the well documented side effects of this treatment. Further studies are required to evaluate the results for the better management of our patients.

CONCLUSION

Peripheral blood eosinophilia can be used to curtail the steroid prescribing practice in Pakistan to avoid potential side effects.

We recommend further studies on a larger population scale to strengthen our data.

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Final Approval of version:	Huma Batool

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

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Original Article

Outcome of Adipofascial Flap in Patients Having Soft Tissue Defects of Lower Third of Leg, Ankle and Hind Foot

Muhammad Bilal Saeed, Ijaz Hussain Shah, Naheed Ahmed

ABSTRACT

Objective: To determine the outcome of Adipofascial flap in patients having soft tissue defects of lower third of leg, ankle and hind foot.

Study Design: Descriptive case series

Place and Duration of the Study: The Study was conducted at the Pak Italian Modern Burn CenterNishtar Medical University and Hospital Multan from January 2017 to December 2017.

Materials and Methods: 75 patients requiring soft tissue reconstruction of the lower leg, ankle, and hind foot**.** Twenty-one patients (70%) were having their defects in ankle area. The next most common site was lower third of leg. Five patients (16.7%) were having their defects located in this area. One patient (3.3%) was having defect on the hind foot**.**

Results: A total number of 75 patients were included in this study. There were 13 (43.3%) male and 17 (56.7%) female patients. The age of the patients ranged from 10-40 years, with the mean age of 29.7 years and a standard deviation of 16.2.heel was found to be the most common site requiring reconstruction. Twenty-one patients (70%) were having their defects in this area. The next most common site was lower third of leg. Five patients (16.7%) were having their defects located in this area. One patient (3.3%) was having defect on the hind foot. The dimensions of flap required were found to be different depending upon the size of the defect. The flap length ranged from 10 to 25 cm with a mean of 18.6 ± 3.9 cm. The flap width ranged from 6 to 12 cm with a mean of 9.8 ± 1.5 cm. In 28 (93.3%) patients, flap survival was noted to be 100 percent. In only 2 (6.7%) patients, it was found to be 90 percent, as the distal 10% of the flap underwent necrosis.

Conclusion: The adipofscial flap is a reliable, thin and pliant flap .It is simple to learn, quick to perform and can provide an excellent aesthetic and functional restoration in the lower third leg ,ankle and foot region with good donor site appearance.

Key Words: Adipofacial, flap, hind foot

Citation of articles: Saeed MB, Shah IH, Ahmed N. Outcome of Adipofascial Flap in Patients Having Soft Tissue Defects of Lower Third of Leg, Ankle and Hind Foot. Med Forum 2018;29(5):46-49.

INTRODUCTION

Lower limb reconstruction, especially in the aquilian and calcaneal regions, represent a therapeutic problem for the surgeon. Appropriate protection to the mobility and vascular structures causing minimum sequelae in the donor site, and promoting constant vascular activity are some of the desired factors in an ideal coverage. [1-6]

Most open fractures of lower 1/3 of tibia are associated with soft tissue defects, because tibia is subcutaneous bone with almost no muscles around its lower 1/3 with tight skin and poor circulation. Heel is another problemsite because of weight bearing properties, hence it needs a full thickness skin cover.

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Different forms of soft tissue cover are available e.g., muscle flap, facial flaps, septocutaneousflaps, axial flaps and free flaps with their ownindications and disadvantages.[7]

A lateral calcaneal artery skin flap is an axialpattern flap that includes the lateral calcaneal artery, lesser saphenous vein and

the sural nerve.[8] Since its developmentin 1981, this flap has been demonstrated to be both an effective and reliable local flap for reconstructingsoft tissue defects about the posterior heel and both malleoli.[9,10]

Modifications of this flap include island arterial flaps,[9-12] distally based flaps [12] and free flaps,[13] all of which have a wide variety of clinical applications. Lin et al.[14] modified this flap as an adipofascial flap and used it toreconstruct soft tissue defects of the posterior heel as wellas the lateral malleolar and lateral supramalleolar areas.

Adipofascial flaps have inherent shortcomings that warrant consideration.[15]These include flap thinness, bleeding or hematoma, monitoring difficulties and skin graft associated problems.[16-18]

MATERIALS AND METHODS

75 patients from both sexes those fulfilling the inclusion criteria were recruited for the study through the Emergency and OPD of Pak Italian Modern Burn Center Nishtar hospital Multan. After taking complete history, general physical, local and systemic examination was done. Routine and specific investigations were carried out. Pre-anesthesia evaluation was done. An informed consent was taken. The procedures were performed under spinal and general anesthesia. X ray was taken when there were underlying fractures. Defects were analyzed and measured pre-operatively. Pre-operatively, a 10 MHZ hand held Doppler probe was used to exactly locate and mark the origin and course of the vessels, and flap design was outlined on the selected donor-site according to the dimensions of the defect. Wound was debrided. Its dimensions were mapped out with the help of a template. The planning in reverse was used to confirm the flap design already marked. The flap was elevated and inset into the defect. Flaps was grafted with split thickness skin graft taken from the thigh. The donor site was closed directly. In all cases back slab was applied.

Flap dressing was opened on fourth postoperative day. All patients were observed for survival of the flap and graft, and any early flap or donor-site complication. The patients were discharged on 7 days after operation. At discharge, study proforma were filled and photographs of the donor and recipient site were taken.

The first follow-up visit was after one week. All the patients were subsequently followed-up at every week for four weeks. At each follow-up, the flap and donor site were examined for any late complications like graft loss (partial or complete) and flap loss (partial or complete), the functional and aesthetic restorations were assessed and donor-site appearance was observed.

All the data collected was entered and analyzed by SPSS version 20. Numerical variables of interest like age was presented as mean and standard deviation. Nominal variables like sex, success of flap were presented as frequency and percentages. Data was stratified for any underlying fracture and duration of injury. Data was presented separately for location of defect (lower third of leg, ankle and hind foot) and flap used (sural artery flap, posterior tibial artery flap and supremalleolar flap).

RESULTS

A total this number of 75 patients were included in study. There were 13 (43.3%) male and 17 (56.7%) female patients, as shown in table 1.

The age of the patients ranged from 10-40 years, with the mean age of 29.7 years and a standard deviation of 16.2.

Table No.1: Age distribution

Sex	Frequency (%)
Male	13 (43.3)
Female	17 (56.7)
Total	**75 (100.0)**

Table No.2: Location of defect

Location of Defect	Frequency (%)
Lower third leg	21 (70.0)
ankle	5 (16.7)
Hind foot	1 (3.3)
Total	**75 (100.0)**

Table No.3: Distribution of Cases by Flap Length

Flap Length (cm)	Frequency (%)
23.0	1 (3.3)
13.0	2 (6.7)
14.0	2 (6.7)
15.0	2 (6.7)
16.0	3 (10.0)
17.0	2 (6.7)
18.0	2 (6.7)
20.0	7 (23.3)
21.0	2 (6.7)
22.0	2 (6.7)

Table No.4: Distribution of Cases by Flap Width

Flap Width (cm)	Frequency (%)
6.0	1 (3.3)
7.0	1 (3.3)
8.0	3 (10.0)
8.5	2 (6.7)
9.0	3 (10.0)
9.5	1 (3.3)

Table No.5: Distribution of Cases by Flap Survival

Flap Survival (%)	Frequency (%)
100	28 (93.3)
90	2 (6.7)
Total	**75**

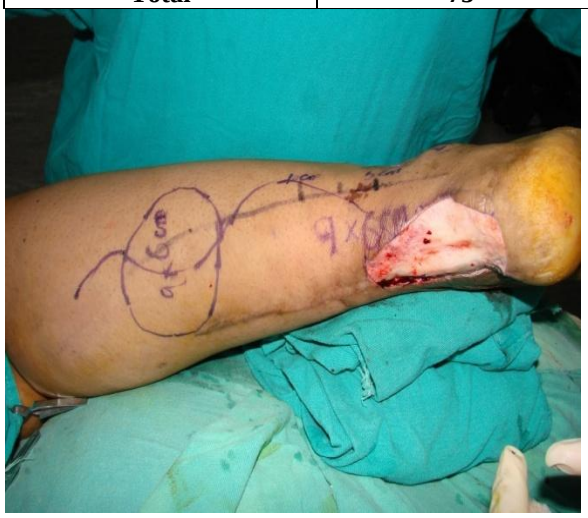

Figure No.1: Defect With Marking of Adipofacial Reverse Sural Artery Flap

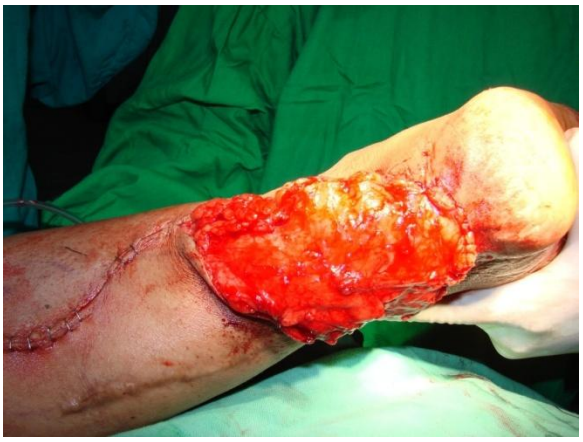

Figure No.2: In setting of Adipofacial Reverse Sural Artery Flap

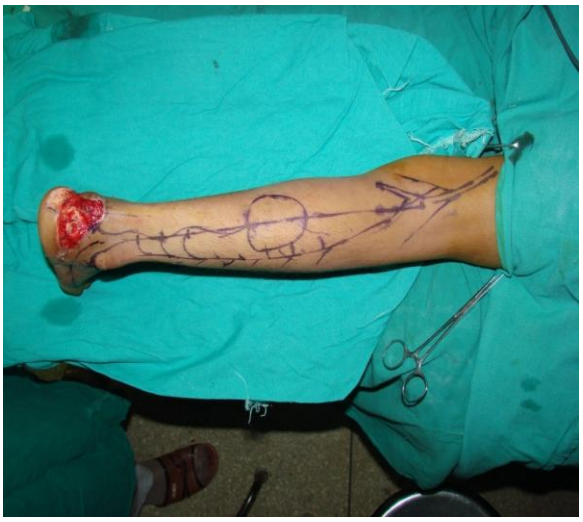

Figure No. 3: Defect with marking of flap

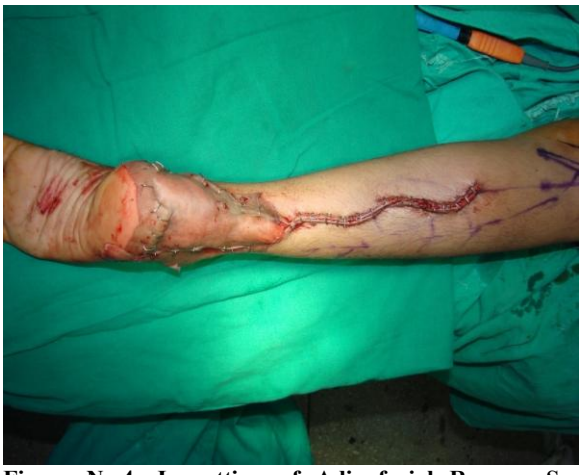

Figure No.4: In setting of Adipofacial Reverse Sural Artery Flap

Heel was found to be the most common site requiring reconstruction. Twenty-one patients (70%) were having their defects in this area. The next most common site was lower third of leg. Five patients (16.7%) were having their defects located in this area. One patient (3.3%) was having defect on the hind foot, as shown in table 2.

The dimensions of flap required were found to be different depending upon the size of the defect. The flap length ranged from 10 to 25 cm with a mean of 18.6 ± 3.9 cm, as shown in table 3. The flap width ranged from 6 to 12 cm with a mean of 9.8 ± 1.5 cm, as shown in table 4.

In 28 (93.3%) patients, flap survival was noted to be 100 percent. In only 2 (6.7%) patients, it was found to be 90 percent, as the distal 10% of the flap underwent necrosis as shown in table no. 5.

DISCUSSION

The third-distal leg and calcaneal region is frequently exposedto trauma and, when cutaneous coverage is made necessary, one ascertains how difficult the reconstruction of this zone may be.[9]Among the adipofascial flaps described in the coverage of the lower limb, Hong and his co-authors used the flap based on the posterior tibial artery, while Yoshima and hisco-authors suggested the peroneal artery and vein flap.

Masquelet and his co-authors described a flap based on cutaneous branches originated from perforating branches of the peroneal artery.8 Adipofascial flaps can be made large, easily reaching the most distal regions in the lower limb. The inclusion of the subcutaneous tissue increases the thickness of the flap and, at the same time, assures its vascularization.[2,3,7]

Adipofascial flaps have inherent shortcomings that warrant consideration.19 These include flap thinness, bleeding or hematoma, monitoring difficulties and skingraft associated problems.[8-10]

An axial pattern adipofascial flap has a rich blood supply for the vessels to run and form a redundant vascular network within the fascia.[8] Therefore, the potential difficulties associated with intraoperativeand postoperative bleeding are a valid concern.[9]

Intraoperative bleeding can be minimized by the carefuluse of bipolar cauterization. The problems associated apostoperative hematoma beneath flaps is best address edusing small-caliber suction drains, as recommended by Brent and Byrd,[11] rather by applying external pressure.[9]

CONCLUSION

Adipofacial flap is very good for coverage of lower limb defects. It is simple, quick to do and provide excellent aesthetic and functional results.

