

Intravenous albumin in treatment of acute on chronic liver failure: Can it be an option for resource constrained situation?

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ABSTRACT

Introduction: Acute on chronic liver failure (ACLF) is a form of acute decomposition of cirrhosis with alarmingly high mortality. This condition is seen in both hemispheres, and despite having varied etiology and despite the differences in standard of care, the prognosis of ACLF is grave in the East and in the West alike. Since there is no definitive treatment for ACLF, other than liver transplantation, as of now, it is important to develop a safe, effective, and easily deliverable treatment for this grave condition.

Materials and Methods: In all 30 ACLF patients for included in this observational clinical study, who were randomized into 2 groups. One group received intravenous albumin infusion plus standard of care, while the other group received standard of care only. Each group included 15 patients.

Results: There was no difference in demographic characteristics and baseline parameters between the patients in the 2 groups. The association between investigations in different follow-ups among the 2 groups was also statistically not significant. At 28 days, 53.3% patients were alive in the albumin plus SOC group and 33.3% in the SOC only group. But a significant survival difference between the two groups was not observed. Hepatic encephalopathy and multi-organ failure were the major causes of death in these 2 groups, respectively. This was also statistically not significant.

Conclusion: The study established the safety of intravenous albumin infusion in ACLF patients and yielded a non-statistically significant survival benefit when intravenous albumin infusion is combined with the standard of care in ACLF.

Keywords: ACLF, intravenous albumin infusion, mortality.

Introduction

The Asian Pacific Association for the Study of the Liver (APASL) defines ACLF as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dl) and coagulopathy (INR ≥ 1.5) complicated within 4 weeks by clinical ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver disease, associated with high 28-day mortality [1]. The etiology of ACLF varies geographically, with infections like hepatitis B (HBV) and hepatitis E (HEV) viruses dominating in the East, while alcohol and drugs are the predominant causes in the West. In Bangladesh, the predominant acute insult for ACLF has been reported to be HEV. It contributes to 21.7% cases [2]. However, irrespective of etiology, the mortality in ACLF remains high from multi-organ failure attributed to immunologic defects in these patients. Mortality from ACLF in hospitalized patients is between 43-89% [3]. It has been proposed that there is a 'golden window' period of 1 week before the development of sepsis and catastrophic extra-hepatic organ failure in ACLF patients, when active intervention may reverse the downhill course of the disease [1].

However, unfortunately, there are few specific therapeutic options for ACLF as of date, with liver transplantation being the principal treatment.

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At present, medical management of ACLF concentrates mainly on management of precipitating events, end-organ support, and complication prevention [4]. The quest for effective treatment of ACLF is therefore ongoing.

Albumin is the most abundant plasma protein, which is encoded on chromosome 4. It consists of a single polypeptide chain of 585 amino acid residues and contains 17 disulfide bonds. The chain is folded into a heart-shaped molecule consisting of 3 homologous domains, each having 2 sub-domains [5]. The molecular weight of albumin is approximately 67 kDa. It is a negative acute-phase protein synthesized by the liver and contributes to 50% plasma protein mass, accounting for approximately 10% protein synthesized by the liver. In other words, the healthy liver produces approximately 10-15 gm of albumin daily [6].

Materials and Methods

Rationale

While liver transplantation is the definitive treatment for ACLF, its utility is limited due to donor organ shortage, high cost, and limited availability. Artificial liver support devices offer no benefit over medical treatment in ACLF. It has been hypothesized that intravenous albumin infusion may be beneficial in reversing ACLF by lowering inflammatory

cytokines. Besides, it can be administered without any specialized setup. This observational clinical study was therefore conducted to assess whether intravenous albumin infusion in addition to the standard of care (SOC) is safe and superior to SOC alone in improving 28-day mortality in ACLF patients.

Outcome

Safety as well as Improvement of 28-day transplant-free survival of ACLF patients with intravenous albumin infusion in addition to SOC to SOC only, was taken as the outcome of this trial.

Inclusion and exclusion criteria

ACLF patients between 18-65 years of age of both genders, fulfilling the APASL definition of the disease, were included in this clinical trial. ACLF patients who had received intravenous albumin infusion within the preceding week, patients with spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS) and paracentesis induced circulatory dysfunction (PICD), patients requiring large volume paracentesis, pregnant women, patients with previous known allergy to albumin and patients with coexistent hepatocellular carcinoma (HCC) and comorbidities like, heart failure and chronic kidney disease (CKD) were excluded.

Sample size calculation and statistical analysis

The formula for comparison of 2 proportions was used to determine the sample size. In all, 30 ACLF patients were included. Qualitative data was analyzed by the Chi-square test and quantitative data by the Student's t-test. Regression analysis was done for the confounding variable to explore the effect on mortality, p-value less than 0.05 was considered to be significant. All data were analyzed by SPSS (version 26.0, IBM Corp: Armonk, NY, USA).

