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CONTENTS

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NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD), a term used for s***teatosis*** (fatty liver), ***non-alcoholic steatohepatitis*** (NASH) and c***irrhosis*** secondary to NASH. It is the most common reason for ***abnormal liver function*** **tests** among adults all over the world, and is on the rise here in Pakistan as well. It affects 30 million of the US population, and of these, 8.6 million have NASH, with nearly 20% having signs of advanced disease (i.e., bridging fibrosis, cirrhosis) on histologic examination. NAFLD is most commonly seen in persons who are overweight / obese (40%), have diabetes mellitus (≥ 20%) and hyperlipidemia – triglyceridemia (20%) in association with insulin resistance as part of metabolic syndrome.

The patients with NAFLD/NASH even have increased risk of developing diabetes when combined with obesity or insulin resistance. Even people of normal weight can develop NAFLD. Risk of NAFLD with metabolic syndrome is 4 to 11 times higher than that of persons without insulin resistance and coffee consumption ion appears to reduce the risk. Risk of NAFLD is also increased in persons with active psoriasis, soft drink consumption, cholecystectomy, drugs like corticosteroids, amiodarone, diltiazem, tamoxifen, irinotecan, oxaliplatin, highly active antiretroviral therapy (HAA-RT), toxins (vinyl chloride, carbon tetrachloride, yellow phosphorus), various endocrinopathies such as Cushing syndrome and hypopituitarism, polycystic ovary syndrome, hypothyroidism, hypobetalipoproteinemia, obstructive sleep apnea (with chronic intermittent hypoxia), excessive dietary fructose consumption-ion, starvation and refeeding syndrome and total parenteral nutrition. Other liver diseases that can present with steatosis are Hepatitis C, Acute hepatitis D, Wilson disease, Hemochromatosis, Lipodystrophy, Lysosomal acid lipase deficiency.

Most patients are asymptomatic or have mild right upper quadrant discomfort. Hepatomegaly is present in up to 75% of patients, but stigmata of chronic liver disease are uncommon. Signs of portal hypertension of advanced liver fibrosis or cirrhosis can occasionally occur in patients with mild and no fibrosis and severe steatosis. Persistently elevated ALT can be associated with disease progression. Patients with normal ALT levels can also develop progressive disease. Up to 80% of NAFLD patients can have normal ALT. In contrast to alcoholic liver disease, the ratio of ALT to AST is almost always greater than 1, but it decreases to less than 1 as advanced fibrosis and cirrhosis develop. Antinuclear or smooth muscle antibodies and an elevated serum ferritin level may each be detected in one fourth of patients with NASH. Elevated serum ferritin levels may signify so - called dysmetabolic iron overload syndrome and mildly increased body iron stores, which may play a causal role in insulin resistance and oxidative stress in hepatocytes and correlate with advanced fibrosis. Iron deficiency is also common and associated with female sex, obesity, increased waist circumference, diabetes mellitus, and black or Native American race.

Ultrasound examination usually reveals bright liver with increased echotexture vs. kidney, vascular blurring, and macrovascular steatosis. Ultrasound findings for fatty liver cannot be distinguished from those of early cirrhosis. CT or MRI Imaging does not distinguish steatosis from steatohepatitis or detect fibrosis. Changes consistent with NAFLD may not be detected if < 20 – 30% of liver contains fat.

Noninvasive assessment of liver fibrosis to guide treatment and monitor progression requires a risk score for predicting advanced fibrosis, known as **BARD**, based on **B**ody mass index >28, AST/ALT **R**atio ≥ 0.8, and **D**iabetes mellitus; it has a 96% negative predictive value (i.e., a low score reliably excludes advanced fibrosis). Another risk score for advanced fibrosis, the **NAFLD Fibrosis Score** based on age, hyperglycemia, body mass index, platelet count, albumin, and AST/ALT ratio, has a positive predictive value of over 80% and identifies patients at increased risk for liver-related complications and death. A **clinical scoring system** to predict the likelihood of NASH in morbidly obese persons includes six predictive factors: hypertension, type 2 diabetes mellitus, sleep apnea, AST greater than 27 units/L (0.54 mckat/L), ALT greater than 27 units/L (0.54 mckat/L), and non-black race.

Liver biopsy is the gold standard to make the diagnosis of NASH, initiate drug therapy, assess prognosis: liver, cardiovascular, etc, stage fibrosis (if imaging or tests are indeterminate), rule out concomitant liver disease like autoimmune, Wilson disease, Drug Induced Liver Injury (DILI), iron overload (ferritin can be high in NAFLD in absence of iron overload).

Lifestyle modifications in NAFLD are difficult to achieve and sustain, and will not be enough for morbidly obese patients. Limiting total caloric intake is ideal and more important than aiming for a specific nutrient composition. Processed carbohydrates like white / brown bread, rice, white / orange potatoes, flour / corn tortillas, pizza / pasta, chips, and fructose - containing sodas and juices should be limited significantly. Physical inactivity is strongly linked to increased body weight, central adiposity, insulin resistance, increased risk of metabolic syndrome, NAFLD and severity of NASH. Exercise associated with a reduction in hepatic fat even in the absence of weight loss, and small studies had suggested that resistance training reduces hepatic fat, improves other metabolic parameters. Current evidence reinforces utility of aerobic or resistance exercise for improving steatosis.

Still no FDA-approved therapies for NASH are available but there are some therapeutic options with proven efficacy like vitamin E, Pioglitazone, Pentoxifylline and Liraglutide. In case of vitamin E therapy liver enzymes are not reliable to assess quiescence or progression and there is increased risk of hemorrhagic stroke as well.

Gastric bypass may be considered in patients with a body mass index greater than 35 and leads to histologic regression of NASH in most patients. Liver trans-plantation for NASH with advanced cirrhosis may be associated with increased mortality from cardiovascular disease and sepsis compared with liver transplantation for other indications.

Fatty liver often has a benign course and is readily reversible with discontinuation of alcohol or treatment of other underlying conditions; if untreated, fibrosis progresses at an average rate of 1 stage every 14 years, with a subset progressing more rapidly. In patients with NAFLD, the likelihood of NASH is increased by the following factors: obesity, older age, non-African American ethnicity, female sex, diabetes mellitus, hypertension, higher ALT or AST level, higher AST/ ALT ratio, low platelet count, elevated fasting C-peptide level, and a high ultrasound steatosis score. NASH may be associated with hepatic fibrosis in 40% of cases with progression at a rate of 1 stage every 7 years; cirrhosis develops in 9 – 25%; and decompensated cirrhosis-sis occurs in 30 – 50% of cirrhotic patients over 10 years. Course may be more aggressive in diabetic persons than in nondiabetic persons. Mortality is increased in patients with NAFLD, correlates with fibrosis stage, and is more likely to be the result of malignancy and ischemic heart disease than liver disease. Risk factors for mortality are older age, male sex, white race, smoking, higher body mass index, hypertension, diabetes mellitus, and cirrhosis. Steatosis is a cofactor for the progression of fibrosis in patients with other causes of chronic liver disease, such as hepatitis C. Hepatocellular carcinoma is a complication of cirrhosis-sis caused by NASH, as it is for other causes of cirrhosis-sis, and has been reported even in the absence of cirrhosis. NASH accounts for a substantial percentage of cases labeled as cryptogenic cirrhosis and can recur following liver transplantation. Central obesity is an independent risk factor for death from cirrhosis of any cause.

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PREVELANCE AND FACTORS ASSOCIATED WITH NEEDLE STICK INJURIES AMONG HEALTH CARE WORKERS IN A TERTIARY CARE LADY READING HOSPITAL PESHAWAR

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ABSTRACT

Introduction: *Due to repeated handling of needle, health care workers (HCW) are more susceptible to needle prick injuries as compared to general population and thus are more prone to transmission of blood borne pathogen. According to World Health Organization (WHO), 2 million health care workers (HCWs) incur needle stick injuries each year. Various risk factors contribute to needle stick injuries (NST). There are numerous causes of needle prick injuries but the most important are unsafe collection, disposal of sharps objects, two handed recapping needles and extreme workload.*

Aims and Objectives: *The sole aim of our is find out the prevalence and factors associated causing needle stick injuries among HCW presenting to tertiary care hospital of Peshawar.*

Methods: *This descriptive cross sectional survey was carried out in Medical Teaching institution, Government Lady Reading Hospital Peshawar. After approval from ethical committee, 285 HCWs were randomly selected and included in the study. Informed consent was taken from participants enrolled in the study. They were asked about their personal experiences in regard to NSI. A pre-designed questionnaire was used as a source of data collection. SPSS standard version was used to interpret data. For all variable frequencies were calculated which provided numbers and percentages of responses. Then cross tabulation was done to analyze the data. p values of 0.05 was taken as statistically significant.*

Results: *Total no. of HCW included in the study were 285, Amongst them 60% (171) were doctors and 40% (n = 114) were nurses and other paramedical staff (Figure 1). Amongst these participants 64.9% (n = 185) had exposure to NSI. 57.3% (n = 106) were doctors and 42.7% (n = 79) were nurses and other paramedical staff. 48.6% (n = 90) were male and 51.4% (n = 95) were female. Majority (63.2%, n = 117) of them had experience of less than 5 years whereas 9.2% (n = 17) had experience of greater than 15 years. 25.9% (n = 48) of HCWs had single needle prick whereas 43.2% (n = 80) had 3 or more pricks during their working period (Table 1). Multiple factors at a time were responsible for NSI in HCWs' (Table 2).*

Conclusion: *It is concluded from our study that health care workers are at high risk of acquiring blood borne pathogens particularly hepatitis B,C and HIV infections as compared to general population. So strict precautions should be followed to limit the transmission of blood borne diseases through needle stick injuries.*

Key words: *Needle stick injury (NSI), Health care worker (HCW).*

INTRODUCTION

For health care workers (HCW) accidental needle prick injuries (NSI) are a professional risk. These workers are more prone to hospital-acquired transmission of various blood borne infections like hepatitis B, C and HIV, malaria, infectious mononucleosis, diphtheria, herpes, tuberculosis, brucellosis, spotted fever and syphilis as a result of contaminated needle injuries.[1]

WHO Reported in 2002 that among 35 million health-care workers, 2 million suffer needle stick injuries every year. Inspite of high prevalence of needle stick injuries about 40 – 70%, cases are not reported[2]. In the UK reported rate of sharps injuries per year vary between 0.8 and 5 per 100 persons while it is 5.5 per100 persons in US.[3,4] In Pakistan annual incidence rate is very high with 12 – 27 NSI per year per 100 doctors.[5]

Due to needle stick injuries, risk of transmission of

HBV is 6 – 30% while it is 3% and 0.3% for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) respectively among the healthcare workers[6]. Moreover, among health-care workers around the world, the risk of transmission of Hepatitis B, C and HIV/AIDS due to needle stick injuries are 37.6%, 39% and 4.4% respectively.[2,7]

There are numerous causes of needle prick injuries but the most important are unsafe collection, disposal of sharps objects, two handed recapping needles and extreme workload. In Pakistan syringes (72%) are the most injury causing instrument while nurses (67%) followed by residents especially working in the surgical department are more commonly prone to needle stick injuries.[5]

OPERATIONAL DEFINITIONS

Health Care Worker

Health care worker is a health care professional who provides medical services in a systematic way to individuals, families or communities in a health care center in the form of preventive, curative, promotional, or rehabilitative *health care* services.

Needle Stick Injury

Needle stick injuries are damages which are produced by needles that puncture/pierce the skin accidentally.

MATERIALS AND METHOD

This descriptive cross sectional survey was conducted in Medical teaching institution Government Lady Reading Hospital (LRH) Peshawar. After approval from ethical committee, 285 health care professionals workin in LRH Peshawar during study period involved in clinical work were selected randomly and enrolled in the study. Before administration of the questionnaire, informed consent was taken from all participants enrolled in the study. All the participants were enquired about their experiences regarding NSI during their carrier.