Author's Contribution:

Concept & Design of Study:	Muhammad Bilal Saeed
Drafting:	Ijaz Hussain Shah, Naheed Ahmed
Data Analysis:	Ijaz Hussain Shah, Naheed Ahmed

Revisiting Critically:	Muhammad Bilal Saeed, Ijaz Hussain Shah
Final Approval of version:	Muhammad Bilal Saeed

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

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Original Article

PSA Levels

Histological Prostatitis and its Correlation with Prostate Specific Antigen Levels

Parkha Rehman[1], Zainab Rehman[2] and Iftikhar Mohammad Khan[1]

ABSTRACT

Objectives: The aim of the study was to find a relationship between Prostate Specific Antigen levels and histological prostatitis in people belonging to our part of the world mainly Khyber Pakhtunkhwa and adjoining areas of Afghanistan.

Study Design: Analytical / cross sectional study

Place and Duration of Study: The study was conducted at the North West Hospital, Peshawar for a period of six months.

Materials and Methods: A total of 200 patients who underwent surgical treatments for Benign prostatic hyperplasia due to obstructive or irritative symptoms were prospectively studied.Patients who complained of chronic pelvic pain or had a history of laboratory exam suggesting acute prostatitis were excluded.Results were analysed using Mann-Whitney rank sum test or Pearson product moment correlation (for Prostate specific antigen vs inflammation) at 95%CI.

Results: In my study of the 200 cases, 98 cases with histological prostatitis had normal PSA levels and 102 cases with histological prostatitis had raised PSA levels. Of the cases with raised PSA levels , most cases were of grade I inflammation with multiple spread and their location was glandular, peri- glandular plus stromal.

Conclusion: It is shown in numerous studies that there is a relationship between PSA levels and Histological Prostatitis .My study revealed that a relationship doesexist between PSAlevels and Prostatitis but it is a weak one.PSA levels can be raised in conditions other than prostatitis.

Key Words: Prostate specific antigen, benign prostatic hyperplasia, Prostatitis

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INTRODUCTION

The prostate gland is derived from the Greek word προστάτης – prostates, which means one who stands before, protector or guardian. (Ayala et al. 1989)[1]. Prostate is an exocrine gland of the compound tubuloalveolar variety (Baade et al. 2009)[2]. Herophilus of Alexandria first used the word prostatitis in 335B.C. to describe an organ present in front of the bladder.(Bennet and Harrison, 1969)[3]. The prostate surrounds the first part of the urethra, the prostatic urethra, and is considered the largest accessory reproductive gland in the males (Bankhoff and Remberger, 1998)[4]. The prostatic part of the urethra surrounds the prostate gland anteriorly It is divided into proximal and distal portions by an angulation of 30degrees in its mid portion. The posterior wall of the gland has a ridge , distal to this angulation, Verumo-ntanum(crista urethralis)[5].

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The ejaculatory ducts that receive about 90% of the ducts of the prostate gland also open in the distal segment of the urethra(Brendler et al., 1992)[6]. The differentiation and the growth of the prostate depends on the androgenic hormones which are synthesized in the testis[7].

The most common benign diseases of the prostate gland include BPH and prostatitis and affect a large majority of men over a period of time. Prostatitis is defined as the presence of pathological infiltration of the prostate by inflammatory cells.

Prostatitis was considered to be the disease of the young men, but now it is proven that it is as common in older men[8]. Compared to men aged 51 and higher the odds of a documented prostatitis diagnosis is only 2-fold greater in younger men[9]. Approximately 8% of men over 50 years of age report atleast some mild prostatitis like symptoms compared to 11% of younger men.

In 1992, 31,681 United States health professional without prostate cancer showed a relationship between the diagnosis of urological diseases and the symptoms of the lower urinary tract. 57.2% of the 5,053 with prostatitis also had a history of BPH and 38.7% of the 7,465 men who had a diagnosis of BPH also had a history of prostatitis[10].

There is a tendency to correlate inflammatory prostatitis with an elevation of PSA.(Irani et al.,2014) studied the

effect of inflammation of prostate on the serum PSA concentration in patients with BPH tissue on prostate biopsies. Inflammatory infiltrate were given the following grades: Grade 0(no inflammatory cells), 1 (inflammatory cells are scattered in the stroma but with absent lymphoid nodules), 2 (non-confluent lymphoid nodules) and 3 (large areas of inflammation with confluence of infiltrate)[11].

It was reported that the inflammation seen in the biopsies of the prostate were not associated with the raised serum PSA levels unless the glandular epithelium isdisrupted[12]. Another research showed that the inflammation of the prostate is an important factor contributing to elevation of serum PSA levels in men with no prostate cancer[13].

Inflammation in the prostate was divided as acute (polymorphonuclear leukocytes with glandular or ductal lumina, their epithelium and/or adjacent stroma) and chronic (mononuclear cell infiltrate in the stroma around prostatic glands) and was graded on a 3-point scale of 0(none), 1(low grade), 2 (high grade). When prostatic inflammation is seen on a biopsy sample of patient with elevated PSA levels, the rise in PSA is attributed to presence of prostatitis[14].

In this study a total of 200 patients who underwent surgical treatments for Benign prostatic hyperplasia due to obstructive or irritative symptoms were prospectively studied.Patients who complained of chronic pelvic pain or had a history of laboratory exam suggesting acute prostatitis were excluded.Results were analysed using Mann-Whitney rank sum test or Pearson product moment correlation (for Prostate specific antigen vs inflammation) at 95%CI.

MATERIALS AND METHODS

A total of 200 patients who underwent surgical treatments for Benign prostatic hyperplasia due to obstructive or irritative symptoms were prospectively studied.Patients who complained of chronic pelvic pain or had a history of laboratory exam suggesting acute prostatitis were excluded.Results were analysed using Mann-Whitney rank sum test or Pearson product moment correlation (for Prostate specific antigen vs inflammation)at 95%CI.All patients underwent a digital rectal examination ,serum prostate specific antigen .Prostate tissue from each case was examined microscopically. For each focus of inflammation the pattern was categorized as glandular, periglandular, stromal and periurethral ,the surface area measured and the intensity of inflammation graded from 1 to 3. Total prostate specific antigen was assayed before transurethral resection procedure using the Bayer Immunolk automated system. Patients with unsuspected prostate cancer on pathological examination were excluded from this analysis.

RESULTS

Results was analysed using the Mann- Whitney rank sum test or Pearson product moment correlation (for Prostate specific antigen vs inflammation)at 95% CI.

Table No.1: Incidence of Prostatitis

Statistics		
Age		
N	Valid	200
	Missing	0
Mean		69.16
Median		70.00
Mode		70
Std. Deviation		9.446
Minimum		40
Maximum		98

Table No.2: Relationship of degree of inflammation and PSA Level

Count		**PSA**				
		Normal (<4 ng/ml)	Mild (4-8 ng/ml)	Moderate (9-12 ng/ml)	Severe (>12 ng/ml)	
inflammation	Acute	1	0	0	1	2
	Chronic	59	28	25	20	132
	Acute + Chronic	37	6	13	9	65
	No Infla	1	0	0	0	1
Total		98	34	38	30	200

Table No.3: Chi Square values of relationship between degree of inflammation and PSA levels

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.506[a]	9	.484
Likelihood Ratio	9.323	9	.408
N of Valid Cases	200		

8 cells (50.0%) have expected count less than 5. The minimum expected count is .15.

In my research of 200 cases, 199 cases had inflammation of which 2 cases (1%) had acute inflammation. In 132 cases (66%) the patient had chronic inflammation and in 65 cases(32.5%) the patient had acute and chronic inflammation. In 1 case (0.5%) the patient had no inflammation. In patients with acute inflammation one case had severely raised PSA

levels i-e more than 12ng/ml. In patients with chronic inflammation 20 cases had severely raised PSA levels, 25 cases had moderately raised PSA levels and 28 cases had mildly raised PSA levels that is less than 4ng/ml. In 59 cases (44.7%) with chronic inflammation the PSA levels were normal. In patients with acute and chronic inflammation 9 cases (13.8%) had severly raised PSA level, 13 cases (20%) had moderately raised PSA levels and 6 cases(9.2%) had mildly raised PSA levels. In 37 cases (56.9%) with acute and chronic inflammation the PSA levels were normal. In 1 patient (100%) with no inflammation the PSA levels were normal. Thus of the total cases 98 cases (49%) had normal PSA levels. 34 cases (17%) had mildly raised PSA levels. In 38 cases (19%) the PSA levels were moderately raised and in 30 cases (15%) the PSA levels were severely raised.

DISCUSSION

Prostate specific antigen (PSA) a "glycoprotein serine protease" was first identified by Wang *et al* in 1979[15]. Although it was first designed as a serum marker for detecting and monitoring patients with prostate cancer it is now proven that it can be raised in other conditions such as prostatitis, BPH and diagnostic and surgical procedures(Pollack, 1991)[16]. PSA which is secreted entirely by the epithelial cells lining the prostatic acini and ducts of prostatic tissue is non specific for prostatic cancer and specific for prostatic tissues (Price H et al. 1990)[17]. Many researches have been carried out all over the world which has proven this fact (Shapiro et al., 1992)[18]. Immunoreactive PSA exist in two forms ((Siegel, 2011)[19]. Major fraction is bound to serum (<PSA) and 10-30% is free (fPSA). Many reports indicate that serum PSA level is elevated in patients with clinical acute prostatitis[20]. The exact reason for the elevation in PSA with inflammation is poorly understood, however there are many theories (Smith MJ, 2006)[21]. One theory is that the inflammatory process may trigger the release of unknown substances that in turn cause the release of PSA from the epithelial cells surrounding the affected area(Stamey et al., 2004)[22]. On the other hand Hasui et al proposed that elevated PSA levels is caused by the leakage of stored PSA in epithelial cells into the stromal tissue and blood circulating after epithelial cell death (Van der Cruijsen-Koeter et al., 2005)[23].

The correlation of histological prostatitis with elevated PSA levels remain controversial. Some researchers support the theory while some studies were unable to establish a correlation between PSA levels and histological prostatitis(Van de Voorde et al., 1995)[24].

One study carried out by Affonso et al in 2006 revealed that abnormal PSA level could not be attributed to the inflammatory process[25]. Of the 183 patients 145 had histological prostatitis and 38 cases had no prostatitis (Venkateswaran and Klotz, 2010)[26]. Similarly another study carried out by Lakhey et al from January 2008 to December 2009 revealed that serum PSA was marginally elevated in patients with BPH without inflammation and active inflammation and high grade lesions were associated with PSA levels more than 5ng/ml[27]. In asymptomatic men the histological evidence of prostatitis is very common(Wasson *et al*., 1995)[28]. There was 98% incidence of prostatitis in 168 asymptommatic patients in a study carried out by Khoen et al[29]. Similarly Nickel et al reported that the material obtained from patients undergoing TURP, there was inflammation in all 80 specimens (Zeegers,2003)[30]. In my research 200 patients who were to undergo surgical treatment were studied. They were categorized as glandular, peri-glandular, stromal and peri-urethral. The intensity of inflammation was graded from 1-3. Total PSA levels were assayed before TURP using the Bayer Immunolk automated system . Those cases were excluded who had preoperative diagnosis of prostatitis, prostatic cancer, previos prostatic surgery or documented UTI. It was found that of the 200 cases undergoing TURP, 2 cases had acute inflammation, 132 cases had chronic prostatitis and 65 cases had both acute and chronic prostatitis. Only one case had no inflammation, signifying that a total of 199 cases who were previously undiagnosed had prostatitis, of these 98 cases had PSA levels in the normal range, that is less than 4ng/ml. 102 cases had PSA levels that were raised, of these 102 cases, 34 cases had PSA levels in the mild range that is between 4-8ng/ml, 38 cases had PSA levels in the moderate range, that is between 9-12ng/ml and 30 cases had PSA levels in the severe range, that is more than 12ng/ml. The extent of inflammation was focal in 43 cases, multiple in 126 cases and diffuse in 28 cases. Of the focal cases 13 cases had PSA levels in the normal range and 30 cases had raised PSA levels. When the extent of inflammation was multiple, 70 cases had PSA levels in the normal range and 56 cases had raised PSA levels. In cases of diffuse inflammation, the PSA levels were normal in 15 cases and 13 cases had raised PSA levels. So when the extent of inflammation is multiple the PSA levels are most raised. In cases of grade I inflammation, of the 140 cases , 68 cases had normal PSA levels and 72 cases had raised PSA levels. In contrast of the 51 cases with grade II inflammation, 26 cases had PSA levels in the normal range and 25 cases had raised PSA levels. Similarly of the 9 cases with grade III inflammation 4 cases had normal PSA levels and 5 cases had raised PSA levels. So of the 200 cases PSA levels were most raised with grade I inflammation. Hence my study revealed that although a relationship does exist between prostatitis and PSA levels ,it is a very weak one and it should not be used as a diagnostic criteria for histological prostatitis. With histologically proven prostatitis, 98 cases had normal PSA levels and in comparison 102 cases had raised PSA levels which is not a significant difference. This data suggests that

incidental finding of histological prostatitis is very common and is not necessarily related with an increased PSA value. It can exist without raised PSA level and PSA levels can be raised in other conditions such as prostatic cancer, BPH or previous surgical intervention.

CONCLUSION

It is shown in numerous studies that there is a relationship between PSA levels and Histological Prostatitis. My study revealed that a relationship does exit between PSA levels and Prostatitis but it is a weak one.PSA levels can be raised in conditions other than prostatitis.

Author's Contribution:

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Revisiting Critically:	Zainab Rehman, Parkha Rehman
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Original Article

Role of Statins on Chronic Kidney Disease

Analysis of Role of Statins on Cardiac Patients with Chronic Kidney Disease and Renal Failure: A Research Analysis

Saad Akmal Bhatti[1], Akmal Khurshid Bhatti[2] and Ahmed Dilawar Khan[3]

ABSTRACT

Objective: The objective of our study is to find the role of statins in CVD and those patients who are suffering from renal failure and chronic kidney disease.

