Evaluation of mannitol as an osmotherapeutic agent in traumatic brain injuries by measuring serum osmolality

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ABSTRACT

BACKGROUND

The effectiveness of mannitol as an osmotherapeutic agent has never been subjected to a controlled clinical trial against placebo. Excessive use of mannitol in brain trauma patients can result in hyperosmolar states, hypernatremia and renal failure. This prospective study was conducted to evaluate the institutional protocol of using mannitol and assess its effects on serum osmolality.

METHOD

Thirty patients with brain injury were included in the study. All the patients were given 100 mL of 20% mannitol three times a day as bolus infusion over 20–30 minutes. Serum osmolality was measured at 12 hourly intervals using Fiske osmometer. Mannitol administration was stopped whenever serum osmolality reached ≥ 320 mOsmol/Kg H₂O. The total dose and duration of mannitol used to reach target osmolality of ≥ 320 mOsmol/Kg H₂O was recorded.

RESULTS

On 33% of all occasions, the patients had a serum osmolality which was in excess of the desired values (i.e. ≥ 320 mOsmol/Kg H₂O). This indicates that the standard protocol of administering 20% mannitol 100 mL three times a day for more than 48 hours is perhaps excessive.

CONCLUSION

The mannitol therapy should be guided by 12 hourly measurement of serum osmolality. Mannitol should be used for 48 hours only if facilities for measuring serum osmolality are not available.

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Key Words: head injury; mannitol; osmotherapy

INTRODUCTION

Traumatic brain injuries (TBI) are a major public health problem especially among the young age group and is the sixth leading cause of death in India.¹ It seems that regardless of the intervention strategy chosen, the outcome from TBI remains bleak.² About 50–70% of severe brain injuries are found to have raised intracranial pressure (ICP). Reduction of raised ICP is the mainstay of treatment in moderate to severe TBI. Osmotically active agents, such as mannitol are widely used for reduction of intracranial pressure in TBI. However, the effectiveness of mannitol as an osmotherapeutic agent remains open to question as it has never been subjected to a controlled clinical trial against placebo. Although there is much data regarding its mechanism of action, there are few studies that validate different regimes of mannitol usage. Excessive use of mannitol in critically injured brain trauma patients can result in hyperosmolar states, severe dehydration, hypernatremia, and renal failure. In this study mannitol was administered as per institutional protocol and further guided by measurement of serum osmolality and serum sodium. The aim of the study was to assess whether the institutional protocol of using mannitol in brain trauma patients is rational or not.

MATERIALS AND METHOD

After Institutional Ethics Committee's approval, this prospective study was performed on 30 patients of traumatic brain injury admitted to intensive care unit of a tertiary care hospital of Armed Forces. Informed consent was obtained from patient's kin before study enrolment. Patients of either sex with moderate (Glasgow Coma Score [GCS] 9–12) to severe brain injury (GCS 3–8) who were administered mannitol were included in the study. Patients younger than 16 years of age, and pregnant patients were excluded from the study. Immediately after admission to the intensive care unit (ICU), all patients were kept head end elevated by $>30^\circ$ and placed on routine monitoring with pulse oximetry, non-invasive blood pressure, and electrocardiogram. Patients were clinically examined and initial GCS, pupillary signs, and neurological deficit was noted. Noncontrasted head computed tomography scan (NCCT head) was performed after stabilising vital signs.

All the patients were administered 20% mannitol 100 mL three times a day irrespective of age and weight as bolus infusion over 20–30 minutes for 5–7 days as per institutional protocol.

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However, mannitol administration was stopped as and when serum osmolality ≥ 320 mOsmol/Kg H_2O or serum sodium ≥ 145 mEq/L was recorded. Trachea was intubated and patients were ventilated using synchronised intermittent modes of ventilation (SIMV-Volume control) if GCS ≤ 8 on admission. Serum osmolality was measured with Fiske's 210 microsample osmometer on admission and recorded as baseline and thereafter at 12 hourly intervals. At the same time serum electrolytes, blood sugar was measured twice a day; blood urea and serum creatinine was measured daily.

Any episode of serum osmolality reaching >320 mOsmol/Kg H_2O was regarded as protocol violation. Counts were made of the number of times osmolality crossed the desired value of 320 mOsmol/Kg H_2O and the number of times serum sodium crossed the target of 145 mEq/L. If the protocol resulted in more than 10% excess, then it was taken as an indication that the protocol followed resulted in an excess of patients put at risk of hypernatremia and hyperosmolality, with no corresponding benefits in terms of reduction of ICP. The total dose and duration of mannitol used to reach target osmolality of 320 mOsmol/Kg H_2O was also noted down. Each reading of serum osmolality and serum sodium was treated as a separate data point for the purpose of statistical acquisition. Simple statistical methods were used for data analysis. Some of the patients received frusemide in addition to mannitol on the discretion of neurosurgeon. A note was made of this point.