Sample Selection

Inclusion Criteria

- Health care workers during study period involved in clinical work irrespective of age and sex after random selection were included.
- Percutaneous injuries of all depths i.e. superficial, moderate and deep were included.
- Amongst sharps, only needle stick injuries i.e. injuries with syringes/needles for IM or IV use or blood sample collection, or by phlebotomist for various purposes, needles for subcutaneous/sub dermal injections or needles used for suturing etc are included in the study.

Exclusion Criteria

- Health care workers exposed to blood or body fluid through all other means e.g., splash were excluded.
- Injuries with sharps other then needle sticks e.g. scalpels, broken glass and other objects contaminated with blood from a source patient were excluded.

Statistical Analysis

A pre-designed questionnaire was used as a source of data collection. The questionnaire consisted of a simple tick box format. The data was analyzed using SPSS version 17. Frequencies were calculated for all variables, which gave the numbers and percentages of responses. The data was then analyzed by using cross tabulation. The significance level is taken as 0.05.

RESULTS

Total no. of HCW included in the study were 285, with 58.9% (n = 168) from the medicine & allied and 41.1% (n = 117) from surgical & allied department. Amongst them 60% (171) were doctors and 40% (n = 114) were nurses and other paramedical staff (Figure 1).

Amongst these participants 64.9% (n = 185) had exposure to NSI. 56.2% (n = 104) of the HCW belonged to medical and allied and 43.8% (n = 81) to surgical and allied department. 57.3% (n = 106) were doctors and 42.7% (n = 79) were nurses and other paramedical staff. 48.6% (n = 90) were male and 51.4% (n = 95) were female. Majority (63.2%, n = 117) of them had experience of less than 5 years whereas 9.2% (n = 17) had experience of greater than 15 years. 25.9% (n = 48) of HCWs had single needle prick whereas 43.2% (n = 80) had 3 or more pricks during their working period. In 66.5% (n = 123) the needle was sterilized and in 33.5% (n = 62) it was used (Table 1).

Multiple factors at a time were responsible for NSI in HCWs. Most of the injuries (66.5%, n = 122) occurred in emergency situation in emergency department due to unexpected body movement (35.1%) of the patients, heavy work load and fatigue (14.6%) and lack of experience (13%). Injuries while suturing or due to improperly disposed sharps by others were responsible in 29.2% and 15.7% of the cases respectively. Other contributing factors include poor lightening at work place (14.6%), handling instruments in OT room (18.9%), removing needle cap (28.6%), recapping needle (41.1%), and bending needle by hand (8.1%). Injuries while inserting IV line occurred in 14.6% (Table 2).

DISCUSSION

HCWs are exposed to numerous occupational hazards such as exposure to various airborne and blood pathogen because of their direct exposure to very sick

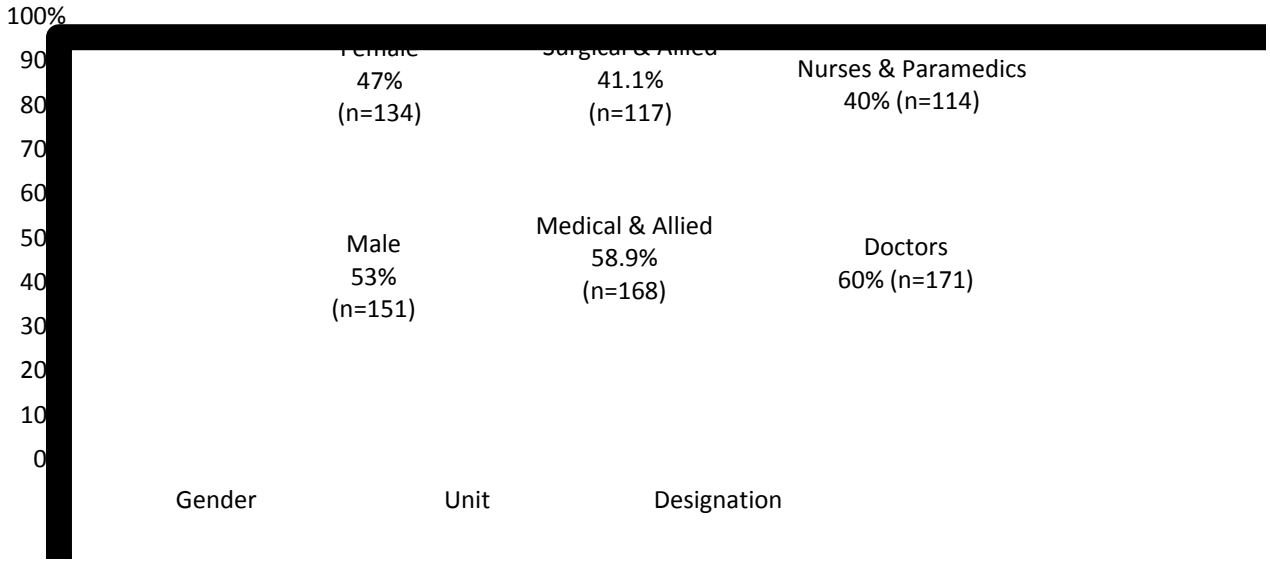

Figure 1:

Table 1: *Characteristics of participants with NSI.*

	No. (%)
Participants with NSI	*N=185 (64.9%)*
Gender Male Female	 N=90 (48.6%) N=95 (51.4%)
Unit Medical & Allied Surgical & Allied	 N=104 (56.2%) N=81 (43.8%)
Experience <5 years 5 – 10 years 11 – 15 years >15 years	 N=117 (63.2%) N=43 (23.2%) N=8 (4%) N=17 (9.2%)
Designation Doctors Nurses & Paramedical staff	 N=106 (57.3%) N=79 (42.7%)
Needle at the time of NSI Sterilized Used but not blood stained Blood stained	 N=123 (66.5%) N=32 (17.3%) N=30 (16.2%)
Number of times of NSI Once Twice Three or more times	 N=48 (25.9%) N=57 (30.8%) N=80 (43.2%)

Table 2: *Prevalence of causative factors:*

	% (no.)
Emergency situation	65.9% (n=122)
Suturing	29.2% (n=54)
Unexpected patient movements	351.% (n=65)
Improper disposable by others	15.7% (n=29)
Heavy work load & fatigue	47% (n=87)
Removing needle cap	28.6% (n=53)
Recapping needle	41.1% (n=76)
Bending needle by hand	8.1% (n=15)
Inserting iv line	14.6% (n=27)
Lack of experience	13% (n=24)
Poor lightening at work place	14.6% (n=27)
Handling instruments in OT	18.9% (n=35)

and dying patients, which, coupled with increasing work-loads, can seriously threaten their health and well-being.

64.9% (n = 185) of the participants had NSI during their working period, which is in comparison (53% & 63%) with various studies conducted in India.[5] A study in Iran conducted on nurses also showed almost similar pattern (63.3%).[5] In Nigeria 41.8% NSI prevalence has been reported.[11] A survey was

conducted on American surgical trainees, it was found that during postgraduate training about 99% respondents had NSI,[9] whereas in other study it was 83%.[9] Moreover another study conducted in South Africa which showed that about 91% of junior doctors have been reported suffering a NSI in the previous 12 months.[8] In a similar study conducted in Karachi, showed 45% of the HCWs had NSI. A study from Rawalpindi conducted on doctors showed comparatively high prevalence (85.1%) of NSI amongst them[5], whereas another study in Rawalpindi conducted on nurses showed prevalence of 67%. Study from Egypt showed prevalence of approximately 64%.[8]

74.1% of the participants had greater than one exposure to NSI and 25.9% had once NSI, whereas a study conducted on nurses in Rawalpindi showed 39% and 11% respectively.[10]66.5% of the participants had injury from sterilized needle and 33.5% from used needle which was blood stained in 16.2% of the cases whereas the rate of injuries from high risk patients is much higher (53%) in other studies.[8]

65.6% of the participants with NSI had experience less than 5 years, whereas participants with >15 year's experience had exposure to NSI of 8.4%. A study from Sindh conducted on needle stick injuries showed that majority of participants (28.5%) who sustained NSI are junior doctors (interns and residents). This is mainly due to the fact that NSI are much more among less experienced HCW as compared to experienced ones.[7] Moreover differences NSI have also been noted regarding gender. There are more chances of NSI (53% Vs 47%) among male than female which is similar to findings in other studies.

HCWs working in medical and allied departments had more needle injuries as compared to HCWs working in surgical and allied department which is how-ever, different from other studies. A study conducted on surgical trainees showed 83% had a needle stick injury during training period.[9] High prevalence (93%) was also noted in American surgeons as compared to our studyfindings.[12] This might be due to the fact that most of the participants were younger with less experience who usually have rotational duties in various departments of the hospital, whereas senior HCWs usually have permanent place of work.

Most of the injuries (66.5%) among the participants occurred in emergency department due to unexpected body movement (35.1%) of the patients which is similar finding to study in Africa (23.9%)[8] however, in contradiction with a study performed in Islamabad which showed NSI prevalence of 9% in ER department.[10]

Heavy work load and fatigue contributed up to 14.6% as a cause of NSI whereas it is reported up to 57% in other study.[8]Lack of experience (13%) is observed more in our study as compared to other study (1.1%)[14] most likely due to immature exposure to clinical work and lack of experience (13%) and inappropriate training program in our set up. In the other part of the world, various studies have been conducted showing that inappropriate training of the HCW resulted in increased risk of NSI so all the health care providers should be given proper training regarding handling sharp objects before joining practical work.

Injuries while suturing was responsible in 29.2%of the cases. Two other studies showed prevalence of 52% and 17.8%.[8,15] Poor lightening at work place (14.6%) which is not a major problem in rest of the world. 18.9% of the injuries occurred while handling instruments in OT room. A study showed 1.1% injuries in operating room,[9] while another study conducted on surgical trainees reported 72% NSI in operating room.[12]

Injuries while removing needle cap (28.6%) and recapping needle (41.1%) is reported more as compared to other studies (4.4% and 7.3% respectively).[8,12] Injuries while inserting iv line occurred in 14.6% as compared to 2.2% in other study.[16]

CONCLUSION

From our study it is concluded that risk of needle stick injuries is significantly higher amongst health care providers than general population. It also identifies the common modifiable factors, which can be easily avoided by awareness of the HCWs and providing them with proper training and education.

RECOMMENDATIONS

Every health care facility should have an infection control program and occupational health department, which educate and bring awareness in HCWs about the hazards of needle stick injuries, report all the cases of NSIs and provide post exposure prophylaxis to the exposed worker.

