Low dose mannitol versus high dose mannitol to achieve brain relaxation in brain tumor surgery: a meta-analysis

Gunna Hutomo Putra¹*, Irwan Barlian Immadoel Haq¹, Rahadian Indarto Susilo¹, Joni Wahyuadi¹

ABSTRACT

Background: Brain edema is one of the common intraoperative problems in neurosurgery. Brain edema is usually treated by administering a hypertonic solution such as mannitol. Some studies mentioned the use of high-dose mannitol (>1 g/kg), but it is important to note that mannitol has several drawbacks. This meta-analysis aims to identify the most effective mannitol dose to reduce intraoperative brain edema among brain tumor cases.

Methods: We searched for all randomized-controlled trials (RCTs) published in English, which compared various doses of mannitol for brain tumors published between 2010-2020. The studies should include adult patients with intracranial tumors who received mannitol to reduce brain edema before opening the dura mater. The primary and secondary outcomes are satisfactory brain relaxation and the need for additional treatment to achieve adequate relaxation, respectively.

Result: Three RCTs were identified using an agreed-upon search strategy. A total of 354 patients were included in the meta-analysis. Satisfactory brain relaxation occurred in 70 of 152 and 154 of 202 patients who received low-dose and high-dose mannitol, respectively (RR 0.64 (95% CI, 0.48 – 0.86, p=0.003). There were 59 of 152 and 71 of 202 patients who needed additional treatment to make the brain adequately relax (RR 1.33, 95% CI 1.097 – 1.83, p=0.08).

Conclusion: A mannitol dose of >1g/kg achieves better brain relaxation. And it required fewer additional measures to relax the brain. These conclusions are drawn from low-quality evidence. Further research on the safety of high-dose mannitol is warranted to ensure its benefit outweighs its harm.

Keywords: Brain Relaxation, Brain Tumor, Dose, Mannitol.

Received: 2022-12-20
Accepted: 2023-01-29
Published: 2023-02-27

INTRODUCTION

A brain tumor can cause significant mass effects due to brain edema.¹ Brain edema is an unpleasing condition that complicates surgery, especially after opening the dura mater.² It is a common practice to administer hypertonic solution to reduce brain edema upon opening the dura mater. One of the most commonly administered agents is mannitol.³ Mannitol increases intravascular osmotic pressure, thus driving water out of brain parenchyma.⁴ Mannitol, however, also has several drawbacks, such as causing further blood-brain barrier disruption field, and it has been associated with acute kidney injury field, especially at a higher dose.⁵-⁷ Electrolyte disturbance and acidosis incidents have also been reported after mannitol infusion.⁸

Therefore, despite its common uses in neurosurgery, it is important to administer mannitol judiciously. Some published studies advocate the use of high doses (>1 g/kg), but some others advised otherwise.⁹-¹² Based on those mentioned above, this meta-analysis aims to identify the most effective mannitol dose to reduce intraoperative brain edema among brain tumor cases.

METHODS

We searched for all randomized-controlled trials (RCTs) published in English, which compared various doses of mannitol for brain tumors published between 2010-2020. The inclusion criteria of the study were:

1. Types of participants
   Adult (≥18-year-old) patients of either gender were diagnosed with intracranial tumors and received mannitol to reduce brain edema before opening the dura mater.
2. Types of interventions
   Intravenous mannitol administration before opening the dura mater. The experimental intervention was low-dose mannitol (<1 g/kg), and the control treatment was high-dose mannitol (≥ 1 g/kg).
3. Types of outcome measure
   a. Primary outcome
      Immediate brain relaxation was evaluated based on a 4-scale Brain Relaxation Score (BRS). BRS values of 1 (relaxed) and 2 (adequate) are deemed satisfactory, while the value of 3 (firm) and 4 (bulging) are unsatisfactory.¹³
   b. Secondary outcome
      The need for additional intervention to achieve satisfactory brain relaxation.
relaxation, e.g., hyperventilation, reverse Trendelenberg position, or additional mannitol.

