

Comparison of The Effects of Mannitol After Anesthesia Induction and Skin Incision on Brain Relaxation in Craniotomy: A Randomized Controlled Trial

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Abstract:

Objective: Effective brain relaxation during craniotomy enhances exposure and minimizes injury. Mannitol reduces intracranial pressure, but the best timing is debated. This study compares 20.0% mannitol administered immediately after anesthesia or at the skin incision on brain relaxation in elective craniotomy patients.

Material and Methods: This randomized controlled trial enrolled 80 patients. Participants received 1.0 g/kg of 20.0% mannitol either immediately after anesthesia induction (Group A, n=40) or at the time of skin incision (Group B, n=40). The primary outcome was the brain relaxation score (BRS), assessed by a blinded neurosurgeon on a four-point scale at the time of durotomy. Secondary outcomes included hemodynamic parameters, electrolyte levels, urine output, and length of stay in the intensive care unit (ICU) and hospital.

Results: Baseline demographic and surgical characteristics were comparable between the two groups (p-value>0.05). Group A demonstrated significantly better brain relaxation compared to Group B, with a mean BRS of 2.02 (S.D. 0.85) versus 2.50 (S.D. 0.73), respectively (p-value=0.004). “Good grade” relaxation (BRS 1–2) was achieved in 73.0% of Group A versus 48.0% in Group B (p-value=0.009). No significant differences were observed in hemodynamic stability, electrolyte imbalances, intraoperative blood loss, or the duration of ICU and hospital stays.

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Conclusion: For patients undergoing elective craniotomy for small-to-medium brain tumors, giving 1.0 g/kg of 20.0% mannitol immediately after anesthesia improves brain relaxation more than at the skin incision. This early use enhances surgical conditions without increasing hemodynamic or electrolyte risks.

Keywords: brain relaxation, craniotomy, intracranial pressure, mannitol, neuroanesthesia

Introduction

Central nervous system (CNS) tumors represent a significant clinical challenge worldwide. While some epidemiological data suggest a higher prevalence of certain primary malignant CNS tumors in males, the gender distribution often varies significantly, depending on the specific tumor pathology and regional demographics¹. In clinical practice, especially for elective craniotomies involving various tumor types, a female predominance is frequently observed in institutional cohorts. Although removing the tumor through craniotomy remains the standard surgical treatment, the procedure is often complicated by increased pressure and swelling inside the brain. To minimize surgical risks, reducing brain pressure is essential². Standard methods to lower pressure include controlled breathing, head elevation, cerebrospinal fluid (CSF) drainage, and mannitol administration³.

Mannitol⁴, typically administered as a 20.0% solution at 1 g/kg, is preferred for its effectiveness in reducing brain tension and its limited side effects⁵. However, the optimal timing for administering mannitol remains unclear. Achieving optimal brain relaxation is critical in neurosurgical anesthesia, as it improves surgical exposure and reduces the need for forceful brain retraction⁶, thereby lowering the risk of postoperative complications.

Mannitol, a hyperosmolar agent, remains the gold standard for reducing intracranial pressure (ICP) and inducing brain relaxation through a dual-phase mechanism⁷. The initial rheological effect occurs almost immediately after administration by lowering blood viscosity and increasing cerebral blood flow. It triggers compensatory

reflex vasoconstriction of the cerebral resistance vessels, leading to a rapid decrease in intracranial blood volume. This is followed by the osmotic effect, which typically begins within 15 to 30 minutes and peaks between 30 and 60 minutes⁸. This delayed phase depends on the formation of an osmotic gradient that draws water from brain tissue into blood vessels, thereby dehydrating the brain tissue^{9,10}. The clinical effects of mannitol typically last from 90 minutes to six hours. Significantly, mannitol may worsen dehydration and lead to electrolyte imbalances^{11,12}.

Despite its routine use, the optimal timing of mannitol administration remains a topic of ongoing clinical debate^{13,14}. If given too late, such as at the time of the skin incision, the full benefit of its osmotic effect may not be realized by the critical moment of dural opening. Conversely, administering it too early might result in a peak effect before it is most needed. This timing discrepancy creates significant uncertainty in neuroanesthetic practice¹⁵. While some studies have examined dosage, few have directly compared the clinical impact of pre-incision versus post-induction timing on brain relaxation quality. Therefore, this study addresses this gap by evaluating the effectiveness of these two timing points in patients undergoing elective craniotomy.

