Chapter 8. Hyperosmolar therapy

I. RECOMMENDATIONS

Strength of Recommendations: Weak. Quality of Evidence: Moderate, based on two moderate-quality class II studies and one poor-quality class III study.

A. Level I

There are insufficient data to support a level I recommendation for this topic.

B. Level II

Hypertonic saline should be considered for the treatment of severe pediatric traumatic brain injury (TBI) associated with intracranial hypertension. Effective doses for acute use range between 6.5 and 10 mL/kg.

C. Level III*

Hypertonic saline should be considered for the treatment of severe pediatric TBI associated with intracranial hypertension. Effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg of body weight per hour administered on a sliding scale. The minimum dose needed to maintain intracranial pressure (ICP) <20 mm Hg should be used. Serum osmolarity should be maintained <360 mOsm/L.

*Although mannitol is commonly used in the management of raised ICP in pediatric TBI, no studies meeting inclusion criteria were identified for use as evidence for this topic.

II. EVIDENCE TABLE (see Table 1)

III. OVERVIEW

Hyperosmolar Therapy for Intracranial Hypertension

Intravenous administration of hyperosmolar agents was shown to reduce ICP early in the 20th century (1). A study by Wise and Chater (2) introduced mannitol into clinical use in 1961. Despite widespread use of a number of osmolar agents (mannitol, urea, glycerol) up until the late 1970s (2), mannitol gradually replaced other hyperosmolar agents in the management of intracranial hypertension. Subsequently, hypertonic saline was introduced and now both are used in contemporary management of intracranial hypertension. In recent studies of hyperosmolar therapy use in pediatric TBI, euvolemia rather than dehydration has been the general therapeutic target based on fluid balance and/or central venous pressure monitoring, and a Foley catheter is routinely used in these patients to quantify urine output and avoid bladder rupture.

The use of hyperosmolar therapy in the management of pediatric severe TBI is a topic in which there was investigation shortly before the 2003 pediatric guidelines, notably studies focused on the use of hypertonic saline for raised ICP (3–5). However, since those guidelines, no new study on hyperosmolar therapy met the inclusion criteria for this guideline.

Mannitol

Mannitol is commonly used in the management of raised ICP in pediatric and adult TBI (6). In a practice survey in the United Kingdom in 2001, it was reported to be used in 70% of pediatric intensive care units, and recently, even in infants with severe TBI, mannitol was reported to be the second most common therapeutic intervention, surpassed only by intubation (7). Despite this fact, mannitol has not been subjected to controlled clinical trials vs. placebo, other osmolar agents, or other therapies in children. Most of the investigations on the use of mannitol have focused on the treatment of adults (8–21). Either children were excluded or the composition or outcome of the pediatric trial was not defined (8–24).

Mannitol can reduce ICP by two distinct mechanisms. Mannitol at 1 g/kg has been shown to reduce ICP by reducing blood viscosity. This effect is immediate and results from a viscosity-mediated reflex vasoconstriction (intact autoregulation), which allows cerebral blood flow to be maintained despite a reduced level of cerebral blood volume (17, 25–27). Thus, cerebral blood volume and ICP both decrease. The effect of mannitol administration on blood viscosity is rapid but transient (<75 mins) (17). Mannitol administration also reduces ICP by an osmotic effect, which develops more slowly (over 15–30 mins), as a result of the gradual movement of water from the brain parenchyma into the systemic circulation. The effect persists up to 6 hrs and requires an intact blood–brain barrier (28, 29). Mannitol may accumulate in injured brain regions (30), where a reverse osmotic shift may occur with fluid moving from the intravascular compartment into the brain parenchyma, possibly increasing ICP. This phenomenon has been suggested to occur when mannitol is used for extended periods of time (31). The gap between serum and cerebrospinal fluid (CSF) osmolality decreased below baseline in some adult patients treated with mannitol for >48–60 hrs (18). Mannitol possesses antioxidant effects (32), but the contribution of this mechanism to its overall efficacy is unclear.

