JPPT | Review

Hyperosmolar Therapy for Severe Traumatic Brain Injury in Pediatrics: A Review of the Literature

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Traumatic brain injury remains a leading cause of morbidity and mortality in children. The use of hyperosmolar therapy to offset increased intracranial pressure (ICP) is described in pediatric guidelines, yet some controversy remains regarding which option to select. A search was conducted using the PubMed, MEDLINE, Cumulative Index of Nursing and Allied Health, Academic Search Premier, PsycInfo, and Cochrane Library databases. Studies were included if they described the hyperosmolar therapy use, involved severe traumatic brain injury (TBI), and patient age was 0 to 18 years. A total of 331 studies published between 1987 and 2017 were retrieved; of these, 9 met the inclusion criteria. Included studies were evaluated for the type and concentration of hyperosmolar therapy, associated mortality outcomes, ICP and coronary perfusion pressure (CPP) measurements, concurrent medications, and reported serum sodium and serum osmolarity or osmolality values. Hypertonic saline was the most commonly reported hyperosmolar therapy. Mannitol was less studied, but collectively demonstrated a higher incidence of mortality than hypertonic saline. There were several studies that did not report monitoring outcomes associated with serum sodium and/or serum osmolarity, despite the use of hyperosmolar therapies. Inconsistencies were noted between the studies in the overall study design as well as reported monitoring parameters and length of stay. Hypertonic saline appears to be safe and efficacious at several concentrations for treatment of increased ICP associated with severe TBI in pediatric patients. The limited available data regarding the use of mannitol do not allow a strong conclusion to be made regarding its use.

ABBREVIATIONS BTF, Brain Trauma Foundation; CINAHL, Cumulative Index of Nursing and Allied Health; CPP, cerebral perfusion pressure; EPTS, early post-traumatic seizure; GCS, Glasgow Coma Scale; HTS, hypertonic saline; ICP, intracranial pressure; LOS, length of stay; PRISM, Pediatric Risk of Mortality; TBI, traumatic brain injury;

