

Mannitol for acute traumatic brain injury (Review)

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[Intervention Review]

Mannitol for acute traumatic brain injury

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ABSTRACT

Background

Mannitol is sometimes dramatically effective in reversing acute brain swelling, but its effectiveness in the on-going management of severe head injury remains open to question. There is evidence that, in prolonged dosage, mannitol may pass from the blood into the brain, where it might cause reverse osmotic shifts that increase intracranial pressure.

Objectives

To assess the effects of different mannitol therapy regimens, of mannitol compared to other intracranial pressure (ICP) lowering agents, and to quantify the effectiveness of mannitol administration given at other stages following acute traumatic brain injury.

Search strategy

The review drew on the search strategy for the Injuries Group as a whole. We checked reference lists of trials and review articles, and contacted authors of trials.

Selection criteria

Randomised trials of mannitol, in patients with acute traumatic brain injury of any severity. The comparison group could be placebo-controlled, no drug, different dose, or different drug. Trials where the intervention was started more than eight weeks after injury, and cross-over trials were excluded.

Data collection and analysis

The reviewers independently rated quality of allocation concealment and extracted the data. Relative risks (RR) and 95% confidence intervals (CI) were calculated for each trial on an intention to treat basis.

Main results

Overall there were few eligible trials. In the pre-operative management of patients with acute intracranial haemorrhage the administration of high-dose mannitol resulted in reduced mortality (RR=0.55; 95%CI 0.36, 0.84) and reduced death and severe disability (RR=0.58; 95%CI 0.45, 0.74) when compared with conventional-dose mannitol. One trial compared ICP-directed therapy to 'standard care' (RR for death = 0.83; 95%CI 0.47,1.46). One trial compared mannitol to pentobarbital (RR for death = 0.85; 95% CI 0.52, 1.38). No trials compared mannitol to other ICP-lowering agents. One trial tested the effectiveness of pre-hospital administration of mannitol against placebo (RR for death=1.75; 95% CI 0.48, 6.38).

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Authors' conclusions

High-dose mannitol appears to be preferable to conventional-dose mannitol in the pre-operative management of patients with acute intracranial haematomas. However, there is little evidence about the use of mannitol as a continuous infusion in patients with raised intracranial pressure in patients who do not have an operable intracranial haematoma. Mannitol therapy for raised ICP may have a beneficial effect on mortality when compared to pentobarbital treatment. ICP-directed treatment shows a small beneficial effect compared to treatment directed by neurological signs and physiological indicators. There are insufficient data on the effectiveness of pre-hospital administration of mannitol to preclude either a harmful or a beneficial effect on mortality.

PLAIN LANGUAGE SUMMARY

Synopsis

There is evidence that mannitol can improve outcomes after severe head injury, but more research is needed on how best to use it, as it can also cause problems

Severe head injury can lead to brain swelling. As space inside the skull is limited, this can cause dangerous pressure on the brain (raised intracranial pressure - ICP). Mannitol reverses the swelling at first, but there is evidence that its prolonged use can eventually worsen the pressure. The review found there is not enough evidence from trials to show how best to use mannitol for people with head injury. For people with raised ICP, mannitol may reduce the chances of death more than pentobarbital (a barbiturate drug). There is not enough evidence to show whether giving mannitol before head-injured people arrive in hospital can improve outcomes.

BACKGROUND

Mannitol is widely used in the control of raised intracranial pressure following brain injury. A 1995 survey of the critical care management of head-injured patients in the United States showed that 83% of centres used osmotic diuretics in more than half of severely head-injured patients (Ghajar 1995), a survey in the United Kingdom showed that 100% of neurosurgical centres used mannitol in the treatment of raised intracranial pressure (Jeevaratnam 1996; Matta 1996). The effectiveness of mannitol for head-injured patients in a critical condition is considered to be well established, without the need for randomised controlled trials.

For other patients, the Brain Trauma Foundation Guidelines Task force of the American Association of Neurological Surgeons and Joint Section in Neurotrauma and Critical Care (Task Force 1995) recommend that mannitol be used only if the patient has signs of raised ICP or deteriorating neurological status as, in these circumstances, adverse effects are most likely to be outweighed by therapeutic benefit. Nevertheless, the guidelines acknowledge that this is an area of considerable clinical uncertainty. There is uncertainty over the optimal treatment regimen, over the effectiveness of mannitol as compared to other ICP-lowering agents and over the usefulness of mannitol given at other stages following head injury, for example in the pre-hospital setting, prior to volume resuscitation.

