

# Chapter 11. Use of hyperosmolar therapy in the management of severe pediatric traumatic brain injury

## I. RECOMMENDATIONS

*A. Standards.* There are insufficient data to support a treatment standard for this topic.

*B. Guidelines.* There are insufficient data to support a treatment guideline for this topic.

*C. Options.* Hypertonic saline is effective for control of increased intracranial pressure (ICP) after severe head injury. 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 ICP <20 mm Hg should be used. Pending multicenter confirmation of effectiveness and lack of toxicity, caution should be exercised in widespread adoption of this therapy.

Mannitol is effective for control of increased ICP after severe traumatic brain injury (TBI). Effective bolus doses range from 0.25 g/kg of body weight to 1 g/kg of body weight.

Euvolemia should be maintained by fluid replacement. A Foley catheter is recommended in these patients to avoid bladder rupture.

Serum osmolality should be maintained below 320 mOsm/L with mannitol use, whereas a level of 360 mOsm/L appears to be tolerated with hypertonic saline, even when used in combination with mannitol.

The choice of mannitol or hypertonic saline as a first-line hyperosmolar agent should be left to the treating physician.

*D. Indications from Adult Guidelines.* Most of the pediatric options regarding mannitol, listed previously, mirror those stated in the adult guidelines (1). The adult guidelines only addressed the use of mannitol and not hypertonic saline. Mannitol administration achieved guideline status for the control of intracranial hypertension in the adult document.

## II. OVERVIEW

Mannitol is a cornerstone in the management of raised ICP in pediatric and adult TBI. In a recent survey that included 70% of the pediatric intensive care units in the United Kingdom (2), mannitol was used in pediatric TBI in all of the units. Despite this fact, mannitol has not been subjected to controlled clinical trials vs. placebo, other osmolar agents, or other mechanism-based therapies in children. Most of the early and recent study on the use of mannitol focused on the treatment of adults (3–15). Either children were excluded or the composition or outcome of the pediatric trial was not defined (3–18). In a key study, low mean ages were reported, indicating the inclusion of many adolescents and/or children (3). Studies in which the pediatric composition is clearly defined are discussed subsequently. The use of hyperosmolar therapy in the management of infants and children with severe TBI, however, is an area in which there has been much contemporary study. This work, discussed subsequently, has reported on the successful use of hypertonic saline to prevent or treat increased ICP in infants and children with severe TBI.

In constructing an evidence-based document on the use of hyperosmolar therapy in pediatric TBI, one must recognize that the guideline level evidence supporting the use of mannitol in adults relies on studies that often included but did not define the proportion of children. There is a large body of clinical experience using mannitol in infants and children but a limited number of pediatric studies (class III only) that document efficacy of mannitol. In contrast, several recent studies support the use of hypertonic saline in infants and children with severe TBI. However, the use of hypertonic saline has been limited to a small number of centers, and clinical experience with the use of hypertonic saline is limited compared with clinical experience with mannitol.

## III. PROCESS

We searched Medline and Healthstar from 1966 to 2001 by using the search strategy for this question (see Appendix A) and supplemented the results with literature recommended by peers or identified from reference lists. Of 46 potentially relevant studies, six were used as evidence for this question (Table 1).

## IV. SCIENTIFIC FOUNDATION

Intravenous administration of hyperosmolar agents was shown to reduce ICP early in the 20th century (19). Wise and Chater (20) introduced mannitol into clinical use in 1961. Despite widespread use of a number of osmolar agents (mannitol, urea, glycerol) up until the late 1970s (20), mannitol gradually replaced other hyperosmolar agents in the management of intracranial hypertension.

Mannitol can reduce ICP by two distinct mechanisms. Mannitol rapidly reduces ICP by reducing blood viscosity with a resultant decrease in blood vessel diameter (21–24). This occurs as a result of cerebral blood flow (CBF) autoregulation. The level of CBF is maintained, despite a reduction in blood viscosity, through reflex vasoconstriction. Thus, cerebral blood volume and ICP decrease. This mechanism is dependent on intact viscosity autoregulation of CBF, which is linked to blood pressure autoregulation of CBF (21, 23, 24). The effect of mannitol administration on blood viscosity is rapid but transient (<75 mins) (22). Mannitol administration also reduces ICP by an osmotic effect, which develops more slowly (over 15–30 mins), due to the gradual movement of water from parenchyma into the circulation. The effect persists up to 6 hrs and requires an intact blood-brain barrier (25, 26). Mannitol may accumulate in injured brain regions (27), where a reverse osmotic shift may occur—with fluid moving from the intravascular compartment into the brain parenchyma—

