Effect of Equiosmolar Solutions of Mannitol versus Hypertonic Saline on Intraoperative Brain Relaxation and Electrolyte Balance


Background: The purpose of the study was to compare the effect of equiosmolar solutions of mannitol and hypertonic saline (HS) on brain relaxation and electrolyte balance.

Methods: After institutional review board approval and informed consent, patients with American Society of Anesthesiologists physical status II–IV, scheduled to undergo craniotomy for various brain pathologies, were enrolled into this prospective, randomized, double-blind study. Patients received 5 ml/kg 20% mannitol (n = 20) or 3% HS (n = 20). Partial pressure of carbon dioxide in arterial blood was maintained at 35–40 mmHg, and central venous pressure was maintained at 5 mmHg or greater. Hemodynamic variables, fluid balance, blood gases, electrolytes, lactate, and osmolality (blood, cerebrospinal fluid, urine) were measured at 0, 15, 30, and 60 min and 6 h after infusion; arteriovenous difference of oxygen, glucose, and lactate were calculated. The surgeon assessed brain relaxation on a four-point scale (1 = relaxed, 2 = satisfactory, 3 = firm, 4 = bulging). Appropriate statistical tests were used for comparison; P < 0.05 was considered significant.

Results: There was no difference in brain relaxation (mannitol = 2, HS = 2 points; P = 0.8) or cerebral arteriovenous oxygen and lactate difference between HS and mannitol groups. Urine output with mannitol was higher than with HS (P < 0.03) and was associated with higher blood lactate over time (P < 0.001, compared with HS). Cerebrospinal fluid osmolality increased at 6 h in both groups (P < 0.05, compared with baseline). HS caused an increase in sodium in cerebrospinal fluid over time (P < 0.001, compared with mannitol).

Conclusion: Mannitol and HS cause an increase in cerebrospinal fluid osmolality, and are associated with similar brain relaxation scores and arteriovenous oxygen and lactate difference during craniotomy.

The hyperosmolar solutions mannitol and hypertonic saline (HS) have both been used for treatment of elevated intracranial pressure in critical care units. The hyperosmolarity of mannitol and HS, combined with the impermeability of the blood–brain barrier (BBB) to mannitol and sodium, provides favorable conditions to move water from the brain to the intravascular compartment. However, the differential effects of these agents on clinical conditions in patients undergoing neurosurgery have not been compared in a rigorous fashion.

Mannitol is considered the standard and is recommended as a first-choice hyperosmotic agent for treatment of increased intracranial pressure in North America and Europe.†,‡ However, a number of prospective clinical trials comparing the effects of mannitol and HS on intracranial pressure have suggested that HS is at least as effective as, if not better than, mannitol in the treatment of intracranial hypertension.†,‡ Two prospective studies comparing mannitol and HS in patients undergoing elective neurosurgery used different osmolar loads of the two agents and reported similar brain conditions between groups.†,‡ Although the results of these studies provided valuable clinical data, they did not address the question of comparative efficacy between HS and mannitol because the study designs did not control for equiosmolar concentrations of the two solutions.

The purpose of our study was to compare the effect of equiosmolar equivolemic solutions of mannitol and HS on intraoperative brain relaxation as the primary endpoint of the study, and brain oxygen metabolism and electrolyte changes as secondary endpoints, in patients undergoing craniotomy for elective and urgent neurosurgical procedures.

Materials and Methods

After institutional review board (University of Washington, Seattle, WA) approval and written informed consent, 40 adult patients were enrolled into this prospec-
tive, randomized, double-blinded study. We included patients scheduled to undergo craniotomy for various neurosurgical pathologies, requiring intraoperative lumbar cerebrospinal fluid (CSF) drainage. Exclusion criteria were age younger than 18 yr, American Society of Anesthesiologists (ASA) physical status V, preoperative hypotension or hypotension (serum Na <130 or >150 mEq/l), treatment with any hyperosmotic fluid (mannitol or HS) in the previous 24 h, or history of congestive heart failure or kidney disease. After randomization using sealed envelopes, patients were assigned to receive 5 ml/kg of either 20% mannitol (1 g/kg, osmolality = 1,098 mOsm/l, mannitol group) or 3% HS (osmolality = 1,024 mOsm/l; HS group) for intraoperative brain relaxation. Both fluids were administered over 15 min using an infusion pump with the type of fluid blinded to both surgeon and anesthesiologist.

