Original Article

Liver dysfunction and its effect on renal function: A hospital based study from Khyber Pakhtunkhaw, Pakistan

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Objective: To study the effect of extent of liver dysfunctions on the renal function in non-pregnant women of Khyber Pakhtun Khwa, Pakistan.
Methodology: The study population comprised of 240 non pregnant women in the age group of 18-60 years. Control Group (CG) consisted of 126 individuals, while 114 were taken as Study Group (SG). The data regarding age, BMI and medical history was collected from the patients through a well-designed data entry form using purposive sampling method. 5 ml of fasting venous blood sample was collected from each patient and was analyzed for ALT, AST, urea and creatinine, using Standard protocols. The data were statistically analyzed on SPSS version 21.0.
Results: Significant differences were found in the serum urea and creatinine of CG & SG. The mean serum urea & creatinine of SG (serum urea: 33.30 mg/dl, CRT: 1.34 mg/dl) was found higher than the CG (serum urea: 28.41 mg/dl, CRT: 1.19 mg/dl).
Conclusions: Renal markers were found higher in Study Group (SG) population than in Control Group (CG). (Rawal Med J 201;43:213-216).
Keywords: Creatinine, urea, aspartate transaminase, alkaline phosphatase.

INTRODUCTION

Chronic liver diseases account for 2.5% deaths worldwide, with hepatitis B the commonest cause in the developing world.[1] Non-alcoholic steato-hepatitis (15%) and fatty liver disease (1024%) are the principal causes of chronic liver disease in the general population of Western world.[2] The available data from different parts of Pakistan shows prevalence rate of hepatitis B to be 2.4% and for hepatitis C is about 3.0%. The hepatitis B & C Virus are believed to be transmitted through the reuse of needle in medical care, drug abuse, unsafe use of blood and its products in Pakistani population. [3]

In seropositive hepatitis C &B populations, the infection has been found to be associated with different renal disease like focal segmental glomerulosclerosis, albuminuria, and membranous nephropathy with or without nephrotic proteinuria, IgA nephropathy, proliferative glomerulonephritidies and progression of chronic kidney disease to end stage renal disease.[4] Women are more vulnerable to liver diseases in developing countries than men[5] because of limited access to health care facilities, poor diet, high body mass index (BMI) and low estrogen receptor concentrations, as in one prospective study, it was found that 67% total 1147 liver patients were women.[6] Women are also 10 times at higher risk of developing Primary Biliary Cirrhosis (PBC) than men and 4 times as likely to have autoimmune hepatitis[7].

The risk factors for the onset of PBC in females as found from different epidemiologic studies, include use of hair dye, frequent urinary tract infections, smoking, and estrogen deficiency, all of which may contribute to increased disease in women.[8,9] The present cross sectional study was conducted to study the effect of extent of liver dysfunction on the derangement of renal function in non-pregnant women of Khyber Pakhtun Khwa in Northern Pakistan.

METHODOLOGY

The study population comprised of 240 non pregnant women in the age group of 18-60 years and the study was carried out in Khyber Teaching Hospital (KTH) Peshawar, Pakistan from March 1, 2014 to March 30, 2015. Control Group (CG) consisted of 126 individuals, while 114 were taken as Study Group (SG). The inclusion criteria for SG was women having at least one test either for ALT or AST (Normal range for ALT& AST was 5-45 IU/L) above

30 and other above 20 IU/L while for inclusion in CG, ALT and AST should be below 20 IU/L. Exclusion criteria for both the group were hypertension, heart ailment and diabetes. Ethical approval of the study was given by the institutional committee and Informed Consent was taken from all participants.

The data regarding age; BMI and medical history was collected from each patient on through a well-designed form using purposive sampling method. 5 ml of fasting venous blood sample was collected from each patient and was analyzed for ALT, AST, urea and creatinine, using IFCC standard methods on chemistry autoanalyser (Erbamannhein chemistry autoanalyser, Germany) using standard Erba kits & protocols[10] The normal range for SGPT& SGOT was 5-45 IU/L and 5-45 IU/L, respectively. Kinetic UV method was used for the determination of Serum urea[16] while serum creatinine was determined by Jaffe method on chemistry auto analyser (Erbamannhein chemistry auto analyser, Germany). The normal range for urea was 05-45 mg/dl and for Creatinine was 0.5-1.5 mg/dl respectively.[11,12]

The data of both the groups was statistically analyzed on SPSS version 21.0. Multiple linear regression & Pearson's correlation analysis for the required parameters was done to determine the kind of association between these parameters. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Table 1 shows the comparative mean age, BMI, Urea, CRT, ALT, AST, ALP of both groups. It is clear from the table that the mean values are higher for SG than CG.