Study Design: Comparative / cross sectional study.

Place and Duration of Study: This study was conducted at the Sialkot Medical College and RHC, Dhullanwala, Gujrat from January 2018 to March 2018.

Materials and Methods: The study was conducted at Sialkot Medical College and RHC, Dhullanwala, Gujrat with the permission of ethical committees and concerned departments. For this study the data was collected from 50 patients who were suffering from cardiovascular and kidney diseases. We made two groups of study for this purpose. One group was control group and the other group was suffering from CVD and kidney problems.

Results: The values of analysis of statin therapy in patients shows the comparison between two groups on the basis of functional values. ROC curve explained the specificity and sensitivity of statin therapy in patients.

Conclusion: The results of this study clearly showed that patients of CKD are at increasing risk for CVD. Also, there is significant evidence depicting that patients with CKD get advantage from statin therapy with improvement of CV outcomes. Nevertheless, in patients who are on dialysis and are of stage 5 CKD, the advantages of statin therapy on CV outcomes are less definite, and further large RCTs may be required to explain this substance.

Key Words: Chronic, CKD, Statin, Patients, Renal Failure

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INTRODUCTION

Chronic kidney disease (CKD) is one of the major public health problems. Cardiovascular disease (CVD) keeps on being one of the major cause of morbidity and mortality among individuals with CKD around the world, with number of cardiovascular occasions and mortality reliably expanding as renal function deranges. Dialysis patients have death rates up to 40-crease higher than the overall public, with CVD being in charge of up to half of these passing.[1] Patients with CKD have increased commonness of various hazard factors for CVD, including lipid variations from the norm, hypertension, stoutness, and diabetes.

Statins are outstanding to decrease the cardiovascular (CV) occasions and mortality in patients having coronary supply route disease.[2]

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The fundamental impact of the statins is to decrease the low-thickness lipoprotein cholesterol (LDL-C) levels. Be that as it may, statins additionally apply critical pleiotropic impacts, including calming and antithrombotic activities, and also change of endothelial capacity.

A few investigations have revealed that the benefits of statins in patients with coronary heart diseases (CHD) are by inhibiting the catalyst 3-hydroxy-3-methylglutaryl coenzyme A reductase. This enzyme is needed for the rate limiting step of cholesterol synthesis, which results in decreasedintrahepatic cholesterol levels. It causes an increase in the movement/atomic translocation of the interpretation factor sterol administrative element which limits protein in our body. Hence, starting the low-thickness lipoprotein receptor (LDLR) quality with resulting up direction of LDLRs, ultimately leading to a lessening in circulatingLDL-C levels over a period of time.[4]

The use of statins in the population with dyslipidemia to decrease cardiovascular (CV) risks and mortality is all around archived. Astonishingly, the patients with chronic kidney disease (CKD), especially those with progressive and advanced renal disease, are by and large stopped from extensive clinical trials due to fear of high morbidity and mortality, and also security issues of the medications.[5] In this regard, the influence of statins on such patients is for the most part from some post hoc subgroup investigation in which the

effects of statins on kidney remainsarguable. Chronic kidney disease is associated to dyslipidemia, involving the whole range of plasma lipoproteins. The particular lipoprotein variations from the normal values found in patients with CKD may be different depending upon the degree and the necessary driver of renal dysfunction, and the type of dialysis in patients having end stage renal disease(ESRD).[6]

MATERIALS AND METHODS

The study was conducted at Sialkot Medical College, Sialkot and RHC Dhullanwala, Gujrat, with the permission of ethical committees and concerned departments. For this study the data was collected from 50 patients who were suffering from cardiovascular disease and kidney disease. For this purpose we made two groups of study. One group was control group and the other group was suffering from CVD and kidney problems. The second group was also getting the statin therapy for the cure of their problem but the control group was not getting any kind of therapy, they just get normal medication. Then we collected the socio economic status and therapy status of both groups. Then we analyzed the data and found that either statin therapy is helpful for patients or not.

Student's t-test was applied to assess the variations in roughness among groups. Two-way ANOVA was carried out to examine the contributions. A chi-square test was performed to study the variations in the distribution of the fracture modes (SPSS 19.0).

RESULTS

The data was collected for further analysis. Table 01 of the data shows the basic values of control group and patients. It shows the BMI, age, Total cholesterol level and other basic values. We can find that cholesterol level is high in patients as compared to normal values. We also showed the comparison of statin group and normal group.

Table No.1: General values of Control group and diseased group

Variable	Diseases Group	Control Group	t Value	*p* Value
Age（Year）	56.56±8.46	53.64±8.36	1.716	0.081
BMI（kg/m2）	24.31±2.26	23.37±2.09	2.195	0.031
SBP（mmHg）	140.36±15.70	116.53±13.46	8.248	0.000
DBP（mmHg）	87.94±10.69	75.81±9.94	5.967	0.000
PP（mmHg）	52.42±12.87	40.72±8.74	5.426	0.000
FBG（mmol/）	5.12±0.65	5.06±0.49	1.764	0.081
TG（mmol/L）	1.74±0.75	1.69±0.86	1.838	0.071
TC（mmol/L）	4.95±0.76	4.88±0.82	1.712	0.090
HDL-	1.30±0.43	1.31±0.56	1.717	0.089
LDL-C	3.46±0.58	3.38±0.66	1.139	0.266

Note： BMI：Body Mass Index；SBP：Systolic Blood Pressure；DBP：Diastolic Blood Pressure；PP：PulsePressure；FBG：Fasting Blood Glucose；TG：Triglyceride；TC：TotalCholesterol；HDL-C：High-DensityLipoprotein；LDL-C: Low-Density Lipoprotein

Tale 02 shows the values of analysis of statin therapy in patients. It shows the comparison between two groups on the basis of functional values. ROC curve explained the specificity and sensitivity of statin therapy in patients (Figure 01).

Table No.2: Comparison between two groups in structural and functional parameters

Group	IMT (μm)	CC(mm^2/ KPa)	α	β
CVD Group	694.88± 77.63	0.89± 0.13	5.68± 1.23	11.25± 1.01
Control Group	586.87± 62.12	0.96± 0.08	4.77± 0.62	9.24± 1.24
T value	7.818	-3.115	4.712	9.004
P value	0.000	0.002	0.000	0.000

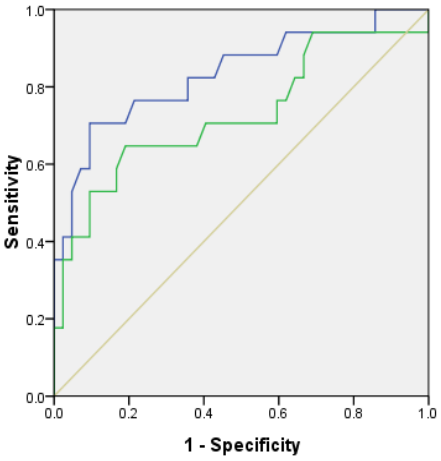

Figure No.1: ROC curve of statin therapy in patients

DISCUSSION

A large quantitative survey, incorporating 31 trials with in excess of 48 000 people, proposes that treatment with statin reduces the danger of cardiovascular occasions crosswise over various levels of kidney work.[7] Major cardiovascular occasions are decreased by 23%, including a 22% lessening in coronary occasions, and 9% decrease in cardiovascular or all-cause passing. No noteworthy impact was seen on the danger of renal disappointment, or on the danger of unfriendly occasions involving disease mortality. End focuses for the assessment of the impact of statin treatment on kidney function in patients with CKD, have included protein discharge and movement of CKD.[8]

Starting examination indicated distinctive rates of expanded protein discharge with different statins. Be that as it may, clinical investigations that particularly assessed the impact of statin treatment on protein discharge yielded clashing outcomes, with some exhibiting a lessening in proteinuria and others demonstrating no impact. There are clashing information regarding the effect of statins on movement of CKD.[9]

Some of the investigations have suggested that statins may limit the rate of decrease in renal function in patients with mellow to direct renal impairment.Although others have found that statins were not better than placebo treatment. In another research which comprised of extremely late substantial meta-examination including 57 randomized controlled trials (RCTs) with143 888 participants, statins did not lessen the risk for renal dysfunction in patients with CKD not on dialysis but rather did unremarkably decreased proteinuria and rate of assessed glomerular filtration rate (eGFR) deterioration.[11-13] These results are consistent with the findings of another exceptionally late meta-examination of 23 randomized controlled trials (RCTs) with 39 419 participants with non– end-organize CKD, showing that statins caused a detectably critical depletion in micro-albuminuria, proteinuria but did not sufficiently moderate the clinical movement of non– end-arrange CKD. Moreover, in another meta-investigation, which examined the sustainability of statins in patients with diabetic nephropathy and included 14 trials with 2866 members. It revealedthat statins lessened albuminuria and this decrease in albuminuria was more significant in patients of type II diabetes mellitus with diabetic nephropathy.[14]

In a vast meta-investigation, which involved 8834 members with organize 1– 3 CKD and 32 846 man a very long time of development, statin treatment was appeared to be helpful for the essential cardiovascular anticipation in CKD.36 More particularly, statins decreased the danger of CVD by 41% ($P < .001$) and diminished aggregate mortality by 34% ($P = .005$) and the danger of CHD by 45% ($P < .001$).38 For arrange 3 CKD just, statins decreased the danger of CVD by 44% ($P < .001$) and diminished aggregate mortality by 38% ($P < .001$), the danger of CHD by 45% ($P < .001$), and the danger of stroke by 57% ($P = .003$).[15-17]

CONCLUSION

The results of this study clearly showed that patients ofCKD are at increasing risk for CVD. Also, there is significant evidence depicting that patients with CKD get advantage from statin therapy with improvement of CV outcomes. Nevertheless, in patients who are on dialysis and are of stage 5 CKD, the advantages of statin therapy on CV outcomes are less definite, and further large RCTs may be required to explain this substance.

Author's Contribution:

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Original Article

Fate of Patients of Hepatitis C on Antiviral Therapy

Effect of Antiviral Therapy in Hepatitis C

Adnan Butt[1], Mian Mansoor[2], Asif Javed[2] and A. Hamid[3]

ABSTRACT

Objective: To study the Fate of patients of Hepatitis C on antiviral therapy.
Study Design: Prospective Study.
Place and Duration of Study: This study was conducted at the Idris Teaching Hospital Sialkot from January 2016-December 2017.
Materials and Methods: One Hundred patients of hepatitis C on antiviral therapy were included in this prospective study. All the patients of hepatitis C were diagnosed by kit method and diagnoses was further confirmed by quantitative PCR before start of antiviral therapy. Liver function tests, quantitative PCR, blood picture were also measured before start of antiviral therapy. Abdominal Ultra sound examination was also conducted to see the exact liver picture. Following antiviral therapy was used in all hepatitis C patients included in the study.
1. Sofsububir 400mg (OD), 2. Daclatasvir 60mg (OD), 3. Rivavirin 400mg (TDS)
These tests were repeated after completion of the therapy. A performa was designed to record age, gender and above tests. An informed consent was also taken by the patients included in the study. Permission of ethical committee of the institute was also considered before collecting and publishing data. The results were analyzed on SPSS version 10.
Results: The frequency of hepatitis C was seen maximum 37 (37%), male 15% and female 22% at age group 31-40 years and it was minimum 04 (04%), male 01% and female 03% at the age group 61 & above years as shown in table no. 1. At the end of therapy 96 (96%), male 45% and female 51% were cured but 04 (04%) patients of hepatitis C were not cured as shown in table no.03. With regard to complications at the end of antiviral therapy it was observed that anemia was seen in 25 (25%) patients, acities were seen 13 (13%) patients, Hepatic Encephalopathy in 03 (03%) and liver cirrhosis in 02 (02%) patients of hepatitis C as shown in table no. 2.
Conclusion: It was concluded on follow up that there were complications (Anemia, Acities, Cirrhosis, Hepatic Encephalopathy etc) in patients of Hepatitis C even treated by antiviral therapy.
Key Words: Hepatitis C, Antiviral Therapy, Fate, PCR.

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INTRODUCTION

Hepatitis C is a major public health concern. With almost 4 million Americans with chronic infection, hepatitis C is the one of the leading causes of chronic liver disease and is the single most common indication for liver transplantation[1,3]. Antiviral therapy is effective in more than half of infected patients, but the actual rate of sustained viral response depends on viral, host, and adherence factors. Viral and host factors tend to be no modifiable, whereas interventions may increase adherence.
However, adverse effects from antiviral therapy directly affect treatment adherence and can decrease the likelihood of a sustained viral response.

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These complications can severely compromise quality of life[7].
Most patients with HCC have an underlying chronic liver disease (often cirrhosis), resulting mainly from chronic infection by hepatitis B virus (HBV), hepatitis C virus (HCV), excessive alcohol consumption, and often an association of these causes. HCC has recently gained more interest due to its increasing incidence in industrialized countries[1,2,3]. Hepato Cellur Carcinoma (HCC) is the most rapidly increasing cause of cancer death, with HCV as the major etiology affecting generally more than half of HCC patients in developed countries such as the USA[1]. These studies clearly highlight the urgent need for identification of undiagnosed HCV infection by implementing HCV screening programs targeting high-risk populations as well as improved access to new generation anti-HCV therapies with reduced costs and streamlined treatment intake and follow-up(2). Retrospective interrogation of previously treated patients mostly by interferon-based regimens revealed several post-SVR HCC-associated clinical variables, most of which are known HCC risk factors in patients with active HCV infection. More advanced liver fibrosis as well as biochemical or

imaging surrogates of histological fibrosis (e.g., serum albumin, platelet count, fibrosis-4 index, aspartate aminotransferase-to-platelet ratio index, elastography-based liver stiffness) before and/or after antiviral treatment are the most prominent features associated with higher post-SVR HCC risk[3]. The goal of primary prevention is to avoid or delay the occurrence of HCC by using medical treatments[4].