Material and Methods

Study design and ethical considerations

This study was designed as a prospective, randomized, parallel-group, single-blind controlled trial. The study protocol was approved by the Center for Ethics in Human Research, Khon Kaen University (Approval number: HE661356) and was conducted in accordance

with the Declaration of Helsinki. The trial was registered with the Thai Clinical Trials Registry (TCTR20250224001). Written informed consent was obtained from all participants or their legal representatives before enrollment. The study took place at Srinagarind Hospital, Khon Kaen University, Thailand, between August 2023 and November 2024.

Participants

Patients were aged 18 to 65 years. We excluded patients older than 65 years to reduce the confounding effect of age-related cerebral atrophy, which could artificially increase brain relaxation scores regardless of the intervention. Participants had an American Society of Anesthesiologists (ASA) physical status of I–III and a Glasgow Coma Scale (GCS) score of 13–15, and were scheduled for elective craniotomy. Tumor size was measured as the largest diameter on preoperative contrast-enhanced Magnetic Resonance Imaging (MRI) (T1-weighted axial plane) to confirm that all the included tumors were small-to-medium-sized supratentorial tumors (<5 cm) scheduled for elective craniotomy. While significant mass effect or a midline shift of >3 mm was not an absolute requirement for inclusion, all participants had radiologically confirmed tumors where intraoperative brain relaxation was clinically indicated to facilitate surgical access. Participants were assessed for eligibility. Exclusion criteria included patients with preoperative electrolyte imbalances (serum sodium <125 or >150 mmol/L), congestive heart failure, respiratory distress, chronic kidney disease (stage 3–5; glomerular filtration rate [GFR] <60 mL/min/1.73 m²), history of extra-ventricular drainage (EVD) or ventriculoperitoneal (VP) shunt, or those who had received mannitol, hypertonic saline, or diuretics within 24 hours before surgery.

Randomization and blinding

Participants were randomly assigned to either Group A or Group B in a 1:1 ratio using a block randomization

method with varying block sizes. An independent researcher employed a computer-based random number generator to create the randomization sequence. To ensure strict allocation concealment, the sequence was kept in sequentially numbered, opaque, sealed envelopes (SNOSE). The primary anesthesiologists enrolled the participants, and the group assignment was made by an anesthetic nurse, who opened the envelopes only after participants had been formally enrolled and met all the inclusion criteria. This study used a double-blind design. The neurosurgeon evaluating the primary outcome (brain relaxation) was blinded to group assignments. The anesthesia team managing the patients could not be blinded due to the nature of the intervention (timing of drug administration), but they were not involved in assessing outcomes.

Interventions and anesthesia protocol

Standard monitoring (electrocardiogram, pulse oximetry, non-invasive blood pressure) was started upon arrival. An arterial line was placed for continuous blood pressure measurement. General anesthesia was induced with fentanyl (1–2 µg/kg) and propofol (1–2 mg/kg), facilitated by cisatracurium (0.1–0.2 mg/kg) for endotracheal intubation. Anesthesia was maintained with target-controlled infusion (TCI) of propofol (Schneider model, Cp 3.5–4.5 µg/mL), fentanyl (0.5–2 µg/kg/h), and cisatracurium infusion. Mechanical ventilation was adjusted to maintain a tidal volume of 6–8 mL/kg of ideal body weight and a positive end-expiratory pressure (PEEP) of 5 cmH₂O. Maintaining mild hyperventilation (EtCO₂ 30–35 mmHg) is a standardized institutional protocol designed to optimize brain relaxation during the critical phases of neurosurgery. To minimize bias, this ventilation strategy was applied strictly and consistently to both study groups, ensuring that any observed differences in brain relaxation scores were primarily attributable to the timing of mannitol administration.

EtCO₂ served as the primary parameter for continuous ventilation control throughout the procedure, while arterial blood gas analysis was performed at baseline, 60, and 120 minutes to obtain PaCO₂ values for calibration and verification of the EtCO₂ readings.

