INTRODUCTION

Osmotherapy is commonly used to achieve satisfactory intracranial pressure (ICP) and achieving brain relaxation.[7] Mannitol is the most popular osmotic agent to reduce ICP intraoperatively.[17]
Reducing surgical compression, local hypoperfusion, and cerebral ischemia are considered as neuroprotective measures that are achieved by brain relaxation.⁹¹⁶¹ Mannitol works through a biphasic mechanism which results in an increased plasma osmolarity and since it is almost impermeable to the blood-brain barrier (BBB), increased plasma osmolarity will shift fluid from the brain parenchyma into the intravascular compartment through an intact BBB. However, mannitol is associated with various adverse events, such as rebound phenomenon, nephrotoxicity through different mechanisms, and hypovolemia due to its diuretic effects. Like mannitol, hypertonic saline (HS) also works through a biphasic mechanism, but HS has an additional benefit which is being less permeable than mannitol across the BBB and has fewer diuretic effects. Yet, HS use is also associated with some adverse events, including metabolic acidosis, and central pontine myelinolysis (CPM) might happen when HS rapidly increases sodium levels, but no cases were reported of CPM after the use of HS to reduce ICP.⁸¹⁹¹²¹

Several randomized controlled trials (RCT) have compared equiosmolar HS and mannitol for brain relaxation in patients undergoing craniotomies, yet there were no consistent results between these trials.¹¹⁰¹¹³¹¹⁶¹²²¹ A previously published study by Zaffer et al. showed that HS had a better brain relaxation score when compared to mannitol to be used during supratentorial brain tumor surgeries.¹⁰¹ Another study by Rozet et al. found that there is no statistically significant difference between HS and mannitol in brain relaxation for different neurosurgical pathologies.¹¹¹ A systematic review and meta-analysis by Fang et al. that included nine studies which compared the efficacy of equiosmolar HS and mannitol for brain relaxation during craniotomies. This study showed HS to be a better option for brain relaxation during craniotomies; however, this systematic review and meta-analysis have included different types of neurosurgical pathologies.³¹

Hence, we aimed to assess the efficacy of equiosmolar HS and mannitol for the degree of brain relaxation and ICP during craniotomies for supratentorial tumors, along with their effect on systematic hemodynamics and electrolytes.

**MATERIALS AND METHODS**

We conducted this systematic review and meta-analysis according to our pre-specified protocol and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist.⁹ The study was protocol was registered in PROSPERO (CRD42021260861).

**Search strategy**

We searched Medline, Embase, and Cochrane Central Register of Controlled Trials with no restriction on the date and included only studies written in English. We used Medical Subject Headings (MESH) terms and keywords according to each database. Our used MESH terms and keyword were as following: “HS,” “Mannitol,” “brain relaxation,” “craniotomy,” “brain tumor,” and “supratentorial neoplasms.” This search was extended through searching the following trial registries: Clinical Trials Registry, MetaRegister of Controlled Trials, Australian New Zealand Clinical Trials Registry, and UMIN Clinical Trials Registry. The bibliographic references of the included studies were explored to find any relevant studies to our review. The last search was done early - July 2021.

**Eligibility and selection criteria**

We included only RCTs that have compared the efficacy of 3% or 3.2% HS and 18% or 20% mannitol for brain relaxation in patients who underwent craniotomy for supratentorial tumors only. We excluded any study that has different neurosurgical pathologies, tumors at any location other than supratentorial, non-equiosmolar HS and mannitol, studies with pediatric age group, and the absence of a full text of the article. For a study to be included in our meta-analysis, the study had to have at least one relevant outcome to this systematic review. Our intended outcomes were the degree of brain relaxation (4-point scale surgeon assessment), monitored ICP, mean arterial pressure (MAP), central venous pressure (CVP), peri-operative fluid input, urine output, and electrolytes levels (Na⁺ and K⁺).

Two investigators independently and in duplicate reviewed the titles and abstracts for articles that met our pre-specified criteria. Later, the included articles were assessed through their full-text, and if the full-text was eligible, the same two investigators extracted all relevant data in a pre-established data collection sheet. In the case of any disagreement, a third investigator was needed to resolve the disagreement or give the final decision.