The intracranial pressure was monitored by inserting intraventricular catheter (Phoenix fifth ventricle intraventricular catheter set) in patients with severe head injury. The catheter was connected to the pressure transducer and continuous monitoring of ICP was carried out using multifunction monitor. Intracranial pressure waveform was recorded as ballistic waveform temporally associated with the systemic blood pressure. Usually a good pressure tracing is recognised, having a pulse pressure of 3–7 mmHg. But we recorded only mean pressure for the purpose of this study. In addition the baseline of ICP waveform fluctuates with breathing whenever the intracranial compliance falls.

Around 1–2 mL of cerebrospinal fluid (CSF) was drained through intraventricular catheter to reduce ICP below 20 mmHg, whenever ICP more than 25 mmHg was found. While using Phoenix fifth ventricle intraventricular catheter set, whenever CSF is drained, the ICP is regulated by the height of the collection bag in relation to the foramen of Monroe. Care was taken to ensure that the bag was securely placed. The intraventricular catheter was removed after 3 days or earlier if it was found to be blocked. Mannitol therapy was not guided based on ICP monitoring.

RESULTS

Thirty patients were enrolled in this study. Most patients were in the age group of 16–45 years. Age wise distribution is shown in Table 1. There were 27 males and three female patients. In 25 patients (83.25%) road traffic accidents was the cause of injury, fall caused injuries in four patients (13.32%), and one patient (3.33%) suffered injury due to boxing. The type of injuries

suffered is shown in Table 2. Most of the patients had other associated injuries, commonly fractures of long bones that were not taken into account for the study purpose. Ten patients (33.33%) suffered severe injuries (GCS ≤ 8) and 20 patients (66.66%) suffered moderate injuries (GCS 9–12). Fifteen patients (50%) required endotracheal intubation and mechanical ventilation. Patients with severe injuries were intubated on admission and five patients with moderate injury required tracheal intubation, either they were restless or needed surgical interventions. During mechanical ventilation effort was made to maintain partial pressure of carbon dioxide in arterial blood ($PaCO_2$) between 32 and 34 mmHg and partial pressure of oxygen in arterial blood (PaO_2) > 90 mmHg.

Six patients (20%) required surgical intervention for drainage of extradural/subdural haematoma and/or craniectomy. In these patients intraventricular catheter was inserted in operation theatre under direct vision. Five patients (15.65%) were transferred from other hospitals after few days of injury. These patients were also included in the study. We were, however, not aware how much mannitol these patients received before admission to our ICU. Four patients (13.32%) were administered frusemide either before transfer to our hospital or after admission to our ICU. The patient's characteristics, average number of day's mannitol administered, average serum osmolality and sodium recorded and outcome of patients in terms of survival is shown in Table 3.

On analysis of the data, it was found that there were total 60 data points. On 33% of all occasions, the patients had a serum osmolality which was in excess of the desired values (i.e. > 320 mOsmol/Kg H_2O ; Figure 1). But only on 10% of all occasions serum sodium was in excess of desired value (i.e. > 145 mEq/L; Figure 2).

ICP catheter was removed after three days. In one patient ICP catheter got blocked and CSF became blood stained hence excluded from the study. Only two patients had high ICP > 25 mmHg, which was treated by aspirating 1–2 mL of CSF. No complications

Table 1 Age wise distribution of study cases.

Age (yr)	Number of patients (%)
16–30	14 (46.66%)
31–45	12 (40%)
46–60	4 (13.33%)
Total	30

Table 2 Types of brain injuries.

Types of injuries	Number of patients
Diffuse axonal injury with cerebral oedema	10
Extradural haematoma	5
Subdural haematoma with/without cerebral contusion	5
Subarachnoid haemorrhage	5
Fracture cranial fossa with/without CSF leak	5

Table 3 Average serum osmolality, serum sodium and outcome.

Number of patients	Mean age (yr)	Average number of days mannitol received	Average serum osmolality (mOsmol/Kg H ₂ O)	Average serum sodium (mEq/L)	Outcome
24	31.5 (18–50)	2.16 (1–4)	328.75 (289–420)	142.58 (136–155)	Survived
6	34.33 (27–48)	3.33 (1–5)	365.00 (327–453)	146.00 (144–149)	Died

Figure 1 Overall serum osmolality values. **Figure 2** Overall serum sodium values.

were noticed due to ICP catheter insertion. Tip of the catheter removed was sent for culture and sensitivity testing. None of the catheter had shown any growth. We did not find any relationship between ICP and mannitol dosing. However, ICP was reduced significantly on aspirating small volume of CSF. Overall mortality was 30% with six patients dead.