Table 1. Evidence table

References	Description of Study	Data Class	Conclusion
James (26), 1980	Retrospective study of 60 patients (1–73 yrs of age) treated with mannitol (0.18–2.5 g/kg per dose) for increased ICP (>25 mm Hg). In 18 patients (12 with TBI, mean age 14 yrs), bolus mannitol was followed by intravenous continuous infusion (6–100 hrs).	III	ICP decreased by $\geq 10\%$ after 116 of the 120 doses. Bolus doses $\geq 0.5$ g/kg produced an ICP reduction 97% of the time. Other concomitant therapies included dexamethasone, neuromuscular blockade and hyperventilation, barbiturates, and hypothermia, in refractory cases.
Miller et al. (35), 1993	Paired comparison of mannitol (0.5 g/kg) hypnotic (thiopentone 5 mg/kg and/or GABA 60 mg/kg) for refractory ICP >25 mm Hg or >30 mm Hg in 17 patients, including six children (3–17 yrs).	III	Mannitol was superior to hypnotic in five cases; hypnotic was superior to mannitol in three cases; both were effective in five cases; and neither was effective in four cases. Hypnotics were more effective in cases of diffuse TBI; mannitol was effective in focal TBI. Other concomitant therapies included neuromuscular blockade and sedation.
Fisher et al. (52), 1992	Double-blind crossover study comparing 3% saline (1025 mOsm/L) and 0.9% saline (308 mOsm/L) in 18 children with severe TBI. Doses of each agent were equal and ranged between 6.5 and 10 mL/kg in each patient.	III (class II for ICP)	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 pressure. Serum sodium concentration increased $\sim 7$ mEq/L after 3% saline.
Khanna et al. (34), 2000	Prospective study of administration of 3% saline (1025 mOsm/L) on a sliding scale to maintain ICP <20 mm Hg in ten children with raised ICP resistant to conventional therapy.	III (class II for ICP)	A significant reduction in ICP spikes and an increase in CPP were observed 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. Reversible renal failure developed in two patients. Sustained hypernatremia and hyperosmolarity were safely tolerated in pediatric patients.
Simma et al. (53), 1998	Open-randomized prospective study of hypertonic saline (598 mOsm/L) vs. lactated Ringer's administered over the initial 3 days in 35 consecutive children with severe TBI.	III (class II for ICP)	Patients treated with hypertonic saline required fewer interventions than those treated with lactated Ringer's to maintain ICP control. The hypertonic saline treatment group also had shorter length of ICU stay, shorter duration of mechanical ventilation, and fewer complications than the lactated Ringer's-treated group.
Peterson et al. (33), 2000	Retrospect study of the use of a continuous infusion of hypertonic saline (3%) titrated to reduce ICP $\leq 20$ mm Hg in 68 infants and children with closed head injury. Doses of 0.1–1.0 mL·kg <sup>-1</sup> ·hr <sup>-1</sup> resulting in mean daily dosages between $\sim 11$ and 27 mL·kg <sup>-1</sup> ·day <sup>-1</sup> were used. There was no control group.	III	Three patients died of uncontrolled ICP, and mortality rate was lower than expected based on trauma and injury severity score. No patients developed renal failure. Concomitant therapy included neuromuscular blockade, fentanyl, sedation, hyperventilation, and barbiturates. CSF drainage was rarely used. Hypertonic saline (3%) appeared safe. Central pontine myelinolysis, subarachnoid hemorrhage, or rebound increases in ICP were not observed.

ICP, intracranial pressure; TBI, traumatic brain injury; GABA,  $\gamma$ -aminobutyric acid; CPP, cerebral perfusion pressure; ICU, intensive care unit.

possibly increasing ICP. This phenomenon has been suggested to be most marked when mannitol is present in the circulation for extended periods of time, supporting the use of intermittent boluses (28). Mannitol possesses antioxidant effects (29), but the contribution of this mechanism to its overall efficacy remains 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 (30–32). 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. Much higher levels of serum osmolarity (365 mOsm) appear to be well tolerated in children when induced with hypertonic saline (33, 34). It is unclear if this threshold for complications with mannitol results from concomitant dehydration, the use of mannitol rather than hypertonic saline, or differences between

adults and children in their susceptibility to nephrotoxicity. As stated in the adult guidelines, few data exist supporting the concomitant use of diuretics and mannitol to reduce ICP (30).

