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Review

Hyperosmolar therapy in pediatric traumatic brain injury: a systematic review

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Abstract

Background: Traumatic brain injury (TBI) is a prominent reason for morbidity and mortality in children. The use of hyperosmolar therapy to manage increased intracranial pressure (ICP) is portrayed in pediatric guidelines; however, there still remains some debate regarding which option to select. The aim of this systematic review was to assess which hyperosmolar therapy – mannitol or hypertonic saline (HTS) – is more effective in terms of lowering ICP and having better outcomes in treating children with TBI.

Methods: A literature search was conducted using MEDLINE (through PubMed), Scopus, and Web of Science. This review included 6 retrospective and prospective studies comparing the use of mannitol and HTS in pediatric patients with TBI.

Results: HTS was the most frequently described hyperosmolar agent, obtaining better results in managing ICP, cerebral perfusion pressure and osmolarity. It also showed to be effective in refractory intracranial hypertension, in situations where mannitol fails to lower ICP. Mannitol was less studied but demonstrated a higher incidence of mortality than HTS. There were several studies that did not report monitoring outcomes associated with serum osmolarity, despite the use of hyperosmolar therapies. Discrepancies were noticed between the studies in the overall study design in addition to reported monitoring parameters and length of stay.

Conclusions: HTS seems to be safe and efficient in the treatment of severe TBI in children. The reduced existing studies regarding the use of mannitol do not permit a strong decision to be made concerning its practice.

For the time being, the choice of hyperosmolar therapy in this context must be individualized and based on clinical practice and experience, not disregarding the latest guidelines that recommend the use of HTS.

Keywords

Pediatric, traumatic brain injury, hyperosmolar therapy, mannitol, hypertonic saline, intracranial pressure.

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Background

Traumatic brain injury (TBI) is a major cause of death and disability all over the world [1]. Pediatric TBI differs from adult TBI in both pathophysiology and management [2]. It is difficult to perform a neurological exam and evaluate a newborn, infant, or toddler more than an adult. Besides that, the younger the child, the thinner and poorer its ability to cushion against external forces, so even a small blood loss can lead to hemorrhagic shock, which may occur without apparent external bleeding. Therefore, children are considered to exhibit a specific pathological response to brain injury and accompanying neurological symptoms [3].

TBI can lead to cerebral edema, increased intracranial pressure (ICP), and a decrease in cerebral perfusion pressure (CPP), which is related to more complications during treatment, worse outcomes, and an increase in morbidity and mortality [4]. ICP can be assessed through clinical observations, such as irritability, headache, and cranial nerve dysfunction, non-invasive examinations, like transcranial Doppler, and direct invasive measures, for example, intraparenchymal monitors. It is important to frequently and carefully assess children with TBI to observe and manage the signs and symptoms of early increased ICP – which can be subtle, like irritability and cranial nerve dysfunction – before the child progresses to later signs, such as Cushing's triad (increased systolic blood pressure due to increased cerebral perfusion, bradycardia due to vagal response triggered by cardiac baroreceptors, and abnormal or irregular respirations) [5].

ICP monitoring is vital in the management of severe TBI, with most guidelines considering values of > 20-25 mmHg demanding treatment [6]. One of the primary treatments to reduce ICP is hyperosmolar therapy, of which mannitol and hypertonic saline (HTS) are the most commonly used agents [7].

Mannitol lowers ICP through two mechanisms: an effect that consists in reducing blood viscosity and promoting plasma expansion and cerebral oxygen delivery, which, due to autoregulation, leads to cerebral vasoconstriction and decreasing of cerebral blood volume, and through the creation of an osmotic gradient across the blood-brain barrier, leading to the movement of water from the parenchyma to the intravascular space; it also acts as an osmotic diuretic, leading to free water clearance and an increase in serum osmolality. It should be administered with an in-line filter to prevent the infusion of crystals. Risks of mannitol administration include the development of acute renal failure and rebound cerebral edema [8, 9]. Current guidelines for the use of mannitol in pediatrics recommend its use in intermittent boluses spaced several hours apart, with appropriate fluid replacement to maintain euvolemia and serum osmolality < 320 mOsm/L [6].

