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Original Article

Mini-dose albumin can reduce renal impairment in cirrhotic patients with spontaneous bacterial peritonitis

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Abstract

Background: Spontaneous bacterial peritonitis (SBP) is one of the most common and life threatening infections in cirrhosis. SBP patients are at high risk of developing renal impairment due to deterioration of systemic hemodynamics, intravenous albumin at a dose of 1.5 g/kg at diagnosis and 1 g/kg 48 h later has been shown to prevent renal impairment and reduce mortality in those patients. Such large dose of albumin is costly and not trouble free so it is important to assess other alternative regimens. The aim of the work is to assess using of mini-dose albumin 20% versus human plasma (as a source of isotonic albumin) in treatment of SBP and assess in hospital morbidity in term of occurrence of renal impairment and in hospital mortality. *Patients and methods:* This study included seventy five patients with decompensated cirrhosis and ascites complicated by SBP were divided into three groups each one included 25 patients as follow: Group (1) patients were administered mini-dose hypertonic albumin 20% (20g/ day) for 3-5 days plus antibiotic, group (2) patients were administered plasma (2 units/ day) for 3-5 days plus antibiotic, group (3) patients were administered antibiotic only. All groups were followed for 5 days (duration of hospital admission) and compared as regards in hospital renal impairment (diagnosed by percentage of serum creatinine elevation) and in hospital mortality. *Conclusion:* mini-dose albumin (20g/d) plus antibiotics reduced significantly renal impairment in cirrhotic patients with SBP while plasma transfusion didn't.

Keywords: Spontaneous bacterial peritonitis, Human albumin, Renal Impairment.

Introduction

Hepatitis C viral infection is endemic in Egypt with the highest prevalence rate in the world. Chronic HCV is the leading cause of cirrhosis, its complications and liver-related death in Egypt[1]. SBP is considered as one of the most common infections in cirrhotic patients with about 32% in-hospital mortality rate[2]. It is defined as an infection of the ascitic fluid in the absence of intra-abdominal source that could be surgically treated in patients with advanced cirrhosis[3]. SBP patients are at high risk of developing renal impairment due to deterioration of systemic hemodynamic parameters with further arterial and splanchnic vasodilatation and the release of high level of vasoactive cytokines in sepsis are the patho-physiological explanation for the association between SBP and renal impairment. Vasoactive cytokine deteriorates the arterial vasodilatation and leads to secondary activation of neurohormonal system. So, the use of concentrated albumin 20% is to maintain intravascular volume and to repair renal perfusion[4]. Albumin administration for patients with SBP is studied as albumin can expand intravascular volume and bind to inflammatory cytokines. It is recommended that antibiotics and intravenous concentrated albumin (20%) at a dose of 1.5 g/kg at diagnosis and 1 g/kg 48 h later inhibits renal impairment and decreases mortality in patients with SBP[5]. The high cost of albumin represents a major limitation to its use in clinical practice[6]. Some studies suggested that lower dose albumin are comparable with albumin standard dose. The aim of the workis to assess using of mini-dose albumin 20% versus human plasma (as a source of isotonic albumin) in the treatment of SPB and assess in hospital morbidity in term of occurrence of renal impairment and in hospital mortality.

Patients and methods

This was a randomized controlled study included seventy five cirrhotic ascitic patients with SBP who were selected from Hepatology Unit of Mansoura Specialized Hospital, in the period between January 2015 and January 2016. The study protocol conformed to the Medical Sciences Ethics Committee of Mansoura Faculty of Medicine and all the included patients had written informed consents. The study included both genders aged between 18-70 years with cytological diagnosis of SBP (ascitic fluid PMN ≥ 250 / mm^3). We excluded cases of secondary peritonitis,

antibiotic treatment within one week before the diagnosis of SBP (except for prophylactic treatment with norfloxacin or trimethoprim/sulfamethoxazole), shock, gastrointestinal bleeding, cardiac failure, and malignant ascites, TB ascites, creatinine level of more than 3 mg/dl, and potential causes of dehydration (such as diarrhoea) within one week before the diagnosis of SBP, hematological disorders, diabetes mellitus and overt hyper or hypothyroidism.

