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Effectiveness of human albumin solution in the treatment of patients with cirrhosis

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Abstract

Aim: Human serum albumin is synthesized in the liver and is the main plasma protein responsible for plasma oncotic pressure. Studies on the use of Human albumin solution (HAS) in patients with cirrhosis, for prevention of cirrhosis complications or for treatment are ongoing. The beneficial role of albumin beyond volume expansion is an evolving topic, and further research is needed to understand its role in modulating biological functions and disease processes, particularly in liver disease and sepsis, but also in other diseases that involve albumin dysfunction.

Materials and Methods: We investigated the effectiveness of HAS through the patients with cirrhosis who received 3 consecutive days (2x1 per day) 190-210 g / L protein were retrospectively analyzed.

Results: Albumin infusion was found to be beneficial for serum albumin levels in the patient with high Child-Pugh scores.

Conclusion: The complications of cirrhosis can be reduced, particularly in patients awaiting transplantation, by support with HAS treatment.

Introduction

Cirrhosis is a chronic diffuse liver disease characterized by the extensive scarring and disruption of the liver parenchyma, an increase in the connective tissue, and the appearance of regeneration nodules, which all typically occur in the course of chronic liver disease. Portal hypertension and hepatocellular failure can also occur in cirrhosis [1], and one of the functions of the liver is the synthesis of albumin [2], which is impaired in cirrhosis due to hepatocellular failure [3]. Albumin is the main plasma protein responsible for plasma oncotic pressure, and its contribution to that pressure is the main reason for its use in clinical practice [2,4]. Human albumin solution (HAS) is frequently used to increase the volume of albumin, although its superiority over crystalloids has not been demonstrated, especially in critically ill patients [5]. Nevertheless, the use of HAS has been shown to correct, through extra-oncotic mechanisms, circulatory disorders caused by the functional impairment of albumin in cirrhosis [6]. The beneficial role of albumin beyond volume expansion is an evolving topic, and further research is needed to understand its role in modulating biological functions and disease processes, particularly in liver disease and sepsis, but also in other diseases that involve albumin dysfunction [7, 8]. In our study, we therefore investigated the effectiveness of HAS in infusion therapy for patients with cirrhosis. As these patients await transplantation, their transplantations can be delayed or they could even die due to complications such as infections, and the aim of our study was to determine whether HAS treatment might be a good option for such transplant candidates.

Materials and Methods

Study design

Patients who have diagnosed cirrhosis and followed up Inonu University Turgut Özal Medical Center Gastroenterology Department, are involved the research. Our study was reviewed retrospectively in accordance with the Helsinki Declaration, patient rights regulation and ethical rules, and with the approval of Malatya Clinical Research Ethics Committee (Approval number: 2019/311). All medical records of eligible patients were retrospectively reviewed and the following independent variables were

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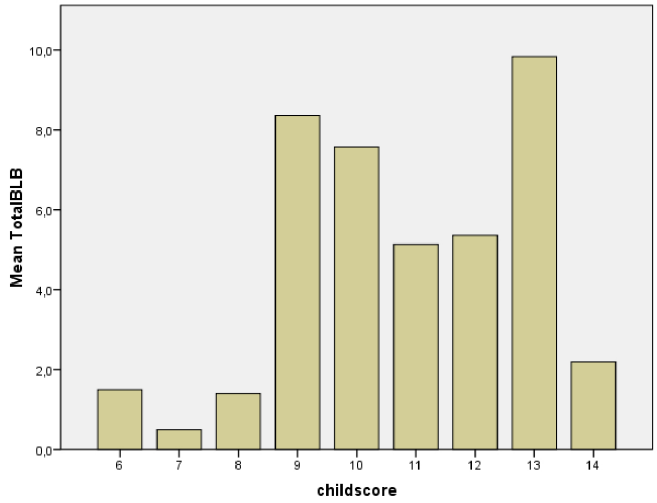

Figure 1. Comparison of child score and total bilurubin values.

collected: demographic data such as age, gender, transplantation etiology (Hepatitis B virus (HBV), Hepatitis C virus (HCV), cryptogenic, alcoholic, sclerosing, cholangitis, autoimmune), transplantation status and Child- Pugh-Turcotte Scores were calculated (Child A: 5-6 points, Child B: 7-9 points, Child C: 10-15 points). First of all, patients who were hospitalized in the Gastroenterology Department were screened. These patients were evaluated according to whether they received albumin therapy or not. And then, patients who received albumin therapy were considered about therapy dosage. Among these patients who received 190-210 g/L protein for three consecutive days and 2x1 per day, were included in the study. (This protein solution was contained 95% albumin.) Among these patients, 30 patients diagnosed with chronic liver cirrhosis were involved the study. Child-Pugh scores were calculated. The albumin values of the patients before the treatment, and on the 7th, 10th and 30th days after the treatment were analyzed. Transplant status, exitus status, hemoglobin and hematocrit values of the patients were determined. Patients who received albumin for any reason after transplantation were excluded. Transplanted patients received albumin therapy in the pre-transplant period.

