Association between Acid Suppressive Therapy and Spontaneous Bacterial Peritonitis in Ascitic Cirrhotic Patients

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Abstract: Background: Risk of spontaneous bacterial peritonitis (SBP) is increased among ascitic cirrhotic patients due to bacterial translocation across the intestinal wall due to impaired small intestinal motility and increased permeability. Acid suppressive therapy (AST) suppresses secretion of gastric acid and hence predisposes to bacterial colonization, overgrowth and translocation. This study aimed to determine whether AST use in cirrhotics with ascites is associated with SBP. **Methods:** In this case-control study, data from 118 cirrhotic ascitic patients (50 with SBP and 68 free from SBP) were compared. Exclusion criteria included HIV infection, prior transplantation, peritoneal or hemodialysis. History of regular AST intake on daily basis for at least two weeks prior to admission was identified and those with justified indication were recorded. Demographic data, Child's class, model for End-Stage Liver Disease (MELD) history of diabetes mellitus, associated melena, hematemesis or encephalopathy was recorded. Serum data between groups were compared and bacteriologic examination ascitic fluid in SBP patients was done using Gram stain. Statistical analysis was done to detect odds ratios (ORs) of association of AST use with occurrence of SBP. **Results:** Patients were matched regarding demographic characteristics and history. Patients with SBP showed significantly worse Child's class and MELD score, higher serum bilirubin, creatinine and INR whilst significantly lower serum sodium and albumin. Users of AST were significantly higher among patients with +ve SBP (37/50 and 20/68 respectively, *P*=0.006). Odds ratio was 6.83 (95% CI: 3.01, 15.50 *P*=0.0001). **Conclusion:** Odds of exposure to SBP in cirrhotic patients with ascites is increased among AST users
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1. Introduction

Risk of spontaneous bacterial peritonitis SBP occurs mostly in liver cirrhotic patients with portal hypertension in spite of efforts for prevention through intestinal bacterial decontamination[1]. It occurs due to increased intestinal permeability to bacteria and carries a grave prognosis[2,3]. Gastric acidity guards against bacterial overgrowth whereas AST has been shown to increase viability, colonization and translocation of pathogenic bacteria in the gastrointestinal tract[4,5].

Studies relating AST use with SBP in ascitic cirrhotic patients are inconsistent and investigators in those studies relied on data obtained from patient's records which might have decreased accurateness[6-9]. We conducted this case control study to investigate the aforementioned association meanwhile guaranteeing direct contact with patients on admission and follow up.

2. Methods

This case control study was approved by our local ethical committee and performed on 118 patients who were admitted to Tanta Hospital of the University with a confirmed diagnosis of liver cirrhosis and ascites. Written informed consent was obtained from all patients. Diagnostic paracentesis is a standard practice performed for those patients regardless of the reason for admission. SBP was diagnosed if a paracentesis was yielding >250 polymorphonuclear leukocytes (PMN)/mL^3 in the ascitic fluid with or without a positive culture. Patients with SBP were put in group A while SBP negative patients (controls) were put in group B. Exclusion criteria included immunosuppressed patients, HIV infection, prior transplantation, patients on peritoneal or hemodialysis and patients with a history of irregular intake of AST. Patients who were either on regular AST intake on dialy basis for at least two weeks prior to admission or those who were not on AST at all for at least two weeks before admission were identified and included. Acceptable indications for AST use included, but not limited to, gastroesophageal reflux disease (GERD), peptic ulcer disease, Barrett's esophagus, Zollinger–Ellison syndrome, and nonsteroidal anti-inflammatory drug use. Patients with justified indication for AST were identified and recorded. Patients were matched for age, weight, height, Child–Pugh–Turcotte (CPT) score and class, (MELD). History of diabetes mellitus and associated melena, hematemesis or

encephalopathy were identified and recorded. Serum examination included bilirubin, albumin, sodium, creatinine and international normalized ratio (INR). ascitic fluid examination was done for pH, specific gravity, glucose, protein, lactate dehydrogenase (LDH), white blood cells (WBCs) count and polymorphnuclear cells (PMNCs) count. Bacteriologic examination of SBP ascitic fluid using Gram stain was done.