Search methods for identification of studies
We searched PubMed and Cochrane Central Register of Controlled Trials (CENTRAL). The search was limited to papers published between 2010 to 2020. The used Mesh keywords were as follows, stated in Table 1. We also searched Google Scholar with the following keywords: Mannitol AND (Craniectomy OR Craniotomy*) AND (Brain neoplasms OR Brain Tumor), search limited to 2010-2020.

Table 1. Search terms used in the study.

<table>
<thead>
<tr>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 MeSH descriptor: [Mannitol] this term only</td>
</tr>
<tr>
<td>2 Craniotomy (Word variations have been searched)</td>
</tr>
<tr>
<td>3 Craniotomy*</td>
</tr>
<tr>
<td>4 MeSH descriptor: [Brain Neoplasms] explode all trees</td>
</tr>
<tr>
<td>5 MeSH descriptor: [Intracranial Pressure] explode all trees</td>
</tr>
<tr>
<td>6 MeSH descriptor: [Intraoperative Period] explode all trees</td>
</tr>
<tr>
<td>7 Brain Tumor</td>
</tr>
<tr>
<td>Combination</td>
</tr>
<tr>
<td>7 #1 AND (#2 OR #3)</td>
</tr>
<tr>
<td>8 #1 AND (#2 OR #3) AND #4</td>
</tr>
<tr>
<td>9 #1 AND (#2 OR #3) AND (#5 OR #6)</td>
</tr>
<tr>
<td>10 #1 AND (#4 OR #7) AND (#5 OR #6)</td>
</tr>
</tbody>
</table>

The Keywords based on PICO are as follows:
P = Brain tumor  
I = Low-dose mannitol  
C = High-dose mannitol  
O = Brain Relaxation Score (BRS), the requirement of hyperventilation, reverse Trendelenberg position, or mannitol adjunct to achieve adequate brain relaxation

Selection of studies
The search results were first excluded based on the relevancy of the titles and then on the relevancy of the abstracts. Non-English publications were automatically excluded. Full-text articles were then assessed by all authors (GHP, JW, IBIH, RIS) for potentially eligible RCTs. The reasons for exclusion were noted and reported.

Data extraction and management
Demographic data about age, sex, diagnosis, mannitol dose, the timing of mannitol administration, and brain relaxation evaluation are collected and presented in Table 2. Concomitant therapy is also noted and reported in the same table.

Assessment of risk of bias in included studies
The risk of bias was assessed by all four authors (GHP, JW, IBIH, RIS). Should the conclusion be unmet, a third party from the neurosurgery department would be asked to give their opinion. Assessed biases are those mentioned in The Cochrane Collaboration Tool for Assessing Risk of Bias in Randomised Trials published in 2011.14

Measures of treatment effect
We undertook statistical analysis using the statistical software Review Manager 5.4 of The Cochrane Collaboration. We used risk ratios (RRs) to measure treatment effect for proportions (dichotomous outcomes) among primary and secondary outcomes. The random-effect model will be used should evidence of significant heterogeneity is present. A statistically significant difference between intervention and control groups was assumed if the 95% CI did not include the value of no differential effect.

Assessment of Heterogeneity
Heterogeneity is addressed by the I² value upon forest plot construction using RevMan 5.4. The statistical model used is switched to random effect should I² yield the value of ≥ 50% as the studies are deemed heterogenous.15

RESULTS
We included three studies in our meta-analysis.13,16,17 All included studies were double-blinded randomized clinical trials. All studies evaluated brain relaxation with the same 4-scale score. One thesis study from India was found and included in the full-text assessment.18 The study was a double-blinded randomized trial. However, the randomization process, allocation concealment, and blinding were not clearly stated. Besides, the data provided in the paper were not dichotomized by the author and were presented in mean scores instead. We then decided to exclude the study. The exclusion processes can be seen in Figure 1. The risk of bias of included studies was assessed using The Cochrane Collaboration Tool for Assessing Risk of Bias in Randomised Trials published in 2011.14 The domain of the biases are as follows: 1) Random sequence generation, 2) Allocation concealment, 3) Blinding of participant and personnel, 4) Blinding of outcome and assessment, 5) Incomplete outcome data, 6) Selective reporting, 7) Other bias.

