

Human Albumin Infusion for Volume Resuscitation: Recommended and Controversial Uses

Abstract

Human albumin (HA) is currently the most expensive substitute for blood plasma and has been used since 1940 as part of volume expansion and resuscitation. HA preparations are administered as volume expander in numerous pathologic conditions, such as in the management of ascites and its complications in cirrhotic patients, in therapeutic plasma exchange, during major operations and in patients with burns, trauma, critical illness or sepsis. However, literature data indicate that HA use is rather empirical than evidence-based. The current review aims to summarize the published literature, enlightening the circumstances where HA infusion can be recommended as an appropriate volume expander and indicating the pathologic conditions where its administration is yet controversial.

Keywords: Volume resuscitation; Cirrhosis; Surgery; Trauma; Burns; Sepsis

Review Article

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Introduction

Human albumin (HA) is a natural colloid which was developed in 1940 and has been since used as part of volume expansion and resuscitation and to correct hypoalbuminaemia [1,2]. Currently, human albumin is the most expensive substitute for blood plasma, and increasing use has resulted to increased expenses, due to costs of production and limited availability [3-5]; for instance, HA 50ml bottle used to be sold for 14-20 dollars in Brazil in 2006, while the price reached 48-66 dollars in 2008 [5]. However, albumin preparations are safer than most plasma products because of the way they are manufactured. There are no reported cases of HBV, HCV or HIV infections and they can be used in spite of blood type, since they do not contain agglutinins or other blood type substances [2,5-7].

Numerous studies have been conducted concerning the advantages and disadvantages of the use of HA in various populations and pathological conditions. Nevertheless, the outcomes are ambiguous resulting in an empirical use of HA rather than evidence based. The latter is verified by a study conducted in 53 US hospitals concluding that the use of HA was inappropriate in 57.8% of adult and 52.2% of pediatric patients [7], while Yim et al. [8] indicated that HA infusion is not supported by consensus guideline recommendations in 62% of cases [8]. Implementation of albumin guidelines is limited basically due to the lack of generalizability of meta-analysis findings, small sample sizes and pooling data of clinically heterogeneous patient groups [9].

Beyond controversies and cost limitations, clinical practice should be guided by specific recommendations, in order albumin use to be selective and effective. Under this scope, the present

review aims to assess the efficacy of HA in clinical practice, indicating the clinical circumstances where albumin infusion is recommended and enlightening the cases where its infusion is considered to be more controversial, based on published literature.

Methods

A systematic search in the electronic database of PubMed using the search terms human albumin treatment or human albumin therapy or human albumin infusion and fluid resuscitation, sepsis, mortality, critical care, intensive care, shock, surgery, trauma, cirrhosis, paracentesis, plasmapheresis, plasma exchange, hypoalbuminemia or plasma substitute was conducted. All articles referred to humans, were written in English and were published in PubMed between 2004 and 2015. In case that a retrieved article cited a paper published earlier than 2004, but which was considered to be very interested and strongly related to the subject, this older article was also retrieved.

Recommended uses of human albumin as volume expander in clinical practice

Expert opinion or international clinical guidelines, are currently recommending HA infusion in the following pathologic conditions:

Management of ascites: Ascites is a major complication, occurring among 50% of patients with "compensated" cirrhosis, and a landmark in natural history of disease which is associated with increased morbidity and hospital admissions [10,11]. Although liver cirrhosis is the most common one (75% of all cases of ascites), other causes include malignancy, heart failure, tuberculosis and pancreatitis [11,12]. Over the recent years

there have been several changes in the management of this complication, under the scope of the constant rising of both the incidence and the associated mortality of ascites.

Published data indicate that in patients with large ascites, HA infusion may be useful for volume expansion after paracentesis. A meta-analysis of 17 randomized trials with 1225 total patients with tense ascites indicated that post-paracentesis albumin infusion decreased the frequency of circulatory dysfunction (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.27-0.55); in the subgroup analysis albumin was found to be superior compared to every other volume expander (e.g. dextran, gelatin, hydroxyethyl starch, and hypertonic saline) regarding this complication. Moreover, there was a decrease in the occurrence of hyponatremia (OR, 0.58; 95% CI, 0.39-0.87) and in mortality risk (OR, 0.64; 95% CI, 0.41-0.98) in albumin group. In these studies the mean volume of ascetic fluid removed was 5.5-15.9 liters [13].