Mannitol is excreted unchanged in urine, and a risk of the development of acute tubular necrosis and renal failure has been suggested with mannitol administration with serum osmolarity levels >320 mOsm in adults (33–35). However, the literature supporting this finding is limited in scope and was generated at a time when dehydration therapy was common. A euvolemic hyperosmolar state generally is targeted with contemporary care.

Hypertonic Saline

In the initial description in 1919 of the reduction in ICP by intravenous administration of hyperosmal agents, hypertonic saline was the agent used (1). Its use in the treatment of increased ICP, however, failed to gain clinical acceptance. Resurgence in interest in this treatment resulted from the report of Worthley et al (36), who described two cases in which hypertonic saline (small volumes of an extremely hypertonic solution, approximately 29% saline) reduced refractory ICP elevations. In the last decade, many have studied the use of small volume hypertonic saline in resuscitation

Table 1. Evidence table

Reference	Study Description	Data Class, Quality, and Reasons	Results and Conclusion
Studies from previous guidelines			
Fisher et al, 1992 (3)	Design: randomized controlled crossover trial N = 18 Age: mean 8.3 yrs (range, 0.6–14.5 yrs) Protocol: comparison of 3% saline (sodium 513 mEq/L, 1027 mOsm/L) and 0.9% saline (308 mOsm/L); doses of each agent were equal and ranged between 6.5 and 10 mL/kg in each patient Purpose: comparison of effect on ICP over 2 hrs exposure Outcome: ICP	Class II Moderate quality: randomization and allocation concealment methods not reported; crossover study lacking reporting on first-period comparison of baseline characteristics; small sample size	During the 2-hr trial, hypertonic saline was associated with a lower ICP and reduced need for additional interventions (thiopental and hyperventilation) to control ICP Serum sodium concentration increased approximately 7 mEq/L after 3% saline
Peterson et al, 2000 (4)	Design: retrospective chart review N = 68 Age: mean 7.8 ± 3.6 yrs Protocol: use of a continuous infusion of 3% hypertonic saline (513 mEq/L, 1027 mOsm/L) titrated to reduce ICP ≤ 20 mm Hg; doses of 0.1–1.0 mL·kg^{-1}·hr^{-1} resulting in mean daily dosages between approximately 11 and 27 mL·kg^{-1}·day^{-1} were used Purpose: assess effect of continuous infusion of hypertonic saline on acute and long-term outcome Outcome: ICP, 6-month Glasgow Outcome Scale score	Class III Poor quality: no control for confounders	Survival rate was higher than expected based on Trauma and Injury Severity Score (41 predicted, 58 actual) 53% had good outcome, 20% moderate, 10% severe, 0.1% vegetative, and 15% died; 3 died of uncontrolled ICP No patients developed renal failure Central pontine myelinolysis, subarachnoid hemorrhage, or rebound increases in ICP were not observed
Simma et al, 1998 (5)	Design: randomized controlled trial N = 35 Age: mean 87 months (± 42; range, 12–173 months) Protocol: comparison of hypertonic saline vs. lactated Ringer's solution Purpose: comparison of 1.7% hypertonic saline (sodium 268 mmol/L, 598 mOsm/L) vs. lactated Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) as a continuous infusion for maintenance fluid administration over a 3-day exposure Outcome: ICP, cerebral perfusion pressure, need for other interventions, fluid requirements, intensive care unit stay, survival rate	Class II Moderate quality: not blinded, insufficient power	There was no difference between groups in survival rate and length of hospital stay Patients treated with hypertonic saline required fewer interventions than those treated with lactated Ringer's solution to maintain ICP control ($p < .01$) The hypertonic saline treatment group had shorter length of intensive care unit stay ($p = .04$), shorter duration of mechanical ventilation ($p = .10$), and fewer complications than the lactated Ringer's-treated group ($p = .09$ for two or more complications, not significant, without p value reported for one complication)

ICP, intracranial pressure.

of hemorrhagic shock and polytrauma with or without TBI in experimental models and in adult humans (37–42). However, the recent National Institutes of Health-funded resuscitation outcomes consortium trial of hypertonic saline in TBI resuscitation in adults was stopped for futility after enrollment of 1073 patients (43).