James (26) carried out a retrospective study of 60 patients (1–73 yrs of age) treated with intravenous mannitol (0.18–2.5 g/kg per dose) for increased ICP (>25 mm Hg). Although cited as class III evidence in the adult guidelines (30), this study included a large number of children. After bolus dosing, ICP decreased by  $\geq 10\%$  for 116 of the 120 doses. Bolus doses of 0.25 g/kg, 0.5 g/kg, and  $\geq 1.0$  g/kg reduced ICP in 25%, 78%, and 98% of cases, respectively. This contrasts the work of Marshall et al. (4), who reported equivalence for doses between 0.25 and 1.0 g/kg in adults. The mean time for the return of ICP to baseline was 196 mins, with the shortest reduction being 40 mins. Other concomitant therapies used for patient management in this study included dexamethasone, neuromuscular blockade and hyperventilation, barbitu-

rates, and/or hypothermia, in refractory cases.

Miller et al. (35) reported a comparison of mannitol (0.5 g/kg) vs. a hypnotic (thiopentone 5 mg/kg and/or gamma hydroxyl butyrate 60 mg/kg) for refractory ICP (>25–30 mm Hg in 17 patients, including six children, 3–17 yrs of age). Response to therapy was defined in each patient in the study, allowing individual assessment of children. Mannitol was found to be superior to the hypnotic in five cases, the hypnotic was superior to mannitol in three cases, and both were effective in five cases. All of the children responded to either or both agents. Hypnotics were more effective in cases of diffuse TBI, whereas mannitol was effective in focal TBI, but the sample size in this study was limited.

In other studies with exclusively pediatric patients (36, 37), mannitol represented a key component of therapy or even defined a specific subgroup; however, the specific effect of mannitol on ICP or outcome was not reported. In contrast, Bruce and coworkers (38) sug-

gested restricted mannitol use in the 1980s and 1990s. Based in part on the suggested hyperemic response to TBI in children (39) and the possible increase in cerebral blood volume with mannitol administration (when pressure and viscosity autoregulation are defective), it was proposed that mannitol administration carried special risk in pediatric patients with diffuse cerebral swelling early after TBI. The authors recommended against the use of mannitol in the absence of a high probability of mass lesion. Since recent studies showed that early posttraumatic CBF generally is reduced, rather than increased, in infants and children (40), this hypothetical risk of mannitol administration in pediatric patients should not *a priori* dissuade clinicians from administration in the initial 48 hrs.

In the initial description in 1919 of the reduction in ICP by intravenous administration of hyperosmolar agents, hypertonic saline was the agent used (19). The use of hypertonic saline in the treatment of increased ICP, however, failed to gain clinical acceptance. Resurgence in interest in this treatment for raised ICP resulted from the report of Worthley et al. (41), who described two cases in which hypertonic saline (small volumes of an extremely hypertonic solution, ~29% saline) reduced refractory ICP elevations. One of those cases involved treatment of a 17-yr-old boy with TBI. In the last decade, numerous laboratories have studied the use of small volume hypertonic saline in resuscitation of hemorrhagic shock with or without TBI in experimental models and in humans (42–45). These studies are summarized in several recent reviews (46, 47).

Like mannitol, the penetration of sodium across the blood-brain barrier is low (46). Sodium thus shares both the favorable rheologic and osmolar gradient effects involved in the reduction in ICP by mannitol. Hypertonic saline also exhibits several theoretical beneficial effects including restoration of normal cellular resting membrane potential and cell volume (48, 49), stimulation of atrial natriuretic peptide release (50), inhibition of inflammation (reviewed in Ref. 46), and enhancement of cardiac output (51). Possible side effects of hypertonic saline include rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage (reviewed in Ref. 46).

Hypertonic saline has been the subject of considerable investigation with three class II studies (for ICP) and one class III

study in >130 pediatric patients with severe TBI. It should be pointed out that none of these studies produced class II data demonstrating a beneficial effect on long-term outcome.

Fisher et al. (52) carried out a double-blind crossover study comparing 3% saline and 0.9% saline 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, serum sodium concentration increased about 7 mEq/L, and hypertonic saline was associated with a lower ICP and reduced need for additional interventions. Concomitant therapies used for patient management in this study included thiopental, dopamine, mannitol, and hyperventilation. Cerebrospinal fluid drainage was not used.

Khanna et al. (34) reported a prospective study with administration of 3% saline (514 mEq/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·L<sup>-1</sup>·day<sup>-1</sup>, and the maximal rate of decrease in serum sodium was 10 mEq·L<sup>-1</sup>·day<sup>-1</sup>. 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 osmolality were 170.7 mEq/L and 364.8 mOsm/L, respectively. The maximum serum osmolality in an individual patient was 431 mOsm/L. Sustained hypernatremia and hyperosmolality 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.

