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Review Article

Mannitol or hypertonic saline in the setting of traumatic brain injury: What have we learned?

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Abstract

Background: Intracranial hypertension, defined as an intracranial pressure (ICP) >20 mmHg for a period of more than 5 min, worsens neurologic outcome in traumatic brain injury (TBI). While several mechanisms contribute to poor outcome, impaired cerebral perfusion appears to be a highly significant common denominator. Management guidelines from the Brain Trauma Foundation recommend measuring ICP to guide therapy. In particular, hyperosmolar therapy, which includes mannitol or hypertonic saline (HTS), is frequently administered to reduce ICP. Currently, mannitol (20%) is considered the gold standard hyperosmolar agent. However, HTS is increasingly used in this setting. This review sought to compare the efficacy of mannitol to HTS in severe TBI.

Methods: The PubMed database was used to systematically search for articles comparing mannitol to HTS in severe TBI. The following medical subject headings were used: HTS, sodium lactate, mannitol, ICP, intracranial hypertension, and TBI. We included both prospective and retrospective randomized controlled studies of adult patients with intracranial hypertension as a result of severe TBI who received hyperosmolar therapy.

Results: Out of 45 articles, seven articles were included in our review: 5 were prospective, randomized trials; one was a prospective, nonrandomized trial; and one was a retrospective, cohort study.

Conclusions: While all seven studies found that both mannitol and HTS were effective in reducing ICP, there was heterogeneity with regard to which agent was most efficacious.

Key Words: Hypertonic saline, intracranial pressure, mannitol, traumatic brain injury

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INTRODUCTION AND BACKGROUND

Sustained intracranial hypertension, defined as an intracranial pressure (ICP) >20 mmHg for a period of more than 5 min, has been demonstrated to worsen neurologic outcome for patients with traumatic brain injury (TBI). While several mechanisms contribute to poor outcome, impaired cerebral perfusion appears

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to be a highly significant common denominator.[9] Current management guidelines from the Brain Trauma Foundation recommend measuring ICP to guide therapy.[3] In particular, hyperosmolar therapy, using infusions of mannitol or hypertonic saline (HTS) is frequently administered to reduce ICP.[12] Currently, mannitol (20%) is considered the gold standard hyperosmolar agent and is by far the most well studied. However, HTS, which comes in a variety of concentrations, is increasingly used in this setting.[11]

The decision to administer hyperosmolar agent is weighed against its potential side effects. Mannitol is a potent diuretic which may increase the risk of kidney injury in hypovolemic patients. While mannitol induces an osmotic diuresis, the initial rapid increase in intravascular volume can paradoxically cause acute hypervolemia (which could precipitate heart failure or pulmonary edema in susceptible patients). HTS can cause a rapid increase in serum sodium concentrations, raising concern for central pontine myelinolysis. Fortunately, this devastating condition has been rarely observed in this setting. In addition, HTS is a volume expander, which could precipitate volume overload. For patients with chronically elevated ICP that require prolonged administration of either agent, the brain attempts to compensate for the osmotic gradient by forming "idiogenic osmoles." While poorly understood, these osmoles are considered oncotically active and highlight the importance of gradually weaning both agents with caution. If discontinued abruptly, the gradient for water transfer is reversed, allowing a rebound increase in intracranial volume and pressure. In addition, disruption in the blood brain barrier can result in the accumulation of osmotically active molecules, which can lead to local edema or rebound increases in ICP. The reflection coefficient is a term used to describe the relative impermeability of each agent with respect to the blood brain barrier. A value of zero suggests that the molecule is freely permeability while a value of one corresponds to complete impermeability. The reflection coefficient for mannitol and HTS are 0.9 and 1.0, respectively.

The PubMed database was used to systematically search for articles comparing mannitol to HTS in severe TBI. The following medical subject headings were used: HTS, sodium lactate, mannitol, ICP, intracranial hypertension, and TBI. We included both prospective and retrospective randomized controlled studies of adult patients with intracranial hypertension as a result of severe TBI who received hyperosmolar therapy (specifically, mannitol, HTS, and hypertonic sodium lactate). We excluded studies that investigated conditions other than TBI or did not compare mannitol with HTS, and we excluded studies that involved pediatric populations. This search strategy yielded seven articles for inclusion that were analyzed from the full manuscript.

