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Human albumin solution for patients with cirrhosis and acute on chronic liver failure: Beyond simple volume expansion

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Abstract

To provide an overview of the properties of human serum albumin (HSA), and to review the evidence for the use of human albumin solution (HAS) in critical illness, sepsis and cirrhosis. A MEDLINE search was performed using the terms "human albumin", "critical illness", "sepsis" and "cirrhosis". The references of retrieved articles were reviewed manually. Studies published between 1980 and 2014 were selected based on quality criteria. Data extraction was performed by all authors. HSA is the main plasma protein contributing greatly to its oncotic pressure. HSA demonstrates important binding properties for endogenous and exogenous toxins, drugs and drug metabolites that account for its anti-oxidant and anti-inflammatory properties. In disease states, hypoalbuminaemia is secondary to decreased HSA production, increased loss or transcapillary leakage into the interstitial space. HSA function can be also altered in disease with reduced albumin binding capacity and increased production of modified isoforms. HAS has been used as volume expander in critical illness, but received criticism due to cost and concerns regarding safety. More recent studies confirmed the safety of HAS, but failed to show any survival benefit compared to the cheaper crystalloid fluids, therefore limiting its use. On the contrary, in cirrhosis there is robust data to support the efficacy of HAS for the prevention of circulatory dysfunction post-large volume paracentesis and in the context of spontaneous bacterial peritonitis, and for the treatment of hepato-renal syndrome and hypervolaemic hyponatraemia. It is likely that not only the oncotic properties of HAS are beneficial in cirrhosis, but also its functional properties, as HAS replaces the dysfunctional HSA. The role of HAS as the resuscitation fluid of choice in critically ill patients with cirrhosis, beyond the established indications for HAS use, should be addressed in future studies.

Key words: Human serum albumin; Human albumin

solution; Critical illness; Cirrhosis; Resuscitation fluid; Large-volume paracentesis; Hepatorenal syndrome; Spontaneous bacterial peritonitis

Core tip: Human serum albumin has several important functions beyond being the principal protein in plasma. In disease states, albumin levels may not only be low but there may also be functional hypoalbuminaemia. This may explain why human albumin solution is helpful in treating the complications of cirrhosis whereas its role (as a volume expander) in critical illness remains limited. However, in the presence of cirrhosis or acute liver failure the restoration of functional albumin may be beneficial, even in critically ill patients. This still needs to be addressed in clinical trials.

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INTRODUCTION

Human serum albumin (HSA) is produced in the liver, and is the main plasma protein fraction responsible for plasma oncotic pressure. Historically, the oncotic property of albumin has been the major determinant of its use in clinical practice. However, it is now clear that albumin is responsible for a number of other important biological functions, and hence should be treated as a drug and not just as a form of fluid used for resuscitation. A close look at the albumin molecule reveals that it consists of three specific domains which act as binding sites for various endogenous and exogenous toxins, and drugs and drug metabolites such that the overall binding capacity of albumin is reflected in its scavenging, antioxidant and anti-inflammatory properties[1]. Acute hypoalbuminaemia is common in hospitalised patients resulting from decreased synthesis due to acute organ dysfunction, malnutrition and increased trans-capillary escape due to increased endothelial permeability secondary to systemic inflammation[2]. This is particularly noticeable in patients who are chronically hypoalbuminaemic from chronic malnourishment, protein losing nephropathy and enteropathies, and cirrhosis of the liver. In cirrhosis, reduced albumin production (quantitative hypoalbuminaemia) is complicated by an increase in the proportion of irreversibly damaged isoforms (functional hypoalbuminaemia) thus further compromising overall binding capacity[3]. While human albumin solution (HAS) are often used for volume expansion and oncotic effect in critically ill patients, their superiority over crystalloid fluids is not established. In cirrhosis, however, because of the functional dysfunction conferred to the albumin molecule, administration of HAS has been consistently shown to improve circulatory dysfunction, through oncotic but also extra-oncotic mechanisms, and survival. The common indications in this setting include large volume ascitic paracentesis (LVP), type 1 hepatorenal syndrome (HRS), and spontaneous bacterial peritonitis (SBP)[4]. The beneficial role of albumin function beyond volume expansion is an evolving field, and further research is required to explore this unique property of albumin in modulating biological functions and disease processes not just in liver disease and sepsis but also in other diseases where albumin dysfunction seems to play a central role in their pathophysiological processes.