General anesthesia was induced with propofol or sodium thiopental, along with opiate and muscle relaxant as determined by the attending anesthesiologist. In addition to standard anesthesia monitors including invasive arterial and central venous pressure (CVP), a retrograde jugular bulb catheter (16 GA, 133 mm, BD Angiocath™; Becton Dickinson Infusion Therapy Systems Inc., Sandy, UT) was inserted as previously described. Anesthetic maintenance included inhalational anesthesia (0.5–1 minimum alveolar concentration of isoflurane or sevoflurane) with oxygen–air mixture, remifentanil infusion (dose range of 0.125–0.375 µg · kg⁻¹ · min⁻¹), and muscle relaxants at the attending anesthesiologist’s discretion. For intraoperative drainage of CSF, a lumbar drain catheter (80 cm, Hermetic Lumbar Catheter Closed Tip; Integra NeuroSciences, Hampshire, England) was inserted into the lumbar subarachnoid space with the patient in the lateral decubitus position. Mechanical ventilation was adjusted to maintain partial pressure of carbon dioxide (PaCO₂) between 35 and 40 mmHg. Plasma electrolyte solution (Baxter; Baxter Healthcare Corp., Deerfield, IL) was given intravenously to maintain CVP at 5 mmHg or greater. After skin incision, the study drug (mannitol or HS) was administered via the central line.

Brain relaxation was scored by the surgeon upon opening the dura on a four-point scale: 1 = perfectly relaxed, 2 = satisfactorily relaxed, 3 = firm brain, 4 = bulging brain. If the surgeon was not satisfied with the degree of brain relaxation on dural opening, a second bolus of 5 ml/kg of the study drug was given, 20 ml CSF was drawn, and hyperventilation was initiated to provide relaxation for surgical access. The level of hyperventilation depended on the attending anesthesiologist’s preferences.

Measured variables included (1) hemodynamic variables, including mean arterial pressure, CVP, and venous pressure in the jugular bulb; (2) perioperative fluid balance; (3) esophageal temperature; and (4) laboratory data, including blood gases, electrolytes, glucose, lactate and osmolality (freezing point depression, The Advanced™ Os-mometer, Model 3900; Advanced Instruments, Inc., Norwood, MA) measured in arterial blood, jugular bulb venous blood, CSF, and urine. All variables were measured and recorded before infusion (T0) and after administration of the study drug at 15 min (T15), 30 min (T30), 60 min (T60), and 6 h (T360) after infusion. Urine output was recorded every hour. Arteriovenous difference of oxygen and lactate were calculated as differences of oxygen content and lactate between arterial and jugular bulb venous blood using standard formulae.

**Statistics**

For calculation of power analysis, we considered a difference of 1 point in brain relaxation score between the groups to be clinically significant. A power analysis based on 95% confidence interval and β error of 20% revealed a sample size of 12 subjects (6 subjects in each treatment group).

Data are presented as mean ± SD. Brain relaxation scores are presented as median (range). One-way analysis of variance with repeated measures and paired Student t test were used for analysis of data within the group (hemodynamic and laboratory variables). Differences between the mannitol and HS groups were analyzed using chi-square (demographic variables), Mann–Whitney U test (brain relaxation scores), and unpaired Student t test with Bonferroni correction for multiple measurements (hemodynamic variables, urine output); multivariate analysis of variance was used for comparison of changes of hemodynamic and laboratory variables (Na, K, osmolality, lactate, glucose, etc.) over time between the groups. To assess the influence of subarachnoid hemorrhage (SAH) and its interaction with hyperosmotic agent, two-way analysis of variance was used. P < 0.05 was considered significant. For comparison of an arteriovenous difference of oxygen, glucose, and lactate between the groups, the data of the patient with arteriovenous malformation (HS group) were excluded from the analysis. Statistical analysis was performed using Intercool STATA 9 (StataCorp, College Station, TX).

**Results**

Forty patients were enrolled in the study. Twenty patients received mannitol, and 20 patients received HS. There was no significant difference between the groups in age, sex, severity of illness, or brain pathology (table 1). All enrolled patients completed the study. In 5 patients (3 in the mannitol and 2 in the HS group), CSF was not obtained at all required time points for various technical reasons (clotted catheter, withdrawal of the catheter before the study was completed, lost data, or no catheter). Therefore, whereas brain relaxation was determined in all 40 patients, osmolality, electrolytes, and CSF lactate were analyzed in 17 patients in the mannitol group.
Table 1. Comparative Data between Mannitol and Hypertonic Saline Groups

<table>
<thead>
<tr>
<th></th>
<th>HS Group (n = 20)</th>
<th>Mannitol Group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, yr</td>
<td>49 ± 13</td>
<td>48 ± 11</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>12 (60)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>ASA physical status, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Brain pathology, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor, supratentorial</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tumor, infratentorial</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular total</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>AVM</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fisher grade 3, 4 SAH (%)</td>
<td>10 (50)</td>
<td>10 (50)</td>
</tr>
</tbody>
</table>

There was no difference in age, sex, severity of illness, and brain pathology between the groups. All of the patients with subarachnoid hemorrhage (SAH) had an aneurysm rupture.