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Introduction

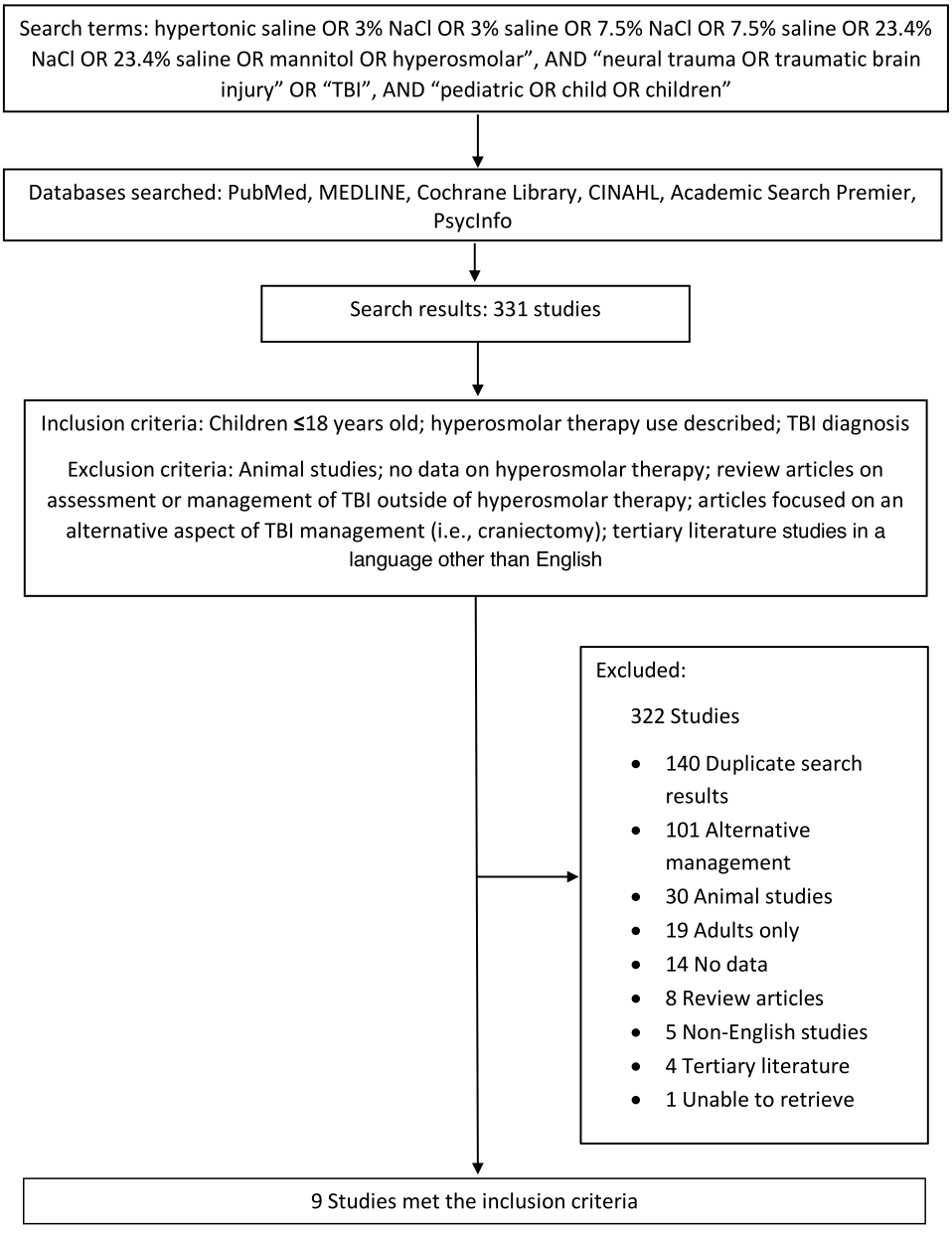
Traumatic brain injury (TBI) remains a significant public health concern and a leading cause of mortality in children.[1] Data from the Centers for Disease Control and Prevention report more than 500,000 traumatic brain injury–related cases in children aged 0 to 14 years between 2002 and 2006.[2] Consequences from TBI can range from mild transient symptoms to significant mental, physical, emotional, and/or intellectual sequelae or death.

The Glasgow Coma Scale (GCS) is a commonly incorporated neurological assessment tool used in the classification of brain injury. The severity of the injury is scored on the basis of the patient's impaired level of consciousness and is grouped into 3 categories: 13 to 15 (mild), 9 to 12 (moderate), and 3 to 8 (severe).[3] For a patient with severe TBI, early complications from the primary injury can include increased intracranial pressure (ICP), decreased cerebral perfusion pressure (CPP), seizures, electrolyte abnormalities, and hypoxemia.[4] Thus, severe TBI requires intensive care, multidimensional management, and interprofessional collaboration.

The fourth edition of the 2016 Brain Trauma Foundation (BTF) guidelines for the management of severe TBI in adults recommends the use of mannitol for ICP reduction and does not specifically support the use of hypertonic saline (HTS).[5] These recommendations are a carryover from the third edition, published in 2007, due to the available evidence not meeting the minimum inclusion requirements of the updated guidelines. In contrast, the 2003 BTF pediatric severe TBI guidelines support the use of hyperosmolar therapy, though the authors state there is insufficient evidence to support utilization of mannitol versus HTS as the first-choice agent.[6] However, the 2012 BTF pediatric guidelines advocate for HTS as either a bolus or infusion with preference over mannitol for this indication.[7]

Despite these pediatric guidelines favoring the use of HTS, mannitol is still commonly used in practice. An international study from 2013 identified use of HTS and mannitol in 96.9% and 90.6% of responding centers in ICP management, respectively.[8] There is limited head-

Figure. Search analysis.