The aim of this review is to provide an overview of HSA structure, kinetics and function, and to explore the pathophysiological basis and clinical evidence for the use of HAS in various diseases, particularly in critical illness, sepsis and liver disease. We conducted a medline search for studies published between 1980 and 2014 using the terms "human albumin", "critical illness", "sepsis" and "cirrhosis". Studies were reviewed and selected for their quality and utility in producing this review.

SYNTHESIS, METABOLISM, DISTRIBUTION AND FUNCTION OF HSA

HSA contributes around 50% of circulating plasma proteins with serum concentrations of 35-50 g/L in healthy subjects. This level reflects the synthesis, metabolism and distribution of HSA, but not its function. HSA synthesis (10-15 g/d) occurs within the hepatocyte from where it is released into the portal tract[5]. Synthesis is regulated by the colloid osmotic pressure of the interstitial fluid bathing the hepatocytes[6]. The rate of synthesis *in vivo* can increase up to 2.7 fold, provided there is adequate available messenger RNA[7].

Only a minority of total body HSA remains within the bloodstream, with most albumin passing into the interstitial space (Figure 1). Injection of radio-labelled HSA demonstrates trans-capillary escape rate (TCER) of 4.5% per hour[8]. In fenestrated capillaries, TCER depends on capillary wall permeability, hydrostatic and oncotic pressure gradients (liver, small intestine, pancreas, bone marrow). In non-fenestrated capillaries, HSA binds to albondin and passes through to the interstitial space. This rate of transfer is increased with long-chain fatty acid binding, cationisation and glycosylation of HSA. Three quarters of extravascular albumin returns to the intravascular space *via* the lymphatic system.

HSA has a half-life of approximately 15 d. Degradation occurs in the liver and kidney, but the majority takes place in the skin and muscle (the main locations of extravascular HSA). Altered or denatured HSA binds to endothelial cell surface receptors; after uptake into intracellular vesicles, fusion with lysosomes results

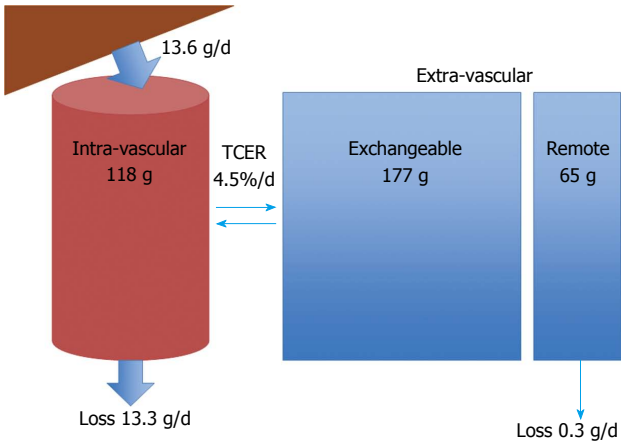

Figure 1 Albumin synthesis and distribution. TCER: Trans-capillary escape rate.

in breakdown into free amino acids. The fractional degradation rate of HSA is 3.7% which parallels the rate of synthesis in health.

The classical physiological role of HSA is to maintain colloid oncotic pressure. The high molecular weight of HSA combined with its concentration in blood result in an 80% contribution to the normal plasma oncotic pressure of around 25 mmHg. This direct osmotic effect provides 60% and the net negative charge 40% of the oncotic pressure. The presence of charged residues and the abundance of HSA account for its function as a physiological buffer. HSA is responsible for approximately half of the normal anion gap, and as such decreasing HSA concentration results in a metabolic alkalosis.

STRUCTURE AND LIGAND BINDING PROPERTIES OF HSA

HSA consists of 585 amino acids with a molecular weight of 66500 Daltons. The globular structure of HSA determined by X-ray crystallography is "heart-shaped" with 17 disulphide bridges cross-linking cysteine residues and uniting the three domains[9,10]. These disulphide bridges give HSA strength, but also facilitate conformational changes in response to ligand binding. There is no carbohydrate moiety, but an abundance of charged lysine, arginine, glutamic acid and aspartic acid residues with a free cysteine and tryptophan residue[1]. The homologous domains (Ⅰ, Ⅱ and Ⅲ) that make up HSA are in turn constructed from two sub-domains (A and B) that possess 6 and 4 α-helices respectively (Figure 2)[1]. Each domain has a binding site with different properties, but nine binding sites for fatty acids have been elucidated with electron magnetic resonance spectroscopy[11]. Flexible loops made of proline residues allow movement of subdomains to accommodate ligands. The HSA molecule serves as the transport vehicle for thyroid and steroid hormones, fatty acids, unconjugated bilirubin, and several drugs[12].