Patients were divided into three groups (25 patients in each group) as follows

Group (1) patients were administered mini-dose hypertonic albumin 20% (20g/ day) for 3-5 days plus antibiotic, **group (2)** patients were administered plasma (2 units/ day) for 3-5 days plus antibiotic and **group (3)** patients were administered antibiotic only. All groups were followed for 5days (duration of hospital admission) and compared as regards in hospital renal impairment (detected by % of serum creatinine elevation) and in hospital mortality. Most patients were treated empirically with IV cefotaxime 1-2g/8-12 hours or cefotriaxone 2g daily for 5 days or until the infection resolved. If necessary the antibiotic was changed according to in-vitro susceptibility of the causative microorganism.

Patients included in this study were subjected to the following

- Detailed history, full clinical examination, radiological investigations (chest X-ray and abdominal ultrasound) and laboratory tests (CBC, liver function tests).
- Renal function was assessed by measuring Serum creatinine level at day 0, 2, 4, 6 and % of creatinine elevation was calculated:

$$\frac{Creatinine\,at\,day6 - Creatinine\,at\,day0}{preCreatinine\,at\,day0} \times 100\%$$

- Ascitic fluid samples (20 ml) were withdrawn under complete aseptic technique and used for, ascitic fluid analysis for neutrophil count, glucose, protein and lactate dehydrogenase (LDH), SAAG (serum-ascites albumin gradient) to ensure that it is above 1.1g/dl i.e portal hypertensive ascites and ascitic fluid culture (10 ml ascitic fluid was inoculated in blood-culture bottles at the patient's bedside) for detection of causative organism, and assess antibiotic sensitivity.
- Second ascitic fluid analysis was done after 48 hour of therapy and treatment failure is diagnosed when there is less than 25% decrease of initial PMN count.

Statistical analysis

All statistical analysis was done using SPSS (statistical package of social sciences) version 20 for windows A2 tailed p value less than 0.05 was considered significant. Continuous data presented as mean ± standard deviation or median (minimum/maximum) for parametric and non-parametric data respectively. Analysis of continuous data was done by one wave anova (followed by Tukey as post-hoc test for parametric data and Kruskoll Wallis test followed separate Mann-Whitney U test for individual group comparisons in non-parametric data categorical data was expressed on (%) and analyzed by Chi-square or Fischer"s test as appropriate comparative analysis between all study groups as regard % of creatinine elevation was done by analysis of covariance with adjustment of confounding variable affecting creatinine elevation All correlation analysis was done by spearman correlation test for continuous data while bi-serial correlation analysis was used for correlation of categorical data with %of creatinine elevation .Significant predictor in correlation analysis will be used as predictors again versus percent of creatinine elevation in forward stepwise linear regression analysis. Univariate logistic regression analysis was done for assessment of association of study intervention with in hospital mortality. Adjustment of confounding variable affecting mortality was done in multivariable logistic regression analysis. Association between clinical and biochemical parameters of this study with in-hospital mortality was analyzed again versus in-hospital mortality by forward log like stepwise logistic regression analysis. Comparison between different study groups as regard change in serum creatinine was done by one way mixed design annova.

