Original Article

A Randomized Controlled Trial to Compare the Effects of Treatment with Fresh Frozen Plasma vs. Human Serum Albumin in Patients with Ascites Due to Cirrhosis of Liver

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Abstract

Background: *Treatment of ascites with diuretic could result in intravascular volume depletion, electrolyte imbalance and impairment of renal function. Several studies demonstrated the additional beneficial effects of human serum albumin (HSA) on diuretic therapy in patients with ascites due to cirrhosis of liver. Fresh frozen plasma could be a cheap alternative to commercially available albumin.*

Objective : *To compare the effects of treatment with fresh frozen plasma versus human serum albumin for the management of ascites due to cirrhosis of liver.*

Methods: *A randomized, open-label, parallel-group, comparative study was carried out in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from April 2015 to March 2016. In this study 90 patients with ascites due to cirrhosis of liver meeting the exclusion and inclusion criteria were purposively included. They were given standard dose of diuretics along with salt and water restriction. Those who lost more than 2 kg weight within 1st 3 days were excluded. Rest 81 patients were randomized to group-A (44 patients) and group-B (37 patients). Group- A received fresh frozen plasma (FFP), 2 units per day for 5 days. Each unit contains 200 ml of FFP. Group-B received human serum albumin (HSA-20% Griffol's), 1 bottle per day for 5 days. Then the clinical and laboratory parameters and adverse events were assessed and compared.*

Results: *The study showed the mean age of the patients was 50.40 years in group A and 53.78 years in group B. Maximum 75% were male in group A and 62.2% were male in group B. Study showed most common cause of liver cirrhosis was HBV; other causes were HCV, wilson's disease and idiopathic in both groups. The mean body weight was 61.68 ±7.74 kg in group A and 61.13±10.16 kg in group B on day 1. After treatment, on day 6, mean weight was 59.71 ±9.03 kg in group A and 58.16±10.30 kg in group- B. Weight loss in group-B was more than that of group-A which was statistically significant. The mean decrease in abdominal girth in group-A was 4.73±0.4 cm and in group-B was 7.05±0.68cm. The mean reduction of abdominal girth was more in group-B than that of group-A and was statistically significant. It was found that the urine output (24 hours) significantly increased from the day-1 to day- 6 in both the treatment groups. The mean increase in serum albumin in group-B (6.66±2.53 g/l) is more than that of group-A(5.55±2.76 g/l) and is statistically significant. The mean excretion of 24 hour urine sodium is more in group-B (82.18±45.17 mEq/L) than that of group-A (50.03±35.02 mEq/L). Regarding adverse effect only one patient have mild articarial transfusion reaction in group-A, but no transfusion reaction happened in group-B. Regarding cost of the treatment it took taka BDT 1400 for collection & screening of 2 unit of FFP whereas equivalent amount of HSA (Grifol's 20% -50 ml) required Taka 3400 BDT. Both in group-A and group-B, decrease in body weight is accompanied by increase in serum albumin but no significant correlation was found in any one of the groups.*

Conclusion: *This study showed that human serum albumin is more effective in improving the clinical and laboratory parameter in cirrhotic patients with ascites. However, the cost/benefit ratio was favorable to fresh frozen plasma.*

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Introduction

Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal regenerative nodule[1]. Cirrhosis becomes decompensated when it is complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy and raised prothrombin time. In Western countries common causes are alcohol and NASH; where as in developing countries, common causes are chronic hepatitis B or C virus infection[2]. Liver cirrhosis accounts for nearly 85% of cases of ascites[3]. In cirrhosis, portal hypertension (PHTN) is the main cause of development of ascites.

Albumin is the ideal plasma expander in this setting, It has the potential to improve the response to diuretics and to prevent complications related to their use, by favouring the net passage of fluid from the peritoneal space to the vascular compartment through an increase in intravascular oncotic pressure. Furthermore, albumin corrects the altered pharmacokinetics of loop diuretics that occurs in cirrhotic patients. In the setting of hypoalbuminaemia, the volume of distribution of furosemide in increased and its renal excretion reduced and/or delayed, while albumin infusion favours the delivery of this drug to the luminal side of Henle's loop, where furosemide exerts its action[4].

Human serum albumin is the most abundant plasma-protein, representing about 50% of the total protein content (3.5–5 g/l). It remains in the blood stream and generates about 70% of the plasma oncotic pressure[5]. More recently, binding, transport, and detoxification capacities of albumin have been found to be severely impaired in cirrhotic patients[6].