**Data synthesis and analysis**

Degree of brain relaxation was assessed using a 4-point scale (I = perfectly relaxed, II = satisfactorily relaxed, III = firm brain, and VI = bulging brain). We defined I and II as positive events while the rest were considered negative events, and we used the risk ratio (RR) to represent the results. All other outcomes were assessed using the standardized mean difference (SMD). The latest value reported in the intended outcomes that have different time point measures was extracted. For example, if a study has reported serum Na⁺ levels in 1 h and 2 h, we extracted 2-h Na⁺ levels. Fluid output was reported as median and range in one study and was converted to mean and standard deviation using the Wan et al. calculator.²⁰²²
We used Reviewer Manager Software version 5.4 to build our meta-analysis and forest plots. The random-effects model was used for all outcomes. Heterogeneity was assessed using I² and P-value of Chi-square while visual inspection of the funnel plot was used to assess the publication bias. P < 0.05 was considered as our threshold for statistically significant results; hence, 95% confidence interval was used. Sensitivity analysis was carried out when there is significant heterogeneity, to determine the source of the heterogeneity. Risk of bias assessment was carried using the Revised Cochrane Risk of Bias Assessment Tool. Two investigators assessed the eligibility of each included RCT independently and in duplicate. Any disagreement was resolved by discussion or the opinion of a third investigator.

RESULTS
A total of 293 total articles were identified from our search. Sixty duplicate articles were excluded. 218 articles were further excluded after the title and abstract screening which left us with 15 eligible articles for full-text assessment. Ultimately, eight articles were excluded while seven articles met our inclusion criteria. All articles were published from 2010 to 2020 with only one study published in 2001 (Figure 1).

Trial characteristics
A total of 531 participants included in the seven studies. Of which 267 (50.2%) were allocated in the HS while
264 (49.7%) were allocated in the mannitol group. Of 531 participants, 282 (53.1%) were male and 249 (46.8%) were females with mean ages ranges from 38.25 to 58-years-old. The details of study characteristics are shown in [Table 1 and Supplementary A].

Risk of bias assessment

Of the seven studies, only one had an overall high risk of bias[3] whereas six had an overall low risk of bias[1,10,12,16,17,22] [Figure 2].

Brain relaxation (4-point scale)

Five studies have reported this outcome with a sample size of 273 participants.[1,10,12,16,17] Overall, there was a tendency for the HS group to achieve a better brain relaxation score than mannitol with no statistically significant result. There was no evidence of significant heterogeneity (RR = 1.13, 95% CI 0.99–1.29; P = 0.08; I² =7%) [Figure 3]. The result of the funnel plot for brain relaxation outcome was symmetrical [Supplementary B].

ICP

Only one study has reported the exact value of the outcome[3] while two have only reported it using figures.[1,17] For that reason, this outcome was not included in our meta-analysis. All studies have demonstrated that there is no difference between the ICP values between the two groups; however, Sokhal et al. have shown that there is a significant difference between HS and mannitol in later timepoints (15 and 20 min after the infusion) and when comparing ICP values to the baseline, Ali et al. have demonstrated that ICP values were significantly reduced from the baseline in the HS when compared to mannitol.

Mean arterial pressure

Five studies have reported this outcome.[1,3,12,16,17] Two of which have reported the exact values while the other two have only reported the outcome using figures. The meta-analysis involving the two studies has shown significant heterogeneity; therefore, we did not perform meta-analysis in this outcome. De Vivo et al. showed that there is a significant MAP reduction in the mannitol group while it did not change in the HS group. Similar results were obtained from Singla et al. which showed that there was a significant reduction in MAP from the baseline in the mannitol group whereas it stayed stable in the HS group. Moreover, Sokhal et al. have shown that there is also a significant fall in MAP in the mannitol group.[17] Yet, Ali et al. and Raghava et al. results demonstrated that there was no significant difference between the two groups MAP and no significant change in MAP in both from the baseline.[1]

CVP

All studies have reported this outcome, but only two studies have reported that exact value while the rest only reported it using figures.[1,3,10,12,16,22] Thus, our meta-analysis only included two studies with a sample size of 89 participants.
### Table 1: Characteristic of patients included in the studies.

| Author          | Study design | Age                  | Sex                        | Number of patients | Pre-operative GCS score | ASA                      |
|-----------------|--------------|----------------------|----------------------------|--------------------|-------------------------|--------------------------|
| Raghava et al. 2015 | RCT          | 41.6±12.9            | M (n=12); F (n=13)         | n=25               | NR                      | II (n=11), III (n=14)   |
| Ali et al. 2018  | RCT          | 50.0±9.7             | M (n=11); F (n=9)          | n=19               | 14.3±0.8                | II (n=14), III (n=15)   |
| Sokhal et al. 2017 | RCT          | 40.8±13.9            | M (n=11); F (n=9)          | n=20               | 4.4±0.68                | II (n=16), III (n=19)   |
| Zaffer et al. 2014 | RCT          | 43.39±13.6           | M (n=28); F (n=30)         | n=56               | NR                      | II (n=40), III (n=35)   |
| De Vivo et al. 2001 | RCT          | 58 years (range 17–75) | M (n=13); F (n=17)       | n=10               | 15                      | II (n=26), III (n=28)   |
| Wu et al. 2010   | RCT          | Median 56 (18–80)    | M (n=56); F (n=60)         | n=122              | NR                      | II (n=96), III (n=88)   |
| Singla et al. 2020 | RCT          | 40.40 (±14.98)       | Male (n=10); Female (n=5) | n=15               | NR                      | I (n=10), II (n=8), III (n=0) |