Following this meta-analysis, the American Society of Gastroenterology updated the guidelines on treatment of ascites to recommend post-paracentesis albumin infusion in a dosage of 6-8 gr per liter of fluid removed, when large volume paracentesis (at least 5 liters) is conducted (level A of evidence) [10]. For single, smaller volume-paracentesis (less than 4-5 liters) the American Society of Gastroenterology recommends that albumin infusion might not be necessary (level C of evidence), since there is not sufficient evidence that has an impact on mortality. As a matter of fact, a small, older study which prospectively assessed the circulatory and neurohumoral responses in 12 patients following a single less than 5 liters total paracentesis concluded that it was safe not to treat these patients with albumin [14]. However, the International Ascites Club recommended that due to the lack of enough evidence a synthetic volume expander should also be used when less than 5 liters of fluid is removed, and this recommendation was based more on consensus than literature data [10,15]. For larger volume paracentesis, the British Society of Gastroenterology also recommends the infusion of HA post-paracentesis, as 20% or 25% solutions at a dose of 8 gr per liter of fluid removed [10].

Spontaneous bacterial peritonitis: Spontaneous bacterial peritonitis (SBP) is the bacterial infection of ascetic fluid in cirrhotic patients [16] and consists the most frequent and most severe infectious complication in this population [17]. Although SPB-attributed mortality has decreased to approximately 20% [18,19], SPB remains a serious complication, especially among hospitalized patients, that has to be early recognized and promptly treated.

Renal impairment is a frequent complication occurring among patients with SBP and is associated with increased mortality [20]. According to current guidelines, albumin infusion is recommended in patients with SBP at a dose of 1.5 g/kg body weight on day 1 and then at a dose of 1 g/kg body weight on day 3, in combination with wide spectrum antibiotics [19]. A recent meta-analysis of 4 randomized control trials including 288 patients with SBP indicated that albumin infusion prevented renal impairment and reduced mortality among patients given albumin, compared to controls [21]. However, whether all patients with SBP should be administered albumin is still under

debate. Poca et al indicated that intravenous administration of albumin increases the survival of patients with high risk (urea >11 mmol/L and bilirubin >68 μmol/L) SBP episodes, while does not seem to be necessary for patients with low risk (urea <11 mmol/L and bilirubin <68 μmol/L) of death [22]. Thus, albumin administration could possibly be avoided among patients with milder SBP episodes. Nevertheless, due to the lack of enough published evidence, the clinical Practice Guidelines for the Study of the Liver (EASL) recommends the administration of albumin to all patients with SBP [19,23]. Nevertheless, the administration of albumin in cirrhotic patients with infections other than SBP remains controversial and has not been included in clinical guidelines.

Hepatorenal Syndrome: Hepatorenal Syndrome (HRS) is a serious complication of advanced cirrhosis and is defined as the development or renal dysfunction due to decrease in effective arterial blood volume [24]. The pathophysiologic mechanism underlying this condition is the severe renal hypoperfusion due to activation of neurohumoral mechanisms, resulting to renal vasoconstriction; thus, HRS is a functional renal failure, associated with high mortality [19].

Therapeutic approach to HRS aims to the expansion of circulating plasma volume, utilizing a combination of vasoconstrictors and a synthetic plasma expander [24]. Of all volume expanders tested, albumin has proven to be the most helpful, while when albumin is administered concomitantly with other plasma expanders, the effectiveness of the latter increases [24-26]. Several vasoconstrictors have been used for the treatment of HRS; however, none was found to be effective enough when administered alone. On the other hand, the combination of HA with intravenous vasoconstrictors seems to be the most effective treatment for HRS. Norepinephrine, dopamine, vasopressin [10,24,27,28] are only some of the vasoactive agents that have been used in combination with albumin for the treatment of HRS, but the combination of terlipressin-albumin is probably the most widely used and studied. According to clinical recommendations, albumin could be given bolus intravenously for 2 days with an initial dose of 1g/kg and then a maintenance dose of 20-25 g/d until the vasopressor is ceased and serum creatinine level has become normal [19,29].

Therapeutic plasma exchange: Therapeutic plasma exchange (TPE) is a term which refers to several procedures all of which involve large plasma volume removal from the patient, such that a significant hypovolemia and circulatory collapse could occur. Therefore TPE is always accompanied by volume replacement. On the other hand, plasmapheresis refers to a procedure where smaller amount of plasma is removed, so that volume replacement is not needed [30,31].