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EPIDEMIOLOGICAL CHANGES IN HEPATITIS C VIRUS GENOTYPES AND THEIR ROUTES OF TRANSMISSION IN PAKISTAN

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ABSTRACT

Background: *Characterization of Hepatitis C virus (HCV) into its genotypes plays a vital role in therapeutic recommendation, geographic characterization and to determine the sources of transmission of the virus*

Objectives: *The present study was arranged to examine the changing epidemiology of different HCV genotypes and their routes of transmission in Pakistan.*

Methods: *The present retrospective cohort study was conducted at the pathology department of Shalamar hospital Lahore from November 2007 to November 2015. HCV genotyping was performed. Genotyping was done by multiplex PCR using type specific primers.*

Results: *Genotype 3 was found the most common type in HCV RNA positive cases (68.10%) followed by genotype 1, 2, 4, 5 and 6 (14.66%, 5.76%, 2.31%, 0.06%, and 0.02% respectively). 5.06% cases remained unclassified and in 4.04% more than one genotype was detected. In last eight years a gradual increasing trend in HCV genotype 1 & 4 and decreasing trend in genotype 2 & 3 was examined. The most probable routs of HCV transmission were noted in dental surgery, general/gynaecological surgery and barbers (22.28%, 20.14% and 11.16%).*

Conclusions: *Downward trend was observed in the prevalence of HCV genotype 3. On contrary, the prevalence of genotype 1 and 4 was observed to be rising. Transmission of HCV was strongly associated with nonsterile razors, general/ gynaecological or dental surgery.*

Key words: *HCV; genotypes; changing epidemiology; Pakistan.*

INTRODUCTION

Hepatitis C is a communicable liver disease caused by the infection of Hepatitis C virus (HCV) and may lead from a mild illness of a few weeks to the severe long lasting disease. More than 185 million individuals in the world are living with HCV chronic infection and more than 350,000 deaths occurs every year with this disease.[1,2] The highest rate of Hepatitis C in the world is reported from Egypt, Pakistan and China (15%, 4.8% and 3.2%).[1,2]

HCV is an enveloped spherical virus with approximately 9600 nucleotides long positive single stranded RNA genome and belongs to the *Flaviviridae* family.[3-5] HCV genome is highly heterogeneous and the variation of the nucleotide sequence is not consistently distributed across the whole genome, some regions are highly variable and some are conserved.[6,7]

HCV genotypes, subtypes and quasispecies are based on three levels of HCV genomic variations. The classification of Hepatitis C virus into its genotypes is based on the first level of genetic variation where the nucleotide sequence of HCV genome shows more than 30% variability. At the second level each major genotype is subdivided into its subtypes when it exhibits more than 20% variation in its nucleotide sequence within the genotype.[8-11] These genotypes and subtypes play a key role to examine the geographical prevalence of different HCV genotypes, their source of transmission, their relation to the particular risk groups,[12] to predict the response of HCV infected patients to Interferon therapy and to decide the therapy duration and management.[13-15]

The frequency of HCV genotypes and their subtypes varies region to region. In North and South America, Europe, Russia, China, Japan, Australia, New Zealand and India the contribution of HCV subtypes la, lb, 2a, 2c, and 3a is considered more than 90%.[16,17] In Egypt, North Africa, Central Africa, and the Middle East the most frequently reported HCV genotype is 4. Genotype 5 and 6 are commonly found in South Africa and South East Asia respectively.[18,19] According to the

studies reported by different groups from Pakistan, Mostly the population of this country is infected with genotype 3 especially its subtype 3a.[14,20-23]

In previous studies reported from different areas of the Pakistan changing epidemiology of different HCV genotypes in this country is not properly addressed. Additionally, except one study reported by Idrees and Riazudin in 2008 all other studies were based upon the small number of samples and were not able to explain the prevalence of all six HCV genotypes (1 to 6).

The following study was arranged to see the frequency of different HCV genotypes, their changing epidemiology and their probable routs of transmission in Pakistan. The present study was based upon a sufficient number of the samples (4981). The findings of this study may play an important role in epidemiological, pathological and viralogical characterization of the virus. It may also help in effective therapeutic management and future planning to eliminate the virus from our population and in vaccine development.

MATERIALS AND METHODS

Patients: Anti-HCV positive (by ELISA) samples were received at the Pathology department of Shalamar Hospital Lahore for further processing to detect HCV RNA and specific genotype of the virus. The age range of the patients was 2 – 70 years both in males and females, while the mean, median and mode was 36 ± 6, 35.5 and 40 respectively. The patient participated in the present study were from different areas of the province Punjab of Pakistan. All the patient information including age, sex, address, previous HCV infection related investigations, foreign tour history and the history of any family member HCV infection was registered.

Statistical Analysis

To analysis the data SPSS version 11 software was used. The results for all variables were set in the form of rates (%). To evaluate the positive association among the categorical variables Fisher's exact and Chi Square tests were used and $p < 0.05$ was defined as significant.

RESULTS

Hepatitis C virus was genetically classified into its six major genotypes (1 to 6) and nine subtypes (1a, 1b, 2a, 2b, 3a, 3b, 4, 5a and 6a) in 4528 (90.90%) out of 4981 HCV RNA positive samples (Fig. 2). In 5.06% HCV RNA positive samples HCV remained unclassified and were declared as untypable. Mixed genotypes (More than one) were detected in 4.04% samples (Table-1).

Genotype 3 was the most prominent type among the HCV infected patients (68.10%). Second and third common genotypes were 1 and 2 (14.66% and 5.76%), while the percentage of genotype 4 was 2.31%. The percentages of genotype 5 and 6 were very low (0.06% and 0.02%). Among the HCV subtypes, the most common subtype was found 3a (47.80%) followed by 3b, 1a, 1b, 2a, and 2b (20.30%, 9.13%, 5.52%, 4.62% and 1.14%) (Table 1 and Fig. 3).

The changing epidemiology of different HCV genotypes was observed from November 2007 to November 2015. Decreasing trend was examined in genotype 2 and 3 in last five years. Decline was 6.80% to 5.63% in genotype 2 and 72.80% to 63.64% in genotype 3. Major instability was seen in genotype 1 (especially its subtype 1a) and genotype 4 where the trend was significantly on increasing side ($p = 0.001$). Because the presentation of genotype 5 and 6 was rare so to assess their epidemiological change during the said period was difficult. All the results regarding the changing epidemiology of different HCV genotypes are revealed in table 4.

The probable source of HCV transmission was observed in 71.22% HCV infected patients. Out of those 22.28% were due to dentists, 11.16% due to barbers, 20.14% due to general or gynaecological surgery, 11.46% due to infected family members, 4.28% due to blood or blood product transfusion and 1.89% were due to piercing or tattooing. In 28.78% cases the source of HCV transmission was unclear (Table 5).

A total of 19.17% HCV patients infected with different HCV genotypes had foreign tour history out of those 12.83% were males and 6.34% females. With 5.52% males and 3.53% females a total of 451 (9.05%) patients had a Middle East tour history, whereas 504 (10.12%) had Europe or USA tour history (7.31% males and 2.81% females) (Table 6).

Table 1: *Presentation of different HCV genotypes and subtypes.*

Genotypes	Subtypes	Males	Females	Total
1	1a	286 (10.24%)	169 (7.73%)	455 (9.13%)
	1b	187 (6.69%)	88 (4.02%)	275 (5.52%)
2	2a	92 (3.29%)	138 (6.31%)	230 (4.62%)
	2b	34 (1.22%)	23 (1.05%)	57 (1.14%)

3	3a	1396 (49.96%)	985 (45.04)	2381 (47.80%)
	3b	556 (19.90%)	455 (20.80%)	1011 (20.30%)
4	4	82 (2.93%)	33 (1.51%)	115 (2.31%)
5	5a	2 (0.07%)	1 (0.05%)	3 (0.06%)
6	6a	1 (0.04%)	0 (0.00%)	1 (0.02%)
Untypable	Untypable	91 (3.26%)	161 (7.36%)	252 (5.06%)
Mixed	Mixed	67 (2.40%)	134 (6.13%)	201 (4.04%)
Total		2794 (56.09%)	2187 (43.91%)	4981 (100%)

Table-2: *Demonstration of mixed HCV subtypes.*

Mixed Subtypes	Males	Females	Total
3a & 3b	17 (25.37%)	49 (36.57%)	66 (32.84%)
3a & 2a	10 (14.93%)	31 (23.13%)	41 (20.40%)
3a & 2b	7 (10.45%)	13 (9.70%)	20 (9.95%)
3a & 1a	16 (23.88%)	19 (14.18%)	35 (17.41%)
3a & 1b	9 (13.43%)	10 (7.46%)	19 (9.45%)
3a & 4	3 (4.78%)	1 (0.75%)	4 (1.99%)
2a & 1a	3 (4.78%)	3 (2.24%)	6 (2.99%)
2a & 2b	2 (2.99%)	8 (5.97%)	10 (4.98%)
Total	67 (33.33%)	134 (66.67%)	201 (100%)

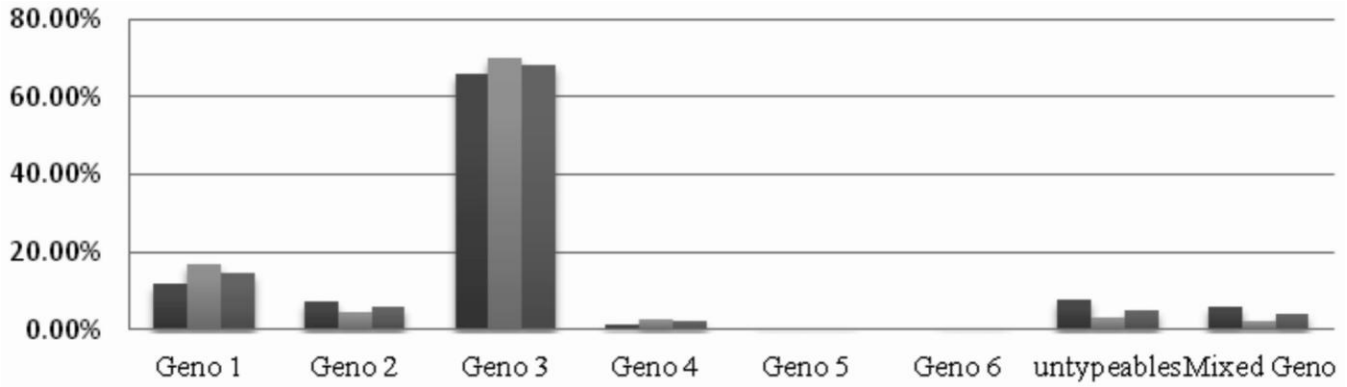

Fig. 3: Presentation of HCV Genotypes in Male and Female Patients.

Table 3: *Presentation of different HCV genotypes reported from different areas of Pakistan.*

Reference	Year	Province	Population Groups	HCV genotype (%)					
				Geno-1	Geno-2	Geno-3	Geno-4	Geno-5	Geno-6
Tong *et al* [25]	1996	Punjab	Patients with CLD, HCC	6.66	-	80	-	-	-

Shah *et al* [22]	1997	Sindh/Karachi	Chronic Hepatitis	6.66	2.23	87	2.22	-	-
Moatter *et al*[21]	2002	Different areas of Pakistan	Patients with HCV	14	-	68	-	-	-
Akhtar and Moatter[26]	2004	Sindh/Karachi	Households of Thalassemic Children	-	-	100	-	-	-
Iqbal *et al*[23]	2007	Punjab(Lahore)	Chronic Hepatitis	4.87	9.32	73.85	2.48	-	-
Idrees and Riazuddin[20]	2008	Different areas of Pakistan	Patients with HCV	11.51	8.41	67.46	1.49	0.18	0.12
Afridi *et al*[27]	2008	Baluchistan	Patients with HCV	7.14	-	60.72	-	-	-
Akhund *et al*[28]	2008	Sindh	Patients with HCV	3.06	-	75.87	-	0.87	-
Husain *et al*[29]	2009	Punjab (Faisalabad)	Patients with HCV	1.09	-	87.10	-	-	-
Ahmad *et al*[30]	2010	Punjab(Lahore)	Patients with HCV	23.61	–	59.09	13.70	-	-
Baig *et al* (44)	2014	Jamshoro/Hyderabad (Sindh)	Patients with HCV	7.50	18.70	72.90	0.9	-	-

Table 4: *Changing epidemiology of different HCV genotypes in last five years (Nov 2007 to Nov 2015).*