Statistical analysis

While evaluating the findings obtained in the study, the software SPSS vs 22.0 (SPSS Inc Chicago, IL, USA) was used for statistical analyses. For the purposes of compliance of permanent variables to normal distribution, Kolmogorov Smirnov test was employed to normal distribution ($p<0.05$). The definitive data was expressed as number (n) and percentage (%). While considering the data in the study, median (min-max) was used in the variables not compliant with the normal distribution. Pearson qi-square, Fisher Exact, Wilcoxon Signed Ranks test was used for statistical analyses while the significance level was accepted as $p<0.05$ and 95% confidence interval.

Table 1. Various characteristics of the patients included in the study.

Sex	N	%
Female	12	40%
Male	18	60%
Age	median(min-max) 63.5 (23-86)	
Etiology		
HBV	13	43.3
HCV	5	16.7
Cryptogenic	7	23.3
Alcoholic	2	6.7
Sclerosing Cholangitis	2	6.7
Autoimmune	1	3.3
Tranplant Status.		
Not Trasnplanted	22	73.3
Transplanted	8	26.7
Child Score		
A	1	3.3
B	7	23.3
C	22	73.3
Total	30	100

Table 2. Distribution of total bilirubin, PT and albumin values of the patients included in the study.

Total Bilirubin	N	%
< 2 mg/dl	5	16.7
2-3 mg/dl	6	20
> 3 mg/dl	19	63.3
INR		
< 1.7	16	53.3
1.7-2.2	8	26.7
> 2.2	6	20
Albumin		
<2 g/dl	25	83.3
2-2.5 g/dl	3	10
>2.5 g/dl	2	6.7
Total	30	100

Results

Patients diagnosed with chronic liver cirrhosis in the Gastroenterology Clinic of Inonu University Turgut Özal Medical Center were screened and 30 patients were included in the study. These 30 patients mean ages is 63.5 (23-86) and of these patients 60% is male. The patients were examined according to their transplant status, while 26.7% were transplanted at any time after albumin treatment, while 73.3% could not be transplanted. When we follow up these 30 patients, 5 of them were died who were not transplanted. When we look at the etiologies, 43%

Table 3. The values of albumin of the patients included in the study after albumin treatment (7th day, 10th day and 30th day).

Statistics					
		ALB	ALB7	ALB10	ALB30
N	Valid	30	30	29	18
	Missing	0	0	1	12
Mean		1.8133	2.6767	2.6207	2.7222
Standart deviation		0.38213	0.44851	0.51157	0.65848
Minimum		1.20	2.00	1.80	1.60
Maximum		2.90	3.80	3.90	3.90
Z			-4,758[a]	-1,007[b]	-0,804[a]
P* value			0,000[a]	0,314[b]	0,421[c]

a: P<0.00 7th day ALB values versus baseline ALB values. b: P>0.31 10th day ALB values versus 7th day ALB values. c: P>0.42 30th day ALB values versus 10th day ALB values.
*Wilcoxon Signed Ranks test was used.

Table 4. Comparision of transplantation status and various characteristics of the patients included in the study.

	Trasnplanted		Not Transplanted		p
	N	%	N	%	
Sex					
Female	7	58.3 %	5	41.7 %	0.21*
Male	15	83.3 %	3	16.7 %	
Etiology					
HBV	9	69.2	4	30.80	0.65**
HCV	4	80	1	20	
Cryptogenic Cirrhosis	5	71.4	2	28.60	
Alcoholic	2	10	0	0	
Sclerosing Cholangitis	2	10	0	0	
Autoimmune	0	0	1	10	
Age Groups					
≤50	4	50	4	50	0.12**
50-65	7	70	3	30	
≥65	11	91.7	1	8.3	

* Pearson qi-square and ** Fisher Exact test were used.