To date, the use of albumin is only recommended in patients with ascites treated with therapeutic paracentesis, for the treatment of spontaneous bacterial peritonitis and for the treatment of hepatorenal syndrome[7]. But treatment of cirrhotic ascites with

diuretics and albumin has been practiced on anecdote and experience for many years. Recently, however, evidence has accumulated from prospective randomized trials and meta-analyses that support the use of albumin in the treatment of ascites and its complications. In such a randomized controlled trial on 126 patients with cirrhosis and ascites showed that, patients receiving diuretics plus albumin had a higher cumulative rate of response and a shorter hospital stay (2061 versus 2462 days) than those given diuretics alone. Treatment with albumin on an outpatient basis (25g/week) resulted in a lower probability of developing ascites and a lower probability of readmission. Patients given albumin also had a better quality of life[8].

Commercially available human serum albumin is a sterile aqueous solusion containing 20% human albumin, on the other hand, fresh frozen plasma (FFP) is a blood component prepared from whole blood or collected by apheresis, frozen within time limits and at a temperature such as to preserve the labile clotting factors adequately. FFP is a hyperosmolar (319mOsm/kg), hyperglycaemic & hypochloraemic solution. Here protein content is 5.5 gm/dl with 60% albumin. (3.3gm/dl). FFP's protien content is the primary consideration for volume expansion[9]. One unit FFP(200-250ml) contains about (6.6-8.25gm) of albumin.

Materials & Methods

A randomized, open-label, parallel-group, comparative study was carried out in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka during the period of April 2015 to March 2016. The study was carried out with the Patients admitted into the Department of Gastroenterology of Bangabandhu Sheikh Mujib Medical University, Dhaka, with cirrhosis due to any aetiology with ascites. Cirrhosis of liver with ascites were diagnosed by history, clinical examination & biochemical findings, abdominal ultrasound, endoscopy and liver biopsy if required. All patients were undergone a 3-day lead-in period in hospital with a low-salt diet (25 g/day), bed rest and diuretic therapy (oral spironolactone 50 mg/day and furosemide 20 mg/day). Patients exhibiting symptomatic improvement, by the disappearance of ascites and/or a weight loss of at least 2 kg during the lead-in period will be excluded from this study. The remaining patients were randomly be assigned to either the group A or group B. Randomization were done by simple random sampling by lottery. Patient in group-B recieved 50 ml 20% human serum albumin, on the other hand group-A received 2 unit FFP(200ml) for 5 days in addition to diuretics**.**

Serum albumin, serum creatinin, serum electrolyte, 24 hour urinary sodium concentration were done at base line before starting treatment with either HSA or FFP and at 6th day after completion of therapy were recorded in the data sheet. Body weight (kg), abdominal girth (cm), 24 hr urinary volume were measured every day during the hospital stay & was recorded in the data sheet. Any occurrence of adverse effects due to either HSA or FFP during the study period was also recorded. Length of hospital stay were recorded during discharge from the hospital. Data were collected using a preformed data collection sheet (questionnaire). All the data were checked and edited after collection. Then the data were entered into computer and statistical analysis of the results being obtained by using windows based computer software devised with Statistical Packages for Social Sciences (SPSS-20) (SPSS Inc, Chicago, IL, USA). Statistical significance was set at $p<0.05$ and confidence interval set at 95% level. Continuous variables were expressed as mean with standard deviation and categorical variables as count with percentage. Groups were compared using student's t-test for continuous variables, and chi-squared test for categorical variables. The correlation between variables were evaluated by means of Pearson's correlation test.

Results

This randomized controlled trial enrolled 90 patients with ascites due to cirrhosis of liver. All patients were treated with bed rest, salt and water restriction and diuretics. Nine patients showed >2 Kg weight loss in first 3 days led-in period and are excluded from the

study. With the help of computer based randomization patients were allocated into two groups. Out of 81 patients, 44 were assigned to Group-A and 37 patient were in group-B. Patients of group A were treated with Fresh frozen plasma (FFP) and those of group-B were treated with human serum albumin (HSA) in addition to above mentioned therapy. 4 patients in group-A and 3 patients in group-B did not respond to protocol based treatment and were also excluded. So, final statistics were done with 40 patients in Group A and 34 patients in group B. The baseline data, outcome and adverse effects were compared by the computer based program SPSS for windows version 20. The mean difference of continuous data was compared by Student t test and categorical data by Chi-square test. P value less than 0.05 was considered as significant. The result and observation were shown in table and graph.

