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Role of albumin in cirrhosis: from a hospitalist's perspective

Saqib Walayat[a], Daniel Martin [b], Jaymon Patel[a], Umair Ahmed [a], Muhammad N. Asghar [a,d], Aparna U. Pai[c] and Sonu Dhillon[b]

[a]Department of Internal Medicine, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL, USA; [b]Department of Gastroenterology and Hepatology, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL, USA; [c]Department of Internal Medicine, Palos Community Hospital, Palos Heights, IL, USA; [d]Department of Medicine, CMH Lahore Medical College, Lahore, Pakistan

ABSTRACT

Albumin, a negatively charged globular protein encoded on chromosome 4, is one of the most abundant proteins in the plasma and accounts for approximately 75% of plasma oncotic pressure. The role of albumin in the management of various disease states has shown to be beneficial historically. Low serum albumin is a predictor of mortality and poor outcomes. In cirrhotics undergoing paracentesis, albumin infusion prevents rapid re-accumulation of ascitic fluid while simultaneously decreasing the risk of post-paracentesis related circulatory dysfunction. Additionally, albumin is utilized in patients with hepatorenal syndrome (HRS) and spontaneous bacterial peritonitis (SBP). Overall, albumin appears to be an effective pharmacological agent in the management of cirrhosis and its complications.

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1. Introduction

Human serum albumin is a negatively charged globular protein encoded on chromosome 4. It typically accounts for 50% of the plasma proteins, and for 75% of plasma oncotic pressure. This is primarily due to the direct osmotic effect of albumin secondary to its high plasma concentration (about 4 g dl^{-1}) and negative charge attracting sodium as well as water. The half-life of albumin is 14–18 days with a significant variability in catabolic states such as sepsis, end-stage liver disease, and various inflammatory etiologies. There are no known reservoirs of albumin in the body. Instead, nearly 10–15 g of albumin is synthesized in the liver daily. This constitutes about 25–30% of hepatic protein synthesis, with 20–30% of liver cells responsible for its synthesis. In times of extreme stress, the liver has the capacity to increase production of albumin by 10-fold.[1] The rate of albumin synthesis is mainly determined by the plasma colloid osmotic pressure and the extra vascular hepatic sinusoidal or parenchymal osmolality. Its synthesis has also been shown to be dependent on hormones such steroids, insulin, and glucagon. Steroids, in particular, have been shown to enhance gene expression for the synthesis of albumin in animal models.[2,3] The catabolism of albumin is incompletely understood, but approximately 40–60% is degraded by the liver, kidney, and muscle.[1]

2. Albumin characterization

About 30–40% of albumin remains within the plasma compartment while the remainder redistributes into the interstitial space at a rate of 4–5% per hour. Once in the interstitial space, the albumin enters the lymphatic channels and ultimately returns to the systemic circulation.[1] The rate at which albumin leaves the plasma compartment is dependent on Starling forces. In cirrhosis, these forces are altered due to increased microvascular permeability, which in turn increases the redistribution rate to 9–11% per hour. Continued sodium and water retention in cirrhotic patients leads to further dilution of albumin. These factors, combined with decreased synthesis by the cirrhotic liver, lead to hypoalbuminemia.[4]

In a meta-analysis by Vincent et al.,[5] low serum albumin was an independent, dose-dependent predictor of poor outcome in acutely ill patients. Normal serum albumin concentration is 3.5–5 g dl^{-1}. Each 1 g dl^{-1} decline in serum albumin was reported to increase the odds of death by 137% and increase morbidity by 89%. This association was found to be independent of the patient's nutritional and systemic inflammatory status.[5] Interestingly, although albumin plays a significant role in maintaining plasma oncotic pressure, randomized trials have shown that it is inferior to crystalloids in plasma expansion.[6,7]

CONTACT Saqib Walayat Saqib.k.walayat@osfhealthcare.org Department of Internal Medicine, University of Illinois Peoria Campus, OSF Saint Francis Medical Center, Peoria, IL 61637, USA

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3. Molecular structure and properties

