Does albumin supply is needed for the management of ascites?

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Albumin has been used in clinical practice in patients with cirrhosis in an attempt to reduce the formation of ascites, to improve circulatory and renal function. While some of these indications are supported by the results of randomized studies, others are based on only clinical experience and have not proved in prospective studies. The paucity of well-designed study, the cost of albumin, lack of clear-cut benefits for survival and fear of transmitting unknown viruses make the use of albumin controversial. Recently, the benefits of albumin infusions are well established in preventing the deterioration in renal function associated with large volume paracentesis, spontaneous bacterial peritonitis and established hepatorenal syndrome in conjunction with vasoconstrictor. In contrast, when circulatory dysfunction is already established, albumin alone is not effective in improving renal function. Efforts should be made to define the indications for albumin use, dose of albumin required and predictors of response, so that patients gain the maximum benefit from its administration.

Keywords: *

Introduction

Albumin is an effective plasma volume expander due to its high oncotic activity and prolonged half-life in the intravascular compartment. Considering these factors, it is not surprising that it has been used for many years in the management of patients with cirrhosis and ascites. There is evidence to support albumin use in the management of complications of cirrhosis, but there are also arguments against its use in cirrhosis, especially since albumin infusions are costly and survival has not been shown to be improved with this treatment. Recently, this debate has been fostered by the results of a meta-analysis showing that albumin administration may increase mortality in critically ill patients. This will review the use of albumin infusions in the management of patients with cirrhosis and ascites on the basis of the current knowledge of the pathogenesis of ascites and renal dysfunction in cirrhosis.

The physiologic functions of albumin

1. Colloidal osmotic pressure

The most important function of albumin is to maintain colloidal osmotic pressure. As albumin contributes to 60% of the
intravascular protein pool, it provides 60% of the colloidal osmotic pressure. Albumin is a negatively charged molecule and, therefore, it attracts sodium ions, which in turn leads to water retention. In patients with hypoalbuminemia (especially when it is associated with inflammation or sepsis) whose capillaries are known to be hyper-permeable, the leakage of albumin into the interstitial space draws water with it, producing edema.

2. Transport

Albumin has a strong negative charge, but binds weakly and reversibly to both cations and anions. Therefore, it functions as a transport molecule for a large number of metabolites including fatty acids, ions, thyroxine, bilirubin and amino acids. Albumin also binds covalently and irreversibly with d-glucose and d-galactose. The glycosylation of albumin, which is to a certain extent age-dependent, has effects upon its charge and therefore may influence capillary permeability characteristics.

3. Antioxidant effects

Albumin is the major extracellular source of thiols. These sulphhydryl groups are scavengers of reactive oxygen and nitrogen species. Albumin also can influence plasma redox status by binding heavy metals such as iron and copper.

4. Endothelial stabilization

Albumin’s ability to reduce injury to the endothelium caused by reactive oxygen and nitrogen species means that it could potentially have a stabilizing effect on the endothelium and help to maintain capillary permeability. Albumin also interferes with neutrophil adhesion to the capillary endothelium, thereby, reduces inflammation and adds to the maintenance of endothelial integrity.

5. Pharmacological interactions, drug binding

Drugs with which albumin interacts in a highly clinically significant fashion owing to their highly protein-bound state and low margins of safety include warfarin, phenytoin, non-steroidal anti-inflammatory drugs, digoxin, midazolam, thiopental and a number of antibiotics. The volume of distribution of drugs bound to albumin may increase in hypoalbuminemic states, thereby reducing their efficacy.

Pathogenesis of ascites and renal dysfunction in cirrhosis

There is a strong evidence indicates that renal dysfunction and ascites formation in cirrhosis are the final consequence of circulatory dysfunction characterized by marked splanchnic arterial vasodilatation causing a reduction in effective arterial blood volume and homeostatic activation of vasoconstrictor and anti-natriuretic mechanisms. The exact mechanism(s) leading to this vasodilatation is not completely understood but may involve increased synthesis/activity of vasodilator factors, including nitric oxide and vasodilator peptides. These splanchnic arterial vasodilatations would be responsible not only for the reduction in total systemic vascular resistance but also for an abnormal distribution of blood volume with reduction of effective arterial blood volume. Reduction of effective arterial volume stimulates the rennin-angiotensin system and vasopressin release which leads to continuous renal sodium and water retention and ascites formation. In contrast, there is no
evidence to support a role for reduced vascular oncotic pressure due to hypoalbuminaemia in the pathogenesis of ascites. Renal dysfunction in cirrhosis is of great clinical importance because its intensity correlates with prognosis.  