Table 1. Comparison of the biochemistry of CG and SG.

Parameter	CG (n=126)		SG (n=114)	
	Mean	SD	Mean	SD
Age	45.98	13.14	46.89	13.35
BMI	23.40	2.82	22.93	2.66
Urea	28.41	10.82	33.30	9.97
CRT	1.19	0.83	1.34	0.73
ALT	18.93	5.18	36.25	21.38
AST	21.31	7.34	34.12	20.42
ALP	134.02	47.01	152.97	46.79

CG: Control Group, **SG**: Study Group, **BMI**: Body Mass Index, **CRT:** creatinine**, ALT**: Alanine Transaminase, **AST**: Aspartate transaminase, **ALP**: Alkaline phosphatase.

Pearson's bivariate correlation analysis was carried to investigate the association of serum urea and creatinine with age, BMI, ALT, AST, ALP and Urea in both the groups, as shown in Table 2. Positive correlation between these parameters and serum urea was found in CG. The correlation of serum urea with ALP was highly significant in CG (p=0.00). Serum creatinine showed positive correlation with age and AST and negative correlation with BMI, ALT, ALP and urea. In SG, urea showed positive correlation with age and negative with ALT, AST and ALP. A very strong positive relation was also found between urea and creatinine (p=0.001).

Table 2. Correlation analysis of Age, BMI and liver enzymes with urea and creatinine in two groups.

Parameter	CG		SG	
	Urea	Creatinnine	Urea	Creatinnine
	r(p)	r(p)	r(p)	r(p)
Age	0.003(0.97)	0.10(.28)	0.11(0.26)	0.10(0.27)
BMI	0.17(.06)	-0.03(.73)	0.08(0.43)	0.02(0.86)
ALT	0.07(0.43)	-0.11(.21)	-0.10(0.31)	-0.04(0.70)
AST	0.17(0.06)	0.02(0.81)	-0.13(0.16)	-0.06(0.55)
ALP	0.330**(0.00)	-0.04(0.64)	0.01(0.89)	-0.09(0.34)
Urea	1	-0.002(0.98)	1	0.30**(0.001)

Pearson Correlation: r, Sig. (2-tailed): p, *. Correlation is significant at the 0.05 level (2-tailed).**. Correlation is significant at the 0.01 level (2-tailed).

Multiple linear regression analysis was performed to see the dependency of renal dysfunctions on Age, BMI, ALT, AST and ALP. Age, BMI, ALT, AST and ALP were taken as independent variables (IV) while Serum urea and creatinine as dependent variables (DV). The results of both the groups are shown in Table 3 & 4.

Table 3. Multiple linear regression analysis in CG.

Model		DV			
		Urea		Creatinine	
		Unstandardized Coefficients		Unstandardized Coefficients	
		B	Std. Error	B	Std. Error
Constant		2.94	9.26	1.53	0.76
IV	AGE	0.02	0.07	0.01	0.01
	BMI	0.46	0.33	-0.01	0.03
	ALT	0.06	0.18	-0.02	0.02
	AST	0.18	0.13	0.01	0.01
	ALP	0.07	0.02	.000	0.00

Table 4. Multiple linear regression analysis in SG.

Model		DV			
		Urea		Creatinine	
		Unstandardized Coefficients		Unstandardized Coefficients	
		B	Std. Error	B	Std. Error
Constant		23.81	9.48	1.18	0.71
IV	AGE	0.11	0.07	0.01	0.01
	BMI	0.27	0.36	0.01	0.03
	ALT	-0.02	0.05	0.00	0.00
	AST	-0.08	0.05	-0.002	0.00
	ALP	0.01	0.02	-0.001	0.00

Urea was found to be positively related with Age, BMI, ALP, ALT and AST in CG while creatinine was positive with Age, ALP, and AST while negative with BMI & ALT in CG respectively. Similarly Urea was found to be positively related with Age, BMI, ALP, and negative with ALT and AST in SG. Creatinine was positive with Age, ALP, and AST while negative with ALP & AST in SG, respectively.