CINAHL, Cumulative Index of Nursing and Allied Health; TBI, traumatic brain injury.

to-head evidence in pediatric patients for evaluating hyperosmolar agents. The purpose of this review is to assess the available literature on the use of hyperosmolar therapy for the treatment of pediatric severe TBI and highlight areas of scholarly need.

Methods

A literature search was conducted by using PubMed, MEDLINE, Cumulative Index of Nursing and Allied Health (CINAHL), Academic Search Premier, PsycInfo, and Cochrane Library databases. The search terms used for each database were "hypertonic saline OR 3% NaCl OR 3% saline OR 7.5% NaCl OR 7.5% saline OR 23.4% NaCl OR 23.4% saline OR mannitol OR hyperosmolar", AND "neural trauma OR traumatic brain injury OR TBI", AND "pediatric OR child OR children". Eligible studies included those published between January 1, 1987, and December 31, 2017, with enrollment of children 0 to 18 years of age who were treated for

TBI with hyperosmolar therapy (HTS or mannitol). The 2 investigators independently conducted the literature searches and confirmed the results with each other prior to abstract evaluation. Abstracts were independently reviewed by each author for study inclusion. Excluded from the review were studies that did not state data on hyperosmolar therapy; review articles on the assessment or management of TBI outside of hyperosmolar therapy; animal studies; articles that focused on an alternative aspect of TBI management such as craniectomy; studies in a language other than English; and tertiary literature such as book chapters. The Figure illustrates the search methodology and results.

Results

A total of 331 articles were retrieved through the database searches (103 from PubMed, 92 from MEDLINE, 77 from CINAHL/Academic Search Premier/PsycInfo, and 59 from the Cochrane Library). Initial review eliminated 140 duplicate articles, leaving 191 studies that underwent abstract review. Of these, 182 studies were excluded, leaving 9 studies meeting the inclusion criteria—5 retrospective studies, 3 prospective studies, and 1 case series. These 9 articles presented data on a total of 229 patients ranging in age from 4 months to 18 years over a period of 27 years. All studies used a GCS of ≤8 to indicate severe brain injury. Three studies also included Pediatric Risk of Mortality (PRISM III) scores. Table 1 lists the study characteristics of the included articles.

Hyperosmolar Therapy and Mortality. Three studies evaluated the use of mannitol compared to HTS;[9–11] 4 studied HTS only;[12–15] 1 studied mannitol use only;[16] and 1 evaluated HTS only after mannitol administration.[17] Mannitol concentration was reported as 20% in all studies except for 1,[16] in which the mannitol concentration was not specified. Hypertonic saline concentrations studied included 3%, 7.5%, and 23.4%; these were administered either as a continuous infusion (only 3% HTS was stated to be administered as a continuous infusion) or as a series of bolus doses. No other concentrations were reported in the literature reviewed. Mortality rates ranged from 6% to 32%, though 1 study's mannitol subgroup of 5 patients had a mortality rate of 80%,[11] and the case series of 2 patients had a 50% mortality rate. The collective mortality rate from all studies was 22% (78/355). There was no distinct difference between the concentration of HTS and mortality outcomes.

ICP and CPP Measurements. Eight studies included ICP measurements as part of their results.[9,10,12–17] The data showed a decrease in ICP with use of 3%, 7.5%, and 23.4% HTS. Mean ICP reductions between studies ranged from −4.2 mm Hg to −10.2 mm Hg at 2 hours after HTS administration, though baseline measurements and time of therapy initiation relative to admission were not always reported. Roumeliotis et al[9] described a decrease in ICP with both 3% HTS and mannitol with no difference between the agents. White et al[16] studied only mannitol and saw an increase in ICP in patients who did not survive. Four studies also reported CPP measurements.[9,10,13,17] Three reported positive outcomes with the use of HTS, showing CPP increases of 7 to 20 mm Hg (baseline ranged from 41 to 61 mm Hg). One study reported no difference between mannitol and HTS on CPP.[9] There were no other described data on the effect of mannitol on ICP or CPP measurements. Table 2 summarizes the outcomes of the studies included in this review.

