



Efficacy of intravenous Albumin Administration in Hypoalbuminemic Patients: Why and When

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The intravenous administration of albumin in hospitalized patients with hypoalbuminemia remains controversial. In fact, this treatment is being recommended less and less, except in some specific situations where prospective studies have demonstrated a positive outcome. Previous disappointing results from intensive care units have been reported in patients who received intravenous albumin for serious injuries following emergency surgery. Some of these reports state that i.v. albumin was used to induce intravascular volume expansion after trauma; abdominal, aortic or cardiopulmonary surgery; thermal injury; and septic or hypovolemic shock. However, these studies did not show any beneficial action compared to the results obtained with standard crystalloid solutions. Similar inefficient outcomes have been reported in hypoalbuminemic patients who developed pulmonary insufficiency due to acute or chronic diseases [1].

The notion of intravenous albumin is based on the concept that adequate oncotic pressure is essential to regulate water and electrolyte balance, renal function and intravascular volume expansion [2]. Moreover, lower blood albumin concentration was the accepted parameter to predict increased frequency of medical and surgical morbidity and mortality [3]. Therefore, it seemed logical to initiate i.v. albumin in the presence of low blood concentrations of albumin in patients with hypercatabolism, peripheral edema, ascites and anasarca, malnutrition and/or pre-renal failure. However, the results of studies evaluating the efficacy of albumin in critically ill patients, as summarized by Finfer et al. [4], did not demonstrate albumin to be beneficial in such conditions. Some reports noted that the outcome with this treatment may even be worse, as detailed in the analysis by the Cochrane Group [5]. In fact, it was recommended that the use of albumin in critically ill patients be eliminated altogether. This conclusion was recently discussed and it was suggested that unpurified preparations of albumin solutions might have played a role in their deleterious action. It is no surprise then that the Wilkes and Novickis meta-analysis [6], based on a subgroup of studies introducing higher quality trials and larger sample size investigations, which also included the results from studies using purified albumins preparations, could not answer the question whether

intravenous albumin improves or worsens survival of critically ill patients. In this arena of conflicting views, the idea of a total halt to the use of albumin because of an increased risk of mortality – as recommended by Offringa [7] and Sikuler et al. [8] – is presently not feasible. However, the administration of purified human serum albumin remains very costly without proven beneficial action. Therefore, there is no cost benefit in the use of i.v. albumin in the management of intensive care patients.

The question that needs to be addressed is: for what conditions is intravenous albumin administration relevant? These can be reduced to two specific entities that are characterized by an increased risk of circulatory dysfunction, which can lead to impairment in the effective arterial blood volume and a decrease in glomerular hydrostatic pressure causing severe renal insufficiency. The short- and long-term prognosis in such situations is modified if the renal functions are maintained at an adequate level, preventing the occurrence of uremia and the need to use a form of renal replacement therapy, and diminishing the frequency of infectious diseases and death.

The first condition ameliorated by i.v. administration of albumin is liver cirrhosis [9]. Numerous publications in recent years have shown that if albumin treatment alone may have a positive effect in patients with cirrhosis, ascites, hyponatremia and normal or slightly impaired renal function [9], in the presence of moderate to severe renal insufficiency, albumin does not affect the evolution of the disease [10]. However, recent studies have demonstrated that safe and large-volume paracentesis may be performed when albumin is given, preventing the development of renal insufficiency and hepatorenal syndrome in a significant number of patients. Intravenous administration of albumin has been recommended also in cirrhotic patients hospitalized for spontaneous peritonitis [11]. In such a situation kidney function was maintained and lives were saved. The benefit of albumin infusion was found particularly in those with advanced liver lesions and severe impairment of renal function [11].

