Albumin: The Cons

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Introduction

Intravenous albumin infusions have long been considered an important option in the treatment of patients with cirrhosis and ascites[1]. Many studies have shown that 20% Human Albumin Solution (HAS) improves circulatory function[2] and it is therefore recommended in international guidelines worldwide for use in hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), as well as in preventing post paracentesis circulatory dysfunction following large volume paracentesis (LVP)[3, 4]. Albumin has also been reported to have beneficial immunomodulatory and endothelial effects and therefore may have a particular beneficial role in sepsis[5, 6]. Finally two trials have been published this year regarding outpatient infusions[7, 8].

Therefore in routine clinical practise, its use often extends beyond these international guidelines. For example to treat low sodium levels, as an adjuvant to diuretic therapy for ascites in patients with renal insufficiency and in alcoholic hepatitis.

Controversy

However albumin use is not without controversy[9, 10] and many countries experience albumin shortages. Albumin is considerably more expensive than other intravenous fluids and theoretically, there is a risk of transmission of prion protein diseases[11]. Non hepatologists rarely use albumin outside of plasmapharesis. The large scale intensive care unit (ICU) studies of fluid resuscitation have largely shown equivalence when albumin was compared to crystalloids with subgroup analyses suggested benefit in patients with severe sepsis and harm in those with traumatic brain injur[12, 13, 14]. Moreover, serious adverse events have been reported with albumin use. In a recent study in patients with non-SBP infection using albumin, pulmonary oedema developed in 8.3% patients in the albumin group, two of whom died[15]. Therefore perhaps an evidence-based re-evaluation of the role of albumin in cirrhosis is timely.

Renal dysfunction, Spontaneous Bacterial Peritonitis and Large Volume Paracentesis

It is widely believed that albumin represents the optimum fluid resuscitation agent in cirrhosis based on its oncotic properties and ability to increase effective circulating volume in order to prevent activation of the sympathetic nervous system and the renin-angiotensin system[3, 4]. Albumin is recommended for acute kidney injury (AKI) not responding to initial measures such as diuretic withdrawal, although notably this is grade III evidence i.e. based on expert opinion[16].

Fluid resuscitation is naturally an integral part of the management of AKI; however, studies to date have not established grade I evidence for an advantage of the use of albumin over

other colloids or crystalloids. Vasoconstrictors and albumin are recommended in all patients meeting the current definition of AKI-HRS stage >1A and there is clinical trial data that demonstrates the combination of vasoconstrictors plus albumin is superior to vasoconstrictors alone[17, 18] but data also supports terlipressin and hydroxyethyl starch for this purpose[19]. Notably clinical guidelines suggest no other fluid aside from albumin.

Furthermore the albumin dosing regimen of 1.5mg/kg on day 1 and 1mg/kg seems on day 3 appears arbitrary and there are no dose finding studies. Indeed in the final paragraph of their seminal paper Sort et al state “Intravenous albumin is expensive and has limited availability in some settings. Therefore, studies should be performed to determine whether treatment of spontaneous bacterial peritonitis with lower doses of albumin or with artificial plasma expanders, which are less expensive, would have similar beneficial effects on renal function and survival”[20]. This approach seems to have been forgotten in our rush to prescribe albumin. Indeed our focus on a fixed weight-based dosing regimen ignores the fact that fluid resuscitation should be a dynamic process. Little mention is made in guidelines about monitoring treatment response, for example, using haemodynamic parameters or blood sampling for lactate or mixed venous oxygen saturation. Surely our clinical care is more sophisticated than to suggest a one fluid resuscitation size fits all for our patients

Albumin is recommended in the treatment of SBP in order to prevent renal failure and this is supported by a meta-analysis of four randomised controlled trials (RCTs) including 288 patients that demonstrated that albumin infusion prevented renal impairment and reduced mortality[21]. However, only 10 patients in the control arm in these trials received *any* fluid at all. These patients received hydroxyethyl starch (HES), which has been subsequently withdrawn from clinical use as it can cause renal failure; this was unknown at the time of this important study[21]. HES was selected as the comparator for albumin because a randomized trial had shown that it was as effective as albumin in the prevention of paracentesis-induced circulatory dysfunction[23] and that HES in combination with terlipressin had been found to be effective in the treatment of hepatorenal syndrome[19]. Moreover the oncotic capacity of 1 g albumin is identical to that of 1 g HES 200/0.5.This study showed that the administration of albumin improved cardiovascular hemodynamics in patients with SBP but that HES had no effect. However the crucial clinical endpoint, serum creatinine improved in both groups and SBP resolved in all patients.

The evidence for large volume paracentesis (LVP) differs in that many of these studies do have an active control arm treated with a plasma expander. Therefore the recommendation for albumin use reaches Grade 1A status in international guidelines[3, 4]. However two different conclusions have been reached by separate groups conducting their meta-analyses for use of albumin in LVP[24, 25]. One group concluded that there was insufficient evidence that albumin infusion after LVP significantly lowered mortality in hepatocellular carcinoma-free patients with advanced liver disease[24] and the other that albumin reduced morbidity and mortality compared with alternative treatments[25]. The primary reason for the lack of statistical significance appears to stem from the inclusion of two studies in the former analysis but not the latter as the authors disagreed as to whether these were appropriate[26]. A recent health economic assessment presented in abstract has suggested that the use of albumin for LVP, SBP or hepatorenal syndrome was cost-effective in both survival and quality adjusted life years (QALYs) across Italy, Spain, and Germany[27]. However only in the LVP model was albumin was compared to another fluid.