Genotypes	**Subtype**	**Nov 2007-Nov 2009 (%)**	**Nov 2009-Nov 2011 (%)**	**Nov 2011-Nov 2013 (%)**	**Nov 2013-Nov 2015 (%)**	**Total (%)**
1	1a	25 (4.47)	59 (5.31)	150 (10.12)	221 (12.08)	455 (9.13)
	1b	21 (3.76)	45 (4.05)	88 (5.94)	121 (6.62)	275 (5.52)
2	2a	31 (5.55)	52 (4.68)	64 (4.32)	83 (4.54)	230 (4.61)
	2b	7 (1.25)	13 (1.17)	17 (1.15)	20 (1.09)	57 (1.14)
3	3a	295 (52.80)	575 (51.8)	685 (46.2)2	826 (45.16)	2381 (47.80)
	3b	112 (20)	258 (23.2)	303 (20.45)	338 (18.48)	1011 (20.30)
4	4	10 (1.79)	22 (1.98)	37 (2.5)	46 (2.52)	115 (2.31)
5	5a	0	1 (0.09)	2 (0.14)	0	3 (0.06)
6	6a	0	1 (0.09)	0	0	1 (0.02)
Untypable	Untypable	35 (6.26)	41 (3.69)	71 (4.79)	105 (5.74)	252 (5.06)
Mixed	Mixed	23 (4.11)	44 (3.96)	65 (4.38)	69 (3.77)	201 (4.04)
Total		559 (100)	1111 (100)	1482 (100)	1829 (100)	4981

Table5: *Possible source of infection of different HCV genotypes (n=4981).*

Major Genotypes	Subtypes	Blood/ Blood Product Transfusion (%)	General/ Gynecological Surgery (%)	Dental Surgery (%)	Barbers (%)	Piercing/ Tattooing (%)	Infected Family Members (%)	Unknown Reasons (%)	Total (%)
1	1a	28 (13.15)	54 (5.38)	59 (5.320	32 (5.76)	19 (20.21)	132 (23.12)	131 (9.13)	455 (9.13)
	1b	31 (14.55)	45 (4.49)	41 (3.69)	20 (3.60)	26 (27.66)	24 (4.203)	88 (6.14)	275 (5.520)
2	2a	10 (4.70)	75 (7.48)	58 (5.23)	10 (1.80)	7 (7.45)	5 (0.876)	65 (4.53)	230 (4.62)
	2b	2 (0.94)	13 (1.30)	11 (0.99)	5 (0.90)	2 (2.13)	3 (0.525)	21 (1.46)	57 (1.14)
3	3a	61 (28.64)	465 (46.40)	543 (48.90)	317 (57.02)	14 (14.89)	321 (56.22)	660 (46.03)	2381 (47.80)
	3b	22 (10.33)	208 (20.70)	287 (25.90)	129 (23.20)	7 (7.45)	66 (11.56)	292 (20.36)	1011 (20.30)
4	4	16 (7.51)	19 (1.89)	22 (1.98)	8 (1.44)	4 (4.26)	3 (0.525)	43 (3.00)	115 (2.31)
5	5a	0	1 (0.10)	2 (0.18)	0	0	0	0	3 (0.06)
6	6a	0	0	0	1 (0.18)	0	0	0	1 (0.02)
Untypable	Untypable	11 (5.16)	46 (4.59)	38 (3.42)	23 (4.14)	9 (9.57)	8 (1.401)	117 (8.16)	252 (5.06)
Mixed	Mixed	32 (15.02)	77 (7.68)	49 (4.41)	11 (1.98)	6 (6.38)	9 (1.576)	17 (1.19)	201 (4.04)
Total		213 (4.28)	1003 (20.14)	1110 (22.28)	556 (11.16)	94 (1.89)	571 (11.46)	1434 (28.78)	4981 (100)

Table 6: *Foreign tour history of Hapatitis C patients infected with different HCV genotypes.*

Genotype	Subtype	Tour to Middle East		Tour to Europe/USA		No Foreign tour (%)	Total
		Male (%)	Female (%)	Male (%)	Female (%)		
1	1a	63 (13.85)	43 (9.45)	89 (19.56)	47 (10.33)	213 (46.81)	455
	1b	51 (18.54)	27 (9.82)	62 (22.55)	37 (13.45)	98 (35.64)	275
2	2a	11 (4.78)	2 (0.87)	12 (5.22)	3 (1.30)	202 (87.83)	230
	2b	3 (5.26)	2 (3.51)	4 (7.02)	2 (3.51)	46 (80.70)	57
3	3a	58 (2.44)	55 (2.31)	132 (5.54)	14 (0.59)	2122 (89.12)	2381
	3b	22 (2.18)	12 (1.19)	16 (1.58)	9 (0.89)	952 (94.16)	1011
4	4	32 (27.83)	9 (7.83)	19 (16.52)	4 (3.48)	51 (44.34)	115
5	5a	1 (33.33)	0	1 (33.33)	0	1 (33.33)	3
6	6a	0	0	1 (100)	0	0	1
Untypable	Untypable	33 (13.09)	11 (4.37)	19 (7.54)	13 (5.16)	176 (69.84)	252

Mixed	Mixed	1 (1.99)	15 (7.46)	9 (4.48)	11 (5.47)	165 (82.09)	201
Total		275 (5.52)	176 (3.53)	364 (7.31)	140 (2.81)	4026 (80.83)	4981

DISCUSSION

Although in this study the most frequent HCV genotype in Pakistani population was found genotype 3 (68.10%) particularly its subtype 3a (47.80%) that was also in accordance with previous studies.[20,30] However in last eight years (2007 to 2015) the prevalence of this type was observed on decreasing side (72.80% to 63.64%). On the other hand, the gradual increase was observed in HCV genotype 1 (1a+1b) i.e. 8.23% to 18.70% (Table 4). The increase in type 1 was examined more than hundred percent which was highly significant (p = 0.001). The same situation was observed in type 4 which increased from 1.79% to 2.52% as demonstrated in table 4, which is in agreement with the previous reports.[20,30] HCV genotype 3 is the most responding type to interferon therapy[31-33] and most of the population of this region is infected with this genotype. Proper management of HCV patients infected with this genotype can be helpful to wipe out the HCV infection of the population of this area as compared to those areas where type 1 and 4 are prominent and are not friendly to Interferon therapy.[31,32]

In 201 (4.04%) HCV infected patient's samples, more than one genotype was found. These mixed genotypes showed the exposure of the HCV infected persons to more than one sources of HCV infection which indicates unawareness of disease in these patients. Untypable cases may be due to the low viral load or new HCV genotype which may not be classified by this method. Untypable HCV cases were also indicated in an earlier study done in Pakistan.[20]

In the present study significant difference (p = 0.005) in males and females was observed regarding the distribution of different HCV genotypes, which was contrasted to the previous study done in this area in which no significant difference was observed.[20] It was interesting to see that in males the ratio of genotype 1 and 4 was higher as compared to females, while the situation was contrasted in genotype 2, where the ratio of this genotype was higher in females. As mentioned before in this part of the study, genotype 1 and 4 are not common genotypes of this region as compared to genotype 2 and 3, which indicates that the source of infection in females may be local while in males foreign source may be possible, because most of the male population of this area visits to foreign countries for business, job and religious purposes as compared to females.

Most of our population visits Saudi Arabia and Iran for religious purposes in which male and female ratio may be same, but a large number, mostly the males visits or stay there especially in Saudi Arabia and UAE for earning purposes, where HCV genotype 1 and 4 is the most common type in the HCV infected population.[34-36] So these countries may be the main source of transmission for genotype1 and 4. The source of genotype 1 may also be Europe and USA, where this type is most common.[37-40] So, future planning to block these probable sources of transmission is the need of the hour. For that, proper screening of those people who return after a long stay in above mentioned countries should be mandatory.

The probable transmission source of HCV infection in this study revealed that most of the people infected with genotype 1 and 4 had a foreign tour history as compared to those people infected with genotype 2 and 3 which provides strength to the above mentioned possibility. It was also important to see that mixed genotypes were more common in females especially in those mostly exposed for surgery purposes. Most of those females had history of more than one gynecological surgeries, which indicates that surgery may be the major source of infection. In single genotype infected population the most common source was suspected barbers and dentists, which was also indicated in previous studies.[41] It shows lack of awareness in our population about HCV transmission sources. It is also important to mention here that only the male population visited the barbers for hair cutting and shaving purpose. So, the data was collected only from the male population not from the females regarding the possible source of HCV infection in this category. Blood trans-fusion and needle source was less common in this study that was contrasted to the previous study.[41] It may be because of proper screening and new needle use awareness, which was a good sign to overcome this infection.

Out of 4981 HCV infected individuals 11.46% had a history of HCV infected family members (Table 5). In this region the joint family system and cousin marriage are very common. Because Hepatitis C disease remained in silent form and infected persons looks healthy which may transfer their infection silently to other family member living with.[42] This can potentially happen through the sharing of razors, toothbrushes, or any sharp instruments that carry HCV infected blood.[43] Therefore, it is important to keep each person's personal use items such as toothbrush and razor in separate areas of the bathroom and each item should be clearly labeled. In this way, the accidental use of the potentially HCV infected household item may be prevented. The proper screening of joint family members should be done to elucidate the infected

member. In 28.78% cases no possible source of HCV transmission was found. In those cases no family member was infected and never visited the barbers for a shave and had no blood transfusion or needle contact history but were infected with HCV. It clearly indicates that there are others, as yet unidentified modes of transmission.

In conclusion a decrease in genotypes 2 and 3 especially subtype 3a and gradual increase in genotypes 1 and 4 in this population was examined. This situation is alarming because genotype 1 and 4 are not so friendly to Interferon therapy as genotype 2 and 3. Therefore, future treatment strategy should be directed towards type 1 and type 4. The probable source of transmission was observed in those cases that had a history of repeated general or dental surgery and visited to barbers. So a proper strategy on the government level to monitor the standard sterilization of surgical instruments in hospitals and awareness campaign for barbers and family members is the need of the hour, which can be helpful in reducing the chances of trans-mission.

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FREQUENCY OF ASYMPTOMATIC SPONTANEOUS BACTERIAL PERITONITIS IN DECOMPENSATED CIRRHOTIC PATIENTS WITH ASCITES

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ABSTRACT

Introduction: *Spontaneous bacterial peritonitis is an infection of ascitic fluid in cirrhotic patients which occurs most commonly due to bacterial translocation from the intestines and inadequate defense mechanisms to counter these bacteria. Most common symptoms are abdominal pain, tenderness, fever, chills however it can be present in asymptomatic patients.*

Objectives: *The objective of the study is to find the frequency of asymptomatic spontaneous bacterial peritonitis in patients of decompensated liver cirrhosis with ascites.*

Study Design: *Cross sectional survey.*

Setting: *Department of Gastroenterology, Medical Unit-III, Services Hospital, Lahore.*

Duration of Study: *Study was carried out over a period of six months from 13-05-2014 to 12-11-2014.*

Subjects and Methods: *A total of 140 cases were included in this study. After taking informed consent ascitic fluid sample was taken and checked for the presence of spontaneous bacterial peritonitis by complete biochemical and cytological examination.*

Results: *Regarding age distribution of patients, 22 patients (15.7%) were 21 – 40 years old, 87 patients (62.15%) were 41-60 years of age while 31 patients (22.15%) were between 61 – 70 years of age. Mean age of the patients was observed 53.27 ± 9 Out of 140 patients, 73 patients (52.1%) were male and remaining 67 patients (47.9%) were female. Frequency of asymptomatic spontaneous bacterial peritonitis was seen in 16 patients (11.4%).*

Conclusion: *It is concluded that frequency of spontaneous bacterial peritonitis is high in asymptomatic patients of decompensated liver cirrhosis with ascites.*

Key Words: *Spontaneous bacterial peritonitis, Translocation, Decompensated liver cirrhosis, Ascites.*

INTRODUCTION

Cirrhosis is a serious and irreversible disease. It usually occurs as an end result of hepatocellular injury that leads to both fibrosis and nodular regeneration. Usual presenting complaints are due to upper gastrointestinal bleed, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular carcinoma and hepatorenal syndrome.[1]

Spontaneous bacterial peritonitis is defined as an infection of previously sterile ascitic fluid, without any apparent intra-abdominal source of infection.[2] Patients with cirrhosis and ascites are more susceptible to bacterial infections, of which spontaneous bacterial peritonitis (SBP) is the most frequent and potentially life threatening.[3] More than 92% of cases of SBP are monomicrobial (aerobic gram negative bacilli being responsible for more than two third of all the cases and Escherichia coli being the most common followed by Klebsiella species).[4]