The intervention involved the administration of 20.0% mannitol at a dose of 1.0 g/kg, infused intravenously over 30 minutes. The dose of 1.0 g/kg was selected based on previous studies (Zhang et al.), which suggest that this dose provides optimal ICP reduction for supratentorial tumors. The infusion was administered via a large-bore peripheral intravenous catheter (18 G or larger) to standardize infusion rates.

Hemodynamic stability was strictly monitored during mannitol infusion. Our safety protocol mandated that mannitol was administered only when the Mean Arterial Pressure (MAP) was maintained above 65 mmHg. In the event of post-induction hypotension, ephedrine was administered to restore hemodynamics before continuing the mannitol infusion. In this study, no patients in Group A required exclusion due to refractory hypotension that precluded mannitol administration.

Group A (Post Induction): Mannitol was started immediately after anesthesia induction.

Group B (Skin Incision): Mannitol was started at the time of skin incision.

Outcome measures

The primary outcome was the Brain Relaxation Score (BRS), assessed by the blinded neurosurgeon immediately after durotomy using a standard four-point scale¹⁵:

Grade 1 (completely relaxed): No cerebral edema.

Grade 2 (satisfactorily relaxed): Minimal edema, adequate space for manipulation.

Grade 3 (firm): Moderate edema requiring intervention.

Grade 4 (bulging): Severe edema requiring aggressive intervention.

BRS was analyzed primarily as an ordinal variable (4-point scale) and secondarily dichotomized into 'Good' (BRS 1–2) and 'Poor' (BRS 3–4) for clinical interpretation. To mitigate inter-rater variability and reduce subjectivity, the assessors were instructed to assign a single, discrete grade and avoid intermediate or ambiguous scores. This was done to ensure clear categorization and to minimize potential bias in the scoring process. The BRS was assessed by a single time point following durotomy by an experienced senior neurosurgeon who was blinded to the group assignment. By using a single assessor, potential inter-rater variability was eliminated, ensuring consistent evaluation of brain tension across all study participants, as this is the critical moment for assessing surgical conditions. It is not a continuous measure that can be repeated. Secondary outcomes included intraoperative hemodynamic parameters and metabolic variables (lactate, electrolytes, and partial pressure of carbon dioxide). These were recorded at three time points: T0 (start of mannitol infusion), T60 (60 minutes post-infusion), and T120 (120 minutes post-infusion). Urine output, blood loss: Complications such as severe electrolyte imbalances, significant hemodynamic instability, and duration of anesthesia and surgery, ICU/hospital stay were also recorded. All the secondary outcomes, including hemodynamic parameters and electrolyte balances, were prespecified in the study protocol. However, it should be noted that the sample size was specifically powered to detect a significant difference in the primary outcome. Consequently, the analysis of the secondary outcomes is considered exploratory, as the study may not be adequately powered to detect statistically significant differences in these variables.

Sample size calculation

The sample size was determined based on the primary outcome (BRS) as a continuous variable. Drawing from the work of Zhang et al.¹⁵, who reported a mean difference in BRS of 0.5 with a standard deviation of 0.75,

we calculated that a minimum of 32 patients per group would provide 80.0% power to detect a similar difference with a two-sided alpha level of 0.05. To account for a 10.0% potential attrition rate, the final recruitment target was set at 40 patients per group (total N = 80). Statistical comparisons were performed using the Independent t-test for normally distributed data and the Mann-Whitney U test for ordinal BRS data.

$$n = \frac{(Z_{\alpha/2} + Z_{1-\beta})^2 \left(\sigma_1^2 + \frac{\sigma_2^2}{r} \right)}{(\mu_1 - \mu_2)^2}$$

The formula used for sample size estimation

n represents the sample size per group; $Z_{\alpha/2}$ represents the critical value of the normal distribution at $\alpha/2$ (for a 95% confidence level, $Z_{0.05/2}=1.96$); $Z_{1-\beta}$ represents the critical value for power (for 80% power, $Z_{0.20}=0.84$); σ_1 and σ_2 represent the standard deviations of the two groups (assumed to be pooled $\sigma=0.75$); $\mu_1-\mu_2$ represents the expected mean difference (effect size=0.5); and r represents the allocation ratio (for this study, $r=1$).