DISCUSSION

According to WHO, the annual death toll from liver diseases is believed to be 563000.[13,14]

Pakistan due to its increasing population is among the worst afflicted nation in the world, especially the women population due to low literacy rate, poverty, social factors, gender discrimination and access to health care facilities. On the global level, there is an increasing concern among the researchers to take into account the sex of the experimental animal/ human in all preclinical and clinical studies,[15] as both the sexes have different biological, cellular & molecular mechanism.[16] Women are reported to have a 1.51.7 time higher risk of acute liver failure than male counterparts and 74% acute liver failures with case fatality rate of about 80% induced by drugs are reported in women in United States.[17]

The purpose of our present work was to investigate the extent of liver dysfunctions in the women population of Khyber Pakhtun Khwa in northern Pakistan and its long term effect on the renal function derangement. Kidney function of both CG & SG was evaluated by measuring concentration of serum urea & creatinine.[18] We found significant differences in the serum urea and creatinine of CG & SG. In other similar studies involving association of liver and renal diseases reduction in the serum creatinine pool was observed. It is believed to be due to decrease synthesis of creatinine in liver, accumulation of extracellular ?uid, edema, malnutrition and loss of muscle mass.[19] The difference in our findings and other studies may be due to age, gender, ethnicity, diet, quality of protein, and importantly liver disease.[20]

Pearson's bivariate correlation analysis of study population indicated that renal functions were directly affected by age, BMI, ALT, AST, ALP and Urea in both the groups. The correlation of serum urea with ALP was highly significant in CG (p=0.00). Serum creatinine showed positive correlation with age and AST and negative correlation with BMI, ALT, ALP and urea. In SG, urea showed positive correlation with age and negative with ALT, AST and ALP.

Findings of other similar studies also indicated that liver disease was strongly associated with an increased incidence of renal diseases that measurement of extent of liver diseases improves risk prediction for CKD, independently of traditional risk factors (age, sex, diabetes duration, hypertension and micro albuminuria.[21]

CONCLUSION

Renal markers were found higher in Study Group (SG) population than in Control Group (CG).

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Original Article

Comparison of effectiveness of pretreatment with beta blocker vs without beta blocker in patients presenting with acute coronary syndrome in terms of early mortality

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Objectives: To compare the effectiveness of pretreatment with beta blocker vs without beta blocker in patients presenting with acute coronary syndrome (ACS) in terms of early mortality.

Methodology: A total of 348 consecutive patients presenting with ACS were included in the study. All patients with diabetes mellitus were excluded. All patients were monitored in the CCU and echocardiograms were performed. All were examined and evaluated for third heart sound and crepitations. Group A (Pretreatment group) was those who are taking beta blocker already for any cause before presentation and Group B (control group) was those who are not taking beta blocker before.

Results: In Group A, mean age was 52±1.27 years where as in Group B it was 54±1.32. In Group A, 62% patients were male and 38% patients were female where as in Group B 60% patients were male and 40% patients were female. In Group A, efficacy was in 90% patients where as in Group B efficacy was in 82% patients.

Conclusion: Pretreatment with beta blocker was more effective then treatment without beta blocker in patients presenting with acute coronary syndrome in terms of early mortality. (Rawal Med J 201;43:217-219).

Key words: Beta blocker, acute coronary syndrome, early mortality.

INTRODUCTION

Beta-blocker (BB) treatment decreases the mortality and morbidity in patients with myocardial infarction (MI).[1] It is currently recommended as a class I-A indication in clinical practice guidelines.[2] The mechanism by which beta-blocker works is by reducing cardiac workload as it has negative chronotropic and ionotropic properties.[3] Due to reduced cardiac workload, it decreases myocardial oxygen demand and hence improve in the compromised blood supply. By limiting ischemic injury, beta-blockers prevent ventricular fibrillation, ultimately decreasing morbidity and mortality.[4]

Short-term effect of early administration of beta blockers in patients with unstable angina or Acute MI remains controversial.[5] In ACS patients, there is a risk that the decreased cardiac output may aggravate the ischemic insult, when the cardiac output is already compromised by stunned myocardium or due to a preexisting cardiomyopathy (ischemia, hypertensive, vulvular).[3]

Chaterjeeet et al in a meta-analysis of sixteen randomized trials showed that hospital mortality was reduced by 8% with intravenous beta-blockers when compared with controls and they reduced the risk of ventricular tachyarrhythmias.[6] Cucli F et al showed that the rate of STEMI was higher in patients in whom beta blockers were started after hospitalization compared to patients taking beta blockers before admission to hospital ($p<0.001$).[5] The aim of this study was to highlight the role of pretreatment of beta blocker in patients with ACS in our set up.