It develops in 10 – 30% of hospitalized patients.[5-6] Initially mortality rate was high > 90% when it was first described. However, with the early recognition of disease and prompt and appropriate antibiotic treatment, the in-hospital mortality of an episode of SBP has been reduced to approximately 20%.[7]

Clinical manifestations of SBP are often non-specific and include abdominal pain or tenderness, fever, chills, hepatic encephalopathy and alterations in gastrointestinal motility (vomiting, ileus, diarrhea).[8] One third of patients with infected peritoneal fluid lack any overt signs or symptoms such as fever or abdominal pain at the time of initial presentation.[9]

Diagnosis is made by ascitic fluid complete examination (cell count and culture sensitivity) after abdominal paracentesis. A raised total leucocyte count >500 cells/mm^3 or absolute polymorph nuclear (PMN) cell count of >250/mm^3 or culture positive is considered to be diagnostic of SBP.[10]

Cirrhotic patients with spontaneous bacterial peritonitis may be asymptomatic i.e. not having the clinical sign and symptoms of peritonitis like abdominal pain, abdominal discomfort and fever. As spontaneous bacterial peritonitis can be silent so in order to make the diagnosis of SBP; abdominal paracentesis is necessary to prevent the complications like septic shock, hepatorenal syndrome, and hepatic encephalopathy.[11]

There are various studies regarding the frequency of asymptomatic SBP but the results vary. An international study quotes that frequency of asymptomatic SBP is low i.e. 3.5%[8] and 5.4%[12] while local studies in Pakistan quote that it is quite high i.e. 10%[13,14] and 21%.[15] Rationale of this study is that there are discrepancies in the above mentioned studies regarding frequency of asymptomatic spontaneous bacterial peritonitis in Pakistan as well as abroad. So this study was conducted to determine the frequency of asymptomatic SBP in the local population.

OBJECTIVE

The objective of the study is to determine the frequency of asymptomatic SBP in patients of decompensated liver cirrhosis with ascites.

MATERIALS AND METHODS

It was a cross sectional survey, conducted in Medical Unit 3, Services Hospital Lahore over a period of six months from 13-05-2014 to 12-11-2014. Total 140 patients, with 95% confidence level & 5% margin of error and taking expected percentage of frequency of asymptomatic SBP 10%, were included.[8]

Inclusion Criteria:

1. Patients of either gender between the ages of 20-70 years.
2. Patients of decompensated liver cirrhosis with ascites (as per operational definitions).
3. Asymptomatic patients i.e. no history of fever or pain in abdomen.

Exclusion Criteria:

1. Patients who had taken antibiotics in last two weeks.
2. Patients who had the procedure of paracentesis in last two weeks.
3. Patients with upper GI bleed or history of bleed in last two weeks.
4. Patients who will not give the consent.

After informed consent, ascitic fluid sample of 10 ml was taken via paracentesis and checked for the presence of SBP.

Data Analysis

Data was analyzed on SPSS version 19. Age was the quantitative variable and its mean and standard deviation was calculated. Presence or absence of spontaneous bacterial peritonitis and gender were qualitative variable and data regarding it was calculated as frequency and percentage.

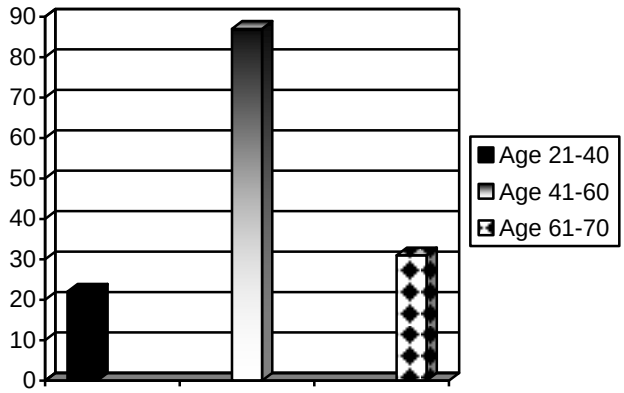
RESULTS

A total of 140 cases were included in current study during the study period of six months from 13-05-2014 to 12-11-2014.

Regarding age distribution of patients, 22 patients (15.7%) were 21 – 40 years old, 87 patients (62.1%) were 41 – 60 years of age while 31 patients (22.1%) were between 61 – 70 years of age. Mean age of the patients was observed 52.14 ± 9.61 (table-2).

Table 1: *Distribution of cases by Age.*

Age (Year)	Number	Percentage
21-40	22	15.7%
41-60	87	62.15%
61-70	31	22.15%
Total	140	100%
Mean ± SD	52.14 ± 9.61	



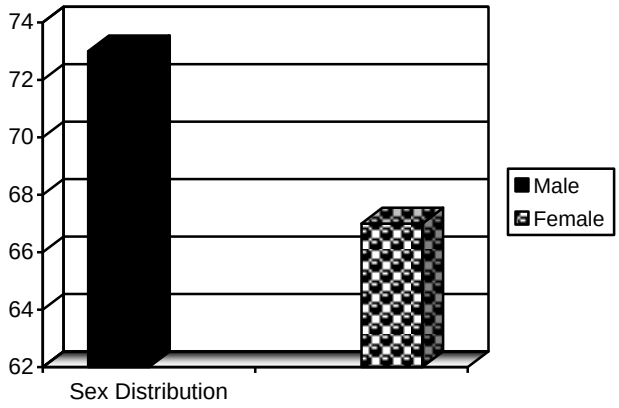
Graph 1: *Distribution of Cases by Age.*

Table 2: *Distribution of Cases by Sex.*

Sex	Number	Percentage
Male	73	52.1%
Female	67	47.9%
Total	140	100%

Out of 140 patients, 73 patients (52.1%) were male and remaining 67 patients (47.8%) were female (table

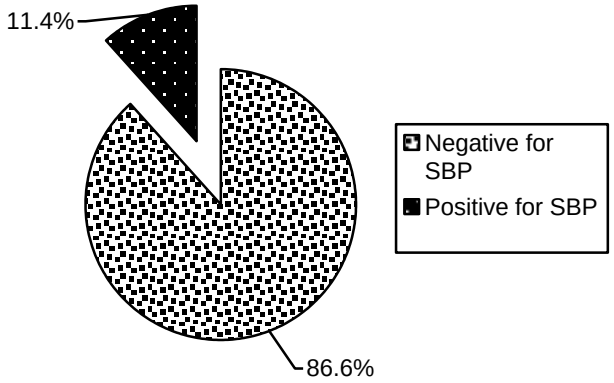
3). Criteria for SBP was positive in 16 patients (11.4%) (table 4).



Graph 2: *Distribution of Cases by Sex.*

Table 4: *Frequency of Asymptomatic SBP.*

Sample Positive for SBP	Number	Percentage
Yes	16	11.4%
No	124	88.6%
Total	140	100.0



Graph 3*: Frequency of Helicobacter Pylori.*

DISCUSSION

Spontaneous bacterial peritonitis (SBP) is a life threatening complication of cirrhosis and results from infection of the ascitic fluid.[3] The decompensated cirrhotic patients who develop ascites, can get this infection by bacterial translocation from the intestine. It develops in 10 – 30% of hospitalized patients.[5-6] Mortality rate is high. However with the early recognition of disease and prompt and appropriate antibiotic treatment, mortality of an episode of SBP can be reduced.[7]

SBP can present with non-specific symptoms like abdominal pain or tenderness, fever, chills, hepatic encephalopathy and alterations in gastrointestinal motility (vomiting, ileus, diarrhea)[8] but about one third of patients with infected peritoneal fluid lack any signs or symptoms such as fever or abdominal pain at the time of initial presentation.[9] As spontaneous bacterial peritonitis can be silent so in order to make the diagnosis of SBP; abdominal paracentesis is necessary even in asymptomatic patients to prevent the complications like septic shock, hepatorenal syndrome, and hepatic encephalopathy.[11] Frequency of asymptomatic SBP in patients of decompensated liver cirrhosis with ascites has been a subject of ongoing debate.

In our study we found the frequency of asymptomatic SBP 11.6%. Similar results were seen in a study conducted in medical units of Khyber Teaching Hospital, Peshawar from July 2008 to Jan 2009. This study showed that the frequency of asymptomatic SBP was 10%.

Another study conducted from India in 2011. H. pylori infection was found in 22 (63%) of 35 patients with MHE.[9]

CONCLUSION

Data from our study has further proven the increased frequency of asymptomatic spontaneous bacterial peritonitis (SBP) in decompensated liver cirrhotic patients. Early diagnosis of SBP and its treatment may prevent serious complications associated with SBP like septic shock, hepatorenal syndrome, and hepatic encephalopathy.[11]

Although testing for SBP in asymptomatic cirrhotic patients with ascites is not in routine, it is important to consider this infection in all asymptomatic cirrhotic patients with ascites in order to improve their quality of life. Further studies are needed to evaluate the arguments in favour of and against the testing for SBP in asymptomatic patients of liver cirrhosis with ascites.

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ORIGINAL ARTICLE

EFFICACY OF RIFAXIMIN IN PREVENTION OF RECURRENT HEPATIC ENCEPHALOPATHY IN LIVER CIRRHOSIS

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ABSTRACT

***Objective**: To determine the efficacy and safety of rifaximin to prevent recurrent episodes of hepatic encephalopathy in patients with liver cirrhosis as compared to lactulose alone.*

***Study Design:** Randomized controlled trial.*

***Place and Duration of Study:** Department of Gastroenterology, Shalamar Hospital, Lahore, from June 2012 to November 2014.*

***Methodology:** We randomly chose 196 Patients who did not have overt hepatic encephalopathy for approximately 4 weeks resulting from cirrhosis of liver to take rifaximin, at a dose of 550 mg twice daily (99 patients), or lactulose only (97 patients). Patients were asked to take the drug orally twice daily for 6 months or until they experience a recurrent episode of hepatic encephalopathy.*

***Results:** Rifaximin markedly decreased the risk of an episode of hepatic encephalopathy, in comparison to lactulose alone, over a six month period. A sudden episode of hepatic encephalopathy was experienced by 19 (19.19%) patients who took Rifaximin, as compared with 49 (50.51%) patients in the lactulose group. A total of 12.6% (8) of the patients in the rifaximin group were hospitalized due to hepatic encephalopathy, as compared with 23.8% (15) patients in the lactulose group. Patients who did not develop hepatic encephalopathy during study period were 79 (79.79%) out of 99 in rifaximin group and 48 (49.48%) out of 97 patients in lactulose group. Most of the patients who developed breakthrough hepatic encephalopathy had MELD score range of 21-25 in both groups. The number of mortalities and morbidities were similar in both groups.*

***Conclusion:** Over a 6 months period, treatment with rifaximin was more effective in maintaining remission from hepatic encephalopathy than lactulose alone. In our study, rifaximin significantly reduced the incidence of hospitalization due to hepatic encephalopathy.*

***Key Words:** Rifaximin, hepatic encephalopathy, cirrhosis.*

INTRODUCTION

Hepatic encephalopathy (HE) a common complication of cirrhosis, has a detrimental effect on health - related quality of life and survival.[1-4] It is the term used to explain the complex and variable changes in neuropsychiatric signs and symptoms that complicate liver disease.[4-6] Recurrent episodes of hepatic encephalopathy are debilitating, require multiple hospitalizations and make the patient incapable of performing activities of daily life.[2,5,8] The increasing number and intensity of such episodes predicts an increased risk of mortality.[1,2,7,8]

The pathogenesis of these events remains unclear.[1,2] Both hepatocellular failure and portosystemic shunting play major role in its development.[1,4,5] Gut related toxins mainly ammonia, escape hepatic detoxification and cross the blood brain barrier, ammonia is then detoxified by astrocytes.[2,7-9] The final result is the development of low-grade cerebral oedema, which eventually effects neuronal function. The goal of treatment has been to lessen the gut-derived ammonia, increased ammonia clearance and control of precipitating factors.[1-3,7-9] Lactulose has been the standard of care while oral antibiotics have been effective only to be related with toxic effects when used on long-term basis.[8-10]

Rifaximin, a synthetic antimicrobial structurally related to rifamycin has broad span of activity against gram-positive, gram-negative and anaerobic enteric bacteria and has a low risk of developing bacterial resistance.[11] systemic absorption is negligible (.4%). It is at least as effective as Lactulose and other non-absorbable antimicrobials, for example neomycin for the treatment of hepatic encephalopathy.[8,9,11]

Rifaximin has a good safety profile, better tolerated than other non-absorbable disaccharides and hence adherence to treatment may be better in longer run. In randomized studies, Rifaximin, used in addition with lactulose was found to be more effective for the prevention of frequent episodes of hepatic encephalopathy. [11,12,17]

The study population in the western world mostly consists of alcohol induced cirrhosis while in our part of the world it is mostly cirrhosis due to viral hepatitis. In addition, the micro flora in the gut in eastern population may be different from that of western population. There is a likelihood of different response to rifaximin in our population compared to the west. If it is found to be efficacious in the local population, it would help decrease the morbidity of the disease.