Like mannitol, the penetration of sodium across the blood–brain barrier is low (39). Sodium thus shares both the favorable rheologic and osmolar gradient effects involved in the reduction in ICP by several theoretical beneficial effects including restoration of normal cellular resting membrane potential and cell volume (44, 45), stimulation of arterial na-

triuretic peptide release (46), inhibition of inflammation (39), and enhancement of cardiac output (47). Possible side effects of hypertonic saline include rebound in ICP, central pontine myelinolysis, renal impairment, subarachnoid hemorrhage, natriuresis, high urinary water losses, hyperchloremic acidosis, and masking of the development of diabetes insipidus (39).

Much higher levels of serum osmolarity (approximately 360 mOsm) may be tolerated in children when induced with hypertonic saline (4, 48) vs. mannitol, although one recent report suggested increases in serum creatinine in children treated with hypertonic saline when serum sodium concentration was allowed

to increase to >160 mmol/L (49). However, the recommendation of an upper safety threshold of 360 mOsm/L for hypertonic saline (in the 2003 pediatric TBI guidelines) (50) was viewed as the item that generated the greatest disagreement among 194 physicians treating pediatric patients with TBI in a recent survey (51).

In 14 adults with severe TBI, a study by Lescot et al (11) suggested important differences in the response of contused vs. noncontused brain tissue to hypertonic saline with reductions in the volume of noncontused brain but increases in the volume of contusions after treatment. Studies of regional effects of hyperosmolar therapy have not been carried out in pediatric TBI.

A second use of hypertonic saline is to treat hyponatremia resulting from cerebral salt wasting (CSW) if it develops in pediatric patients after TBI. Hyponatremia can result in cell swelling and seizures, both of which can compromise the injured brain (52). Hyponatremia in pediatric TBI can result from several mechanisms including CSW, the syndrome of inappropriate antidiuretic hormone secretion, sodium losses (from renal, CSF drainage, or other sources), or iatrogenic causes. It can manifest between 48 hrs and 11 days after injury, and the mechanistic underpinnings appear to involve increases in atrial natriuretic peptide (53, 54). Confirmation of the diagnosis is essential because management of CSW can differ greatly from the syndrome of inappropriate antidiuretic hormone or other causes of hyponatremia (55). The diagnosis is made by demonstrating hyponatremia and increased urine sodium concentration in the face of polyuria and hypovolemia (56). Dramatic examples of CSW in pediatric TBI show profound hyponatremia (serum sodium as low as 98 mmol/L) and marked polyuria ($\geq$15 mL/kg/hr) requiring large volumes of combinations of 0.9% and 3.0% saline to match urinary losses and address the hyponatremia (53, 54). Some have suggested to limit the rate of correction of serum sodium concentration to <12 mmol/L per day (50) related to concerns about myelinolysis. The optimal rate of correction of hyponatremia in a child with severe TBI is unclear.

IV. PROCESS

For this update, MEDLINE was searched from 1996 through 2010 (Appendix B for search strategy), and results were supplemented with literature recommended by peers or identified from reference lists. Of 35 potentially relevant studies, no new studies were added to the existing table and used as evidence for this topic.

V. SCIENTIFIC FOUNDATION

Two class II studies (3, 5) and one class III study (4) met the inclusion criteria for this topic and provide evidence to support the recommendations.

Hypertonic Saline

A study by Fisher et al (3) was carried out as a double-blind crossover study comparing 3% saline (513 mEq/L, 1027 mOsm/L) and 0.9% saline (154 mEq/L, 308 mOsm/L) in 18 children with severe TBI. Bolus doses of each agent were equal and ranged between 6.5 and 10 mL/kg. During the 2-hr trial, hypertonic saline use was associated with an approximate 7-mEq/L increase in serum sodium concentration, lower ICP, and reduced need for other interventions. Concomitant therapies used for patient management in this study included thiopental, dopamine, mannitol, and hyperventilation. CSF drainage was not used. As a result of design flaws (see evidence table; Table 1), the evidence from this study is class II.