Domain Ⅰ contains the single cysteine residue that is not a part of the structural disulphide bridges[13].

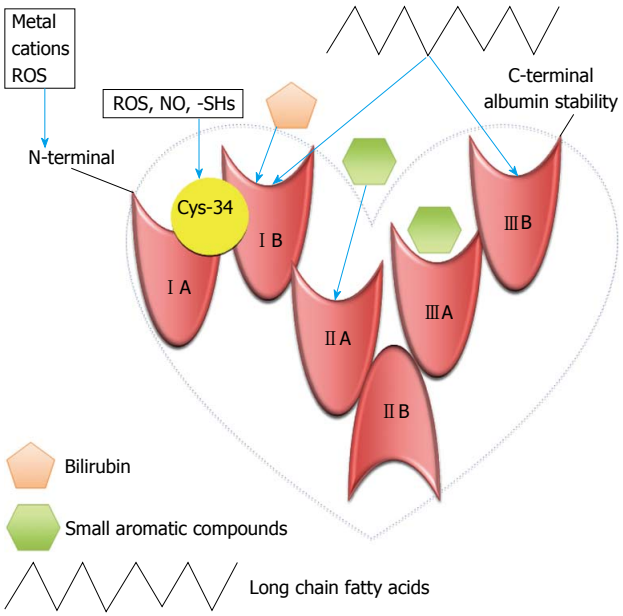

Figure 2 Human serum albumin structure and binding sites. ROS: Reactive oxygen species; NO: Nitric oxide; SH: Sulfhydryl.

This creates a reactive thiol group which can form intermolecular bridges and bind with metals, such as copper and iron. Covalent binding with molecules such as D-penicillamine may occur. There is a metal-binding site involving the N-terminus that can neutralize free copper and iron cations restricting catalysis of free radical production[14]. HSA contains two further functional cation binding sites, multi-metal binding site A and B[15]. The former lies in the interface of domain Ⅰ and Ⅱ binding zinc and cadmium. The latter is thought to be a secondary binding site and its location remains uncertain.

There is a single binding site for unconjugated bilirubin in domain Ⅰ B within a narrow hydrophobic cavity. Usually, there are two fatty acids loaded on an HSA molecule. The long-chain fatty acid binding sites are found in subdomains Ⅰ B and ⅢB. These sites can also bind bacterial endotoxins so reducing their activity[16].

The hydrophobic cavities in subdomains ⅡA and ⅢA are the principal ligand binding sites for small heterocyclic or aromatic compounds. Subdomain ⅡA has a lone tryptophan residue that limits solvent accessibility. It is one of the principle binding sites of pharmacological agents (*i.e.,* Sudlow site 1) and shows affinity for bulky heterocyclic molecules, including drugs such as warfarin and furosemide[17]. Subdomain ⅢA, corresponding to Sudlow site 2, demonstrates greater stereo-selectivity, but is less flexible and binds aromatic molecules, including diazepam and non-steroidal anti-inflammatory drugs[17]. The subdomains ⅡA and ⅢA actually face each other, and ⅡA binding can utilise residues in subdomains ⅡB and ⅢA. An important pharmacological consequence of this configuration is that competitive displacement can then occur. Many compounds will also utilise secondary binding sites. Despite modern techniques there are aspects of the

HSA-drug interactions that remain unclear, such as the binding site of digoxin. The ligand binding activity of HSA may also generate a pseudo-enzymatic activity whereby HSA plays an active role in pro-drug modification by hydrolysis.

Most HSA exists with a free redox-active thiol group (due to the cysteine residue in domain Ⅰ A), referred to as mercaptoalbumin. Due to the relative abundance of HSA this constitutes 80% of available plasma thiols and is a scavenger of many reactive oxygen and nitrogen species[18]. Oxidative stress initially converts HSA into the mixed disulfide non-mercaptalbumin-1 (HNA-1) as reactive oxygen species are scavenged. The quantity of HNA-1 increases with aging[19]. HNA-1 can be further oxidised into HNA-2, which is thought to be an irreversibly damaged form. Nitroalbumin, the product of nitric oxide binding to the thiol group, may be a vasodilator and inhibitor of platelet aggregation.