Statistical analysis data analysis was performed using STATA version 18.0 (StataCorp, College Station, TX, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data were presented as mean and standard deviation (S.D.) and compared using an independent-samples t-test. Non-normally distributed data were presented as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and analyzed using Pearson's Chi-square test or Fisher's exact test, as appropriate. A p -value<0.05 was considered statistically significant.

Results

Following eligibility screening, 80 patients were enrolled in the study, with no exclusions. The participants

were randomly assigned to either Group A (post-induction of anesthesia) or Group B (skin incision), with each group containing an equal number of patients (Figure 1). Baseline characteristics and surgical data (Table 1) were analyzed for all participants, and no significant differences were observed between the two groups.

Regarding the timing of the intervention, the mean duration from the start of mannitol infusion to the dural opening was significantly longer in the post-induction group than in the skin-incision group (58.4 ± 7.2 min vs. 26.8 ± 5.5 min; p -value<0.001). This finding confirms that Group A achieved dural opening closer to the anticipated peak osmotic effect of mannitol.

The primary outcome analysis revealed that the mean BRS was significantly lower in Group A (post-induction) compared to Group B (skin incision) [2.02 (S.D. 0.85) versus 2.50 (S.D. 0.73), respectively; Mann-Whitney $U=492.0$, $Z=2.88$, p -value=0.004]. Furthermore, the proportion of patients achieving 'good' brain relaxation (BRS 1–2) was significantly higher in Group A (post-induction) than in Group B (skin incision) (73.0% versus 48.0%; Pearson's $\chi^2=6.82$, $df=1$, p -value=0.009) (Table 2).

For the other measured parameters, including bispectral index, partial pressure of carbon dioxide, heart rate, mean arterial pressure, serum lactate levels, pulse pressure variation, and urine output, no statistically significant differences were observed between the two groups (Table 3).

In terms of safety, no severe intraoperative electrolyte imbalances (specifically severe sodium or potassium abnormalities and acidosis) or significant hemodynamic instability requiring vasoactive support were observed in either group. Furthermore, there were no significant differences regarding total urine output, estimated blood loss, or the duration of ICU and hospital stays (Table 4).

