

Mannitol for Resuscitation in Acute Head Injury: Effects on Cerebral Perfusion and Osmolality

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ABSTRACT

Objective: To review the use of mannitol during initial resuscitation following traumatic brain injury and to determine the effects of mannitol on subsequent management following resuscitation and commencement of neuromonitoring.

Methods: A retrospective audit of patients presenting to a tertiary hospital with severe head injury (Glasgow coma score ≤ 8). Patients were divided into two groups according to whether they received mannitol during initial resuscitation. Measurements included initial plasma osmolality, cerebral perfusion pressure (CPP), intracranial pressure (ICP) and jugular venous saturation (SjO₂).

Results: Forty patients were identified: 19 received mannitol prior to admission to the intensive care unit. Of these, only 2 patients fulfilled acceptable neurological indications for mannitol. The mannitol patients received a mean dose of 237 mL of 20% mannitol (47.4g) and had significantly higher initial osmolalities than the patients who did not receive mannitol (293 vs 279 mosmol/L, $p < 0.05$). No significant difference in initial CPP, ICP, or SjO₂ was identified. The mannitol patients were further subdivided into two 12-month periods (1994 and 1995). A dose related, significant difference in initial osmolalities was identified (140 vs 344 mL and 284 vs 304 mosmol/L respectively, $p < 0.05$). The latter group ($n = 9$) had significantly lower initial CPPs (72 vs 59 mmHg) and higher ICPs (14 vs 18 mmHg). No difference in 6 month Glasgow outcome scores between groups was demonstrated.

Conclusions: The empirical overuse of mannitol is common. Mannitol did not exert any beneficial effect on CPP, ICP or SjO₂ in the initial phases of management. Larger doses (i.e. $> 20g$) are associated with increased osmolality which may reduce CPP. (**Critical Care and Resuscitation 2000; 2: 14-18**)

Key Words: Mannitol, traumatic brain injury, resuscitation, cerebral perfusion, osmolality, jugular bulb saturation

Mannitol has an established place in the clinical management of traumatic brain injury, which has probably developed more from habit rather than science. The theoretical benefits of the acute use of mannitol in treating intracranial hypertension in neurotrauma relate to its effect on reducing viscosity¹ and resultant increase in cerebral blood flow²⁻⁴ (CBF) rather than specific reduction in intracranial pressure (ICP) due to cerebral

osmotic dehydration.^{5,6} The injudicious use of mannitol may result in hyperosmolal states, hypovolaemia and hyperviscosity which may negate these beneficial effects.^{6,7} The induction of an inappropriate osmotic diuresis during initial resuscitation of the traumatised patient with head injury may complicate subsequent fluid and electrolyte management during the period when patients undergo emergency surgery and

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subsequent transfer to the intensive care unit. Recently, guidelines have been published outlining evidence-based indications for the use of mannitol in traumatic brain injury.⁸

The aim of this study was to review the use of mannitol used during resuscitation in head injured patients presenting to a tertiary referral trauma centre and to determine the effects of mannitol on subsequent management in the intensive care unit (ICU) following resuscitation and commencement of neuromonitoring.

MATERIALS AND METHODS

Over a two year period, patients admitted to the trauma resuscitation bay of a tertiary referral trauma centre with severe closed head injury and who were subsequently admitted to the ICU were retrospectively studied. Severe head injury was defined as a presenting Glasgow coma score (GCS) ≤ 8 following non-surgical resuscitation. The indications for, and dose of mannitol administered during resuscitation were recorded.