Other Medications Used. All studies listed additional medications patients received during their admission. However, only broad drug classes were documented in several of these studies, specifically, sedatives, vasopressors, non-depolarizing muscle relaxants, paralytics, and loop diuretics. The most commonly reported specific medications used were pentobarbital, thiopental, propofol, and fentanyl.

Tracking of Serum Sodium Concentrations. Six studies evaluated patient serum sodium concentrations.[9,12–15,17] Two studies reported a 7 mEq/L increase from baseline (normal values, 135–145 mEq/L),[14,17] while 2 reported no change.[9,12] Nakagawa et al[13] reported a mean sodium value of 141.1 mEq/L and 155.7 mEq/L in 2 different patients with a maximum serum sodium value of 144 mEq/L and 170 mEq/L, respectively. These maximum serum sodium values were obtained 4 hours and 7 hours after administration of HTS. Khanna et al[15] described a range of mean maximum serum sodium values of 157 to 187 mEq/L (mean 170.7 mEq/L), the highest range of all studies.

Four studies evaluated serum osmolality or osmolarity.[12–15] Nakagawa et al[13] reported serum osmolality of 1 patient reaching a mean of 341 mOsm/kg and a maximum of 369 mOsm/kg (normal values, 275–295 mOsm/kg). Fisher et al[14] prospectively evaluated the effect of HTS on ICP and reported a mean serum osmolarity increase from baseline of 12 mOsm/L at 30 minutes and 6 mOsm/L at 120 minutes post administration of 3% HTS. The mean baseline serum osmolarity was 300.8 mOsm/L. Khanna et al[15] described a mean maximum serum osmolarity of 364.8 mOsm/L. Piper et al assessed serum osmolarity with mannitol and reported a mean value of 305.7 mOsm/L.[12]

Discussion

This review identified a paucity of data regarding comparisons of outcomes with HTS and mannitol. There are inconsistencies in practice regarding the use of these agents and limited strong comparisons between HTS and mannitol. Optimal monitoring strategies and parameters in pediatric TBI patients have not been established, including measurement of ICP, CPP, serum sodium, and serum osmolarity and/or osmolality. Additionally, the optimal concentration of HTS to correct elevated ICP has not been defined, and there are