A study by Simma et al (5) was carried out as a randomized controlled trial of 1.7% hypertonic saline (sodium 268 mmol/L, 598 mOsm/L) vs. lactated Ringer's solution (sodium 131 mmol/L, 277 mOsm/L) administered over the initial 3 days in 35 children with severe TBI. Patients treated with hypertonic saline required fewer interventions (including mannitol use) to control ICP than those treated with lactated Ringer's solution. Patients in the hypertonic saline treatment group also had a shorter length of pediatric intensive care unit stay ($p = .04$), shorter duration of mechanical ventilation ($p = .10$), and fewer complications than the lactated Ringer's-treated group ($p = .09$ for two or more complications, nonsignificant for one complication). As a result of design flaws and insufficient power (see evidence table), the evidence from this study is class II.

A study by Peterson et al (4) was a retrospective study on the use of a continuous infusion of 3% saline (sodium 513 mEq/L, 1027 mOsm/L) titrated to reduce ICP to $\leq$20 mm Hg in 68 infants and children with TBI. The mean daily doses of hypertonic saline over a 7-day period ranged between 11 and 27 mEq·kg^{-1}·day^{-1}. There was no control group. Three patients died of uncontrolled ICP, and mortality rate was lower than expected based on Trauma and Injury Severity Score categorization. No patient with a serum sodium concentration >180 mEq/L had a good outcome. No patients developed renal failure. Concomitant therapies included sedation, neuromuscular blockade, mannitol, hyperventilation, and barbiturates. CSF drainage was used in three children. The mean daily dose of mannitol was 1–2 g·kg^{-1}·day^{-1}. Rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage was not seen.

In the three papers cited as evidence for hypertonic saline, several limitations should be recognized. These studies originated from only two centers and there was limited use of ventriculostomy catheters and CSF drainage; instead, hyperventilation and barbiturates were used. Also, the children were enrolled between 16 and 26 yrs ago. Finally, the report by Simma et al (5) compared 1.7% hypertonic saline with lactated Ringer's solution, which is hypotonic. It should be recognized that the therapeutic window, safety profile, and optimal doses or osmolar levels of hypertonic saline remain to be determined.

VI. INFORMATION FROM OTHER SOURCES

A. Indications From Adult Guidelines

Based on an evidence table in the adult guidelines (57) (one class II and seven class III studies), mannitol was deemed to be effective for controlling increased ICP after severe TBI at doses ranging from 0.25 g/kg to 1 g/kg of body weight. Serum osmolarity <320 mOsm/L was recommended with mannitol use. Several key studies were cited. In the one class II study, Eisenberg et al (58) reported that a therapeutic regimen with mannitol was effective for ICP control in 78% of patients (n = 73). In addition, a study by Schwartz et al (21) was carried out as a randomized comparison of mannitol vs. barbiturates in 59 adults with severe TBI. Cerebral perfusion pressure was better maintained in the mannitol-treated group. Use of mannitol for TBI was subjected to Cochrane review, and no conclusion could be reached regarding efficacy vs. placebo or any other therapy (59). Two class III level studies of hypertonic saline were cited in the adult guidelines (57). The body of work on hypertonic saline in pediatric TBI showing beneficial effects on ICP was discussed as was the pediatric guidelines level III recommendation of continuous infusion of 3% saline. However, it was stated that limited data on hypertonic saline in adults with severe TBI did not allow for conclusions.

B. Information Not Included as Evidence

Mannitol. When constructing an evidence-based document on the use of hyperosmolar therapy to control ICP in pe-

diatric TBI, one must recognize that evidence supporting the use of mannitol in adults relies on studies that often included but did not explicitly define the proportion of children. Mannitol was used concomitantly to control ICP in the aforementioned studies of hypertonic saline in the evidence table. One must thus weigh the value of long-standing clinical acceptance and safety of a therapy (mannitol) that has no evidentiary support for its efficacy against a newer therapy (hypertonic saline) with less clinical experience but reasonably good performance in contemporary clinical trials (two class II studies for ICP and one class III study) (3–5, 48).

