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Effectiveness of Mannitol vs Hypertonic Saline for Intracranial Hypertension from Traumatic Brain Injury

Jennifer Saephanh
University of the Pacific

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By

Jennifer Saephanh

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Introduction

Traumatic brain injury (TBI) is one of the primary causes of death and disability.[1] TBI occurs from sudden head injury that damages the brain and interrupts its normal functioning. The severity of a TBI ranges from "mild" (i.e., loss of consciousness shorter than 30 minutes) to "severe" (i.e., extended period of unconsciousness usually greater than 6 hours).[1] According to the US Centers for Disease Control and Prevention (CDC) in 2014, over 2 million TBI-related emergency department visits and hospitalizations occurred with over 56,000 of them leading to death.[1] Mortality rates after brain injury are highest in those with severe TBI. The vast number of hospitalizations and deaths from TBI is attributed to complications such as posttraumatic seizures, deep vein thrombosis, chronic traumatic encephalopathy (CTE), and intracranial hypertension (ICH).[1] ICH is often present in the acute setting and is associated with poor neurologic outcomes and death. Hence, treating this disorder is critical.

Elevated intracranial pressure (ICP), which is caused by cerebral edema, is a serious potential complication of TBI resulting in ICH. Thus, effective and reliable guidelines for the management of patients with elevated ICP should be identified. In order to prevent potential damages due to ICH, prompt recognition, urgent assessment, and expeditious therapy directed at reducing ICP are required. In adults, normal ICP is $\leq$ 15 mmHg and pathologic ICH is present at pressures $\geq$ 20 mmHg, with normally lower ICP values in children.[2] The intracranial contents consist of 80% brain parenchyma, 10% cerebrospinal fluid, and 10% blood.[2] With normal intracranial compliance, ICP is autoregulated to maintain normal pressures. This autoregulatory ability malfunctions in pathologic states such as TBI resulting in cerebral edema and increases in ICP.[2]

When ICP rises, signs and symptoms can include pupillary asymmetry, fixed and dilated pupils, decorticate or decerebrate posturing, peripheral hypertension, bradycardia, respiratory irregularity, headache, decrease in consciousness, and vomiting.[2] Patients who exhibit these signs and symptoms require urgent ICP monitoring and prompt initiation of treatment. Current recommendations for care of acute severe TBI, based on recent guidelines, include admission to the intensive care unit along with airway management and ventilation (to avoid hypoventilation), monitoring of vital signs (especially temperature, pulse oximetry, respiratory rate, and blood pressure; watching for fever, hypoventilation, and hypotension), antifibrinolytic therapy (if indicated), glucose monitoring (to avoid hyperglycemia), antiepileptic drugs (to prevent seizures), electroencephalography (EEG), and maintenance of euvolemia via IV fluids.[3]

Since elevated ICP is complicated by higher mortality and serious neurologic deficits, its prevention and treatment are key. Osmotic agents can decrease cerebral edema and thus, ICP. This therapy is used in TBI patients who have clinical manifestations of cerebral edema and ICH or have a documented elevated ICP.[3] Specifically, two osmotic agents, hypertonic saline (HTS) and mannitol (MNT), have been shown to be effective for ICP.[3] Nonetheless, whether one agent is superior to the other has yet to be determined. Each osmotic agent has theoretical advantages. HTS has several theoretical advantages over MNT including intravascular volume replenishment and prevention of hypovolemia.[3] Moreover, HTS appears to improve tissue oxygenation of the brain more than MNT since HTS has less chance of leaking into brain parenchyma and interfering with the functional tissue of the brain.[3] A theoretical advantage of MNT is its effects on brain circulation. Although the mechanism of action of MNT isn't fully understood, it is thought to lower ICP by reducing blood viscosity. This in turn helps cerebral blood flow and ultimately reducing cerebral blood volume and ICP.[3] Additionally, MNT reduces ICP by

withdrawing water from the brain parenchyma and is excreted in urine. [3] Examining the currently available evidence may establish which osmotic agent is more effective.

Discussion

Administration of hyperosmolar agents, such as mannitol (MNT) and hypertonic saline (HTS), creates an osmotic gradient within the blood brain barrier and allows cerebrospinal fluid to flow out of the cranium leading to a decrease in ICP.[3] MNT was historically the treatment of choice but HTS is becoming the preferred treatment for elevated ICP.[4] Many studies have shown that both osmolar therapies are effective for decreasing ICP; however, choosing one over the other as the gold standard therapy is difficult because of conflicting findings in the available research.

In a systematic review article by Boone et al., seven studies including five prospective, randomized trials; one nonrandomized, prospective trial; and one retrospective cohort study all found that both osmolar therapies were effective in reducing ICP but the heterogeneity among these studies precluded determination of which agent was more efficacious.[4] Most of these studies showed that both HTS and MNT were equally effective, while some of the studies found that HTS was superior to MNT because it decreased ICP more quickly or to a greater extent or both.[4] Many of these published studies had major limitations because they only focused on ICP management without considering additional factors such as cerebral perfusion pressure and clinical outcomes.