| Author          | Study design | Dose                  | Groups                    | Infusion method   | Peri-operative complication                          | Post-operative complication                               |
|-----------------|--------------|-----------------------|---------------------------|-------------------|------------------------------------------------------|----------------------------------------------------------|
| Raghava et al. 2015 | RCT          | 5 ml/kg               | 3%                       | Central line      | Hypotension (n=0), pulmonary edema (n=0), decreased urine output (n=1), Paesis (n=2), Deep Vein Thrombosis (n=2), seizure (n=1), Pneumocephalus (n=1), Hematoma (n=0) | Nausea, vomiting, headache, disorientation, restlessness, convolution, weakness of limbs, and aphasis |
| Ali et al. 2018  | RCT          | 5 ml/kg               | 3%                       | Central line      | Hypotension (n=2), pulmonary edema (n=1), decreased urine output (n=0), Paesis (n=2), Deep Vein Thrombosis (n=0), seizure (n=3), Pneumocephalus (n=1), Hematoma (n=1) | Nausea, vomiting, headache, disorientation, restlessness, convolution, weakness of limbs, and aphasis |
| Sokhal et al. 2017 | RCT          | 5.35 ml/kg            | 3%                       | Central line      | Hypotension (n=0), pulmonary edema (n=0), decreased urine output (n=1), Paesis (n=2), Deep Vein Thrombosis (n=2), seizure (n=1), Pneumocephalus (n=1), Hematoma (n=0) | Nausea, vomiting, headache, disorientation, restlessness, convolution, weakness of limbs, and aphasis |
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The meta-analysis showed that HS is more likely to have higher CVP values than mannitol, but no statistical threshold was reached (SMD = 0.42, 95% CI 0.00–0.85; \( P = 0.05; \ I^2 = 0\%\) [Supplementary C].

**Perioperative fluid input**

Fluid input has been reported by three studies with a sample size of 402 participants.\(^{10,12,20}\) In comparison to HS, the mannitol group was associated with higher fluid inputs; however, it was not a statistically significant result. No heterogeneity was noticed (SMD = −0.18, 95% CI −0.37–0.02; \( P = 0.08; \ I^2 = 0\%\) [Figure 4]. The funnel plot for fluid input was symmetrical [Supplementary D].

**Urine output**

Five studies reported the urine output with a sample size of 471 participants.\(^{1,10,12,16,22}\) Higher urine output was significantly associated with the mannitol group compared to HS. No significant heterogeneity was present (SMD = −1.33, 95% CI −1.56–−1.10; \( P < 0.01; \ I^2 = 12\%\) [Figure 5]. The urine output funnel plot was symmetrical [Supplementary E].

**Na\(^+\) levels**

Four studies have reported this outcome with a sample size of 139 participants.\(^{1,3,12,16}\) There was a significant tendency for the HS group to have higher Na\(^+\) levels compared to the mannitol group, yet there was significant heterogeneity in this outcome (SMD = 1.21, 95% CI 0.53–1.89; \( P < 0.01; \ I^2 = 69\%\) [Figure 6]. Thus, sensitivity analysis was carried out to detect the source of the heterogeneity. The result of the outcome after the sensitivity analysis was similar and it is shown in [Supplementary F] (SMD = 1.47, 95% CI 0.86–2.09; \( P < 0.01; \ I^2 = 53\%\). The funnel plot for this outcome was symmetrical [Supplementary G].

**K\(^+\) levels**

Three studies have reported the outcome with a sample size of 100 participants.\(^{1,12,16}\) Mannitol group tended to have higher K\(^+\) levels when compared to HS with no significant \( P\)-value and there was significant heterogeneity (SMD = −0.29, 95% CI −1.09–0.52; \( P = 0.48; \ I^2 = 73\%\) [Supplementary H]. The sensitivity analysis was carried out the result is shown in [Supplementary F] (SMD = 0.08, 95% CI −0.39–0.55; \( P = 0.74; \ I^2 = 0\%\). Symmetrical funnel plot was observed in this outcome [Supplementary I].