MATERIALS AND METHODS

One Hundred patients of hepatitis C on antiviral therapy were included in this prospective study. All the patients of hepatitis C were diagnosed by kit method and diagnoses was further confirmed by quantitative PCR before start of antiviral therapy. Liver function tests, quantitative PCR, blood picture were also measured before start of antiviral therapy. Abdominal Ultra sound examination was also conducted to see the exact liver picture. Following antiviral therapy was used in all hepatitis C patients included in the study.

1. Sofsububir 400mg (OD)
2. Daclatasvir 60mg (OD)
3. Rivavirin 400mg (TDS)

These tests were repeated after completion of the therapy. A performa was designed to record age, gender and above tests. An informed consent was also taken by the patients included in the study. Permission of ethical committee of the institute was also considered before collecting and publishing data. The results were analyzed on SPSS version 10.

RESULTS

The frequency of hepatitis C was seen maximum 37 (37%), male 15% and female 22% at age group 31- 40 years and it was minimum 04 (04%), male 01% and female 03% at the age group 61 & above years as shown in table no. 01. At the end of therapy 96 (96%), male 45% and female 51% were cured but 04 (04%) patients of hepatitis C were not cured as shown in table no.3. With regard to complications at the end of antiviral therapy it was observed that anemia was seen in 25 (25%) patients, a cities were seen 13 (13%) patients, Hepatic Encephalopathy in 03 (03%) and liver cirrhosis in 02 (02%) patients of hepatitis C as shown in table no. 2.

Table No. 1: Age & Gender Distribution in Patients of Hepatitis C using antiviral treatment

S#	Age(Years)	Male(Cases)	Female(Cases)
1	**20-30**	10 (10%)	06 (06%)
2	**31-40**	15 (15%)	22 (22%)
3	**41-50**	10 (10%)	08 (08%)
4	**51-60**	12 (12%)	13 (13%)
5	**61 & above**	01 (01%)	03 (03%)
	Total	**48 (48%)**	**52 (52%)**

Table No. 2: Distribution of complications in patients of Hepatitis C using antiviral treatment

S#	Complications	Cases	Percentage%
1	Anemia	25	25%
2	As cities	13	13%
3	Hepatic Encephalopathy	03	03%
4	Liver Cirrhosis	02	02%
	Total	41	41%

Table No. 3: Treatment Response of Antiviral Therapy in Hepatitis

S#	Age (Years)	End Treatment Response (Cured)		Sustained Viral Response	
		Male	Female	Male	Female
1	20-30	10 (10%)	06 (06%)	10 (10%)	06 (06%)
2	31-40	14 (14%)	22 (22%)	14 (14%)	21 (21%)
3	41-50	09 (09%)	08 (08%)	09 (09%)	08 (08%)
4	51-60	11 (11%)	12 (12%)	11 (11%)	12 (12%)
5	61 & above	01 (01%)	03 (03%)	01 (01%)	03 (03%)
	Total	45 (45%)	51 (51%)	45 (45%)	50 (50%)

DISCUSSION

The treatment of HCV infection was revolutionized in mid-2011 with the addition of direct-acting antiviral agents (DAAs)—the protease inhibitors boceprevir (Vic-trelis, Merck) and telaprevir (Incivek, Vertex)—to the decade-long standard-of-care (SOC) therapy of pegylated interferon α-2a/b and ribavirin. This advance resulted in a tremendous demand for HCV therapy, leading to resource rationing and treatment triage[5,6]. The concept of distributive justice with scarce resources suggests that patients with cirrhosis have the greatest need for treatment and thus should receive the highest priority for treatment, with asymptomatic patients with minimal fibrosis being at the other end of the spectrum[7,8]. Our initial experience with DAA therapy refects this urgency: Of the first 98 consecutive HCV-infected patients we started on tela-previr, almost 40% had advanced fibrosis or cirrhosis[9,10,11]. This review will examine the data on DAAs in patients with cirrhosis and will describe the evolution of HCV therapy in this special group from the SOC therapy of the past decade into the new era of DAAs.

Hepatitis C has become a curable disease with the use of antiviral agents (>95%)[12,13].

Hematologic side effects are the most recurrent abnormal laboratory values that can lead to dosage reductions and premature treatment termination[14,15,16]. Because of its myelosuppressive effect, interferon can

affect hemoglobin, white blood cell, and platelet values. However, the anemia seen during combination treatment is mostly associated with ribavirin-induced hemolytic anemia.

In our study with regard to complications at the end of antiviral therapy it was observed that anemia was seen in 25 (25%) patients, acities were seen 13 (13%) patients, Hepatic Encephalopathy in 03 (03%) and liver cirrhosis in 02 (02%) patients of hepatitis C.

CONCLUSION

It was concluded on follow up that there were complications (Anemia, Acities, Cirrhosis, Hepatic Encephalopathy etc) in patients of Hepatitis C even treated by antiviral therapy.

Author's Contribution:

Concept & Design of Study:	Adnan Butt
Drafting:	Mian Mansoor
Data Analysis:	Asif Javed, A. Hamid
Revisiting Critically:	Adnan Butt, Mian Mansoor
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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 Intraventicular Hemorrhage in Premature Neonates According to Mode of Delivery

Sami ul Haq[1], Samiullah[2] and Hazrat Bilal Khan[3]

ABSTRACT

Objective: To determine frequency of intraventricular hemorrhage in premature neonates according to mode of delivery.

Study Design: Descriptive/ cross-sectional study.

Place and Duration of Study: This study was conducted at the Pediatric Medicine Department, DHQ Hospital Faisalabad from 12.05.2011 to 11.11.2011.

Materials and Methods: This study included 300 premature neonates. The neonates were divided in two separate groups. In the 1st group, neonates born with vaginal delivery and the 2nd group, neonates born with cesarean section were included. All the patients were evaluated for the presence of IVH which was described as frequency distribution table. Data was collected in a specially designed proforma.

Results: The mean gestational age of the neonate in the study was 29.81 $\pm$ 3.36 weeks including 177 (61%) male and 123 (39%) female. Total 67 (22.3%) infants had IVH. 19 (10.7%) patients in cesarean section group and 48 (39%) neonates in the other groupdeveloped IVH, showing significant differences($p< 0.05$).

Conclusion: The frequency of IVH is low among neonates born with cesarean section as compared to those born with vaginal delivery.

Key Words: Premature infants; intraventricular hemorrhage; cesarean section; vaginal delivery.

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INTRODUCTION

Delivery before 37 weeks from first day of last menstrual period is called prematurity delivery.[1] The incidence of prematurity in Pakistan is not known with certainty, but it is estimated as 11-13%.[2] Respiratory distress syndrome, infections, necrotizing enterocolitis, patent ductus arteriosus, intraventricular hemorrhage, and other signs of brain injury as apnea and bradycardia are among the acute complications of prematurity.[3,4]

Intraventricular hemorrhage (IVH) is most often seen in premature babies[5]. Intraventricular hemorrhage can be defined as intracranial hemorrhage that originates in the periventricular subepindymal germinal matrix with subsequent entrance of blood into the ventricular system[4].

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It is reported that approximately 12,000 premature infants develop intraventricular hemorrhage every year in the United States alone[6]. The incidence of IVH in very low birth weight (VLBW) infants (<1500 g) has declined from 40 to 50% in the early 1980s to 20% in the late 1980s[7]. However, in the last two decades the occurrence of IVH has remained stationary[8].

Incidence of intraventricular hemorrhage is inversely proportional to gestational age, but the prevalence of germinal matrix intraventricular hemorrhage is approximately 47.5%[9]. In extremely premature infants weighing 500–750 g, IVH occurs in about 45% of neonates[8]. Thus, IVH continues to be a major problem of premature infant in modern neonatal intensive care units (NICUs) worldwide.

Intraventricular hemorrhage (IVH) is an important cause of morbidity and mortality in preterm infants[10]. More than 50% of bleeding episodes occur during the first 24 hours of life, with <5% occurring after day 4 and 5. Although the incidence of IVH is decreasing[11], it remains a serious problem in the VLBW infant. It is classified into four groups i-e Grade I,II III and IV, and higher the grade more severe is the bleeding. Signs and symptoms vary, child may be asymptomatic especially in some cases of Grade I and II IVH, but may present with apnea, pallor, poor muscle tone, decreased reflexes, excessive sleep, lethargy, weak suck, bulging fontanell and coma. A number of risk factors have been proposed for the development of IVH. Low birth weight and

gestational age, maternal smoking, breech presentation, gender, premature rupture of membranes, [11,12] intrauterine infection, prolonged labour, postnatal resuscitation and intubation, early onset of sepsis, metabolic acidosis, and high-frequency ventilation, respiratory distress syndrome, pneumothorax [12] are some named risk factors.

Beside, other commonly cited risk factors, that alter the risk for intraventricular hemorrhage, include mode of delivery, maternal hypertension, premature or prolong rupture of membranes, maternal fever and bleeding, prenatal steroid administration, maternal magnesium sulphate (MgSO4) therapy, and that in neonate, 1 and 5 mints Apgar scores, need for delivery room resuscitation, sepsis, use of high frequency ventilation, pneumothorax and patent ductus arteriosus[9].

Clinical presentation is variable may be asymptomatic or may present with bulging fontanell, sudden pallor, apnea, bradycardia, acidosis, seizures, change in muscle tone or level of conciousness[13].Diagnosis of intraventricular hemorrhage is made on the basis of clinical assessment and cranial ultrasonography.[5,6] Management is mostly supportive and may include the correction of anemia, acidosis, and hypotension[14].

The cause of intraventicular hemorrhage is multi factorial but stress of labour is considered as one of the contributing factors and the rate of the intraventicular hemorrhage is 7.7% for cesarean delivery and 13.6% in vaginal delivery [15]and in other study the rate of intraventricular hemorrhage was 33% for vaginal delivery and 67% for cesarean delivery[16]. However the role of mode of delivery in occurrence of intraventricular hemorrhage is unclear.

The rationale of present study is to determine the occurrence of intraventricular hemorrhage in premature neonates delivered by normal vaginal delivery and c-section, which will be helpful in choosing the safest modes of delivery to reduce mortality and long term morbidities of intraventricular hemorrhage in premature neonates.

MATERIALS AND METHODS

This Descriptive case series was carried out at Paediatric Medicine Department, DHQ Hospital Faisalabad, in six month duration, from 12/05/2011 to 11.11.2011.

By using WHO sample size calculator, a total of 300 samples were calculated.

- Prevalence of intraventricular hemorrhage = 7.7%
- Absolute precision required = 3%
- Confidence level = 95%
- Sample size = 300

Sampling Technique: Non-Probability, Purposive Sampling

Sample Selection: Samples were selected, using the following inclusion and exclusion criteria.

Inclusion Criteria

- Premature infants of either sex
- Age limit first 3 days.

Exclusion Criteria

- Infants who had congenital cranial abnormalities
- Infants who died within 3 days

Data Collection Procedure: After taking approval from hospital ethical committee, children of either sex presenting with prematurity below 34 weeks in Neonatology Unit were enrolled. Exclusion criteria were strictly followed to control confounding variables. The purpose, procedure, risks and benefits were explained to the parents of children and informed consent was taken. Inclusion and exclusion criteria were met by taking history and by examining the patients. After detailed history and examination, data was registered as per proforma. Ultrasound cranial was done on 3rd day of admission by radiologist in radiology department DHQ Hospital Faisalabad. All the information were recorded on proforma and mode of delivery was confirmed on the basis of history.

Data analysis Procedure: Data was entered and analysed by using SPSS V-16and level of significance was determined. Descriptive statistics was calculated for all variables. Mean and standard deviation were calculated for all quantitative variables like age (in days) and gestational age (at which is delivered). Frequency and percentage were calculated for all qualitative variables like gender, intracranial hemorrhage and grades of hemorrhage and mode of delivery. Frequency was calculated for intraventricular hemorrhage based on mode of delivery.

RESULTS

The results of the study are tabulated at tables1-4 and figures I-2.

Distribution of patients by Gestational age: The mean gestational age of the premature neonates was 29.81 $\pm$ 3.36 weeks. [Range 26 – 36]. There were 14 (4.6%) premature neonates of gestational age 26 weeks, 26 (8.7%) neonates of age 27 weeks, 29 (9.7%) neonates of gestational age of 28 weeks, 37 (12.3%) neonates of age 29, 25 (8.3%) of gestational age of 30 weeks, 26 (8.7%) neonates of age 31 weeks, 30 (10%) patients of gestational age 32 weeks, 36 (12%) patients of age 33 weeks, 23 (7.7%) patients of age 34 weeks, 21 (7%) patients of gestational age 35 weeks and 33 (11%) patients of gestational age 36 weeks. (Table 1)

Distribution of patients by sex: There were 177 (59%) male neonates and 123 (41 %) female neonate in the study. The male to female ratio was 1.44:1.

Distribution of patients by Intraventricular hemorrhage: Among the 300 premature neonates in the study, Intraventricular hemorrhage was present among 67 (22.3%) premature infants, while this was absent among 233 (77.7%) neonates. (Figure I)

Distribution of patients by age of development of IVH: There were 67 neonates who developed IVH. There were 26 (38.8%) neonates who developed IVH during 1st day of life, 19 (28.4%) neonates who developed IVH during 2nd day of life and 22 (32.8%) neonates who developed IVH during 3rd day of life. (Table 2).