METHODOLOGY

This study was conducted at Department of Cardiology, Bolan Medical College/Sandeman Provincial Hospital, Quetta, Pakistan. Study design was randomized controlled trial and duration of study was one year. The total sample size was 278

(139 in each group) using 47.6% P1 proportion of patients with ACS and not on prior beta blocker treatment and 62.4% P2 proportion of patients with ACS on beta blocker treatment among patients, 5 power of study 80 % with 95% confidence interval and 8% margin of error using WHO sample size calculations. Consecutive (non probability) sampling was used for sample collection. Patients of both gender and age >18 <60 years, presenting with ACS were included. Patients with asthmatic problems, patients with bradycardia (Heart Rate <60/min), patients with heart failure (NYHA class III & IV), patient with AV block, patients with hypotension (Systolic BP < 100 mm Hg), patients with pulmonary edema were excluded. This study was conducted after approval from hospital ethical and research committee and a written informed consent was obtained.

Patients were divided in two groups. Group A (Pretreatment group) was those who are taking beta blocker already for any cause before presentation. Group B (control group) was those who are not taking beta blocker before. A detailed history was taken from all the patients followed by routine physical examination and baseline investigation. All patients were followed up for one month for primary and secondary outcomes. All the analysis was done using SPSS version 17. Chi-square Test was applied to compare effectiveness in both groups. Keeping p-value < 0.05 was considered significant.

RESULTS

The study had 348 patients. Mean age was 52± 1.27 years (Table 1). In Group A, 86 (62%) patients were male and 53 (38%) patients were female where as in Group B 83 (60%) patients were male and 56 (40%) patients were female (Table 2).

Table 1. Age distribution (n=278).

Age	Group A (n=139)	Group B (n=139)
30-40 years	25 (18%)	28 (20%)
41-50 years	50 (36%)	49 (35%)
51-60 years	64 (46%)	62 (45%)
Total	139	139
Mean and SD	52 years ± 1.27	54 years ± 1.32

Table 2. Gender distribution (n=278).

Gender	Group A (n=139)	Group B (n=139)
Male	86 (62%)	83 (60%)
Female	53 (38%)	56 (40%)
Total	139	139

Table 3. Efficacy (n=278).

Efficacy	Group A (n=139)	Group B (n=139)	P-Value
Effective	125 (90%)	114 (82%)	0.057
Not effective	14 (10%)	25 (18%)	
Total	139	139	

Table 4. Efficacy with respect t0 age (n=278).

Age	Efficacy	Group A (n=139)	Group B (n=139)	P Value
30-40 years	Effective	25	28	0.000
	Not effective	0	0	
Total		25	28	
41-50 years	Effective	46	40	0.127
	Not effective	4	9	
Total		50	49	
51-60 years	Effective	54	46	0.158
	Not effective	10	16	
Total		64	62	

Table 5. Efficacy with respect to gender (n=278).

Gender	Efficacy	Group A (n=139)	Group B (n=139)	P Value
Male	Effective	77	67	0.114
	Not effective	9	16	
Total		86	83	
Female	Effective	48	47	0.284
	Not effective	5	9	
Total		53	56	

Efficacy of two groups was analyzed as Group A was effective in 125 (90%) patients and was not effective in 14 (10%) patients where as in Group B was effective in 114 (82%) patients and was not effective in 25 (18%) patients (Table 3). Stratification of efficacy with age and gender is shown in Table 4 and 5.

DISCUSSION

Our study showed that in Group A beta blocker was

effective in 90% patients and was not effective in 10% patients where as in Group B it was effective in 82% patients and was not effective in 18% patients. Similar results were observed in another study by CuculI F et al[7] in which 7,684 patients (29.4%) had previous blocker therapy, and in 6,234 of these patients this therapy was continued after admission (group A; in 1,450 patients blockers were stopped after admission); in 12,344 (47.2%) patients blocker therapy was started at admission (group B); 6,131 (23.4%) patients never received blocker therapy (group C). The mean age of all patients was 65.6 years (13.2) and 72.3% of them were males. Patients of group A were significantly older than patients of group B (67.6 vs. 62.5 years, p (0.001) but had a similar age as patients of group C (68.4 years). Patients of group A had a higher proportion of diabetes (24.3 vs. 15.8% in group B and 22% in group C, p (0.001) and a higher proportion of arterial hypertension (79.9 vs. 45.2% in group B and 50.4% in group C). The rate of STEMI was higher in patients of groups B and C (62.4 and 62.8%) compared to patients of group A (47.6%, p=0.001)
Similar results were observed in another study by Chatterjee et al[8] in which sixteen studies enrolled 73,396 participants. In-hospital mortality was reduced 8% with intravenous beta-blockers, RR=0.92 (95% CI, 0.86-1.00; p=0.04) when compared with controls. Moreover, intravenous beta-blockade reduced the risk of ventricular tachyarrhythmias (RR=0.61; 95 % CI 0.47-0.79; p=0.0003) and myocardial reinfarction (RR=0.73, 95 % CI 0.59-0.91; p=0.004) without increase in the risk of cardiogenic shock, (RR=1.02; 95% CI 0.77-1.35; p=0.91) or stroke (RR=0.58; 95 % CI 0.17-1.98; p=0.38). Moreover, he concluded that intravenous beta-blockers early in the course of appropriate patients with ACS appears to be associated with significant reduction in the risk of short-term cardiovascular outcomes, including a reduction in the risk of all-cause mortality.

