Annals of Hepatology 28 (2023) 101150

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Opinions

Intravenous albumin in cirrhosis: Updated clinical uses and novel perspectives

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ARTICLE INFO

Keywords:
Albumin
Hepatorenal syndrome
Spontaneous bacterial peritonitis
Ascites

Albumin, the most abundant plasma protein, is produced by the liver and represents around 50% of circulating proteins. Albumin has oncotic and non-oncotic properties (Fig. 1). The oncotic property is essential for the stabilization of intravascular volumes. Thanks to its structural characteristics, albumin is responsible of about 70% of oncotic plasma pressure and this function explains its principal medical use as plasma volume expander. Besides oncotic function albumin owns a lot of other biological properties in immunomodulation, antioxidation, endothelial stabilization, antithrombotic function and binding and transport of molecules [1]. Cirrhosis is characterized by reduced levels of serum albumin due to both reduced hepatic synthesis and other factors, such as hemodilution caused by renal and water retention [2,3]. Furthermore, there is an increased trans-capillary escape of albumin to the extravascular space. Hypoalbuminemia is a strong predictor of prognosis associated with poor prognosis [4]. Remarkably, in advanced liver diseases there is not only a quantitative but also a qualitative alteration of albumin due to its structural and functional changes (oxidation, truncation or glycation of the molecule) [5]. Those alterations impair albumin function and are strongly prognostic indicators. Recently, the concept of "effective albumin concentration" has been postulated, highlighting that the overall albumin function is not dependent only to the quantity but also to the functionality of the protein. Functional and structural alterations are increased in patients with decompensated cirrhosis and acute on chronic liver failure (ACLF) being strongly affected by the severity of systemic inflammation [6]. Effective albumin concentration proved to be better than total albumin concentration in predicting mortality in patients with decompensated cirrhosis.

Human albumin solution (HAS) administration is frequently used in the management of patients with advanced liver disease. The use of albumin is not only correlated with its capacity as a plasma expander but also to the antioxidant and immunomodulatory function of albumin, which is not owned by other plasma expanders. Currently, established therapeutic indications for albumin in cirrhosis are three (Table 1): prevention of paracentesis induced circulatory dysfunction (PICD); diagnosis and treatment of hepatorenal syndrome acute kidney injury (HRS-AKI); treatment of spontaneous bacterial peritonitis (SBP). After large volume paracentesis (LVP) some patients develop a circulatory dysfunction due to a decrease in peripheral vascular resistance and arterial blood pressure accompanied by an increased activation of renin-angiotensin and sympathetic system. PICD is associated with a rapid recurrence of ascites, renal failure, a high incidence of HRS-AKI, dilutional hyponatraemia, hepatic encephalopathy and decreased survival [7]. The administration of human albumin at the dose of 8 g per liter of ascites removed can prevent PICD and is more effective than other plasma expanders [8]. In a meta-analysis of randomized controlled trial, HAS showed to reduce risk of mortality vs. other strategies in patients undergoing LVP [9]. The benefits of albumin were shown in patients undergoing LVP>5 l, however, more recently albumin administration prevented PICD in patients with ACLF undergoing LVP < 5 l and should be recommended in these patients [10].

In patients with SBP the use of albumin at a dose of 1.5 g/kg of body weight at the diagnosis and 1 g/kg of body weight at day 3 plus antibiotics was associated with a reduction of incidence of acute kidney injury (AKI) and mortality than antibiotics alone [8]. In patients with SBP, albumin is more effective than other plasma expanders being able to increase stroke volume and decrease systemic inflammation [11]. Evidence from experimental models of cirrhosis suggest that the beneficial effect of albumin is linked to the non-oncotic

Abbreviations: ACLF, acute on chronic liver failure; HAS, human albumin solution; PICD, paracentesis induced circulatory dysfunction; HRS-AK, hepatorenal syndrome acute kidney injury; SBP, spontaneous bacterial peritonitis; LVP, large volume paracentesis; AKI, acute kidney injury; SMT, standard medical treatment; HE, hepatic encephalopathy

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https://doi.org/10.1016/j.aohep.2023.101150