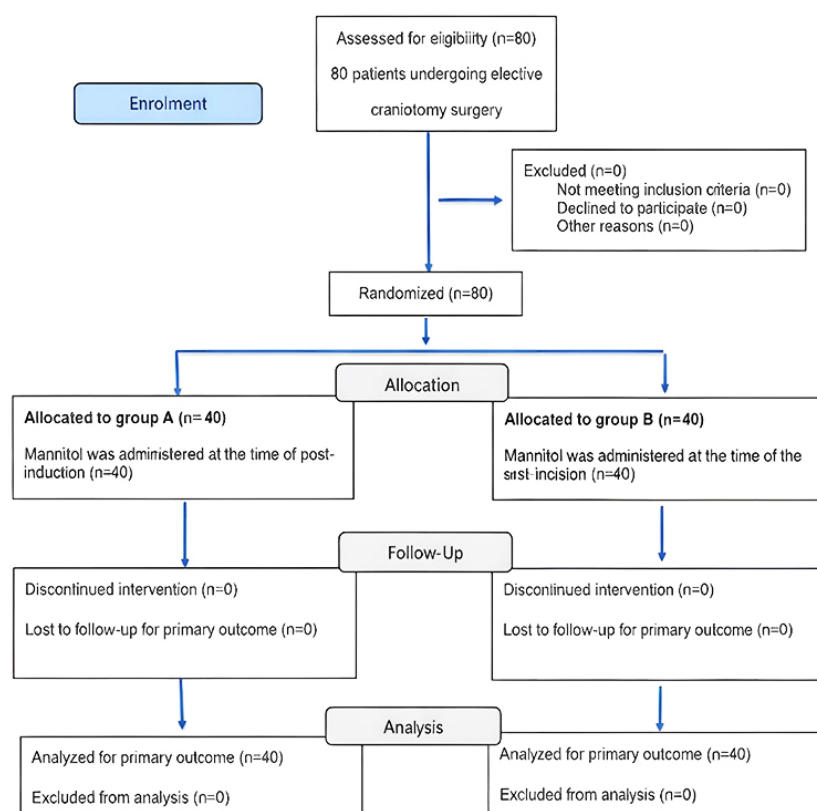


Figure 1 Consort diagram

Table 1 Baseline demographic and clinical characteristics of the participants

Characteristics	Group post- induction (n=40)	Group skin incision (n=40)	p-value
Age (years), mean (S.D.)	54.45 (12.38)	56.1 (13.06)	0.559
Gender (Male/female), n	16/24	13/27	0.485
Weight (kg), mean (S.D.)	60.218(10.35)	61.24 (11.20)	0.662
Height (cm), mean (S.D.)	158.55 (7.22)	157.65 (8.35)	0.648
BMI (kg/m ²), mean (S.D.)	23.95 (3.75)	24.60 (4.10)	0.463
ASA physical status (I/II/III), n	23/15/2	24/15/1	0.658
Tumor location, n (Frontal/temporal/parietal/other)	12/10/8/10	11/12/7/10	0.945
Type of tumor, n (Meningioma/Schwannoma/Glioma/Others)	22/7/0/11	25/8/6/1	0.922
Tumor size (cm), mean (S.D.)	3.52 (1.20)	3.38 (1.15)	0.596
Midline shift (mm), mean (S.D.)	3.20 (2.10)	3.05 (1.95)	0.742
Preoperative GCS*, n	15 (14–15)	15 (14–15)	0.812
Position of surgery, n (Supine/Lateral/Prone)	32/4/4	32/5/3	0.299

Data are presented as mean (S.D.), or median (IQR)*, S.D.=standard deviation, cm=centimeter, mm=millimeter, kg=kilogram, kg/m²=kilograms per square meter, mmol/L=millimoles per liter, IQR=Interquartile range, GCS=Glasgow coma scale, n=number, p-value=probability value

Table 2 Comparison of brain relaxation scores

Variable	Group post-induction (n=40)	Group skin incision (n=40)	Mean difference (95% CI)	p-value
Brain relaxation score (n)				
Grade 1	12	3	—	—
Grade 2	17	16	—	—
Grade 3	9	18	—	—
Grade 4	2	3	—	—
Good Grade (score 1–2)	29 (73.0%)	19 (48.0%)	—	0.009*
Mean score in good grade				—
Poor Grade (score 3–4)	11 (27.0%)	21 (52.0%)	—	0.009*
Mean score in poor grade				
Overall mean BRS, mean (S.D.)	2.02 (0.85)	2.50 (0.73)	0.48 (0.29–0.67)	0.004*

Data are presented as numbers (%), mean (S.D.), and mean difference (95% CI), S.D.=standard deviation, CI=confidence Interval, BRS=brain relaxation score, *Statistically significant difference (p-value<0.05), p-value for “Good Grade” proportions was calculated using Pearson’s Chi-square test, p-value for “Overall Mean BRS” was calculated using the Mann-Whitney U test

Table 3 Intraoperative hemodynamic and laboratory parameters

Parameter	Group post-induction (n=40)	Group skin incision (n=40)	Mean difference (95% CI)	p-value
Heart rate (bpm)				
T0 (Baseline)	85.55 (10.10)	90.54 (12.22)	4.99 (2.36–7.62)	0.156
T60	79.50 (12.54)	85.14 (11.56)	5.64 (2.48–8.80)	0.140
T120	84.48 (12.11)	89.84 (12.05)	5.36 (2.29–8.43)	0.228
Mean Arterial Pressure (mmHg)				
T0	84.43 (11.56)	81.08 (10.85)	3.36 (0.13–6.49)	0.363
T60	82.40 (10.15)	89.03 (12.55)	6.63 (4.07–9.19)	0.408
T120	79.13 (12.45)	81.08 (13.59)	1.95 (–0.62–4.25)	0.107
Pulse pressure variation (%)				
T0	9.48 (3.56)	9.60 (5.45)	0.12 (–1.68–1.92)	0.295
T60	8.15 (4.05)	7.85 (6.76)	0.30 (–0.60–1.20)	0.348
T120	8.85 (3.98)	7.95 (5.93)	0.90 (–0.05–1.82)	0.414
BIS				
T0	37.40 (6.10)	39.60 (7.22)	2.20 (0.82–3.58)	0.615
T60	37.55 (7.15)	38.65 (8.35)	1.10 (–0.73–2.93)	0.517
T120	39.15 (6.25)	38.60 (7.75)	0.55 (–1.48–2.58)	0.328
PaCO ₂ (mmHg)				
T0	35.22 (4.25)	38.65 (8.35)	2.20 (0.44–1.92)	0.856
T60	34.81 (4.12)	38.60 (7.75)	1.10 (0.07–1.53)	0.736
T120	34.32 (4.11)	35.65 (3.52)	0.55 (0.74–1.92)	0.755
Lactate (mg/dL)				
T0	12.55 (5.98)	15.85 (6.12)	3.30 (1.42–1.58)	0.365
T60	11.93 (6.05)	14.93 (6.45)	3.00 (1.36–4.64)	0.323
T120	12.40 (6.25)	13.95 (5.15)	1.55 (0.05–3.05)	0.228