Currently, HA infusion is recommended as replacement fluid after TPE [30]. A solution of 4%-5% of HA with normal saline is used, with the majority of the solution given at the end of the procedure, as approximately 2/3 of any volume substitute is removed during the TPE, if given at the beginning. Although albumin replacement fluid significantly increases the cost of TPE, it is a safer volume substitute than plasma, since potential transfusion reactions are avoided [30,32].

Controversial uses of human albumin as a volume expander in clinical practice

Data on HA infusion in other medical or surgical patients are currently controversial, regarding both its superiority as volume expander, compared to other colloids, and its impact on morbidity and mortality in several pathologic conditions.

Albumin infusion in patients who undergo cardiac surgery: In cardiac surgery patients the use of volume expanders is guided by the potential of major blood loss and the need of balanced volume replacement, in order circulatory collapse to be avoided without resulting in pulmonary oedema. In these patients HA infusion has been previously considered as an appropriate treatment approach. Previous studies indicated a lower risk of bleeding after the use of HA solutions, compared to older synthetic colloids, such as dextrans or first generation hydroxyethyl starch (HES) [33-36], while in the study of Sedrakyan et al. [37] the administration of HA as a volume expander after coronary artery bypass graft surgery reduced mortality by 25%, compared to the use of non-protein colloids [37]. In a meta-analysis conducted in 2012 among 970 patients who had undergone cardiac surgery, HES solution of 450/0.7 or 200/0.5 increased postoperative blood loss and increased the need for red blood cells, fresh frozen plasma and platelets infusion, compared to HA administration [38].

On the contrary, in a more recent prospective study which included 240 cardiac surgery patients, 5% HA infusion was compared to 130/0.4 HES and no significant difference in postoperative rate of bleeding and need of transfusion rate was found between these two colloids. In this study patients who were treated with a crystalloid (Ringer Lactate) only, although presented with a more positive perioperative fluid balance, required less blood products transfusion, possibly due to the limited interference of crystalloids with blood coagulation factors, compared to colloids [39]. Furthermore, in a prospective cohort of 984 patients with normal preoperative renal function who underwent on-pump cardiac surgery, HA administration postoperatively was associated with significantly increased risk of acute kidney injury, which was dose-dependent and remained significant after adjustment for all other cofounders [40]. Under the scope of these conflicting results and due to its high cost, HA is usually recommended to be used among cardiac surgery patients as last resort after crystalloids and non- protein colloids fail to restore circulating volume [3,41].

Volume replacement in cases of burns: Severe burns, extended at least 20 to 25% of total body surface area are associated with increased capillary permeability and decreased intravascular volume, which if left untreated could result to circulatory collapse, organ hypoperfusion, acute renal failure and death. These abnormalities are more severe during the first 24 hours and dictate an optimal fluid resuscitation [42]. Hypoalbuminemia is a frequent complication of burns and has been associated with increased mortality [43].

Under this scope, human albumin administration could be potentially beneficial for patients with extensive burns. In a retrospective study by Park et al. [44], early albumin administration among patients with burn size of at least 20% of total body surface area who needed more than 6 ml/kg per

cent burn of fluids to resuscitate, resulted in decreased mortality and the use of less vasopressor agents [44]. However, in another study, hypoalbuminemia correction with HA infusion resulted to increased costs of hospitalization, with no impact on hospital length of stay, wound healing, or mortality [45]. According to a Cochrane Database systematic review, analysis of 70 randomized controlled trials indicated that there is no evidence that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, among patients with trauma, burns or following surgery. For HA infusion, in specific, the pooled relative risk was 1.0 (95%CI 0.92-1.09) [46].

Currently, the majority of burn centers are using isotonic crystalloid solutions for initial fluid resuscitation. According to American Burn Association Practice guidelines 2 to 4 ml/kg body weight/% total body surface area of a crystalloid solution during the first 24 hours is recommended for fluid volume resuscitation in burn patients. The addition of colloid-containing fluid, such as albumin, after the first 12 to 24 hours post-burn may decrease overall fluid requirements [42]. Following the controversy regarding the efficacy of albumin infusion in burns, several burn resuscitation protocols in other countries have also moved from previously used colloid-based resuscitation to crystalloid-based resuscitation protocols, in agreement to what is currently used in United States [41,47].