HTS can be administered in various concentrations, but 3% is the most commonly used. HTS creates an osmotic force to bring water from the interstitial compartment of the brain parenchyma into the intravascular compartment in the presence of an intact blood-brain barrier, therefore reducing intracranial volume and ICP. Adverse effects of HTS administration involve rebound elevation in ICP, central pontine myelinolysis due to rapid correction of hyponatremia, hyperchloremic metabolic acidosis, and hematologic abnormalities [8, 9]. Pediatric guidelines recommend the use of HTS up to a serum osmolality of 360 mOsm/L [6].

The recently published third edition of the pediatric severe TBI guidelines recommends a bolus of 3% HTS at a dose of 2-5 mL/kg over 10-20 minutes for ICP control (class II) [6]. They also advise a continuous 3% HTS infusion for ICP control, with a dose range of 0.1-1.0 mL/kg per hour, with a minimum dose for maintaining ICP less

than 20 mmHg suggested (class III). For refractory ICP, the guidelines suggest a bolus of 23.4% HTS, with dosing of 0.5 mL/kg and a maximum of 30 mL. Like in the second edition of the guidelines (2012) [10], the third edition also says that there are no studies meeting inclusion criteria for mannitol, despite it being commonly used in clinical practice [6]. Since then, it has been existing a significant variation of clinical practice in the treatment of intracranial hypertension in pediatric severe TBI.

Methods

Eligibility criteria

This review included randomized control trials and retrospective studies, with the target population being children with TBI. Articles were included if they compared the effect of HTS to mannitol for the management of elevated ICP in this context. Articles were excluded if they included animal or adult studies, were not published in English, had no distinction between adults and children, had outcomes not concerning hyperosmolar therapy, or not comparing HTS and mannitol. Duplicate articles, editorial letters, and those not related to the purpose of this review were also excluded. The number of population or the date of publication were not exclusion criteria for this review.

Information sources and search strategy

A comprehensive literature search was conducted with the purpose of identifying all reported articles comparing mannitol and HTS in children with TBI, according to the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. This search was conducted on the databases MEDLINE (PubMed), Web of Science, and Scopus. The search query, which took place in September of 2021, included the following terms and keywords: ("children" or "pediatric") and ("hyperosmolar therapy" or "mannitol" or "hypertonic saline") and ("traumatic brain injury").

Study selection and risk of bias assessment

Two investigators independently assessed whether the studies addressed the topic in question and if all inclusion/exclusion criteria were met. Initially, this was done according to the screening phase, where only the title and the abstract were analyzed. After this process, 48 articles were eligible. This was followed by the inclusion phase, where the integral text was fully evaluated. Any doubtful situation was solved by consensus between the authors, after which, concerning study eligibility, 100% agreement between authors was seen in each step of the study assessment. A flowchart showing the literature search method can be seen in **Fig. 1**.

Risk of bias was assessed according to the National Institutes of Health reporting guideline using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (**Tab. 1**) and the Quality Assessment of Controlled Intervention Studies (**Tab. 2**).

