Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries

Clinical article

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Object. The purpose of this study was to compare the effects of mannitol and hypertonic saline in doses of similar osmotic burden for the treatment of intracranial hypertension in patients with severe traumatic brain injury.

Methods. The authors used an alternating treatment protocol to compare the effect of hypertonic saline with that of mannitol given for episodes of increased intracranial pressure in patients treated for severe head injury at their hospital during 2006–2008. Standard guidelines for the management of severe traumatic brain injury were followed. Elevated intracranial pressure (ICP) was treated either with mannitol or hypertonic saline. Doses of similar osmotic burden (mannitol 20%, 2 ml/kg, infused over 20 minutes, or saline 15%, 0.42 ml/kg, administered as a bolus via a central venous catheter) were given alternately to the individual patient with severe brain injury during episodes of increased pressure. The dependent variables were the extent and duration of reduction of increased ICP. The choice of agent for treatment of the initial hypertensive event was determined on a randomized basis; treatment was alternated for every subsequent event in each individual patient. Reduction of ICP and duration of action were recorded after each event. Results obtained after mannitol administration were statistically compared with those obtained after hypertonic saline administration.

Results. Data pertaining to 199 hypertensive events in 29 patients were collected. The mean decrease in ICP obtained with mannitol was 7.96 mm Hg and that obtained with hypertonic saline was 8.43 mm Hg (p = 0.586, equal variances assumed). The mean duration of effect was 3 hours 33 minutes for mannitol and 4 hours 17 minutes for hypertonic saline (p = 0.40, equal variances assumed).

Conclusions. No difference between the 2 medications could be found with respect to the extent of reduction of ICP or duration of action. (DOI: 10.3171/2010.5.JNS091685)

Key Words • mannitol • hypertonic saline • trauma • brain injury • intracranial hypertension • osmotic burden

Hypertonic saline has been used to treat intracranial hypertension in patients with severe head injuries. Its results are comparable to those of mannitol, which is the standard treatment in cases of severe head injury with intracranial hypertension. A direct comparison of the 2 agents using the same osmotic burden has not been performed until now. A recent review article for the use of hyperosmolar agents in neurosurgical practice, published in Neurosurgery, states that “There is only one head-to-head comparison of mannitol and HS [hypertonic saline] bolus therapy for TBI … Analysis of the authors’ study is complicated by the fact that different osmolar loads of HS and mannitol were used.”

Our purpose is to compare mannitol with hypertonic saline, using the same osmotic burden, in the treatment of intracranial hypertension in patients with severe head injury. This kind of comparison is necessary because the main mechanism of action of both agents is increased osmolality of the blood, which causes collection of fluid from the brain toward the vessels.
Methods

All patients treated for severe head injury (GCS score ≤ 8) during the time period 2006–2008 in our hospital, except those in brain death or shock, were included in the study. We used an alternating treatment protocol to compare the effects of the 2 osmotic agents, comparing results for distinct increased ICP events rather than comparing different treatments given to separate groups of patients. Thus our analysis focused on comparison of treatment results for hypertensive events treated with mannitol versus events treated with hypertonic saline.

In general, we treated our patients according to the Brain Trauma Foundation Guidelines. Hypotension and hypoxia were treated. Those who had an indication for intracranial surgery were treated surgically. Intracranial pressure and cerebral tissue oxygenation monitoring were initiated. Analgesics, hypnotics (midazolam or propofol), sedatives, and muscle relaxants were used as usual, and the patient’s head was elevated at 30°.

Normocapnia was maintained on the first day after injury. Thereafter, our protocol allowed for the use of hypocapnia (PaCO2 30–35 mm Hg) in case of intracranial hypertension.

Vasoconstrictive agents (noradrenaline) could be used to maintain the cerebral perfusion pressure above 60 mm Hg. No corticosteroid agents were used for the treatment of the head injury. Antiepileptic drugs (mainly diphenylhydantoin) were used as long as the patient was in critical condition and were then used therapeutically only if necessary for seizure control.

Based on theoretical calculation and measurements using an osmometer, we determined that mannitol 20% administered at a dosage of 2 ml/kg has the same osmotic burden as hypertonic saline 15% administered at 0.42 ml/kg.

Mannitol was infused over 20 minutes, while hypertonic saline was administered as a bolus via a central venous catheter.

When the ICP was greater than 20 mm Hg for 5 minutes, we gave one of the two medications, with the selection determined on a random basis. The randomization was performed by the first author (N.S.), who was not in charge of the patient’s care. Thereafter the choice of osmotic agent was alternated for each successive intracranial hypertension event. That is, patients who were initially treated with mannitol would be treated with hypertonic saline during the next hypertensive event, and those initially treated with hypertonic saline would be treated with mannitol during the next event. Alternation of treatments was continued for successive events.