ASA = American Society of Anesthesiologists; AVM = arteriovenous malformation; HS = hypertonic saline.

and in 18 patients in the HS group. There were no differences in PaCO₂, Pao₂, and esophageal temperature between the two groups during the study period (table 2).

Mannitol and HS had similar effects on brain relaxation (table 3). To improve brain relaxation, 6 patients in the mannitol group and 6 patients in the HS group were given a second bolus of the study drug on surgical request. All of these patients had substantial SAH (Fisher grade 3 or 4) and poor brain relaxation grading of 3 or 4 after the first bolus of study drug. Mannitol had a more profound diuretic effect than HS, especially in the first 3 h after the bolus (table 3).

There was no difference in mean arterial pressure between the groups (table 2). In patients with SAH, CVP and jugular bulb pressure were higher than in patients without SAH, but there was no difference between the mannitol and HS groups. CVP significantly increased after both HS and mannitol at the end of infusion at T15 (P < 0.001). When subgroups with and without SAH were analyzed, a significant increase of CVP at T15 was observed only in patients without SAH, but without difference between the mannitol and HS groups (table 2).

**Osmolality**

Both mannitol and HS resulted in similar increase in serum osmolality, with the peak effect at 15 min after administration and remaining elevated above baseline for 6 h (fig. 1). In CSF, an increase in osmolality over time was only observed at 6 h, with no difference between HS and mannitol (fig. 1).

**Electrolytes and pH**

Mannitol caused an immediate decrease in sodium in blood and an increase in potassium over time (figs. 1 and 2). In contrast, HS resulted in an immediate increase in sodium (sustained for 6 h) and an immediate, but transient, decrease in potassium (figs. 1 and 2). In CSF, an increase in sodium over time was observed in HS group, compared with the mannitol group (F(df1), (df2) = 18.9, P < 0.001; fig. 1).

In both groups, pH did not change over time during study period and did not differ between the groups (baseline values for blood pH for mannitol: 7.43 ± 0.2 vs. for HS: 7.42 ± 0.0). There was no pH gradient between venous (jugular bulb) blood and CSF, irrespective of the study group.

**Lactate**

Compared with HS, a significant increase in arterial blood lactate over time was observed with mannitol, when compared with HS (F(df1), (df2) = 34.09, P < 0.001; fig. 3). In patients with SAH, CSF lactate was significantly higher than that in patients without SAH (P < 0.001). An increase in CSF lactate over time was observed with mannitol in patients with SAH (F(df1), (df2) = 11.5, P < 0.001). In patients without SAH, there was no difference in pattern of changes of CSF lactate between HS and mannitol, whereas in both groups, an increase of lactate was observed at T360 (fig. 3).

There was no difference in blood glucose between the groups (fig. 2), nor was there any difference in cerebral arteriovenous difference of oxygen or lactate between groups (fig. 4).

**Discussion**

We compared effects of equiosmolar boluses of HS and mannitol on the clinical brain condition and chemistry in blood and CSF in patients with and without SAH undergoing intracranial neurosurgical procedures. The major findings of our study are that during craniotomy, (1) equiosmolar solutions of mannitol and HS provide a similar effect on brain relaxation and cerebral arteriovenous oxygen content difference; (2) compared with HS, mannitol has a more prominent diuretic effect, which is associated with a less positive fluid balance, an increasing lactemia over time, and an increase in CSF lactate in patients with extensive SAH; and (3) HS and mannitol result in an increase of blood and CSF osmolality, and with HS this is associated with an increase in CSF Na concentration.

