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Current indications for the use of albumin in the treatment of cirrhosis

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ABSTRACT

The role of proteins in the maintenance of colloid osmotic pressure has been described by Starling since 1896. For many decades, the importance of albumin was associated exclusively to its colloid osmotic function. More recently, other properties of albumin have been demonstrated, such as: carrying different substances, anti-inflammatory activity, preserving capillaries permeability, anti-oxidant role. It is noteworthy that, in decompensated cirrhosis, there is qualitative and quantitative decrease in albumin function. This is why, when we use it, we must have in mind its pharmacological role, as well as its colloid osmotic function. Currently, albumin has three major indications in the treatment of cirrhosis. The first would be in the treatment of tense or refractory ascites, when large-volume paracentesis are accomplished, maily when more than 4-5L of ascites are drained, in order to avoid post-paracentesis dysfunction. The second would be in cases of spontaneous bacterial peritonitis, avoiding renal impairment and increasing survival; it is formally indicated when bilirubin is greater than 4 mg/dL or creatinine is greater than 1 mg/dL. Finally, we understand its use associated to terlipressin seems to be the best treatment strategy for type I hepatorenal syndrome. Hence, its judicial use is of great relevance and benefit in the treatment of these complications of the cirrhotic patient.

Key words. Hepatorenal syndrome. Refractory ascites. Spontaneous bacterial peritonitis. Paracentesis.

INTRODUCTION

In 1896, Starling, in his classic study, suggested that the exchange of fluids between blood and tissular space was determined by the difference between capillary hydrostatic pressure, determining filtration, and the osmotic pressure of plasma proteins that favored resorption.[1]

It is known that patients with cirrhosis show a protein deficit due to inadequate synthesis of albumin related to an impaired hepatocellular function. Normal liver synthesizes 11 to 15 g of albumin/day. However, in patients with cirrhosis that capacity can be reduced by approximately 60 to 80%. Protein levels can drop even more since salt and water are retained at the renal level, due to dilution of the colloidal component of the extracellular space, and because of sequestration of part of the circulating albumin in the ascitic fluid.[2] Thus, for a long time the role of albumin was highlighted primarily on its coloidosmotic properties. For this reason, albumin would be one of the factors to play a role in peripheral artery vasodilation, as was originally described by Schrier, *et al.*[3] in their explanation of ascites formation.

Albumin is a 66 KDa protein, representing 50% of total proteins. However, it is known that, apart from its coloidosmotic function, albumin has several other properties, which include its role in the transport of fatty acids, nitric oxide, bilirubin, drugs and metals, its anti-inflammatory role, maintenance of capillary permeability, maintenance of the pool of thiol, its antioxidant role (thiol in cys 34 position), etc.[4,5] Thus, albumin should be considered a drug and not a single agent which, by its osmotic role, can influence the balance of fluids. In regarding this, it is important to emphasize the study of

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Jalan, *et al.*,[6] which evaluated the role of albumin in 22 patients with decompensated cirrhosis, 12 patients with compensated cirrhosis and 80 blood donors as controls. It was shown that the effectiveness of albumin in transport was 10% in relation to the control group, that there was a reduced effectiveness of albumin in detoxification associated with reduced binding capacity, as well as an alteration of the three-dimensional structure and a decrease in the effective concentration of albumin (which are all also reduced in treated cirrhosis). Thus, in cirrhosis a quantitative and qualitative decrease of albumin function is present, which should always be considered. Alterations of albumin were previously described in patients with advanced hepatic diseases.[7]

Under our opinion, according to the existing evidence in the literature, there are three main situations in which albumin should be used in cirrhotic patients, i.e. in the treatment of patients with ascites, in spontaneous bacterial peritonitis (SBP) and in hepatorenal syndrome (HRS).