The aim behind this study was to evaluate the efficiency and safety of Rifaximin in the local population to avoid recurrent episodes of hepatic encephalopathy.

METHODOLOGY

This study took place at the Department of Gastroenterology, Shalamar Hospital Lahore, from June 2012 to November 2014. It was a comparative study. Patients with cirrhosis of any cause, of all ages and both gender and with a history of at least two episodes of hepatic encephalopathy in the last 6 months with a West Haven criteria of grade 0 or 1 and score of 25 or less on the model for end stage liver disease scale presenting to OPD or getting admitted to ward were included in the study. Patients admitted with hepatic encephalopathy (HE), which was precipitated by active spontaneous bacterial peritonitis (SBP), a potassium level of < 2.5 mmol/l, or intercurrent infection, gastrointestinal hemorrhage, constipation and electrolyte imbalance due to diuretic use were selected once these conditions were corrected. It was made sure, however, that this episode leading to admission was at least the second episode of HE with West Haven criteria of ≥ 2 in the past 6 months. Those patients who had known hypersensitivity to rifamycin, a calcium level > 10 mg/dl, hepatocellular carcinoma and co morbidities such as chronic kidney disease, respiratory insufficiency and cerebrovascular injury were excluded. Patients were counseled regarding the study and its implications and an informed consent was taken for participation in the study. History and clinical examination were carried out at the time of patient registration. Previous history of hepatic encephalopathy was assessed clinically with use of West Haven criteria (score 0: no abnormality detected; score 1: trivial lack of awareness, shortened attention span and anxiety; score 2: lethargy, apathy, and disorientation; score 3: somnolence, stupor, confusion: score 4: coma). MELD score was calculated.

Patients up to the mark of inclusion criteria were randomly assigned to either treatment group (Rifaximin 550 mg and Lactulose) or Lactulose only group.

Patients were requested to take the drug orally twice daily for 6 months or until they developed a sudden episode of hepatic encephalopathy or had to withdraw the drug due to some other reason. Breakthrough episode of hepatic encephalopathy was defined as West Haven criteria ≥ 2 precipitated by progression of disease, constipation or electrolyte imbalance. All enrolled patients and their attendants were informed about the possible side effects of Rifaximin and were advised to get in touch with the investigator if any new symptoms developed while on study drug. Patients developing detrimental events including intercurrent infections such as pneumonia, bacterial peritonitis or variceal hemorrhage leading to HE were asked to discontinue the study drug. Concomitant administration of Lactulose was permitted during the study.

After screening and randomization, patients were required to visit Gastroenterology-Hepatology Out-door on day 7 and every 4 weeks thereafter through 168 days. Telephonic monitoring was carried out during the week without visits to outpatients department. Safety assessments were carried out on each visit in particular infection, including infection of respiratory and gastrointestinal tract. Assessment of response to therapy on day 0 and on subsequent visits was done by West Haven criteria. The information was collected through a specifically designed performa.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 20.

RESULTS

A total of 196 patients were randomly chosen to take the study drug. Majority of patients had cirrhosis due to chronic hepatitis C. baseline characteristics were similar. A greater number of patients fell in the age group of 41 – 65 years and gender distribution in both groups was similar. Most of patients had MELD score in the range of 11 – 20 in both groups (table 1).

All enrolled patients received at least one dose of study drug and underwent at least one safety assessment after enrollment. The study medicine was stopped at the time of first sudden episode of hepatic encephalopathy or if the patients developed severe harmful events. All except 9 patients in rifaximin group and 8 patients in the other group were not using diuretics due to absence of ascites. There were however, incidences of self-medication with metronidazole and ciprofloxacin/ levofloxacin for uninvestigated episodes of either diarrhea, abdominal pain or cough productive of sputum by 16 patients in Rifaximin group and 12 patients in Lactulose group. All enrolled patients were adherent to the use of study

drug and the follow-up visits to gastroenterology outdoor except for one patient in each group who was lost to follow-up. Breakthrough episodes were reported in 19 (19.19%) of 99 patients in treatment group and 49 (50.51%) of 97 patients in Lactulose group. The difference turned out to be significant with a p-value of< 0.001 (table III). There is a relative decrease in the risk of a break through episodes by 57% with rifaximin in comparison with lactulose group during the 6-months study periods.

Most common cause of HE in both groups was progression of disease (Table 4). There are 16 patients in both groups, who were investigated for all known precipitating causes of hepatic encephalopathy and none were found. An average rise of MELD score by 9 in Lactulose group and 6 in rifaximin group was noted when these patients presented with PSE during the study. A total of 8 (12.6%) patients in the Rifaximin group were admitted in the hospital involving hepatic encephalopathy as compared with 15 (23.8%) patients in lactulose group. There is a reduction of 48% with rifaximin as compared with lactulose group hepatic encephalopathy, as compared with 15 (23.8%) patients in the risk of hospitalization.

The incidence of harmful events reported during the study was similar in both groups. Study drug was discontinued once severe detrimental events were reported. Most adverse events were either due to progression of disease or complications of cirrhosis and were managed along lines of prescribed standard of care (table 4). The symptoms of nausea/vomiting, generalized weakness, sore throat and fatigue resolved once study drug was discontinued. The patients in treatment group who developed abdominal pain were investigated for SBP and no such evidence was found on ascitic fluid analysis. Abdominal pain resolved on discontinuation of study drug.

One patient in treatment group who died of acute on chronic hepatitis had a baseline bilirubin of 1.9 mg/dl which rose to 15.9 mg/dl and MELD rose from 16 to 34 in Lactulose group, acute on chronic hepatitis was precipitated by hepatitis E. He was asked to discontinue the study medicine and was managed on lines of prescribed standard of care. There were 14 deaths during the study. Seven patients died in Treatment group and 7 in Placebo group. Most of the deaths were related either to progression of disease or secondary to infection (Table 4). All patients had at baseline, apart from hepatic encephalopathy, one or more signs of decompensated cirrhosis i.e. ascites, edema or history of variceal bleed.

Table 1: *Basic Demographics.*

	Lactulose Group (n = 97)	**Rifaximin Group (n = 99)**
Age in years		
<50	60	66
≥50	37	33
Mean ± SD	44.45 ±3.43	43.97 ± 3.54
Gender		
Male	47 (48.45%)	46 (46.46%)
Female	50 (51.54%)	53 (53.53%)
Range of MELD score		
0 - 10	8 (8.24%)	9 (9.09%)
11 - 20	51 (52.57%)	49 (49%)
21 - 25	38 (39.17%)	41 (41.41%)
Mean ± SD	17.74 ± 2.98	15.45 ± 3.45
Number of episodes of encephalopathy in the past		
2 episodes	45 (46.39%)	51 (51.51%)
> 2 episodes	52 (53.60%)	48 (48.48%)
Etiology of cirrhosis		
Hepatitis C	88 (90.72%)	87 (87.87%)
Hepatitis B	6 (6.18%)	5 (5.05%)
Ethanol	2 (2.06%)	3 (3.03%)
Other	1 (1.03%)	2 (2.02%)

MELD = Model for End Stage Liver Disease

Table 2: *Subgroup analysis of patients free of PSE during trial.*

	Lactulose Group 48 (49.48%)	Rifaximin Group 79 (79.79%)	p-value
Age (in years)			
< 50	36 (75%)	58 (73.41%)	0.833
≥ 50	11 (25%)	21 (26.5%)	
GENDER			
Male	22 (45.83%)	37 (46.83%)	0.913
Female	26 (54.17%)	42 (53.16%)	
Range of MELD score			
0 – 10	6 (12.5%)	6 (7.59%)	0.633
11 – 20	37 (77.08%)	63 (79.74%)	
21 – 25	5 (10.41%)	10 (12.65%)	
Number of episodes of encephalopathy in the past			0.275
2	21 (43.75%)	43 (54.43%)	
> 2	27 (56.25%)	36 (45.56%)	

Table 3: *Subgroup analysis of patients with breakthrough PSE.*

Total	Control Group 49 (50.51%)	Treatment Group 19 (19.19%)	p-value < 0.001
Age (in years)			
	49	19	0.418
< 50	25 (51.02%)	07 (36.84%)	Insignificant
≥ 50	24 (48.97%)	12 (63.15%)	
Gender			
Male	21 (42.85%)	11 (57.85%)	0.270
Female	28 (57.14%)	07 (42.10%)	Insignificant
Range of MELD score			
0 – 10	1 (2.04%)	0	0.290
11 – 20	16 (32.65%)	3 (15.78%)	Insignificant
21 – 25	32 (65.30%)	16 (84.21%)	
Number of episodes of encephalopathy in the past			0.118
2	9 (18.38%)	07 (36.84%)	Insignificant
> 2	41 (83.67%)	12 (63.15%)	

Table 4: *Cause of PSE and adverse events and deaths.*

Causes of PSE	Control Group	Treatments Group
Constipation	11	8
Sepsis due to pneumonia	3	2
Hypokalemia due to overdiuresis	11	7
Progression of disease	21	15
SBP	8	6
SBP + HRS	3	3 (5.88%)
Variceal bleed	9	4

Acute on chronic hepatitis	6	3
Adverse events / deaths	-	-
Death due to persistent PSE	2 (18.18%)	1 (7.69%)
Death due to HRS	2 (18.18%)	2 (15.38%)
Death due to acute on chronic hepatitis	-	1 (7.69%)
Death due to pneumonia	1(9.09%)	1 (7.69%)
Death due to cellulitis	1(9.09%)	-
Death due to variceal bleed	1(9.09%)	2 (15.83%)
Abdominal pain	-	1 (7.69%)
Nausea and vomiting	2 (18.18%)	3 (23.08%)
Sore throat / fatigue	1(9.09%)	-
Gen. weakness	-	1 (7.69%)
Missing data	1(9.09%)	1 (7.69%)
Self – medication with other antibiotics	10/63 (15.8%)	4/63 (6.3%)

SBP = Spontaneous Bacterial Peritonitis; HRS = Hepato Renal Syndrome; PSE = Portosystemic encephalopathy.