Upon arrival in the ICU plasma osmolality, ICP, cerebral perfusion pressure (CPP) and jugular venous oxygen saturation (SjO₂) were measured following placement of monitors. Intracranial pressure (ICP) was measured by intraparenchymal strain gauge monitor (Codman Microsensor[®]) placed through a frontal burr hole. The CPP was defined as the difference between mean arterial pressure and ICP. Mean arterial pressure was measured directly using intra-arterial cannulation. All pressures were zero referenced to the aortic root with the patient at 30° head elevation. Jugular venous saturation was measured by fiberoptic catheter (Abbott, Oximetrix 3[®]), with the internal jugular venous cannulation performed according to a previously published protocol.⁹

Outcome was assessed at six months following injury by physicians unaware of the data and grouped according to Glasgow outcome scores,¹⁰ identifying groups according to the classification of good recovery and moderate disability, severe disability and vegetative state, and death.

Statistical analysis was used using a commercial software package (Excel, Microsoft Corporation[®]) using paired Student's *t* test, where statistical significance was accepted at a $p < 0.05$. Permission to perform this case note audit was obtained from the institutional ethics committee of the Royal Adelaide hospital.

RESULTS

Over the two year period, 40 patients were identified. There was no difference in demographics or median presenting GCS between these two groups. (Table 1)

In 17 of the 19 patients who received mannitol, empirical reasons such as closed head injury or traumatic coma were cited as the indications for its use. Two patients had clinical features suggesting intracranial hypertension which were regarded as acceptable reasons to receive mannitol. These features included lateralising signs (e.g. ipsilateral pupillary mydriasis) in addition to a witnessed neurological deterioration in an appropriately resuscitated patient.

Table 1. Patient demographic data

	received mannitol n = 19	no mannitol n = 21
Age (mean years)27		29
Gender (M:F)	16:3	17:7
Initial GCS	4	5

Patients in the mannitol group received a mean dose of 237 mL of 20% mannitol (47.4g) resulting in significantly higher initial plasma osmolalities compared with the group that did not receive mannitol (293 vs 279 mosmol/L, $p < 0.05$). No significant differences in initial measured ICP, CPP and SjO₂ between the mannitol group and group that did not receive mannitol were demonstrated (Figure 1).

The mannitol patients were further subdivided into two 12 month periods (i.e. 1994 and 1995). A dose related, significant difference in initial osmolalities was identified between the two groups (144 vs 344 mL of 20% mannitol and 284 vs 304 mosmol/L respectively, $p < 0.05$). The latter group (i.e. those who received the larger mannitol dose) had a significantly lower initial CPP (72 vs 59 mmHg) and higher ICP (14 vs 18 mmHg, $p < 0.01$) (Figure 2).

Outcomes as defined by Glasgow outcome score at six months were not significantly different between the two groups (Figure 3).

DISCUSSION

The place of osmotherapy in acute head injury has been reappraised in the light of evidence based medical guidelines.⁸ Evidence in support of osmotherapy relates primarily to beneficial rheological effects and improved CBF which may or may not reduce ICP.¹⁻⁶ Mannitol will only work in areas of the brain that have an intact blood brain barrier and requires an adequate perfusion and osmotic gradient to exert its effect. There is no evidence that induced dehydration in any form improves outcome in neurotrauma.^{8,11,12}

The beneficial effects of mannitol are not dose related, although there is a causal relationship between