Previously, the effect of mannitol and HS on the brain in patients without increased intracranial pressure has been investigated in two studies in patients undergoing elective craniotomies for various neurological procedures.⁸,⁹ Gemma et al.⁸ reported satisfactory brain relaxation in all cases, when a similar osmolar load but different volume of 7.5% HS (n = 25) and 20% mannitol (n = 25) was given to patients. De Vivo et al.⁹ compared three different regimens and combinations of mannitol
and HS: (1) 0.5-g/kg bolus of mannitol (n = 10) versus (2) 0.25-g/kg bolus of mannitol followed by continuous infusion of 3% HS (n = 10) versus (3) bolus of 3% HS followed by continuous infusion of 2% and 1% HS (n = 10). Using the scale of brain relaxation similar to ours, the authors did not find any difference between the groups.9 In our study, all patients without SAH had satisfactory brain relaxation after the bolus of hyperosmotic fluid, whereas 60% of patients with extensive SAH in both groups did not have adequate brain relaxation necessitating a second bolus of hyperosmotic fluid and hyperventilation. We also maintained $\text{PaCO}_2$ between 35 and 40 mmHg to avoid an influence of carbon dioxide on the brain bulk, until it was assessed by the surgeon. Then, if needed, hyperventilation was initiated by the attending anesthesiologist’s choice.

Physiologic effects of hyperosmotic fluids on the brain have been compared in multiple animal and human studies with various brain pathologies, including SAH.12,13 The principal mechanism of action of both mannitol and HS solutions is the creation of an osmolar gradient across the BBB due to impermeability of the BBB to mannitol and Na. Therefore, an intact BBB is required for intravascular water absorption. Indeed, a
decrease in intracranial pressure with increased serum osmolality, and decreased brain water content with hypoperosmotic treatment in healthy, but not injured, brain tissue has been shown in animals.14–18 In humans, a correlation between an increased concentration in serum sodium and osmolality and a decrease in intracranial pressure and brain water content in noninjured brain areas has been shown in patients with traumatic brain injury and brain tumors, treated with either HS or mannitol.19–21 In this regard, our data showing equally effective brain bulk reduction with HS and mannitol in patients without SAH (and likely, with intact BBB) is consistent with the classic theory of hyperosmotic therapy.

The effectiveness of the hyperosmolar solute depends on its “reflection coefficient” determining the relative impermeability of the BBB to the solute, where 1 means an absolutely impermeable solute and 0 means an ideally permeable solute. Because the reflection coefficient of sodium is 1 and that of mannitol is 0.9,12 HS may have potential advantages over mannitol. There are some data in animal and human studies suggesting HS is more effective than mannitol in reducing an increased intracranial pressure,3–7 but unfortunately, differences in the osmolar load between solutions, as well as differences in study design, did not allow definitive conclusions.

In our study, the equiosmolar load of mannitol and HS led to similar acute increases in serum osmolality by the end of infusion, which is consistent with the data of Erard et al.22 who compared an equiosmolar load but different volumes of 7.5% HS and 20% mannitol.

### Table 3. Brain Relaxation and Fluid Balance in Hypertonic Saline and Mannitol Groups

<table>
<thead>
<tr>
<th></th>
<th>HS Group (n = 20)</th>
<th>Mannitol Group (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brain relaxation (n = 40)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with grade 1/2/3/4 (total)</td>
<td>6/8/6/0 (20)</td>
<td>5/9/4/2 (20)</td>
<td>0.86</td>
</tr>
<tr>
<td>Median grade (range)</td>
<td>2 (1–3)</td>
<td>2 (1–4)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-SAH (n = 20)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with grade 1/2/3/4 (total)</td>
<td>6/4/0/0 (10)</td>
<td>5/5/0/0 (10)</td>
<td>0.66</td>
</tr>
<tr>
<td>Median grade (range)</td>
<td>1 (1–2)</td>
<td>1.5 (1–2)</td>
<td></td>
</tr>
<tr>
<td><strong>SAH (n = 20)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with grade 1/2/3/4 (total)</td>
<td>0/4/6/0 (10)</td>
<td>0/4/4/2 (10)</td>
<td>0.6</td>
</tr>
<tr>
<td>Median grade (range)</td>
<td>3 (2–3)</td>
<td>3 (2–4)</td>
<td></td>
</tr>
<tr>
<td>Blood loss, ml</td>
<td>309 ± 45</td>
<td>305 ± 107</td>
<td>0.97</td>
</tr>
<tr>
<td>Fluid input, ml</td>
<td>4,335 ± 581</td>
<td>6,648 ± 1,346</td>
<td>0.16</td>
</tr>
<tr>
<td>Urine output 3 h, ml</td>
<td>908 ± 829</td>
<td>2,248 ± 1,443</td>
<td>0.001</td>
</tr>
<tr>
<td>Ureciose 3 h, ml</td>
<td>1,500 ± 509</td>
<td>2,969 ± 1,600</td>
<td>0.06</td>
</tr>
<tr>
<td>Fluid balance 3 h, positive, ml</td>
<td>3,230 ± 1,543</td>
<td>1,638 ± 1,620</td>
<td>0.004</td>
</tr>
<tr>
<td>Fluid balance 6 h, positive, ml</td>
<td>2,850 ± 2,654</td>
<td>2,519 ± 1,330</td>
<td>0.7</td>
</tr>
<tr>
<td>Number of patients given two boluses (%)</td>
<td>6 (30)</td>
<td>6 (30)</td>
<td>1</td>
</tr>
</tbody>
</table>

Four-point scale score of brain relaxation: 1 = perfectly relaxed, 2 = satisfactorily relaxed, 3 = firm (leveled) brain, 4 = bulging brain. Intravenous fluids included crystalloids and colloids. There was no difference between groups.

