

Original Article

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Comparing the Effects of Hydroxyethyl Starch and Albumin in Cirrhotic Patients with Tense Ascites; a Randomized Clinical Trial

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Abstract

Introduction: Large-volume paracentesis is one of the usual treatments for cirrhotic patients with tense ascites, which may cause different complications including decreased cardiac preload, suppressed renin angiotensin system, inactivation of sympathetic nervous system, electrolyte imbalances, etc.

Objective: The aim of this study was to compare the effects of administrating hydroxyethyl starch (HES) and albumin in cirrhotic patients with tense ascites in order to reduce the paracentesis complications.

Methods: In the present randomized clinical trial, 108 cirrhotic patients with tense ascites were enrolled. The patients were randomly divided into 3 groups. In group A, albumin 20% with 5 g/L dose of paracentesis fluid, in group B, HES 6% dissolved in saline were administered, and in group C, a combination of albumin 20% and HES 6% with half the dosage administrated to two other groups were prescribed. Then biochemical panel, and liver function tests and renal and electrolyte complications were compared between the groups.

Results: The results obtained after intervention did not show significant differences between the groups regarding weight ($p=0.102$), heart rate and platelet count (both $p=0.094$), hematocrit ($p=0.09$), creatinine ($p=0.421$), serum sodium ($p=0.743$) and potassium ($p=0.147$), total bilirubin ($p=0.375$) and urine volume ($p=0.421$). Additionally, we concluded that mean arterial pressure of patients who had received albumin was higher than the other 2 groups ($p < 0.001$).

Conclusion: The results of the present study showed the similar effects of HES and albumin in cirrhotic patients with tense ascites undergoing large-volume paracentesis.

Key words: Albumins; Ascites; Hydroxyethyl starch derivatives; Liver cirrhosis; Serum albumin

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INTRODUCTION

Ascites is defined as accumulation of more than 25 cc liquid in the peritoneal cavity, which has various reasons including cirrhosis, anomaly, congestive heart failure, Budd-Chiari syndrome, tuberculosis, and pancreatitis. Ascites is one of the most common complication that manifests in about 60% of cirrhotic patients within 10 years (1, 2). Various treatment methods have been proposed including diuretics, paracentesis, and trans-jugular intrahepatic portosystemic shunt (TIPS) placement, but none improved the survival of cirrhotic patients (3, 4). Among the treatment options, paracentesis is the most common one that could lead to various problems in the circulatory system by increasing cardiac output and decreasing cardiac preload (5). Thus, finding other treatment methods for these patients is still

necessary. Albumin is the most common protein found in blood and has various functions such as maintaining intravascular volume and colloid osmotic pressure, anti-oxidant, anti-inflammation, stabilizing endothelial wall, and might play an important role in treatment of ascites caused by cirrhosis (6-8). The effects of albumin in cirrhotic patients with tense ascites vary and include prevention of dysfunction after paracentesis, decreased autonomous bacterial peritonitis, prevention of kidney injury and increasing survival. On the other hand, hydroxyethyl starch (HES) is used for treatment and prevention of hypovolemia by sustaining water in the plasma and increasing blood volume. It has recently been used as plasma expander in cirrhotic patients with tense ascites (9). Considering the complications caused

by paracentesis, the need to find a safe, non-invasive and cheap treatment method is still present. In addition, to the best of our knowledge, there are not enough prospective studies in this regard and moreover, contradicting results have been presented in this era. Therefore, the present study aimed to evaluate and compare the results of HES and albumin in cirrhotic patients with tense ascites in order to reduce the paracentesis complications.

METHODS

Study design

This randomized clinical trial was performed in Alzahra Hospital, Isfahan, Iran, from January to May 2017. The study protocol was approved by the ethical committee of Isfahan University of Medical Sciences and the code of 395092 was assigned to it. All the participants signed the written consent form. The authors were fully adhered to the Declaration of Helsinki Principles throughout the study.

Study population

Inclusion criteria consisted of cirrhotic patients with tense ascites that were diagnosed by the emergency physician based on clinical criteria and ultrasonography findings (including cirrhosis of patients and presence of ascites fluid) and referred to the hospital, serum creatinine <1.4 mg/dL, serum sodium >120 mEq/dL, giving consent for participation in the study.

Having any comorbid diseases in addition to cirrhosis, history of gastrointestinal (GI) bleeding in the past 2 weeks, presence of portosystemic anastomosis or peritoneal shunt, receiving plasma expander or paracentesis in the past 10 days, creatinine increasing to more than 2 mg/dL during the study, hepatic anomaly encephalopathy, severe cardiac, pulmonary, and renal diseases, infectious disease, hypotension (systolic blood pressure (SBP) <80 mmHg), severe hemodynamic disorder, withdrawing from participation in the study and patients' data not being complete were all considered as the exclusion criteria.