Albumin is primarily composed of alpha helices (67%). It contains 35 cysteine residues which form disulfide bridges and one free cysteine residue at position 34 which accounts for a redox thiol capable of thiosylation, nitrosylation and oxidation. The antioxidant effect of albumin is due to this sulphydryl group which accounts for 80% of extracellular thiol, which in turn has an intense affinity for reactive nitrogen and oxygen species and endotoxin neutralization ability. Due to these scavenging and free-radical neutralizing reactions, the baseline biological shape of albumin becomes altered and the concentration of reduced albumin (human mercaptalbumin) is decreased. These changes in the biochemical structure of albumin and decreased availability of the reduced form may be associated with its impaired oxidative function, altered transport role and short half-life in medical conditions including chronic inflammatory states, endocrinopathies, and liver and kidney disease. In addition, the circulatory dysfunction in conditions such as sepsis or acute liver failure may partly be due to impaired binding of oxidized albumin to nitric oxide (NO).[8,9]

4. Role as a transporter

Albumin is also involved in the transport of various compounds. These include metal cations such as copper and zinc as well as poorly water-soluble molecules such as cholesterol, bilirubin, and thyroxine. Additionally, drugs such as cisplatin, N-acetyl cysteine, antiepileptics, and anticoagulants are transported via albumin. Changes in homeostatic conditions can profoundly alter these properties. For example, ischemia alters the biochemical structure of albumin in a manner that prohibits it from binding cobalt. In fact, this property is being investigated as a marker of early myocardial ischemia.[1]

5. Role in hepatorenal syndrome

Hepatorenal syndrome (HRS) in patients with cirrhosis is classified into two types. Type 1 HRS is defined as the severe, rapid deterioration in renal function characterized by the doubling of serum creatinine value in less than two weeks and attaining a final value greater than 2.5 mg dl^{-1} in the absence of other causes of renal failure. This usually occurs secondary to an acute insult such as SBP or acute gastrointestinal bleed and carries a poorer prognosis than type 2 HRS.[10–12]

Type 2 HRS is characterized by a more indolent course with a slow progressive deterioration of renal function with creatinine levels ranging between 1.5 and 2.5 mg dl^{-1}. Although it may be triggered by a precipitating event, it usually occurs spontaneously. These patients usually have recurrent ascites and hyponatremia. Type 2 HRS can transition into type 1 in the presence of an acute insult such as SBP. In a study by Gines et al., the incidence of HRS was found to be around 18% at one year and 39% at five years in 234 non-azotemic patients with cirrhosis and ascites.[11,12]

The may be due to systemic vasodilation in cirrhotics due to presence of nitric oxide, reduced cardiac output or marked intra-renal vasoconstriction leading to reduced renal blood flow and glomerular filtration rate (GFR). While vasoconstrictors and transjugular intrahepatic portosystemic shunt (TIPS) are effective to some degree in improving renal function, liver transplant remains the only definitive therapeutic option. Administration of albumin may play a crucial role in enhancing survival in these patients.[12,13]

Vasoconstrictors in the absence of albumin have reported to produce suboptimal results.[12,14] Albumin in combination with a pressor such as ornipressin, terlepressin, midodrine, octreotide, or norepinephrine has been shown to be beneficial in improving renal perfusion and function.[15] Patients treated with albumin plus terlipressin had a greater response rate then terlipressin alone (77% vs. 25%).[16] Albumin was noted to enhance serum sodium concentration, arterial pressure, central venous pressure, and reduce renin aldosterone levels in patients treated with albumin and terlipressin versus patients treated with terlipressin alone.[12,14,17]

According to the European Society of liver disease, patients with Type 1 HRS should receive 1 g kg^{-1} body weight of albumin followed by 20–40 g day^{-1} until serum creatinine normalizes to less than 1.5 g dl^{-1}. Although the evidence for treatment for Type 2 HRS is insufficient, terlepressin plus albumin appears to be effective in 60–70% of patients. Since terlepressin is not available in the USA, AASLD recommends the administration of albumin plus norepinephrine for critically ill patients with Type 1 HRS (Class IIa, level A recommendation) or albumin infusion plus the administration of octreotide and midodrine (Class IIa, level B recommendation).[13,18,19]