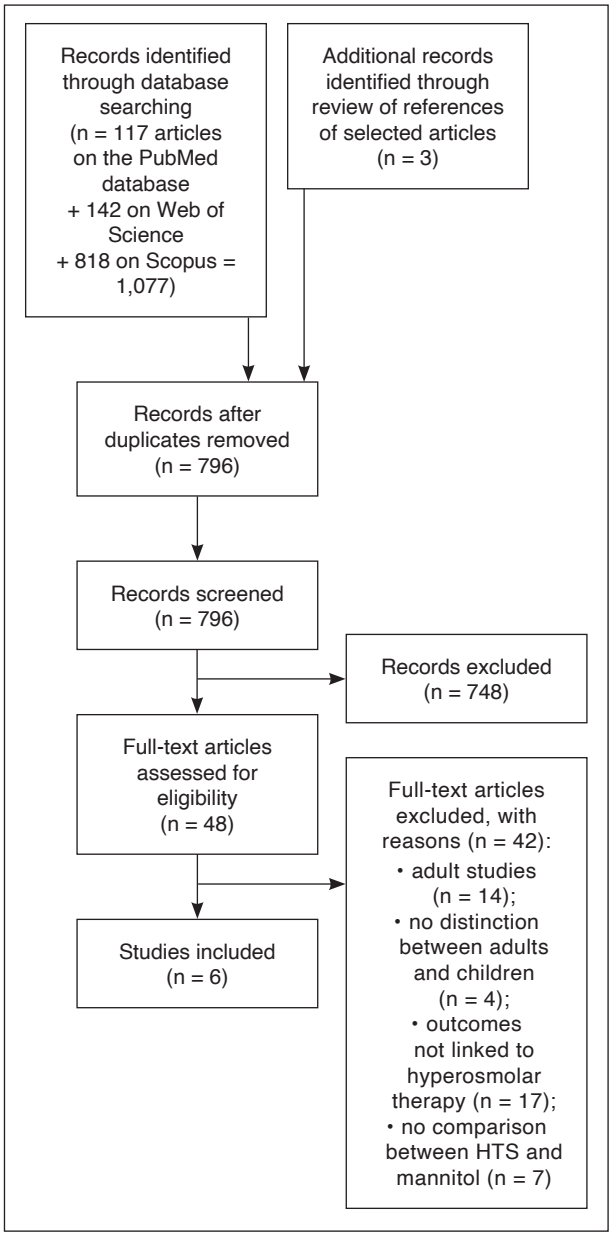

Figure 1. Flowchart showing literature search method.
HTS: hypertonic saline; n = number of articles.

Table 1. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (continues in the next column).

	Vats et al., 1999 [12]	Khanna et al., 2000 [13]	Taha et al., 2015 [17]	Roume-liotis et al., 2016 [15]	Shein et al., 2016 [14]
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y	Y	Y
3. Was the participation rate of eligible persons at least 50%?	Y	Y	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y	Y	Y
5. Was a sample size justification, power description, or variance and effect estimates provided?	NR	NR	NR	Y	NR
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	NR	NR	NR	NR	NR
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Y	Y	Y	Y	Y
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	NR	Y	Y
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y
10. Was the exposure(s) assessed more than once over time?	Y	Y	Y	Y	Y
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	Y	Y
12. Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR
13. Was loss to follow-up after baseline 20% or less?	Y	Y	Y	Y	Y
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Y	Y	NR	Y	Y

NR: not reported; Y: yes.

Table 2. Quality Assessment of Controlled Intervention Studies.

	Kumar et al., 2019 [16]
1.Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Y
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	Y
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	Y
4. Were study participants and providers blinded to treatment group assignment?	NR
5. Were the people assessing the outcomes blinded to the participants' group assignments?	Y
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Y
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Y
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Y
9. Was there high adherence to the intervention protocols for each treatment group?	Y
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Y
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Y
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	NR
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	Y
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	Y

NR: not reported; RCT: randomized controlled trial; Y: yes.

Data collection process and outcomes

Two independent authors performed the article selection, data extraction, and article analysis. Discrepancies between authors were resolved by consensus. The following data were extracted from each study: publication year, study design, objective, number of patients, study population, type of hyperosmolar therapy used, route of administration, and clinical outcomes. Outcomes varied across studies, including the number of interventions and doses administered, management of ICP and CPP, length of stay in the Intensive Care Unit (ICU), number of complications, mortality rate, Glasgow Outcome Scale score, and duration of comatose state. The primary outcome studied was the management of ICP after administration of hyperosmolar therapy.

Results

A total of 6 articles were included in this systematic review, each comparing the use of HTS and mannitol in the management of elevated ICP in children with TBI. A total of 223 patients were assessed. Study characteristics are summarized in **Tab. 3**.

The main outcome reviewed was the management of ICP after administration of hyperosmolar therapy. Vats et al. [12] and Khanna et al. [13] showed a significant decrease in ICP after administration of HTS and mannitol, with Shein et al. [14] proving only a significant decrease of ICP with 3% HTS. Roumeliotis et al. [15] and, more recently, Kumar et al. [16] concluded that both HTS and mannitol were associated with reducing ICP but were not statistically significant. Taha et al. [17] focused on ICU length of stay and disposition status on discharge in the comparison of hyperosmolar therapies, settling on the benefit of administering combined treatment of mannitol and 3% HTS. Other outcome variables studied were CPP and osmolarity. Not all studies reported these, which translated into not very thorough results and conclusions. More detailed outcomes are summarized in **Tab. 4**.

Table 3. Study characteristics of literature reviewed.