HSA also has a role in clotting, transporting both anti-thrombin and heparin cofactor Ⅱ, both of which increase the anticoagulant activity of natural heparinoids and exogenous heparins, by inhibiting thrombin generation. Hypoalbuminaemia has been linked to platelet hyper-aggregation in peritoneal dialysis patients[20], and may play a role in the procoagulant tendency reported in acute on chronic liver failure, and with acute kidney injury[21,22]. HSA influences several immune pathways and may enhance intracellular protection from inflammation and oxidative stress. In experimental studies HSA inhibits tumor necrosis factor-alpha (TNF-α) induced upregulation of vascular cell adhesion molecule 1 and nuclear factor-κB activation[23]. Intravascular HSA may promote endothelial stability by reducing oxidative stress, dampening inflammation and reducing neutrophil adhesion to endothelial cells. Vascular integrity may be aided by HSA binding in the sub-endothelium reducing endothelial permeability.

Isoforms of HSA as a result of genetic variation do occur but are not typically associated with disease. Exceptions are the variants with high affinity for tri-iodothyronine and levothyroxine, which are responsible for familial dysalbuminemic hypertri-iodothyroninaemia and hyperthyroxinaemia, respectively[24]. Patients with these clinical syndromes are euthyroid. Another isoform has been discovered with increased affinity for nitric oxide which has demonstrated anti-bacterial and anti-apoptotic properties.

HYPOALBUMINAEMIA IN DISEASE

Disease can alter the synthesis, distribution and degradation of HSA. Decreased HSA synthesis occurs in malnutrition and malabsorption as a result of amino acid deficiency, and hypoalbuminaemia is often used as a surrogate of nutritional status[25]. In advanced liver disease, hepatocyte dysfunction or loss results in decreased HSA synthesis. HSA is a component of the Child-Pugh-Turcotte score[26], a disease severity score widely used for patients with cirrhosis, although the more recent model for end-stage liver disease (MELD) does not include HSA[27]. Hypoalbuminaemia is common in inflammatory disorders, as HSA synthesis is suppressed by pro-inflammatory cytokines, including interleukin 6 (IL-6) and TNF-α, in the context of the acute phase response[28].

Increased HSA shift into the interstitial space occurs in cases of increased endothelial permeability. Vasodilatation and increased capillary leakage are the hallmarks of severe sepsis, and contribute greatly to multiple organ dysfunction[29,30]. Several vasoactive and pro-inflammatory mediators produce vasodilatation and loss of endothelial integrity in sepsis, such as endotoxins, TNF-α, IL-1, IL-6, prostacyclin and nitric oxide, leading to a three-fold increase in HSA TCER[2]. This leakage of HSA into the interstitial space is not associated with a concomitant increase in lymphatic return into the intravascular compartment; rather there is increased sequestration in the non-exchangeable sites in the body. Plasma HSA falls faster after a bolus of 20% HAS in patients with sepsis compared with healthy volunteers[31]. Furthermore, a reduction in HSA mRNA transcription occurs in the context of the acute phase response, mediated by IL-6 and TNF-α.

HSA DYSFUNCTION IN CIRRHOSIS

HSA concentration is used as a surrogate of liver function, and hypoalbuminaemia is a common feature in patients with cirrhosis. Recent research has shown that the function of HSA is impaired in patients with cirrhosis (Figure 3)[32]. HSA dysfunction may be due to either saturation with bilirubin or allosteric and structural modifications.

A recent study assessed post-transcriptional changes in HSA in patients with cirrhosis and healthy controls[33]. Seven isoforms of HSA resulting from post-transcriptional structural modification were identified in patients with cirrhosis, whereas the native unmodified HSA was reduced in the same group compared to controls. The presence of isoforms was associated with the severity of liver disease. The presence of oxidized and N-terminal truncated isoforms was associated with complications such as ascites, renal dysfunction and bacterial infections. The native HSA isoform was associated with greater one-year survival, and was a better predictor of survival than total HSA concentration, supporting the concept of the "effective HSA concentration".