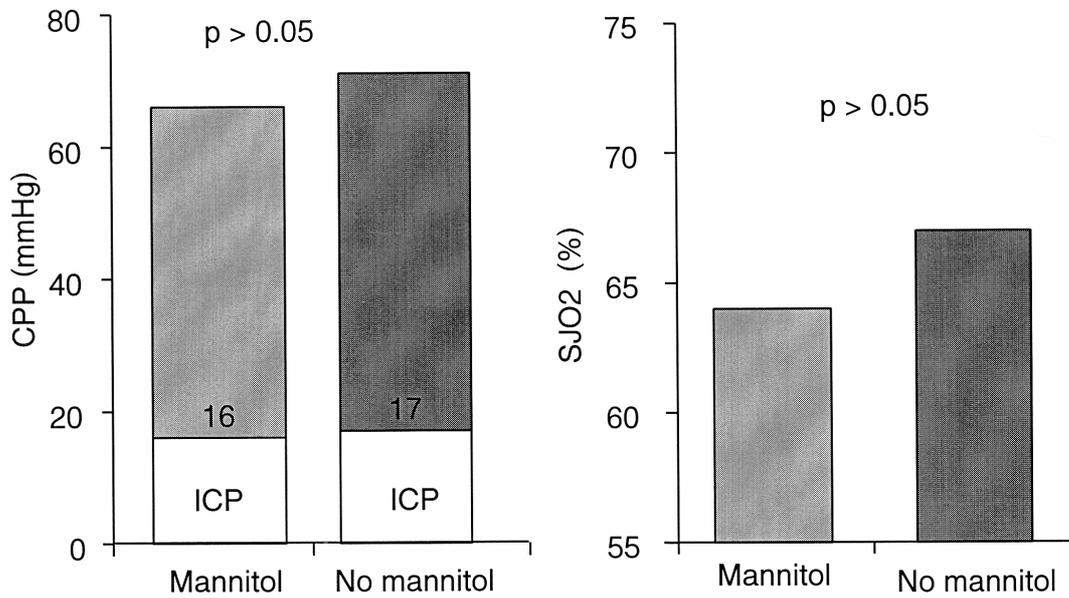


Figure 1. Effects on initial cerebral perfusion pressure (CPP) and jugular venous saturations (SjO₂) between patients who received mannitol during resuscitation and those who did not. Intracranial pressure (ICP) is recorded in the CPP column. No statistically significant difference was identified ($p > 0.05$).

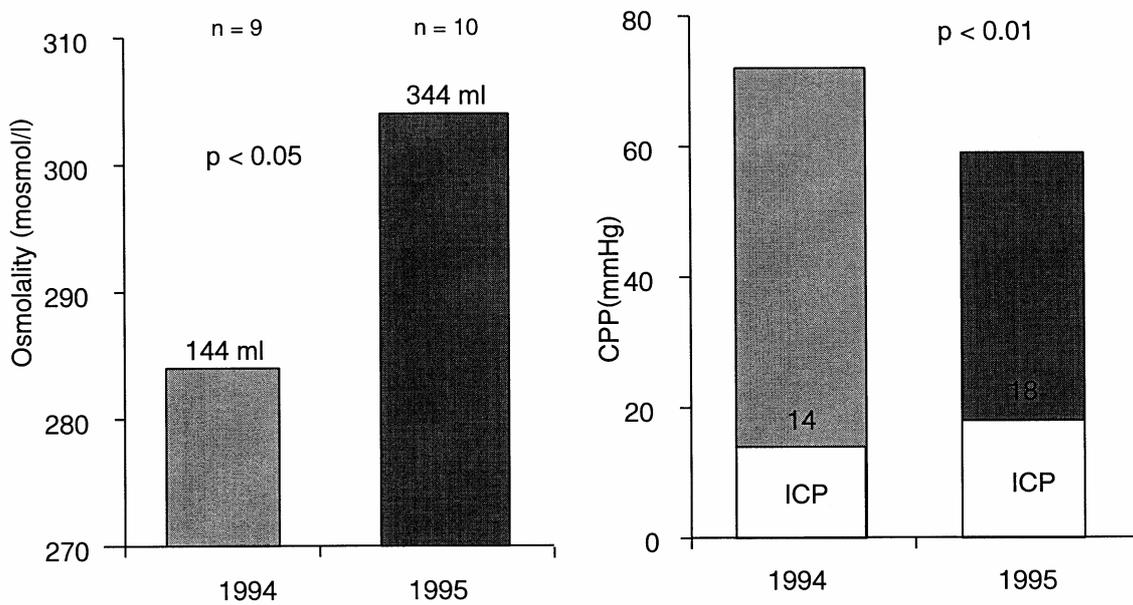


Figure 2. Subset analysis of the group who received mannitol. There was a significant difference in the average mannitol dose (left hand panel) administered during the two 12 month periods causing a significant difference in plasma osmolality. The effects of this on initial CPP and ICP are shown in the right hand panel.