Study	Study design	No. of patients	Mean of patient ages (range)	Type of hyperosmolar therapy	Dose of hyperosmolar therapy	Route of administration	Severity of TBI
Vats et al., 1999 [12]	Retrospective review	55 HTS: 25 Mannitol: 18 Both: 12	Not reported (1-16 years)	3% HTS vs 20% mannitol	HTS: 5 mL/kg Mannitol: 0.5 g/kg or 1 g/kg	Bolus	Mild, moderate and severe
Khanna et al., 2000 [13]	Prospective cohort	10	6 years (0.3 months - 13 years)	3% HTS vs "standard therapy"	Unknown	Continuous infusion	Severe
Taha et al., 2015 [17]	Retrospective review	96 HTS: 34 Mannitol: 5 Both: 18 Therapy: 39	13 years (8-18 years)	3% HTS vs 20% mannitol	Unknown	Bolus	Severe
Roumeliotis et al., 2016 [15]	Retrospective review	16	13 years (9-15 years)	3% HTS vs 20% mannitol	HTS: 1.8 mL/kg Mannitol: 0.6 g/kg	Bolus	Severe
Shein et al., 2016 [14]	Prospective cohort	16	5 years (3-14 years)	3% HTS vs 20% mannitol vs fentanyl vs pentobarbital	3 mL/kg	Bolus and continuous infusion	Severe
Kumar et al., 2019 [16]	Randomized controlled trial	30 HTS: 14 Mannitol: 16	Not reported (2-16 years)	3% HTS vs 20% mannitol	HTS: 2.5 mL/kg Mannitol: 2.5 mL/kg	Bolus	Severe

HTS: hypertonic saline; TBI: traumatic brain injury.

Table 4. Summary of study outcomes.

Study	Type of hyper-osmolar therapy	ICP	CPP	Osmolarity	ICU LOS	Conclusions
Vats et al., 1999 [12]	3% HTS vs 20% mannitol	HTS and mannitol both reduced ICP significantly ($p < 0.05$ at 30 min after HTS, $p < 0.01$ at 60 and 120 minutes after HTS and/or mannitol)	Only HTS increased CPP significantly ($p < 0.01$), with no change after mannitol	Not reported	Not reported	HTS produces a significant and sustained reduction in ICP
Khanna et al., 2000 [13]	3% HTS vs "standard therapy"	Significant reduction in ICP at 6, 12, 24, 48, 72 hours ($p < 0.01$)	Significant increase in CPP at 6, 12, 24, 48, 72 hours ($p < 0.01$)	Significant increase in serum osmolarity at 12 hours ($p < 0.05$) and at 24, 48, 72 hours ($p < 0.01$)	Not reported	HTS effectively controlled intracranial hypertension resistant to conventional therapy, including mannitol and sodium thiopental coma
Taha et al., 2015 [17]	3% HTS vs 20% mannitol	Not reported	Not reported	Not reported	No significant difference between those who received hyperosmolar therapy and those who did not (regarding ICU LOS $p = 0.48$ and discharge disposition status $p = 0.15$). Patients who received mannitol only had the shortest ICU LOS followed by the mannitol plus 3% HTS group, whereas the 3% HTS only group had the longest ICU LOS ($p = 0.031$)	Administering a combined therapy of mannitol and HTS proved to be beneficial in treating elevated ICP in severe TBI patients. Children who received mannitol plus 3% HTS had the greatest number discharged home ($p = 0.02$)
Roumeliotis et al., 2016 [15]	3% HTS vs 20% mannitol	No significant change in ICP (mannitol $p = 0.055$ and HTS $p = 0.096$)	No significant change in CPP after HTS or mannitol	No significant change in serum sodium after mannitol or HTS	Not reported	Both 3% HTS and mannitol were associated with decrease in ICP, but did not achieve statistical significance
Shein et al., 2016 [14]	3% HTS vs 20% mannitol vs fentanyl vs pentobarbital	Significant decrease in ICP after 3% HTS ($p < 0.05$) and no change in ICP after mannitol	Significant increase in CPP after HTS ($p < 0.05$) and no change after mannitol	Not reported	Not reported	HTS was associated with the most favorable cerebral hemodynamics and fastest resolution of intracranial hypertension
Kumar et al., 2019 [16]	3% HTS vs 20% mannitol	Decrease in ICP for both treatment groups, with no difference between groups ($p > 0.05$)	Increase of CPP for both treatment groups, with no difference between groups ($p > 0.05$)	No significant difference in serum creatinine or sodium between groups ($p > 0.05$)	Not reported	There was no significant difference in reduction in ICP between mannitol and HTS groups, with both having similar functional outcome

CPP: cerebral perfusion pressure; HTS: hypertonic saline; ICP: intracranial pressure; ICU: Intensive Care Unit; LOS: length of stay; TBI: traumatic brain injury.

