Hyperoncotic Human Albumin Solution in Traumatic Brain Injury

Subjects: Critical Care Medicine

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Fluid resuscitation with human albumin solution (HAS) corrects low serum albumin levels and aids in preserving euvolemia in non-brain-injured intensive care units and in perioperative patients. Ischemia, hypotension, hypoxia, and energy dysfunction are important determinants of the outcomes following a severe traumatic brain injury (TBI). Cerebral edema and increased intracranial pressure (ICP) are frequently observed after TBI, leading to cerebral ischemia.

albumin brain injury intracranial pressure

1. Introduction

Despite continuous advances in intensive care, the mortality and permanent disability rates after head injuries remain high [1][2]. Ischemia, hypotension, hypoxia, and energy dysfunction are important determinants of the outcomes following a severe traumatic brain injury (TBI). Cerebral edema and increased intracranial pressure (ICP) are frequently observed after TBI, leading to cerebral ischemia. A complex series of pathological events triggers the propagation of this secondary injury cascade to cerebral areas that are initially not involved in TBI [3]. The mortality among patients with TBI is significantly increased in the presence of intracranial hypertension (ICP ≥ 20 mmHg), regardless of the cerebral perfusion pressure (CPP) [4], and patient management has focused on preventing or ameliorating the secondary injury that occurs in the ensuing hours and days following the primary initial trauma. An overarching goal of medical management is to ensure optimal cerebral perfusion and oxygenation [5].

Intravenous fluids play a central role in the management of TBI, allowing adequate CPP to be maintained and helping to avoid intracerebral edema and elevated ICP. However, fluids can have both favorable and unfavorable consequences because of the potential risks of hyperhydration and hypo- or hyperosmolar conditions, which may affect the clinical course and outcome of TBI [6].

2. Use of Human Albumin Solutions in Fluid Management of Traumatic Brain Injury (TBI)

Recent evidence of the low risk of bias confirmed that the use of 20–25% (hyperoncotic) human albumin solution (HAS) to correct low serum albumin levels aids in preserving euvolemia in non-brain-injured intensive care units and perioperative patients [7][8]. Previously, an infusion of 25% HAS was shown to prevent intracerebral edema in patients with TBI [9] and decrease ICP after craniotomy [10].

An ICP-targeted treatment concept for TBI was developed by investigators in Lund, Sweden, utilizing hyperoncotic HAS to maintain euvolemia and colloid osmotic pressure [11]. However, HAS as a replacement fluid in acute brain injury patients is not used in most centers worldwide and is not recommended in international clinical guidelines because of reports of adverse outcomes of HAS infusion [12][13][14]. Specifically, the SAFE-TBI study (a post-hoc follow-up analysis of 290 patients from the randomized SAFE trial) reported higher mortality in those receiving 4% HAS [15]. The researchers of this post-hoc analysis suggested that increased albumin may have crossed the damaged blood–brain barrier into the brain tissue, resulting in a greater net outflow of fluid from the cerebral intravascular space into the interstitial brain tissue. An increase in cerebral edema, increase in cerebral pressure, more frequent use of cerebral pressure-lowering measures and, finally, increased mortality in the 4% HAS group compared to the group receiving physiological saline for volume therapy were observed [15][16].

These findings remain the subject of debate, because the patients were not enrolled in the SAFE study according to any specific set of TBI-related criteria, and the use of a hypotonic preparation of 4% HAS, particularly in conjunction with the liberal use of vasopressors and relatively high hydrostatic pressure, may have been suboptimal for the patients with severe TBI [17]. The mean change in ICP from randomization to 14 days post-randomization was subsequently analyzed in a post-hoc subgroup of 209 patients of the 290 patient SAFE-TBI study subgroup associated with the use of 4% HAS with increased ICP on day 7 but not on day 3, day 14, or overall [18]. In this subgroup analysis of a subgroup, the initial mean ICP was 21% higher in the group allocated to 4% HAS (p = 0.06), and no attempt was made to adjust for this imbalance [18]. Experimental findings directly comparing the commercially available hypotonic 4% HAS used in the SAFE study (4% Albumex (278 mOsm/kg)) with a novel isotonic 4% HAS (288 mOsm/kg) finally confirmed that the tonicity of 4% HAS, rather than the albumin itself, was responsible for increasing the ICP [19].

