Review Article

Role of Albumin in Chronic Liver Diseases and in Medical Practice

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ABSTRACT

Albumin is a small protein circulating between the intravascular and extravascular spaces. Serum albumin level is a strong predictor of morbidity and mortality in critically ill and post-operative patients. The superiority of colloids (albumin, etc.) over crystalloids with regard to fluid resuscitation in critical conditions has not been confirmed. The formation of ascites in cirrhosis is due to elevated hydrostatic pressure related to portal hypertension and reduced oncotic pressure from hypoalbuminemia. Albumin infusion prevents post-circulatory dysfunction after large-volume paracentesis. Albumin administration during spontaneous bacterial peritonitis prevents the progression to hepatorenal syndrome and reduces mortality. Several studies of hepatorenal syndrome showed that albumin treatment combined with vasoconstrictors improved renal function markedly, leading to improved post-liver transplant survival and renal function.

Key words : albumin, cirrhosis, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome

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INTRODUCTION

Albumin is one of the most abundant plasma proteins derived from hepatic protein synthesis. It was introduced as a treatment in the 1950s.[1] Albumin infusion has been used in multiple critical conditions such as shock, burn, hypoalbuminemia, acute respiratory distress syndrome and during hemodialysis. The clinical benefit of albumin in critical conditions was repeatedly reviewed in randomized controlled trials and meta-analyses. Albumin became widely used for the treatment of cirrhosis with ascites and hepatorenal syndrome during the 1950s and 1960s.[1]

The fundamental properties of albumin

Albumin is a small, multifunctional, non-glycoselated, negatively charged plasma protein.[2-4] It contributes over 50% of total plasma protein. Human albumin is a 66-Kd globular protein consisting of 585 amino acids with excess charged residues such as lysine and aspartic acids. Nearly seventy percent of plasma oncotic pressure is contributed by the high concentration of albumin in plasma and its strong negative charge property.[2-4] Albumin is synthesized in the liver at a rate of 9-12 g per day in normal adults.[2-4] Rate of albumin production is controlled by alterations in colloid os-

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motic pressure and the osmolality of the extravascular space. Albumin degradation occurs in the vascular endothelium of tissues at a rate of 9-12 g (or 4% of total body albumin) per day.[2-4] Factors that accelerate albumin degradation are protein and calorie malnutrition, stress, trauma and septicemia. Albumin is predominantly an extravascular protein with a total mass of 160 mg and a total intravascular mass of 120 mg, leaving the plasma albumin concentration of 40 g/L.[2-4] Albumin is circulated from the intravascular space into the interstitial space, and returns to the intravascular space through the lymphatic system. Albumin has a circulation half-life of 16-18 hours.[2-4] A decrease of albumin level may result from accelerated redistribution, decreased synthesis and increased catabolism.

The important physiologic functions of albumin include.[4]

1. *Colloid osmotic pressure effect*

As albumin contributes 60% of the intravascular protein, it provides 60% of the colloid osmotic pressure.[4] Albumin attracts sodium ions by means of the negatively charged property, resulting in water retention and colloid osmotic pressure effect.[4]

2. *Binding and transport of molecules*

With a strong negative charge, albumin can bind weakly and reversibly to drugs and metabolites including bilirubin, fatty acid, thyroxin, etc. In hypoalbuminemia, the volume of drug distribution may increase, thus reducing the drug efficacy.[3] As a result, the administration of loop diuretics (furosemide) in combining with albumin is encouraged in cirrhotic patients with ascites with hypoalbuminemia.[3]

3. *Free radical scavenging*

Abundant sulphydryl groups in albumin are scavengers of reactive oxygen and nitrogen species.

4. *Platelet function inhibition and anti-thrombotic effects*

Albumin inhibits the rapid inactivation of nitric oxide and allows prolongation of its anti-aggregatory effects on platelets.

5. *Capillary membrane permeability*

Albumin may directly influence vascular integrity by binding in the interstitial matrix and subendothelium and by altering permeability of these layers to large molecules and solutes.[2-4]

Commercially available human albumin is produced from pooled human plasma. Complications relating to albumin infusion include fluid overload, coagulation defects, hemolysis, allergic reaction and myocardial depression. Other minor complaints are nausea, fever and chill.[2-4]

Clinical use of albumin in critical care

Albumin has been used as plasma substitutes for volume expansion and replacement in critical conditions such as shock, trauma, burn, hypoalbuminemia, etc. Several reviews and meta-analysis reported the comparison of the outcome of fluid replacement between crystalloids and colloids. Crystalloids decrease oncotic pressure and may increase the risk of pulmonary edema.[4,5] On the other hand, colloids solution theoretically should remain within the intravascular space and provide an oncotic gradient leading to water flow from the interstitial space.[4,5] Nevertheless, a small study in septic patients showed that albumin and 0.9% normal saline augmented the interstitial fluid volume equally.[6]