New updated reports suggest that an adapted treatment for hepatorenal syndrome must consider volume expansion and selective vasodilation of the renal circulation. This vasodilator

agent must not affect the splanchnic circulation, which is always vasodilated in this setting. However, no specific drugs have been developed to date. Therefore, it was proposed that the action of splanchnic vasoconstrictors be evaluated, which may, indirectly, ameliorate the systemic vascular system. Agonists of the V_1 vasopressin receptors were indeed evaluated [12,13], and it was found that the administration of terlipressin in association with i.v. albumin is more efficient in leading to an improvement in renal function, and has fewer side effects. In these studies plasma renin activity and blood aldosterone concentration decreased, and urinary volume and urinary sodium excretions as well as blood levels of atrial natriuretic peptide increased [13]. The probability of survival after entry into the study was associated with reversal of HRS, which was more frequent in those receiving terlipressin and albumin. The survival rate in the number of patients reaching liver transplantation increased – a very important target in the treatment of patients with such severe liver decompensation (HRS type 1).

Other models of vasoactive therapy in association with albumin infusion have been implemented successfully. Noradrenalin, which has a predominant α -adrenergic activity, is the drug of choice for vasoplegic shock. It has been used in cases of type 1 HRS at a starting dose of 0.5 mg/hour up to a maximum of 3 mg/hour, the change in dosage based on the increase in blood pressure and urine output. Infusions were given for a mean duration of 10 days (up to 15 days). The results obtained by Duvoux et al. [14] with this therapy were comparable at least to those reported with terlipressin and albumin. This treatment allows the patient to reach liver transplantation after a more prolonged survival rate, as mentioned previously. In conclusion, albumin will continue to be a major adjunctive efficacious therapy to prevent and treat circulatory dysfunctions and HRS in patients with liver disease.

The second condition that may justify the use of intravenous albumin administration is very severe nephrotic syndrome. In specific conditions where hypovolemia, acute renal failure and sodium retention occur rapidly, infusion of albumin may reverse the hypovolemia-related clinical manifestations [15]. Even if “several observations have argued against a primary role of circulatory underfilling – hypovolemia,” due to hypoalbuminemia and low oncotic pressure, in the development of sodium retention and edema formation in nephrotic syndrome [15], no doubt in some circumstances such as lipoid nephrosis, a reduced plasma oncotic pressure can cause hypovolemia, low glomerular filtration rate and sodium retention [16]. Infusion of albumin may be attempted to expand plasma volume when symptomatic hypovolemia is present, or if the administration of classic loop diuretics, thiazides and/or potassium-sparing diuretics is inefficient in the presence of extreme fluid overload. However, it should be noted that the addition of i.v. albumin to diuretic therapy has also been successful in cases of nephrotic syndrome due to other glomerular diseases [17,18] and not only in patients with lipoid nephrosis. In these studies, increased diuresis [17,18] and natriuresis [17] were demonstrated after infusion of albumin and furosemide. Elevations of blood level of atrial natriuretic peptide and albumin, and effective renal plasma

flow were noted [17]. These observations were in patients with mildly [17] and severely [18] diminished blood levels of albumin, using different timing of albumin administration – the first using both drugs in parallel, the second infusing albumin before starting the diuretic drug. Therefore, the administration of albumin may be given before or during furosemide therapy. Based on these two recent and well-conducted investigations, the effect seems significant. However, we must mention that other studies could not detect the relevant action of albumin administration in nephrosis. If intravenous albumin is indicated when symptomatic hypovolemic nephrotic syndrome occurs, as found in nephrosis, this treatment should be considered also for other forms of nephrotic glomerulopathies, probably by modifying the pharmacokinetics of the diuretic medication [18].

In summary, the use of intravenous albumin for the management of hypoalbuminemic patients was introduced in the 1950s. Purification of albumin preparations improved during the last decade but the indications for this therapy became more limited. We may conclude according to convincing data that i.v. albumin remains relevant in cirrhotic patients with ascites, renal failure and hepatorenal syndrome awaiting a liver transplantation. In those with nephrotic syndrome, the standard therapy with a low salt diet and diuretics remains adequate and successful in most cases. In exceptional cases characterized by severe symptomatic hypovolemia, or when anasarca is unresponsive to standard management, initiating treatment with i.v. albumin and loop diuretics (or mannitol as used in the past) may be attempted – keeping in mind that a mild diuretic and natriuretic effect can be expected. At the present time no other acute or chronic medical condition can be considered appropriate for albumin therapy.

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HRS = hepatorenal syndrome

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