CONCLUSION

Our study showed that pretreatment with beta blocker was more effective then treatment without beta blocker in patients presenting with acute coronary syndrome in terms of early mortality.

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Original Article

Evaluation of Typhidot test in the diagnosis of enteric fever in symptomatic children keeping blood culture as gold standard

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Objective: To evaluate the validity of typhidot test in the diagnosis of enteric fever in symptomatic children keeping blood culture as gold standard

Methodology: This descriptive cross sectional study was conducted at pediatric ward of Liaquat National Hospital, Karachi, Pakistan from July 30, 2013 to January 31, 2014. Patients of either gender with age between 1-12 years with fever 38°C and above lasting for at least 3 days were included. All had Typhidot and blood culture. Provisional diagnosis of enteric fever was made on the basis of history of fever ? 38°C lasting at least 3 days with or without abdominal pain, coated tongue, vomiting, constipation/diarrhea, splenomegaly, hepatomegaly, and rose spots.

Results: Total number of patients was 129. Mean age was 7.75±4 years. Mean duration of fever was 6.73±1.99 days. There were 89 (69%) male patients and 40 (31%) females. Vomiting was observed in 44 (34.1%) patients, coated tongue 64 (49.6%), constipation 11 (8.5%), diarrhea 31 (24%), splenomegaly 35 (27.1%), Hepatomegaly 58 (45%) and rose spots 75 (58.1%). Typhidot IgM was positive in 94 (72.9%) and blood culture was positive in 108 (83.7%) patients. Overall validity of typhidot showed that sensitivity was 83%, specificity 81%, PPV 96% and NPV 49%.

Conclusion: The validity of typhidot test in the diagnosis of enteric fever in symptomatic children was found to be satisfactory. (Rawal Med J 201;43:220-223).

Keywords: Typhidot test, enteric fever, fever in children.

INTRODUCTION

Enteric fever is termed for both typhoid fever and paratyphoid fever. Typhoid fever is caused by salmonella typhi, whereas paratyphoid fever is caused by S. paratyphi A, B and C. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, which resulted in 216,000 deaths, of which more than 90% morbidity and mortality occurred in Asia.[1,2] According to WHO, the incidence of typhoid fever in Pakistan is 421 cases per 100,000 populations per year and it represents fourth most common cause of death in Pakistan.[3] A study from Karachi claims the prevalence of the typhoid fever in symptomatic cases as 61.5%.[4]

The presenting signs and symptoms of typhoid fever in children differ significantly from those in adults. The diagnosis in emergency department is usually based on clinical signs and symptoms with basic or no laboratory testing.[2] Blood culture is the gold standard for the diagnosis and gives information about antibiotics sensitivity of isolate but in best of the circumstances it carry 70-75% diagnostic yield. The widespread use of antibiotics in the community makes it difficult to isolate the organism on blood culture and alternative methods of diagnosis such as bone marrow culture may be required.[5] Therefore, there is a real need for simple and rapid serological diagnostic test for enteric fever.

Culture of bone marrow aspirate is 90% sensitive.[3] Blood, intestinal secretions (vomitus or duodenal aspirate), and stool culture results are positive for S typhi in approximately 85%-90%.[4] The dot-enzyme immunoassay (dot-EIA) is a new serological test that shows specific IgM and IgG antibodies against salmonella typhi strains. It separately identifies IgM and IgG antibodies.[6] Typhidot test has been reported to be highly sensitive and specific test in diagnosing typhoid fever in some studies, other studies report variable results.[7] Its sensitivity and specificity of has been reported as 92.85% and 90%.[8] Therefore the rationale of this study to evaluate the validity of typhidot test in the diagnosis of enteric fever in

symptomatic children keeping blood culture as gold standard.