Study procedure

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (approval number 3847). The study was conducted at the Department of Hepatology, Bangladesh Medical University (BMU) from September 15, 2022, to May 31, 2023. Written informed consent was obtained from every patient. Thirty ACLF patients were included in the study. They were randomized into 2 groups by block randomization. In group A, 15 patients received intravenous infusion of 20% human albumin 40 gm on day 1 (*i.e.*, loading dose) followed by 20 gm/day intravenously for 7 days and then every alternate day till day 28, in addition to SOC. In group B, another 15 patients were assigned SOC only.

SOC included close clinical assessment (*i.e.*, appetite, sleep pattern, level of consciousness, bowel habit, color of stool and

urine, abdominal pain, fever, jaundice, flapping tremor, ascites, hematemesis and melaena etc.), early use of broad-spectrum antibiotics in case of suspicion of infection, oral non-absorbable disaccharide (*e.g.* lactulose), rifaximine and L-ornithine L-aspartate (LOLA) to treat hepatic encephalopathy, maintenance of blood sugar, trace element and mineral supplementation and so on. Blood tests (*i.e.*, complete blood count (CBC), serum alanine transaminase (ALT), serum aspartate transaminase (AST), serum total bilirubin, international normalized ratio (INR), serum albumin, serum creatinine, and serum electrolyte) were checked at day-0, 7, 14, and 28 as well as at the time of deterioration.

Both groups were followed up for 28 days or up to death, whichever was earlier. The cause of death of patients who died within 28 days was documented. Biochemical, Hematological, and Virological tests were performed at the Departments of Biochemistry, Hematology, and Virology of BMU, while abdominal ultrasonography and endoscopy of the upper gastrointestinal tract were performed at the Departments of Radiology and Imaging and Hepatology of the same university, respectively. Data was collected in a preformed data collection sheet approved by the IRB.

Maintaining confidentiality

Each study subject was assigned a unique identity number, which was followed throughout the study. All research data were coded and stored in a locked cabinet, accessible only to the research team and IRB members. Contact details and cell phone numbers of the patients and their near to kin were recorded.

Results

It was observed that in group A, 1 (6.67%) patient was between 18-30 years, and 2 (13.3%) in group B were in this age range. 9 (60%) patients were between the age group 31-50 years in both groups. Five (33.33%) patients in group A and 4 (26.67%) in group B were above 50 years old. The majority of patients were male in both group A and group B, which is 14 (93.3%). The majority 14 (93.3%) patients were married in group A and all (100%) in group B. In group A, 2 (13.3%) were bachelor's and above, 3 (20%) passed HSC, 5 (33.3%) passed SSC. On the other hand, in group B 2 (13.3%) were bachelor and above, 2 (13.3%) passed HSC, 5 (33.3%) passed SSC. 46.7% patients were service holders in group A and 33.3% in group B. The difference was statistically not significant ($p > 0.05$) between the two groups. In group A 5 (33.3%) of the patients had a monthly income above 20000 BDT and 7 (46.7%) had a monthly income between 10001-20000 BDT. In group B, 4 (26.7%) had a monthly income above 20000 BDT and 4 (41.5%) had a monthly income between 10001-20000 BDT. The difference was also not statistically significant ($p > 0.05$) between the two groups (Table-1).

Table-1: Association between demographic variables between two groups (n=30)

Demographic variable	Group A (n=15)		Group B (n=15)		p-value	Statistical test
	n	%	n	%		
Age in years						chi-square test and student 't' test
18-30	1	6.67	2	13.33		
31-50	9	60	9	60		
≥50	5	33.33	4	26.67	0.935	
Mean±SD	46.80±10.02		43.46±10.28			
Sex						
Male	14	93.3	14	93.3		0.377
Female	1	6.7	1	6.7		
Marital status						
Married	14	93.3	15	100.0	0.551	

Unmarried	1	6.7	0	0.00		chi-square test and student 't' test
Education						
Illiterate	2	6.7	0	20.0		
Primary	3	46.7	5	33.3	0.090	
SSC	5	6.7	6	40.0		
HSC	3	20.0	4	36.7		
Bachelor and Above	2	13.3	0	00		
Occupation						
House wife	1	6.7	0	00		
Service	7	46.7	5	33.3	0.090	
Farmer	1	6.7	6	40.0		
Business man	3	20.0	4	36.7		
Others	3	20.0	0	00		
Monthly income						
5001-10000	3	20.0	7	46.6		
10001-20000	7	46.7	4	26.7	0.282	
Above 20000	5	33.3	4	26.7		

p-value<0.05 was considered as significant

The mean hemoglobin (Hb) was found 11.16±2.07g/dl in group A and 11.22±1.09 g/dl in group B. The mean bilirubin was 20.30±10.79mg/dl in group A and 18.53±8.14mg/dl in group B. The mean INR of group A and group B were 2.24±0.59 and 2.03±0.61 respectively. There was no statistically significant difference among baseline parameters between the patients in the 2 groups (Table-2).