We conducted a systematic review of randomised controlled trials that compared different mannitol treatment regimens, or compared mannitol to alternative interventions or placebo, at any stage in the acute management of head injury.

OBJECTIVES

1. To compare the effectiveness of mannitol therapy when given in different doses and for different durations.
2. To quantify the effectiveness of mannitol compared to other ICP-lowering agents.
3. To quantify the effectiveness of mannitol administration given at other stages following head injury.

RESULTS

One trial compared ICP-directed therapy to 'standard care', in which mannitol therapy was directed by neurological signs (Smith 1986). The study was randomised and allocation concealment was by the use of sealed envelopes. For ICP-directed treatment compared to treatment based on neurological signs, the RR for death

was 0.83 (95% CI 0.47,1.46); this trial demonstrated a similar effect for death or severe disability (RR=0.88; 95%CI 0.55,1.38).

One trial compared mannitol to pentobarbital (Schwartz 1984). This trial was randomised and single blind. Only patients with known raised ICP were included. For mannitol compared to pentobarbital in the treatment of patients with raised ICP, the RR for death was 0.85 (95%CI 0.52,1.38) . No trials identified that compared mannitol to other ICP-lowering agents.

The effectiveness of pre-hospital administration of mannitol against placebo was investigated in Sayre 1996. This study was randomised and allocation concealment was through pharmacy prepared blinded solutions. For pre-hospital infusion of mannitol compared to placebo in patients with head injury and multiple trauma, the RR for death was 1.75 (95%CI 0.48, 6.38).

Two trials (Cruz 2001; Cruz 2002) compared high-dose and conventional-dose mannitol in the pre-operative acute care of patients with intracranial haemorrhages. In both studies there were fewer deaths in the high-dose mannitol group, with a pooled relative risk of death of 0.55 (95%CI 0.36, 0.84). In both trials, the proportion of patients who were dead or severely disabled at six months was lower in the high-dose mannitol group, with a pooled relative risk of death or severe disability of 0.58 (95%CI 0.45, 0.74).

DISCUSSION

There were few eligible trials of mannitol therapy in head-injured patients.

ICP-directed treatment showed a small beneficial effect on mortality when compared to treatment directed according to neurological signs and physiological indicators (RR=0.83; 95%CI 0.47, 1.46). The method of allocation concealment in this study was adequate to prevent fore-knowledge of treatment, and was unlikely to have led to bias. Owing to small patient numbers, the effect measure is imprecise. It must be noted that in this study the ICP-directed protocol initiated mannitol only when the ICP rose to above 25mmHg and therefore these results cannot be extrapolated to ICP-directed protocols which initiate mannitol therapy at a lower level.

Pre-operative administration of high-dose mannitol results in reduced mortality and morbidity compared with conventional-dose mannitol. However, in both of the eligible trials, allocation concealment was not described and the possibility of selection bias is open to question.

Mannitol therapy may have a beneficial effect on mortality when compared to pentobarbital therapy. However, the single trial which tested this (Schwartz 1984) yielded an imprecise effect measure, which also may be compatible with no difference, or a beneficial effect of pentobarbital. The trial was testing an initial treatment of mannitol compared to pentobarbital as some patients later received the alternate therapy if the allocated therapy failed to control ICP. There were no trials of mannitol compared to other ICP-lowering interventions.

The single trial which compared pre-hospital administration of mannitol to placebo showed an increase in mortality amongst the mannitol-treated patients (RR=1.75; 95%CI 0.48, 6.38). The estimate yielded by this trial is imprecise owing to the small sample size; the effect measure also may be compatible with no difference, or a beneficial effect of pre-hospital administration of mannitol.

AUTHORS' CONCLUSIONS

Implications for practice

High-dose mannitol appears to be preferable to conventional-dose mannitol in the pre-operative management of patients with acute intracranial haematomas. However, there is little evidence about the use of mannitol as a continuous infusion in patients with raised intracranial pressure in patients who do not have an operable intracranial haematoma.

Implications for research

There are many unanswered questions regarding the optimal use of mannitol following acute traumatic head injury. The widespread current use of mannitol, and lack of clarity regarding optimal administration present an ideal opportunity for the conduct of randomised controlled trials.

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* Indicates the major publication for the study

SOURCES OF SUPPORT

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INDEX TERMS

Medical Subject Headings (MeSH)

Brain Injuries [complications; *drug therapy]; Diuretics, Osmotic [*therapeutic use]; Intracranial Hypertension [etiology; *prevention & control]; Mannitol [*therapeutic use]; Randomized Controlled Trials

MeSH check words

Humans