Original Research Article

Study of etiology, clinical profile and predictive factors of spontaneous bacterial peritonitis in cirrhosis of liver

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ABSTRACT

Background: Spontaneous bacterial peritonitis (SBP) is one of the potentially lethal complication of liver cirrhosis and is defined as infected ascites in the absence of any recognizable secondary cause of infection. Majority of the SBP cases are caused by organism from the gastrointestinal tract mainly aerobic gram-negative organisms- Escherichia coli being the most common etiological agent.

Methods: It was a prospective observational study done over a period of 1 year in a tertiary care hospital. 50 patients from medical and gastroenterology wards were included in the study. Patients above 12 year of age with diagnosed cirrhosis of liver and documented evidence of SBP were included. Pregnant females, patients who refused to give consent, patients with a documented evidence of intra-abdominal source of infection or patients with ascitis due to non-hepatic causes were excluded.

Results: The high serum bilirubin and creatinine levels were associated with higher mortality rate. Hepatic encephalopathy is associated with worse outcome. The outcome of the patient in relation to the grades of ascitis, liver enzymes, prothrombin time, international normalised ratio (INR), Child pugh grades, ascitic fluid polymorphism nuclear leucocyte count, ascitic fluid culture and blood culture were not statistically significant.

Conclusions: A high index of suspicion should exist for SBP in patients with cirrhosis and ascitis. Serum creatinine and bilirubin levels are strong predictors of mortality. Hepatic encephalopathy has a strong association with mortality in patients with spontaneous bacterial peritonitis.

Keywords: Liver cirrhosis, SBP

INTRODUCTION

Cirrhosis was named by Laennec in 1826 means orange or tawny in Greek.3 Spontaneous bacterial peritonitis (SBP) is a very common bacterial infection in patients with liver cirrhosis (LC) and ascites which requires prompt recognition and treatment. The earliest description of SBP was in 1907-1908. It was first described by Conn and Fessell, as a syndrome of infected ascitic fluid in patients with hepatic cirrhosis.2 The infecting organisms are usually those found among the normal intestinal flora. When first described, its mortality exceeded 90% but it has been reduced to approximately 20% with early diagnosis and treatment.3,8 All the patients with cirrhosis and ascites are at risk of SBP. The prevalence of SBP varies in out-patients it is 1.5-3.5% and about 10%-30% in hospitalized patients.5,6 Half of the episodes of SBP are present at the time of hospital admission while the rest are acquired during hospitalization.5 In-hospital mortality for the first episode of SBP ranges from 10% to 50%, depending on various risk factors.7,8 Earlier known as a complication of
alcoholic cirrhosis, spontaneous bacterial peritonitis is now known to affect patients with cirrhosis from any other cause like heart failure, Budd-Chiari syndrome or nephrotic syndrome.

METHODS

It was a prospective observational study done over a period of 1 year from August 2012 to July 2013 in a tertiary care hospital. 50 patients from medical and gastroenterology wards were included in the study. After obtaining institute’s Ethics committee approval and valid written informed consent patients were enrolled in the study. Patients above 12 year of age with diagnosed cirrhosis of liver and documented evidence of SBP in the form of ascitic fluid PMN>250 cells /mm³ and ascitic fluid culture positive or ascitic fluid PMN count >250/mm³ and ascitic fluid culture negative or ascitic fluid PMN count <250 cells/mm³ and ascitic fluid culture positive were included. Pregnant females, patients who refused to give consent, patients with a documented evidence of intra-abdominal source of infection or patients with ascitis due to non-hepatic causes like nephrotic syndrome and congestive cardiac failure were excluded. All the patients included in the study were interviewed in detail with particular attention to abdominal pain, increasing abdominal distension, diarrhoea, fever, haematemesis, malena and oliguria. Detailed history of addictions including alcoholism was taken. Pre-existing illnesses like hepatitis B and hepatitis C were also noted.