Table 1. Study Demographics

Reference (Design; Sample Size)	Age (% Male)	GCS at Admission (PRISM III)	Inclusion Criteria	Primary Outcome (Secondary Outcomes)	Complications	Comparators
Rallis[17] (retrospective chart review; n = 29)	8.9 ± 4.6 yr* (52)	6†; IQR 5–7 (12.9 ± 7.8)	≤14 yr; GCS ≤ 8; primary closed TBI; continuous ICP monitoring; ICP ≥ 20 for ≥15 min after supportive tx; 7.5% HTS for raised ICP	ICP and CPP response at 30, 60, and 120 min post HTS (serum sodium alterations; neurological outcome mortality)	Pt already treated with 20% mannitol; mannitol and HTS doses were not equimolar (HTS > osmolarity); small sample size	None
Roumeliotis[9] (retrospective chart review; n = 16)	9–15 yr (75)	6†; range: 4–7 (NA)	1 mo–18 yr; GCS ≤ 8; invasive ICP monitoring followed by hyperosmolar agent within 48 hr of PICU admission	Effect of 20% mannitol and 3% HTS on ICP and CPP (NA)	No control for interventions prior to ICP monitor placement; did not account for cointerventions possibly reducing ICP; did not look at sedation, opioid or benzodiazepines use, or hyperventilation	Mannitol 20%; 3% HTS
Shein[10] (prospective observational; n = 16)	102 mo†; IQR: 43–168 mo (66)	5†; range: 3–7 (18; 12–22)	<18 yr; admitted 12/2011 to 02/2013; GCS ≤ 8; ICP monitoring	Fentanyl, 3% HTS, mannitol, and pentobarbital decrease ICP without significantly decreasing CPP (none)	Did not address long-term functional outcome; limited data on mannitol due to clinical practice of institution; could not account for infusions of fentanyl, HTS, and pentobarbital; other medications were used concurrently	Pentobarbital; fentanyl; mannitol 3% HTS
Piper[12] (retrospective cohort; n = 32)	14 yr†; range: 8 mo–17 yr (63)	4†; range: 3–15 (NA)	<18 yr; primary diagnosis of TBI; ICP monitor; ICP > 20 for >5 min and not responding to stepwise head injury tx protocol; 23.4% HTS administered to control ICP	Efficacy and consequences of 23.4% HTS (NA)	Small sample size; lower ISS than some other studies; did not account for maintenance or bolus fluids	23.4% HTS; mannitol
Nakagawa[13] (case report; n = 2)	23 mo*; 4 yr† (50)	3 and 6 (NA)	NA	NA (NA)	One patient received 2 doses of mannitol in addition to 3% HTS (1° therapy); used 3% and 23.4% HTS	3% HTS vs. 23.4% HTS
Taha[11] (descriptive retrospective chart review; n = 96)	13 yr†; range: 8–18 yr (70.8)	3†; range: 3–8 (NA)	Age 8–18 yr; admitted with severe TBI (GCS 3–8); abnormal head CT scan on admission; documented high ICP (>20 for >5 min)	ICU LOS (discharge disposition in children admitted with TBI)	NA	Mannitol; 3% HTS; mannitol + 3% HTS
Fisher[14] (prospective observational; n = 18)	7.7 yr†; range: 0.6–14 yr (NA)	6†; range: 3–10 (NA)	TBI, admitted to San Diego Children's Hospital	Effect of HTS on ICP (NA)	ICH in 13 pts; 5 pts died	0.9% NaCl vs. 3% HTS to all groups
Khanna[15] (prospective interventional; n = 10)	5.8*; range: 0.33–12 yr (80)	4†; range: 3–7 (NA)	TBI, admitted to San Diego Children's Hospital, receiving ICP monitoring, intracranial HTN unresponsive to conventional tx	Effect of continuous 3% HTS infusion on ICP (NA)	Failed conventional tx including mannitol with loop diuretic	NA
White[16] (retrospective cohort; n = 136)	0–17 yr (56.6)	3†; range: 3–8 (18, survivors; 27, non-survivors)	Severe, non-penetrating head injury; GCS ≤ 8	Survival (PICU LOS; cost of hospitalization)	NA	NA

CPP, cerebral perfusion pressure; CT, computed tomography; GCS, Glasgow Coma Scale; HTN, hypertension; HTS, hypertonic saline; ICH, intracranial hypertension; ICP, intracranial pressure; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay; NA, not available; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality; pts, patients; TBI, traumatic brain injury; tx, treatment

* Mean ± SD.

† Median.