RANDOMIZED CLINICAL STUDIES

Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol[30]

This is a prospective, randomized study which evaluated 20 consecutive patients admitted with severe TBI (Glasgow Coma Scale [GCS] ≤8). The aim of the study was to evaluate the number and duration of episodes of ICP >25 mmHg while maintaining a cerebral perfusion pressure (CPP) of >70 mmHg. Treatment goals were directed at decreasing ICP (<25 mmHg) or increasing CPP (>70 mmHg). Prior to administration of the hyperosmolar agent, an algorithmic approach to achieve these goals included: Increasing sedation, fluid administration or initiating vasoactive medications, and hyperventilation. When these goals were not met, patients were then randomized to receive isovolumetric solution of either 7.5% HTS or 20% mannitol. Both the number and duration of daily episodes of ICP >25 mmHg was greatest in the mannitol group. The mannitol group also needed more cerebrospinal fluid (CSF) drainage than the HTS group (18.4 ± 14.3 vs. 5.3 ± 4.8 times/opened/day). Treatment failures occurred in 7 out of 10 patients in the mannitol group versus 1 out of 10 in the HTS group. While the primary outcome was satisfied, there were no statistical differences in secondary outcomes (mortality or neurological outcome at 90 days). One limitation to this study was the osmolar difference between the solutions; the patients in HTS arm received a higher osmolar load than the mannitol arm (361 mOsm vs. 175 mOsm). This may limit the validity of the study.

Sodium lactate versus mannitol in the treatment of intercranial hypertensive episodes in severe traumatic brain-injured patients[12]

This is a prospective randomized controlled study that compared the efficacy of an equiosmolar and isovolumetric dose of either sodium lactate (1100 mOsm/L) or 20% mannitol (1160 mOsm/L) in reducing ICP. Thirty-four eligible patients with TBI (GCS ≤8, ICP >25 mmHg for >5 min, refractory to other interventions) were randomized to receive either mannitol or sodium lactate.

Treatment was considered "successful" if ICP decreased by more than 5 mmHg or decreased to below 20 mmHg 15 min after the end of the infusion. If ICP remained elevated for >15 min, a cross-overdose was administered (mannitol after lactate and vice versa).

Out of the 17 patients who were randomized in each group, 9 patients received only mannitol, 12 received only sodium lactate, and 13 patients crossed over and received both mannitol and sodium lactate.

Compared to mannitol, the effect of sodium lactate solution on ICP was significantly more pronounced (7 vs. 4 mmHg), more prolonged (4^{th}-hour-ICU decrease: −5.9 ± 1 vs. −3.2 ± 0.9 mmHg) and more frequently successful (90.4 vs. 70.4%)

The authors concluded that a sodium-lactate-based hyperosmolar solution is significantly more effective in reducing ICP than an equivalent osmotic load of mannitol.

Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury.[2]

This is a prospective, cross-over, and randomized controlled study that compared the efficacy of an equiosmolar dose of HTS and dextran solution with 20% mannitol for reduction of increased ICP. Nine patients with either TBI (6) or subarachnoid hemorrhage (3) rapidly received either 200 mL of 20% mannitol (249 mOsm dose) or 100 mL of 7.5% saline and 6% dextran-70 solution (250 mOsm dose).

If ICP increased to >20 mmHg for more than 5 min (and was not associated with painful stimulation or systemic derangement), each patient was randomized to receive either two treatments of mannitol followed by two treatments of HTS or two treatments of HTS followed by two treatments of mannitol.

Both mannitol and HTS significantly reduced ICP, but HTS caused a significantly greater decrease in ICP than mannitol (13 mmHg vs. 7.5 mmHg). In addition, HTS had a longer duration of effect than mannitol; the median subthreshold ICP for mannitol was 89.5 min compared to 148 min for HTS.

The authors concluded that HTS is more effective than mannitol in reducing elevated ICP, both by degree and duration of ICU reduction.

Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension[19]

This is a prospective, nonrandomized, and cross-over study that compares the effects on brain tissue oxygen tension ($PbtO_2$) of mannitol and HTS. Twelve consecutive patients with 42 episodes of intracranial hypertension (ICP > 20 mmHg for more than 10 min) were studied. All patients received mannitol (25%, 0.75 g/kg, 412 mOsmol/dose, infused over 20 min) as first line treatment (n = 28 boluses). HTS (7.5% solution, 250 mL, 641 mOsmol/dose, infused over 30 min) was given for repeated episode of intracranial hypertension (n = 14).

Mannitol and HTS were both associated with a significant ICP reduction. However, at 60 and 120 min, HTS treatment was associated with lower ICP and higher CPP than mannitol.