**DISCUSSION**

We aimed in this systematic review and meta-analysis to evaluate the efficacy of HS and mannitol in producing...
a satisfactory brain relaxation in patients undergoing supratentorial tumors craniotomies. Our review provided a high level of evidence since we included well-designed RCTs. Our review focused only on supratentorial tumors craniotomies rather than different brain pathologies. The difference between brain tumors and other brain pathologies is that brain tumors are space-occupying lesions and can induce peritumoral edema. The increase in ICP from brain tumors depends on different tumor factors, such as histological grade, and the degree of brain invasion. These factors are associated with a defective BBB and compromised venous outflow. Our result demonstrated no significant difference between HS and mannitol with respect to brain relaxation scores. Mannitol was associated with higher urine output while HS was associated with higher levels of Na⁺.

Our study showed that HS has a higher tendency to produce better brain relaxation scores; however, our results were not statistically significant which contradict previous systematic review and meta-analysis done on the same issue. Fang et al. and Shao et al. concluded that HS have significantly better odds in producing a good brain relaxation score when compared to mannitol. These studies have included both 3- and 4-point brain relaxation scores as well as various brain pathologies which all can contribute to the difference between our results and their results. In this review, we were unable to perform a meta-analysis for ICP values due to the lack of a report of the exact values. However, different reviews compared HS and mannitol using ICP. First, Schwimmbeck et al. compared both interventions in traumatic brain injuries (TBI) and concluded that there is no significant difference between HS and mannitol in terms of ICP at 30–60 min after the treatment. Yet they also demonstrated a significant reduction in ICP in favor of HS at 90–120 min after the treatment. This study was on patients with TBI, and there was no mentioning of equiosmolar doses of HS and mannitol. Another study done by Shao et al. showed that HS significantly reduces intra-operative ICP in patients undergoing neurosurgical procedures with different brain pathologies. These results all indicate that HS may have better chances to reduce ICP when compared to mannitol and that it could be due to the additional mechanisms of HS. Theoretically, HS has higher osmotic reflection coefficient, which results in more osmotic activity and less permeability to the BBB.

We demonstrated in this review that HS was associated with significantly higher Na⁺ levels whereas mannitol was associated with significantly higher urine output. The increase in serum Na⁺ will increase serum osmolarity leading to activation of osmo receptors in the hypothalamus which activates the release of antidiuretic hormone contributing to fewer diuretic effects of HS. Singla et al. suggested that the increase in Na⁺ levels in HS will return to normal within
48 h. On other hand, the increase in urine output by mannitol may lead to hypovolemia and increase the need for intraoperative fluid input. These results were consistent across most studies that compared both HS and mannitol. As for K⁺ levels, our study showed that there is no significant difference between HS and mannitol. Rozet et al. demonstrated that HS lead to a transient decrease in K⁺ levels while mannitol lead to a gradual increase in K⁺.

Our review found that HS was associated with non-significantly higher levels of CVP. This is consistent with the previous systematic reviews. Fang et al. concluded the mannitol significantly reduced CVP, but with comparable MAP in patients undergoing neurosurgical procedures for different brain pathologies. It is logical to think that this result may be similar in patients undergoing craniotomies for supratentorial tumors. In fact, this evidence is supported by many RCTs in craniotomies for supratentorial tumors not included in our meta-analysis. Dostal et al. performed a study comparing HS and mannitol for different intracranial tumors and suggested that mannitol significantly reduced CVP at the end of the surgical procedure.

We acknowledge that our systematic review and meta-analysis had some limitations. First, our main outcome was subjectively assessed across all studies. Second, many studies have only reported their results using figures which limited our meta-analysis in different outcomes. Third, brain relaxation can be affected by different anesthesiologist measures. Finally, we were limited by the small sample size and the small number of studies.

CONCLUSION

Both HS and mannitol can produce a satisfactory brain relaxation with a non-statistically significant tendency for HS to achieve better relaxation scores. Mannitol was associated with higher diuretic effect whereas HS was associated with higher Na⁺ levels. Lower perioperative fluid input and higher CVP were found to be associated with HS. We recommend the use of HS in favor of mannitol in patients undergoing supratentorial tumor surgeries that do not demonstrate any electrolytes disturbances as HS has an edge over mannitol also HS can maintain an acceptable hemodynamics stability. Further high quality RCTs with a large sample size, an objective measurement of ICP, and standardized anesthesiologist measures are required to provide a more satisfactory conclusion.