Detailed clinical examination was performed. Vital parameters like temperature, pulse, blood pressure, respiratory rate, mental status examination and presence or absence of signs of liver cell failure were noted. Complete blood count, blood urea nitrogen, serum creatinine, serum electrolytes, random blood sugar, total protein and serum albumin, total and direct bilirubin, SGOT, SGPT, alkaline phosphatase and prothrombin time and INR (international normalized ratio) were done. Ultrasonography of abdomen to look for liver size and architecture, spleen size, ascitis grade and localised collection of focus of infection was done. Hepatoportal Doppler to rule out Budd Chiari syndrome or portal vein thrombosis was done if indicated. CECT of the abdomen was done if intra-abdominal source of infection was suspected but not localised on ultrasonography. Ascitic fluid examination was done for its appearance, proteins, cells-total and differential count and ascitic fluid culture. All the patients received standard antibiotic regimen. The necessary changes in antibiotics were made once culture reports were available. Patients were monitored for complications and were followed up till discharge. Data thus obtained were statistically analyzed.

RESULTS

This was a prospective study carried out over a period of 1 year. 50 patients were included in the study. Males were 40 (80%) and females were 10 (20%). Out of the males 24 survived (60%) and 16 expired (40%). Amongst the females 4 survived (40%), and 6 expired (60%). The mean age was 40.7 years with the maximum number of patients in the age group of 40-50 years (20 i.e 40%) followed by 30-40 years (12 ie 24%). The most common etiology of cirrhosis was alcoholic liver disease (56%) and cryptogenic cirrhosis was found to be the second most common cause (30%). The other causes for cirrhosis were HBV related (6%), Wilson’s disease (4%), HCV related and chronic Budd chiari syndrome contributed to 2% each. The commonest symptom at presentation was progressively increasing abdominal distension (80%), abdominal pain being the second frequent symptom (66%), fever (56%), encephalopathy at presentation (44%), GI bleeding (40%) and diarrhoea (10%). 8% patients were asymptomatic and were diagnosed on investigations.

Table 1: Ascitic fluid bacteriological profile and outcome.

<table>
<thead>
<tr>
<th>Ascitic fluid profile</th>
<th>Survived (n=28)</th>
<th>Expired (n=22)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive</td>
<td>18 (64.2%)</td>
<td>9 (40.9%)</td>
<td>27</td>
</tr>
<tr>
<td>CNNA</td>
<td>10 (35.8%)</td>
<td>13 (59.1%)</td>
<td>23</td>
</tr>
<tr>
<td>MMNNA</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>22</td>
<td>50</td>
</tr>
</tbody>
</table>

The outcome of the patients with respect to the grades of ascitis was assessed. 2 patients had grade 1 ascitis (4%), 22 with grade 2 (44%) and 26 with grade 3 ascitis (52%). Mortality in grade 3 ascitis group was 54.55% grade 2 ascitis group was 45.45%. There was no mortality seen in grade 1 ascitis group. However, the number of patients in grade 1 ascitis was too small to correlate. This value was not statistically significant (p=0.659). Out of 28 patients who survived only 5 patients had serum bilirubin more than 5 mg% and amongst the 22 expired only one patient had serum bilirubin less than 5 mg%.

The mean serum bilirubin amongst the survived was 3.88 mg% and amongst the expired was 10.03 mg%. The difference was statistically significant (p=0.000). Out of 28 patients who survived only 3 patients had serum creatinine value more than 1 mg% and out of the 22 patients who expired only 2 patients had serum creatinine value less than 1 mg%. The mean value of serum creatinine amongst the survived was 0.86 mg% and amongst the expired was 2.50 mg%. Thus, high serum bilirubin and creatinine levels were associated with higher mortality rate and were statistically significant (p =0.000). The other lab parameters like liver enzymes, serum protein, prothrombin time were not statistically significant with respect to outcome of patients. According to Child Pugh grade, 2 patients were in grade A (4%), 20 patients (40%) in B and 28 (56%) in grade C. There was 1(50%) mortality in grade A, 9(45%) in grade B and 12(42.85%) in grade C. However, this was not

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statistically significant (p = 0.974). Of the 22 patients with encephalopathy 16 expired (62.5%) and of the 28 without encephalopathy 6 (21%) expired. This difference in the outcome was statistically significant (p < 0.000).

The relation between the ascitic fluid bacteriological profile and outcome was not statistically significant (p = 0.268).

*E. coli* was the 2 (7.1%) each. No growth was seen in 10 (35.7%). Amongst those who expired 13 (59.1%) did not show commonest organism in ascitic fluid in those who survived 14 (50%) followed by *S. pneumoniae* and *Klebsiella* in any growth, *E. coli* 6 (27.3%), *S. pneumoniae* 2 (9.1%) and *Anaerobes* 1 (4.5%). However, there was no significant relationship of organism grown in ascitic fluid with the patient outcome. *E. coli* was grown in the ascitic fluid in 20 patients (40%) and only 6 (12%) had blood culture positive for *E. coli*. This difference was significant (p = 0.0014) indicating that the *E. coli* isolation in ascitic fluid culture is significantly higher than the blood culture.