In the consensus conference for the treatment of ascites,[8] the importance of the subject is highlighted since it is the most frequent cause of decompensation in a patient with cirrhosis. Around 50% of patients with cirrhosis develop ascites within 10 years, and expected mortality in the presence of ascites is 50% in 2 years, and 75% in 1 year when refractory ascites has been diagnosed. In a study we conducted, average survival of cirrhotic patients with ascites was 25.89 ± 23.43 months and 3.57 ± 7.61 months when the ascites was refractory.[9]

The role of albumin in the therapy of ascites was controversial until the beginning of 1950. However, it has been adopted as therapy after randomized studies demonstrated its value when comparing therapeutic paracentesis with diuretics.[10-13]

Albumin plays an important role in the prevention of postparacentesis circulatory dysfunction.[14] In this case, together with the reduction in systemic vascular resistance, late hemodynamic disturbances can take place and lead to renal failure (RF), portotsistemic encephalopathy (PSE), hypotension, and hyponatremia. Considering that the diagnosis of this disorder is difficult (it is often subclinical), by default it should be carried out using renin level determination that will be increased by up to 50% from the baseline, with values > 4ng/mL/h.[15] Generally, the increase is irreversible, favoring the recurrence of ascites and decreasing the survival of these patients. When performing therapeutic paracentesis, administration of albumin would reduce the incidence of this complication.

However, it is important to emphasize the study of Wong, *et al.*[16] which systematically reviews the role of therapeutic paracentesis with or without albumin and/or synthetic expander. After evaluation of nine prospective randomized studies with 806 paracentesis, there was no difference in the occurrence of hyponatremia and RF; after evaluation of seven prospective randomized studies with 666 paracentesis, there was no difference in the incidence of PSE; and after evaluation of seven prospective randomized studies with 678 paracentesis, no difference in mortality was observed. Thus, the authors conclude that there is no evidence that the use of albumin is superior to the use of synthetic expanders in regard to morbidity and mortality, despite existing a lack of evidence for any conclusion when the use of plasma expanders are compared with saline or placebo.

A reflection should be made when interpreting these results, once the main studies in the present review, when evaluated, do not agree with these ideas. Thus, in the study of Ginès, *et al.*[17] when comparing therapeutic paracentesis with or without the use of albumin in 105 patients with tense ascites, it was observed that isolated paracentesis favored an increase in the uremia, renin and aldosterone as well as a decrease in serum sodium. Also, a significant incidence in RF and/or severe hyponatremia was noted, as well as a decreased survival of patients due to complications. Another important prospective, multicenter, controlled study by the "International group for the study of ascites (IAC)", with 289 patients with cirrhosis and ascites paracentesis,[15] compared albumin with dextran 70 and with Haemaccel®. The group of patients which used albumin had the lowest incidence of renin alteration, which represents hemodynamic stability. In the follow-up of patients with post-paracentesis circulatory dysfunction, the average time before readmission (1.3 ± 3.5 months), and survival (9.3 ± 16.9 months) were longer in patients who used albumin. In this study the authors conclude that dextran or Haemaccel® should only be used when paracentesis is less than 5 L. Thus, although there are no randomized studies which assess the higher survival of patients treated with albumin in comparison with other plasma expanders,[14] increased number of patients evaluated would allow this benefit to be demonstrated.

When the effect of total paracentesis with albumin replacement was assessed by our group in cirrhotic patients with refractory ascites with average drained volume of 8.2 ± 5.6 L (3.1 to 24.8 L), no difference in the parameters studied was observed in

the hemodynamic evaluation (renin and aldosterone and Swans-Ganz catheter monitoring) nor in the kidney function evaluation (urea, creatinine, the corrected creatinine clearance, glomerular filtration rate measured with 51Cr-EDTA) before and after paracentesis (18), which indicates that the total paracentesis with albumin infusion is a safe procedure and can be used in the treatment of tense ascites and in refractory ascites.

In the Practice Guideline of the American Association for the Study of Liver Disease (AASLD)[19] treatment of refractory ascites with paracentesis and replenishment of albumin (6-8 g/L) is recommended when this is greater than 4-5 L.