There is no study that met the inclusion criteria for this guideline, for either ICP or neurologic outcome, that documents efficacy of mannitol in infants and children with severe TBI. In several reports (29, 60–62), the specific effect of mannitol on ICP or outcome was not reported, the sample size was very small, or mannitol was shown to reduce ICP reliably, but the sample represented a mixture of adults and children (29).

Hypertonic Saline. One additional study was not included as evidence because it represented a prospective observational study with an inadequate sample size (n = 10). A study by Khanna et al (48) administered 3% saline (sodium 513 mEq/L, 1027 mOsm/L) on a sliding scale to maintain ICP <20 mm Hg in ten children with increased ICP resistant to conventional therapy. The maximal rate of increase in serum sodium was 15 $mEq \cdot L^{-1} \cdot day^{-1}$, and the maximal rate of decrease in serum sodium was 10 $mEq \cdot L^{-1} \cdot day^{-1}$. A reduction in ICP spikes and an increase in cerebral perfusion pressure were seen during treatment with 3% saline. The mean duration of treatment was 7.6 days, and the mean highest serum sodium concentration and osmolarity were 170.7 mEq/L and 364.8 mOsm/L, respectively. The maximum serum osmolarity in an individual patient was 431 mOsm/L. Sustained hypernatremia and hyperosmolarity were generally well tolerated in the children. Two patients, both with sepsis and/or multiple organ failure, developed acute renal failure. Both received continuous venovenous hemofiltration and recovered renal function. One patient died of uncontrolled intracranial hypertension. Despite its exclusion from the evidence table, the findings of this report are consistent with our recommendations supporting the use of 3% saline.

Hypertonic saline in pediatric patients with severe TBI is also used in the management of hyponatremia from CSW. No publications meeting the inclusion criteria for this guideline and addressing treatment of CSW were identified. Most reports suggest aggressive replacement of urine salt and water losses, but only case reports in pediatric TBI or case series with various diagnoses (including severe TBI) have been reported (53, 54, 63). The sodium replacement used ranged in dose between 0.1 and 2.4 mmol/kg/hr.

VII. SUMMARY

There is class II evidence supporting the use of hypertonic saline (3%) for the acute treatment of severe pediatric TBI associated with intracranial hypertension and class III evidence to support its use as a continuous infusion during the intensive care unit course. There is insufficient evidence to support or refute the use of mannitol, concentrations of hypertonic saline >3%, or other hyperosmolar agents for the treatment of severe pediatric TBI. One must thus weigh the value of longstanding clinical acceptance and safety of mannitol, which has no evidence to support its efficacy that met the inclusion criteria for this guideline, against hypertonic saline, for which there is less clinical experience but reasonably good performance in contemporary clinical trials.

VIII. KEY ISSUES FOR FUTURE INVESTIGATION

- Documentation of the effect of hyperosmolar therapy on ICP, cerebral perfusion pressure, and outcome in studies of infants and children.
- Studies comparing mannitol administration with hypertonic saline, particularly studies evaluating long-term outcome. This should include assessment of the combination of mannitol and hypertonic saline.
- Study of the use of hyperosmolar therapy vs. other therapies such as CSF drainage or barbiturates, including investigation of both control of ICP and long-term outcome.
- Studies as to whether or not hyperosmolar therapy can be effective in the setting of herniation.
- Study of the prevention of intracranial hypertension by continuous infusion of hypertonic saline vs. treatment in response to spikes and its impact on long-term outcome.
- Additional mechanistic studies in children with severe TBI examining issues such as the serum–CSF osmolar gap, regional effects of hyperosmolar therapies on contused vs. noncontused brain tissue using computed tomography or advanced magnetic resonance imaging, and their effects on other surrogate markers of brain injury such as blood flow, metabolism, and biomarkers.
- Studies of the use of hyperosmolar therapy across various etiologies (abusive vs. nonabusive) and head computed tomography injury patterns (contusion vs. diffuse injury) in children.
- Optimal dosing and better definitions of treatment threshold for the development of nephrotoxicity, rebound intracranial hypertension or hyponatremia, central pontine myelinolysis, and other complications with mannitol and hypertonic saline.
- Studies on the use of hypertonic saline in the management of CSW and other causes of hyponatremia in pediatric patients with TBI.

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