On comparison of the present study (50 patients) with that of Melvin et al (28 patients), and Hoefs et al (43 patients) the clinical profile of the patients was similar in many aspects.

**DISCUSSION**

Cirrhosis is a condition in which there is irreversible scarring of the liver. As a result of chronic damage, non-functional scar tissue replaces functional liver tissue. Patients with Cirrhosis of liver are at high risk of developing bacterial infections due to the reduced activity of phagocytic cells in the hepatic reticuloendothelial system and bacterial influx into the general circulation through portocaval shunts. Infection of ascitic fluid without any apparent intra-abdominal foci of sepsis - spontaneous bacterial peritonitis (SBP) - is often fatal complication of cirrhosis. Most cases of SBP are caused by gram-negative enteric organisms, such as *Escherichia coli* and *Klebsiella pneumoniae*. Risk factors for the development of SBP include ascitic fluid total protein less than 1 g/dl, gastrointestinal haemorrhage, and previous history of SBP. 50 patients were included in our study. Males were 40 (80%) and females were 10 (20%). There were 88 males (88%) and 12 females (12%) patients in a study by Mane et al. In a study by Purohit et al the total number of males with SBP was 49 (69%) while that of females with SBP was 22 (31%). Thus, there is male preponderance seen in all Indian studies. In a study by Oladimeji et al there was no gender difference in the occurrence of SBP. This difference in gender distribution could be due to alcoholism being more common in males than females in India.

The mean age was 40.7 years with the maximum number of patients in the age group of 40-50 years (20 i.e. 40%) followed by 30-40 year (12 patients or 24%). In a study by Mane et al the age of patients ranged between 20 to 80 years, majority of the patients were in the age group of 30-60 years. Age distribution was almost similar in both studies. In our study the etiology of cirrhosis was alcohol in 28 (56%), cryptogenic 15 (30%), hepatitis B 3 (6%), Wilson’s disease 2 (4%), HCV and Budd Chiari 1 each (2%). In a study by Nadagouda SB et al of 9 patients, 6 patients (66.67%) had alcoholic cirrhosis, in 2 patients aetiology was not found (cryptogenic), 1 patient (11.11%) had hepatitis-B associated cirrhosis, and no patient had hepatitis-C associated cirrhosis. In the study conducted by Andreu et al from Spain alcohol was noted in 81.70% by Guarner et al and 67% by Baheti R et al from Jodhpur. Thus alcohol was found to be the most common risk factor worldwide for the development of cirrhosis of liver and SBP as its complication.

Abdominal distension was the most common symptom with which the patients presented (80%), abdominal pain was seen in 66%, fever in 56%, encephalopathy was seen in 44%, GI bleeding in 40% diarrhoea in 10% and 8 were asymptomatic. In a study by Nadagouda SB et al abdominal pain was seen in 7 (77.78%) patients, fever was seen in 6 (66.67%) patients, hepatic encephalopathy in 6 (66.67%) patients, rebound tenderness in 5 (55.55%) patients, absent bowel sounds in 3 (33.33%) patients, upper G.I. bleeding in 3 (33.33%) patients, and hypotension in 2 (22.22%) patients. The presenting complaints of the patients are similar in both the studies. The outcome of the patients with respect to the grades of ascitis was assessed, 2 patients with grade 1 ascitis (4%), 22 with grade 2 (44%), and 26 with grade 3 ascitis.

### Table 2: Microorganism against outcome.

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Survived</th>
<th>Expired</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Count</td>
<td>Percentage</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td><em>Anaerobes</em></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No growth</td>
<td>10</td>
<td>35.7</td>
</tr>
</tbody>
</table>
(52%). There was 45.45% mortality in the grade 2 ascites group and 54.55% in the grade 3 ascites group. However, it was not statistically significant (p=0.659).