Discussion

The studies included in this systematic review demonstrated different conclusions about the best type of hyperosmolar therapy in terms of treatment for children with TBI. Mannitol and HTS are usually used for decreasing ICP in severe TBI and, although there are many articles and randomized controlled trials about the adult population about the best way of treatment and use of these therapies, this revision shows the lack of studies about children and its best course of treatment with TBI and elevated ICP. The majority of the studies concluded the positive effects of mannitol and even better HTS or the use of both these agents simultaneously in decreasing ICP and increasing CPP [12-14].

Although mannitol was first recommended to reduce the ICP in TBI [18, 19] and it is frequently used in clinical practice, there are few studies verifying its effectiveness in practice and comparing it with other agents in hyperosmolar therapy. The 2019 guidelines for pediatric severe TBI clearly state this, acknowledging its use, but not recommending it due to lack of data [6]. Instead, HTS is suggested for the treatment of intracranial hypertension due to its efficiency and the amount of data supporting it [13, 14, 16]. HTS is also suggested in refractory intracranial hypertension at a higher concentration when mannitol is no longer successful [13, 20-22]. Considering that the landscape for pediatric severe TBI management with hyperosmolar therapy has long suffered from limited data, the consequence is that each doctor and institution has developed their own treatment plan for these patients, a decision that is more subjective rather than evidence-based.

On the other hand, it seems that there are many more publications and studies about the use of hyperosmolar therapy in adult patients [23-26]. However, there is also no specific agreement regarding dosage and which agent to use, due to different hyperosmolar therapy and concentrations, diverse study designs, and distinctive outcome measurements [1].

The studies in this systematic review have some limitations due to being single-center investigations and having a small population. Since we tried to find a comparison between the effect of HTS and mannitol in the management of children with TBI, very few studies met our eligibility criteria; furthermore, we did not include unpublished studies or studies published in other languages than English, so our review might have publication bias. Only one study is a randomized control trial [16], while the others are retrospective reviews [12-15, 17]. This could explain the diverse results obtained through this review, due to differences in patient population characteristics and clinical practice disparity outside the use of hyperosmolar therapy. As the majority of studies in the present review are retrospective studies, the limitations include those intrinsic to this kind of studies, including an absence of data on confounding factors and losses to follow-up, which can also lead to selection bias in these studies. Nevertheless, a strong point of this review is the randomized controlled studies and retrospective studies included, that compared HTS with mannitol and other osmolar agents to comprehend a better potential therapy in providing an improved outcome for children with cerebral edema, in TBI. Also, there were no restrictions on the date of publication year.

Conclusion

Although mannitol seems to be widely used in clinical practice, few studies prove it is the most effective hyperosmolar agent in reducing ICP and having a better outcome in treating TBI in children. On the other hand, HTS is, by the current guidelines [6], the hyperosmolar agent of choice in the treatment of these patients. Even though some studies show its effectiveness and favorable outcome in the reduction of ICP [12-14, 27], later studies, such as Roumeliotis et al. [15] and Kumar et al. [16], failed to demonstrate statistical significance in a reduction in ICP between mannitol and HTS. There are many reasons for these outcomes (such as selection, performance, detection, and reporting bias), but one thing is necessary: larger studies and more clarification on the duration of effect, comorbidities, and detailed outcomes with these hyperosmolar therapies. This review showed that HTS proved to have a more effective approach in reducing ICP and increasing CPP, thus leading to a better outcome in these cases. For now, it seems that the choice of hyperosmolar therapy for children with TBI should be individualized and based on one's practice and experience, not disregarding the latest guidelines that suggest the use of HTS.

Declaration of interest

The Authors report no conflicts of interest. The Authors did not receive any funding for the present study.

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