HS = hypertonic saline; SAH = subarachnoid hemorrhage.
both agents, we observed a sustained increase in blood osmolality for 6 h, and an increase in CSF osmolality 6 h after the treatment. Because the composition of CSF is highly dependent on the integrity of the BBB, an observed increase of osmolality in CSF with both agents and an increase of Na in CSF with HS may reflect an impaired permeability of the BBB. On the other hand, it may suggest dynamics of mannitol and sodium over time across the BBB. Recently, Ito et al. reported an increase in CSF sodium over time after a single bolus of HS in dogs with an intact BBB. With an impaired BBB, aggravation of cerebral edema with HS has been reported, suggesting a potentially detrimental effect of HS due to leakage of sodium through the BBB. With regard to mannitol, an increase in CSF osmolality had been reported to correlate with the dose of mannitol after repeated treatments. However, even without an increase in CSF osmolality, detectable concentrations of mannitol in CSF had been reported after a single intravenous bolus during craniotomies. Measurement of mannitol concentration in CSF might be helpful for assessment of the integrity of the BBB, but this is beyond the scope of our study. Nevertheless, in our study, the clinical effect of equiosmolar load of mannitol and HS on brain relaxation in patients with an impaired BBB (with SAH) was similar. However, the precise mechanisms involved in the effect of mannitol and HS on the brain, as well as the exact role of CSF composition in reducing cerebral edema, are not clear. Along with the hyperosmotic mechanism, an improved blood rheology with the shrinkage of erythrocytes, and a decrease in CSF production, antiinflammatory and other properties of both mannitol and HS are believed to play a role in their therapeutic action on healthy as well as injured brain.

The patients in our study remained hemodynamically stable, without significant changes in mean arterial pressure with both mannitol and HS infusions. It is possible that blood pressure fluctuations were controlled by anesthesia management, masking an acute response to...
Study solutions, but this is considered unlikely because no specific hemodynamic pattern emerged during the study. CVP was increased by both agents at the end of infusion, consistent with an initial intravascular volume expansion, determined by the increase in serum osmolality. Despite the similarities in hemodynamic response in the groups, the use of mannitol did result in a more profound diuretic effect and a less positive fluid balance, and this was associated with an increase in blood lactate over time, whereas no changes in blood lactate were observed with HS. The negative fluid balance with mannitol suggests that the increase in lactate may be secondary to relative hypovolemia. On the other hand, our finding of high baseline lactate in CSF in patients with SAH hemorrhage is a well-known phenomenon, and the clinical relevance of relative blood hyperlactemia in patients with SAH remains unknown, because brain metabolism of oxygen and lactate stayed within normal limits and did not differ between the groups.

Hypertonic saline caused an increase in blood sodium, which was sustained for 6 h, and acute, but transient, hypokalemia. In contrast, mannitol caused an acute hyponatremia, but a stepwise increase of potassium over time. Different changes of potassium such as hypokalemia and hyperkalemia have been previously reported with mannitol. Hyperkalemia after mannitol administration has been reported, but the exact mechanism of this phenomenon is unknown. One of the suggestions includes a cellular potassium efflux with the water, as a result of hyperosmolar condition. The development of hypokalemia with HS can be explained as a compensatory mechanism to maintain electrical neutrality in circumstances of induced hyperchloremic acidosis associated with the infusion.

Although there have been several comparative studies of mannitol and HS, to our knowledge, this is the first prospective double-blind randomized human study demonstrating the comparative effect of equiosmolar and equivolemic solutions of mannitol and HS on intraoperative brain relaxation, brain oxygen metabolism, fluids, and electrolytes. HS may be recommended as a safe alternative to mannitol for intraoperative brain debulking in patients with and without SAH, especially in hemodynamically unstable patients and/or when excessive fluid shifting should be avoided.
The authors thank Loretto Lollo, M.D. (Anesthesia Attending from the Department of Anesthesiology, Harborview Medical Center, University of Washington, Seattle, Washington), for his translation of the article by Erard et al. 22

References