Data are expressed as mean ± SD. Statistical analysis was performed using unpaired t test to compare normally distributed and continuous data, whereas the Fisher's exact test was used to compare data expressed as percentages. Logistic regression was performed to determine ORs of developing SBP associated with use of AST. Data analysis was performed using SPSS, version 16 (IBM, Somers, NY, USA). A probability level of 0.05% was considered significant.

3. Results

One hundred and eighteen patients were included in our study: Fifty patients had SBP while 68 had not. The etiology of cirrhosis (group A/group B) was: schistosomiasis± hepatitis C (Number (N)=34/49, *P*=0.8851), hepatitis B (N=11/13, *P*=1.000), NASH/Cryptogenic (N= 5/6, *P*=1.000).

Patient characteristics, number of diabetics and associated melena, hematemesis and encephalopathy were comparable between both groups. CPT classification, CPT and MELD scores were significantly worse in group A (Table 1). Serum billirubin, creatinine and INR were significantly higher in group A whereas serum albumin and sodium were significantly lower (Table 2). ascitic fluid examination revealed that group A had significantly lower pH and protein at the same time as significantly higher LDH, WBCs and PMNCs whereas comparable values of specific gravity and glucose were shown between groups (Table 3).

Table 1. Demographic characteristics of Patient

Variable	Group A (N=50) SBP positive	GroupB (N=68) SBP negative	***p***
Age (years)	55.460±3.6152	55.000±3.761	0.620
Weight	74.360±8.4388	74.808±8.1757	0.967
Height	161.280±5.9179	161.441±5.7294	0.475
Male/Female	34/16	40/28	0.6559
Diabetes mellitus	15	18	0.843
Melena	8	6	0.3947
Haematemesis	8	8	0.5593
Encephalopathy	5	7	1.000
CPT classification: B/ C	17/33 (38%/62%)	38/30 (53%/47%)	0.0250*
CPT score	10.280±1.7732 Median = 11 (range 5-13)	9.191±1.4584 Median = 9 (range 5-13)	0.007*
MELD score	24.160± 2.2710 Median=24 (range 19-28)	19.632±2.9468 Median=19 (range 15-27)	0.038*

Values are given as as number (n) or mean±SD; mediam + range *=Significant: P < 0.05; SBP: Spontaneous bacterial peritonitis; C= hepatitis C virus; B= hepatitis B virus; MELD =: Model for End-Stage Liver Disease; CPT = Child-pugh-turcotte

Table 2. Serum data

Variable	Group A (N=50) SBP positive	GroupB (N=68) SBP negative	*P*
Serum bilirubin (mg/dL)	3.098±1.1746	2.050±0.8764	0.002*
Creatinine (mg/dl)	2.290±0.6044	1.642±0.4264	0.008*
INR	2.056±0.6188	1.792±0.3868	0.003*
Serum albumin g/dL	2.360±0.3077	2.550±0.4592	0.020*
Serum sodium mEq/L	130.640±2.7830	135.205±3.8885	0.013*

INR = international normalized ratio; SBP = Spontaneous bacterial peritonitis

Bacteriologic growth in ascitic fluid was confirmed in 18 patients (36%) of group A: Gram-positive organisms were found in 8 patients (Staphylococcus species [4], Enterococcus [2], and Streptococcus species [2]), and Gram-negative organisms were found in 10 patients (*Escherichia coli*

[3], Klebsiella [2], Serratia [2], Pseudomonas [1] and Enterobacter [2]. In both groups, 57 patients received AST, 35 of them (61.4%), had no documented indication for AST. Twenty two patients had clear indications for AST use (12 in group A and 10 in group B *P*=0.2359). Indications were: esophageal variceal banding 13, GERD 5, peptic ulcer disease 3 and Barrett's esophagus 1 (Figure 1). Patients in group A had significantly higher incidence of AST use (37/50 while 20/68 in group B, (*P*=0.006). Odds ratio for the development of SBP among AST users versus non users was 6.83 (95% CI: 3.01, 15.50 *P*=0.0001). Five patients with SBP had died during admission due to sepsis and hepatic failure.