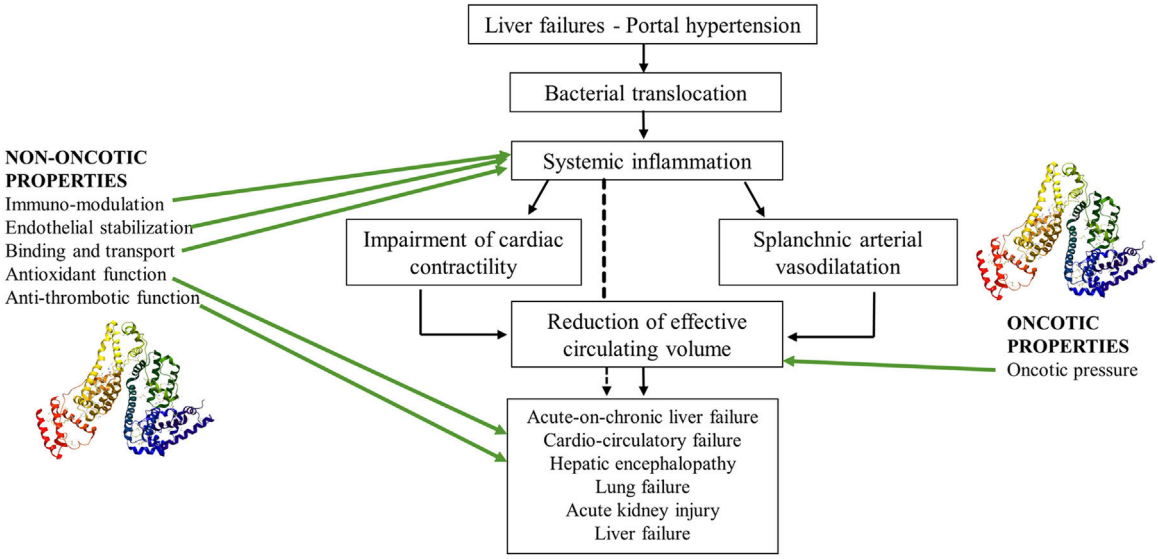

Fig. 1. Pathophysiology of complications of cirrhosis and protective properties of albumin.

Table 1
Established and promising indications for use of albumin in cirrhosis.

CLINICAL CONDITION	DOSE OF ALBUMIN
ESTABLISHED INDICATIONS	
Prevention of PICD	8 g/l of ascites removed in case of large volume paracentesis (>5 l)
Hepatorenal syndrome	Diagnosis: 1 g/kg bw for 2 consecutive days Treatment: 20–40 g/day in association with vasoconstrictor
Spontaneous bacterial peritonitis	1.5 g/kg bw at the diagnosis + 1 g/kg bw at day 3
PROMISING INDICATIONS	
Hepatic encephalopathy	1.5 kg on day 1 plus lactulose
Sepsis induced hypotension	250 ml (5%) intravenous bolus, 250 ml over 15–30 min, maintenance 50 ml/h
Long term treatment in ascites	40 g twice weekly for 2 weeks, and then 40 g weekly

PICD, paracentesis induced circulatory dysfunction; BW, body weight.

properties of the molecules. Indeed, albumin administration, but not starch increase cardiac contractility in cirrhotic rats, an effect mediated by the downregulation of tumor necrosis factor-alpha induced increase in nitric oxide in the heart [12].

In patients with AKI grade 2 or higher, plasma volume expansion (1 g per kg of body weight for two days) is recommended to treat pre-renal AKI and diagnose HRS-AKI. In patients with HRS-AKI, the medical treatment of choice is the combination of vasoconstrictors and albumin. Indeed in a case control study, HAS enhances the efficacy of terlipressin [13]. In these patients albumin is used at the dose of 20–40 g/day and aims to counteract the severe reduction of effective circulating volume and to improve cardiac output. Treatment should be continued until a complete response (SCr below 1.5 mg/dl). Albumin should be withdrawn in patients developing circulatory overload or pulmonary edema during treatment.

The accumulating evidence supporting the beneficial effects of human albumin in counteracting systemic inflammation [14] and immune dysfunction [15,16] in patients with decompensated cirrhosis led to explore other potential indications for this treatment [1].

Infections other than SBP has a high risk of AKI. In this setting, the administration of human albumin has been tested in three randomized controlled trial with controversial results.

In the first multicenter randomized controlled trial, patients receiving albumin had a significant reduction in serum creatinine and plasma renin after 7 days of treatment and a reduced adjusted risk of mortality [17]. Another multicenter randomized controlled trial showed no significant difference in renal function and survival between patients treated with or without albumin. Episodes of pulmonary edema were reported in albumin group [18]. The last multicenter randomized controlled trial, showed that patients treated with albumin reached a significant reduction in plasma renin concentration after 3–7 days of treatment, while no significant changes were observed in the standard medical treatment (SMT) group. The cumulative incidence of death was not significantly different between patients treated or not with albumin. A reduction in ACLF grade was shown in the subgroup of patients with ACLF. Therefore, nowadays albumin use cannot be recommended in patients with infections other than SBP [19].