Declaration of patient consent

Patient’s consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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| Study               | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Outcomes                                                                 |
|--------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Rghava et al. 2018 | Patients with age group 18–65 years, with GCS>13, and ASA physical status 1–3 were included in the study. | Patients with the presence of raised ICP, electrolyte imbalance. Patients with severe cardiac, respiratory, or renal disease. Patients who are already on mannitol or HS treatment. | Brain relaxation (4-point scale), CVP (120 min), MAP (120 min), Na (120 min), K (120 min), urine output (6 h), fluid intake |
| Singla et al. 2020 | American Society of Anesthesiologists physical statuses I–III, aged 18–65 years with clinical or radiological evidence of raised ICP, and scheduled to undergo supratentorial tumor resection | Pre-operative hyponatremia or hypernatremia, intake of any hyperosmotic fluid in the previous 24 h, history of congestive heart failure, kidney disease, or surgery for ventriculoperitoneal shunt. | Brain relaxation (4-pint scale), MAP (180 min), CVP (180 min), urine output (3 h), K (48 h), Na (48 h). |
| Ali et al. 2015   | Adult patients (aged 18–65) scheduled to undergo elective craniotomy for supratentorial brain tumors were enrolled | (ASA) physical status over III, History of cranial operations, Pregnancy or morbid obesity (BMI<40kg/m²), Abnormal preoperative sodium levels, Patients who were treated with hyperosmotic fluids in the 24 h before surgery, Patients who had a Gordon-Firing scale score<2. | Brain relaxation (4-point scale), ICP values, MAP (45 min), CPP (45 min), CVP (45 min), Na (45 min), ICP (45 min), urine output, fluid infusion (45 min) |
| Wu et al. 2010    | Two hundred thirty-eight patients who were scheduled to undergo elective craniotomy for supratentorial brain tumors | Less than 18-years-old, GCS less than 13, ASA physical status IV and V, sings of increased ICP, perioperative hypo- or hypernatremia, history of treatment with any hyperosmotic fluids within the 24 h preceding the surgery, and history of congestive heart failure or severe renal function impairment. | Brain relaxation (3-point scale), perioperative fluid input, urine Output, serum sodium concentration. |
| Zaffer et al. 2014 | ASA II and III, >18 years of either sex, scheduled to undergo elective craniotomy for supratentorial brain tumor | History of unstable angina or myocardial infarction within past 6 months, congestive cardiac failure, GCS<13, uncontrolled diabetes, severe renal impairment, preoperative hyponatremia or hypernatremia. | Brain relaxation (4-point scale), CVP, Fluid input (360 min), urine output (360 min) |
| Sokhal et al. 2017 | 40 adult patients belonging to either sex, scheduled to undergo elective craniotomy for supratentorial brain tumors | Preoperative GCS<14, (ASA) physical status IV/V, Preoperative hypo- or hypernatremia, History of treatment with hyper osmotic fluids (HS or Mannitol) within 24 h before surgery, History of congestive heart failure, renal function impairment, and diabetes mellitus, Patient posted for seller and suprasellar surgeries, Patient with history of any intracranial surgery. | Brain relaxation (4-point scale), ICP values, MAP, CVP, Na levels, K levels, Fluid input, and urine output. |
| De Vivo et al. 2001 | Patients who scheduled for intracranial supratentorial tumor surgery | NR | ICP values, MAP (72 h), K (72 h), Na levels |

ASA: American Society of Anesthesiologists, GCS: Glasgow Coma Scale, NR: Not reported, HS: Hypertonic Saline
Abdulhamid, et al.: Equiosmolar hypertonic saline and mannitol for brain relaxation in patients undergoing supratentorial tumor surgery

**Supplementary B:** Brain relaxation funnel plot.

**Supplementary C:** CVP forest plot.

**Supplementary D:** Fluid input funnel plot.

**Supplementary E:** Urine output funnel plot.

**Supplementary F:** Results after the sensitivity analysis.

| Outcomes | Number of studies | Number of patients | Standardized mean difference | 95% CI | P-value | I² |
|----------|-------------------|--------------------|-----------------------------|--------|---------|----|
| Na levels | 3                 | 119                | 1.47                        | 0.86, 2.09 | <0.001 | 53% |
| K levels  | 2                 | 70                 | 0.08                        | −0.39, 0.55 | 0.74   | 0%  |
Supplementary G: Na⁺ level funnel plot.

Supplementary H: Serum K⁺ levels forest plot.

Supplementary I: K⁺ level funnel plot.