A prospective randomized trial of the optimal dose of mannitol for intraoperative brain relaxation in patients undergoing craniotomy for supratentorial brain tumor resection

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OBJECTIVE Mannitol is used intraoperatively to induce brain relaxation in patients undergoing supratentorial brain tumor resection. The authors sought to determine the dose of mannitol that provides adequate brain relaxation with the fewest adverse effects.

METHODS A total of 124 patients were randomized to receive mannitol at 0.25 g/kg (Group A), 0.5 g/kg (Group B), 1.0 g/kg (Group C), and 1.5 g/kg (Group D). The degree of brain relaxation was classified according to a 4-point scale (1, bulging; 2, firm; 3, adequate; and 4, perfectly relaxed) by neurosurgeons; Classes 3 and 4 were considered to indicate satisfactory brain relaxation. The osmolality gap (OG) and serum electrolytes were measured before and after mannitol administration.

RESULTS The brain relaxation score showed an increasing trend in patients receiving higher doses of mannitol (p = 0.005). The incidence of satisfactory brain relaxation was higher in Groups C and D than in Group A (67.7% and 64.5% vs 32.2%, p = 0.011 and 0.022, respectively). The incidence of OG greater than 10 mOsm/kg was also higher in Groups C and D than in Group A (100.0% in both groups vs 77.4%, p = 0.011 for both). The incidence of moderate hyponatremia (125 mmol/L ≤ Na+ < 130 mmol/L) was significantly higher in Group D than in other groups (38.7% vs 0.0%, 9.7%, and 12.9% in Groups A, B, and C; p < 0.001, p = 0.008, and p = 0.020, respectively). Hyperkalemia (K+ > 5.0 mmol/L) was observed in 12.9% of patients in Group D only.

CONCLUSIONS The higher doses of mannitol provided better brain relaxation but were associated with more adverse effects. Considering the balance between the benefits and risks of mannitol, the authors suggest the use of 1.0 g/kg of intraoperative mannitol for satisfactory brain relaxation with the fewest adverse effects.

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KEY WORDS brain tumor; brain relaxation; mannitol; hyponatremia; osmolality gap; oncology

Mannitol is widely used to reduce intracranial pressure (ICP) in patients with cerebral edema.2 Mannitol reduces ICP by decreasing brain water content, improving cerebral microcirculation, reducing cerebral blood flow via vasoconstriction, and decreasing cerebrospinal fluid volume.11 However, mannitol has several adverse effects, including hypochloremic metabolic alkalosis associated with volume contraction and diuresis, hypernatremia, hypokalemia, and renal failure.11 Because of tumor size, brain edema, or increased ICP, satisfactory brain relaxation can be required before tumor resection.10 Satisfactory brain relaxation improves the surgical approach in patients undergoing craniotomy.1 Mannitol is generally administered intravenously at doses be-
tween 0.25 and 1.5 g/kg, but the optimal dose has not been established. A previous meta-analysis found a weak linear relationship between mannitol dose and change in ICP. In contrast, another study found a dose-response effect of mannitol with ICP reduction in patients who had sustained traumatic brain injury; however, the mannitol doses (50 and 100 g) were not standardized based on body weight. Although the dose-response relationship between mannitol and intraoperative brain relaxation was investigated in a previous study conducted by Quentin and colleagues, the proportion of patients with midline shift on brain CT, which is an important sign of increased ICP, was not balanced across treatment arms in their study. The authors showed no difference in brain relaxation score between the high-dose (1.4 g/kg) and low-dose (0.7 g/kg) mannitol groups. However, after adjustment for the presence of midline shift, the high-dose mannitol group had a better brain relaxation score than the low-dose mannitol group.

We hypothesized that mannitol has a dose-related effect on brain relaxation. In the present study, we prospectively assessed the effect of different doses of mannitol on intraoperative brain relaxation and adverse effects in patients undergoing craniotomy for the removal of supratentorial brain tumors. We also sought to determine the mannitol dose to provide adequate brain relaxation with the fewest adverse effects.

Methods

A total of 124 adult patients (age range 20–80 years) scheduled for craniotomy for supratentorial brain tumor resection under general anesthesia at Seoul National University Hospital were enrolled in the study between June 2014 and May 2015. All patients harbored a unilateral lesion and showed a midline shift (> 3 mm) on brain MRI, which was determined by a blinded radiologist. The protocol for our prospective randomized study was registered at clinicaltrials.gov (NCT02168075). The institutional review board approved our study, and written informed consent was obtained from all participants.