Similarly, findings from another study by Francony et al. were comparable to previous reports. In a parallel, randomized, control trial, a total of 20 patients with ICP > 20 mmHg received an equimolar dose of 20% MNT or 7.45% HTS. The times required to effect ICP

changes were similar in the two groups. At 60 minutes MNT reduced ICP by 45% ± 19% (mean ± standard deviation) and HTS reduced ICP 35% ± 14% compared with baseline values at 0 minutes.[5] This study demonstrated that 20% MNT was equally effective as 7.45% HTS for reducing ICP in patients with brain injury.[5] There were no significant differences in effectiveness of ICP with MNT or HTS to preclude one method over the other. Additionally, the study highlighted other possible effects of hyperosmolar therapy. For instance, MNT had beneficial effects on brain circulation through possible improvement in blood viscosity whereas HTS caused elevations of serum sodium and chloride, both adverse effects.[5] The researchers suggested that MNT could be the first line treatment in patients with cerebral hypoperfusion and that hypertonic saline could be reserved for patients with hypovolemia or hyponatremia.[5] When considering the available choices for osmolar treatment of ICP, these additional unintended effects from therapy should be weighed. These disparate unintended effects could explain the difficulty in determining which therapy is superior.

Other studies, with findings contrary to the above studies, found evidence for superiority of one agent compared with another. In a prospective, randomized, controlled pilot study by Battison et al. evaluating nine patients with ICH both MNT (median decrease, 7.5 mmHg, 95% confidence interval, 5.8-11.8) and HTS (median decrease, 13 mmHg; 95% confidence interval, 11.5-17.3) reduced ICH, but HTS provided a significantly greater reduction in ICP ($p = .044$) and had a longer duration of effect ($p = .044$) than MNT. Both were given in equimolar concentrations and by rapid, intravenous infusion.[6] Limitations of this study included lack of generalizability and low quality evidence because of its small sample size. In a prospective observational study by Shein et al., 16 children < 18 years old with severe TBI, GCS score < 8 who had ICP monitoring were treated with HTS, fentanyl, or phenobarbital. HTS administration

was associated with the most rapid resolution of ICH compared to the other inventions.[7] Although the sample size was small, the data consisting of > 2,700,000 individual time points provided a strength. The small sample size and the observational design of this study limited its ability to suggest causality. Moreover, long-term outcomes were not followed. In addition, the exclusion criteria eliminated participants who received MNT so a comparison with HTS was not available.[7] In a 2008 prospective randomized study by Vialet et al., participants with refractory post-traumatic ICH were treated with increasing osmotic loads of HTS. In this study, increasing osmotic load by giving 2mL/kg of 7.5% saline was more effective than giving 2mL/kg of 20% MNT and the failure rate of HTS was comparatively lower than that in MNT.[8] The researchers suggested that HTS is an effective and safe initial treatment for ICH since there were fewer episodes of ICH and shorter durations of ICH in the HTS group than in the MNT group.[8] No clinically significant perturbations in serum sodium (osmolality) were found. Although ICP was measured, clinical outcomes were not assessed. [8] In a randomized control trial using MNT in comparison with other ICP lowering agents such as HTS, MNT increased the likelihood of death.[9] Given this finding, it is imperative to find more effective and reliable alternatives, possibly HTS, for reducing ICP. Although the sample size in this trial was too small for deducing a reliable conclusion, the possible risk of death after infusion of MNT is too serious to dismiss when selecting an ICP lowering agent. In a retrospective study looking at data from ten earlier studies, this study assessed the impact of HTS administration on TBI outcomes and hypothesized that favorable outcomes would be associated with larger amounts of 3% saline.[10] Beneficial outcomes were associated with the administration of larger amounts of HTS in specific groups of patients with complex TBI, including higher trauma center survival, greater ICH containment, and better ability to follow commands at three months when given larger quantities of HTS.[10]

Principal limitations were the retrospective study design and patient information gathered from only one institution. A prospective study is needed to provide an independent set of observations to see if similar results are found. Since research on side effects of HTS is still limited, considering other clinical factors is still required to determine which osmolar agent is best for each patient.

Summary

Most of these studies found that HTS was superior to MNT for osmotic treatment of ICH due to TBI. Potential adverse effects were less with HTS. The studies were limited because of the small sample sizes, the short-term follow-up, and the focus on ICH changes rather than long-term clinical outcomes, such as death and neurologic sequelae. Although risks are inherent with either treatment, weighing the risks versus benefits across both treatment options points to better ICP management with HTS. These studies were limited because they examined surrogate outcomes such as ICP rather than clinical outcomes such as mortality, disease progression, patient's symptoms and overall effect on function or quality of life. Moreover, the small sample sizes of these studies limited their power and generalizability. Although the studies provided evidence that HTS may be superior to MNT, both of their risks of adverse effects attenuate this evidence. Further research is necessary before HTS can be definitively recommended over MNT. No specific hyperosmolar treatment protocol has been shown to improve function outcome or mortality in clinical trials. Different types of HTS solutions and different methods of administration, continuous versus bolus dose, need to be evaluated to effectively recommend one osmotic agent over the other. Specific trials are needed to determine whether certain types of patients respond better to HTS than MNT, and vice versa. Although MNT proves to be

comparable to HTS in some studies, it comes with a greater risk of mortality that most providers may not be willing to take.

Conclusion

The question of whether to use MNT or HTS therapy for ICH due to TBI has not been fully answered. MNT was the preferred treatment decades ago, but HTS is beginning to establish itself as the initial option for treatment of elevated ICP based on these data. Most of the available studies support the contention that ICH due to TBI can be reduced with osmotic therapy and that HTS, instead of MNT, may be recommended as the treatment of choice (or the first-line treatment). Future investigations should determine the definitive osmolar therapy for treatment of ICH from TBI, or at least set parameters for which agent would better in different clinical situations. Additional research is warranted with larger sample sizes and randomized controlled trials since uncertainty remains over the optimal therapy. At this point, lacking reliable evidence precludes definite recommendations for the use of HTS over MNT. Nonetheless, as evidenced in recent studies, HTS may be preferred in patients who are hypovolemic or hyponatremic.

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