Distribution of patients by Grading of IVH: Of the 67 patients in the study, there were 29 (43.4%) neonates who had developed IVH of Grade I, 15 (22.4%) neonates who had IVH of grade II, 14 (20.8%) neonates who had grade III and 9 (13.4%) patients who developed IVH of grade IV. (Table 3)

Distribution of neonates by mode of delivery: There were 123 (41%) mothers who delivered their baby by vaginal delivery while 177 (61%) had cesarean section. Figure II)

Table No.1:Distribution of patients by age (n=300)

Gestational Age (weeks)	No. of patients	Percentage
26	14	4.6
27	26	8.7
28	29	9.7
29	37	12.3
30	25	8.3
31	26	8.7
32	30	10
33	36	12
34	23	7.7
35	21	7
36	33	11
Mean + SD	29.81 ± 3.36	
Range	26 – 34	

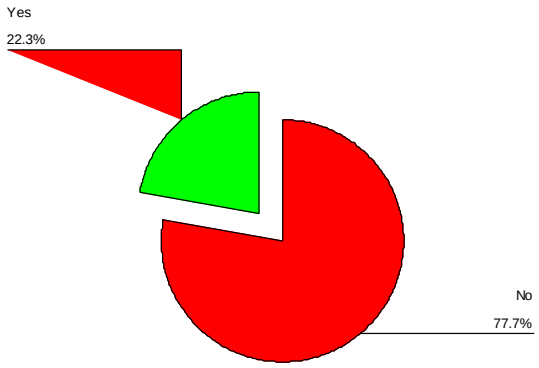

Figure No.I: Distribution of neonates by intraventricular hemorrhage (n= 300)

Table No.2: Distribution of patients by age of development of IVH (n = 67)

Age of developing IVH	No. of patients	Percentage
1st day	26	38.8
2nd day	19	28.4
3rd day	22	32.8

Cross tabulation of neonates with IVH with mode of delivery: Of the 177 neonates born to the mothers who had cesarean section, IVH developed in 19 (10.7%) neonates, while 158 (89.3%) infants did not developed IVH. Among the 123 neonates born through par vaginal route, IVH was present among 48 (39%) neonates, while 75 (61%) neonates did not suffere from IVH. study, The two groups were compared with each other for any statistical significance. Chi – square test was applied. P value was 0.000 (significant). (Table 4)

Table No.3: Distribution of patients by grade of IVH (n=67)

Grades of IVH	No. of patients	Percentage
G – I	29	43.4
G – II	15	22.4
G – III	14	20.8
G - IV	9	13.4

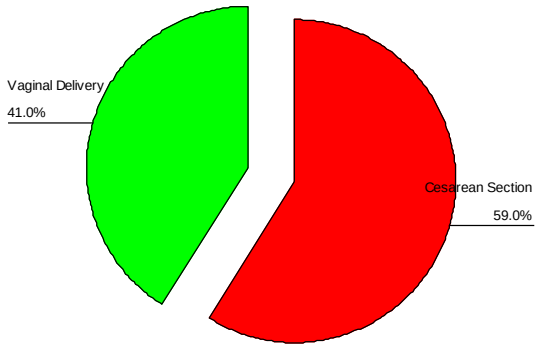

Figure No.2: Distribution of patients by mode of delivery (n=300)

Table No.4: Cross tabulation of neonates with IVH with mode of delivery (n=67)

Intraventricualr hemorrhage	Mode of delivery			
	Vaginal delivery (n=177)		Cesarean section (n = 123)	
	No.	%	No.	%
Yes	19	10.7	48	39
No	158	89.3	75	61
P-value	0.000*			

* Chi – square test

DISCUSSION

Intraventricular hemorrhage is a major neuropathologic lesion in premature infants. Since, prematurity have shown significant association with IVH, this study was conducted with the aim to determine the frequency of IVH among premature infants according to its mode of delivery. The overall frequency of IVH was 22.3%. The results of this study showed that IVH among neonates born with cesarean section was 10.7% while that with vaginal delivery was 39%.

Few studies have been reported which have determined the frequency of IVH among premature infants. However, the frequency of IVH varies among different authors.Sonkusare S, *et al*[17] performed a study which included a total of 113 pregnant women and 124 neonates who delivered from 30 to 35 weeks of

gestation were enrolled and outcomes of 70 neonates born vaginally were compared to 54 neonates born by caesarean. They found that IVH occurred in 1.4% neonates with vaginal delivery while 3% in neonates with cesarean section. They found andobserved a higher frequency of IVH with vaginal delivery, but the difference was not significant and the sample size of the study was too short. However, in another study of larger scale by Heuchan *et al*, [6] among 5712 infants of 24-30 weeks gestation. They found IVH more common (19%) in SVDs as compared to LSCS which was found to be 11%.

Sabir S, *et al*[18-19]conducted a study in which 100 preterm babies were included. Mean gestational age was 32.3 weeks (SD=2.12). Maximum number of the patients (70%) was in the age group of 30 weeks of gestation. Mean birth weight of the babies was 1637.7gm (SD=349.25) and male to female ratio was 1:1. Sixty-one (61%) of babies were delivered by SVD, while 39 (39%) babies were born by LSCS. Intraventricular hemorrhage was diagnosed among 11% cases of IVH in 100 preterm babies. IVH was detected in 7 babies on third day of life, while in rest of 4 babies on day 7. However, none of the patients in our study was found having IVH at 7th day of life. Mode of delivery affects frequency of IVH and we found IVH more common (13%) in babies delivered by SVD as compared to (7.6%) babies delivered by LSCS.

Present study showed that 38.8% IVH occurred in first 24 hours of birth, while no much difference was observed in other two days, i.e. 28.4% and 32.8% in 2nd and 3rd day. Chen HJ in their multi-centre study, having 147 preterm found that 90% IVH occur in 1st 72 hours of life[19], which is much higher as reported in our study.. Kleigman et al[20] in their study found that IVH is rarely present at birth. 80 to 90% of cases occurred between birth and 3rd day of life. Their study showed that 50% cases occurred on the 1st day, while our study showed that 38.8% neonates had IVH in first 24 hours of birth. Their study also showed that IVH was rare beyond 1st month of life.

A study was conducted by Sajjadian N, *et al*[21] which included 57 infants who were born premature. The prematurity was defined if the birth weight was less than 1500 grams or gestational age was less than 37 weeks. They found that IVH was common among 61.4% patients. This was quite higher than our study i.e. 22.3%. Forty percent of patients with intraventricular hemorrhage had grade I, 11% grade II, 25.7% grade III, 2.8% grade VI. These results have some similarity with our results i.e. grade I IVH was the most common and was seen among 43.4% patients, followed by grade II in 22.4%.

CONCLUSION

This study concludes that frequency of IVH was found to be high among premature infants. So, it should be detected among all patients with prematurity. Moreover, the frequency of IVH was high among neonates born with vaginal delivery as compared to cesarean section. So, a cesarean section should be offered to the mother with premature fetuses.

Author's Contribution:

Concept & Design of Study:	Sami ul Haq
Drafting:	Samiullah
Data Analysis:	Hazrat Bilal Khan
Revisiting Critically:	Samiullah, Sami ul Haq
Final Approval of version:	Sami ul Haq

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

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Original Article

Comparison of the Efficacy of IV Iron versus Oral Iron Therapy in Postpartum Anemia

Sidrah Batool[1], Khiaynat Sarwar Hahsmi[1] and Mahham Janjua[2]

ABSTRACT

Objective: To compare the efficacy of parenteral and oral iron therapy in post partum anemia.
Study Design: Randomized controlled trial study
Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynaecology, Bahawal Victoria Hospital, Bahawalpur from 1st August 2017 to 31 January 2017.
Materials and Methods: A total of 82 patients with postpartum anemia, having age range of 20 to 35 years were included in the study. The patients were randomly placed into two groups i.e. Group A (intravenous iron) and Group B (oral iron), by using lottery method. All patients were followed till 6 weeks and efficacy (deemed as yes if there was rise in hemoglobin levels >3.5g/dl after 6 weeks of therapy) was noted.
Results: There was rise in hemoglobin levels >3.5g/dl after 6 weeks of the rapy in 36 patients in intravenous route foe iron therapy while in oral route, it was seen in 27 patients. So, efficacy was 87.80% in group A (intravenous iron) and 65.85% in group B (oral iron) with p-value of 0.018.
Conclusion: Intravenous iron therapy is more effective than oral iron in treating postpartum anemia due to good compliance and better tolerance.

Key Words: Iron deficiency anemia, hemoglobin, parenteral iron,oral iron

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INTRODUCTION

Anemia is defined as level of haemoglobin falling 11gm/dl and a haematocrit of less than 33%.[1] Mild to moderate anemia is associated with vague symptoms like tiredness, weakness, easy fatiguability or shortness of breath. Anemia that is severe has greater symptoms which may include: confusion, dizziness, inability to concentrate and an increased desire to drink fluids. There may be additional symptoms depending on the underlying cause.[2]

Anemia in pregnancy accounts indirectly for 40-60% of the maternal deaths in the developing countries.[3] Its incidence is 18% in pregnant women of the developed and 35- 75% of pregnant women in developing countries.[1,4] Postpartum mild anemia i.e. haemoglobin (Hb) levels of <10 g/dl is seen in up to 30% of women, severe anaemia (Hb <8 g/dl) seen in 10%.[5] The main cause of anemia is iron deficiency because of the iron deficit that occurs because of increased iron consumption to fulfil the increased iron demand by the placenta and growing fetus and also increased red cell mass in patients.[6] This fall in iron levels are usually recovered in 4-6 weeks postpartum but the women belonging to low socioeconomic class remain at increased risk to suffer from anemia in post partum period for a longer time. Lately oral iron therapy, intramuscular iron therapy, intravascular iron therapy and blood transfusion have been used to treat anemia during pregnancy and in postpartum period[7] because of the risks of blood transfusion and financial constraints, oral (by mouth) and parenteral (by intravenous, intramuscular or subcutaneous injection) have remained attractive.

The oral iron has remained first line of treatment because of easy availability and easy administration.[8] Ferrous sulfate among all available preparations is used mostly.[9] In conditions where oral iron therapy is not effective because of increased demand, poor compliance or poor tolerance as seen in patients with inflammatory bowel disease (e.g. ulcerative colitis, Crohn disease), need arises for parentral iron therapy in anemic pregnant and post natal women. intravenous iron has been used safely and effectively.[10] The intravenous iron therapy,can provide a greater and more rapid iron supply than oral iron supplementation.[6,11]

As there was no local study available on this so, this study was conducted to compare the efficacy of intravenous iron therapy with oral iron therapy in postpartum anemia in local population, so our population might get benefit. Moreover, the results of this study would provide us with more efficacious regimen among two for managing postpartum anemia.

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MATERIALS AND METHODS

This randomized controlled trial study was carried out at Department of Obstetrics and Gynaecology, Bahawal Victoria Hospital, Bahawalpur from 1st August 2017 to 31 January 2017. A total of 82 patients with postpartum anemia, having age range of 20 to 35 years were included in the study. The patients were randomly placed into two groups i.e. Group A (intravenous iron) & Group B (oral iron), by using lottery method.

Group A received intravenous iron over 30 minutes,200mg repeated weekly in 100 ml of normal saline0.9%) . Group B received oral iron (tab. Ferrous sulfate, 325 mg three times daily by mouth for 6 weeks). All patients were followed till 6 weeks and efficacy (deemed as yes if there was rise in hemoglobin levels >3.5g /dl after 6 weeks of therapy) was noted by the researcher. The data was entered and analyzed by SPSS-20.

RESULTS

In group A average age of patients was 26.36±4.30 years and in group B it was 26.31±4.69 years on an average, with majority of the patients 41 (50%) in age range of 20 to 25 years as shown in Table 1. Tables 2 & 3 showed the number and % of patients according to parity and haemoglobin levels respectively. 36 (87.80%) patients in Group A (intravenous iron) showed a rise in hemoglobin levels >3.5g/dl after 6 weeks of therapy while 27 (65.85%) patients in Group B (oral iron), So, efficacy was 87.80% in group A (intravenous iron) and 65.85% in group B (oral ir on) with p-value of 0.018 as shown in Table 4. Table 5 shows stratification of age groups with respect to efficacy while Table 6 has shown the hemoglobin levels stratification with respect to efficacy.