of the patients have liver cirrhosis due to HBV, 16% are due to HCV, 23% are cryptogenic, 3% are due to autoimmune hepatitis, 6.7% are due to alcoholic hepatitis, and 6.7 % had chronic liver cirrhosis due to primary sclerosing cholangitis (Table 1). The mean child scores of the 30 chronic liver patients included in the study were as follows: 73.3% of the patients had a score of child 10 Ⓒ and higher, 7% had a score of 9 (B) and 3.3% had a score of 6-8 (A) (Table 1). Therefore, the majority of our patients are patients with advanced cirrhosis and many of them are candidates for transplantation. When the bilirubin values of the patients were examined, while ,63.3% of the patients had total bilirubin of the 3 mg/dl and above, only 5% of the patients' bilirubin values below 2 mg/dl, and the remaining 6% of the patients had bilirubin values between 2 and 3 mg/dl. (Figure 1 and Table 2). When the international normalized ratio (INR) values of the patients were examined, while 20% of the patients had the INR values of 2.2 and above, 53.3% of the patients values below 1.7, and the INR value of the remaining 26.7% patients was between 1.7 and 2.2 (Figure 2 and Table 2). When the albumin values of the patients are examined; while 6.7% of the patients' serum albumin levels were above 2.5 g/dl, 83.3% of the patients' value below the 2 g/dl, and the albumin value of the remaining 10% patients was between 2 and 2.5 g/dl (Figure 3 and Table 2). When the values before and after albumin treatment were compared, the mean initial serum albumin value was 1.8 ± 0.38 g/dl, while the serum albumin value was 2.67 ± 0.44 g/dl at the end of 1 week with 3 times daily 200 g albumin replacement. Then we examined tenth day and thirtieth day albumin values.

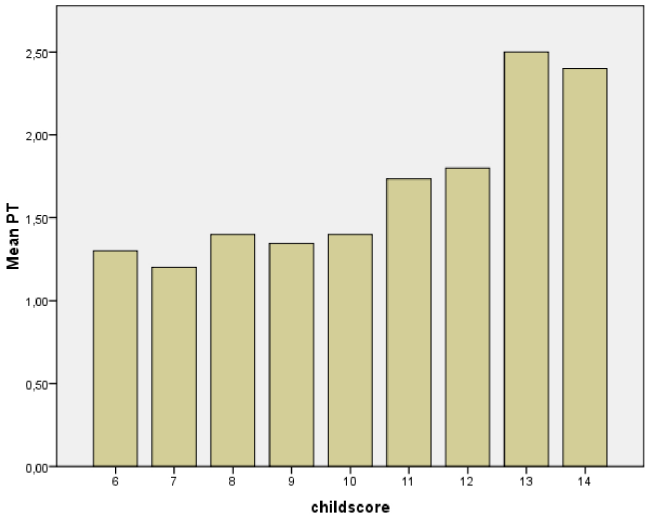

Figure 2. Comparison of child score and INR values.

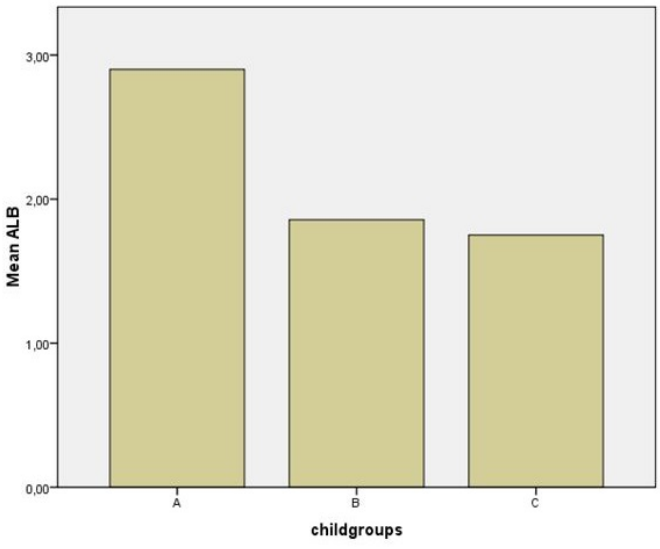

Figure 3. Comparison of child score and albumin values.