Albumin administration as plasma expander has been studied in patients with cirrhosis and septic shock. Philips *et al* investigated 5% albumin vs. saline in patients with sepsis-induced hypotension. Patients randomized to receive albumin had higher rate of reversal of hypotension and a very short-term survival benefit [20]. Maiwall *et al* randomized 100 patients to receive either 20% albumin or plasmalyte. Patients receiving 20% albumin had a faster improvement in hemodynamics and lactate clearance than those receiving plasmalyte. No difference in survival was shown between the two groups [21]. Eleven patients in albumin group had to withdrawn albumin because of occurrence of respiratory complications (pulmonary edema or bronchospasm). Therefore albumin may help to control hypotension, but should be used with caution in patients with sepsis induced hypotension.

Albumin administration in patients with overt hepatic encephalopathy (HE) has been explored in two randomized controlled trials. In the first one, patients were randomized to receive albumin at the dose provided for SBP or saline. Albumin did not improve the resolution of hepatic encephalopathy, but improved survival [22]. In the second trial, Sharma *et al* randomized patients with over HE to

receive either albumin (1.5 kg on day 1) plus lactulose or lactulose alone [23]. Patients receiving albumin had a higher rate of resolution of HE and lower mortality rate. Both trials were unpowered to show survival benefit, therefore other studies are needed before a strong recommendation about albumin use in over HE can be made. Finally, the use of albumin has been explored in outpatients with prior episodes of over HE and/or covert HE and hypoalbuminemia [24]. Forty-eight patients were randomized to receive 25% HAS (1.5 g/kg once a week for five weeks) or saline. Albumin use was associated with improved cognitive function test and quality of life.

Since albumin showed to restore immune response in decompensated cirrhosis [15], China *et al* explored the use of daily infusion of 20% albumin solution to restore albumin concentration above 30 g/L in hospitalized patients with decompensated cirrhosis [25]. Patients were randomized to either albumin for 14 days or standard of care. Albumin infusion did neither reduce the incidence of infections nor improve survival. More severe or life-threatening serious adverse events occurred in the albumin group than in the standard-care group. Therefore short-term albumin infusion should be discouraged in acutely decompensated patients without clear evidence based indications.

The long-term albumin use has been explored in patients with cirrhosis and ascites. Romanelli *et al* randomized 100 patients with cirrhosis and first onset ascites to receive albumin (25 gr per week for 12 months, followed by 25 gr every 2 weeks thereafter) or standard of care [26]. Patients receiving albumin had a significantly higher probability of survival, although the study was unpowered for this endpoint. In the ANSWER trial, 440 patients with ascites requiring antialdosteronic drugs and furosemide to receive either SMT or SMT plus HAS (40 g twice weekly for 2 weeks, and then 40 g weekly) for up to 18 months. Overall 18-month survival was significantly higher in the SMT plus albumin than in the SMT group. The incidence of refractory ascites, hepatorenal syndrome, SBP, non-SBP infections and hyponatremia was significantly lower in albumin group than in control group. Patients showing the highest benefit were those achieving albumin concentration > 40 g/L after one month of treatment [27]. In a case control study, albumin (20 gr twice a week) showed to reduce the cumulative incidence of mortality and reduce the incidence of hospitalization for complications of cirrhosis in patients with refractory ascites [28]. On the contrary, in a randomized placebo controlled trial human albumin (40 g every 15 days) plus midodrine (15–30 mg/day) did not reduce incidence of complications of cirrhosis versus placebo in patients with cirrhosis on liver transplant waiting list. The discrepancy between the latter and the ANSWER study, is likely related to the different population, study design, the dose of albumin used, the duration of treatment and the effect on serum albumin concentration [29]. Logistics and costs are barriers to long-term use of albumin in patients with cirrhosis; however, it can be cost effective in some countries [30]. Even in case of establishment of logistics and willingness to pay, it should be highlighted that albumin is a plasma-derived molecule that relies on plasma donation and shortage of albumin stocks may present a severe challenge for patients and clinician and alternative solution should be explored.

Funding

Salvatore Piano received funding from the Italian Ministry of Health (GR-2021-12374075).

Declaration of interests

RG, NZ, have no conflict of interest; SP received fees from Mallinckrodt (advisory board), Plasma Protein Therapeutics association (consulting fees); Grifols (speaking fees).

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