Simma et al. (53) carried out an open randomized prospective study of hypertonic saline (598 mOsm/L) vs. lactated Ringer's solution 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 shorter length of intensive care unit stay, shorter duration of mechanical ventilation, and fewer complications than the lactated Ringer's-treated group.

Peterson et al. (33), reported a retrospective study on the use of a continuous infusion of 3% saline titrated to reduce ICP to ≤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 mL·kg<sup>-1</sup>·day<sup>-1</sup>. There was no control group, but only 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, but cerebrospinal fluid drainage was used in only three children. The mean daily dose of mannitol was 1–2 g·kg<sup>-1</sup>·day<sup>-1</sup>. Hypertonic saline appeared to be safe. Rebound in ICP, central pontine myelinolysis, and subarachnoid hemorrhage were not seen.

### Key Elements from the Adult Guidelines Relevant to Pediatric TBI

Based on an evidence table in the adult guidelines (30) (two class I and five class II studies), mannitol was deemed to be effective for controlling increased ICP after severe TBI, with effective doses ranging from 0.25 g/kg to 1 g/kg of body weight. Limited data in adults suggest that intermittent boluses may be more effective than a continuous infusion. Several key studies were cited. Schwartz et al. (3) carried out a randomized comparison of mannitol vs. barbiturates in 59 adults with severe TBI. Cerebral perfusion pressure was better maintained in the mannitol-treated group. Gabb et al. (54) and Rosner and Coley (11) reported similar effects. Fortune et al. (14) compared mannitol, ventriculostomy drainage, and hyperventilation to control ICP in 22 adults. Mannitol was the most effective. Use of mannitol for TBI recently was subjected to Cochrane review, and no conclusion could be reached regarding efficacy vs. placebo or any other therapy (55).

### V. SUMMARY

Two class III studies support the use of mannitol in pediatric TBI. Neither of these studies included exclusively pediatric patients. One must thus weigh the value of long-standing clinical acceptance and safety of a therapy (mannitol) that

**O**ne must thus weigh the value of long-standing clinical acceptance and safety of a therapy (mannitol) that has limited evidentiary support (two class III studies) of its efficacy against a newer therapy (hypertonic saline) with a limited clinical experience but reasonably good performance in contemporary clinical trials (three class II studies for intracranial pressure and one class III study).

has limited evidentiary support (two class III studies) of its efficacy against a newer therapy (hypertonic saline) with a limited clinical experience but reasonably good performance in contemporary clinical trials (three class II studies for ICP and one class III study). Bolus administration of mannitol or continuous infusion of 3% saline is supported. Thus, in pediatric TBI, there is guideline-level support for hypertonic saline to treat increased ICP but limited clinical experience. In contrast, there is only class III evidence for mannitol, despite long-standing clinical acceptance. Until one or more direct comparisons between these two therapies are carried out in infants and children with severe TBI, the choice of either mannitol or hypertonic saline in the management of pediatric TBI is a matter of physician preference.

## VI. KEY ISSUES FOR FUTURE INVESTIGATION

Additional investigation is needed comparing mannitol administration with hypertonic saline, particularly studies evaluating long-term neurologic outcome. Similarly, study of the use of more

aggressive hyperosmolar therapy with other second-tier therapies is needed, including investigation of the prevention of intracranial hypertension by continuous infusion of hypertonic saline vs. treatment in response to spikes. Documentation of the effect of mannitol in studies restricted to infants and children is needed. Similarly lacking are studies in victims of child abuse. Despite the overall quality of the investigations assessing the effect on ICP, the use of hypertonic saline has been limited to a small number of pediatric centers, and a number of factors involved in patient management, such as the use of concomitant therapies like cerebrospinal fluid drainage and the extent of use of specific second-tier therapies, varies greatly between centers. Additional study is needed. Optimal dosing and better definitions of treatment threshold are needed for the development of nephrotoxicity, rebound intracranial hypertension, central pontine myelinolysis, and other complications with mannitol and hypertonic saline.

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## APPENDIX: LITERATURE SEARCH STRATEGIES

### SEARCHED MEDLINE AND HEALTHSTAR FROM 1966 TO 2001

#### Chapter 11. Hyperosmolar Therapy

1. exp craniocerebral trauma/
2. head injur\$.tw.
3. brain injur\$.tw.
4. 1 or 2 or 3
5. hyperosmolar therapy.mp.
6. hyperosmolar treatment.mp.
7. Fluid therapy/ or “fluid therapy”.mp.
8. saline solution, hypertonic/
9. osmolar concentration/
10. 5 or 6 or 7 or 8 or 9
11. 4 and 10
12. limit 11 to (human and english language)
13. limit 12 to (infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
14. from 13 keep 1–13