6. Role in ascites

Ascites, defined as the presence of greater than 25 ml of fluid in the peritoneal cavity, is divided into three grades depending on severity. Grade I ascites is minimal and detectable only via ultrasonography while grade III is defined by marked abdominal distention. Although many etiologies for ascites exist, the most common is cirrhosis secondary to high portal pressures which results in increased transudation of fluid into the peritoneal space. The development of ascites is extremely common in cirrhosis, occurring in nearly

50% of patients within 10 years of diagnosis of cirrhosis, and portends a poor prognosis.[20,21]

6.1. A historical overview

The significance of albumin in ascites has been established since the 1940s. It was observed that patients with cirrhosis and albumin levels less than 3 g dl^{-1} almost ubiquitously developed ascites while patients with albumin levels greater than 4 g dl^{-1} did not.[22,23]

In one of the earliest published studies demonstrating the benefit of albumin in ascites, 105 patients with tense ascites were randomly divided into two groups. One group received 40 g of albumin after each paracentesis while the other group received placebo. Patients in the placebo group developed significant impairment in renal function, electrolyte abnormalities, elevation in renin aldosterone levels and decreased renin activity when compared to those who received albumin. However, no difference in mortality was noted between the groups.[24] Although other plasma expanders such as hemacel and dextran 70 have been compared to albumin due to its high cost and limited availability, albumin has been reported to be the best in reducing post-paracentesis related circulatory dysfunction (PPCD).[25–27] PPCD is defined as an increase in plasma renin value of greater than 50% of the pretreatment value within six days of large-volume paracentesis and is associated with rapid re-occurrence of ascites, impairment of renal function, readmission to the hospital and shorter survival. The incidence has been reported to be as high as 75–80% in patients who have large volume paracentesis without albumin.[10,28] Norepinephrine, terlipressin, octreotide and midodrine have also been studied in preventing PPCD in combination with albumin in various studies.[29–31]

In a small pilot study, 10 patients with refractory ascites were given a combination of midodrine, octreotide and albumin(50 g thrice weekly) for one month with an observed significant reduction in plasma renin and aldosterone concentration as well as a reduction in the volume of ascitic fluid and no change in renal function.[31,32] However, larger randomized studies are needed to further understand the benefit of the combination of albumin and vasoconstrictors to reduce ascitic fluid accumulation and PPCD.

In another meta-analysis of 17 randomized trials, the efficacy of albumin was assessed versus alternative treatments including dextran, gelatin, hydroxyethyl starch, hypertonic saline, terlipressin, epinephrine, and midodrine in patients undergoing large-volume paracentesis. Albumin usage was associated with a significantly reduced risk of PPCD, reducing odds by 66%, and morbidity and mortality, reducing odds of death by 36%.[33]

6.2. Impact on survival

The role of albumin administration on long term survival of cirrhotic individuals remains incompletely understood. In a randomized controlled trial of 100 patients, long-term albumin administration (25 g $week^{-1}$ for one year followed by 25 g once every two weeks) in combination with diuretics to cirrhotic patients after their first ascitic episode significantly reduced the risk of recurrence of ascites (51% vs. 94%) and improved transplant-free survival.[34] Another study by Gentilini and colleagues demonstrated decreased hospital length of stay and reduced ascites recurrence but did not show any difference in mortality between the two groups when followed over a period of three years.[35]

6.3. Albumin dosage

The albumin dosage used in most of the above studies was approximately 8 g l^{-1}, but doses of 4 g l^{-1} have also been shown to be effective in a pilot study, suggesting that lower doses may be similarly efficacious while reducing cost.[36]

Per the current guidelines of EASL and AASLD, the recommended infusion is 8 g of albumin per liter of ascitic fluid removed after large volume paracentesis (≥5 l).[19] Also, long-term albumin infusion may result in improvement of ascites and resolution of edema in patients who are not suitable for TIPS.[37]