Table 3.Ascitic fluid Data

Variable	Group A (N=50) SBP positive	GroupB (N=68) SBP negative	*P*
pH	7.178±0.2503	7.483±0.17	0.006*
Protein gm/dl	1.618 ±0.723	2.691±.4021	0.001*
LDH mg/dl	69.820 ±13.07	43.397±18.6948	0.011 *
WBCs /mm^3	1071.000 ±200.31	211.838±65.4827	0.000*
PMNCs /mm^3	806.800 ±193.311	66.823±14.4376	0.000*
Specific Gravity	1011.500 ±3.908	1012.764±3.7100	0.656
Glucose mg/dl	71.100 ±6.370	69.720±5.4247	0.358

WBCs = white blood cells PMNCs = polymorphnuclear cells LDH = lactate dehydrogenase * = significant

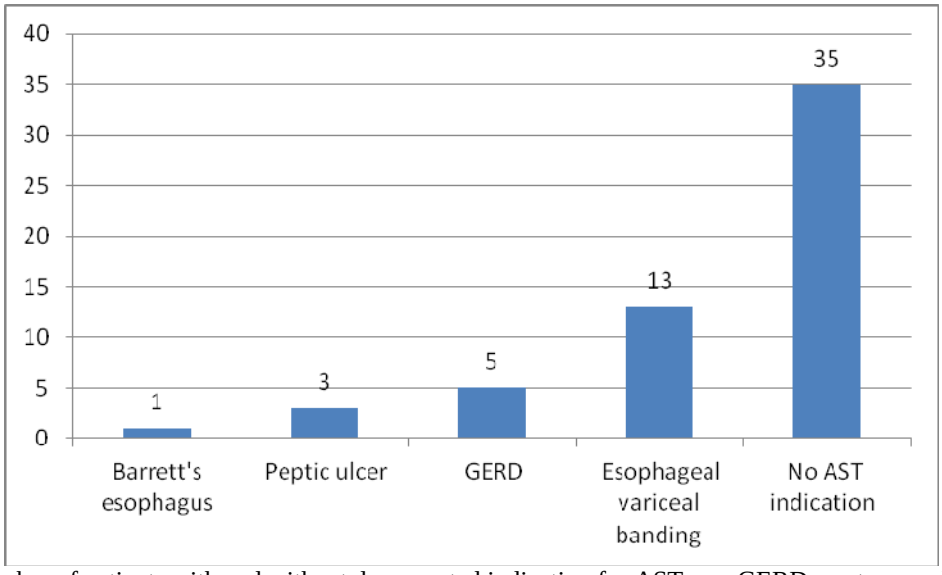

Figure 1: Number of patients with and without documented indication for AST use. GERD=gastro-esophageal reflux disease

4. Discussion

Data in our study demonstrate that use of AST in ascitic cirrhotic patients was associated with significantly increased odds of acquiring SBP, a finding in harmony with some observations[4,7-9] but not with others[6]. In 2001, a small-scale study[4] (29 patients) examined this association as a secondary outcome; on basis of quantitative cultivation of jejuna aspirates and hinted an increased risk of SBP with the use of AST, however, their results were not significant (hazard ratio = 7.0, *P* = 0.08). In 2008, Campbell *et al.* [6] published another study specifically designed to investigate this issue and included more patients (116) than the previous one to improve the precision of their point estimates. They did not find a causal relationship between AST and the development of SBP in their patient population and they suggested further studies to confirm their results. Three studies[4,7-9] followed afterward included 140,403 and 113 patients respectively and challenged the results of Campbell *et al.* Pooling of the four previous studies[6-9] into a meta-analysis[10], that involved a total of 772 patients, found a significant association between the use of AST and the development of SBP (OR 2.77, 95% CI 1.82–4.23). Goel *et al.* [11] published another study in 2012 on 130 patients where they did not exclude patients receiving antibiotics so as to reflect more accurately the real-world experience. Their results supported the

association between AST and SBP and, in addition, they found no diminution of SBP incidence among patients receiving antibiotics who are, in fact, had a higher prevalence of SBP. In our study, we broadened the real world further by including those with gastrointestinal bleeding besides those patients on antibiotics.