The use of the osmotic agents was continued as long as the ICP was elevated above 20 mm Hg or until osmolality reached 320 mOsm/L.

In each department, one physician gave the medication and another performed the measurements of its duration of action and the change in ICP, each was blinded to the actions of the other.

We used the Codman ICP monitoring system, with the catheter placed inside the brain parenchyma. We continuously measured 2 parameters: the maximum reduction of the ICP in mm Hg and the duration of the effect, measured from the point at which the ICP started to diminish and including the entire period during which it remained under 20 mm Hg.

If the ICP continued to be pathologically elevated, hyperventilation, blood pressure elevation, barbiturate coma, or decompressive craniotomy could be used. In such cases, events were paired in such a way that results obtained under similar conditions were compared.

Blood pressure, heart rate, ICP, cerebral perfusion pressure, and cerebral tissue oxygenation (PtO2) were continually measured with the aid of the Licox (Integra) brain tissue oxygen monitoring system.

We also measured the hematocrit, PaO2, PaCO2, glucose, creatinine, osmolality, sodium, potassium, pH, prothrombin time, partial thromboplastin time, and platelet count. Finally, we studied the GCS and Glasgow Outcome Scale scores of our patients, their Apache II scores, and their length of stay in the intensive care unit.

We used paired t-test statistical analysis for both our dependent variables as well as the paired samples correlation index. Statistical power was assessed by the Lehr formula and the Altman nomogram. Our study design was reviewed and approved by the ethics committee of our hospital.

Results

All patients who met our criteria were included. Two patients were in shock and were not included in the series, because they only received hypertonic saline. In 5 patients, the ICP remained under 20 mm Hg.

Twenty-nine patients were included in the study, and these patients had a total of 199 hypertensive events. The mean GCS score in these patients was 5.4. Their ages ranged from 14 to 82 years (mean 36 years). Ten patients underwent surgery for treatment of acute subdural hematoma, 2 for treatment of epidural hematoma, 2 for treatment of traumatic intracerebral hematoma and contusions, and 2 for decompressive craniotomy. In 13 cases, no surgery was performed for the treatment of intracranial pathology. There was no significant difference between the 2 groups of events in all other clinical or laboratory parameters that were measured.

The mean decrease in ICP was 7.96 mm Hg (SD 5.79 mm Hg, SEM 0.65 mm Hg) with mannitol treatment and 8.43 mm Hg (SD 6.65 mm Hg, SEM 0.54 mm Hg) with hypertonic saline with equal variances assumed, for a difference of −0.47 mm Hg (95% CI −2.15 to 1.22 mm Hg, t = −0.547, 2-tailed significance p = 0.586, with equal variances assumed). The paired-sample correlation (for 82 paired samples) was 0.265 (p = 0.018).

The mean duration of effect was 3 hours 33 minutes for mannitol (SEM 31 minutes) and 4 hours 17 minutes (SEM 50 minutes) for hypertonic saline, a relative reduction of 44 minutes (assuming equal variances, 95% CI −2 hours 29 minutes to 1 hour 1 minute, t = −0.84, 2-tailed significance p = 0.40). The paired-sample correlation between the 2 variables for duration of action was 0.234, which is statistically significant (p = 0.034). Thus, there was no statistically significant difference in the reduction of ICP or the duration of the effect achieved with the 2 medications.
Mannitol versus hypertonic saline in brain injury

Outcome at 3 months, as measured by the Glasgow Outcome Scale, was death in 7 patients, vegetative state in 1, bad in 1, moderate in 8, and good in 11. One death was attributed to pulmonary embolism.

One patient developed hyperosmolarity and electrolyte disturbances after mannitol administration and another after hypertonic saline treatment, necessitating temporary withdrawal of the treatment in both cases.

Discussion

Hyperosmolar therapy is standard practice in most neurosurgical centers worldwide. Neurotrauma guidelines currently recommend 20% mannitol infused over 20 minutes for trauma patients with elevated ICP.

Hypertonic saline entered the trauma literature as a potentially more effective alternative to normal saline in the initial resuscitation of patients with hemorrhagic shock. A survival benefit has been shown with its use for patients with both hemorrhagic shock and TBI, but such patients were excluded from our study.

Head-to-head comparison of mannitol and hypertonic saline therapy for the treatment of TBI in human patients has been reported by only a few investigators. In the study of Viallet et al., patients in the mannitol group experienced more frequent intracranial hypertension episodes, but no difference in clinical outcome could be demonstrated between the 2 groups.