7. Infection

7.1. Spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis, a common complication of cirrhosis with a prevalence of 10–30%, is defined as the presence of ≥250 neutrophils in ascitic fluid cell count. Approximately 75% experience recurrence over two years after the first incidence of SBP.[38,39] Nearly a third of patients with SBP have been reported to develop renal failure despite treatment of the underlying infection, with renal impairment being the strongest predictor of in-hospital mortality in such patients. Mortality rates have been reported to be as high as 22–50% in patients developing renal failure after SBP.[40,41]

Albumin has shown to have an effective role in preventing SBP and decreasing its renal complications. Sort et al. [42] randomized 126 patients with SBP to receive daily cefotaxime alone or cefotaxime plus 1.5 g kg^{-1} body weight of 20% albumin at the time of diagnosis of SBP followed by another 1 g kg^{-1} on day 3. The incidence of circulatory dysfunction and renal impairment in the non-albumin group was approximately 35%, while that in the albumin group was 10%. There was also a significantly decreased mortality rate in the albumin group both inpatient (10% vs. 29%, $p < 0.01$) and after three months of

follow up (22% versus 41%, $p < 0.03$).[42] Other studies have shown that the benefit of albumin in preventing renal failure is most pronounced in high risk patients (bilirubin > 4 mg dl^{-1}, Cr > 1 mg dl^{-1}, plasma urea ≥ 60 mg dl^{-1}).[43,44]

7.2. Mechanism of improvement

One proposed mechanism is improved cardiac preload and increased peripheral vascular resistance.[45] This may be due to the ability of albumin to bind vasodilators such as NO, IL-6 and TNF-a. Significantly reduced levels of these inflammatory markers have been seen in plasma and ascitic fluid of patients with SBP post albumin infusion.[45,46] Patients receiving both ceftriaxone and albumin have an increase in left ventricular stroke index, mean arterial pressure, systemic vascular resistance, decrease in heart rate and a suppression in plasma renin and creatinine levels. The serum albumin levels were also significantly elevated seven days after resolution of infection, supporting sustained albumin retention within the plasma as well as decreased catabolic activity.[45]

Furthermore, the benefit seen in HRS may be due to its effect on the cardiovascular system, with albumin producing an increase cardiac output and central blood volume thus enhancing renal perfusion.[46,47]

Improved transport function of the new non-oxidized albumin may also play a role.[8] This is supported by the observation that patients with SBP who were given plasma expanders other than albumin did not have the aforementioned improvements in circulatory and renal function. An endothelial stabilizing effect of albumin is also one of the suggested reasons.[48,49]

According to the AASLD current guidelines, all patients with SBP who have serum creatinine >1 mg dl^{-1}, BUN > 30 mg dl^{-1} or total bilirubin > 4 mg dl^{-1} should be treated with broad spectrum antibiotics and intravenous albumin (1.5 g kg^{-1} within six hours of diagnosis and 1 g kg^{-1} on day 3) (Class IIa B recommendation).[19]

7.3 Other infections

Albumin also appears to play a beneficial role in cirrhotics with infections other than SBP. In a randomized study, in cirrhotic patients with infection other than SBP, the administration of albumin (1.5 g kg^{-1} on diagnosis and 1 g kg^{-1} on day 3) together with antibiotics led to improved renal and circulatory function and was an independent predictor of survival after adjustment for other prognostic factors. In addition, patients treated with albumin had a lower incidence of Type I HRS.[50]

8. Role in cirrhotic cardiomyopathy

Circulatory dysfunction in cirrhotics was first described in the 1950s and termed 'cirrhotic cardiomyopathy'. It is characterized by decreased cardiac contractile function, impaired conductance, prolonged QT, ventricular hyporesponsiveness, and hypertrophy of the atria and ventricles. These appear separate from the effects of alcohol and occur even in its absence.[51] These may be due to persistent elevation in sympathetic activity, alteration in beta-adrenergic function, direct bilirubin-induced toxicity, and the other toxic metabolites in cirrhotics. Albumin infusion has been shown to improve cardiac function in such individuals.[51–53] In two small pilot studies in patients with advanced cirrhosis, infusion of 200 ml of 20% albumin after paracentesis resulted in increased cardiac output likely from increased preload.[54,55] In an experiment on rats with cirrhosis, infusion of albumin showed significantly increased cardiac contractility by reducing the negative inotropic effects of NF-kB-iNOS-NO pathway and by counteracting negative effects of oxidative stress.[56]