Results

The present study was conducted on seventy five patients with SBP as listed in **tab$_s$. (1, 2, 3 & 4)** and **fig$_s$. (1 & 2).** Where, Table (1)shows that, there was no significant difference between all studied groups as regard clinical data (age, gender, MELD, Child Turcotte–Pugh score, systolic blood pressure, diastolic blood pressure, in hospital renal impairment and in hospital mortality (P value > 0.05) for all. Table 2 shows laboratory data of the studied groups, there was no significant difference as regards serum creatinine, serum albumin, serum bilirubin, INR, serum Na and ascitic fluid WBCs (PMN). As regards serum creatinine elevation, it was found to be significantly lower in albumin group compared to plasma group (P value 0.001). After adjustment of confounding variables (age, gender, MELD, SBP and DBP). The percentage of serum creatinine elevation was significantly lower in albumin group compared to plasma group (p1= 0.024),

however, no significant change was found between albumin group versus control group and between plasma group and control group. Figure (2) shows that, there was a significant difference between the studied groups as regard changes in serum creatinine. There was no significant association between each of albumin or plasma groups versus control group with in-hospital mortality even after adjustment of other confounders (P value was >0.05) for all.

Table 1. Clinical features of the studied groups

Clinical Characteristic	Mini-dose albumin group N=25 Mean ± SD	Plasma group N=25 Mean ± SD	Control group N=25 Mean ± SD	P value
Age (ys)	56.8±7.6	55.8±6.2	57.6±7.6	P1=0.865 P2=0.661 P3=0.933
Gender n (%) Male	12(48)	12(48)	13(52)	P1=1.000 P2=0.777 P3=0.777
MELD	18.8±7.7	18.1±7.6	18.2±5.8	P1=0.931 P2=0.955 P3=0.962
Child Turcotte–Pugh score	10(6-13)	9(6-12)	10(8-12)	P1=0.961 P2=0.395 P3=0.385
Systolic Blood Pressure (mmHg)	108.0 ±10.0	104.8±11.6	104.0±7.6	P1=0.490 P2=0.956 P3=0.330
Diastolic blood pressure(mmHg)	68.8±6.0	66.8± 8.5	66.8 6.3	P1=0.575 P2=1.000 P3=0.575
In hospital renal impairment n (%) Yes	4 (16)	11(44)	9(36)	P1=0.062 P2=0.564 P3=0.196
In hospital mortality n (%) Yes	4 (21)	4(21)	5(20)	P1=1.000 P2=1.000 P3=1.000

***P1**= significance between albumin group and plasma group, **P2**= significance between plasma group and control group, **P3** significance between albumin group and control group*

Table 2. Laboratory data of the studied groups

Clinical characteristic	Mini-dose albumin group N=25	Plasma group N=25	Control group N=25	P value
		Serum Creatinine		
Day 0	1.3(0.7-2.4)	1.1(0.4-2.2)	1.2(0.7-2.3)	P1=0.396 P2=0.445 P3=0.845
Day 2	1.2(0.7-3)	1.2(0.4-2.5)	1.3(0.7-2.5)	P1=0.915 P2=0.612 P3=0.514
Day 4	1(0.7-3)	1.2(0.4-3.2)	1.3(0.7-3)	P1=0.471 P2=0.763 P3=0.121
Day 6	1(0.7-4)	1.2(0.4-4.3)	1.3(0.7-3)	P1=0.385 P2=0.977 P3=0.108
% of Cretinine elevation	-10.5(-50-142)	11.1(-45.5-166.7	0(-47.-228.6)	P1=0.001* P2=0.103 P3=0.215
Serum.Na (mmol/L)	128.7±6.4	129.2±4.3	126.3±6.5	P1=0.962 P2=0.205 P3=0.320
Albumin (g /del)	2.5±0.4	2.3±0.4	2.3±0.4	P1= 0.231 P2= 0.997 P3= 0.260
Bilirubin (mg/del)	5.5(0.4-15)	4.7(0.9-15)	4(1.2-15)	P1=0.503 P2=0.884 P3=0.547
INR	1.6±0.4	1.7±0.5	1.5±0.4	P1=0.725 P2=0.497 P3=0.929
Ascitic fluid WBCs (PMNL)	1380 (450-4300)	1520 (450-3600)	1200 (450-3000)	P1=0.490 P2=0.414 P2=0.838

***P1**= significance between albumin group and plasma group, **P2**= significance between plasma group and control group, **P3**= significance between albumin group and control group*

Table 3. Comparative analysis between the studied groups as a regard % of serum creatinine elevation (adjusted for confounders).