Table 2. Summary of Study Outcomes

Reference	Effect on ICP and CPP Monitoring	Mortality	Other Medications Used	ICU LOS, Average Days (Range)	Effect on Serum Sodium (Mean)	Effect on Serum Osmolality (Mean)
Rallis[17]	ICP significantly decreased after 2 hr in pts tx with 7.5% HTS (29 to 18, $p < 0.001$). CPP significantly increased after 2 hr in pts given 7.5% HTS (50 to 58, $p < 0.001$)	5 (17%)	Sedation with benzodiazepines; analgesia with opiates; fluid expansion, inotropes, and/or vasopressors. Initially given 20% mannitol—if tx failed, escalated to 7.5% HTS	NA	Increased (142 to 149, $p < 0.001$)	NA
Roumeliotis[9]	Mannitol and 3% HTS decreased ICP 4 hr after 2 boluses, but was NS. No change in CPP post bolus for mannitol or HTS	5 (31%)	11 pts: "cointervention" to decrease ICP; 2 pts: concomitant 3% HTS; 2 pts: propofol infusion; 2 pts: thiopental infusion	NA	NS change with mannitol or 3% HTS	NA
Shein[10]	5 min after HTS bolus start: decreased ICP (−2.49 mm Hg, $p = 0.004$); CPP increased after 3% HTS (+4.10 mm Hg, $p = 0.005$); 5 min after bolus: HTS decreased ICP (−5.86 mm Hg, $p < 0.001$); CPP increased (+7.66 mm Hg, $p = 0.001$).	8 (32%)	Fentanyl, hyperosmolar agents, pentobarbital, vecuronium, cisatracurium	NA	NA	NA
Piper[12]	Mean ICP reduction: 10.2 ± 8 mm Hg	2 (6.25%)	10 pts received mannitol, thiopentone infusion, propofol in >12 yr, opiates, benzodiazepines, non-depolarizing muscle relaxant, inotropes, 3% HTS in 1 pt for cerebral salt-wasting syndrome; depressive craniectomy in 2 cases	10*	No correlation between HTS and peak sodium/sodium increase; initial mean 139 mmol/L	Mannitol: 305.7 mOsm/L (range: 281–333 mOsm/L)
Nakagawa[13]	Pt 1: mean ICP change: −6.2 mm Hg (range: −2 to 12) Pt 2: mean ICP change: −11 mm Hg (range: 6 to 20)	1 (50%)	Pt 1: NE, sedation, paralytics, pentobarbital; Pt 2: midazolam, morphine, fentanyl, pentobarbital, phenobarbital	NA	Pt 1: Max: 170 mEq/L, mean: 155.7 mEq/L Pt 2: Max: 144 mEq/L, mean: 141.1 mEq/L	Pt 1: Max: 369 mOsm/kg; mean: 341 mOsm/kg; Pt 2: NA
Taha[11]	NA	Mannitol: 4 (80%); HTS: 12 (35.3%); 3% HTS + mannitol +3 (6.7%)	Sedation	Mannitol: 1.3† (0.6–3.1) 3% HTS: 5.04† (0–97.9) Mannitol + 3% HTS: 4.03† (0.21–23.5)	NA	NA
Fisher[14]	3% HTS: mean ICP change: −4.2 mm Hg; 0.9% NaCl: mean ICP change: +0.7 mm Hg	5 (27.8%)	Thiopental, dopamine, epinephrine	NA	Mean: +7 mEq/mL	3% HTS: 6–12 mOsm/L 0.9% NaCl: 0.2 mOsm/L
Khanna[15]	NA	1 (10%)	Mannitol, loop diuretic, pentobarbital	NA	157–187 mEq/mL (170.7)	330–431 mOsm/L (364.8)
White[16]	Maximum ICP; survivors: 26 ± 18 mm Hg; non-survivors: 59 ± 33 mm Hg	32 (23.5%)	Vasopressors, pentobarbital, phenytoin	2† (0–46)	NA	NA

CPP, cerebral perfusion pressure; HTS, hypertonic saline; ICP, intracranial pressure; ICU, intensive care unit; LOS, length of stay; NA, not applicable; NE, norepinephrine; NS, not significant; pts, patients; tx, treatment

* Mean.

† Median.

inconsistencies regarding the overall management of severe TBI in children. Outcomes data for all hyperosmotic therapies are lacking. Limited data and inconsistent evaluation of therapy success make designing an optimized management plan challenging.

Hyperosmolar Therapy and Mortality. The literature reported use of several HTS concentrations, the most common of which was 3%. This concentration was evaluated in 5 studies, 3 of which compared HTS to mannitol; 1 compared HTS to normal saline; and 1 compared HTS to other medications used in the treatment of TBI (fentanyl, pentobarbital, mannitol). Intracranial pressure was consistently improved with use of 3% HTS, though data linking a morbidity or mortality benefit remain unclear. An additional 3 studies evaluated HTS concentrations greater than 3%.[12,13,17] Rallis and colleagues[17] studied the effect of 7.5% HTS and noted no substantial harm while demonstrating improvement in ICP and CPP. Concentrations of 23.4% NaCl were assessed in 2 studies, showing reductions in ICP with no harm described by either group. In the limited available evidence, higher-concentration HTS may be an option for fluid-restricted patients.[12,13]