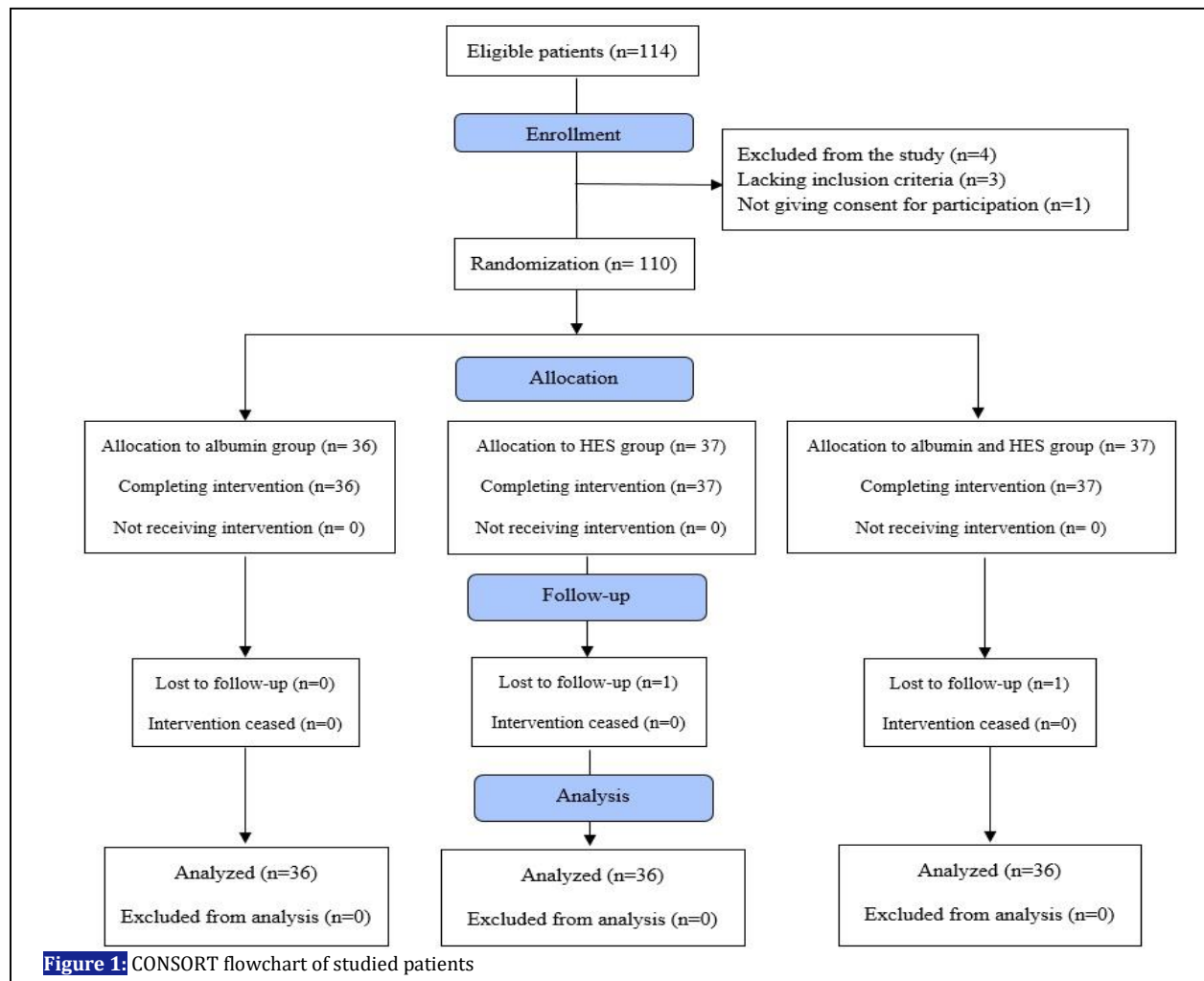


Figure 1: CONSORT flowchart of studied patients

The eligible patients were divided into 3 groups: group A received albumin, group B received HES, and group C received a combination of albumin and HES. Allocation of patients was via blocks, therefore since our studies included 3 groups, blocks of 12 included 4 participants that were allocated to albumin group, 4 participants in HES group and 4 participants of albumin and HES group, and this pattern went on until sample size was reached. CONSORT flowchart of the study has been shown in figure 1. Overall, 114 patients with the diagnosis of cirrhosis with tense ascites were eligible and 110 cases were allocated for each group: 36 in albumin group, 37 in HES group and 37 in albumin and HES group. In the end, 6 patients were excluded and 108 participated in the study. Those who prescribed the drugs were independent from those who gathered patient data and both were blind to the type of drugs prescribed

Intervention

Patients did not receive diuretics and vasoactive agents for at least 5 days before paracentesis. Liquid intake before paracentesis was not more than 115 L per day. Patients were fasting before paracentesis and electrolyte levels, serum creatinine, complete blood count (CBC), and liver function tests were evaluated before paracentesis. Ascites fluid samples were sent to the hospital laboratory for undergoing routine tests such as culture, cell count, and biochemical tests.