Data are presented as mean (S.D.), S.D.=standard deviation, CI=confidence interval, PaCO₂=partial pressure of arterial carbon dioxide, BIS=bispectral index, T0=start of mannitol infusion, T60=60 minutes post-infusion, T120=120 minutes post-infusion, Statistical analysis performed using an independent t-test.

Table 4 Intraoperative data and secondary clinical outcomes

Parameters	Group post-induction (n=40)	Group skin incision (n=40)	p-value
Duration of surgery (min)	185.50 (45.20)	180.25 (42.15)	0.592
Duration of anesthesia (min)	210.40 (48.35)	205.15 (44.50)	0.612
Intraoperative urine output (mL)	850.50 (210.45)	825.25 (195.80)	0.584
Intraoperative blood loss (mL)	600.50 (180.25)	625.75 (195.50)	0.551
ICU stay (days)	1.25 (0.54)	1.32 (0.62)	0.592
Hospital stay (days)	7.42 (2.15)	7.68 (2.40)	0.612

Data are presented as mean (S.D.), S.D.=Standard Deviation, *Statistically significant, p-value<0.05, min=minute, mL=millilitre

Discussion

This study demonstrated that administering mannitol immediately after induction produced greater brain relaxation than administering it at the time of skin incision, as evidenced by lower brain relaxation scores. This finding warrants discussion of the potential mechanisms underlying mannitol's effects on brain relaxation, its integration into contemporary neuroanesthesia practice, its safety profile, and the clinical implications of this study's results.

Our findings are consistent with those of Zhang et al. (2021), who also reported superior brain relaxation when 1.0 g/kg of mannitol was administered immediately after induction rather than at the time of skin incision. While Zhang's study focused on high-risk patients with significant midline shift, our results demonstrate that this benefit extends to a broader population undergoing elective craniotomy for small- to medium-sized tumors. The alignment of results between these two studies reinforces the pharmacodynamic importance of the 'induction-to-durotomy' interval, which should ideally be around 50–60 minutes to capture the peak osmotic effect. For cases with prolonged surgical approaches, the timing may require further adjustment, whereas for standard elective craniotomy, the 60-minute window appears optimal.

Comparative effectiveness and clinical significance

While mannitol has been used extensively, comparative studies evaluating the effectiveness of different timing strategies are limited. This study directly compared two common approaches for administering mannitol: post-induction versus at the time of skin incision. The results suggested that the former approach was more effective at inducing brain relaxation, as indicated by lower BRS scores. Early administration could reduce the need for other interventions to induce cerebral relaxation during surgery, such as further hyperventilation or additional osmotic agents. However, the magnitude of the difference and its clinical implications warrant further investigation to enable comparisons with other approaches, such as hypertonic saline. The clinical significance of our findings lies in the potential to optimize surgical conditions and to improve patient outcomes during supratentorial tumor resection. Superior brain relaxation is associated with improved surgical exposure, reduced risk of intraoperative brain injury, and potentially shorter operative times. The current clinical practice is varied. The study's findings suggest that employing mannitol administration immediately post-induction of anesthesia should be considered. Also, reducing retraction pressures can minimize post-operative

neurological deficits. Implementing a standardized protocol for mannitol administration and incorporating the timing considerations identified in this study could lead to more consistent and predictable surgical outcomes.