Albumin binding capacity (ABiC) refers to assessment of binding site Ⅱ by binding of a fluorescent marker (usually dansylsarcosine). ABiC was reduced (< 40%) in 22 patients with cirrhosis and high bilirubin[34], and correlated inversely with the severity of liver disease and short-term mortality. This study showed improved ABiC in patients treated with the Molecular Adsorbents Recirculating System (MARS).

Cobalt binding assays can demonstrate defective metal cation scavenging N-terminal corresponding to ischaemia-modified albumin (IMA). Fatty acid binding

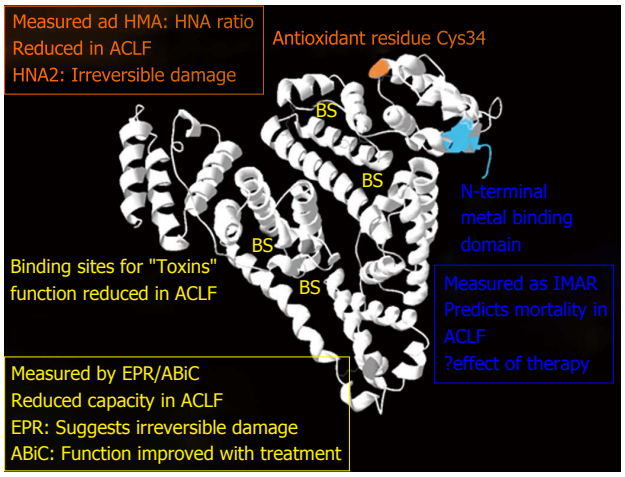

Figure 3 Impaired albumin function in cirrhosis. ACLF: Acute-on-chronic liver failure; HMA: Mercaptoalbumin; HNA: Non-mercaptalbumin; IMAR: Ischaemia-modified albumin ratio; EPR: Electron paramagnetic resonance; ABiC: Albumin binding capacity.

capacity can be assessed using electron paramagnetic resonance spectroscopy. A study in 34 patients with acute-on-chronic liver failure (ACLF) assessed binding sites associated with main HSA functions using both these methods[3]. This study demonstrated impaired HSA ability to transport HSA-bound substances in ACLF. The ratio of IMA to normal HSA (IMAR) was significantly higher in non-survivors compared to survivors. The role of this ratio in novel prognostic scores is currently under investigation. MARS™ treatments did not improve HSA function or IMAR in this study.

Another study assessed the functional status of the HSA thiol moiety by measuring non-oxidized mercaptalbumin, reversibly oxidized HNA-1 and irreversibly oxidized HNA-2 with chromatography according to the redox state of cysteine-34[35]. ABiC assessed with dansylsarcosine as ligand was reduced in patients with cirrhosis and was associated with parameters of liver dysfunction. The proportion of oxidised forms was also increased in patients with cirrhosis. The irreversibly damaged HNA-2 form was a strong predictor of 30- and 90-d mortality with predictive accuracy comparable to MELD.

These studies demonstrated impaired HSA function in patients with cirrhosis, which increased with severity of underlying liver disease. Oxidative changes may account for the reduced binding capacity resulting in impaired detoxifying and antioxidant function. Extracorporeal liver support systems, MARS™ and Prometheus™, were developed to remove HSA-bound toxins, such as bilirubin and bile acids, but they are unable to restore HSA function, due to irreversible damage[36]. Although initial studies reported some improvement in ABiC with MARS™ treatments, subsequent studies did not show any benefit. Plasma exchange, on the other hand, removes and replaces damaged HSA, and has shown more encouraging clinical outcomes.

Impaired ABiC has been also demonstrated in patients with chronic kidney disease, and correlates with the degree of renal dysfunction[37]. HSA dysfunction may contribute to the accumulation of HSA-bound uraemic toxins leading to uraemic complications. Renal dysfunction is not uncommon in patients with advanced liver disease, and may further aggravate HSA function. The impact of renal failure on HSA function in ACLF needs to be addressed in future studies.

