Mannitol for Traumatic Brain Injury: Searching for the Evidence

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals*' Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane database of systematic reviews and a commentary by an emergency physician knowledgeable in the subject area. The source for this systematic review abstract is: Wakai A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2007;Issue 1:CD001049. DOI: 10.1002/14651858. The *Annals*' EBEM editors assisted in the preparation of the abstract of this Cochrane review, as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

The objectives of this review were to assess the effects of mannitol therapy on overall mortality after traumatic brain injury. Comparisons were made between mannitol and other intracranial pressure–lowering agents, different doses of mannitol, and mannitol administration during different stages after head injury.

DATA SOURCES

The authors searched the Cochrane Injuries Group Specialised Register, Cochrane Register of Controlled Trials (Central, Issue 1, 2006), MEDLINE (to April 2005), EMBASE (to March 2006), Science Citation Index (to March 2006), and Web-based trials register. The reviewers also checked the reference lists of all relevant articles, and a letter was sent to the first author of all relevant articles to ask for assistance in identifying any further trials that may have been published by them or other investigators.

Quasirandomized controlled trials examining the time or dose of mannitol administration in patients with clinically defined traumatic brain injury were included. Studies in which mannitol was given to the treatment group in any dose for any duration at any time within 8 weeks after injury were included. The control group received a nonmannitol intracranial pressure–lowering agent or placebo or standard care only. The reviewers also considered studies that guided mannitol administration according to clinical signs versus direct intracranial pressure measurements.

The primary outcome was all-cause mortality. Additional outcomes included disability and vegetative state.

DATA EXTRACTION AND ANALYSIS

Each reviewer independently determined trial eligibility and quality of study concealment of allocation and completed data extraction. Data were analyzed by comparing (1) intracranial pressure–directed treatment, (2) mannitol versus phenobarbital therapy, (3) mannitol versus hypertonic saline solution therapy, and (4) out-of-hospital administration of mannitol. Mortality data were expressed as relative risk of death, with associated 95% confidence intervals.

RESULTS

Four trials met the authors' inclusion criteria. One trial compared intracranial pressure–directed mannitol treatment versus treatment based on neurologic signs and physiologic indicators. Another trial compared mannitol versus phenobarbital treatment. The third trial compared mannitol with hypertonic saline solution. The last trial compared out-of-hospital mannitol treatment with placebo. All 4 studies were randomized; however, only 2 studies reported blinding (1 double- and 1 single-blinded). Three trials reported the method of allocation concealment. The status of heterogeneity and the reason for not pooling the results are not reported.

A summary of the results for each of the reviewed trials is presented in the Table.

CONCLUSIONS

According to the 4 trials included in this review, the authors concluded that there is insufficient evidence to make reliable recommendations on the use of mannitol in the management of patients with acute traumatic brain injury.

Mannitol therapy for raised intracranial pressure might be beneficial compared to pentobarbital treatment but could have a detrimental effect on mortality compared to hypertonic saline solution. Intracranial pressure–guided treatment also could be more beneficial compared to treatment directed by neurologic signs and physiologic indicators. There are insufficient data on the effectiveness of out-of-hospital administration of mannitol.

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Table. Summary of reported mortality data for mannitol therapy versus other agents, out-of-hospital administration of mannitol, and intracranial pressure–guided therapy.

Study	Study Population	Mortality, Relative Risk (95% CI)
Schwartz et al, 1984[1]	59 Patients with severe TBI (GCS score <8); mannitol vs phenobarbital	0.85 (0.52–1.38)
Vialet et al, 2003[2]	20 Patients with severe TBI (GCS score <8); 20% mannitol vs 7.5% hypertonic saline solution	1.25 (0.47–3.33)
Smith et al, 1986[3]	77 Patients with severe TBI (GCS score <8); ICP-guided therapy vs standard care	0.83 (0.47–1.46)
Sayre et al, 1996[4]	41 Patients with moderate to severe TBI (GCS score <11); out-of-hospital mannitol administration vs standard care	1.75 (0.48–6.38)
Harutjunyan et al, 2005[8]*	40 Patients at risk of increased ICP after TBI; 15% mannitol vs 7.2% hypertonic saline solution hydroxyethyl starch	1.46 (0.72–2.94)

CI, Confidence interval; *TBI,* traumatic brain injury; *GCS,* Glasgow Coma Scale; *ICP,* intracranial pressure.
*Not included in the systematic review.

COMMENTARY: CLINICAL IMPLICATION

Traumatic brain injury contributes to a substantial number of deaths and permanent disability annually. Of the 1.4 million individuals who sustain a traumatic brain injury each year in the United States, 235,000 are hospitalized and 50,000 die.[5] There are 2 types of brain insults that occur after traumatic brain injury. The primary insult is caused by the initial traumatic impact and cannot be reversed. The secondary insults occur as a result of worsening ischemia caused by increased intracranial pressure, brain edema, hypoxia, and so on. It is these secondary insults that emergency physicians have the potential to influence, and interventions that reduce them and improve outcomes are the subject of considerable interest.