Mannitol use has not been extensively studied in pediatric patients over the last 30 years. In 3 studies examined in this review, patients had failed mannitol and were being administered higher-concentration HTS as a second-line therapy.[12,15,17] Only 1 study evaluated mannitol alone, while another compared it to HTS. White et al[16] studied various factors' impact on survival from severe TBI, one of which included administration of mannitol. This study identified mannitol use as an independent predictor of *increased* mortality. Of note, there were statistically significant differences between survivors and non-survivors in several evaluative categories, including GCS at 6 hours, admission pediatric trauma score, and admission PRISM III score. Survivors were less likely to need and therefore receive mannitol, which may have skewed the results.

In a retrospective chart review, Taha et al[11] compared mannitol to 3% HTS and mannitol + 3% HTS head-to-head, in addition to a no-hyperosmolar therapy group. All patients were admitted with a TBI and a GCS score of 3 to 8. Of the 4 groups, the no-hyperosmolar therapy group had the shortest length of stay (LOS) and lowest mortality rate at 15%, though the authors believed this was due to these patients having less severe TBI. For the patients who received hyperosmolar therapy, the mannitol-only group had the lowest median LOS (1.30 days) and highest incidence of mortality (80%); however, only 5 patients were in this group. The combined mannitol + 3% HTS group had a shorter LOS than the 3% HTS–only group (4.03 vs. 5.04 days) and lower mortality rate (3/18, 16% vs. 12/34, 35%).

ICP and CPP Measurements. The 2012 pediatric BTF guidelines for severe TBI recommend consideration of ICP monitoring for severe TBI in pediatrics (Level III) and considering treatment of ICP at a level of 20 mm Hg (Level III).[7] One study reviewed did not describe ICP monitoring at all; however, one of their inclusion criteria was a documented ICP exceeding 20 mm Hg for at least 5 minutes.[12] Amongst studies that monitored ICP, there was consensus mean improvement in ICP from HTS therapy varying from −4.2 to −11 mm Hg. There does not seem to be a dose-dependent relationship between milliequivalents of sodium administered and ICP change; that is, there was no observed relationship between the concentration of saline used and the decrease in ICP. Administering a higher concentration of saline did not appear to result in a proportionally similar decrease in ICP.[10,12,17]

These guidelines also have a Level III recommendation of monitoring CPP in children with a minimum target of 40 mm Hg.[7] Only 4 studies reported CPP measurements in their outcomes, with improvement noted in 3 studies.[9,10,13,17] While evidence supporting the monitoring of ICP and CPP is limited in pediatrics, data in adult patients show improvement in 2-week mortality with such monitoring.[5]

Other Medications Used. The guidelines identify other pharmacologic interventions in these patients in addition to hyperosmolar therapy. Classes of such medications include analgesics, sedatives, neuromuscular blockade, and antiseizure prophylaxis agents. Most studies in this review described to some extent the implementation of these medications, though they broadly listed medication classes rather than specific medications. Additionally, most studies did not control for other medications used in the medical management of these pediatric TBI patients, making it more challenging to determine the true effect of HTS compared with mannitol.

Shein et al[10] extracted data regarding the use of fentanyl specifically in a prospective study. They showed increased ICP and decreased CPP outcomes at the 5-minute time point, which is contradictory to ICP and CPP treatment goals for severe TBI and warrants consideration for study to see if the results can be duplicated. Utilization of other opioid medications such as morphine may be prudent given this outcome, owing to its hypotensive effect.[18]

While some studies used pentobarbital to reduce ICP, it was not specifically stated for its use for seizure prophylaxis except for White et al.[16] Current literature suggests use of phenytoin for early posttraumatic seizure (EPTS) prophylaxis.[7] Other research has identified levetiracetam, phenobarbital, and valproic acid for EPTS prophylaxis in addition to phenytoin and fosphenytoin.[19,20] In a 2016 publication evaluating the use of levetiracetam for EPTS prophylaxis, the authors reported 17% of patients having EPTS with levetiracetam, which was higher than reported EPTS with phenytoin.[21] However, since the studies in this review were often not specific about the agents used, the purpose of these

antiseizure agents (i.e., reduction in ICP or antiseizure prophylaxis) is often unclear in this setting.