Table I: Age distribution of the study subjects

Age in years	Group A (n=44)		Group B (n=37)		P value
	No	%	No	%	
Mean±SD	50.40±11.41		53.78±10.89		0.178

Group A: Fresh frozen plasma

Group B : Human serum albumin

Table II: Sex distribution of the study subjects

Age in years	Group A (n=44)		Group B (n=37)		P value
	No	%	No	%	
Male	33	75	23	62.2	
Female	11	25	14	37.8	0.213

Group A: Fresh frozen plasma

Group B : Human serum albumin

Table III : Cause of liver cirrhosis

Cause	Group A (n=44)		Gr oup B (n=37)		P value
	No	%	No	%	
HBV	26	59.1	24	64.9	
HCV	9	20.5	7	18.9	0.955
Wilson	3	6.8	2	5.4	
Idiopathic	6	13.6	4	10.8	

Group A: Fresh frozen plasma

Group B : Human serum albumin

Table IV: Body weight of the study population between two groups

Weight in Kg	Group A (n=40)	Group B (n=34)	Mean changes	P value
	Mean±SD	Mean±SD	Mean±SD	
Day 1	61.68±7.74	61.13±10.16	-0.55	0.805
Day 6	59.71±9.03	58.16±10.30	1.55	0.499
Mean change	-1.97±1.81	-2.96±2.62		0.016
P value	0.001	0.001		

Group A: Fresh frozen plasma Group-B B : Human serum albumin.

Table showing mean wt loss in group-B is more than that of group-A

Table V: Abdominal girth of the study population between two groups

Abdominal girth (cm)	Group A (n=40) Mean±SD	Group B (n=3 4) Mean±SD	Mean changes	P value
Day 1	85.77±8.43	84.59±6.57	1.18	0.502
Day 6	80.91±8.08	77.86±5.48	3.05	0.059
Mean change	-4.71±1.84	-6.59±4.54		0.014
P value	0.001	0.001		

Group A: Fresh frozen plasma Group B : Human serum albumin

Table VI: Urine output (24 hours) of the study population between two groups

Urine output (24 hours)	Group A (n=40)	Group B (n=34)	Mean changes	P value
	Mean±SD	Mean±SD		
Day 1	1041±301	958±432	83	0.354
Day 6	1400±270	1629±522	229	0.026
Mean change	349±209	680 ±342		0.001
P value	0.001	0.001		

Group A: Fresh frozen plasma Group B : Human serum albumin**.**

Table showing The mean increase in 24 hour urine volume was significantly more in group-B than in group-A.

Table VII: Serum albumin of the study population between two groups

Serum albumin (g/l)	Group A (n=40)	Group B (n=34)	Mean change	P value
	Mean±SD	Mean±SD		
Day 1	23.76±2.87	23.84±2.46	0.08	0.899
Day 6	28.76±3.13	30.55±2.85	1.79	0.012
Mean change	5.55±2.76	6.66±2.53		0.002
P value	0.001	0 .001		

Group A: Fresh frozen plasma Group B : Human serum albumin.

Table showing Albumin increase in group-B was significantly more than that of group-A

Table VIII: Urinary sodium (24 hours) of the study population between two groups

Urinary sodium (2 4 hours)	Group A (n=40)	Group B (n=34)	Mean changes	P value
	Mean±SD	Mean±SD		
Day 1	67.52±14.89	60.01±18.82	7.51	0.065
Day 6	119.67±36.87	143.23±43.32	26.56	0.015
Mean changes	50.03±35.02	82.18±45.17		
P value	0.001	0.001		

Group A: Fresh frozen plasma Group B : Human serum albumin.

Table showing Excretion of 24 hour urine sodium is more in group-B than that of group-A

Table IX: Adverse event (incidence)

Transfusion reaction	Group A (n=40)		Group B (n=34)	
	No	%	No	%
Mild (Articarial)	1	**2.5**	0	0 0
Febrile reactions	0	0	0	00
Severe anaphylactic	0	00	0	00
None	39	**97.5**	34	100

Group A: Fresh frozen plasma Group B: Human serum albumin.

Table showing only one patient had mild articarial transfusion reaction in group-A which is 2.5%, but no adverse reaction occurred in group-B

Table X: Correlation between albumin and weight in different group

	Group A		Group B	
	r value	p value	r value	p value
Weight loss versus change in serum albumin	-0.058	0.717	-0.166	0.339

Group A: Fresh frozen plasma Group B : Human serum albumin

r → pearson correlation coefficient)

Table showing that in both group-A and group-B, decrease in body weight is accompanied by increase in serum albumin, but no significant correlation was found

Discussion

Two predominant factors in the formation of ascites are portal hypertension and hypoalbuminaemia. In the current study, the patients of both groups were followed the first-line treatment modalities for ascites; bed rest, salt restricted diet, water restriction and standard dose of diuretics. We attempted to increase the response to diuretics through the administration of low doses of albumin either in the form of Human serum albumin (HSA) in group-B or cheap alternative the fresh frozen plasma (FFP) in group-A. We compared the two groups on the basis of clinical response (reduction in body weight, decrease in ascites reflected by abdominal girth measurement and increase in 24-hour urine output) and laboratory data (serum albumin and 24-hour urinary sodium).