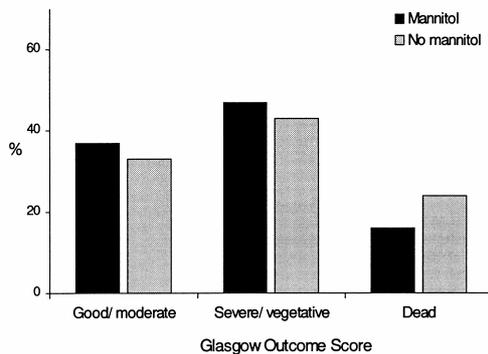


Figure 3. The mean Glasgow outcome scores measured at six months according to whether patients received mannitol during the pre-intensive care unit period. No statistical difference was detected.

dose and toxicity.⁷ The dose of mannitol required to achieve an improvement in CBF and reduction in ICP is often less than the frequently quoted 0.5 - 1 g/kg.¹³ One hundred mL of a 20% solution of mannitol (20g) will usually suffice for most adult patients.^{1,2}

Current guidelines recommend osmotherapy during resuscitation only in euvoalaemic, normotensive and oxygenated patients with clinical signs of intracranial hypertension with herniation. In patients without clinical signs of raised ICP, mannitol should be withheld until resuscitation and neuroimaging is completed, and/or neuromonitoring is in situ.⁸ It is well established that any intervention directed at controlling intracranial hypertension should not compromise cerebral perfusion, particularly during the first 48 hours where cerebral oligoemia is common following injury.¹⁴ Cerebral hypoperfusion following hypotension is associated independently with an adverse outcome.¹⁵

Despite these recommendations and guidelines, the use of mannitol during resuscitation of head injury remains variable. This audit of practice highlights the frequent use of empirical mannitol during resuscitation that resulted in initial increased plasma osmolalities and no discernible beneficial effect on clinically measured neurophysiological parameters or outcome.

On review of the patients who received mannitol for clinical evidence of raised ICP, it was interesting to note that once these patients were intubated, ventilated and resuscitated, the pupillary signs normalised. Furthermore, patients who received the larger doses of mannitol had persistent hypovolaemia, inappropriate polyuria and hyperosmolal states that required vigorous fluid resuscitation well into the first 48 hours after arriving in the ICU with one patient developing transient renal failure as a result. On a more detailed review, 6 of these patients were given 500 mL (i.e. 100g) of mannitol. Whether this was deliberate, or as a result of the infusion accidentally running to completion, is not

known. The resulting, possibly inadvertent, hyperosmolal states may reduce the potential beneficial use of mannitol in controlling intracranial hypertension as the plasma osmolality approaches 300 - 320 mosmol/L beyond which further osmotherapy has reduced efficacy.¹⁶ In addition, large doses of mannitol induce an osmolal gap, so that in order to monitor the effect on osmolality, frequent measured plasma osmolalities are required.

The level of evidence outlined in this study is not sufficient to make a strong scientific statement, due to the retrospective design of the study and small numbers used in the subset analysis. However, there are some conclusions that may be deduced from these observations. Despite evidence and guidelines to the contrary, the empirical overuse of osmotherapy is common during resuscitation of head injured patients. In accordance with previous studies and published guidelines, no beneficial effects from mannitol on cerebral perfusion or control of intracranial pressure were demonstrated. Larger doses are associated with an increased osmolality that may reduce cerebral perfusion.

Furthermore, two recommendations for the use of mannitol during resuscitation of head injured patients may be made. Firstly, clear guidelines about indications for osmotherapy, in accordance with existing data should be instituted to reduce the empirical use of mannitol. Secondly, solutions of mannitol should be changed from 500 mL to 100 mL bags to prevent accidental overdosing during resuscitation. Alternatively, smaller volumes of hypertonic saline may provide the same degree of theoretical benefit without posing the potential risk of hyperosmolality and potential cerebral hypoperfusion.^{16,17}

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