According to Harutjunyan et al., hypertonic saline is more effective than mannitol in the treatment of intracranial hypertension. Part of the advantage was due to the fact that hypertonic saline increases the systemic blood pressure and consequently increases cerebral perfusion pressure. They suggest that the rest of the advantage might be explained by local osmotic effects, because there were no clinically relevant differences in hemodynamic or chemistry parameters.

Mainly on the basis of the study by Harutjunyan et al. and 3 others, a recent Cochrane review concludes that “mannitol therapy for raised ICP may have a beneficial effect on mortality when compared to pentobarbital treatment, but may have a detrimental effect on mortality when compared to hypertonic saline.”

We undertook this study because it would be important for those treating patients with TBI to know if saline is more effective than mannitol in the treatment of intracranial hypertension. Our study has 2 key differences from the previous ones: 1) we used events and not patients as our units of statistical analysis, to avoid stratification; and 2) we used the same osmotic load for both medications. The design of our study is very strong for the purpose of answering the question of differences between the 2 agents in the treatment of intracranial hypertension, because it requires no stratification and allows the use of the paired t-test.

Our results show that hypertonic saline and mannitol, when used in the same osmotic burden, are equivalent in the treatment of intracranial hypertension in severe brain injury. The mean difference between the 2 treatments with respect to reduction of ICP was only 0.47 mm Hg. If we want to exclude a Type 2 error (false negative result) with a power of 80%, Lehr’s formula gives the following calculation for the number of pairs of events necessary (n): n = 16/(sd)² where, for the paired t-test, sd = standardized difference equals twice the minimal accepted difference that is clinically important/standard deviation of differences in response. If we assume a minimal accepted difference of 2 mm Hg and as we have a standard deviation of about 6 mm Hg, our research has an 80% power of detecting such a difference. In post hoc power analysis, by using the obtained sample size and effect size of 0.47 mm Hg, assuming the effect size in the sample is equal to the effect size in the population, we should need about 680 pairs of events to achieve an 80% power. The usefulness of retrospective techniques in power analysis is controversial.

Our results are in accordance with the main pathophysiological mechanism of action of the 2 agents in intracranial hypertension, which is the same. The beneficial effect of hypertonic saline on systemic blood pressure is not likely to have been a factor in our study, because we have excluded patients remaining in shock after resuscitation, where this effect would be important. On the other hand, even transient reductions of cerebral perfusion pressure were treated in this study according to the standard guidelines, including use of vasoconstrictive agents.

There was no difference between the 2 groups of events in all other clinical or laboratory parameters measured. The complications were also similar.

The very strong correlation between the 2 groups of events (with respect to both the effect of the 2 osmotic agents and their duration of action) also supports a very similar mechanism of action.

The use of events instead of patients does not allow us to draw conclusions about complication rates, morbidity, and mortality, because every individual patient received both medications alternately. A prospective study with stratification of patients and not events is necessary for this purpose, even if it seems improbable that statistically significant results will be found, when no difference in intracranial hypertension treatment exists.

Osmotic effects are not the only possible mechanism of action of the 2 medications. Lowered blood viscosity is a similar, well-known mechanism of action.

In experimental studies, there is a significant reduction in calpain and apoptosis activity and in the neuroinflammatory response in animals receiving hypertonic saline. Although mannitol proved to significantly decrease the neuroinflammatory response and calpain activity, it did not affect apoptosis, and its effect was significantly less than that of hypertonic saline.

In another experimental study, mannitol, but not hypertonic saline, decreased the deleteriously increased levels of malondialdehyde, catalase, and glutathione peroxide after head trauma.

It is therefore likely that in special environments mannitol or hypertonic saline can have a beneficial effect compared with the other, independent of their osmotic action. In everyday clinical practice and as far as we are concerned with the acute effects of the 2 osmotic agents on ICP, however, it is unlikely that there would be a clinically important difference.
Conclusions

By using the rest of the standard guidelines for the management of severe TBI, we have compared mannitol with hypertonic saline for the treatment of intracranial hypertension. No difference between the 2 medications could be found with respect to the effect on ICP or the duration of action.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sakellaridis, Vlachos. Acquisition of data: Pavlou, Karatzas, Chroni, Vlachos, Chatzopoulos, Dimopoulou, Kelesis, Karauli. Analysis and interpretation of data: Sakellaridis, Pavlou, Karatzas, Chroni. Drafting the article: Sakellaridis. Critically revising the article: Pavlou, Karatzas, Chroni, Vlachos. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Sakellaridis. Administrative/technical/material support: Vlachos.

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