Infections are of great significance based on the fact that 30-50% of cirrhotic patients present infection during the patient's stay in hospital, that 65% of cirrhotic patients with bleeding will present infection and that infections are responsible for 25% of deaths among patients with cirrhosis. When the prevalence of infection in 451 consecutive admissions of patients with cirrhosis was evaluated by our group, the prevalence of deaths was 25%, being SBP responsible for 25.9% of cases. In addition, mortality was significantly higher in the majority of patients with infection. Thus, infection is common in the cirrhotic patient, significantly contributing to their prognosis.[20]

In another study, carried out in our Department to assess the prevalence and prognosis of the SBP in 1030 consecutive admissions of patients with cirrhosis and ascites,[21] a prevalence of 11.1% was found; in these patients mortality was 21.9% despite the fact that the infection was controlled in 91.1% of cases. Hence it is possible to conclude that SBP is frequent and worsens the prognosis of patients with cirrhosis and ascites.

The classic treatment of this infection should be done with third generation cephalosporins, more specifically with cefotaxime.[19] However, some of these patients do not survive even with control of the infection. In this context it is important to note that when evaluating 114 consecutive episodes of SBP,[22] we observed that 24% of the cases had a stable or progressive loss of renal function, with mortality being significantly higher in patients with RF compared to those who did not have an impaired renal function.

In this scenario, it is essential that reference is made to the study of Sort, *et al.*[23] in which prospective, controlled and randomized assessment of the role of albumin in the prevention of the RF in patients with SBP was performed. This study evaluated 126 SBP patients: 63 treated with cefotaxime with albumin administration (1.5 g/kg on the first day in 6 h and 1.0 g/kg on the third day) and 63 with cefotaxime only. It was noted that there was a small increase of renin, renal failure (10% x 33%) and hospital mortality (10% x 29%) in the group with combination therapy. The authors concluded that the albumin prevents RF and improves survival in patients with SBP.

When the role played by the plasma expanders in 20 patients with SBP was evaluated in a prospective, randomized pilot study,[24] there was an improvement of circulatory and renal function only in the group that used albumin. Thus, it seems that albumin, and not synthetic expanders, prevents hemodynamic deterioration in patients with SBP.

In spite of these studies, it is still unclear whether albumin should be used in all patients with SBP or only in a selected population. The restriction of its use is perhaps derived from a study that assessed the role of albumin in 38 episodes of SBP.[25] Here patients were considered as being of risk for the development of RF when they presented with altered bilirubin or creatinine. In low risk patients, SBP was resolved and RF did not appear. In high risk patients, albumin had a protective role in the development of RF and mortality was lower than expected when not using albumin. In another interesting, though retrospective, study,[26] 127 patients with SBP were assessed, 64% of whom had bilirubin greater than 4 mg/dL or creatinine higher than 1 mg/dL. The presence of RF in 23% of the high-risk patients compared with 2.6% of the low-risk patients, and a mortality rate of 23% among those with a high risk and 6.5% among those with a low risk, were observed.

With respect to albumin in patients with SBP, both IAC (27), and American Association for the Study of Liver Diseases (AASLD) Practice Guidelines,[19] indicate that albumin should always be used in patients with bilirubin greater than 4 mg/dL or creatinine higher than 1 mg/dL (maximum dose on the first day = 150 g and on the third day = 100 g).