Table-2: Association of baseline parameters between two group (n=30)

Baseline parameter	Group A (n=15)	Group B (n=15)	P value	Statistical test
	Mean±SD	Mean±SD		
Hb	11.16±2.07	11.22±1.09	0.930	Student 't' test
TC	1140.91±4387.27	8.48±2.25	0.326	
Neutrophil	70.53±10.41	73.40±8.03	0.406	
ESR	37.46±21.38	37.53±28.64	0.994	
Platelet	137.73±41.18	158.66±83.11	0.390	
Serum bilirubin	20.30±10.79	18.53±8.14	0.616	
ALT	278.86±367.71	263.26±225.77	0.890	
AST	373.13±479.71	303.10±246.911	0.619	
INR	2.24±0.59	2.03±0.61	0.350	
Serum albumin	20.99±8.53	22.24±6.83	0.660	
AFP	15.65±14.44	20.49±19.17	0.442	
Serum creatinine	1.62±0.99	1.21±0.56	0.170	
Serum electrolyte sodium	132.33±6.05	132.60±5.86	0.903	
Serum electrolyte potassium	4.45±1.56	3.83±0.92	0.196	

p-value<0.05 was considered as significant

Association between investigations in different follow-ups among the 2 groups were compared. It was observed that all parameters were statistically not significant (p>0.05) between baseline to at 3rd follow-up at 28 days among the 2 groups (Table-3).

Table-3: Investigations in different follow up among two groups

Baseline parameter	Group A (n=15)	Group B (n=15)	P value	Statistical test
	Mean±SD	Mean±SD		
Serum bilirubin				student 't' test
At 1 st follow up (7 days)	11.38±1.99	11.13±1.15	0.704	
At 2 nd follow up (14 days)	12.15±10.94	10.26±9.08	0.719	
At 3 rd follow up (28 days)	7.47±6.64	4.34±2.35	0.342	
ALT				
At 1 st follow up (7 days)	208.07±197.01	176.53±114.88	0.623	
At 2 nd follow up (14 days)	117.87±68.57	111.00±55.11	0.844	
At 3 rd follow up (28 days)	91.71±50.84	66.20±36.47	0.362	
AST				
At 1 st follow up (7 days)	217.92±226.54	211.30±131.87	0.928	
At 2 nd follow up (14 days)	173.87±101.47	126.33±67.78	0.342	
At 3 rd follow up (28 days)	144.14±100.73	69.40±30.02	0.143	
INR				
At 1 st follow up (7 days)	1.87±0.45	1.92±0.60	0.824	
At 2 nd follow up (14 days)	1.76±0.74	1.58±0.55	0.629	
At 3 rd follow up (28 days)	1.42±0.20	1.36±0.34	0.729	
Serum albumin				
At 1 st follow up (7 days)	21.83±1.65	22.50±5.05	0.845	
At 2 nd follow up (14 days)	21.57±9.94	20.50±9.09	0.829	
At 3 rd follow up (28 days)	23.05±9.76	27.60±4.21	0.356	
Serum creatinine				
At 1 st follow up (7 days)	1.15±0.42	1.28±0.40	0.442	
At 2 nd follow up (14 days)	1.30±0.61	1.16±0.37	0.646	
At 3 rd follow up (28 days)	1.03±0.22	1.12±0.28	0.551	

p-value<0.05 was considered as significant

When the outcome of the patients at 28 days after albumin infusion plus SOC and SOC only was studied, it was observed that 8 (53.3%) patients were alive in group A and 5 (33.3%) in group B. But significant survival difference between two groups was not observed in any follow up ($p>0.05$) (Figure-1).

It was observed that hepatic encephalopathy 4 (50%) in group A and multi-organ failure 4 (40%) in group B were the main cause of death. The difference was, however, statistically not significant ($p>0.05$) between the two groups (Table 4).

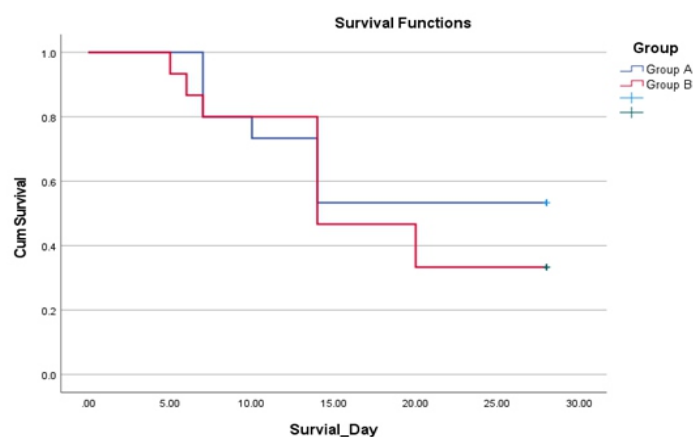


Figure 1: Cumulative survival rate percentage of patients in the Albumin +SOC and SOC only groups at baseline to 28 days.