DISCUSSION

To prevent hepatic encephalopathy is an important aim in the treatment of patients with liver ailment,[1,2,4,6,7] especially since symptoms of overt encephalopathy are associated with great morbidity and noncompliance to a therapeutic regimen, which in turn leads to repeated hospitalizations, and a poor quality of life.[1-4,12,14,15,18] Our study showed that rifaximin reduced the risk of a sudden episode of hepatic encephalopathy during the time period of 6-month among patients in remission who had a recent history of frequent overt hepatic encephalopathy (≥ 2 episodes within the previous 6 months) before enrollment. Our study shows the superiority of rifaximin treatment over lactulose therapy alone. More than 90% of patients also received concomitant lactulose during the study period, and a significant treatment effect was noted within 28 days after randomization. In contrast, a recent local study of 126 patients showed that rifaximin treatment has no role in the avoidance of frequent hepatic encephalopathy.[17]

In our study, rifaximin therapy decreased the risk of hospitalization secondary to hepatic encephalopathy, depicting the clinical significance of our efficacy findings. Also, the reduced risk of hospitalization means lower hospital costs.[26,27,28,30]

The incidences of adverse events were same in the rifaximin group and the lactulose group. The safety profile of rifaximin appears to be superior to that of systemic antibiotics, particularly for patients with liver ailment.[29,30] The nephrotoxicity and ototoxicity associated with the use of aminoglycosides (e.g., neomycin and paromomycins), nausea and peripheral neuropathy with prolonged use of metronidazole minimizes their use in patients with advanced hepatocellular disease.[19,21,and22]

The risk of bacterial resistance appears to be lower with rifaximin than with systemic antibiotics because plasma levels of rifaximin are miminal.[23,24,and25] In addition, whereas resistance to other antimicrobial agents is plasmid-mediated, resistance to rifaximin is carried out through reversible genomic change. Both in vitro and in vivo studies of the effects of rifaximin on commensal flora describes that Rifaximin resistant organisms have low viability.[19,21,30].

In summary, this study shows a significant protective effect of rifaximin against episodes of hepatic encephalopathy. Rifaximin also decreases the risk of hospitalization involving hepatic encephalopathy.

CONCLUSION

Over a 6-month period, treatment with Rifaximin maintained remission from hepatic encephalopathy more efficiently than did lactulose. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy.

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ORIGINAL ARTICLE

EFFICACY OF SINGLE SESSION OF HISTOACRYL INJECTION IN ACHIEVING HEMOSTASIS IN PATIENTS PRESENTED WITH ACUTE UPPER GASTROINTESTINAL BLEEDING SECONDARY TO GASTRIC VARICES

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ABSTRACT

Background: *Gastric variceal bleed is one of the most dreadful emergency carrying high mortality without intervention. Gastric varices are difficult to diagnose and their treatment can be challenging due to their location and complex structure. Histoacryl injection is one of the entity for arresting gastric variceal bleed. In this study we retrospectively analyzed, the effectiveness of single session of Histoacryl injection in achievement of hemostasis in patients presenting with upper gastrointestinal bleeding secondary to gastric fundal varices.*

Objective: *The aim of our study is to assess the efficacy and long term outcome of single session of cyanoacrylate injection in patients who had gastric variceal bleeding.*

Methods: *It is a retrospective cohort study. The medical records of patients who presented with active gastric variceal bleeding between 01/01/2011 and 31/12/2015 in a tertiary care setting were evaluated retrospectively and the eventual outcome(s) (initial hemostasis, rebleeding, and mortality rate) was assessed at least 1 year after the index bleed. Non probability consecutive sampling was used.*

Results: *A total 70 patients were enrolled in our study of whom mean ages were 41 years, 64% were male. The most common cause of gastric variceal bleed was liver cirrhosis constituting about 63% of the total numbers of patients. It has been found that single session of cyanoacrylate injection is successful in achieving hemostasis (91%). One patient (1.42%) died while admitted. Rebleeding was seen in five patients (7%) when followed for one year. these patients were then successfully treated with repeated injection of cyanoacrylate.*

Conclusion: *it has been concluded from our study that a single session of cyanoacrylate injection is successful in achieving and maintaining hemostasis in majority of the patients admitted with gastric variceal bleed.*

Key Words: *Histoacryl, Gastric varices, upper gastrointestinal bleeding, endoscopy.*

INTRODUCTION

Throughout the world one of the main causes of admission to hospital is acute upper gastrointestinal bleed, its incidence is reported as 50 – 150 episodes per 100,000 individuals per year. Mortality rate associated with acute upper gastrointestinal bleeding is 10–14%.[1] It should be remembered that variceal bleed is one of the life threatening complications of portal hypertension causing about one third deaths in cirrhotic patients.[2] Gastric variceal bleed is usually less common than esophageal variceal bleed and is associated with a greater management challenge, with higher reported transfusion requirements, rates of rebleeding and mortality.[2] An international study reported that there are numerous causes of upper gastrointestinal bleed but the most common causes are esophageal varices 57.7%, peptic ulcer disease 18.2%, portal hypertensive gastropathy 9.5%, gastric varices 5.1%, Mallory - Weiss tear 2.9%, reflux esophagitis 2.9% and erosive gastropathy 1.5%.[3] Recent studies conducted in Pakistan reported gastric fundal varices as cause of upper gastrointestinal bleeding in 3.1% of general population[4] and gastric varices accounted for upper gastrointestinal bleeding in 12.3% in cirrhotic patients. There are various options of treating gastric fundal varices which include both surgical and radiological interventions carry significant risk of mortality and morbidity.[5] In 1986 Sohendra et al first reported that bleeding from gastric fundal varices could be controlled by injecting cyanoacrylate in the respective varices, however, after that many authors have used various agents including N-butyl-2

cyanoacrylate, 2-octyl cyanoacrylate, ethanolamine oleate injection, thrombin, gastric variceal banding, and sodium tetradecyl sulfate to achieve hemostasis in bleeding from gastric fundal varices.[6] The main objective of our study is to share our experience regarding efficacy of cyanoacrylate injection into gastric fundal varices in achieving hemostasis in patient presenting in gastroenterology department LRH, Peshawar. The knowledge of efficacy of N-butyl-cyanoacrylate in local population will enable us to administer the best possible treatment modality for this fatal emergency.

MATERIALS AND METHODS

A total of 70 patients were enrolled in our study using WHO software for sample size distribution (95% confidence interval and 5% margin of error). The patients for study were included from Gastroenterology and Hepatology department unit MTI-LRH being admitted with upper GI bleed. Moreover informed consent was taken from every patient included in this study. Patients, in whom the cause of upper GI bleed is other than gastric varices that is peptic ulcer disease, esophageal varices etc, were excluded from study. After cyanoacrylate injection successful homeostasis were defined using BAVENO V guidelines as an absence of upper GI bleed for 1st 120 hours (5 days) after injecting cyanoacrylate into gastric fundal varices. Any bleeding after 120 hours (5 days) of cyanoacrylate injection is defined as rebleeding. Similarly unsuccessful hemostasis was also defined using BAVENO V guidelines as death or the need to change treatment due to hematemesis or aspiration (if NG is in situ) of equal to or more than 100 ml fresh blood 2 hours after the therapy either drug or endoscopic or development of shock (hypovolemic) or a drop in hemoglobin by 3 g within any 24 hours period in the absence of transfusions. Senior consultant gastroenterologists with experience of 200 esophagogastroduodenoscopies performed the procedure on all patients using standard forward viewing video scope (Pentax EG 2910). After mixing lipiodol with N-butyl cyanoacrylate in a ratio of 1:1 it was then injected into gastric fundal varices. The volume used was 0.5 to 4 ml.

RESULTS

Patients included in study were having age ranging from 15 to 70 years with mean age of 41 years and male to female patients 45 and 25 respectively. Seventy patients included in the study, sixty four (91%) patients had successful achievement of homeostasis with single session of Histoacryl injection. Five patients (7%) had rebleeding who were managed by repeated sessions while one (1.42%) patient died during hospital stay.

DISCUSSION

The source of upper GI bleed in Patients with portal hypertension is mostly either esophageal or gastric varices, the later accounts for about 20% but only few bleed.[1-3] Unfortunately gastric variceal bleed is catastrophic and mostly causing heavy upper GI bleed[7] and therefore requires great amounts of blood transfusion. It has been found that single session of cyanoacrylate injections is effective in treating gastric varices related upper GI bleed. The percentage of successfully treated patients was significant when compared to the national and international studies. In Karachi, a recent study was carried out to assess the efficacy of single session of cyanoacrylate in gastric varices in 97 patients it was found that eighty three patients were managed successfully in controlling bleeding. Rebleeding was observed in twenty four patients while seven patients died during the hospital stay.[8]In a study conducted in China, Wu Q et al found that, out of eleven enrolled patients, a single session of Histoacryl was sufficient in eliminating gastric varices in ten patients. No major complication was seen during or after the procedure.[9] Seewald S, a retrospective study, in Germany reported that 100% (131) of the patients achieved initial homeostasis and gastric variceal obliteration with single session of Histoacryl and not a single patient developed any complication during the procedure.[10] Although N-butyl-cyanoacrylate is not used in USA as it is not yet FDA approved, it is administered in Canada, North America , Germany and Japan and they have reported excellent short and long term efficacy rates.[2] Similarly Updated guidelines have also recognized that N-butyl-cyanoacrylate is considered to be the most effective and 1st line treatment to control gastric variceal bleed.[8] Upon the basis of our study and the results, when compared to the other national and international studies, show excellent response of N-butyl cyanoacrylate in gastric variceal bleeding control.

CONCLUSIONS

From our study it is concluded that single session of cyanoacrylate is considered to be the most effective treatment in controlling gastric fundal variceal bleed.

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ORIGINAL ARTICLE

FREQUENCY OF CULTURE-NEGATIVE NEUTROCYTIC ASCITES IN CHRONIC LIVER DISEASE PATENTS PRESENTING TO TERTIARY CARE HOSPITAL, PESHAWAR, PAKISTAN

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ABSTRACT

There is increased morbidity and mortality in cirrhotic patient having ascitic fluid infection. There are two types of ascitic fluid infection i.e. spontaneous bacterial peritonitis (SBP) and culture negative neutrocytic ascites (CNNA). By definition, in Culture-negative neutrocytic ascites (CNNA) polymorphonuclear cells count is more than or equal to 250/mm3 with negative results of ascitic fluid culture and absence of any intra-abdominal source of infection. Secondary causes like pancreatitis, peritoneal carcinomatosis, tuberculous peritonitis etc should be excluded. CNNA is a type of ascitic fluid infection which was first described in 1984. It has been shown that SBP has same prognostic, clinical and therapeutic characteristics. However it has been shown that CNNA has lower mortality as compared to spontaneous bacterial peritonitis. Third generation cephalosporin is considered to be the most effective drug in treating SBP. The following criteria is used for the diagnosis of CNNA (1) neutrophil count more than 250/mm3 (2) culture negative ascetic fluid (3) lack of any intra-abdominal infection (4) no antibiotic received in the last one month (5) no clinical evidence of pancreatitis. Due to increased mortality it is suggested to treat CNNA with antibiotic as early as possible. A descriptive cross sectional study was conducted on CLD patients admitted with ascites in Lady Reading Hospital, Medical Teaching Institutions, Department of Gastroenterology, from 1st September 2011 to 31st August 2016. The aim of our study is to determine the frequency of CNNA in patient of chronic liver disease presenting to tertiary care hospital. The cause of cirrhosis in most case was hepatitis C followed by hepatitis B etc. Most patients were in Child-Pugh Class C stage. Sampling was done by non probability consecutive sampling technique. A total two hundred patients were enrolled in this study among which 120 were male and 80 female. Culture negative neutrocytic ascites was found in 118 (59%) patients. In the prevalence of CNNA, no considerable difference was found regarding age, sex and duration of CLD.