Exclusion Criteria

Patients with an American Society of Anesthesiologists Physical Status Score ≥ IV, Glasgow Coma Scale < 13, severe hyponatremia or hypernatremia (Na⁺ < 120 mmol/L or > 155 mmol/L, respectively), cardiac dysfunction (i.e., congestive heart failure, left ventricle ejection fraction < 40%), renal dysfunction (glomerular filtration rate < 60 ml/min/1.73 m²), or preoperative mannitol use were excluded from the study. Furthermore, patients who had undergone extraventricular drainage or ventriculoperitoneal shunt treatment were also excluded.

Randomization and Group Assignments

The randomization sequence was generated by an anesthesiologist blinded to this study before the patients were enrolled. Randomization was performed in blocks of 4 or 8 patients using randomization software. Patients were randomly assigned to one of 4 groups (allocation ratio 1:1:1:1) according to the dose of mannitol administered: 0.25 g/kg (Group A), 0.5 g/kg (Group B), 1.0 g/kg (Group C), and 1.5 g/kg (Group D). The mannitol dose was calculated using a patient’s total body weight, and the participating surgeons were blinded to dose.

Anesthesia Induction and Maintenance

No patient received medication preoperatively. After arriving at the operating room, the patient was monitored using noninvasive blood pressure, pulse oxygen saturation, and electrocardiogram measurements. Anesthesia was induced using remifentanil (effect-site concentration, 4.0 ng/ml) and propofol (effect-site concentration, 4.0 μg/ml) continuous infusion using a target-controlled infusion device (Orchestra Bass Primera, Fresenius Kabi) and preoxygenation with 100% oxygen via a facial mask. Rocuronium (0.6 mg/kg) was administered to facilitate tracheal intubation, and then a radial artery was catheterized to directly monitor continuous arterial pressure. After intubation, an esophageal stethoscope (DeRoyal) was placed in the esophagus to monitor core temperature. Both lungs were mechanically ventilated with a 50% oxygen–air mixture, and total fresh gas flow was maintained at 2 L/min throughout surgery. Tidal volume and respiratory rate were adjusted to maintain arterial carbon dioxide partial pressure between 35 and 40 mm Hg. No positive end-expiratory pressure was applied in this setting.

All patients were in the supine or supine-lateral position without severe neck flexion, extension, or rotation. The confluence of sinuses was positioned higher than the heart level in all patients.

During surgery, anesthesia was maintained by continuous infusion of propofol and remifentanil. During surgery, the propofol and remifentanil doses were adjusted to maintain a mean blood pressure within 20% of baseline.

Mannitol Administration and Outcome Measurement

The primary end point was the trend in proportions of satisfactory brain relaxation. A predetermined amount of 20% mannitol by each corresponding group was intravenously administered over 15–20 minutes at the time of skin incision. Three neurosurgeons participated in the present study, and one of them rated each case. In other words, 3 neurosurgeons who were blinded to the mannitol dose assessed the degree of brain relaxation immediately after opening the dura. The assessment was performed using a 4-point scale, with 1 denoting bulging or the condition that additional methods for brain relaxation are immediately and always required in order to continue the surgical procedure because of brain swelling; 2, firm or the condition that additional methods for brain relaxation are occasionally required to continue the surgical procedure; 3, adequate; and 4, perfectly relaxed. In all patients, the degree of brain relaxation was assessed at the time of dural opening and satisfactory brain relaxation was defined as a brain relaxation score of 3 or 4. If neurosurgeons required a greater degree of brain relaxation in patients without satisfactory brain relaxation at the time of evaluating the degree of brain relaxation, additional methods such as administration of additional mannitol (0.25 g/kg), hyperventilation (PaCO₂ between 30 and 35 mm Hg), and the reverse Trendelenburg position were used.
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Assessed for eligibility (N = 135)

Excluded (N = 11)
- Not meeting inclusion criteria (N = 3)
- Decline to participate (N = 8)

Randomized (N = 124)

Group A (Mannitol 0.25 g/kg) (N = 31)
Group B (Mannitol 0.5 g/kg) (N = 31)
Group C (Mannitol 1.0 g/kg) (N = 31)
Group D (Mannitol 1.5 g/kg) (N = 31)

Follow-up (N = 31)
Follow-up (N = 31)
Follow-up (N = 31)
Follow-up (N = 31)

Data analyzed (N = 31)
Data analyzed (N = 31)
Data analyzed (N = 31)
Data analyzed (N = 31)

FIG. 1. A CONSORT flow diagram.

