Review

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Human serum albumin, systemic inflammation, and cirrhosis

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Summary

Human serum albumin (HSA) is one of the most frequent treatments in patients with decompensated cirrhosis. Prevention of paracentesis-induced circulatory dysfunction, prevention of type-1 HRS associated with bacterial infections, and treatment of type-1 hepatorenal syndrome are the main indications. In these indications treatment with HSA is associated with improvement in survival. Albumin is a stable and very flexible molecule with a heart shape, 585 residues, and three domains of similar size, each one containing two sub-domains. Many of the physiological functions of HSA rely on its ability to bind an extremely wide range of endogenous and exogenous ligands, to increase their solubility in plasma, to transport them to specific tissues and organs, or to dispose of them when they are toxic. The chemical structure of albumin can be altered by some specific processes (oxidation, glycation) leading to rapid clearance and catabolism. An outstanding feature of HSA is its capacity to bind lipopolysaccharide and other bacterial products (lipoteichoic acid and peptidoglycan), reactive oxygen species, nitric oxide and other nitrogen reactive species, and prostaglandins. Binding to NO and prostaglandins are reversible, so they can be transferred to other molecules at different sites from their synthesis. Through these functions, HSA modulates the inflammatory reaction. Decompensated cirrhosis is a disease associated systemic inflammation, which plays an important role in the pathogenesis of organ or system dysfunction/failure. Although, the beneficial effects of HAS have been traditionally attributed to plasma volume expansion, they could also relate to its effects modulating systemic and organ inflammation.

Keywords: Cirrhosis; Human serum albumin; Paracentesis-induced circulatory dysfunction; Spontaneous bacterial peritonitis; Hepatorenal syndrome; Systemic inflammation; Organ inflammation; Oxidative stress; Decompensated cirrhosis; Acute-on-chronic liver failure.

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Abbreviations: HSA, human serum albumin; HRS, hepatorenal; PICD, paracentesis-induced circulatory dysfunction; SBP, spontaneous bacterial peritonitis; RCT, randomized controlled trial; LPS, lipopolisaccharide; TLR4, Toll-like receptor 4; PAMPs, pathogen-associated molecular paterns; DAMPs, damaged-associated molecular paterns; ROS, reactive oxygen species; RNS, reactive nitrogen species; HMA, human-mercapto-albumin; NMA, non-mercapto-albumin; NO, nitric oxide; CRP, c-reactive protein; RAS, renin-angiotensin system; SNS, sympathetic nervous system; ADH, antidiuretic hormone; PGs, prostaglandins; BDK, bradikinin; ACLF, acute-on-chronic liver failure; TNFα, tumor necrosis factor α.

Human serum albumin (HSA) and the management of decompensated cirrhosis: Background and current indications

History

Diuretics, antibiotics, and HSA are the most frequently used treatments for the management of patients with cirrhosis. According to the CANONIC study database [1], a prospective European investigation in 1348 patients with decompensated cirrhosis, HSA was indicated in 60% of the patients during hospital admission (Table 1).

The history of HSA started in 1940, when a long-term stable substitute of blood was required by the US military authorities to treat shock on the battlefield during the World War II [2]. It was used for first time in December 1941 in seven severely burned sailors after the attack on Pearl Harbor. At that period, the association of portal hypertension, hypoalbuminemia, and ascites was already known. Not surprisingly, ascites was one of the first indications of HSA. Three studies published between 1946 and 1949 assessing the effect of short- and long-term i.v. infusion of HSA in cirrhotic patients with ascites defined the first indications of HSA in cirrhosis [3–5]. Serum albumin concentration and urine volume increased in most patients. Peripheral edema also improved. However, only some patients showed improvement of ascites. First indication of HSA was, therefore, hypoalbuminemia in patients treated by frequent paracentesis. The introduction of spironolactone and furosemide in the early 1960's and the article by Hecker and Sherlock [6] first describing hepatorenal syndrome (HRS) lead to great changes in the management of ascites. The concept that paracentesis could be followed by rapid reformation of ascites and renal failure extended rapidly through the medical community and therapeutic paracentesis was formally proscribed. Only in 10% of patients not responding to diuretics (refractory ascites) was HSA prescribed to increase the plasma volume and diuretic effect [7]. In the 1970's LeVeen designed the first peritoneo-venous shunt [8]. It consisted in a multi-perforated intra-peritoneal tube connected to a unidirectional valve and to a second tube that subcutaneously reached the superior vena cava through the internal

Table 1. Use of albumin in patients with acute decompensation of cirrhosis in Europe. Results from the CANONIC study database.