Group A: Albumin 20% with 5 g/L dose of parasythesized liquid (5g/L albumin in each liter of parasythesized liquid) was injected intravenously (to prevent liquid increase in vessels, half of the required albumin was prescribed during paracentesis and the other half during 6-8 hours after paracentesis) (10).

Group B: HES 6% with 5 g/L dose of parasythesized liquid (5g/L HES in each liter of parasythesized liquid) was injected intravenously (to prevent liquid increase in vessels, half of the required HES was prescribed during paracentesis and the other half during 6-8 hours after paracentesis) (10).

Group C: A combination of albumin 20% and HES 6%, with half the dose injected in groups A and B, was given. This means that each of the compounds (albumin 20 and HES 6%) were prescribed with 2.5 g/L dose and similar to protocol A.

Four days after paracentesis, weight, mean arterial pressure, heart rate, urinary output, and level of consciousness were evaluated. In addition, in this time period biochemical tests (platelet, hematocrit, 24-hour urine volume, fasting blood sugar (FBS), potassium, sodium, albumin, bilirubin, and

prothrombin time) and liver function tests were done for all the patients.

The complications that manifested after paracentesis and were important to us included: renal failure defined as more than 50% increase in serum creatinine ($> 1.5\text{mg/dL}$), hyponatremia where sodium concentration was less than 130mEq/dL , hyperkalemia (potassium concentration $> 5.5\text{mEq/dL}$), infection, especially spontaneous bacterial peritonitis, encephalopathy, and cardiac diseases associated with paracentesis.

Statistical analysis

All patient data including demographic factors and paraclinical symptoms were recorded in a checklist designed by the researcher and entered to SPSS 22 software; statistical analyses were presented in descriptive and analytic sections. In the descriptive section, mean and standard deviation of the laboratory variables and frequency of side effects were presented as the main variable in different groups and all demographic and clinical data of the patients were reported based on descriptive criteria. In the analytic section, based on statistical assumptions, proper parametric and non-parametric tests were applied. To analyze qualitative findings chi-square and for comparison of quantitative data independent t-test were used. If the initial assumptions, such as normality of data, were not true, non-parametric Mann-Whitney test was used. All tests were evaluated at 5% error level and p-value < 0.05 considered significant.

RESULTS

Finally, 108 patients completed the survey. The mean age of studied patients was 45.48 ± 3.95 years and 62 cases (57.4%) were male. Table 1 reports values of the studied variables in the 3 groups of patients before and after intervention. The mean age ($p=0.218$) and sex ratio ($p=0.767$) were not statistically different. Before intervention, there was no significant difference between the groups regarding the variables except for prothrombin time index, which stayed the same after intervention ($p=0.001$).

In the results obtained after intervention, there was no significant difference in the variables such as weight, 24-hour urine volume, bilirubin, heart rate, platelet, hematocrit, sodium, and potassium ($p>0.05$), but mean arterial pressure was significantly different in the albumin receiving group compared to the other 2 groups, which indicates that albumin is good for patients with hemodynamic disorders. In addition, no dangerous and negative side effect was detected in any of the groups.

Table 1: Values of studied variables in the 3 groups of patients before and after intervention