Mini-dose albumin group N=25	Plasma group N=25	Control group N=25	P value
5.8 (11.3)	30.9 (11.3)	21.8 (11.3)	P1=0.024 P2=0.573 P3=0.087

***P1**= significance between albumin group and plasma group, **P2**= significance between plasma group and control group, **P3**= significance between albumin group and control group*

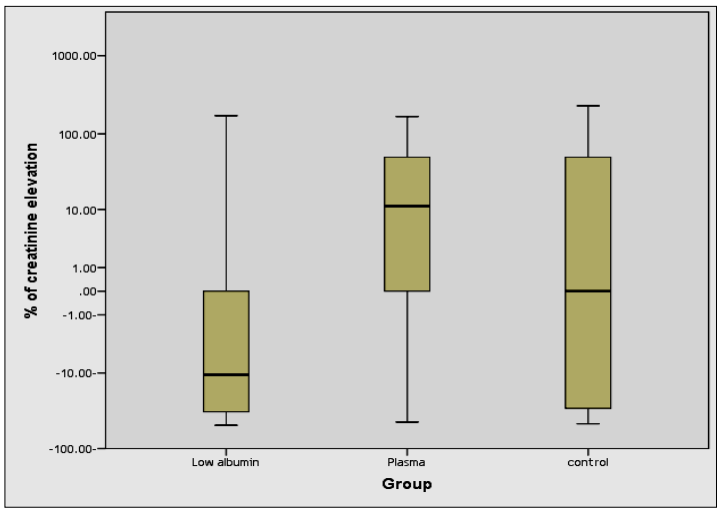

Figure 1. Box plot chart showing a comparison between all study groups as regard % of serum Creatinine elevation**.**

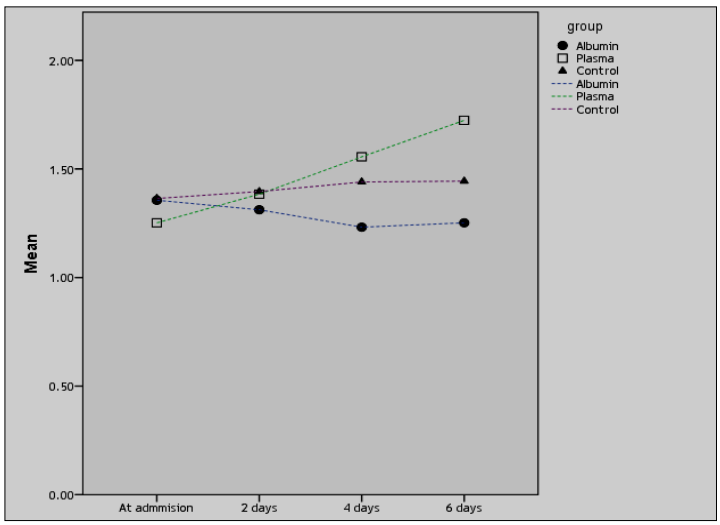

Figure 2. Changes in serum creatinine level with therapy

Discussion

Spontaneous bacterial peritonitis (SBP) is one of the most common and life threatening infections in patients with end-stage liver disease[7]. SBP is associated with a high incidence of renal impairment and mortality. Renal impairment is probably related to systemic hemodynamic alteration that leads to reduced effective arterial blood volume [5]. Early diagnosis and effective treatment of SBP is essential to shorten hospital stay and reduce mortality rate in those patients especially in patients on the waiting list for liver transplantation. The European Association for the Study of the Liver (EASL)[8] and The American Association for the Study of Liver Diseases (AASL)[3] guidelines for SBP treatment advise administration of antibiotic plus human albumin (1.5 g/kg at diagnosis and