Association of AST use with SBP might suggest a causal relationship; however, other explanations are still plausible. Our study showed significantly higher serum bilirubin, creatinine and INR and significantly lower serum sodium and albumin, in patients with SBP denoting more advanced liver disease and thus those patients are-probably, more prone to develop serious complications such as SBP. Also, patients having symptoms requiring AST such as abdominal pain, dyspeptic symptoms or after banding or sclerotherapy of oesophageal varices may have a greater predisposition to SBP as such patients may have pre-existing bacterial overgrowth predisposing to SBP[10,12]. However, this study does not favor this assumption since no significance was detected between numbers of patients using AST with clear indication in both groups. Also, and in agreement with previous studies[6,11] patients with SBP had a significantly higher CPT and MELD scores and significantly worse CPT classification. These results may simply reflect the fact that patients with more advanced liver disease are more likely to develop SBP. However, an alternative credible explanation is that SBP may lead to transiently worsening hepatic synthetic and renal functions, resulting in a higher CPT and MELD scores and worse CPT classification on presentation.

In this study, patients with no documented indications for AST use were 61.4%. AST is frequently prescribed in cirrhotic patients without clear evidence[13] and, moreover, self-medication with AST has also become common because of its perceived safety[14]. Use of AST was found to cause bacterial translocation in the cirrhotic rats, but not in non-cirrhotic controls [15]. Chang *et al.* [16] showed a high prevalence of bacterial overgrowth and impaired small bowel motility in humans with SBP compared with those without SBP. More to the point, a positive association between AST use and the development of *Clostridium difficile*-associated diseases was demonstrated[14,17]. The addressed relationship between AST and the aforementioned infection risks, and the risk of SBP revealed in our study, raises the importance of clinical question about the risk-benefit of its use in this patient population.

As in our study, Characteristics of ascitic fluid, excepting specific gravity and glucose, help in diagnosis of SBP. Low ascitic fluid pH was shown to have a good diagnostic value with 93% specificity and 100% sensitivity[18]. Previous studies suggested that WBCs >1000/mm^3 and PMNCs >250/mm^3 in the ascitic fluid are diagnostic of SBP[19,20]. Low ascitic fluid protein concentration was shown to represent a high risk factor for development of SBP[21,22]. Lower level of glucose in the peritoneal fluid probably reflects the consumption of this substance by bacteria and were shown to be the least reliable of all tests evaluated for the diagnosis of SBP whereas the high concentration of LDH reflects a high degree of peritoneal inflammation[23,24]. Regarding the microbial agents identified, our results were similar to previous reports showing that gram negative bacteria, particularly Escherichia coli, as the most prevalent agent[23,25].

Our study has an important strength compared to the previous studies. We did not rely on nursing and physician notes in the patient's records to identify AST exposure and patient's history with possible decreased reporting accuracy. Instead we investigated the association between SBP and AST through direct contact with all patients on admission with thorough history taking. On the other hand, a potential limitation to our study warrants consideration. We did not carry out separate analyses for different AST formulations because our sample size is limited and we also think that no obvious reason why the risk, if any, would be different among different AST formulations. However, further studies are still possibly needed to clarify this issue. Lastly, we did not perform an analysis based on AST dosage and frequency of administration due to lack of sufficient statistical power. Therefore, we instead reported patients who were regularly taking AST on daily basis before hospital admission.

In conclusion, there is a potential association between AST intake and development of SBP in cirrhotic ascitic patients. More judicious use of AST for cases with only clear evidence based therapeutic benefits may thus be warranted in this patient population.

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