Table No.1: Frequency and percentage of age (n=82)

Age (years)	Group A (n=41)		Group B (n=41)	
	No.	%	No.	%
20-25	20	48.78	21	51.22
26-30	13	31.71	11	26.83
31-35	8	19.51	9	21.95
Mean±SD	26.36±4.30		26.31±4.69	

Table No.2: Frequency and percentage of parity (n=82)

Parity	Group A (n=41)		Group B (n=41)	
	No.	%	No.	%
1	8	19.51	9	21.95
2	13	31.71	13	31.71
3	11	26.83	12	28.27
4	6	14.63	5	12.19
5	3	7.32	2	4.88

Table No.3: Percentage of patients according to hemoglobin levels

Hemoglobin level (mg/dl)	Group A (n=41)		Group B (n=41)	
	No.	%	No.	%
≤ 7	22	53.66	18	43.90
>7 <10	19	46.34	23	56.10
Mean±SD	7.11±1.37		7.46 ± 1.23	

Table No.4: Efficacy in Group A compared with Group B

Efficacy	Group A (n=41)		Group B (n=41)	
	No.	%	No.	%
Yes	36	87.80	27	65.85
No	5	12.20	14	34.15
P value	0.018			

Table No.5: Stratification of age groups with respect to efficacy

Age (years)	Group A		Group B		P value
	Yes	No	Yes	No	
20-25	18 (90%)	2 (10%)	13 (61.9%)	8 (38.1%)	0.036
26–30	11 (84.6%)	2 (15.4%)	7 (63.7%)	4 (36.4%)	0.237
31-35	7 (87.5%)	1 (12.5%)	7 (77.8%)	2 (22.3%)	0.600

Table No.6: Stratification of hemoglobin levels with respect to efficacy

Hb level (mg-dl)	Group A		Group B		P value
	Yes	No	Yes	No	
≤ 7	18 (81.8%)	4 (18.2%)	10 (55.6%)	8 (44.5%)	0.071
>7-<10	18 (94.8%)	1 (5.3%)	17 (73.9%)	6 (26.1%)	0.071

DISCUSSION

A lot of energy is required in post natal period while recovering, taking care of the new born .Tiredness is expected after childbirth but is alarming when lasts more than six weeks after delivery and keeps the woman from performing normal routine. These symptoms if present depict post partum anemia. Iron deficiency being the most likely cause. The risk factors for developing post partum anemia are if the woma n was having iron deficiency anemia in antenatal period, had large amount of blood loss, twin pregnancy or low socioeconomic class.[19] The additional symptoms for this condition include dizziness, easy fatiguability, infections ,problems with breast feedin g and thus a longer hospital stay.[13]

Oral iron supplementation is the first line of management for post partum anemia but non compliance and intolerance seen in gastrointestinal upset are its main limitations.[14] Alternative treatment methods for anemia include intravenous (IV) iron therapy or blood transfusion. Blood transfusions are very costly and risky, inclining the choice of treatment towards IV iron therapy.[15]

Hemoglobin and ferritin measure the effect of therapy and they are rapidly elevated after IV iron use improving the general condition of the patients and also replenishing the iron stores of the body. Out of many options available, IV iron therapy with Iron Sucrose has better availability and larger safety data.[16] Intravenous iron is administered in a dose of 200 mg in 100 ml of normal saline 0.9% over 30 minutes safely. Some authors are convinced about rapid improvement in haemoglobin and better replenishment of iron stores after IV iron use particularly iron sucrose for iron deficiency anaemia in pregnancy as compared with oral therapy.[6,17]

In the present study 36 (87.80%) patients in Group A (intravenous iron) showed a rise in hemoglobin levels >3.5g/dl after 6 weeks of therapy while 27 (65.85%) patients in Group B (oral iron). So, efficacy was 87.80% in group A (intravenous iron) and 65.85% in group B (oral iron) with p-value of 0.018.

In a similar study by Aggarwal et al[18] intravenous iron therapy was found more effective in achieving target hemoglobin in 80% patients as compared to only 40% observed in oral iron group. Bayomeu et al[20] in France conducted a prospective ,random study involving 50 patients at 6 month of gestation, comparing intravenous iron sucrose versus oral route, showed an increase in haemoglobin from 9.6±0.7 g/dl to 11.11±1.3 g/dl after 4 weeks of treatment (P<0.001)in IV route group. Van Wyck et al[12] in his study has shown the efficacy i.e. improvement in targeted hemoglobin levels, of intravenous iron as 90.5% and oral iron therapy as 68.6% in postpartum anemia.

Halimi et al[1] in his study showed a rise in hemoglobin concentration from 9.35±1.62 to 11.20±0.28 gm/dl in oral group and from 9.20±1.69 to 12.65±1.06 gm/dl in intravenous group on day 30.

Breymann et al[11] concluded intravenous iron as a safe and effective treatment option for patients with postpartum iron deficiency anemia, IV iron is better tolerated ,ensures compliance and rapid achievement of the target haemoglobin.

In another study mean Hb level increased from 7.5 to 11gm/dl by IV iron sucrose in iron deficiency anemia of pregnancy. It was carried out by Raja et al[21] at Rawalpindi. On the whole it is concluded that intravenous iron is the preferred route of administration in treating iron deficiency anemia in pregnant women as it is more efficacious in terms of rise in hemoglobin levels.

CONCLUSION

This study concluded that intravenous iron therapy is more effective than oral iron in treating postpartum anemia due to good compliance and better tolerance.

Author's Contribution:

Concept & Design of Study:	Sidrah Batool
Drafting:	Khiaynat Sarwar Hahsmi
Data Analysis:	Khiaynat Sarwar Hahsmi, Mahham Janjua
Revisiting Critically:	Sidrah Batool, Khiaynat Sarwar Hahsmi
Final Approval of version:	Sidrah Batool

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

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Original Article

Frequency, Pattern of Injuries and Weapon used in Medico Legal Cases

Abid Karim[1], Hakeem[2], Hydat ur Rehman[3] and A. Hamid[4]

ABSTRACT

Objective: To study the frequency, Pattern of Injuries and weapon used in Medico legal cases.
Design of Study: Retrospective observational study.
Place and Duration of Study: This study was conducted at the Sardar Begum Teaching Hospital Sialkot, and forensic department Khyber Medical College, Peshawar from January 2015 to December 2016.
Materials and Methods: Two thousand and fifteen cases were included in the study. The Performa was designed to record age, sex, socio economic status, area of the victim, type of injury, number of injuries and weapon used. The fully informed consent of every patient was recorded before examination. The permission of ethical committee of the institute was also taken. The data was analyzed by SPSS version 10.
Results: There were maximum (64.2%) n=1413 medico legal cases at age 21-30 years, (59.8%) n=1317 male and (4.4%) n=96 female. Minimum medico legal cases (0.7%) n= 17 at the age of 61-70 years, (0.6%) n= 14 male and (0.1%) n=3 female as shown in table no. 1. It was seen that maximum (77.3%) n= 1704 from urban area (72.9%) n= 1607 male and (4.4%) n= 97 female medico legal and medico legal cases rural area were (22.6%) n= 498, (19.6%) n=432 male and (3.0%) n=163 female as shown in table no.2. Medico legal cases of firearm were at the top (68.8%) n= 1517, (65.84%) n= 1450 male and (3.04%) n= 67 female in the society but punctured wound medico legal cases were minimum (0.3%) n= 07, (0.22%) n= 05 male and (0.09%) n=2 female in the society as shown in table no. 3. The weapon used in medico legal cases was firearm at the top (68.8%) n=1517 and pointed end weapon was used minimally (0.3%) n=07 as shown in table no .4. There were (75%) n=1651 cases of homicide, (0.6%) n= 15 cases of suicide and (24.4%) n= 536 cases of accident in the study as shown in table no.5.
Conclusion: The study showed that (75%) cases were of homicidal in nature, (0.6%) cases of suicidal nature and (24.4%) cases of accidental in nature.

Key Words: Injuries, Medico legal, weapon.

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INTRODUCTION

The standard definition of an injury as utilized by World Health Organization is injuries area unit caused by acute exposure to physical agents like energy, heat, electricity, chemical or ionizing radiation interacting with the body in amounts or at rates that exceed the brink of human tolerance. In some cases (e.g., frost bite and drowning), injuries result from unexpected lack of essential agents like oxygen or heat.[1] Injuries account for 16% of the planet burden of malady.

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In 1990, five million folks died thanks to trauma and injuries. The quantity is anticipated to rise to eight.4 million by year 2020.[2] Low and middle financial gain countries account for ninetieth of the overall burden of injuries with geographical area and western pacific regions having the best variety of injury deaths worldwide. Road traffic accidents are the second commonest reason for incapacity within the developing world.[3,4] The people most venerable to receive injuries ranges from 17–25 years with male preponderance.[5] The top and face is that the most typically concerned region in trauma because it is that the most accessible and exposed region within the social violence.[6] The frequency varies from place to put reckoning on high gun possession.[7] Only a few studies on the extent and pattern of injuries are conducted in Asian nation.[8,9] Therefore the aim of our study to research the categories of Injuries, weapon used and frequency of medico legal cases reportable at Sardar Baigum Teaching Hospital Sialkot and rhetorical department of Khyber Medical faculty, Peshawar.

A medico-legal case (MLC) may be a case of injury or unwellness wherever the attending doctor, once eliciting history and examining the patient, thinks that some investigation by enforcement agencies is important to ascertain and fix responsibility for the case

in accordance with the law of the land.[10] Common medico-legal cases embody alleged cases of assault, road traffic accidents, burns, poisoning, snake bite, bite, industrial accidents, alcoholic intoxications etc. Medico legal cases area unit an integral a part of practice in emergency departments of major hospitals. identification of medico legal cases is an integral facet for the hindrance of preventable causalities in future and to check the rate in space.[11]

MATERIALS AND METHODS

Two thousand two hundred and two cases were included in the study during the January 2015 – August 2016. The study was conducted at Sardar Begum Teaching Hospital Sialkot and forensic department of forensic medicine department Khyber Medical College Peshawar.

The charts were reviewed, and age, sex, area of the victim, type of injury, and weapon used were recorded on designed Performa. The fully informed consent of every patient was recorded before medico legal examination. The permission of authority of the institute was also taken. The data was analyzed by SPSS version 10.

RESULTS

There were maximum (64.2%) n=1413 medico legal cases at age 21-30 years, (59.8%) n=1317 male and (4.4%) n=96 female.

Table No. 1: Age and Sex distribution in Medico Legal Cases

Sr No	Age (Years)	No Of Patients (%)	Male (%)	Female (%)
1	10-20	157 (7.1%)	123 (5.6%)	34 (1.5%)
2	21-30	1413 (64.2%)	1317 (59.8%)	96 (4.4%)
3	31-40	557 (25.2%)	537 (24.3%)	20 (0.9%)
4	41-50	37 (1.6%)	31 (1.4%)	6 (0.3%)
5	51-60	21 (1.0%)	17 (0.7%)	4 (0.1%)
6	61-70	17 (0.7%)	14 (0.6%)	3 (0.1%)
	Total	**2202 (100%)**	**2039 (92.4%)**	**163 (7.6%)**

Table No. 2: Area Distributions in Medico Legal Cases

Sr No	Area	No of Patients	Male %	Female %
1	Urban	1704 (77.3%)	1607 (72.9%)	97 (4.4%)
2	Rural	498 (22.6%)	432 (19.6%)	66 (3.0%)
	Total	**2202 (100%)**	**2039 (92.6%)**	**163 (7.4%)**

Table No. 3: Pattern of Injuries/ Means in Medico legal cases

Sr No	Pattern of Injury	Cases (Percentage %)	Male (%)	Female (%)
01	Firearm	1517 (68.8%)	1450 (65.84%)	67 (3.04%)
02	Incise(cuts)	13 (0.5%)	6 (0.27%)	7 (0.31%)
03	Stab	27 (1.2%)	21 (0.95%)	6 (0.27%)
04	Punctured	07 (0.3%)	5 (0.22%)	2 (0.09%)
05	Blunt	63 (2.8%)	48 (2.17%)	15 (0.68%)
06	Chemical Burn	11 (0.4%)	8 (0.36%)	3 (0.13%)
07	Dry Flame Burn	13 (0.5%)	8 (0.36%)	5 (0.22%)
08	Poising	15 (0.6%)	8 (0.36%)	7 (0.31%)
09	Road Traffic	536 (24.3%)	485 (22.02%)	51 (2.31%)
	Total	**2202 (100%)**	**2039 (92.6%)**	**163 (7.4%)**

Table No.4: Weapon/Mean used in Medico legal cases

Sr.	Weapon/Mean	Cases	Percentage %
01	Firearm	1517	(68.8%)
02	Sharp Edge	40	(1.81%)
03	Pointed End	07	(0.3%)
04	Blunt	63	(2.8%)
05	Acid /Alkali	11	(0.4%)
06	Dry Flame	13	(0.5%)
07	Poison	15	(0.6%)
08	RTA	536	(24.3%)
	Total	**2202**	**100%**

Table No. 5: Medico Legal Type of Cases

Sr No	Medico Legal Types	No of Patients	Percentage %
1	Homicidal	1651	75.0%
2	Suicidal	15	0.6%
3	Accidental	536	24.4%
	Total	**2202**	**100%**

Minimum medico legal cases (0.7%) n= 17 at the age of 61-70 years, (0.6%) n= 14 male and (0.1%) n=3 female as shown in table no. 1. It was seen that maximum (77.3%) n= 1704 from urban area (72.9%) n= 1607

male and (4.4%) n= 97 female medico legal and medico legal cases rural area were (22.6%) n= 498, (19.6%) n=432 male and (3.0%) n=163 female as shown in table no.2. Medico legal cases of firearm were at the top (68.8%) n= 1517, (65.84%) n= 1450 male and (3.04%) n= 67 female in the society but punctured wound medico legal cases were minimum (0.3%) n= 07, (0.22%) n= 05 male and (0.09%) n=2 female in the society as shown in table no. 3. The weapon used in medico legal cases was firearm at the top (68.8%) n=1517 and pointed end weapon was used minimally (0.3%) n=07 as shown in table no .4. There were (75%) n=1651 cases of homicide, (0.6%) n= 15 cases of suicide and (24.4%) n= 536 cases of accident in the study as shown in table no.5.

DISCUSSION

Present study showed that maximum medico legal cases came to casualty were firearm. This finding was consistent with other studies.[1,2,6-8,10,11] Malik Y [3].But it was stated Hussain SN[5] study also showed maximum number of case reported to casualty were of burn which was differ to our study.

In our study maximum numbers of cases reported to casualty were from age group 21-30 years (64.02%) followed by 31-40 years (25.02%) and minimum at the age 61-70years (0.7%), similar to other authors studies.[2-5,9-11] This may be due to fact that individual of adult age group lead more active life and take risk but in old age the people are spent sedentary.