The clinical benefit of albumin administration in critically ill patients with shock, burn or hypoalbuminemia is still controversial. In 1998, the Cochrane Injuries Groups Albumin published a systematic review of albumin given in critically ill patients comparing with crystalloids.[7] Thirty randomized trials of 1,419 patients were reviewed. The pool relative risk of death was 1.68 (1.26-2.23).[7] The pool difference in the risk of death with albumin was 6% (95% CI: 3%-9%).[7] The authors concluded that there was no benefit from albumin infusion in critically ill patients, and that albumin may increase mortality in critically ill patients with shock, burns and sepsis.[7] The results from subsequent randomized-controlled and meta-analysis studies are in agreement with the conclusion of earlier studies.[8,9] In critically ill patients, albumin and normal saline should be considered as equivalent choices of treatment for volume resuscitation.[8,9]

Albumin levels drop rapidly in critically ill patients from altered distribution and decreased synthesis. Serum albumin level was the strongest predictor of morbidity and mortality in critically ill and postoperative patients.[4] From meta-analyses, there was only a trend toward reduced morbidity by giving albumin as a part of nutritional supplement in hypoalbuminemic patients.[10]

Clinical use of albumin in chronic liver diseases

1. *Volume expansion*

Common circulatory abnormalities in patients

with decompensate cirrhosis are portal hypertension, peripheral vasodilatation, increased cardiac output, hyperdynamic state, expanded total plasma and blood volume, fluid retention, ascites and peripheral edema.[11,12] Although total and splanchnic blood volume is increased, effective vascular blood volume trends to decrease, resulting in functional hypovolemia.[11,12] Vasoconstrictor hormones such as renin-angiotensin, aldosterone and sympathetic nervous systems are markedly elevated. In late stage cirrhosis, impaired free water clearance can also be seen. To correct the low plasma osmotic pressure from hypoalbuminemia, volume expansion by albumin treatment is attempted in cirrhosis-related ascites. Previous studies reported that high oncotic pressure from albumin infusion did not reduce ascites in spite of a shift of fluid from the interstitial space into the plasma volume.[11-13] This finding suggests that increased hydrostatic pressure due to portal hypertension, not hypoalbuminemia, is the principal cause of ascites formation.[11-13] Therefore, albumin treatment should not be used in cirrhosis with the aim of facilitating the reduction of ascites.[11-13]

2. Large-volume paracentesis

Marked stimulation of vasoconstrictor hormones and sodium retention is found after large-volume paracentesis.[11,12] Post-paracentesis circulatory dysfunction (PCID) is associated with rapid ascites accumulation, hepatorenal syndrome, dilutional hyponatremia, increased portal pressure and a shortened survival.[11,12] Albumin is more effective than other plasma expanders in the prevention of PCID after large-volume paracentesis. Albumin should be the plasma expander of choice when more than 5 liters of ascites are removed. It is unfortunate that the evidence of survival improvement after albumin administration is scanty.[4,5,11,12]

3. Spontaneous bacterial peritonitis (SBP)

One-third of cirrhotic patients who have SBP can develop circulatory changes and renal dysfunction.[4,5,11,12] A prospective, randomized control study in patients with SBP showed that circulatory changes, renal failure and mortality rate were much lower in those who received antibiotic with albumin infusion (of 105 g on day 1 and 70 g on day 3) than in those receiving antibiotic therapy alone.[14]

4. Hepatorenal syndrome

Hepatorenal syndrome (HRS), an extreme presentation of circulatory alteration in cirrhosis, is characterized by marked arterial hypotension, over-activity of vasoconstrictor hormones and severe renal vasoconstriction.[4,5,11,12] Previous studies suggested that administration of vasoconstrictor hormones with albumin improves renal function in patients with HRS.[4,5,11,12] Impaired circulatory function of splanchnic blood flow is corrected by vasoconstrictor drugs, and low central blood volume is augmented by albumin infusion.[4,5,11,12] Current evidence suggests that albumin improves the efficacy of vasoconstrictor action, and combining vasoconstrictors with albumin is more effective than giving vasoconstrictors alone.[4,5,11,12]

CONCLUSIONS

Albumin treatment has been used both in critically ill patients and in patients with decompensate cirrhosis. Multiple studies confirm the advantage of albumin administration in large-volume paracentesis, spontaneous bacterial peritonitis and hepatorenal syndrome. Because of the high cost of albumin, the decision of treatment with albumin infusion requires judicious consideration.

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