<table>
<thead>
<tr>
<th>TABLE 1. Demographics in the 124 patients included in this study</th>
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<tbody>
<tr>
<td>Variables</td>
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<td>-----------</td>
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<tr>
<td>Mean age in yrs (range)</td>
</tr>
<tr>
<td>Male sex</td>
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<tr>
<td>Mean height, cm</td>
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<tr>
<td>Mean weight, kg</td>
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<tr>
<td>Mean BMI, kg/m²</td>
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<tr>
<td>Tumor type</td>
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<tr>
<td>Anaplastic astrocytoma</td>
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<tr>
<td>Glioblastoma</td>
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<tr>
<td>Oligodendroglioma</td>
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<tr>
<td>Other glioma</td>
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<tr>
<td>Meningioma</td>
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<tr>
<td>Metastasis</td>
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<tr>
<td>Other</td>
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<tr>
<td>Tumor location</td>
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<tr>
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<td>Temporal</td>
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<tr>
<td>Parietal</td>
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<tr>
<td>Occipital</td>
</tr>
<tr>
<td>Sphenoidal</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Mean max tumor diameter, mm</td>
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<tr>
<td>Mean midline shift, mm</td>
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<tr>
<td>Peritumoral edema &gt;10 mm</td>
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</tbody>
</table>

The administered dose of mannitol is 0.25 g/kg in Group A, 0.5 g/kg in Group B, 1.0 g/kg in Group C, and 1.5 g/kg in Group D. Values are presented as the number of patients (%) unless indicated otherwise. Mean values are presented as the mean (SD) unless indicated otherwise.
Laboratory data, including electrolytes and serum osmolality, were recorded at 4 specific time points: immediately before mannitol administration, and at 30, 60, and 180 minutes after the end of mannitol administration. Because mannitol shows a peak effect 30 minutes after administration, the correlation between the degree of brain relaxation and serum osmolality level at this time point was investigated. The osmolality gap (OG) was calculated as serum osmolality – calculated osmolality (2 × [Na⁺, mmol/L] + [glucose, mg/dl]/18 + [BUN, mg/dl]/2.8). OG > 10 mOsm/kg was considered high.

Radiographic parameters were analyzed on brain MR images using a picture archiving and communication system (PACS; M-view, version 5.4; Infinitt Healthcare). The maximal intersecting diameter of the mass was measured using T1-weighted enhanced images for contrast-enhancing tumors or T2-weighted images for contrast nonenhancing tumors. Peritumoral edema was assessed using measurement of the shortest straight line between the tumor margin and the far point of peritumoral edema on FLAIR images. The degree of midline shift was defined by the maximal distance from the imaginary midline of brain to the deviated septum pellucidum.

### Statistical Analysis

A previous study found that the incidence of satisfactory brain relaxation was 70% after administration of a 1.0-g/kg dose and 55% after a 0.7-g/kg dose of mannitol. Assuming 40%, 50%, 70%, and 80% incidences of satisfactory brain relaxation in Groups A, B, C, and D, respectively, and assuming a Type I error rate of 0.05 and power of 80%, we calculated that at least 26 patients were required for each group by the Cochrane-Armitage test for linear trend in proportions. Furthermore, assuming a dropout rate of 20%, a total of 124 patients were needed for the study. The data were screened for normality using the Shapiro-Wilk test. Continuous variables with normal distribution were compared using ANOVA with Bonferroni correction at each time point. A p value < 0.05 was deemed to indicate statistical significance.

### Results

The study included 124 patients (Fig. 1). The demographic data were comparable among groups (Table 1). There was an increasing trend in the brain relaxation score in patients receiving high-dose mannitol (p = 0.005). The incidence of satisfactory brain relaxation was significantly higher in Groups C and D than in Group A (67.7% and 64.5% vs 32.3%, p = 0.011 and 0.022, respectively; Fig. 2), but not in Group B (51.6%). The overall incidence of additional methods for further brain relaxation was comparable among the 4 groups (Table 2). There was a significant correlation between the degree of brain relaxation and serum osmolality at 30 minutes after the end of mannitol administration (correlation coefficient 1.43, p = 0.036).

Serum osmolality (median [IQR]) measured at 30 minutes after the end of mannitol administration was significantly higher in Group D than in other groups (315 [310–317] vs 303 [301–309], 303 [300–307], and 306 [303–310] mOsm/kg in Groups A, B, and C, respectively) and was higher in Group C than in Group B (p = 0.008, Table 2).