Table 1 Composition of human plasma and different intravenous fluids

	Human plasma	4% albumin solution	0.9% saline solution	Hartmann's solution
Osmolarity (mOsm/L)	291	250	308	280.6
Sodium (mmol/L)	135-145	148	154	131
Chloride (mmol/L)	94-111	128	154	111
Potassium (mmol/L)	4.5-5.0	0	0	5.4
Calcium (mmol/L)	2.2-2.6	0	0	2
Lactate (mmol/L)	1-2	0	0	29
Octanoate (mmol/L)	0	6.4	0	0

HAS COMPOSITION

HAS, produced by plasma fractionation since 1941, has been widely used in clinical practice - despite criticism - mainly for its intravascular volume expansion properties. There are differences that should be taken into consideration between HAS and endogenous HSA, as well as between different HAS formulations. HAS is hypo-osmolar compared to human plasma but with higher sodium and chloride concentrations (Table 1). There may also be differences in oxidation and metal ions among different HAS products, and storage conditions may lead to biochemical changes. These may not be relevant for volume expansion but could modify albumin function. Quantitative analysis of octanoate in HAS showed levels within 20% of the quoted product label value in 132 of 138 HAS tested[38]. Octanoate is used as a stabiliser but variations in levels are associated with embryotoxicity. It can also bind to HSA (binding site 1) inducing allostery and displacing compounds, such as non-steroidal anti-inflammatory drugs, at binding site 2[39,40]. The stability and binding capacity of different HAS preparations has been investigated for the use of albumin in liver support dialysis systems[41]. HAS is available in different concentrations, and experiments in a murine model of endotoxaemia suggest that only albumin at physiological concentrations of 4%, and not 20% HAS, had a protective effect[42].

Recombinant human HAS has shown pharmacokinetic equivalence in studies, but has only been licensed as a pharmacological excipient due to concerns about immunogenic host cell products[43]. Industrial manufacture of recombinant HAS is currently not cost-effective. However, the potential production of genetic isoforms of HAS with desirable characteristics, such as antibacterial properties or bilirubin affinity, may expand the utility of recombinant HAS in the future.

EVIDENCE FOR HAS USE IN CRITICAL ILLNESS AND CIRRHOSIS

Critically ill patients

The utility of HAS in the management of critically ill patients has been a matter of great debate. A Cochrane meta-analysis of 30 clinical trials published in 1998 showed a 6% absolute increase in risk of death with HAS administration compared with crystalloid solutions in patients with hypovolaemia, burns or hypoalbuminaemia[44]. However further clinical trials and meta-analyses failed to confirm these findings.

The Saline *vs* Albumin Fluid Evaluation (SAFE) study was a large double-blind randomised trial comparing 4% HAS with normal saline (NS) fluid resuscitation in approximately 7000 critically ill patients[45]. This study did not show any difference in mortality, number of failing organs, length of intensive care unit (ICU) or hospital stay, or need for renal replacement therapy at day 28. In the subgroup of patients with severe sepsis 28-d mortality was lower in the HAS group (30.7%) compared to the NS group (35.3%), but this difference did not reach statistical significance. In multivariate analysis HAS administration was an independent predictor of survival in the same subgroup of patients. In the subgroup of patients with traumatic brain injury, however, mortality at 24 mo was higher in the HAS group (33.2%) compared with 20.4% in the NS group[46].

Another study investigated the administration of 20% HAS in critically ill patients for the first seven days of ICU stay[47]. One hundred patients with hypoalbuminaemia were randomized to either 20% HAS or no HAS, with target HSA of 30 g/L. There was significant improvement in organ function, as assessed using the Sequential Organ Failure Assessment score, in the HAS group with a less positive fluid balance. There was, however, no significant difference in 28-d mortality (24% in the HAS *vs* 30% in the control group) and length of hospital stay.

A subsequent meta-analysis including 38 studies did not show any mortality benefit with HAS administration in critically ill patients with hypovolaemia, burns or hypoalbuminaemia[48]. The results of this meta-analysis were greatly influenced by the SAFE study population. A more recent meta-analysis compared colloid *vs* crystalloid fluid for resuscitation in critically ill patients[49]. Twenty four studies that compared HAS with crystalloid fluid were included in the analysis. There was no difference in mortality between the two groups. According to the results of the above meta-analyses, the administration of HAS in critically ill patients cannot be justified in view of the failure to demonstrate survival benefit and the higher cost of HAS.