METHODOLOGY

This descriptive cross sectional study was conducted at pediatric ward of Liaquat National Hospital, Karachi, Pakistan from July 30, 2013 to January 31, 2014 through Non probability consecutive sampling technique. With prevalence as 61.5%[4] to 90%[8] using 95% level of confidence and 7% absolute precision total sample size calculated was 129. Inclusion criteria were patients of either gender with age between 1-12 years with fever 38°C and above lasting for at least 3 days. Patients with fever of 38 °C or above with clear focus of infection, patients with MP positive, those with history of recent typhoid immunization, with history of immunosuppression and taking any type of antibiotics during this illness were excluded from the study. Informed consent was taken from legal guardians of each child.

Patient's history and physical examination was conducted and the responses were marked on a pre-designed Performa (annex) comprising of demographic features and clinical diagnostic features of enteric fever and its duration. Typhidot was collected within 24 hours and the Blood Culture was followed for the maximum of 10 days until it turns to be positive for salmonella.

Data were analyzed using SPSS version 17. Sensitivity, Specificity, Positive predictive value, and Negative predictive value and Accuracy of clinical diagnosis were calculated for typhidot (Ig M) positive, taking positive blood culture as gold standard. Effect modifiers were controlled through stratification of age, gender, duration of fever to see the effects of these on outcome.

$p<0.05$ was taken as significant.

RESULTS

Total numbers of patients were 129. Mean age was 7.75±4 years. Mean duration of fever was 6.73±1.99 days. 77 (59.7%) patients were in >7 years age group. There were 89 (69%) males and 40 (31%) females. Vomiting was observed in 44 (34.1%) patients, coated tongue in 64 (49.6%), constipation in 11 (8.5%), diarrhea in 31 (24%), splenomegaly in 35 (27.1%), Hepatomegaly in 58 (45%) and rose spots in 75 (58.1%). Typhidot IgM was positive 94 (72.9%) and blood culture positive in108 (83.7%) patients (Table).

Table. Clinical Features and validity of Test (n=129).

Clinical Features	Yes n (%)	No n (%)	P-Value
Vomiting	44 (34.1%)	85 (65.9%)	-----
Coated Tongue	64 (49.6%)	65 (50.4%)	-----
Constipation	11 (8.5%)	118 (91.5%)	-----
Diarrhea	31 (24%)	98 (76%)	-----
Splenomegaly	35 (27.15%)	94 (72.9%)	-----
Hepatomegaly	58 (45%)	71 (55%)	-----
Rose Spots	75 (58.1%)	54 (41.9%)	-----
Typhoid IGM Positive	94 (72.9%)	35 (27.1%)	-----
Blood culture positive	108 (83.7%)	21 (16.3%)	-----
Overall Validity of Typhoid Yes No	 90 18	 18 17	**0.001**
Age group ≤7 years and validity of typhoid Yes No	 46 4	 2 0	**1.00**
Age group >7 years and validity of typhoid Yes No	 42 14	 4 17	**0.001**
Duration of fever ≤5 days and validity of typhoid Yes No	 22 7	 4 11	**0.003**
Duration of fever >5 days and validity of typhoid Yes No	 68 11	 0 6	**0.001**

Overall validity of typhidot showed that sensitivity was found to be 83%, specificity 81%, PPV 96% and NPV 49% (p=0.001). Age group ?7 years sensitivity was 92%, specificity 0%, PPV 96% and NPV 0% (p=1.00). Age group >7 years sensitivity was 75%, specificity 81%, PPV 91% and NPV 55 (p=0.001). With duration of fever ?5 days sensitivity

was 76%, specificity 73%, PPV 85% and NPV 61% (p=0.003). With duration of fever >5 days sensitivity was 86%, specificity 100%, PPV 100% and NPV 35% (p=0.001).

DISCUSSION

In this study, overall sensitivity was found to be 83%, specificity 81%, PPV 96% and NPV 49%. Chi-square test was applied and sufficient evidence of significant relationship was observed as p-value was less than level of significance. Typhidot was positive in 72.9% children. In a study from Rawalpindi, Typhidot was positive in 55.2% and negative in 44.8% children.[8] This difference may be due that they included adolescents and adults along with children in their study. In another local study Typhidot was positive in 856 (42.9%) children [9]. In another local study Typhidot was positive in 266 (48.36%) children [10]. 16 (4.5%) were positive in the age group 0-1 year whereas in 1-5 years age positive with 17.12% prevalence. patients of 5-10 years of age had 22.2% prevalence. While patients of 10-15 years of age were found positive with 26.9% prevalence. In Adolescent group, 27(25%) were positive.