In our study we observed that male (92.04%) and female (7.6%) as seen in others.[2-5,9-11] This is because males are more vulnerable to accident or injuries.

Present study showed that maximum number of medico-legal cases reported to casualty between 12 p.m. to 6 p.m. because in this time of day most of people are maximally involved into their activities[13].

We observed in our study that firearm weapon was used maximally (68.8%) in medico legal cases in the society which was similar to other studies conducted in Pakistan and even in develop countries.[14]

CONCLUSION

The study showed that (75%) cases were of homicidal in nature, (0.6%) cases of suicidal nature and (24.4%) cases of accidental in nature.

Author's Contribution:

Concept & Design of Study:	Abid Karim
Drafting:	Hakeem
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Revisiting Critically:	Abid Karim, Hakeem
Final Approval of version:	Abid Karim

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

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Original Article

Unusual Incidental Histopathological Findings of Appendectomy Specimens

Inayatullah Memon and Attiya Memon

ABSTRACT

Objective: To determine the unexpected incidental histopathological findings ofsurgically removed appendectomy specimens.

Study Design: Observational study

Place and Duration of Study: This study was conducted at the Department of Pathology, Indus Medical College Tando Muhammad Khan from February 2017 to January 2018.

Materials and Methods: A sample of 200 appendectomy specimens was collected according to inclusion and exclusion criteria. Gross examination of specimens was noted. 5 µ tissue sections were stained with Hematoxylin and Eosin and examined under microscope. A structured proforma was designed for the collection of data. Data variables were typed on the Microsoft excel sheet in Windows 7.0 software. Data was analyzed onStatistix 8.1(USA) at 95% confidence interval ($P \leq 0.05$).

Results: Mean Age was noted as 27±10.56 years. Male to female ratio was 5.6:1 (P=0.0001). Acute appendicitis was noted in 30.5%, suppurative appendicitis in 8%, gangrenous appendicitis in 5%, perforation in 9.5%, tuberculosis in 8.5%, lymphoid hyperplasia in 5.5% and fecolith in 7.5% of cases. Unusual histopathological findings noted were Crohn`s disease (1.5%), benign tumors (6%), carcinoid (1%), Adenocarcinoma (7%), endometriosis (3.5%) and Enterobiusvermicularis (6.5%).

Conclusion: Incidence of unexpected histopathological findings was high in appendectomy specimens.The present study emphasizes the importance of histopathological examination of every single resected appendectomy specimen to avoid missing any clinically important and treatable disease.

Key Words: Appendectomy,Tuberculosis, Enterobius, Histopathology

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INTRODUCTION

Acute appendicitis is commonly encountered surgical problem in emergency,[1] while the appendectomy is widely performed surgical procedure. Negative histopathological examination is reported in 20% of patients who underwentappendectomy.[2] Negative histopathological examination of appendectomy specimens is common in female compared to male. Making diagnosis of acute appendicitis is a surgical dilemma, especially in females because of internal genitalia. Misdiagnosis of acute appendicitis is very common in female who are non-pregnant of child bearing age.[3]Peak age incidence of acute appendicitis is in teenage and early 20s. Incidence of acute appendicitis is similar among male and female before puberty. In adult age, the incidence in male is more frequent with male to female ratio of 3:2, this decreases with advancing age. Obstruction of appendix lumen is dominant factor in the pathology of acute appendicitis. Obstruction may occur due to worm, fecolith, fibrosis and or lymphoid hyperplasia in youngsters. Unusual causes had also been reported.[3,4]Practice of histopathological examination of surgically removed appendectomy specimens varies. Some authors[5]are of opinion that it is not necessary to perform routine histopathological examination of appendectomy specimens until or unless gross abnormality is not observed in the appendix.[5]While others[6,7] suggest performing routine histopathological examination of appendectomy specimensis mandatory. Histopathological examination remains the gold standard procedure for confirmation of appendicitis. It is necessary to be performed for each appendectomy specimen because occasionally sinister findings such as worms, tumors, tuberculosis and rare causes are encountered, which are confirmed by histopathological examination only. Such findings necessitate the pathological examination of each and every resected appendectomy specimen.[8]

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MATERIALS AND METHODS

The present case control study was conducted at the Department of Pathology, Indus Medical College Tando Muhammad Khan. The study covered duration of one year i.e. from Feb. 2017 to Jan. 2018.

Appendectomy specimens of acute appendicitis surgically removed either by open or laparoscopic surgery was included in the study protocol. Chronic/recurrent appendicitis, or appendix removed during some other surgical procedure was exclusion criteria. Incompletely filled patient proforma, not labelled properly and delayed specimens were also excluded. Surgeons were approached and communicated about the purpose so that they could provide completely filled proforma of the patient's histopathological examination. A sample of 200 appendectomy specimens were collected and studied. Appendectomy specimens were collected with proper protocol.5µ tissue sections were prepared, stained with Hematoxylin and Eosin (H & E) and examined under microscope.Consent form was signed from only selected cases where it was considered essential. Volunteers were informed about the purpose of study.Ethical permission was taken from institute before commencing the study. A structured proforma was designed for the collection of data in a systemic way to avoid any deficiency in collection of research variables. This proforma was also approved by the panel of ethical review committee for its completeness in comparison to the objectives of the study and possible findings. Confidentiality of patient data was secured by keeping the record locked and only authorized researcher were allowed to access the results and biodata of patients. Data variables were typed on the Microsoft excel sheet in Windows 7.0 software. Once the data was complete, it was checked carefully by all the authors. Then it was copied to the Statistix 8.1(USA) sheet. Proper statistical tests were discussed by authors and were used to analyze data properly. Continuous variables (e.g. age) and categorical variables (e.g. gender) were analyzed by the Student`s t-test and the Fischer`s exact test respectively. 95% confidence interval was considered statistically significant($P \leq 0.05$).

RESULTS

Age (mean±SD) of total 200 subjects was noted as 27±10.56 years. 45% of subjects belonged to the second decade, followed by 17.5% in third decade and 12.5% in fifth decade (table 1) (P=0.0001).

Table No.1: Age distribution of study subjects (n=200)

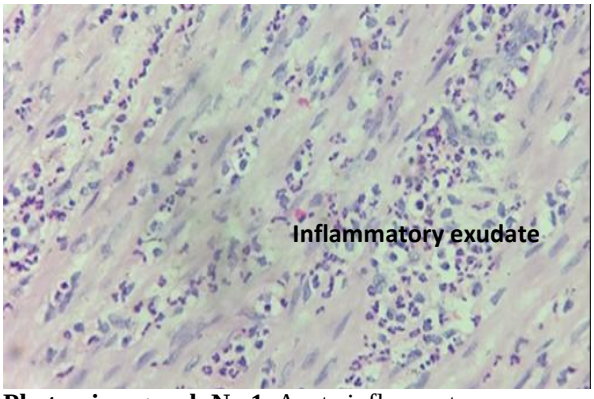
Age (years)	No.	%	P-value
10 - 19.9	90	45.0	0.0001
20 - 29.9	35	17.5	
30 - 39.9	19	9.5	
40- 49.9	25	12.5	
50 -59.9	19	9.5	
≥60	12	6.0	
Total	200	100.0	

Table No.2: Histopathological findings(n=149)

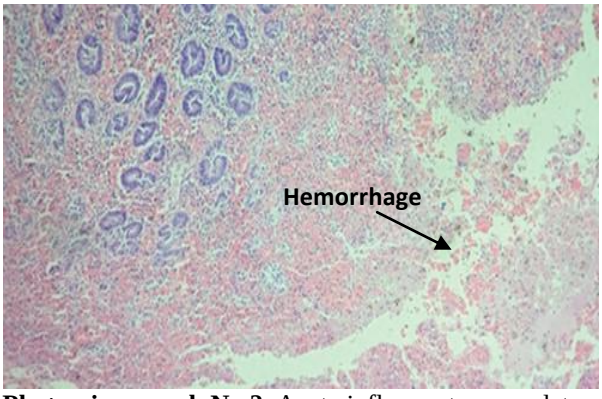
	No.	%	P-value
Suppurative appendicitis	16	8.0	0.0001
Gangrenous appendicitis	10	5.0	
Perforation	19	9.5	
Tuberculosis	17	8.5	
Lymphoid hyperplasia	11	5.5	
Fecolith	15	7.5	
Acute inflammation	61	30.5	
Total	149	74.5	

Table No.3: Unexpected incidental histopathological findings (n=51)

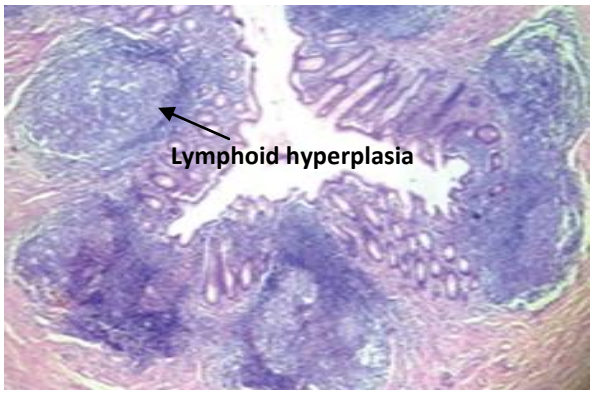
	No.	%	P-value
Crohn`s disease	3	1.5	0.0001
Benign tumors	12	6.0	
Carcinoid	2	1.0	
Adenocarcinoma	14	7.0	
Endometriosis	7	3.5	
Enterobius	13	6.5	
Total	51	25.5	



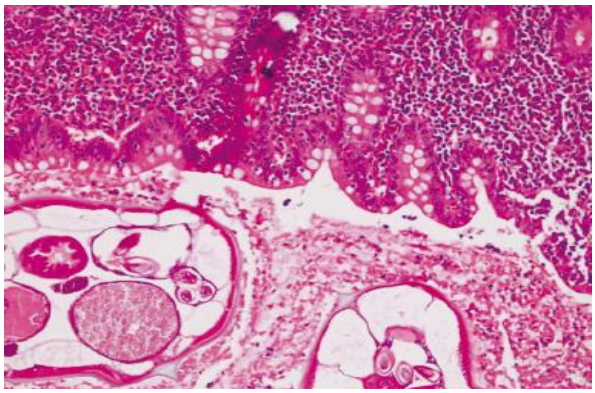
Photomicrograph No.1. Acute inflammatory exudates showing neutrophil infiltration (H& E x100)



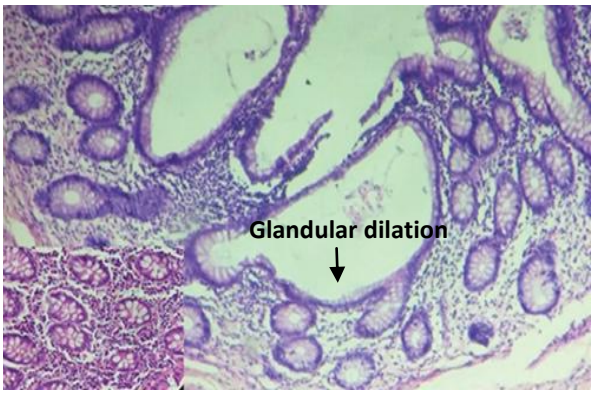
Photomicrograph No.2. Acute inflammatory exudates showing hemorrhage & necrosis (H& E x100)



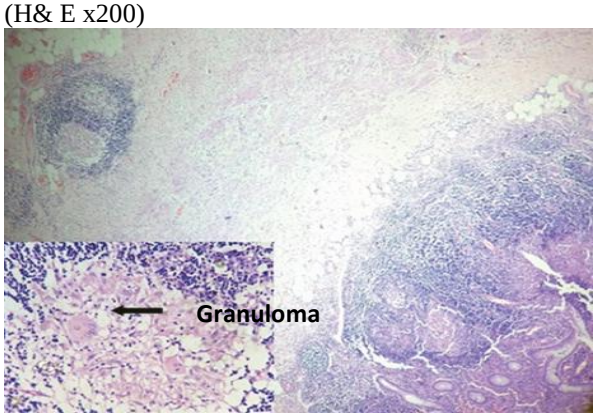
Photomicrograph No.3. Lymphoid hyperplasia seen in the acute appendicitis (H& E x100)



Photomicrograph No.4. Enterobiusvermicularis is seen in the Appendicular lumen & wall (H& E x200)



Photomicrograph No.5: Mucin secreting glandular dilatation showing goblet cell metaplasia (H& E x100)



Photomicrograph No. 6: Chronic granulomatous inflammation showing caseous necrosis (H& E x400)

Of total 200, 170 (85%) were male and 30 (15%) were female. Male to female ratio was 5.6:1 (P=0.0001). Histopathological findings are shown in table 2 and 3. Acute appendicitis (acute inflammatory exudate) was noted in 30.5% of cases. Remaining specimens revealed suppurative appendicitis in 8%, gangrenous appendicitis in 5%,, perforation in 9.5%, tuberculosis in 8.5%, lymphoid hyperplasia in 5.5% and fecolith in 7.5% of cases (table 2) (P=0.0001). Otherunexpected incidental histopathological findings noted were Crohn`s disease (1.5%), benign tumors (6%), carcinoid (1%), Adenocarcinoma (7%), endometriosis (3.5%) and Enterobiusvermicularis (6.5%). Histopathological examination is shown in Photomicrograph 1-5.Acute inflammatory exudates showing neutrophil infiltration, acute inflammatory exudates showing hemorrhage & necrosis, lymphoid hyperplasia,Enterobiusvermicularis, glandular dilatation with goblet cell metaplasia and Chronic granulomatous inflammation with caseous necrosis were observed in the histopathological examination.