9. Role in management of hyponatremia

Hyponatremia, an effective predictor of survival in cirrhotics both in observational and randomized controlled trials, is a common complication in advanced cirrhosis due to an impaired renin angiotensin mechanism. Serum sodium less than 130 mmol l^{-1} has been associated with poorer prognosis, increased incidence of hepatic encephalopathy, as well as other neurological, renal and infectious complications. While salt and fluid restriction, use of aldosterone antagonists, diuretics and paracentesis are the mainstay of therapy, their efficacy is variable. Other attempted therapies with variable results include vaptans, demelocycline, and hypertonic saline.[57–60]

In a small randomized pilot study, 24 patients with refractory ascites with serum sodium <130 mmol l^{-1} treated with 40 g of albumin revealed significantly improved serum sodium levels (mean increase 9 mmol l^{-1}), increased free water clearance and reduced serum vasopressin levels when compared with matched controls treated with fluid restriction. The incidence of infection, hepatic encephalopathy, and in-hospital mortality was also reduced as compared to controls.[61] In a meta-analysis by Bernardi et al. [33] albumin infusion post-paracentesis decreased the risk of hyponatremia by 42%.

10. Role in hepatic encephalopathy

In the presence of hepatic failure in cirrhosis, the kidney becomes an important site for excretion of ammonia as the kidney has both glutamine synthase

and glutaminase.[62] In a clinical trial comprising of 15 patients with diuretic-induced hepatic encephalopathy, infusion of 4.5% human serum albumin showed a marked improvement in hepatic encephalopathy along with a reduction in oxidative stress markers as compared to colloid group. There was a decrease in plasma ammonia levels and increased urinary excretion of ammonia due to volume expansion. The marked improvement in the albumin group may suggest an antioxidant role of albumin in treating hepatic encephalopathy.[63]

In a recent multicenter prospective double blind control trial, 56 cirrhotic patients with acute hepatic encephalopathy were randomized to receive either albumin (1.5 g kg^{-1} on day 1 and 1 g kg^{-1} on day3) or isotonic saline in addition to the standard treatment. Although no difference in percentage of patients with encephalopathy were noted on day 4 (albumin 57.7% vs. 53% in saline), there was a significantly better survival rate after three months of follow-up in the albumin group.[64]

In addition, extracorporeal albumin dialysis has been associated with earlier and more frequent improvement in hepatic encephalopathy.[65] In another prospective randomized controlled multicenter trial, albumin dialysis with molecular adsorbent recirculating system showed improvement in hepatic encephalopathy, but the effect was non-significant.[66] A trial is currently underway to assess the long-term efficacy of albumin in preventing hepatic encephalopathy recurrence and decreasing re-hospitalization rate, as well as improving mortality and improving circulatory values in patients with hepatic encephalopathy (clinical trials identifier: NCT02401490).

11. Conclusion

Albumin is an important compound as it constitutes nearly 50% of the total plasma protein. While its role in maintaining oncotic pressure in the plasma is well known, there are many intriguing properties that remain unexplained. It has shown evidence of improving mortality in PPCD, SBP and hepatorenal syndrome and is therefore useful in the management of cirrhotic complications. Further investigation is needed to investigate its role in cardiac myopathy, hyponatremia and encephalopathy. Research trials are currently underway to assess the role of albumin in hepatic encephalopathy and preventing recurrence of ascites. Overall, the pharmaco-therapeutic use of albumin seems to be beneficial in cirrhotics.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Daniel Martin http://orcid.org/0000-0003-3242-6762
Umair Ahmed http://orcid.org/0000-0002-3841-7368
Muhammad N. Asghar http://orcid.org/0000-0002-0566-2543

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