HTS treatment was associated with an increase in $PbtO_2$ (from baseline 28.3 ± 13.8 mmHg to 34.9 ± 18.2 mmHg at 30 min, 37.0 ± 17.6 mmHg at 60 min and 41.4 ± 17.7 mmHg at 120 min) while mannitol did not affect $PbtO_2$ (from baseline 30.4 ± 11.4 to 28.7 ± 13.5 at 30 min, 28.4 ± 10.6 mmHg at 60 min, to 27.5 ± 9.9 mmHg at 120 min). In addition, compared with mannitol, HTS was associated with lower ICP, higher CPP, and cardiac output.

The authors concluded that when given as a second tier therapy for elevated ICP, HTS is associated with a significant improvement in brain oxygen, CPP and cardiac output in patients with severe TBI and intracranial hypertension refractory to previous mannitol administration.

Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury[5]

This was a prospective, randomized controlled trial (RCT) that evaluated the effect of HTS and mannitol on ICP, cerebral blood flow and neurologic outcomes. Forty-seven patients with severe TBI and ICP >15 mmHg were randomized to receive equiosmolar doses of either mannitol or HTS. Infusions were administered in <20 min. The baseline characteristics between groups were similar.

Mannitol and HTS were equally effective in reducing ICP. However, while both osmolar agents increased cerebral blood flow, the magnitude of augmentation was greater in the HTS group. There was no difference in neurologic outcome between groups at 6 months using the Glasgow Outcome Score.

Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries[24]

This was a prospective trial that compared two hyperosmolar regimens (mannitol 20%, 2 mL/kg and HTS 15%, 0.42 mL/kg) of similar osmotic loads given to patients with severe TBI who developed sustained intracranial hypertension (>20 mmHg for 5 min). Patients were generally treated according to the Brain Trauma Foundations' 2007 guidelines. The initial choice of osmolar agent was randomly determined, then alternated for repeated episodes of elevated ICP. A Codman ICP monitor was used to measure ICP. The primary endpoints were maximum reduction in ICP and duration of effect.

Twenty-nine patients were enrolled and had 199 episodes of intracranial hypertension. Sixteen of these patients underwent craniectomy. The mean reduction in ICP for mannitol was 7.96 mmHg ± 5.79 and for HTS was

8.43 mmHg ± 6.65. The mean effect duration was 3 h 33 min (standard error of mean [SEM] 31 min) for mannitol and 4 h 17 min (SEM 50 min) for HTS.

No statistically significant difference in either maximum reduction nor in duration of ICP was observed. The authors concluded that when the same osmotic load is administered, mannitol and HTS are equally effective in treating intracranial hypertension in patients with severe TBI.

Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe traumatic brain injury[15]

This was a retrospective cohort study that compared the efficacy of mannitol and HTS to decrease intracranial hypertension in patients with severe TBI. The authors chose to measure efficacy against cumulative and daily ICP burden as opposed to discrete events. Cumulative ICP burden was defined as the sum of the number of days a patient had an ICP > 25 mmHg. Daily ICP burden was defined as hours per day where ICP exceeded 25 mmHg. Patients received either mannitol or HTS (not both), were stratified according to equiosmolar dosing and matched according to initial GCS, hypotension, pupil reactivity, and surgical lesions. They found that both daily and cumulative ICP burden was lower in the HTS group: Daily burden (0.3 ± 0.6 h/day mannitol vs. 1.3 ± 1.3 h/day HTS, $P = 0.001$), cumulative burden (36.5 ± 30.9% mannitol vs. 15.2 ± 19.9% HTS).

The authors concluded that HTS was superior to mannitol in reducing both the daily and cumulative ICP burden.

EXPERT OPINION

Argument for using hyperosmolar agents in an intracranial pressure-directed manner

Since the cranium is a fixed vault, expansion of one of its components – the brain, intravascular blood, or CSF – must be at the expense of a reduction in another component. For example, the response to increased brain volume (e.g., from TBI) forces CSF from the cranial subarachnoid spaces and lateral ventricles into the spinal subarachnoid space.[22] As ICP continues to rise, this compensatory mechanism is exhausted which leads to compression of blood vessels and reduced (and even total stagnation) of cerebral blood flow.

It is not surprising, then, that elevated ICP has consistently been associated with poor outcome, and, therefore, it is well accepted that elevated ICP should be treated promptly. To-date, the cornerstone therapy in neurological emergencies with intracranial hypertension is ICP reduction.

In 1919, Weed and McKibben first described the effect of osmotherapy in laboratory animals by showing that hypertonic fluids reduced brain bulk and ICP.[32,33] Clinicians quickly adopted this therapy and different compounds were tried (saline, glucose, sucrose, magnesium sulfate, urea, glycerol, and others).[28] Mannitol, which was introduced in the 1960s, has been the main therapeutic intervention through the 1980s and remains the *de facto* gold standard for medical management of intracranial hypertension. However, in the past few decades there has been growing interest in HTS as an alternative to mannitol in treating elevated ICP.