1g/kg on day 3). As albumin at this dose has been shown to prevent renal impairment and reduced mortality and is recommended for all cirrhotic patients having SBP[9]. According to EASL and AASL recommendation, ascitic cirrhotic patient weighted 70 kg will need about 105 g I.V albumin in the first day and about 75 g in the third day of admission, such large dose of albumin is costly, its supply is very limited because it is derived from human plasma besides being not trouble-free as it carries a theoretical risk of transmitting known and unknown infections, so it is important to assess alternative regimens[5]. EASL Guidelines on management of ascites, hepatorenal syndrome and SBP stated that, it isn't known if albumin could be replaced by crystalloids or artificial colloids for prevention of hepatorenal syndrome in SBP patients, and recommended more studies for evaluation of albumin as well other volume expanders[8]. So the aim of our study is to assess the effect of mini-dose hypertonic albumin (albumin 20%) in the treatment of SPB patients regarding effect on renal impairment and in-hospital mortality. Also, we tried to assess the role of plasma transfusion (as a source of isotonic albumin 3-5%) in treatment of SBP patients as it is more available in our locality than albumin. This study found that, there was a statistically significant difference between the studied groups as a regard % of creatinine elevation which was significantly lower among patients treated with antibiotic and mini-dose hypertonic albumin versus other groups. So even treatment with mini-dose albumin that we used can prevent the development of renal impairment in SBP patients. This finding is in agreement with de Araujo et al, who reported that reduced dose regimen of IV albumin (1.0g/kg at diagnosis and 0.5g/kg 48h later) was as effective as the standard regimen (that is the recommended in EASL 2010)[10] in preventing renal failure and hepatorenal syndrome in cirrhotic patients with SBP, although our patients administered much lower dose of albumin compared with their patients. The most likely explanation is that, albumin therapy maintains the effective arterial blood volume and prevents the subsequent activation of vasoconstrictor systems and prevents circulatory dysfunction. However, it cannot be ruled out that the beneficial effects of albumin involve mechanisms other than plasma expansion[6] like binding of inflammatory cytokines that worsen arterial vasodilatation and results in secondary activation of neurohormonal system[4] beside preservation of functional integrity of the microcirculation, scavenging and detoxification of reactive oxygen and nitrogen species[11]. Also, we found that, the percentage of creatinine elevation was higher among patients treated with plasma transfusion (as source of isotonic albumin) than among patients treated with mini-dose hypertonic albumin which is statistically significant, moreover changes in serum creatinine were the worst among patients treated with plasma transfusion. This finding supports the report of Liumbruno, et al.[12] who stated that use of plasma transfusion for circulatory volume expansion, hypoproteinaemia, is inappropriate. Moreover the use of plasmatransfusions may results in volume expansion with subsequent increase in portal vein pressure, add more decompansation and increases the risk of rebleeding from oesophageal or gastric varices if present[13].So malpractice that use plasma transfusion instead of albumin for circulatory volume expansion in cirrhotic patients with SBP should be avoided. Regarding in-hospital mortality, which is the second point of outcome. The study demonstrated non significant differences between the three studied groups in-hospital mortality rate in the 3 groups, it was about 20% the same result was previously reported by Babu, et al[14], they stated that, the hospital mortality rate in patients with SBP is about 20%. Although treatment with mini dose albumin (20gm/d) for 3- 5 days intravenously plus antibiotic decreased renal impairment in cirrhotic patients with SBP it didn't reduce in-hospital mortality. This is in contrast with de Araujo, et al[10] as they concluded that low dose albumin was effective as standard dose albumin as it prevents renal impairment and decreased SBP associated mortality. Further studies with large sample size are needed to ensure the effect of such mini dose albumin (20 g/ day for 3-5 days) on SBP patients in general and in high risk SBP specifically.

Conclusion

Mini-dose albumin significantly decreases renal impairment in cirrhotic patients with SBP. Malpractice that uses plasma transfusion (as source of isotonic albumin) instead of albumin in patients with SBP should be avoided.

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