The result of the assessment can be seen in Figure 2. All studies have clear randomization processes. Li S et al. used a computer-generated randomization table prepared by someone not involved in the trial.16 Quentin C et al. used a computer-generated random list of blocks of 4 patients in sealed envelopes created by research assistants.13 However, we deemed the study by Quentin C et al. had an unclear risk of allocation concealment as it was not clearly stated who prepared the mannitol doses. Randomization in the study by Seo H et al. was done by a blinded anesthesiologist using randomization software.17 All three studies clearly stated that the neurosurgeons and anesthesiologists were blind to the mannitol doses.13,16,17 Two studies reported data on all participants.13,17 Li S et al. reported that some study participants were unavailable for analysis, but we considered this a potential source of analytic bias.16 We found that all outcomes mentioned in the methods section were reported in the
studies.\textsuperscript{13,16,17} Li S et al. gave preoperative mannitol or steroid to some patients.\textsuperscript{16} Quentin C et al. gave preoperative steroids to all patients.\textsuperscript{13} The findings from each study and the quality of evidence for each outcome are shown in Tables 2 and 3, respectively.

All three included studies reported their results on brain relaxation and the need for additional treatment. Li S et al. amassed 204 patients but were only able to include 179 in the analysis. This incomplete data was considered a potential risk of bias. This study compared mannitol at 0.7, 1.0, and 1.4 g/kg and placebo. Therefore, we included only 150 patients for this meta-analysis, as the other 49 were in the placebo group. Some of the patients also received preoperative mannitol or corticosteroid.\textsuperscript{16} Quentin C et al. had a smaller number of subjects (80). Mannitol doses compared in this study were 0.7 g/kg and 1.4 g/kg. The investigators administered intravenous corticosteroids prior to surgery. The inclusion criteria of this study\textsuperscript{13} were identical to those of Li’s except in preoperative hyperosmolar therapy administration.\textsuperscript{16} Seo H et al. studied 124 subjects equally distributed to four dose groups; they are 0.25 g/kg, 0.5 g/kg, 1.0 g/kg, and 1.5 g/kg. The investigators had relatively different inclusion criteria in that they had a wider range of serum natrium (120 – 155 mmol/L) and a more limited ejection fraction (≥ 40%).\textsuperscript{17}

The differences between studies based on the tumor type and size are elaborated in Table 4. Li et al. had 28 gliomas, 20 meningiomas, and 2 other tumor types for the low-dose group. On the other hand, there were 51 gliomas, 46 meningiomas, 2 metastatic, and 1 other type of tumor for the high-dose group.\textsuperscript{16} There were 14 gliomas, 13 meningiomas, and 13 metastatic tumors in the low-dose group of Quentin’s study. In the high-dose group, there were relatively more gliomas (22), fewer meningiomas (10), and fewer metastatic tumors (8).\textsuperscript{13} Seo H et al. had 23 gliomas, 26 meningiomas, 8 metastatic tumors, and 5 other tumor types in the low-dose group. There were an equal number of gliomas (23), meningioma (26), and another type of tumor (7), but less metastatic tumors (6) in the high-dose group.\textsuperscript{17}

Effects of interventions

The effect of the intervention can be seen in Figure 3. All studies did assess brain relaxation based on a 4-scale Brain Relaxation Score. All patients who received mannitol and were included in the analysis of each respective study were included for meta-analysis (354 patients). Satisfactory brain relaxation was achieved in 70 of 152 and 154 of 202 patients who received low-dose and high-dose mannitol, respectively. These three studies yield a risk ratio (RR) value of 0.64 (95% CI, 0.48 – 0.86, p=0.003), indicating that a mannitol dose of < 1.0 g/kg is not as effective as a mannitol dose of ≥ 1g/kg. There is considerable heterogeneity among studies for this outcome ($I^2=55\%$).

These three studies were considered homogenous ($I^2=15\%$) regarding the need for additional treatment to achieve satisfactory brain relaxation. There were 59 of 152 and 71 of 202 patients who

![Figure 1](image-url)  
**Figure 1.** Study flow diagram.
needed additional treatment to make the brain adequately relax (RR 1.33, 95% CI 0.97 – 1.83, p=0.08). This result indicated that a mannitol dose of ≥ 1 g/kg would less likely require additional treatment to achieve adequate brain relaxation.