	Patients with hospitalization follow-up*	Patients receiving albumin during hospitalization
Patients (n)	699	425 (60.8%)
Bacterial infections (n)	398 (56.9%)	152 (38.2%)
SBP (n)	107 (15.3%)	53 (49.5%)
Non-SBP infections (n)	291 (41.6%)	65 (22.3%)
Paracentesis (n)	291 (41.6%)	225 (77.3%)
<5 L (n)	158 (22.6%)	107 (67.7%)
5-9 L (n)	137 (19.5%)	123 (89.8%)
>9 L (n)	55 (7.8%)	51 (92.7%)
HRS (n)	179 (25.6%)	75 (41.9%)

*The CANONIC study was made in 1348 patients. The table only includes patients with hospitalization follow-up. There were patients with more than one complication requiring albumin administration.

jugular vein. The positive abdominal pressure and the negative intra-thoracic pressure facilitated the opening of the valve and the continuous passage of ascites into the circulation. LeVeen shunt was widely used in the management of refractory ascites for more than a decade. Following the introduction of LeVeen shunt, HSA disappeared from the therapeutic armamentarium of cirrhosis for more than a decade.

Current indications of albumin

Management of ascites

In 1988 a Spaniard inter-hospital group [9] demonstrated that paracentesis, if performed in association to HSA, was an effective and safe therapy of ascites. They compared repeated large volume paracentesis (4 liters/day) associated with HSA (8 g per liter of ascitic fluid removed) *vs.* diuretics. The incidence of renal impairment, hyponatremia and encephalopathy was significantly lower in the paracentesis group. No significant change in plasma renin activity was observed indicating no impairment in effective blood volume. Survival probability was similar in both groups. In a second investigation, total paracentesis (complete removal of ascites in only one tap) associated with HSA was also found to be safe [10]. Treatment of ascites was therefore considerably simplified. Instead of requiring 2–4 weeks in hospital to compensate a tense ascites with diuretics, patients could be managed by paracentesis in a single day hospitalization regime [11]. Paracentesis associated with HSA was subsequently compared to peritoneo-venous shunting in patients with refractory ascites [12]. Peritoneo-venous shunting was superior to paracentesis in the long-term control of ascites. However, due to the high rate of complications associated with the prosthesis, the total time in hospital and the probability of survival was similar with both treatments. Based on these data, paracentesis plus HSA was considered the treatment of choice for tense ascites.

When paracentesis is performed without HSA or if HSA is substituted by synthetic plasma expanders, a high proportion of patients develop marked activation of the renin-angiotensin system, a feature known as paracentesis-induced circulatory dysfunction (PICD) [13–15]. The prevalence of PICD in patients not receiving volume expansion is 70%. In patients receiving dextran or polygeline it is also high (37.8%). PICD is due to an accentuation of the arterial vasodilation already present in cirrhosis and a lack of appropriated cardiac response [16–18] (Fig. 1). PICD, although asymptomatic, is a serious complication. It is not spontaneously reversible and is associated with shorter time to hospital readmission, higher incidence of renal failure, and shorter probability of survival [15]. A recent meta-analysis (17 trials, 1,225 patients) comparing HSA *vs.* alternative treatments (no volume expansion, synthetic plasma expanders or vasoconstrictors) has shown that HSA significantly reduces the incidence of PICD and mortality [19].

Prevention of type-1 HRS associated with spontaneous bacterial peritonitis (SBP)

Despite infection resolution, 20–40% of patients with SBP develop type-1 HRS in relation to arterial vasodilation, acute impairment in cardiac function, and compensatory activation of the renin-angiotensin and sympathetic nervous systems [20–23] (Table 2). Type 1 HRS also develops in cirrhotic patients with other type of bacterial infections although the prevalence is lower [24–26]. The reason why SBP is such a frequent precipitating event of type-1 HRS is multifactorial. First, an exaggerated inflammatory response to sepsis occurs in patients with cirrhosis and ascites with an increase in plasma levels of cytokines 20-fold greater than in individuals without cirrhosis [26]. This feature has also been observed in experimental animals in which doses of bacterial endotoxin that do not produce any change in systemic hemodynamics in healthy rats, induce arterial hypotension and increase the plasma levels of cytokines by 100-fold in rats with cirrhosis and ascites [27]. Second, the inflammatory response to bacterial infection persists for a longer duration in cirrhosis. Finally, patients with cirrhosis and ascites already have severe impairment in cardio-circulatory and renal function, which predispose these patients to further deterioration in organ function [28]. In support to this contention, patients with SBP who have increased serum creatinine concentration or dilutional hyponatremia prior to infection, and those with intense inflammatory response (high concentration of polymorphonuclear leukocytes, tumor-necrosis-factor alpha and interleukin-6 in plasma, and ascitic fluid) are at high risk of developing type-1 HRS [23,29,30]. If untreated, type-1 HRS in patients with SBP is associated with a mortality rate approaching 100% [31].

In 1999 we reported the use of HSA (1.5 g/kg b.wt. at infection diagnosis and 1 g/kg b.wt. at the third day) in SBP [31]. HSA prevented cardiovascular dysfunction and this was associated with a dramatic decrease in the prevalence of type 1 HRS and hospital mortality (10% in the HSA group and 30% in the control group). A recent meta-analysis has confirmed these findings [32].

Treatment of type-1 HR

The use of vasopressin analogs and HSA for the treatment of type-1 HRS was based on two features. First, arterial vasodilation in cirrhosis occurs in the splanchnic circulation and vasopressin analogs act preferentially in this area [28]. Second, studies using