Integration with contemporary Neuroanesthesia practice

Our findings suggest that the strategic timing of mannitol administration can be a valuable adjunct to these practices. The standard use of mannitol in elective supratentorial tumor resection aligns with current practices, which aim at facilitating surgical access and minimizing brain injury.

Safety profile and clinical implications

Mannitol is generally considered safe when administered judiciously. However, potential complications include electrolyte imbalances (hyponatremia, hypo- or hyperkalemia), acidosis, and hemodynamic changes, which must be carefully monitored and managed^{16,17}. In our study, no significant complications were reported, suggesting that the timing of mannitol administration did not alter its overall safety profile. However, it is crucial to acknowledge that mannitol administration can affect hemodynamics, which could potentially influence anesthesia decisions. Furthermore, there were no significant differences regarding total urine output, estimated blood loss, or the duration of ICU and hospital stays. The clinical implication of our findings is that optimizing the timing of mannitol administration can potentially improve surgical conditions and reduce the risk of brain injury during supratentorial tumor resection.

We acknowledge that quantitative volumetric analysis of peritumoral edema using T2-weighted or FLAIR MRI sequences was not performed in this study¹⁸. However, the randomized controlled design was strictly adhered to, ensuring a balanced distribution of baseline characteristics

between the two groups. As demonstrated in Table 1, there were no statistically significant differences in tumor size, midline shift, or histopathological subtypes (including dural-based tumors) between the post-induction group and skin incision group. Consequently, it is reasonable to infer that the baseline severity of peritumoral edema was comparable between the two cohorts. Therefore, the significant improvement in the BRS observed in the post-induction group is primarily attributable to the optimized pharmacodynamic timing of mannitol rather than the pre-existing disparities in brain edema.

Including both supratentorial and infratentorial tumors may introduce physiological variability, as a 3.5 cm tumor in the posterior fossa has a greater mass effect than a similarly sized tumor in the supratentorial compartment. However, the distribution of tumor locations and sizes did not differ significantly between the post-induction group and skin incision group. (p -value>0.05). Subgroup analysis indicated that the benefit of early mannitol administration remained consistent across different anatomical locations, suggesting that the timing of administration is a key determinant of brain relaxation regardless of the specific surgical compartment.

Recommendations

Based on our findings, we recommend administering mannitol immediately after induction of anesthesia in patients undergoing elective supratentorial tumor resection, provided that the patient's hemodynamic status and electrolyte balance are carefully monitored.

Limitations

The registration of this trial was postponed. Following ethical clearance, unforeseen difficulties and ambiguities in the TCTR's registration process led to a misunderstanding of the required protocol. These issues were subsequently resolved, but they were the primary cause for the delay in registering the trial.

Our study population was intentionally narrowed to patients with tumors less than 5 cm in diameter—this methodological decision aimed to minimize confounding by ensuring sample homogeneity. However, a key limitation of this approach is that our conclusions may not be directly generalizable to the broader clinical population, particularly patients with large tumors or pronounced intracranial hypertension.

Future research directions

Future research should focus on utilizing objective neuromonitoring, such as direct intracranial pressure probes or cerebral tissue oxygenation sensors, to correlate clinical relaxation scores with physiological data. Additionally, longitudinal studies are needed to determine if the improved brain relaxation achieved by earlier mannitol timing translates into a reduction in postoperative cognitive dysfunction or long-term neurological morbidity. Finally, investigating this timing strategy in more complex cases, such as large tumors with significant midline shift or emergency decompressive craniectomies, would further validate these findings.

Conclusion

This randomized controlled trial demonstrates that administering 20.0% mannitol (1.0 g/kg) immediately after anesthesia induction provides significantly greater brain relaxation than its administration at the time of the skin incision in patients undergoing elective craniotomy for supratentorial tumors. By aligning the peak osmotic effect with the moment of dural opening, this early administration strategy optimizes surgical exposure and minimizes the potential for brain retraction injury. These findings suggest that the timing of hyperosmolar therapy is as critical as the dose itself, and we recommend the routine adoption of post-induction mannitol administration to enhance neurosurgical outcomes.

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Conflict of interest

The authors declare that they have no competing interests or potential conflicts of interest regarding the publication of this article.

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