DISCUSSION

The present observational study reports on the unexpected incidental histopathological findings of acute appendectomy specimens. The histopathological examination is essential because appendix may have different disease for which the management differs. For example the management of tuberculous appendicitis and parasitic appendicitis will be different and a misdiagnosis may lead to failure of symptoms or a flare up of original disease such as the tuberculosis, Crohn`s disease, carcinoid tumors, etc. Acute appendicitis is a surgical emergency and appendectomy is its mainstay of treatment. In Western countries, appendectomy accounts for 40% of all surgical procedures. Incidence of appendicitis is increasing in urban areas of developing countries due to adoption of western diets. Incidence of appendicitis varies according to age, sex, hygiene, race, geographical areas and socioeconomic status.[9]In most cases of appendicitis, obstruction of appendix lumen caused by fecolith or worm results in acute inflammation and symptoms of appendicitis. Appendix lumen obstruction facilitates the bacterial proliferation of various Enterococci species. Lymphoid hyperplasia may also occlude the appendix lumen as in young leading to appendicitis. Lumen obstruction builds the pressure on the wall of appendix resulting in ischemia and obstruction of lymphatic flow.[9] Histopathological examination of appendectomy

specimens serves 2 purposes; first- it allows proper diagnosis, second- it may reveal incidental findings which affect the subsequent clinical therapy.[10] Appendicitis affects 7% of general population in their life with peak incidence noted during first three decades of life.[9]The present observational study reports different unexpected incidental histopathological findings of appendectomy specimens such as the Crohn`s disease, carcinoid, adenocarcinoma, endometriosis and Enterobiusvermicularis (6.5%). Age (mean ± SD) of study subjects was noted as 27±10.56 years. 45% of subjects belonged to the second decade, followed by 17.5% in third decade and 12.5% in fifth decade (P=0.0001). This finding is consistent with Sinha et al[11]which had reported peak incidence of acute appendicitis of 2nd decade in male and 4th decade in female. Other previous studies[12-14]reported 80% of cases belonged to <40 years of age. In present study, of total 200, 170 (85%) were male and 30 (15%) were female. Male to female ratio was 5.6:1 (P=0.0001).Male dominancy is in agreement with previous studies.[11,12]Acute appendicitis (acute inflammatory exudate) was noted in 30.5% of cases (Photomicrograph 1,2). Remaining specimens revealed suppurative appendicitis in 8%, gangrenous appendicitis in 5%,, perforation in 9.5%, tuberculosis in 8.5%, lymphoid hyperplasia in 5.5% and fecolith in 7.5% of cases (P=0.0001). Our findings are consistent to previous studies.[15-17] Suppurative and gangrenous appendicitis is due to delay health seeking behavior of public. Incidence of perforation was 9.5% which is higher than previous studies.[11,12] Reason could be differences of health provision facilities and socio economic status which results in delayed clinical presentation. Sinha et al[11] reported 40% incidence of fecolith in their study which is higher than that of 7.5% noted in present study. However, the suppurative and gangrenous appendectomy specimens are consistent to reported studies.[15-17] Granulomatous inflammation suggestive of tuberculosis was noted in 8.5%of cases which is higher than reported incidence of 0.1-0.6%.[18] Granuloma, caseation necrosis and Langhan`s cells as shown in Photomicrograph 6 are suggestive of primary tuberculous infection of appendix. Eosinophilic inflammation by Enterobiusvermicularis was noted in 6.5% cases. Presence of Enterobiusvermicularis within appendix lumen mimics the symptoms suggestive of acute appendicitis. The finding is in keeping with World incidence of 0.2 – 41.8% of Enterobius infestation in acute appendicitis.[19] Goblet cell metaplasia (Photomicrograph 5) is in agreement with previous study.[11,20,21]Sinha et al[11] reported Crohn`s disease in 7.14% cases which is very high compared to 1.5% noted in the present study.A few of limitations of present research are a small sample size and particular ethnicity; hence findings cannot be generalized. However, findings highlight the importance of histopathological examination of appendectomy specimen, to reach at a proper diagnosis as the clinical management of tuberculosis, Enterobius infestation, Crohn`s disease, etc are different.

CONCLUSION

Incidence of unexpected histopathological findings was high in appendectomy specimens. Incidental findings included the tuberculosis, Crohn`s disease, carcinoid tumors, adenocarcinoma, endometriosis and Enterobiusvermicularis. The present study emphasizes the importance of histopathological examination of every single resected appendectomy specimen to avoid missing any clinically important and treatable disease.

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

Nimesulide Induced Oxidative Stress and Herbal Remedy

Afsheen Siddiqui[1], Yasir Gaillani[1] and Saadia Shahzad Alam[2]

ABSTRACT

Objective: To find the antioxidant activity of Picrorhiza Kurroa(Pk) in liver against nimesulide induced oxidative stress.

Study Design: Experimental animal study on mice

Place and Duration of Study: This study was conducted at the National Institute of Health, Islamadad from Feb 2013 to March 2014.

Materials and Methods: Heapatotoxicity was induced in mice by giving 750 mg/kg body weight of nimesulide foe 3 days and for establishing hepatoprotective activity, Picrorhiza kurroa was given for 14 days in two doses of 250 mg/kg and 500 mg/kg. Liver function analysis was carried out and serum glutathione peroxidase levels were measured to assess the antioxidant role of Picrorhiza Kurroain liver.

Results: Our study showed significant results for serum bilirubin and alanine aminotransferase (ALT) in mice receiving the two doses of Picrorhiza Kurroa. Similarly significant result was seen in serum glutathione peroxidase (GPx) showing Pk as a potent antioxidant against nimesulide toxicity.

Conclusion: This study demonstrated Pk as a strong antioxidant against nimesulide induced hepatic damage and the mechanism of hepatoprotection is by production of free radicals.

Key Words: Nimesuide, Picrorhiza Kurroa (Pk), hepatotoxicity, oxidative stress, glutathione peroxidase

Citation of articles: Siddiqui A, Gaillani Y, Alam SS. Nimesulide Induced Oxidative Stress and Herbal Remedy. Med Forum 2018;29(5):79-81.

INTRODUCTION

Hepatotoxicity occurs either due to an insult by a medicinal agent or other non-infectious agents leading to deranged liver function.[1] Incidence of drug induced hepatotoxicity in general population was recently noted to be 14/100,000. Drugs are responsible for causing acute liver damage in10- 52 % of patients.[2] NSAIDs are among the agents displaying very simple chemical structure but manifesting potent analgesic, antiplatelet, antipyretic and anti-inflammatory response. However bleeding tendency, severe gastric upset, kidney and liver damage are their few common side effects.[3]

Many research studies have shown that an apoptotic event starts due to the presence of intracellular reactive oxygen species and may serve as an important indicator of NSAIDs associated liver damage. Due to excessive production of these reactive particles an environment of oxidative stress is produced leading to cell dysfunction and death of cell.[4]Other reason of mitochondrial failure is covalent modification of proteins by reactive oxidative species. Further aggravating factors are sensitivity to drug and gene related factors.

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Research demonstrates a positive role of nimesuide in generating oxidative stress in liver. Biochemical assays of many antioxidant enzymes are greatly reduced by nimesulide[5]

Picrorhiza kurroa (common name Kutki) is widely used both in modern medicine and in traditional medicine for asthma, jaundice and liver disorders. Apart from hepatoprotective activity other distinct properties of Pk are anti-inflammatory, anti-anaphylactic and free radical scavenging activities.[6]Picrorhiza kurroa has proved its hepatoprotective effect in several investigations against different hepatotoxic chemicals and convincing results were seen.[7]

Many animal studies have confirmed antioxidant effect of Picrorhiza kurroa. In one study different free radicle scavenging assays were used to establish antioxidant activity of aqueous extract of Pk against ethanol.[8] Picrorhiza kurroa methanolic and aqueous extracts obtained from the rhizome are able to show antiapoptotic and cytotoxic activity apart from strong antioxidant potential.[9]

When pretreatment of rats was done with Picrorhiza kurroa, they depicted significant p values of glutathione peroxidase activity.[10]Picroside II is an isolated glycoside obtained from Picrorhiza kurroa is also helpful in preventing liver damage in animals. This was established by noticing markedly decreased levels of ALT against paracitamol and carbon tetrachloride induced hepatotoxicity. Picroside II showed its antioxidant potential by lowering the concentration of malonaldehyde in serum remarkably, whereas serum glutathione and superoxide dismutase levels were

increased. Furthermore increased activity of ATPase and histological improvement was shown by Picroside II against paracitamol.[11]

At yet we have no alternative for detoxification of nimesulide induced damage. One such herb we can rely is Picrorhiza kurroa. No scientific research data documents the hepatoprotective potential for Pk and its glycosides against nimesulide. We conducted our study to note the hepatoprotective effect of Pk glycosides and how they produce hepatoprotection.

MATERIALS AND METHODS

We conducted this study at animal house of National Institute of Health, Islamabad from Feb 2013 to March 2014. Our experimental model for this study was adult Balb C mice. Standard laboratory diet was provided to mice in proper ventilated rooms. Stas Ottos method for glycosidal extraction was used for obtaining glycosidal extract of Pk.[12]There were four groups of 20 mice. Pk was administered to group 1 in a dose of 250 mg/kg for 14 days. 750 mg/kg nimesulide was administered for 3 days to group 2.[13] For group 3, 750 mg/kg nimesulide was given for 3 days and then 250 mg/kg[14]Pk for two weeks and in group 4, 3 days nimesulide administration was followed by 14 days administration of Pk in a dose of 500 mg/kg. At the end liver assesment and serum glutathione peroxidase were assessed by using colorimetric assay.

RESULTS

Animal model of hepatotoxicity was made administring 750 mg/kg nimesulide in high doses to mice. Nimesulide led to significant (p value < 0.000) increase in serum bilirubin from 0.69 mg/dl in group 1 to 1.78 mg/dl in group 2 and serum ALT (p value < 0.000) from 31.9 IU/L in group 1 to 163.2 IU/L in group 2. When nimesulide was given serum GPx levels were lowered from mean value of 91.8 m U/ dl in control group to 63.3 m U/ dl in nimesulide group.

Table No.1: Comparison of ALT between Different Groups

Groups	Mean ALT(IU/L)	P value
Control	31.9	0.000
Nimesulide	163.2	
Nimesulide	163.2	0.000
Low dose Pk	33.0	
Nimesulide	163.2	0.000
High dose Pk	31.7	

Results were analysed by using Tukey's test for serum GPx which demonstrated significant p value (0.000) when group 1 and 2 were compared. Pk demonstrated its curative potential by reversing serum bilirubin. Serum bilirubin was significantly (p value < 0.000) lowered to 0.33mg/dl in group 3 and 0.32 mg/dl in group 4. Similarly mean serum ALT was significantly (p value < 0.000) decreased to 33.0 IU/L in group 3 and 31.7 IU/Lin group 4. Similarly for serum GPx significant p value was seen when comparison of group 2 was made with group 3 and 4.

Table No.2: Comparison of GPx between different Groups

Groups	Mean GPx (mU/dl)	P value
Control	91.8	0.000
Nimesulide	63.3	
Nimesulide	63.3	0.000
Low dose Pk	92.0	
Nimesulide	63.3	0.000
High dose Pk	91.5	

DISCUSSION

Nimesulideis a frequently prescribed NSAID having nitroaromaticsulphonanilide structure which gives nimesulide marked analgesic, anti-inflammatory and antipyretic qualities. Despite therapeutic usefulness, safety profile and dire necessity of NSAIDs, many case reports of idiosyncratic drug induced hepatic injury have been noted.[15]

Literature search demonstrates nimesulide induced hepatotoxicity. Both biochemically and histologically, in doses as low as 20 mg/kg in rats.[16]

In our study nimesulide treated group showed significantly higher values of bilirubin than mean bilirubin of control group. There was 146% increase from normal in serum bilirubin,indicating hepatotoxicity. Pk administration on daily basis in low and high dose groups decreased the high levels of bilirubin (p value 0.000) showing a 52% decrease. Similarly ALT showed 409% increase in nimesulide group and then a decrease to 6.4 % by Picrorhiza kurroa.

Nimesulide induced oxidative stress in group 2 in terms of decreasing GPx significantly upto 45% when comparison was made with control group. Interestingly group 3 and 4 recovered from oxidative stress showing p value < 0.000.

Results of our study were supported by a research work conducted by Jeyakumar R where bilirubin and ALT was decreased by Pk. In that study the mechanism of hepatoprotection against antitubercular drugs was through Pk antioxidant activity in rats.[17]

Furthermore Girish C et al in his research also demonstrated that altered histological and biochemical parameters caused by paracitamol were reversed by prior treatment of mice with picrolive, which is a Pk glycoside against silymarin.[18]

A recently conducted study by K Kant demonstrated same results of Pk activity present in the leaves of Pk instead of using rhizomes of Pk establishing a new source of naturally occurring antioxidants.[19]

The protective potential of Picrorhiza kurroa on liver in cases who are prescribed lipid lowering drugs is also demonstrated by Harban S and Sharma where it proved itself as anticholestatic, antioxidant and demonstrated reduction in glutathione depletion.[20]

However no supporting or refuting data is available in literature to show the protective effect of Pk on plasma GPx activity after nimesulide administration.

CONCLUSION

It is concluded that the antioxidant effect of Picrorhizakurroa on liver occurred by potentiating the activity of antioxidant enzyme GPx which lead to an increased scavenging of free radicals which were produced by nimesulide. Based on these protective qualities of Pk we can give the community a better therapeutic alternative for nimesulide induced hepatorenal toxicity.

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

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