A recently published BaSICS study in Brazil confirmed this hypothesis [20]. When comparing a balanced infusion solution (Plasma-Lyte 148®, Baxter Hospitalar, Brazil) to isotonic saline, a subgroup analysis of the patients with TBI showed that a significantly higher 90-day survival rate was observed under isotonic saline than in patients treated with the balanced solution [21]. Compared to the 0.9% saline solution, the balanced solution used had a theoretical osmolarity of 296 vs. 308 mOsmol/L, whereas the measured osmolality showed an osmolar difference of 271 vs. 296 mOsmol/kgH_2O [22].

The European Society of Intensive Care Medicine (ESICM) consensus and clinical practice recommendations suggest against the use of 4% or 20% HAS as the resuscitation fluid in acute brain injury patients with low blood pressure independent of HAS tonicity (weak recommendation) [14], despite the existence of suggestive evidence that the Lund concept of normalization of plasma oncotic pressure with slowly infused 20–25% HAS may lower the mortality rate compared with alternative approaches in TBI. Several studies have consistently reported low mortality rates ranging from 8% to 20% in patients with severe TBI [23][24][25][26][27][28][29][30][31][32][33], whereas the mean percentages of all injury-related mortality caused by or associated with TBI in Europe and the United States are 37% and 30.5%, respectively [34].

3. Mechanistic Considerations for the Use of Hyperoncotic HAS in TBI

The physiological considerations of intravenous HAS as a replacement fluid and the extant clinical evidence for and against its use within the various facets of modern neuroanesthesia and neurocritical care practice were recently explored and reviewed by Ma and Bebawy [13]. The recommendation was made so that, in the absence of definitive data to either support or dissuade from the use of HAS in most neurosurgical scenarios, practitioners should consider the potential risks and benefits of HAS administration. In the narrative research, no mention was made of the ICP-targeted treatment of TBI utilizing 20–25% HAS [13], suggesting that data on HAS administration in the context of the Lund concept have not been taken into consideration.

HAS infusion to maintain normal serum albumin levels is the cornerstone of the Lund concept [11][12]. HAS is an effective volume expander and, along with erythrocyte transfusions, aids in preserving euvolemia, reducing reliance on vasopressors, and thereby averting intracranial hypertension. Additionally, as the chief endogenous colloid of human plasma, albumin sustains oncotic forces that retain the fluid in the intravascular compartment, consequently minimizing tissue edema in the injured brain and the rest of the body. The administration of concentrated albumin prevented or reduced cerebral edema in two randomized trials [9][35] and in a nonrandomized controlled study [36].

Research has identified a wide range of putative roles for HAS in modifying inflammation, maintaining vascular endothelial integrity and the acid–base balance, and ligating endogenous and exogenous compounds [37], which may all play important roles in the pathophysiology of severe TBI. Albumin can offer protection from inflammatory processes and the associated damage to the microcirculation and tissues, with an impact on the outcome [38].

In addition, supporting the utility of HAS is the observation that hypoalbuminemia is independently associated with increased mortality among severe TBI patients [39]. The kinetics of albumin involves a transcapillary leak and breakdown, leading to hypoalbuminemia, which is associated with the worse outcomes in a broad spectrum of conditions [40]. The correction of hypoalbuminemia with hyperoncotic HAS infusion can be beneficial, as it improves the hemodynamic stability in patients with sepsis [41] and prevents acute kidney injury in cardiac surgery patients [42]. Intravenous hyperoncotic HAS has been determined to be safe for use as resuscitation fluid in most critically ill patients [7].

Neuroinflammation is recognized as an interaction between central and peripheral components that is influenced by age, sex, type of TBI and its severity, and other factors, including the timing of the diagnostic and therapeutic interventions that may have a significant impact on the outcome [43]. Although HAS therapy in TBI may have neuroprotective potential [44], no data supporting this hypothesis are currently available. Moreover, the colloids used in the Lund concept were not restricted to hyperoncotic 20% HAS but also included 4% HAS, plasma, and packed red blood cells (no synthetic colloids were used) [45]. If the timing of 20% HAS administration, i.e., early vs. late in TBI, is important remains speculative.

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