**DISCUSSION**

This meta-analysis sought to identify the ideal mannitol dose to achieve satisfactory brain relaxation during brain tumor surgery. We included only studies published within the last 10 years. Three studies were included in qualitative and quantitative analysis, amassing 354 patients.

Satisfactory brain relaxation was our primary outcome. The 4-scale Brain Relaxation Score is subjective and might vary greatly based on experience. However, this scoring system is universally used.\(^\text{19–22}\) Besides, this scale is probably more applicable in our country (Indonesia) than the intracranial pressure (ICP) value because continuous intraoperative ICP monitoring is rarely practiced here.\(^\text{23,24}\) Risk ratio of 0.64 (95% CI, 0.48 – 0.86, p=0.003) indicated that a mannitol dose < 1 g/kg is not as efficient as a high dose in achieving brain relaxation. However, it is important to note that these studies were considerably heterogeneous regarding brain relaxation.

The need for additional treatment was more frequent in patients who received low-dose mannitol (RR 1.33, 95% CI 0.97 – 1.83, p=0.08). That said, it is important to note that all studies’ CI did touch or cross the line of no effect, indicating that high dose mannitol gave only slight benefit in terms of the necessity to do additional intervention after the initial mannitol infusion. Despite the high dose of mannitol seemingly being better in both primary and secondary outcomes, it is important to note that a dose of ≥ 1 g/kg is not commonly practiced in neurosurgery. The usual dose of mannitol is within the range of 0.25 – 1 g/kg.\(^\text{25}\) Two studies previously reported the benefit of 1.4 g/kg mannitol for patients with brain herniation due to diffuse brain swelling.\(^\text{10,26}\) Our study did not analyze if the risk of developing adverse effects such as electrolytes disturbance and acute kidney injury are linearly correlated with mannitol dose.

The overall methodological quality of these studies is considered good. There was, however, considerable heterogeneity with respect to the primary outcome. We deem that the conclusion for our primary and secondary outcomes belongs to low-quality evidence due to at least one type of bias in any of the studies. The studies were also heterogeneous. One study yields an RR of 0.85 (95% CI, 0.59 – 1.11), indicating inconsistent findings among these studies. For the secondary outcome, despite being homogenous, the weight of these studies was imbalanced as one study found a virtually higher event rate. We are unaware of any such meta-analysis or review which compare the different dose of mannitol for brain tumor surgery.

Further research is advised to assess the safety of high-dose mannitol in brain tumor surgery. It is also as important to address the ideal timing of mannitol administration prior to opening the dura, as it is also among the points not covered by this meta-analysis. Several limitations apply to our study. This meta-analysis included a limited study of RCTs. The results of the analysis can be altered by the quality of the research. Additionally, the outcomes analyzed were clinical outcomes, and inter-examiner may be subjective.

**CONCLUSION**

Mannitol dose of ≥ 1 g/kg achieves better brain relaxation. Mannitol at a high dose might need less additional intervention to relax the brain. However, this conclusion is not firm enough as we consider the available evidence low-quality. Careful monitoring of any possible drawbacks of mannitol administration is warranted.

**CONFLICTS OF INTEREST**

The authors declare that they have no conflicts of interest.

**ETHICS APPROVAL**

Not applicable.

**FUNDING**

This study did not receive any grant or funding from any organization.