Conclusion: *It is concluded that 59% (118 out of 200) of the patients with chronic liver disease and ascites presenting to tertiary care hospital have culture negative neutrocytic ascites.*

Keywords: *Culture-Negative Neutrocytic Ascites, Chronic Liver Disease, portal hypertension.*

INTRODUCTION

Chronic liver disease progresses to cirrhosis of liver characterized by fibrosis, scarring and nodule formation. SBP is considered to be the foremost complication in cirrhotic patient.[1] Patients with cirrhosis are at high risk of developing many complications and have decreased survival.[2] Among the patients with CLD, the major complications include ascites, portosystemic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, coagulopathy, SBP, hepatocellular carcinoma etc which are due to either portal hypertension, abnormal synthetic functions or both.[3] Among the major complications of cirrhosis, ascites seems to be the most frequent one, along with hepatic encephalopathy and the hemorrhage caused by the rupture of the esophageal varices.[4] In patients with cirrhosis, the complication most frequently develops is ascites along with portosystemic encephalopathy and variceal bleed. These patients are increasingly susceptible to develop infections primarily due to poor defense mechanisms. The most common and serious complication is SBP followed by UTI, lower respiratory tract infections etc. There is still controversy in clinical importance and prognosis of CNNA in patient with cirrhosis. There should be Low threshold for SBP to be investigated and treatment should be instituted as early as possible without waiting for culture and sensitivity report but it is essential to take ascitic fluid for routine examination and culture and sensitivity testing in all cirrhotic patients with clinical impression

of spontaneous bacterial peritonitis before commencing treatment because of evolving resistance due to injudicious use of antibiotics, *E. coli* and *Klebsiella* are the most common organism being reported to be implicated-ted in causation of SBP and treatment should be directed against these organisms, however, after culture and sensitivity report, treatment must be tailored accordingly.

SBP was described in 1970, since that time SBP related mortality has significantly declined from 80% to 30% this is mainly due early diagnosis and immediate treatment.[5] SBP is the infection of the ascitic fluid that occurs in the absence of a visceral perforation and in the absence of an intra abdominal inflammatory focus such as abscess, acute pancreatitis or cholecystitis. In patients with SBP it is of utmost importance to have one germ being isolated on C/S testing if positive.[6-8] However polymicrobial infections on C/S testing would raise the suspicion of secondary peritonitis.[9] CNNA is another type of ascitic fluid infection in which C/S test is negative but rest of the diagnostic criteria is same as for SBP and other causes of neutrocytic ascites (pancreatitis, peritonitis, tuberculosis and peritoneal carcinomatosis) must be excluded.[10]

METHODOLOGY

After approval from ethical committee of Medical Teaching Institution, Lady Reading Hospital Peshawar, 200 patients meeting inclusion criteria admitted at Gastroenterology and Hepatology unit MTI Lady Reading Hospital were included Patients admitted with clinical presentation of ascitic fluid infection and also those patients with asymptomatic infection were also included in the study. Data regarding patient age, sex, clinical presentation, complications as well as laboratory findings were collected and Child-Pugh Class was calculated. 200 patients with ascitic fluid infections fulfilling the criteria of SBP or CNNA were enrolled while patients who had non cirrhotic causes of ascites, secondary peritonitis / tuberculous peritonitis or malignancy or those who had received antibiotic within one month were excluded from the study. Diagnostic tap was done by sterile method on bed side using 20cc disposable syringe and the specimen was then put in EDTA tube and analyzed within 3 hours. The specimen was then centrifuged for 3 minutes in laboratory for total and differential count, total proteins. Gram staining and C/S testing of 10 ml ascitic fluid were also performed using aerobic and anaerobic culture bottles containing trypticase soy broth and then processed. At the same time blood was also taken in aerobic and anaerobic culture bottles for C/S testing before commencing antibiotics.

Statistical Analysis

Statistical analysis was done with the help of SPSS (standard version) program. For clinical features, a descriptive analysis was performed and results were presented as mean/standard deviation and percentages for quantitative and qualitative variables respectively. Moreover Chi square and t tests were used to find out the difference between qualitative and continuous data respectively. p - values of < 0.05 were considered to be statistically significant.

RESULTS

Mean age of the patients was 45.0 ± 25.0 years. There were 120 (60%) males and 80 (40%) females. Mean duration of CLD was 8.43 ±1.37 months. Dominant part of the patients 114 (57%) had > 8 months of duration of CLD. Culture negative neutrocytic ascites was found in 118 (59%) patients. Comparison was done to see the effect of age, gender and duration of CLD on the outcome. Chi-square test was applied. Results were shown in below tables.

Table 1: *Age of the Patients n = 200.*

Mean ± SD	Minimum	Maximum
45 ± 25	20	70

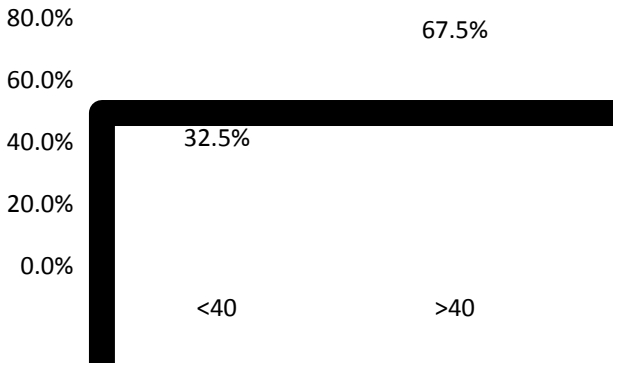

Figure 1: *Age Group (in Years).*

Table 2: *Duration of CLD (in Months) n = 200.*

Mean ± SD	Minimum	Maximum
8.43 ± 1.37	6	11

DISCUSSION

Patient with cirrhosis are at increased risk of many complications and have a decreased life expectancy. One of the main complications of cirrhosis with ascites is SBP and its prevalence is 6-30%.[11-12]

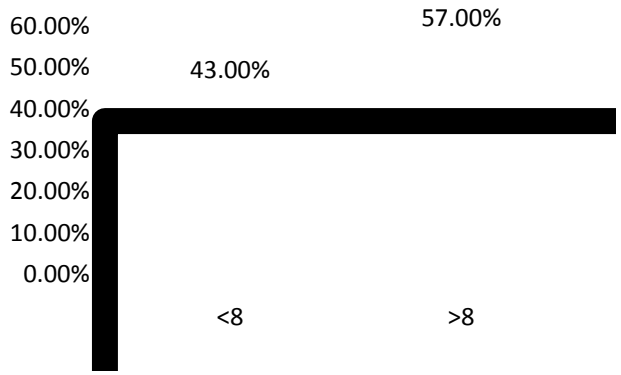

Figure 2: *Duration of CLD (in Months).*

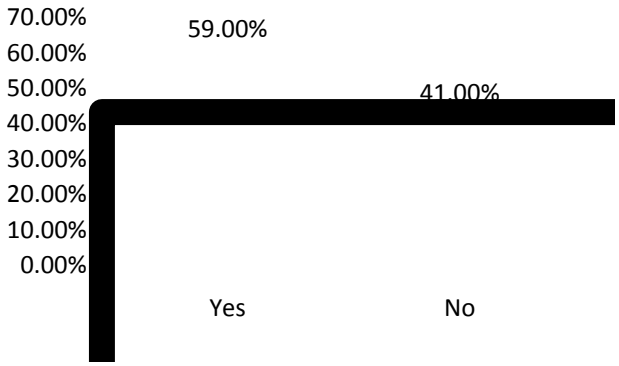

Figure 3: *Culture Negative Neutrocytic Ascites.*

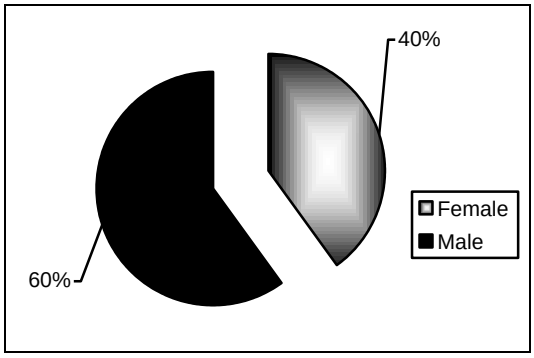

Figure 4: *Gender Distribution.*

Table 3: *Comparison of Culture Negative Neutrocytic Ascites & Age n = 200.*

Age (Years)	Culture-Negative Neutrocytic Ascites		Total	P-Value
	Yes	No		
≤ 40	38 (32.92%)	27 (32.92%)	65 (32.5%)	0.984
> 40	80 (67.80%)	55 (67.07)	135 (67.5%)	
Total	118 (100%)	82 (100%)	200 (100%)	

Table 4: *Comparison of Culture Negative Neutrocytic Ascites & Gender distribution n = 200.*

Duration of CLD (in Months)	Culture-Negative Neutrocytic Ascites		Total	P-Value
	Yes	No		
Male	70 (59.32%)	50 (60.97%)	120 (60%)	0.721
Female	48 (40.68%)	32 (39.02)	80 (40%)	
Total	118 (100%)	82 (100%)	200 (100%)	

Table 5: *Culture-Negative Neutrocytic Ascites and Duration of CLD (in Months) n = 200.*

Duration of CLD (in Months)	Culture-Negative Neutrocytic Ascites		Total	P-Value
	Yes	No		
< 8	47 (39.83%)	39 (47.56%)	86 (43%)	0.873
> 8	71 (60.17%)	43 (52.44)	114 (57%)	
Total	118 (100%)	82 (100%)	200 (100%)	

In our study, culture negative neutrocytic ascites was found in 118 (59%) patients. In another study, among the cultured samples of presumed SBP, 123 (66.2%) presented negative cultures and 63 (33.8%) had positive results.[13]

In a local study on CLD patients the classical SBP was present in 50 (39.06%), Bacterascites in 6 (4.68%) and Culture Negative Neutrocytic Ascites (CNNA) in 72 (56.25%).[14] In another local study 22 patients were found to have SBP among which 11 were culture negative and the remaining were culture positive.[15]

Among fifty patients, 28 (56%) were found to have SBP or its type, however classic SBP was found only in 11 (39.28%) patients, CNNA was present in 16 (57.14%) patients, one patient (3.57%) had bacteracites.[16] In patients with cirrhosis SBP pathogenesis is thought to be the major consequence of bacteria translocation (BT). In bacterial translocation bacteria or their products enter into intestinal lumen and then pass in mesenteric lymph nodes or extra-intestinal area leading inflammatory reaction and ultimately infection. Moreover BT is also to be implicated in aggravating hemostasis disorders and hyperdynamic state. Proposed mechanisms being involved in BT in cirrhotic patients are structural and functional alterations in mucosal barriers, the deficiencies of local

immune response and intestinal bacterial overgrowth. Intestinal bacterial overgrowth is considered to be the main factors involved in BT. There are some other factors which seem to be causing decreased intestinal motility, sympathoadrenal stimulation, increased NO formation and the oxidative stress. Remember, normally there is significantly reduced microbial activity in small intestinal as compared to that of colon however this is reversed in cirrhotic patients.[17]

The clinical presentation of SBP is extremely variable, mostly present with fever pain abdomen and altered GI motility, others may have hepatic encephalopathy or renal failure, patients with SBP may be even asymptomatic so it is strongly recommended to perform diagnostic ascitic tap in all cirrhotic patients with ascites which has significantly reduced the episode of SBP.[2]

A similar prevalence of SBP (22%) in admitted patients had been reported by Amarapurkar DN et al.[33,34] However the prevalence of SBP depends upon the extent of liver disease, it is considered to be higher in severe liver disease. The prevalence of SBP was 34.92% among 63 patient (of Child-Pugh Class C) reported by Jain et al. out of 63 patients. All patients who had SBP were in child class C.[18] Out of 70 patients, 21 had SBP or its type and about 77% had Child-Pugh Class C reported by AS et al.[18-19] In patients with de-compensated liver disease, triggering factor like SBP can lead to death. It is worth mentioning that physicians should have high index of suspicion and low threshold for diagnosis of SBP.[18,20]

RECOMMENDATIONS

From our study it is concluded that Majority of the CLD patients presenting to tertiary care hospital have culture negative neutrocytic ascites so patient fulfilling the criteria of spontaneous bacterial peritonitis should be treated empirically without waiting for culture and sensitivity report. Cefotaxime is still drug of choice to treat SBP.

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