Controversy still exists regarding which therapy is "better." While the prospective studies reported in this manuscript, along with a whole body of literature not reported here, demonstrate that both mannitol and HTS reduce ICP, HTS may be advantageous over mannitol in the management of intracranial hypertension secondary to TBI. Overall, it appears that HTS decreases ICP faster, to a greater degree and for a longer duration than mannitol.

Both therapies have similar mechanisms of action in the brain, using an osmotic gradient – induced shift of extravascular to intravascular water across the blood – brain barrier. However, the comparative effects of these two agents on cerebral physiology, rather than ICP alone, should be evaluated.

There are several advantages for using HTS over mannitol in the management of TBI-induced intracranial hypertension.

Hemodynamic effects

Hypotension should be avoided in patients with head trauma (isolated or with multiple trauma), as it doubles the mortality in this setting.[13,16] In contrast to mannitol – an osmotic diuretic – HTS maintains and even improves mean arterial pressure in various forms of shock.[20] The increase in blood pressure is due to plasma volume expansion, as well as centrally mediated increase in cardiac output.[8] Isotonic fluid resuscitation in the trauma setting requires high fluid volume, which can increase ICP. The advantage of HTS in this setting is maintenance of blood pressure with low volume resuscitation and thus avoiding potentially iatrogenic ICP increase.[31]

Immunomodulatory effects

HTS can play a role in brain cell immune modulation, which may lead to anti-inflammatory effects and potentially better outcome for patients with TBI. Severe trauma activates the inflammatory cascade, inducing the systemic inflammatory response syndrome. In addition, specifically to TBI, cerebral leukocytes migrate to injured areas, leading to peroxidase-and-protease-mediated cell death.[7] Finally, release of inflammatory mediators such as eicosanoids from activated leukocytes can

lead to vasospasm and interstitial edema.[10] HTS blunted neutrophil activation and changed the cytokine production profile in a hemorrhagic shock study; the pro-inflammatory tumor necrosis factor-α cytokine production was reduced while the anti-inflammatory cytokines interleukin (IL)-ra and IL-10 were increased. Together, these processes shift the balance toward anti-inflammatory processes.[21]

Neurochemical effects

HTS reduces the accumulation of extracellular excitatory amino acid (glutamate), thus preventing glutamine toxicity and neuronal damage. The initial brain injury that occurs from trauma leads to extensive neuronal depolarization, increasing extracellular glutamate. The ischemia that follows reduces available energy (in the form of adenosine triphosphate [ATP]), which interferes with cellular homeostasis.[14,18,29] The normal Na^+/K^+ active exchange pump becomes dysfunctional, leading to reduced extracellular Na^+. This, in exchange, reverses the direction of the Na^+/glutamate passive cotransporter, increasing the levels of extracellular glutamate. In addition, there are other processes that support leakage of glutamate out of cells, leading to glutamine toxicity. HTS, by increasing the extracellular Na^+ levels restores cellular action potential and returns the Na^+/glutamate pump to its normal function. Thus, HTS prevents pathological levels of damaging extracellular glutamate.

Vasoregulatory and microcirculatory effects

HTS increases capillary vessel diameter and plasma volume (thus increasing cerebral blood flow) counteracting hypoperfusion and vasospasm. As mentioned above, ischemia dysregulates cell homeostasis by decreasing available ATP molecules. This leads to dysfunction of endothelial cell membrane ion exchange pump, which in turn leads to intracellular water accumulation,[6] narrowing of capillary lumen and reduced capillary blood flow (in essence "endothelial edema"). HTS, by significantly increasing intravascular osmolarity, promotes fluid shift from endothelial cells to capillary lumen, reducing endothelial thickness, and increasing capillary diameter and blood flow (in essence leading to "endothelial dehydration"). In addition, red blood cells size becomes smaller, allowing for their easier flow through the capillaries. The net effect is improved cerebral blood flow and oxygen delivery.[25,26]

In summary, mannitol is considered the "gold standard" therapy for TBI-induced intracranial hypertension mostly due to its historical use and not due to its superiority over HTS. Physiologically, HTS has many theoretical advantages over mannitol. Clinically, HTS appears to be more efficacious than mannitol in reducing ICP both by degree and length of reduction. Finally, HTS appears to improve tissue oxygenation of the brain more than mannitol. All of these advantages suggest that HTS should be studied extensively so it can possibly be used instead of mannitol as first line therapy for the management of high ICP in patients with TBI.