Patients with cirrhosis

Contrary to the controversial indications for HAS use in critical illness, there is robust evidence to support its use for the treatment or prevention of certain complications of cirrhosis. Although initially the oncotic properties of HAS were thought to be of great benefit in cirrhosis, the emerging knowledge on the HSA binding properties and the idea of the "effective albumin concentration" shifted interest towards the non-oncotic properties of HAS.

Circulatory dysfunction is a hallmark of cirrhosis. Splanchnic vasodilatation in the arterial circulation, decreased vascular resistance and "effective intravascular blood volume", increased cardiac output and hyperdynamic circulation are the main features of this circulatory dysfunction, and are probably related to overproduction of vasoactive substances, mainly nitric oxide[50]. These changes lead to homeostatic activation of the renin-angiotensin system and the sympathetic nervous system, and increased release of antidiuretic hormone, resulting in sodium and water retention. Renal perfusion is reduced due to local vasoconstriction, and glomerular filtration rate decreases. Although HRS is often thought to be a vasomotor nephropathy, there is in addition an inflammatory component, with increased Toll like receptor expression in the renal tubules[51]. The use of HAS in cirrhosis has been largely based on its oncotic properties that increase the "effective intravascular blood volume" and improve the circulatory dysfunction. The European Association for the Study of the Liver guidelines suggest administration of HAS in patients with cirrhosis for the following indications[4].

LVP to prevent paracentesis-induced circulatory dysfunction: Diuretic-refractory or diuretic-intolerant ascites occurs in 10% of patients with cirrhosis, and is associated with poor survival. LVP and transjugular intrahepatic portosystemic shunt (TIPS) are the main treatment options for these patients. TIPS not only is more effective in the treatment of refractory ascites compared to LVP, but has been also shown to improve transplant-free survival, as it addresses the underlying portal hypertension[52]. However, TIPS is associated with increased incidence of hepatic encephalopathy, thus it is contra-indicated in these patients, as well as in patients with severely impaired liver function or significant cardiac dysfunction[53]. TIPS may not be technically feasible in cases with non-compatible vascular anatomy or vascular occlusions.

It is evident that LVP remains the only available treatment option for a proportion of patients with refractory ascites. LVP, however, exacerbates the circulatory dysfunction already present in these patients by accentuating the arteriolar vasodilatation leading to overactivation of the compensatory endogenous neuro-humoral vasoactive systems[54]. This paracentesis induced circulatory dysfunction and effective reduction in blood volume may have detrimental effects in cirrhosis including: Rapid re-accumulation of ascites, development of dilutional hyponatraemia, HRS, increased portal pressures and shortened survival[55]. A randomised study comparing LVP with or without HAS administration as plasma expander showed that paracentesis without HAS was associated with higher frequency of renal

impairment, higher plasma renin activity and aldosterone concentration, and higher incidence of hyponatraemia[55]. Several strategies to prevent post-LVP circulatory dysfunction have been tested including administration of HAS, colloid fluids and vasoconstrictor agents. A meta-analysis including data from 17 randomised trials demonstrated significantly lower incidence of post-LVP circulatory dysfunction with HAS compared to each of the other treatment modalities[56]. The incidence of post-LVP hyponatraemia, and mortality were also lower in the HAS group. Current guidelines suggest HAS replacement at a dose of 8 g for every litre of ascitic fluid removed with LVP.

Treatment of HRS: HRS type 1 is characterised by progressive renal failure and is associated with increased mortality. Treatment of HRS includes vasoconstrictors (primarily terlipressin, or noradrenaline, or if these are not available then midodrine and octreotide) in combination with HAS. Terlipressin, a vasopressin analogue, is the vasoconstrictor most commonly used. A randomised, double-blind, placebo-controlled trial showed reversal of type 1 HRS in 34% of patients treated with terlipressin and HAS, *vs* 12% of those treated only with HAS[57]. HRS reversal in this study was associated with improved 6-mo survival. These results were confirmed in a randomised study published almost simultaneously by a different research group[58]. In this study renal function improved in 44% of patients treated with terlipressin and HAS, but only in 9% of those treated with HAS. Improvement in renal function was again an independent predictor of 3-mo survival.

The efficacy of terlipressin without HAS in treatment of HRS has been also assessed. HRS reversal was achieved in 77% of patients receiving terlipressin and HAS, and in 25% of those receiving terlipressin alone[59]. Improvement in arterial pressure and suppression of the renin-angiotensin system was observed only in the combination group, but not in the terlipressin monotherapy group. The recommended dose of HAS in HRS is 1 g/kg of body weight on day 1, followed by 20-40 g/d.