The HRS represents a 15-20% of cases of RF in patients with cirrhosis. Most frequent causes of RF in this patient population are: hypovolemia, acute tubular necrosis and iatrogenic renal toxicity.[28]

In a study in which 234 cirrhotic patients with ascites were followed-up,[29] the cumulative probability of HRS was 18% in a year, and 39% in 5 years. Retrospectively, HRS is observed in 17% of the patients admitted to a hospital and in 50% of the ones who die. When the survival of cirrhotic patients

with ascites was evaluated by our group, HRS was the fourth most common cause of death.[30]

In 1994 the IAC defined the main diagnostic criteria for HRS which was divided into HRS type I and type II.[31] More recently, these criteria have been reformulated[27] and it is now considered necessary to characterize HRS: the presence of cirrhosis and ascites, a decreased glomerular filtration rate (or more than 1.5 mg/dL of creatinine), absence of shock and nephrotoxic drug use, unchanged renal function after 48 h diuretics suspension and expansion of plasma volume with albumin (1 g/kg/d, maximum 100 g/d), and absence of renal parenchymatous disease as defined by: less than 500 mg proteinuria, less than 50 erythrocytes by field and normal renal ultrasonography.

However, the role of albumin in HRS is not only limited to its use in the diagnosis of this complication: albumin seems to be of great relevance in its treatment. Here the treatment of HRS type I will be primarily focused and the main drug that seems to us to be used in these patients, terlipressin, will be highlighted. The importance of the use of albumin with this vasoconstrictor agent became emphasized in literature after a study that compared albumin combined with terlipressin vs. terlipressin alone in HRS.[32] This prospective study was not randomized and evaluated only 21 patients, but showed that kidney function and survival were most significantly improved in the group receiving the combined therapy. It is likely that the beneficial effect of albumin on the kidney function and at systemic hemodynamic level is not related only to the plasma volume expansion but to a vasoconstrictor effect, mainly in the peripheral blood circulation.[33]

It should be noted that combination therapy is superior to the use of albumin alone. This was demonstrated in two recent prospective, controlled and randomized studies.[34,35] Although, in both studies, improved renal function was observed both have failed in observing an increase in survival. In order to add more information, a meta-analysis was made with 5 prospective, controlled and randomized studies, assessing 243 patients.[36] An increase in the regression of the HRS was found; although it was not possible to demonstrate the impact on survival (a higher number of patients would be needed). However, a recently published systematic review / meta-analysis of 10 trials with vasoconstrictor, in which 376 patients were included,[37] showed that the use of vasoconstrictors reduces mortality (the effect was found in the first 15 days) and the decline was related to the reversal of the HRS. This study also found more side effects using the vasoconstrictors; a reason for which patients should be carefully selected. The study concludes that the best strategy is the association of terlipressin with albumin and that the effect on mortality has been observed only in the HRS type I.

It is of interest to emphasize the study of Nazar, *et al.,*[38] which evaluated the indicators of response to combined therapy in 39 patients with HRS: a basal bilirubin less than 10 mg/dL and an increase in mean arterial pressure of at least 5 mm Hg on the third day of treatment were found as independent response factors. Although other vasopressive drugs can be used,[39,40] studies with a higher number of patients to obtain a definitive answer are needed.

In the HRS AASLD Guideline,[19] it is indicated that the use of albumin in association with vasoactive drugs should be considered, particularly in patients in which liver transplantation is indicated.

The use of albumin in hyponatremia in patients with refractory ascites[41] seems to induce an improvement of serum sodium level, an increase of free water removal, reduced incidence of infections, reduced incidence of EPS and RF and a reduced mortality. However the degree of evidence for this indication still needs more studies to be verified.

In summary, in selecting the main indications of albumin currently described in the Clinical Practice Guidelines of European Association for the Study of the Liver (EASL) in which the evidence and recommendations are classified according system GRADE (Grading of Recommendations Assessment Development and Evaluation),[42] it can be concluded that:

- In the treatment of ascites, when therapeutic paracentesis is carried out, albumin must be infused in order to prevent post-paracentesis circulatory dysfunction, mainly when paracentesis is larger than 5 L (level A1).
- Albumin infusion is indicated in SBP since albumin increases survival and reduces the possibility of HRS (level A1).
- Terlipressin in association with albumin should be considered as first line treatment in HRS (level A1).
- Albumin infusion may be effective in hyponatremia (level B2).

DISCLOSURE OF CONFLICT OF INTERESTS

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