Argument against using hyperosmolar agents in an intracranial pressure-directed manner

The use of hyperosmolar agents to reduce an elevated ICP is one of several therapies recommended by the Brain Trauma Foundations guideline on the management of severe TBI.[9] These guidelines have gained widespread, international acceptance. It is clear that hyperosmolar agents, whether HTS or mannitol, are effective in reducing ICP. What remains unanswered is whether these agents contribute toward better neurological outcomes; the tiered, algorithmic approach employed in many of these trials makes it difficult to determine which therapy conveys benefit, or possibly, harm. The concept of guiding treatment by ICP monitoring was recently challenged in a study by Chesnut *et al*.[4] In their study, patients with severe TBI were randomized to treatment based on ICP versus clinical examination and frequent head computed tomography's. While both treatment arms received aggressive ICP treatment, there was no difference in outcome based on their treatment protocol. So this raises the question of looking at each component of a traditional ICP algorithm to determine the relative benefit.

A less well-established method of managing severe TBI offers a competing strategy, known as the "The Lund Concept."[1] While both strategies use ICP values to guide therapy, treatment patterns are quite different. The Lund concept specifically avoids the use of hyperosmolar agents to decrease ICP. Instead, it focuses on employing methods to decrease hydrostatic capillary pressure, which is thought to contribute to vasogenic edema. To accomplish this, a lower limit for CPP is often tolerated (as low as 50 mmHg). Vasopressor infusion to increase CPP above a lower limit threshold is avoided. In fact, antihypertensives are often employed to decrease elevated CPP. There is an aggressive effort to render the patient euvolemic through oncotically active volume expanders such as albumin and red blood cell transfusion. Many of these treatment modalities remain controversial and one, in particular, the use of albumin in patients with TBI, was demonstrated to worsen outcome in large study.[23] One small study that examined the microdialysate of patients with severe brain injury using the Lund approach demonstrated improved normalization of lactate/pyruvate levels and glycerol concentration relative to standard therapy.[27] While scant evidence exists to suggest superiority of the Lund concept in managing severe TBI, it does offer a compelling physiologically-based alternative which warrants further study.

Recently, the Cochrane collaborative reviewed the evidence that supports the Lund concept to treat patients

with severe TBI.[17] The goal of their review was to examine the literature to find studies that compared the Lund concept to both ICP and CPP-targeted therapies. After reviewing 374 potential articles, the reviewers were unable to find any RCTs that met their inclusion criteria. Based on this finding, the authors concluded that the Lund concept should not be used to treat severe TBI until additional RCT data is published.

EDITORIAL SUMMARY

"While simplifying the therapeutic strategy to a single optimal agent that is, universally applicable is attractive from an algorithmic perspective, it is more likely that distinct hyperosmolar agents may exert optimal therapeutic effects in different clinical context." Clark C. Chen, University of California, San Diego.

The critical importance of ICP in the management of traumatic head injuries and nontraumatic neurologic diseases (e.g., stroke, brain cancer, etc.) cannot be overemphasized. However, it is equally important to understand that the ultimate goals of ICP management are to optimize CPP for the preservation of cerebral metabolism and neurologic function. As such, it is nonrational to blindly focus on ICP without consideration of other pertinent physiologic variables (e.g., CPP, oxygen utilization, clinical outcome, etc.). This is a major flaw in many published RCTs with focus on hyperosmolar therapy.

Irrespective of the specific agent used, the efficacy of hyperosmolar therapy as a strategy for acute ICP management has been validated by both clinical experience and RCTs. The most commonly utilized hyperosmolar agents are mannitol and HTS. It is critical to note that distinct physiologic properties have been reported for these agents, including differential effects on blood rheology, inflammation, neurochemistry, and hemodynamic regulation. While simplifying the therapeutic strategy to a single optimal agent, that is, universally applicable is attractive from an algorithmic perspective, it is more likely that distinct hyperosmolar agents exert optimal therapeutic effects in different clinical contexts. For instance, given that HTS expands the systemic volume status while mannitol depletes it, what is the relative merit of their respective use in patients with congestive heart failure who suffered from elevated intracranial hypertension. Trials should also test equiosmolar agents infused over the same time period as to mitigate the effects of molarity and infusion time. Such thoughtful considerations are sorely absent in the existing literature.

Ultimately, judgment and careful dissection of individual clinical scenario in the context of a rigorous interpretation of the existing literature will be needed to best serve the needs of our patient. In general, many ICP-focused treatment algorithms that seem "evidence-based" on surface are actually intellectually arbitrary upon careful scrutiny. Dogmatic and universal adherence to such algorithms (which may be useful for educational purposes or as "guidelines") should not replace clinical judgment and experience.

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