Variable		Albumin group	HES group	HES and albumin group	p
		(n=36)	(n=36)	(n=36)	
		Mean ± SD			
Weight (Kg)	Before	77.36 ± 12.91	81.61 ± 14.43	74.05 ± 15.09	0.081
	After	72.19 ± 12.71	76.16 ± 14.22	69.05 ± 14.93	0.102
Mean arterial pressure (mmHg)	Before	83.81 ± 3.09	84.35 ± 2.41	84.16 ± 1.90	0.651
	After	84.67 ± 2.59	82.24 ± 2.43	80.56 ± 3.05	<0.001
Heart rate (/min)	Before	80.11 ± 6.49	78.33 ± 5.70	81.55 ± 6.76	0.102
	After	77.05 ± 5.72	74.61 ± 5.49	77.5 ± 6.69	0.094
Platelet count (/mm ³)	Before	250.14 ± 57.1	226.78 ± 61.47	228.86 ± 81.87	0.273
	After	301.41 ± 61.11	273.52 ± 61.12	275.66 ± 82.29	0.166
Hematocrit (%)	Before	36.68 ± 3.32	37.13 ± 3.30	35.29 ± 4.34	0.093
	After	38.05 ± 3.34	38.49 ± 3.33	36.63 ± 4.35	0.09
Serum sodium (mEq/L)	Before	135 ± 2.98	134.67 ± 2.96	134.75 ± 3.43	0.896
	After	134.16 ± 3.07	133.58 ± 3.05	133.88 ± 3.47	0.743
Serum potassium (mEq/L)	Before	4.36 ± 0.32	4.46 ± 0.32	4.28 ± 0.36	0.094
	After	4.21 ± 0.32	4.30 ± 0.34	4.13 ± 0.38	0.147
Total bilirubin (mg/dL)	Before	5.76 ± 1.57	6.22 ± 1.99	5.75 ± 2.11	0.494
	After	4.3 ± 1.59	4.88 ± 2.02	4.35 ± 2.15	0.375
Prothrombin time index (%)	Before	62.22 ± 14.17	70.44 ± 8.85	63.97 ± 12.43	0.011
	After	59.5 ± 13.96	67.63 ± 8.67	61.22 ± 12.15	0.011
Urine volume (ml/day)	Before	1065.37 ± 282.54	1044.44 ± 257.67	1129.16 ± 268.69	0.385
	After	1358.33 ± 281.7	1358.33 (±287.72)	1434.72 (±281.02)	0.421

DISCUSSION

Based on the obtained results, there was no significant difference between the groups regarding the studied variables. However, we concluded that in patients with hemodynamic disorders, albumin is a better choice. This study showed that prescription of HES, albumin and even both simultaneously has the same effects in treatment of cirrhotic patients with tense ascites.

A study by Abdel-Khalek, et al. showed that in cirrhotic patients with tense ascites who have undergone paracentesis HES 6% is as effective and safe as albumin for prevention of renal and electrolyte complications and just like the current study they concluded that transients hypotension after paracentesis is more common in HES group (10).

In a study performed by Alsebaey et al. it was shown that Terlipressin and HES have the same effects as low dose albumin regarding prevention of hemodynamic disorder following large-volume paracentesis, but they cost less than albumin. Additionally, they concluded that plasma renin activity in HES group increases less than the other groups and urinary output was significantly higher than baseline at the time of discharge, but there was no significant difference between the groups in this regard (11).

Altman et al. also showed that in cirrhotic patients HES is tolerated better than albumin. They also found out that there is no difference between HES and albumin regarding prevention of complications associated with large-volume

paracentesis. They also concluded that weight loss occurs less in HES group (12). Fernandez et al. showed that albumin, but not HES, improves the hemodynamic status of patients with spontaneous bacterial peritonitis (13). These results were similar to our findings, which showed that albumin prescription is better in patients with hemodynamic disorder and did not show any differences between HES and albumin administration regarding biochemical, and liver function tests and renal complications.

In a meta-analysis performed by Bernardi et al. it was shown that albumin decreases the morbidity and mortality of cirrhotic patients with tense ascites undergoing large-volume paracentesis. In addition, they compared replacement treatments such as dextran 70, 6%, gelatin 3.5%, HES 6%, dextran 40, 10%, Terlipressin 3mg, saline 3.5%, norepinephrine 0.5-3 mg, and Midodrine 12.5 mg (14). These results are in line with our findings. However, we followed patients for a shorter period of time, which was one of the limitations of this study and there is a need for further studies and increased follow-up period to evaluate the patients regarding mortality rate with various methods. The results of the present study showed the similar positive effects of HES and albumin in cirrhotic patients with tense ascites undergoing large-volume paracentesis. We concluded that in patients with hemodynamic disorders, albumin is better and based on the patients' condition it should be used as an additional treatment on the side of standard treatment, which leads to a significantly

better control of biochemical and liver function tests and renal and electrolyte complications.

Limitations

Since there are many items on the exclusion criteria of this study (so that the results of the study will not be affected and confounding factors are eliminated) it is difficult to generalize the aforementioned findings to emergency patients. Therefore, it is suggested to carry out a study with a bigger sample size and include patients with various clinical statuses to generalize the findings of the study and evaluate the effects of the drugs applied in this study more accurately. Among other limitations of the study is the lack of long-term evaluation of the drugs' effects (1 week and 1 month later) regarding need for re-admission, or re-injection of the drug and the required dose to determine the real effects of both drugs. Therefore, another study is suggested to evaluate and follow the patients for a long period of time.

CONCLUSIONS

The results of the present study showed the similar effects of HES and albumin in cirrhotic patients with tense ascites undergoing large-volume paracentesis. Therefore, it can be concluded that albumin should better be prescribed for patients

with hemodynamic disorders based on the status of the patients and as an adjunct treatment in addition to standard treatment.

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AUTHORS' CONTRIBUTION

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.

CONFLICT OF INTEREST

None declared.

FUNDING

None declared.

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