**AUTHORS CONTRIBUTIONS**

GHP, IBIH, RIS, and JW contributed to the study concept and design. GHP, IBIH, and RIS contributed to abstract and/or full-text screening, quality assessment, and data acquisition. IBIH, RIS, and JW...
**Table 2. Summary of findings from each study.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Mannitol dose</th>
<th>Concomitant therapy</th>
<th>Satisfactory relaxation (n)</th>
<th>Relative effect (95% CI)</th>
<th>Need of Additional Treatment (n)</th>
<th>Relative effect (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li S et al., 2019</td>
<td>204 patients</td>
<td>LD 0.7 g/kg</td>
<td>Preoperative steroid (28)</td>
<td>22</td>
<td>RR 0.51 (0.37 – 0.70)</td>
<td>36</td>
<td>RR 1.26 (0.99 – 1.61)</td>
<td>Only 179 were included in the analysis</td>
</tr>
<tr>
<td></td>
<td>50 patients</td>
<td>and 1.4 g/kg</td>
<td>Preoperative mannitol (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 patients</td>
<td>Midazolam, Sufentanil, Rocuronium, Propofol, Remifentanil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quentin C et al., 2013</td>
<td>80 patients</td>
<td>LD 0.7 g/kg</td>
<td>Preoperative steroid (61)</td>
<td>87</td>
<td>RR 0.85 (0.59 – 1.21)</td>
<td>10</td>
<td>RR 1.11 (0.51 – 2.44)</td>
<td>No. of patients requiring hydroxyethyl starch and/or blood transfusion was not made clear.</td>
</tr>
<tr>
<td></td>
<td>40 patients</td>
<td>and 1.4 g/kg</td>
<td>Preoperative mannitol (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 patients</td>
<td>Midazolam, Sufentanil, Rocuronium, Propofol, Remifentanil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seo H et al., 2017</td>
<td>124 patients</td>
<td>LD 0.25 g/kg</td>
<td>Propofol, Sufentanil, Rocuronium, Desflurane, Hydroxyethyl Starch, Blood transfusion</td>
<td>22</td>
<td>RR 0.63 (0.45 – 0.89)</td>
<td>12</td>
<td>RR 2.6 (0.99 – 6.86)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>62 patients</td>
<td>and 0.5 g/kg</td>
<td>Remifentanil, Propofol, Rocuronium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and 1.5 g/kg</td>
<td>62 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ASA: American Society of Anesthesiologist Physical Status; Na: Natrium; LD: Low Dose; HD: High Dose
Table 3. Quality of evidence for each outcome.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Relaxation</td>
<td>RR 0.64 (0.48 to 0.86)</td>
<td>354</td>
<td>☧ ☧ ☧ ☧ low</td>
<td>The presence of bias and imprecision is indicated by the range of confidence interval (CI)</td>
</tr>
<tr>
<td>Additional Treatment</td>
<td>RR 1.33 (0.97 to 1.83)</td>
<td>354</td>
<td>☧ ☧ ☧ ☧ low</td>
<td>Presence of bias and imprecision indicated by the range of confidence interval (CI) and the considerably lower event rate in two studies</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence

High quality: Further research is unlikely to change our confidence in the effect estimate.

Moderate quality: Further research is likely to impact our confidence in the effect estimate and may change the estimate.

Low quality: Further research is very likely to impact our confidence in the effect estimate and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Table 4. Types and size of the tumor and the extent of midline shift.

<table>
<thead>
<tr>
<th>Author</th>
<th>Glioma n(%)</th>
<th>Meningioma n(%)</th>
<th>Metastatic n(%)</th>
<th>Other n(%)</th>
<th>Tumor Size</th>
<th>MLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2019</td>
<td>28(56)</td>
<td>20(40)</td>
<td>0(0)</td>
<td>2(4)</td>
<td>Mean volume 54 (33-85) mm³</td>
<td>Median 3 mm</td>
</tr>
<tr>
<td>Quentin2013</td>
<td>14(35)</td>
<td>13(32.5)</td>
<td>13(32.5)</td>
<td>0(0)</td>
<td>Mean diameter 41.1±15.9 mm</td>
<td>Mean 7.2±4.3 mm</td>
</tr>
<tr>
<td>Seo 2017</td>
<td>23(37.1)</td>
<td>26(41.9)</td>
<td>8(12.9)</td>
<td>5(8.1)</td>
<td>Mean diameter 50.6±14.4 mm and 45.5±15.4 mm³</td>
<td>Mean 9.2±4.3 and 10.0±6.7 mm²</td>
</tr>
</tbody>
</table>

Note: *1.0 and 1.4 g/kg group, respectively; 0.25 and 0.5 g/kg group, respectively; *1.0 and 1.5 g/kg group, respectively; Green row indicates low dose group; Yellow row indicates high dose group; MLS= Midline shift.

REFERENCES


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