Volume replacement in trauma patients: Trauma patients are very often in need of emergency fluid resuscitation, especially when they present with acute hypovolemic shock due to hemorrhage, and albumin infusion, like other colloid solutions, has been used as a volume replacement in these patients. Previous small studies in animal models indicated that albumin may also protect lungs from injury during acute hypovolemic/hemorrhagic shock resuscitation [48,49]. However, current literature data from human studies do not support any benefit in survival when albumin solutions are used instead of other volume substitutes [7]. A recent meta-analysis of randomized controlled trials involving more than 9000 critically ill patients concluded that there is no evidence that HA infusion improves survival among trauma patients [46]. Moreover, several practical issues are related with the use of HA as a volume expander, as it is stored in a glass vial that is not easy to use when large volumes of fluids need to be administered with quick flow to a patient, such as in multiple trauma [7].

Previous studies on animal models indicated that albumin infusion may have a beneficial effect in the treatment of brain injury hypovolemia. Several resuscitation techniques were used in Sprague-Dawley rats with traumatic head injury and hemorrhage. In this animal model, albumin infusion exhibited the greatest beneficial effect on mean arterial pressure, regional tissue oxygenation and arterial PO₂ compared to either normal saline or other colloids [50]. However, later studies on human subjects did not confirm these preliminary results. The SAFE (Saline versus Albumin Fluid Evaluation) study suggested that the infusion of HA solutions may increase brain volume and intracranial pressure, due to their low osmolality [51]. Following up of 460 patients with traumatic brain injury indicated that the ones treated with normal saline presented with lower relative risk of dying, compared to the ones treated with HA [52].

In conclusion, due to the lack of evidence on the beneficial effect of albumin as a volume substitute in trauma patients and to its potential harmful effects among specific trauma groups, such as patients with head injury, some authors propose that injured patients under hypovolemic shock can be treated with albumin only if there is a lack of response to crystalloid or colloid solutions in full doses or when there is any contraindication to the use of non-protein colloids [41].

Albumin use in sepsis: Severe sepsis and septic shock often complicate the clinical course of critically ill patients, leading to increased mortality [53-55]. Early, adequate volume expansion is crucial for the treatment of these patients, and thus HA is often administered in addition to other colloid or crystalloid solutions for this purpose [56]. However, literature data are currently controversial regarding the impact of albumin infusion on short and long term mortality of septic patients. The SAFE (Saline versus Albumin Fluid Evaluation) randomized controlled study concluded that albumin administration did not impair renal or other organ function and might have resulted in reduced risk of death, compared to saline, among patient with severe sepsis; nevertheless, this was a result of a pre-defined subgroup analysis [57]. On the other hand the more recent multicenter, open-label ALBIOS (Albumin Italian Outcome Sepsis) trial where 1818 patients were randomly included to receive either 20% HA and colloid solutions or colloid solutions alone, concluded that in patients with severe sepsis albumin administration in addition to crystalloids did not improve survival rate at either 28 or 90 days [58].

Against this background of uncertainty Jiang et al conducted a meta-analysis of 15 randomized controlled trials, which concluded that the use of albumin-containing fluids for the resuscitation of septic patients of any severity was not associated with any significant survival advantage [59]. However, Xu et al. [56] utilizing more strict criteria regarding the quality assessment of the included studies, conducted another meta-analysis, of a total 3658 severe sepsis and 2180 septic shock patients. This meta-analysis concluded that there was a trend to reduced 90-day mortality when albumin infusion was used for the resuscitation of severe sepsis patients (OR 0.81 95% CI=0.67-0.97, p=0.03), compared to crystalloids and saline [56].

Currently, Surviving Sepsis Campaign International guidelines recommend initial fluid resuscitation with crystalloids (level 1B of evidence) and consideration of the addition of albumin in septic patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure (level 2C of evidence) [60]. Giving the low level of recommendation regarding the use of albumin among septic patients and the somehow conflicting results regarding the impact of colloid versus crystalloid solutions on mortality among critically ill patients [61,62], further prospective studies are needed in order to draw definite conclusions.

Conclusion

HA is an expensive plasma substitute widely used as a volume expander. Management of ascites among cirrhotic patients, spontaneous bacterial peritonitis, hepatorenal syndrome and

therapeutic plasma exchange are the most important indications for HA administration, according to existing guidelines. Nevertheless, HA solutions have also been used in order to treat hypovolemia and occasionally concurrent hypoalbuminemia in patients with burns, trauma, sepsis or postoperatively, although conflicting data from published literature cannot adequately support the inferiority of albumin solutions compared to other colloids or crystalloids, regarding short and medium term mortality. Much of the diversity of these results comes from the high variation in the population included and the methods of analysis applied. Since the cost of using HA is constantly growing, along with the burden of critically ill patients, further prospective studies are needed in order the specific patient characteristics who would benefit most from HA infusion to be accurately defined.

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