The results of our study gives similar picture to the previous study. In our study, the mean weight loss on day-6 (after 5 days HSA) was 2.96±2.62 Kg which is consistent to the study by Nakamura T[10]. where weight loss was 3.06 kg. In group-A, that is with FFP, the mean weight loss was 1.97±1.81 kg which is lower than that of group B. In this study the mean ±SD abdominal circumference in group-A was 85.40±8.61cm and in group-B was 84.19±6.53cm, those are similar to previous study (Nakamura T)[10]. They showed that the mean abdominal circumference were 87.46±9.78 cm and 88.12±2.34 cm. The mean decrease in abdominal girth in group-A was 4.73±0.4 cm and in group-B was 7.05±0.68 cm, both are statistically significant (P value 0.001). The mean decrease in abdominal girth was more in group-B than in group-A, and was statistically significant. It was also found that on day 1, the mean urine output (24 hours) in group A(with FFP) was 1041±301 ml and in group-B 958±432 ml. On day 6, mean urine output (24 hour) in group A was 1400±270 and in group-B was 1629±522 ml. The similar result was found in the previous study (Nakamura T).[11] The mean increase in 24 hour urine volume was 349±209ml in group-A and 680±342 ml in group-B, both are statistically significant (p= 0.001). The mean increase in 24 hour urine volume was more in group-B than in group-A.

Study showed that mean increase in serum albumin in group-A was 5.07±0.12 and in group-B was 6.65±0.03. Both are statistically significant (P value 0.001). Albumin increased more in group-B than that of group-A, that was statistically significant (P = 0.003). In the study of Gentilini[4] the serum albumin in group-B (with albumin) was 29.6±0.7g/l on day1 and, 34.3±0.6g/l on day-6. Serum albumin at the end of the treatment was higher in group B than in group A (34.3±0.6 vs. 31.2±0.6 g/l, p<0.0l).

Study also showed that the mean increase in 24 hour urinary sodium was 50.03±mEq/L in group-A which was statistically significant(P value 0.001) and the

mean increase of 24 hour urinary sodium in group-B was 82.18±45.17 mEq/L which was statistically significant (P value 0.001). Excretion of 24 hour urine sodium was more in group-B than that of group-A, and the difference between two groups was statistically significant (p = 0.006). Similar result was found in the study by Gentilini P[4]. and by Nakamura T[11]. The study by Gentilini showed that The mean increase in 24 hour urinary sodium was 86.82±9.42 mEq/L which is statistically significant($p<0.05$). So urinary sodium was more in albumin group.

Only one patients had mild articarial transfusion reaction in group A (treated with FFP) which is 2.2%. but no transfusion reaction happened in group-B (with albumin). Similar result was found in the study by Gentilini where No patients of the study had side-effects to treatment with albumin.

In our study statistical correlation between increases in serum albumin and decreases in body weight was not found that is also consistent with the previous study (Nakamura T)[12].

The number of non-responder patient in group-A was 4 out of 44(9.09%) and that of group-B is 3 out of 37 (8.10%). This finding is similar to previous study result (Gentilini)[8]. These patients may require high dose of diuretics and albumin for their treatment.

The most outstanding finding of this study was that the HSA (group-B) was more effective than FFP (group-A). We gave the same treatment modalities in both the groups except HSA or FFP. Both the groups were age and sex matched. All patients were admitted in hospital, so there was less chance to be influenced by third variable. Therefore we can say that the variation in results between two groups was due to effects of either fresh frozen plasma (in group-A) or human serum albumin (in group-B). All the measured outcome variables (Decrease in Body weight (kg), Decrease in abdominal girth (cm), Increase in 24 hr urinary volume (cc), Increase in Serum albumin (g/dl) & Increase in 24 hour urinary sodium (mmol/L) showed better effects with statistical significance in group-B (with human serum albumin). Though the cost of FFP is low, effect is also low. So it can be tried to use FFP as an alternate cheap source of human albumin in selective patient with cirrhosis of liver.

Conclusion

The results of this randomized, controlled trial indicate that in addition to diuretics low doses of human albumin either in the form of human serum albumin (Griffol's 20%) or alternative the fresh frozen plasma(FFP) are effective. But the results of the outcome variables showed better with HSA. The correlation between increases in serum albumin and decreases in body weight was not found in this study**.** The previous study showed that the plasma rennin concentration is an important factor which may be a target for future research.

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