The use of albumin in general clinical practice

Albumin has been used in many clinical scenarios, especially those in which there is a need to improve the colloid osmotic pressure (e.g. shock and sepsis). However, since Cochrane Review reported that albumin administration to critically ill patients might increase the risk of death, the use of albumin in clinical practice, especially in the critical-care setting had many controversies. In addition, a large clinical trial that included 7,000 critically ill patients showed that normal saline was equally as effective as 4% albumin as a resuscitation fluid—there was no difference in morbidity, length of stay in either critical-care units or in hospital, and survival. With the added concern of potential transmission of known and unknown infections via administration of human albumin, and the cost of albumin transfusions, the use of albumin in general clinical practice remains controversial.  

The use of albumin in liver cirrhosis

1. For the management of cirrhotic ascites

The standard treatment for cirrhotic ascites is sodium restriction and diuretic therapy. One randomized, controlled trial assessed the effects of albumin plus standard diuretic therapy in cirrhotic patients with ascites; weekly infusions of 25 g of albumin produced a significantly better diuretic response, shorter hospital stays, and a lower likelihood of readmission to hospital than treatment with standard therapy. Suppression of the activity of anti-natriuretic systems, particularly the renin-angiotensin-aldosterone system, probably accounts for an increase in the natriuretic response to diuretics in patients treated with repeated albumin infusions. Survival, however, was not affected by the addition of albumin. Moreover, comparing the simple way performing paracentesis in a day-care unit, the logistic problems of intravenous albumin administration on a weekly basis, and the lack of cost-effectiveness render this indication unjust and impractical in clinical practice. Infusions of albumin plus diuretic therapy, therefore, cannot be recommended as the standard of care for these patients.  

2. For the prevention of renal dysfunction in patients with cirrhosis and ascites

To date, two different situations that may further impair circulatory function in cirrhotic patients with ascites have been identified; large volume paracentesis and spontaneous bacterial peritonitis

1) Large volume paracentesis

The removal of large amounts of ascitic fluid is characterised by early favorable hemodynamic effects with suppression of vasoconstrictor and anti-natriuretic factors and increased plasma natriuretic peptide levels. However, this is followed by a second phase characterized by marked activation of vasoconstrictor and anti-natriuretic factors in the absence of changes in plasma volume, consistent with impairment of effective arterial blood volume. This paracentesis induced circulatory
dysfunction (PCD) occurs in most patients treated with large taps (more than 5 liter), is not spontaneously reversible, and is associated with impairment of renal function and decreased survival. The prevention of PCD is the most controversial indication for albumin use, but the most important quantitatively. In the single, randomized, controlled trial that has compared paracentesis plus albumin infusion (10 g/l of ascitic fluid removed) with paracentesis alone, the incidence of circulatory dysfunction was significantly decreased in the paracentesis plus albumin group (16%) compared with the paracentesis-only group (30%). Other plasma expander (such as, dextran 70) were compared with albumin, albumin was more effective only when more than 5 liter paracentesis performed. A single relatively large-volume paracentesis (less than 5 L) without albumin replacement was shown to have no deleterious consequences and no adverse disturbances in systemic as well as renal hemodynamics.

Since severely critically ill cirrhotic patients usually stay more than one day in the hospital, repeated small-volume paracentesis less than 5 liter will lessen the need for albumin infusion. In addition, no study to date has demonstrated a significant advantage of total paracentesis on repeated smaller volume paracentesis.

AASLD recommended that albumin infusion should be given with dose 6-8 g/1 ascites fluid removed for paracentesis volumes of greater than 5-6 liters. Fifty percents should be given in the first 1 hour (maximum 170 mL/hr) and the remain in the next 6 hours. The uses of substitute fluid for albumin such as hydroxyethyl starch (HES) that can prevent circulatory failure after paracentesis is still controversy.