The mean OG peaked at 30 minutes after the end of mannitol administration and then gradually decreased in all groups (Fig. 3). The OG (mean [SD]) at this time point was significantly higher in Group D than in the other groups (38 [5] vs 13 [6], 18 [5], and 25 [8] mOsm/kg in Groups A, B, and C, respectively). The incidence of a high OG (OG > 10 mOsm/kg) was higher in Groups C and D than in Group A (100.0% in both groups vs 77.4%, p = 0.011 for both; Table 3). The serum sodium concentration (mean [SD]) in Group A was higher than that of all other groups at this time point (138 [3] vs 135 [4], 134 [3], and 131 [4] mmol/L in Groups B, C, and D; p = 0.014, p < 0.001, and p < 0.001, respectively). The in-
We found that the incidence of satisfactory brain relaxation increased as the dose of mannitol increased; however, imbalances in the OG and serum electrolytes also increased in high-dose mannitol.

Mannitol is widely used to reduce ICP and improve brain relaxation in patients undergoing brain tumor resection. When the blood-brain barrier is intact, mannitol may induce brain relaxation by removing water from brain tissue or by decreasing cerebral blood flow. However, mannitol has several adverse effects, such as electrolyte imbalances, volume contraction, and renal failure. Increased serum osmolality can result in outward movement of water, leading to extracellular volume expansion, dilutional hyponatremia, and hyperkalemia. Thus, when using mannitol, the risk-benefit balance should be carefully considered.

Several previous studies have shown a relationship between mannitol dose and the degree of ICP reduction. Sorani et al. found that a higher dose of mannitol produced a greater reduction in ICP; however, the data were collected retrospectively in an intensive care unit in patients with traumatic brain injury. Moreover, the 2 fixed mannitol doses (50 and 100 g) were not adjusted for body weight, and adverse effects, such as electrolyte imbalance,
were not investigated. Quentin et al. found that a 1.4-g/kg dose of mannitol resulted in greater brain relaxation than did a 0.7-g/kg dose. However, the authors did not control for the number of patients exhibiting a midline shift on the brain CT or MRI, which is an important sign of increased ICP. In contrast, our prospective study used 4 incremental doses of mannitol, and the number of patients with midline shift was well controlled.

Mannitol administration affects serum osmolality and causes electrolyte imbalances, such as hyponatremia and hyperkalemia. The OG is an indicator of unmeasured serum osmoles, such as mannitol, and can be used to monitor osmolality change with mannitol administration. When using mannitol, the OG should be less than 55 mOsm/kg because of its nephrotoxicity. We found that the mean OG was significantly higher in Group D than in the other groups at all time points, and the maximal OG was 48 mOsm/kg 30 minutes after mannitol administration. Although we administered 1.5 g/kg of mannitol as the highest dose in the present study and none of the patients exhibited renal dysfunction, nephrotoxicity must be taken into consideration in the use of mannitol, particularly when repeat administration of a high dose of mannitol was required. Mannitol can cause a dose-dependent increase in hyponatremia. Similarly, serum sodium levels decreased after the administration of mannitol in this study. Compared with the other groups, the serum sodium levels in Group D were significantly lower at 30 and 60 minutes but returned to baseline 180 minutes after the administration of the drug. Although hyponatremia has been shown to return to preadministration levels within a day following a high dose of the drug, acute changes in serum sodium levels may be harmful because rapid-onset hyponatremia can become symptomatic. Hyperkalemia caused by an increase in intracellular potassium concentration as a result of cellular water loss and subsequent passive outflow of potassium is another serious adverse effect of mannitol. We observed a transient increase in serum potassium levels after mannitol administration in all groups. In Group D, the mean potassium level in-
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Conclusions

This study showed that the higher doses of mannitol provided better brain relaxation but were associated with more anticipated adverse effects. Therefore, when using mannitol in clinical practice, the balance between benefits and risks should be considered. This study suggests that 1.0 g/kg of mannitol may be the optimal dose for satisfactory brain relaxation with the fewest complications in patients undergoing craniotomy for supratentorial brain tumor removal.
References


Disclosures

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

Conception and design: HP Park, Seo, E Kim, Jeon. Acquisition of data: HP Park, Seo, E Kim, Jung, JW Kim, CK Park, Se. Analysis and interpretation of data: HP Park, Seo, Lim, CK Park, Se, Hwang. Drafting the article: Seo. Critically revising the article: HP Park, Lim, JW Kim, Jeon, Hwang. Reviewed submitted version of manuscript: HP Park. Approved the final version of the manuscript on behalf of all authors: HP Park. Statistical analysis: Seo. Administrative/technical/material support: E Kim, Jung. Study supervision: HP Park.

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