After cerebral tissue damage, the normal cellular homeostasis in the brain is deranged. As a result of this change, tissue edema occurs within a closed space (the intracranial space), leading to increased intracranial pressure. Adequate brain perfusion depends on the cerebral perfusion pressure. Cerebral perfusion pressure is equal to the mean arterial pressure minus intracranial pressure; as intracranial pressure increases, the cerebral perfusion pressure decreases, leading to worsening of cerebral ischemia. Brain herniation ultimately follows if intracranial pressure remains uncontrolled. Therefore, interventions should be aimed at preventing systemic hypotension and at lowering intracranial pressure.[6]

A variety of interventions are routinely used in patients with traumatic brain injury, including positioning, hyperventilation, and transfusions. Mannitol, an osmotic agent that causes diuresis, is one potential adjunct in this approach to reduce intracranial pressure.[6] This agent reduces cell volume and initially causes a transient volume expansion that results in improved cerebral blood flow and oxygenation.[6] Ultimately, mannitol may also cause some adverse effects such as decreased total body water and sodium, decreased intracellular volume in the brain, and lower intracranial pressure.[7]

This systematic review used robust search methods to avoid publication bias and appropriate methods to reduce selection bias. The review identified only 4 trials that met the preselected inclusion criteria. From these, there is insufficient evidence guiding the dosing and timing of mannitol treatment for traumatic brain injury. Moreover, it is not clear whether mannitol is the osmotic agent of choice for controlling intracranial pressure in head-injured patients. As indicated by the presented data, hypertonic saline solution might be superior to mannitol in reducing the risk of mortality after traumatic brain injury. A recent randomized control trial that was not cited in this Cochrane review supports this statement. Harutjunyan et al[8] compared 15% mannitol to 7.2% hypertonic saline solution hydroxyethyl starch in reducing intracranial pressure (<15) in traumatic brain injury patients at risk of increased intracranial pressure after head trauma. This study found that hypertonic saline solution hydroxyethyl starch decreased intracranial pressure more than mannitol.[8] As far as the clinical effects on electrolyte concentration and osmolarity of the blood are concerned, mannitol and hypertonic saline solution were equally safe.

The most recent (2007) Brain Trauma Foundation recommendations[6] for the administration of mannitol in head trauma state that it should be given to patients with signs of transtentorial herniation or progressive neurologic deterioration in the absence of extracranial causes and if systolic blood pressure is greater than 90 mm Hg. They also recommend a dose of 0.25 to 1 g/kg. These are level II and III recommendations (which translate in this guideline into recommendations derived from class II and III evidence, respectively, meaning that the efficacy of the treatment is questionable). There is a clear need for large, pragmatic, randomized, controlled trials to determine the appropriate use of hyperosmolar agents in traumatic brain injury.

TAKE-HOME MESSAGE

Preventing severe disability and death after traumatic brain injury relies on preserving adequate cerebral blood flow. Mannitol has classically been used to lower intracranial pressure for this purpose. Unfortunately, there is little evidence to support the dosing and timing of this medication. In addition, other accessible agents may eventually be found to be superior to mannitol. There is a need for large randomized trials in this area, and until such time as they are conducted, emergency physicians should follow guidelines such as those developed by the Brain Trauma Foundation,[6] which caution the use of mannitol in patients at risk for hypotension. In addition, emergency physicians should be aware that other agents, such as hypertonic saline solution, may replace mannitol in the future.

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EBEM TEACHING POINT

Included Study Quality Assessment

In evidence-based medicine, clinical decisions are made on the basis of research-driven evidence, rather than on expert opinion or clinical experience alone. However, poor-quality studies subject to various biases may provide exaggerated or overestimated effect sizes. Obviously, this issue will significantly affect the clinical recommendations based on practice developed from such studies.

Systematic reviews represent a rigorous method of assembling scientific evidence to answer focused questions, usually relating to issues of treatment or diagnosis. The unique aspect of systematic reviews is that they are designed to minimize bias, such as selection and publication biases. This methodological effort is also applied when included studies are evaluated; high-quality systematic reviews typically assess the methodological quality of the included studies and evaluate the strength of the evidence proposed by them.

The quality components most frequently analyzed in trials included in systematic reviews are randomization, allocation concealment, blinding, and losses to follow-up. However, controversies exist on what components of quality assessment to include, how to evaluate them, what tools (scales or checklists) to use, and how to use the results once tabulated. Although there are several established methods for quality assessment of randomized controlled trials, the lack of consistency of study classification and lack of clearly defined and agreed-on criteria present a challenge to the authors and readers of systematic reviews. Finally, not only are the approaches to quality assessment of primary studies by systematic reviews heterogeneous and lacking in consensus but also more than 50% of systematic reviews do not specify the methods with which the quality assessments are performed.[9] In this Cochrane review, the authors evaluated randomization, blinding, and allocation concealment in the included trials; however, the methodology of quality assessment was not discussed in detail.

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