2) Spontaneous bacterial peritonitis

In patients with SBP, there is a risk that their systemic hemodynamic parameters can deteriorate, with further arterial and splanchnic vasodilatation. These patients are, therefore, at high risk of developing renal insufficiency. In the only study to assess the effect of albumin infusion on renal function and survival in patients with SBP, 126 patients were randomly allocated to receive either cefotaxime alone or cefotaxime plus albumin infusions. Albumin was given at a dose of 1.5 g/kg body weight within 6 h of SBP being diagnosed, followed by a further infusion of 1 g/kg body weight on day 3. This strategy resulted in a large albumin infusion of 105 g on day 1 and 70 g on day 3 in a 70 kg patient. Patients who were given cefotaxime plus albumin infusions showed no increase in plasma renin activity, a decreased incidence of renal failure and a decreased mortality rate from 29% to 10% when compared with patients who were given cefotaxime alone. Criticisms of the study were the inclusion of more sick control patients than those who received albumin with cefotaxime. Secondly, a central venous pressure line was inserted only in patients with signs of hypovolemia. Thirdly, no comparison was done with other much cheaper plasma volume expander. These results suggest that the benefits of albumin infusion apply only to a subset of patients with more advanced liver disease. The amount of albumin used in this study was also substantially high, making this strategic therapy costly and impractical. To address these criticisms, the authors of the original study compared infusions of albumin with infusions of hydroxyethyl starch (HES) for the prevention of renal failure in patients with SBP. The findings supported the superiority of albumin in preventing the development of renal failure in patients with SBP. Another studies comparing albumin, crystalloid fluid and artificial colloid give the same result. Although albumin has a significant role in SBP patients with severe disturbance of liver and renal function, but its use is still debated because of the relative high dose and cost. Nevertheless, the development of renal failure in cirrhotic patient with SBP carries a high risk of morbidity and mortality, the use of albumin infusion as an adjunctive therapy in the treatment of patients with SBP will continue until further trials are completed.
3. For the management of renal dysfunction in patients with cirrhosis and ascites

Administration of albumin to patients with cirrhosis and ascites causes an increase in total blood volume followed by a moderate reduction, but not normalization, of the activity of vasoconstrictor and anti-natriuretic systems. These circulatory changes are associated with favorable effects on renal function. However, these renal effects are modest and limited only to patients with normal or slightly impaired renal function, whereas patients with severe renal dysfunction do not show any beneficial response. The reason why albumin infusion alone fail to consistently improve circulatory and renal function is that albumin cannot increase effective arterial blood volume efficiently because of the extreme vasodilatation present in the splanchnic circulation.\(^1\)

HRS is characterised by very low arterial pressure and total systemic vascular resistance, marked over-activity of vasoconstrictor factors and marked arterial vasoconstriction in the kidney and other vascular territories (muscle, skin, and brain).\(^2\) For many years, HRS was considered a terminal irreversible event in patients with decompensated cirrhosis. However, it was demonstrated that patients with HRS type 1 may be effectively treated with a combination of vasoconstriction and plasma volume expansion.\(^3\) The use of albumin appears to increase the efficacy of vasoconstrictor drugs. Two studies have shown that when cirrhotic patients with hepatorenal syndrome are treated for several days or weeks with a combination of vasoconstrictors and plasma volume expansion with albumin, a marked improvement in circulatory and renal function occurs in most cases with normalization of plasma levels of vasoconstrictor factors and serum creatinine.\(^4,5\) However, it is unclear whether a plasma expander agent is necessary as a co-therapy. The administration of vasoconstrictors with albumin has been shown to reverse type 1 HRS and normalize renal function in 60-70% of treated patients. But, these studies comprised a small number of patients, some of whom were not randomized, and the impact on long-term survival (more than 1 month) has not been shown. Available data on the treatment of type 2 HRS are much scarcer than for type 1 HRS.\(^6\) Whether or not albumin is required to achieve the beneficial effect of vasoconstrictor therapy in HRS is not known. However, two lines of evidence suggest that albumin improves the therapeutic efficacy of vasoconstrictors. First, the improvement in circulatory function is more marked in patients treated with terlipressin and albumin than that in patients treated with terlipressin without albumin. Second, the improvement in renal function is also greater in patients receiving terlipressin and albumin than in those receiving terlipressin alone. Given the fact that albumin has volume expanding, ligand-binding and antioxidant properties, it seems prudent to use albumin infusions in the treatment of HRS unless there is evidence that albumin actually does some harm. Currently, AASLD recommended that albumin infusion plus administration of vasoactive drugs such as ocreotide and midodrine should be considered in the treatment of type 1 HRS (level II-1).

**Conclusion**

The use of albumin in cirrhosis has been reactivated during the last two decades. During this period investigations have shown that albumin (1) prevents circulatory dysfunction in patients with massive ascites treated by paracentesis, (2) prevents circulatory dysfunction and type-1 HRS and increases survival in patient with SBP, and (3) in association with vasoconstrictors normalizes circulatory function and serum creatinine and increases survival in patients with type 1 HRS. Despite this, controversies still remain as to the best use of albumin infusions in the management of patients with cirrhosis. Albumin
infusions are expensive to use and carry a theoretical risk of transmitting known and unknown diseases. Future efforts should concentrate on establishing when, how much, and for what indications albumin should be used.

Reference