The albumin value was found to be 2.62± 0.51 g/dl on the 10th day and 2.72± 0.65 on the 30th day (Table 2). The baseline values of the patients included in the study were compared with the 7th day, 7th day and 10th day and again 10th day and 30th day values. While albumin values between the first and seventh days were statistically significant (p:0.00), there was no statistically significance difference between the seventh and tenth days (p:0.31) and the tenth and thirtieth day (p:0ö42) (Table 3). Considering the transplant status of our patients after albumin treatment, 58.3% of the women were transplanted while 41.7% could not be transplanted. While 83.3% of male patients were transplanted, 16.7% could not be transplanted (p:0,21). And also, when we evaluated the transplanted patients' etiologies after the albumin treatment, 80% of the patients were HCV related, while 69% were HBV-related and 71% had criptogenic liver cirrhosis, 10% were alcoholic and 10% had liver cirrhosis on the basis of primary sclerosing cholangitis (p:0,65) (Table 4). Therefore, transplantation etiology and patient's gender are not associated with the albumin treatment effectiveness. When the ages of the patients who were transplanted after albumin treatment were examined, half of the patients under the age of 50 have been transplanted. In patients aged between 50-65 years, 70% had been transplanted and finally, in patients over 65 years of age, 91.7% of the patients have been transplanted. In elderly patients with cirrhosis, there was no statistically significance between albumin treatment and pre-transplant age groups (Table 4). The mean serum albumin levels of 30 patients, whose mean initial serum albumin level was 1.8 g/dl, reached 2.6 g/dl on the 7th day after treatment. It persisted at these levels for 30 days. The statistical significance of the values that changed with albumin treatment was evaluated with the non-parametric Wilcoxon Signed Ranks Test. The difference between the baseline values and the 7th day values of the cases was found to be statistically significant ($p<0.00$). In the follow-ups after the 7th day, it was observed that the albumin values did not decrease. However, this finding is not statistically significant.

Discussion

Since the recognition of hypoalbuminemia as a key element in the development of ascites, the use of HAS for therapeutic purposes in patients with cirrhosis has come to the fore [9]. Growing knowledge of high cardiovascular abnormalities in patients with advanced cirrhosis over the past two decades has prompted researchers to consider increasing the effective intravascular capacity by using exogenous HAS [10]. Many studies have therefore been conducted and various international guidelines and recommendations for the use of HAS have been formulated. Albumin has been recommended in circulatory disorders, renal failure, spontaneous bacterial peritonitis, and hepatorenal syndrome and after large-volume paracentesis, but it is unclear whether patients other than those with these conditions can be successfully treated with HAS. Although it can be used in cases of circulatory disorders or organ dysfunction caused by decompensated cirrhosis [11], there is no clear consensus regarding the use of HAS in patients with liver cirrhosis and chronic liver disease. In addition to its colloid function, HAS also acts as an antioxidant, binds and transports endogenous and exogenous substances, regulates endothelial functions, and contributes to the inflammatory/immunological system; albumin also binds prostaglandin E2 (PGE2), an immune-suppressive mediator that plays a role in ascites formation and acute decompensation [12,13]. Our study therefore aimed to investigate whether the use of HAS is beneficial in patients with liver cirrhosis. In our study, the albumin levels of 30 patients with mean initial serum albumin levels of 1.8 g/dl achieved a mean level of 2.6 g/dl on the 7th day after treatment, which was a significant improvement. Albumin levels were again checked on the 10th and 30th days, and their averages were found to be 2.62 g/dl and 2.72 g/dl, respectively. Although the changes after the first week were not statistically significant, the maintained serum albumin levels suggest a therapeutic benefit. Also, we had evaluated the transplantation etiologies, transplanted's gender and ages associations to albumin treatment effectiveness. But there was no significant relationship between these parameters. Albumin infusion was thus found to improve serum albumin levels in patients with cirrhosis, especially in our patient group, which was characterized by high Child–Pugh scores. It is therefore plausible that HAS treatment could reduce the complications of cirrhosis, particularly in patients with high Child–Pugh scores awaiting transplantation because, as they await transplantation, their transplantations can be delayed or they might even die due to complications, such as infections. Five of the 30 patients in our study died after albumin treatment, but eight have since undergone transplantation, and the remaining 25 are still alive and waiting. HAS can therefore be used as a supportive and transition therapy before transplantation. While there are studies supporting the use of HAS in managing the complications of cirrhosis, there are also studies that do not support its use and some that oppose it because it is costly and has not yet been proven to contribute to survival. Despite such disagreements, the role of albumin has at least been proven, but there is no consensus regarding dosage. Statistically significant improvements to serum albumin levels were observed in patients to whom the standard treatment dose was administered, but there is not enough data on individualized doses, about which research is still needed.

Ethics approval

Our study was reviewed retrospectively in accordance with the Helsinki Declaration, patient rights regulation and ethical rules, and with the approval of Malatya Clinical Research Ethics Committee (Approval number: 2019/311).

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