DISCUSSION

Hyperosmolar therapy is a key intervention for the management of cerebral edema and raised ICP after traumatic brain injury (TBI). It is particularly indicated for acute rise in ICP as it has a rapid effect. Mannitol, an osmotic diuretic is commonly employed and the immediate efficacy is likely to result from a plasma-expanding effect and improved blood rheology due to reduction in haematocrit. However repeated administration of mannitol can result in renal dysfunction caused by hyperosmolality and dehydration.³ Fiske's osmometer used in the study for measuring osmolality, uses the technique of freezing-point depression to measure osmolality. Osmolality is the osmols of solute particles per kilogram of pure solvent and is usually expressed in mOsmol/Kg H₂O. Osmometers measure the number of solute particles irrespective of molecular weight or ionic charge. On the other hand osmolarity is osmols of solute particles per litre of solution.

The present study indicates that the current protocol of using 20% mannitol 100mL three times a day for 5–7 days is excessive.

In this study we have observed that even one day of 20% mannitol 100mL three times a day administration can result in osmolality >320 mOsmol/Kg H₂O, this was noticed in 16.66% of our patients. Hypernatremia may occur in the long term as a result of hyperosmolar state, but is often compensated by an increase in anti-diuretic hormone. Probably that is the reason in our study we found 33% incidence of hyperosmolality and only 10% incidence of hypernatremia. This is in line with current recommendations of the brain trauma foundation, which states that mannitol has not been adequately tested with respect to placebo and is level II and III recommendation.⁴ The Cochrane review could find no evidence to support the use of mannitol in head-injured patients.⁵ Various studies have been published suggesting that administration of high dose mannitol (1.4g/Kg) is associated with improved outcome compared with normal dose (0.7g/Kg) after traumatic brain injury. However, serious questions have been raised about the conduct of these studies.⁶

Whenever hyperosmolar state occurs because of overzealous use of mannitol and frusemide the return to normal osmolality should approximately match the duration of the hyperosmolar state. Otherwise rebound cerebral oedema may occur if a hyperosmolar state is reversed too quickly. While correcting hyperosmolality cautious use of isotonic (0.9%) saline is safer than hypotonic fluids such as 5% dextrose solution. In this study mannitol administration was guided on the basis of serum osmolality. Though ICP monitoring was performed in 10 patients, ICP was not used to guide osmotherapy. Though we did not calculate the cerebral perfusion pressure (CPP) specifically, it was presumed that if patient was not hypotensive and ICP was not raised then CPP was maintained.

Ventricular catheters have been considered a gold standard for ICP monitoring; however, they are the most invasive of alternatives and it is associated with higher risk of infection and intracranial haemorrhage.⁷ Parenchymal monitors have some advantages over ventriculostomy catheter but they cannot be used to drain CSF and control ICP.⁸ The active management of ICP guided by ICP monitoring has not shown a consistent benefit in outcome. In our study only a very small number of patients were subjected to ICP monitoring. Therefore we cannot make any recommendation about the role of ICP monitoring in brain trauma patients.

Hypertonic saline is increasingly used as an alternative to mannitol. It is available in a range of concentrations from 1.7% to 29.2% and numerous regimens have been described, making it difficult to draw conclusions about the optimal dose or concentration required to control ICP. The favourable effect on cerebral

water content after administration of hypertonic saline has been demonstrated by a reduction in lateral displacement of the brain on serial CT scans in patients with head injury.⁹ Furthermore, hypertonic saline has proven efficacious in controlling ICP in patients' refractory to mannitol.¹⁰ Viallet et al compared mannitol to hypertonic saline and found that mannitol may have detrimental effect on mortality when compared to hyper-tonic saline.¹¹ Horn et al in their study highlighted the frequent use of empirical mannitol during resuscitation that resulted in increased plasma osmolality and no beneficial effects as far as outcome is concerned.¹² They did not find any beneficial effects on CPP, ICP or jugular venous oximetry (SjVO₂) in the initial phases of management. On the contrary larger doses (i.e. >20g) are associated with increased osmolality which may reduce CPP.¹² However, as per the Brain Trauma Foundation Guidelines 2007 there are no strong evidences to recommended use, concentration, and method of administration of hypertonic saline in brain trauma.⁴

This study has its own limitations. The sample size was small and we did not compare mannitol against placebo. Some of the patients were transferred from other centres and some were administered frusemide on the discretion of neurosurgeon. These two factors could act as confounders and affect overall results. A fixed dose of mannitol was advised to all the patients irrespective of age or body weight. We cannot suggest ideal dose of mannitol in terms of gram per kilogram body weight. Patients were followed for a week only. We cannot comment on long-term neurological outcome or mortality. But despite its limitation this study suggests that mannitol should be used for first 48 hours with caution if facility for measuring serum osmolality is not available.

Intellectual Contributions of Authors

Study concept: Gp Capt RM Sharma

Drafting and statistical analysis: Gp Capt RM Sharma

Statistical analysis: Col R Setlur

Technical support: Col MN Swamy

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CONFLICTS OF INTEREST

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