An unsimilar study from India revealed 15.6% children were culture positive and in 31.1% Typhidot was positive.[11] In a local study, only 25.26% samples were positive for Typhidot test. The peak seropositivity rates were found during the months of AprilJune, while fewer cases were observed from January to March. Age wise distribution of typhoid fever reflected that age groups of 1015 years were at higher risks of developing enteric fever.[12]

A study from India showed the overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the Typhidot-IgM test and Enter screen-IgM test considering blood culture as gold standard were 97.29% and 88.13%, 97.40% and 87.83%, 98.18% and 92.03%, 96.15% and 82.27%, respectively.[13] While in another study, in 41 children diagnosed with typhoid fever, 37 were positive for IgM anti S. typhi, but only 18 were positive for S. typhi in blood culture. IgM anti S. typhi (cut-off ?4) test had an Area under the Curve (AUC) of 59%, sensitivity of 100% and specificity of 17.39%. IgM anti S. typhi with cut-off >8 showed the highest AUC with sensitivity of 55.56% and specificity of 73.68%.[14]

In another study, Salmonella typhi was isolated from 82 (30.4%) and the remaining 188 (69.6%) were blood culture negative. Typhidot-M was positive in 136 (50.4%). Typhidot-M test had a sensitivity of 81.7%, specificity of 84.6%, PPV of 69.8%, and NPV of 91.4%.[15] In our study, Rose Spots were common findings; present in 58.1% cases, vomiting in 65.9%, coated tongue in 49.6%, constipation in 91.5%, diarrhea in 76%, splenomegaly in 76% and hepatomegaly in 55% children. A study from India showed anorexia was the common symptoms along with toxic look, coated tongue.[11] Another study from Bangladesh reported abdominal pain in 21%, loss of appetite in 58% and coated tongue in 18%, myalgia was in 15%, headache in 12% and loss of appetite was in 58% children.[16]

CONCLUSION

The validity of typhidot test in the diagnosis of enteric fever in symptomatic children was found to be satisfactory. Even though Typhidot is rapid, easy and affordable, its use should be followed with care and should have backup test in certain circumstances.

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Original Article

Frequency of cytomegalovirus (CMV) in post renal transplant patients: A single center experience

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Objective: To retrospectively analyze post renal transplant patients to see the frequency of CMV infection, risk factors, its prevention and treatment at our Institutution.

Methodology: This study was done from January 2008 to January 2017 at Institute of Kidney Diseases, Peshawar, Pakistan. Clinical records and laboratory data were collected. CMV viral load was monitored by CMV quantitative nucleic acid testing.

Results: A total of 200 patients with 178 male and 22 females were studied. The frequency of CMC was 13.5 % (27 patients). All of these were seen after 3 months of renal transplantation.

Conclusions: The CMV infection is more common in patients with intense post renal transplant immunosuppression with induction therapy. Ganciclovir is an effective treatment against CMV infection. All patients who receive induction therapy must be given ganciclovir as a prophylaxis. Frequent CMV PCR should be done post prophylaxis where there is increase chance of CMV vireamia. (Rawal Med J 201;43:224-226).

Keywords: Cytomegalovirus, kidney transplantation, ganciclovir.

INTRODUCTION

Cytomegalovirus (CMV) is a Herpesviridae virus with a worldwide seroprevalence ranging from 30 to 97 %.[1] The seroprevalence of CMV is higher in developing countries up to 100% due to close contacts, low socio-economic status and over-crowding.[2] It is one of the major causes of morbidity, graft loss and mortality after renal transplantation.[3] With the advent of newer technologies, CMV infection is diagnosed earlier and treated promptly. This infection typically occurs within the first three months after transplantation.[4] The CMV related complications in post renal transplant patients is related to serostatus of the donor (D) and recipient (R). Renal transplant from a seropositive donor (D+) to a seronegative recipient (R-) has highest risk of CMV infection.[5] The CMV D+/R+ transplantation and CMV D-/R+ transplantation are considered to be of intermediate risk for the development of disease, and CMV D-/R- transplantation is considered low risk (5%).[6] The CMV is associated with chronic allograft loss, atherosclerosis and malignancy especially post renal transplant lymphoproliferative disorders (PTLDs) by direct cytopathic effect or indirect immunological injury.[7,8]

Current guidelines suggest ganciclovir or valciclovir prophylaxis for 3 months for D+/R+ and D?/R+ recipients and 6 months for D+/R? recipients, while no need for prophylaxis for sero-negative donor and recipient.[8] Risk of CMV disease, morbidity and mortality has been reduced with CMV prophylaxis in renal transplant recipients.[9] However, it is noted that 35% of the patients become vireamic within a year of post renal transplantation in spite of 3-6 months of ganciclovir prophylaxis.[4] The efficacy of the oral ganciclovir and intravenous ganciclovir is the same in preventing CMV infection and disease.[7] The data regarding CMV in post renal transplant patients is lacking in our country. The purpose of this study was to determine the frequency of CMV in post renal transplant patients in our transplant center.