In Khanna et al,[15] the investigators prospectively evaluated patients who received a continuous infusion of 3% saline targeting a specific serum sodium level. Simultaneously, thiopental was infused continuously while assessing ICP, serum sodium, and osmolarity. The study showed that coadministration of HTS significantly reduced the need for mannitol and thiopental. While multiple studies mentioned that propofol may have been administered to the patient, often at the discretion of the prescriber, the effects of propofol alone were not explicitly reported.

Tracking of Serum Sodium and/or Osmolarity. Current guideline recommendations are to maintain serum osmolarity below 360 mOsm/L; there is no recommendation for a target serum sodium level.[7] Six of the 8 studies that used HTS reported serum sodium values and noted an unsurprising increase with the use of HTS, though the amount of increase varied from no significant change to a maximum recorded value of 170 mEq/L. The studies also did not consistently describe the rate of increase in serum sodium values. Owing to the potential of central pontine myelinolysis with too rapid an increase in sodium, this complication is of concern. There does not seem to be a dose-dependent association with hypernatremia and concentration of HTS used. Similarly, while there was variability in the patients' changes in sodium level in response to HTS, most patients did not become significantly hypernatremic.

In the studies that did document serum osmolarity, it is clear that administration of HTS or mannitol increases serum osmolarity. However, it is impossible to fully determine the etiology of the rise in serum osmolarity—while hyperosmolar therapy may be the culprit, other factors such as diabetes insipidus, cerebral salt wasting, and syndrome of inappropriate antidiuretic hormone may also be responsible. Additionally, many patients received additional agents that affect osmolarity, including loop diuretics and vasopressors. While mannitol and HTS have a clear influence on serum osmolarity, the amount they affect this metric is challenging to conclusively determine without conducting a more robust analysis of these mitigating agents and their additional impact on serum osmolarity.

Limitations

This study has several limitations. The 3 most common HTS concentrations were included as specific search parameters in addition to broader terms, yet the search did not return literature describing any other concentrations. There is a possibility that some institutions use different HTS concentrations, but these were not found with the listed search terms. There is also a possibility that limiting the evidence search to publications dating from 1987 forward limits the available data on any of these therapies, specifically mannitol. There are limited available data comparing hyperosmolar agents, and the data that do exist use many different outcome measures, making comparisons between studies challenging. The collective number of participants included in this review was low, which makes it difficult to draw strong conclusions. The study designs and manners in which data were reported also varied widely between the included analyses, again confounding the aggregation of data. Similarly, many studies used multiple medications and interventions in addition to hyperosmolar therapy. This was not accounted for in these studies' analyses, making it difficult to extract the potential impact of these interventions on the variety of endpoints studied. Baseline measurements were not always reported in the studies, so it is impossible to discern if decreases in ICP and increases in CPP were significant from baseline or just significant in general. Finally, neither the timing of hyperosmolar therapy nor ICP and CPP measurements were described in the literature, meaning patients included in these studies may not have initially needed or received these interventions upon admission. As a result, the impact of the interventions may have been influenced.

Conclusions

This review provides insight into the current understanding of treatment approaches to increased ICP related to severe TBI in pediatrics. Hypertonic saline seems to be efficacious at multiple concentrations in reducing ICP and improving CPP, but there is a need for further controlled study. Mannitol is significantly understudied, and while the limited data suggest more harm than benefit, it is not possible to make a definitive statement without stronger evidence. Data are lacking in several areas, including the comparative safety effects of different concentrations of HTS, adverse effects related to hyperosmolar therapy, and consistency in reporting monitoring parameters.

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