The mean serum bilirubin level was 6.5 mg/dl and the mean serum albumin was 2.2 gm/dl. The highest concentration of protein in ascitic fluid observed was 3.5 gm/dl and the lowest was 0.6 gm/dl and the mean ascitic protein was 1.67 gm/dl. In a study by Nadagouda SB et al the mean serum bilirubin level was 6.48±4.2 mg/dl, mean serum albumin was 2.41±0.39 gm/dl. Highest concentration of protein in ascitic fluid observed in their study was 1.9 gm/dl and lowest was 0.40 gm/dl. Mean ascitic fluid protein concentration was 0.93±0.44gm/dl.18

A high serum bilirubin (above 2.5 mg/dl) and a low ascitic fluid protein concentration (less than 1.0 g/dL) have been shown to be strong predictors the development of SBP in cirrhotic for both initial episodes of SBP as well as for the recurrence.22,23 As for the significance of ascitic fluid proteins, Runyon demonstrated that cirrhotic patients with ascitic protein concentrations below 1 g/dl were 10 times more likely to develop SBP than individuals with higher concentrations.23 It is thought that the antibacterial, or opsonic activity of ascitic fluid is closely correlated with the protein concentration.24 Thus, patients with low protein levels are at higher risk for SBP. Conversely, patients with ascitic fluid of typically high protein content, such as those with malignant ascites are relatively resistant to SBP.25,26 Additional studies have confirmed the validity of the ascitic fluid protein concentration as the best predictor of the first episode of SBP.22,31 The association of the high serum bilirubin to increased incidence of SBP is probably indirect, as elevated serum bilirubin levels are seen in advanced or severe stage of disease.

In present study, the mean serum creatinine value was 0.86±0.19 mg/dl and 2.50±1.84 mg/dl amongst those who expired. This difference was statistically significant (p=0.000). In a study by Müsskopf MI et al the mean serum creatinine value was 1.2±0.3 mg/dl among those who survived and 1.8±0.8 mg/dl among those who expired (p=0.009).27 Thus creatinine was significantly higher in patients who died during hospitalization than in survivors. A review of English-language articles has shown that renal dysfunction, usually defined as creatinine > 1.5 mg/dl, was the most robust predictor of death among prognostic parameters for in-hospital mortality in patients with SBP.28

In present study, there were 2 patients in Child Pugh grade A (2%), 20 (40%) patients in grade B and 28(56%) in grade C. In study by Nadagouda SB et al out of 9 patients of SBP and its variants, 8 (88.89%) patients were in Child Pugh's Class C and only 1 (11.11%) case was in Child Pugh's Class B. In a study by Syed VA et al eighty five percent (n=17) cases were in Child’s class C and 15% (n=3) were in Child’s class B. In present study, the mortality however did not correlate with the Child Pugh grade. Serum bilirubin is one of five markers used to stage the severity of liver disease according to Child-Pugh rankings.29 The higher the number in these rankings, the greater the risk of SBP.30 This helps to explain why 70% of cases of SBP are seen in patients with Child-Pugh class C cirrhosis.30

The ascitic fluid culture was positive in 27 (54%), CNNA was seen in 23 (46%). E coli was the most commonly found organism in ascitic fluid (40%), followed by streptococcus pneumoniae (8%), Klebsiella (4%), and anaerobe was seen in 2% cases. In a study by Mane et al out of 51 cases of spontaneous bacterial peritonitis 23 samples of ascitic fluid showed positive culture reports. E. coli was isolated from 13 (13%) cases; Klebsiella spp. was isolated from 6 (6%) cases, Acinetobacter was isolated from 2 (2%) cases, Pseudomonas aeruginosa was isolated from 1, (1%) case and proteus was isolated from 1 (1%) cases. In a study by Nadagouda SB et al out of 9 cases of SBP, 7 (77.78%) were of culture negative neutrocyctic ascites (CNNA), followed by 1 (11.11%) each of classic spontaneous bacterial peritonitis (CSBP) and mono-microbial non-neutrocyctic bacterascites (MNBA). Taj et al reported E. coli (61.55%) and Streptococci in (15.38%) in their study.31 Haider et al, reported E. coli 30%.32 In a study by Tsung PC et al Eschericia coli (12 of the 47 cases, 25.5%), Klebsiella species (9 cases, 19.1%) and Streptococcus species (9 cases, 19.1%) were the most common organisms in this study, Enterococcus species (6 cases, 12.8%).33 In our study the types of cultured bacterial organisms did not affect the survival rates of cirrhotic patients with SBP.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES
