Review Article

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Hypertonic Saline In Traumatic Brain Injury: Current Status

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Abstract: Traumatic brain injury is among the leading causes of mortality today. Systemic hypotension and intracranial hypertension are major contributors towards morbidity and mortality in these patients. The primary goal of resuscitation is to maintain adequate blood pressure while attenuating the expected rise in intracranial pressure. The type of fluid to be used for this is much debated even today. Mannitol is the most popular agent, but there are limitations to its administration. Interest is now focusing on the utility of other hyperosmolar agents like hypertonic saline, that combat raised intracranial pressure and support intravascular volume. However, no standards exist regarding its indications or optimal administration regimen in the treatment of traumatic brain injury. A review of literature regarding the postulated mechanism of action and current status of its role in traumatic brain injury is discussed.

Keywords: head injury, hypertonic saline, traumatic brain injury, intracranial pressure, resuscitation

Traumatic brain injury is among the leading causes of mortality today. Out of these patients, 60-90% have diffuse cerebral edema, herniation or necrosis[1]. This secondary brain injury is attributable to a decrease in cerebral oxygen delivery as a result of hypoxia, systemic hypotension or relative hypoperfusion produced by intracranial hypertension[2]. On the basis of available prospective, randomized controlled studies, it is apparent that while treating a brain-injured patient, hypoxia, systemic hypotension and intracranial hypertension must be avoided[3,4]. The primary goal of resuscitation is therefore to maintain adequate blood pressure while attenuating the expected rise in ICP.[1] The type of fluid to be used for this resuscitation and its rate of administration are much debated even today.

Hyperosmolar therapy is the cornerstone of treatment for raised ICP. Mannitol is the most popular agent but there are limitations to its administration. Although mannitol can decrease ICP in TBI, prolonged administration may lead to intravascular dehydration, hypotension, prerenal azotemia as well as reduction of cerebral blood flow[5]. For these reasons and because standard therapy and barbiturates do not always control ICP, interest has now been focusing on the utility of other hyperosmolar agents that can not only combat raised intracranial pressure but also support intravascular volume[6]. Weed and Mckibben first reported a reduction in ICP following use of hypertonic saline, in 1919[7]. In models of brain injury, animals resuscitated with HTS exhibit resolution of shock, reduction of intracranial pressure and alleviation of cerebral edema[8,9]. In human studies also, similar effects have been reported along with enhanced cardiovascular performance[10,11]. However, no standards exist regarding the indications or optimal administration regimen for HTS in the treatment of TBI. A review of literature regarding the potential mechanisms of action and the current status of its role in TBI is presented

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Mechanisms of Action

The exact mechanism by which HTS acts on the injured brain remains to be fully elucidated. Animal and human studies suggest that HTS possesses osmotic, vasoregulatory, haemodynamic, neurochemical and immunologic properties. TBI is a multifactorial disorder and HTS works on several areas simultaneously. Some of the postulated mechanisms are as follows-

1) Haemodynamic effects:

In TBI, secondary ischaemia often results from hypoperfusion of the injured brain[12]. Moreover, neurotrauma itself may alter compensatory mechanisms and increase susceptibility to shock and multiorgan failure[13]. The ability of HTS to improve and maintain mean arterial pressure occurs as a result of plasma volume expansion. In addition there may also be centrally mediated effects on the cardiac output, possibly via changes in circulating hormone levels[14]. This improvement in blood pressure does not come at the expense of high infusion volumes and increased ICP as in the case of isotonic resuscitation[15]. Thus, cerebral perfusion pressure maybe improved with HTS, leading to better perfusion of the injured brain.

2) Intracranial pressure effects:

The osmotic effect of HTS on the injured brain improves

perfusion by drawing fluid from the tissue into the intravascular compartment[16]. Both animal and human studies have demonstrated this ability of HTS to lower ICP, whether given as a bolus or continuous infusion[17,18]. Agents like mannitol also dehydrate edematous tissue. However, the blood brain barrier is better able to exclude HTS because of tight gap junctions and its higher polarity, resulting in a reflection coefficient of 1.0 for sodium chloride as compared to 0.9 for mannitol[17]. Also, HTS does not possess the osmotic diuretic properties of mannitol and subsequent problems with volume depletion and hypotension maybe avoided.

Osmolytes, a group of organic solutes have an important role to play in the action of HTS. These organic solutes include certain amino acids, polyhydric alcohols and methylxanthines[19]. They can be released from or transported into cells in response to changes in extracellular osmolarity[20]. Animal studies document extrusion of these osmolytes into the extracellular space by several mechanisms including cell depolarization, cell membrane leakage and reversal of sodium dependent cotransporters[21,22]. An increase in extracellular sodium helps restore cotransporters and normal cell polarity[23]. In addition, HTS helps draw fluid from the edematous brain, which contains extruded osmolytes, to the vascular compartment, thereby decreasing ICH[24]. The cells respond to the increase in extacellular osmolarity by pulling osmolytes intracellularly. This process requires active transport and takes three or more days to achieve[25]. This explains the results of human trials where tolerance to effects of HTS was seen. A 10-15 mEq/l rise in serum sodium was found to lower ICP for approximately 72 hrs[26].

3) Vasoregulatory effects:

Vasomotor dysfunction and resultant cerebral ischaemia is a significant contributor to secondary brain injury[27]. In addition, endothelial cell edema occurs after trauma. HTS appears to counter this hypoperfusion and vasospasm by increasing the vessel diameter and expanding plasma volume[28].

4) Immunomodulatory effect:

HTS has been shown to have immunomodulatory effects in patients with trauma. Inflammation is an important component of the pathophysiology of TBI. Cerebral leukocytes migrate to the injured areas of the brain leading to peroxidase and protease mediated cell death. Also, release of inflammatory mediators like ecosanoids cause vasospasm and interstitial edema[29]. In animal models, HTS has been found to counteract this chain of events and increase the circulating levels of cortisol and ACTH[30,31].

5) Neurochemical effects:

Following TBI, neuronal depolarization occurs accompanied by a concomitant rise in extracellular glutamate. Further, cerebral ischaemia leads to a decrease in ATP, lowering the amount of substrate available to sodium and potassium exchangers. This leads to a decrease in extracellular sodium levels and a reversal of the normal sodium/glutamate cotransporter thereby further raising extracellular glutamate[32]. HTS acts by decreasing the influence of glutamate after TBI. The raised extracellular sodium interrupts the feedback loop and helps to reestablish the normal direction of sodium/glutamate cotransporter[23].

HTS to control ICP

Animal models demonstrating the efficacy of HTS in reducing ICP are plentiful. Human trials are relatively few and mainly limited to patients who have failed conventional management.

Worthley et al reported two patients with TBI who had ICP elevations refractory to mannitol[33]. They successfully treated the ICH with 20 ml of 29.9% HTS. Einhaus et al reported a similar experience in a TBI patient where a single bolus of 7.5% HTS was used[34]. Suarez et al[35] described 8 patients in whom 23.4% HTS was used for ICP control after failure of mannitol therapy. Although only one patient had TBI in this study, a significant decrease in ICP was noted in all the patients and the effect lasted several hours. A significant observation was the absence of a rise in serum sodium despite repeated administrations of 30 ml boluses of this HTS.

Horn et al[36] studied the effects of a bolus dose of 7.5% HTS on elevated ICP refractory to both barbiturates and mannitol. A decrease in ICP from a mean of 33 mm Hg to 19 mm Hg was observed after one hr and the effect lasted about three hours. Mean serum sodium levels rose by only 2 mEq/l[37].

Simma et al[37] were the first to perform a prospective randomized trial to evaluate HTS in pediatric head injuries using either 1.7% HTS or Ringer Lactate as the maintenance fluid therapy for the first 72 hrs after injury. Patients receiving HTS had lower ICP values and required fewer interventions to manage ICP elevations. Less fluid was required to maintain blood pressure in the HTS group, which also displayed improved survival. This study was of particular significance as it was the earliest in which HTS was given over the entire 72 hr period and the results were not modified by the use of isotonic maintenance fluids.

Qureshi et al[16] evaluated the effects of continuous HTS in 8 patients with ICH due to various causes. They administered 3% HTS to raise the serum sodium from 145

to 155 mEq/l. An inverse relationship between serum sodium and ICP was observed in TBI or postoperative edema. The beneficial effect lasted 3 days following which 4 patients required pentobarbital for rebound increase in ICP. The same group retrospectively studied 36 patients of severe TBI who received continuous infusion of 2% or 3% HTS to achieve a serum sodium of 145 to 155 mEq/l.[38] These were compared to a control group who did not receive HTS. Once again, more patients in the HTS group required barbiturate coma and had higher hospital mortality. They concluded that continuous infusion might not be the ideal method of administering HTS and recommended bolus administration.

Khanna and coworkers[26] tried a continuous infusion of 3% HTS in pediatric cases of severe TBI and intracranial hypertension refractory to other treatment modalities. The target serum sodium was continually increased as needed to control ICP. Mean serum sodium levels of 170 mEq/l were reached. An inverse relationship between serum sodium and ICP was observed. Furthermore, an increase in serum sodium was associated with decreased requirements for other therapies to control ICP. Overall outcome was excellent with no adverse effects.

Peterson et al[39] did a retrospective study on the effect of a continuous infusion of 3% hypertonic saline on ICP control in pediatric closed head injuries. They found that the treatment effectively lowered ICP in all except 3 of the 68 patients. No adverse effects were noted. They concluded that administration of hypertonic saline in pediatric head injuries appears to be a promising therapy for control of cerebral edema. They recommended further control trials to determine the optimal duration of treatment before widespread use is advocated.

HTS for prehospital resuscitation in TBI

Head injury often occurs in a setting of polytrauma and maybe accompanied by hemorrhagic shock. Traumatic brain injury by itself can blunt cardiac and vascular compensatory responses to shock, leading to profound hypotension even in the absence of hemorrhage[40]. The injured brain is especially vulnerable to ischemic injury from hypoperfusion following hypotension. Thus the primary goal of acute resuscitation in TBI includes maintaining adequate blood pressure while attenuating the rise in ICP[41].

Vassar et al[11] were among the first to evaluate HTS as a prehospital resuscitation fluid. Dextran(4.2%) was added to HTS on the basis of its potential to augment favourable haemodynamic effects of HTS. Twenty trauma patients were randomized to receive either 7.5% HTS-Dextran or Lactated Ringer (250ml each), followed by supplemental Lactated Ringer as needed, to maintain a SBP of 100mmHg or greater. They observed a significant increase in SBP and overall survival in patients receiving HTS. The same group conducted another prospective randomized trial in 258 trauma patients where they administered 7.5%HTS, 7.5% HTS with 6% Dextran or NS (250ml each)[42]. Once again they observed improvement in SBP as well as increased survival in the HTS group. The addition of dextran however, afforded no additional survival benefit over HTS alone. The same results were put forward after a multicentric trial by this group using 7.5% HTS, 7.5% HTS/6% dextran, 7.5% HTS/12% dextran and Lactated Ringer (250ml each)[43].

Following these encouraging results, Cooper et al conducted a double-blinded trial using HTS as a prehospital resuscitation fluid in 229 patients with TBI and hypotension[44]. Patients were randomly assigned to receive a rapid infusion of either 250 ml of 7.5% saline or 250 ml of Ringer Lactate. In addition conventional IV fluids and resuscitation protocols were followed. At hospital admission mean serum sodium level was 149 mEq/l for HTS patients vs 141 mEq/l for Ringer Lactate .Although the duration of inotropic support was less in patients receiving HTS, no significant difference was found with respect to duration of CPP >70 mm Hg or neurological outcome at 6 months after injury.

It maybe premature however, to abandon prehospital research with HTS based on this study alone. It is important to remember that therapies that are effective in the hospital may not work in the prehospital setting[45]. Further studies which are larger in size need to be carried out with the goal of determining if a larger or more prolonged effect on ICP and cerebral perfusion can be achieved along with improvement in neurological outcome.

Adverse effects of HTS

The primary concerns with use of HTS are osmotic demyelination syndrome (ODS), acute renal insufficiency and hematologic abnormalities including increased hemorrhage, coagulopathy and red cell lysis.

The pathophysiology of osmotic demyelination syndrome involves destruction of myelinated structures after a rapid rise in serum sodium. The deep matter in the pons is the most susceptible. Studies on animal models have recommended avoidance of a rate of change in serum sodium greater than 10- 20 mEq/l/day[46,47]. Human trials using HTS for ICP control generally avoid rapid rises in serum sodium and ODS has not been reported[26,37]. Khanna et al[26] reported 10 patients with TBI in whom a peak serum sodium value of 171 mEq/l was attained. In 4 patients in whom MRI was done, no evidence of ODS was seen. With

bolus doses of HTS, elevated serum sodium values have not been associated with ODS. Thus it appears that HTS is safe with regard to ODS when very rapid rises in serum sodium are prevented.

Renal insufficiency is a major concern with the use of mannitol and has been reported with HTS as well Huang et al observed a fourfold increase in renal failure with the use of HTS vs Ringer lactate in patients with TBI[48]. Khanna et al[26] also reported temporary renal insufficiency in 2 out of 10 patients receiving HTS. However, both these patients were in sepsis and the renal failure may not have been osmotically induced. In animal models, renal insufficiency has not been observed when upto 5 times the therapeutic human doses were used[49]. Further studies with varying dosage regimes will better define this risk with the use of HTS.

Bleeding complications following rapid fluid resuscitation have been described with both HTS and isotonic fluids[50,51]. This concern exists primarily when active hemorrhage cannot be controlled due to unavailable resources. This may not be valid in a setting of TBI where hypotension is not well tolerated and maybe detrimental to neurological outcome.

A rebound rise in ICP has been described with use of HTS for ICP control, both when given as a bolus or after cessation of continuous infusion[26]. However, it is still unclear whether this rise in ICP is truly a "rebound" effect or simply a reflection of the limited half-life of the osmotic agent.

CONCLUSION

The ability of HTS to treat raised ICP appears to occur through a variety of mechanisms including optimization of systemic and cerebral hemodynamics, reduction of cerebral edema and modulation of cerebral immunology and neurochemistry. The adverse effects of HTS are common to all osmotic agents including concern for ODS, renal insufficiency and rebound ICH. The relative safety and efficacy of HTS vs. mannitol has yet to be proven in human trials although animal studies seem to be favorably inclined towards HTS. The use of HTS for resuscitation in trauma patients is less well defined and there is still paucity of well controlled studies in prehospital trials. The ability of HTS to restore blood pressure without increasing cerebral edema and ICP is more definite. What remains less clear is whether HTS really offers a significant advantage over isotonic fluids in general trauma. In the case of TBI, HTS salvage therapy has been resorted to mostly when other measures like mannitol and barbiturates have failed to decrease ICP. Further human studies need to be carried out to ascertain whether HTS really has a significant advantage when compared to mannitol in human subjects with TBI. In addition, the optimal regimens for HTS, whether bolus or continuous infusion as well as the ideal concentration to be used need to be addressed.

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