SBP to prevent renal dysfunction: One third of patients with SBP, another common complication in patients with cirrhosis and ascites, develop renal dysfunction secondary to rapidly progressive impairment in systemic haemodynamics[60]. SBP is also associated with increased mortality, in particular in the subgroup of patients who develop renal impairment. A randomised study assessed renal function and mortality in 126 patients with SBP treated with antibiotics with or without HAS[61]. HAS was administered at a dose of 1.5 g/kg of body weight at the time of diagnosis, followed by 1 g/kg of body weight on day 3. Renal impairment developed in 33% in the group treated only with antibiotics, and in 10% in the HAS group, and 3-mo mortality was 41% and 22%, respectively. Following this landmark study, the combination of antibiotics with HAS was established for the treatment of SBP, and the recommended dose of HAS is that used in the initial study.

The beneficial effect of HAS has also been assessed in patients with cirrhosis and bacterial infections other than SBP[62]. A small study showed improvement in circulatory function in patients treated with antibiotics and HAS compared to those treated only with antibiotics, and a trend towards improved renal function, but no difference in 3-mo survival. Unless future studies provide more robust evidence, currently there is not enough evidence to support HAS administration in non-SBP infections.

Treatment of hypervolaemic hyponatraemia: Hyponatraemia in cirrhosis can be hypovolaemic or hypervolaemic according to extracellular fluid volume status[63]. Hypervolaemic or dilutional hyponatraemia is primarily the result of increased secretion of antidiuretic hormone resulting in greater renal water retention compared to sodium[64]. Hyponatraemia is a poor prognostic marker associated with high mortality. Treatment options are limited as fluid restriction is rarely effective, and crystalloid fluids are only indicated in hypovolaemic hyponatraemia. Previous studies have shown improvement in serum sodium concentration with HAS administration, most likely related to its volume expansion effect[65], therefore HAS can be used for the treatment of hyponatraemia despite the scarcity of strong evidence. Preliminary reports have shown that increasing solute-free water excretion can improve hyponatraemia by blocking distal renal tubular vasopressin 2 receptors. The efficacy and safety of this class of drugs in patients with cirrhosis are currently under investigation, as too great a loss of water may lead to hypovolaemia and acute renal injury[66].

Finally, the effect of HAS on hepatic encephalopathy has been investigated, with studies failing to show that HAS administration improved hepatic encephalopathy, although it was associated with improved 3-mo survival[67].

Critically-ill patients with cirrhosis

The prognosis for patients with cirrhosis admitted to the ICU is poor with mortality rates of approximately 30% reported in contemporary patient cohorts and up to 80% in older ones[68]. Terlipressin and TIPS have improved outcomes, but mortality still remains high. The role of HAS in this setting has not been investigated. The same indications for HAS administration apply to critically-ill patients with cirrhosis in the ICU setting. Beyond the established indications for HAS, however, the question regarding the optimal resuscitation fluid in these patients has not been addressed. HAS administration has been shown to improve circulatory dysfunction and survival in patients with cirrhosis. The use of HAS is limited in critical illness by the absence of survival benefit as demonstrated by the SAFE study and subsequent meta-analyses, and the higher economic cost. We strongly feel that the efficacy of HAS as the primary resuscitation

fluid in critically-ill patients with cirrhosis should be reassessed in prospective randomised studies.

CONCLUSION

Beyond its well-known oncotic properties, HSA entails important binding capacity for endogenous and exogenous toxins which accounts for its antioxidant and anti-inflammatory properties. HSA concentrations are reduced in several disease states. There is increasing interest in HSA function in disease. In cirrhosis, hypoalbuminaemia is a common feature, but evolving research also suggests that HSA detoxifying function is impaired. The rationale for HAS administration in disease has been largely based on its volume expansion properties. In critical illness, however, fluid resuscitation with HAS has not been found to be superior to crystalloid fluids. In patients with cirrhosis, on the other hand, there are well-acknowledged indications for HAS, namely LVP, HRS and SBP. In critically ill patients with cirrhosis the optimal resuscitation fluid remains unknown. As such, future research should focus on the potential beneficial role of the functional properties of HAS, beyond simple volume expansion.

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