Albumin infusions are clearly beneficial for the above indications but we cannot comprehensively conclude that an alternative plasma expander would not have a similar effect on the most important clinical end points, renal failure and mortality. Even HES, a fluid that has been subsequently withdrawn from use in critical care patients appeared to have beneficial properties.

Adverse Effects

In cirrhotic patients with infections other than SBP, albumin infusion, using the 1.5mg/kg day 1 and 1mg/kg day 3 regimen, was associated with pulmonary oedema and did not improve survival at 3 months[15]. The authors recommended that infusion of large amounts of albumin should be cautiously administered in the sickest cirrhotic patients. A rise in portal pressure following large volumes of albumin may also theoretically precipitate a variceal bleed. In a feasibility trial in acute decompensation (AD) and acute-on-chronic liver failure (ACLF) patients given a less aggressive albumin regimen there were no episodes of pulmonary oedma and 5% of patients experienced a variceal bleed during the study treatment period which is similar to previously reported rates[28, 29].

Outpatient Albumin Infusions

There have been two large scale RCTs published in 2018 examining the efficacy of weekly or 2-weekly outpatient 20% HAS infusions[7, 8]. The MACHT trial (**m**idodrine and **a**lbumin for **c**irr**h**otic patients in the waiting list for liver **t**ransplantation)[8] showed that in patients with cirrhosis awaiting liver transplantation, treatment with midodrine and albumin (40g every 2 weeks) slightly suppressed vasoconstrictor activity, but did not prevent complications of cirrhosis nor improve survival. This was a double blinded placebo controlled trial using opaque bags and intravenous sets to administer albumin or placebo (Normal Saline). However, only 9 patients were treated for the entire year and the median length of treatment was 80 days. This demonstrates how challenging studies in liver transplant candidates are, as transplantation frequently interrupts the course of the patients' disease. However, given their notable achievement with regard to blinding, midodrine and albumin should certainly not be prescribed for patients with a likely 3 month or less wait on the transplant list.

The ANSWER trial (The human Albumin for the treatmeNt of aScites in patients With hEpatic cirrhosis)[7] which impressively managed to include 431 patients in their modified intention-to-treat analysis, did demonstrate a survival benefit in patients with cirrhosis and ascites using a treatment regimen of 40g of albumin weekly rather than every two weeks for up to 18 months[12]. The MACHT authors detected suppression, but not normalization, of renin-angiotensin-aldosterone system activity and perhaps a greater dose of albumin or longer duration of treatment is required to benefit patients. The forthcoming PRECICIOSA[27] trial (Effects of Long-Term Administration of Human Albumin in Subjects With Decompensated Cirrhosis and Ascites) in which the treatment arm will receive 1.5 g/kg body weight albumin every 10 ± 2 days may clarify this. However neither ANSWER nor PRECICIOSA are blinded placebo controlled trials and therefore the control groups have no fluid or weekly medical care which introduces an inherent bias in intensity of medical supervision. Finally, weekly infusions are a significant challenge to patient and health care providers alike. The ANSWER authors did demonstrate that albumin was cost-effective by preventing hospital admissions, but economic and quality of life burden associated with weekly travel to hospital was not considered.

Reversing Immune Dysfunction

Although many promising laboratory studies have shown a beneficial immune effect for albumin, the important clinical endpoints are incidence and outcome from infection. The best data on this subject has emerged from the ANSWER study that showed a striking 68% and 30% risk reduction for SBP and non-SBP infection respectively[7]. This provides very strong support for a beneficial role for albumin in prevention of infection, although no fluid was given to the control arm. The primary composite endpoint for ATTIRE (Albumin To prevenT Infection in chronic liveR failure)[31] includes development of nosocomial infection and laboratory studies using samples from their feasibility study supported improved immune dysfunction in AD/ACLF following 20% HAS intravenous infusions. This trial is due to complete next year and the control group receive fluid.

Conclusions

In conclusion, there is little supportive data using clinically robust endpoints to use HAS over other plasma expanders outside of LVP and even this is disputed. Furthermore many studies outside of LVP have administered no fluid to the control arm, which seems counterintuitive in a vasodilatory condition. However a sense of pragmatism is required. No one doubts that HAS is an effective plasma volume expander, the question is whether it is clinically more effective than other fluids, and this is important given its expense. Trials in patients with advanced liver disease are extremely challenging and gaining equipoise over which alternative fluid to use would be difficult. The Barcelona group have demonstrated that a placebo controlled trial of HAS against normal saline is possible[8]. Although this study randomised 196 patients and Kutting et al in their meta-analysis (that included 1277 patients) calculated at least 1550 additional patients need to be recruited in order to detect or disprove a 25% mortality effect for the use of albumin in LVP[25]. Studies at this scale require substantial funding and although the establishment of The European Foundation for the Study of Chronic Liver Failure have provided a great opportunity to enable this process, these studies are in reality rarely performed. It is hoped that as data systems evolve “real-world” clinical trials will enable studies of this magnitude to be performed more straightforwardly and at significantly reduced cost. All that will be required are some hepatologists that are prepared to use a different fluid to albumin.

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