Table 4: Cause of death among two groups (n=17)

Cause of death	Group A (n=7)		Group B (n=10)		p-value	Statistical test
	n	%	n	%		
Hepatic encephalopathy	4	57.1	3	30.0	0.366	chi-square test
Variceal haemorrhage	2	28.57	3	30.0		
Multi-organ failure	1	14.28	4	40.0		

$p\text{-value}<0.05$ was considered as significant

Discussion

Currently, modern medical science is quite helpless in managing ACLF patients, more so in resource-constrained set-ups like that of ours. When we say, resource constraint, we do not necessarily refer to constrain of financial resources only. In a country like Bangladesh, which is graduating to middle-income status, many can afford expensive treatment. However, the constraint lies elsewhere, namely the lack of advanced centers and most importantly the lack of specialists and skilled manpower. We do not have access to liver transplantation as of now. Liver support devices like molecular absorbent recirculating system (MARS) and Prothymus devices are not only very expensive, they are also not superior to medical management for ACLF [1]. Besides, in Bangladesh, such devices are also not present.

Plasma exchange (PLEX) can be beneficial in such patients [7, 8]. However, although PLEX can be offered in a tertiary care center like ours, in a country like Bangladesh, where there are only a handful of Hepatologists and health care facilities are predominantly centered around the major urban centers, even PLEX is difficult to perform in peripheral hospitals.

Subcutaneous injections of granulocyte colony-stimulating factor (G-CSF) are one option, which may help ACLF by mobilizing bone marrow-derived CD34+ cells [9], however, it is yet to be an established modality of treatment for ACLF, due to conflicting results from studies conducted in different parts of the world, particularly the West, where outcomes with G-CSF injections in ACLF were not rewarding. As such, it is imperative to look for a treatment option for ACLF, which will not only be safe and effective, but also be as such that it can be delivered in a peripheral center in a resource-constrained situation like ours, where there is extreme scarcity of specialists and specialized centers.

Although mainly responsible for maintaining colloidal osmotic pressure, several other physiologic functions of albumin are well recognized. It has, among others, antioxidant, anti-inflammatory, and immune-modulatory functions. It attenuates prostaglandin E2 (PGE2) mediated immune dysfunction in decompensated liver cirrhosis [10]. Albumin also exerts an immune-modulatory effect by down regulating the expression

of tumor necrosis factor (TNF α) and nuclear factor κ -B [11]. It scavenges reactive oxygen and nitrogen species [12].

Intravenous albumin has wide indications in liver cirrhosis in SBP, PICD, and HRS, to name a few. However, the ability of albumin to bind proinflammatory molecules like pathogen-associated molecular patterns (e.g. gram-negative bacterial byproduct lipopolysaccharide), prostaglandins, nitric oxide (NO) and oxygen and nitrogen species makes it a likely candidate for treatment of ACLF, as these molecules play a role in the pathogenesis of systemic inflammation and circulatory and organ failures seen in ACLF [13, 14].

Our study observed that intravenous albumin infusion was safe in ACLF patients. We did not experience any significant adverse event in any of our patients. Our study demonstrated a higher survival rate among patients treated with intravenous albumin infusion plus SOC compared to those receiving standard of care only, which is 53.3% against 33.3%. This is in line with the observation from an earlier study [15]. That group, however, using a different schedule of albumin infusion and with a larger number of patients, found no improvement in short-term ACLF mortality, but a significantly higher percentage of patients in that study had ACLF resolution (82.3% versus 33.3%). When we stratified our patients, we observed that 50% ACLF patients in group A were alive at the end of the study, compared to 20% survival among patients in group B. However, this was not a statistically significant survival benefit. We also experienced high 28-day mortality among our patients, which is similar to findings of previous studies, which vary between 42-48% [3]. Hepatic encephalopathy, variceal hemorrhage, and multi-organ failure were the leading causes of mortality in both groups.

Limitations of the study

This was a single-center observational study with a comparatively small sample size, which is one of our limitations. Besides, as we did not have liver transplantation facility at our center, we could not offer this definitive treatment option to our patients.

Conclusion

Our study, despite its inherent limitations, is a promising one. It established the safety of intravenous albumin infusion in ACLF patients. It also yielded, to some extent, a promising result. Multi-center study using intravenous albumin infusion in addition to SOC involving a larger number of ACLF patients may establish this as a definitive treatment modality for ACLF, which can be accomplished in a simple setup.

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