METHODOLOGY

This retrospective analysis of 200 post renal transplant patients with stable renal functions was done from January 2008 to January 2017 at Institute of Kidney Diseases, Peshawar, Pakistan. Institute of Kidney Diseases (IKD), Peshawar is the only single

center doing the renal transplantation in KPK at the moment. All transplants were living related with good HLA matches. All donors and recipients were CMV seropositive before transplant. All received intravenous basliximab as an induction therapy. All were on triple immunosuppressive regime i-e cyclosporine, mycophenolate mofetil (MMF) and prednisolone. All recipients were given ganciclovir prophylaxis.

The patients with suspected CMV infection upon clinical presentation, physical examination, and laboratory results were diagnosed by detection of quantitative CMV PCR viral load more than 600 copies per milliliter in whole blood samples. All these patients were treated with IV ganciclovir with dose adjustments according to renal functions for 3 weeks. Response of the treatment was confirmed by doing whole blood CMV PCR that was negative.

RESULTS

A total of 200 renal transplant recipients were enrolled from January 2008 to January 2008. All were living related kidney transplantation from the close family members. Out of 200 patients, 178 were male and 22 were female recipients. Mean age of the recipient was 34.2 years and donor was 30.7 years (Table).

Table. Characteristics of transplant recipients.

Patients (Total):	200
Male	178(89%)
Female	22(11%)
Mean age:	
Recipients	34.2 years
Donors	37.7 years
Frequency of CMV	27 (13.5%)

The frequency of cytomegalovirus vireamia was noted in 27 (13.5%) patients. All patients (recipients and donors) were CMV IgG seropositive status. All recipients were on triple regime cyclosporine, MMF and prednisolone. There was no rejection noted in patients with CMV vireamia. All responded well with intravenous ganciclovir with CMV PCR negative after 3 weeks of treatment without any complication.

DISCUSSION

Cytomegalovirus infection is the most common post-renal transplant viral infections in 1st 3-6 months. It causes increased morbidity, mortality and graft loss.[6] CMV infections can develop in 10% to 60% of kidney transplant patients without prophylaxis and treatment. It occurs early during the first 3 months after transplantation at the time of the highest immunosuppressive load.[10]

In our study, the prevalence of CMV disease was 13.5%, which is much lower than other studies.[11] In our study, all kidney transplant donors (D+) and recipients (R+) were seropositive, which is well studied in different developing countries with seropositivity of 100% due to low socioeconomic status and overcrowding.[12] However, it is quite low in developed countries like Europe and USA.[13] But some studies also had a higher prevalence than our study (14% to 38%).[13] The reason for this difference was due to the serologic incompatibility of CMV, which lead to the highest risk of CMV disease.[14]

In our study, there was no effect of the type of immunosuppressive regimen on the CMV prevalence. Also, diabetes mellitus and hypertension were not associated with the incidence of CMV disease.[15]

Although exact duration of prophylaxis is not defined but the current recommendations suggest 3 months, which can be extended to 6 months in patients who receive induction therapy like ATG and basliximab.[16] All these patients with CMV infection were treated with 2-3 weeks course of 5mg/kg intravenous ganciclovir every 12 hours in patients with normal renal allograft function.[17] While dose reductions was made in patients with low renal functions.[18] there were no complications noted during treatment of CMV infection.

The study limitations include the sample size of the patients may be not big and we did the study at a single center. However, we need to do more studies on CMV in post renal patients at a multi-center level with bigger sample size.

CONCLUSION

The frequency of CMV disease in kidney transplant recipients in our region is relatively low (13.5%). Diabetes and hypertension were not risk factors for

CMV disease as well as no effect of the type of immunosuppressive regimens. The frequency of CMV disease was more in patients with induction therapy with ATG and basliximab. All patients with CMV diseases responded well with intravenous ganciclovir for 3 weeks. The first 6 months after transplantation are considered high risk period for CMV disease, hence monitoring of the patients by PCR is highly recommended. All patients should be given Ganciclovir prophylaxis for 3-6 months according to serostatus of the CMV.

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