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Review Article

Equiosmolar hypertonic saline and mannitol for brain relaxation in patients undergoing supratentorial tumor surgery: A systematic review and meta-analysis

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ABSTRACT

Background: Hypertonic saline (HS) and mannitol are hyperosmolar agents that are usually used to reduce intracranial pressure (ICP) and provide a satisfactory brain relaxation. The aim of the study was to perform a systematic review and meta-analysis to compare the efficacy of HS and mannitol on brain relaxation intraoperatively in patient undergoing craniotomies for supra-tentorial brain tumors.

Methods: A systematic review and meta-analysis of randomized control trials. We included randomized control trials that compared equiosmolar HS and mannitol in supratentorial tumors craniotomies and reported at least one of the following outcomes: degree of brain relaxation, ICP, central venous pressure, mean arterial pressure, perioperative fluid input, urine output, Na+ levels, and K+ levels. We searched Medline, Cochrane Central Register of Controlled Trials, and Embase using MESH terms and keywords. The bibliographic references of included studies and trial registries were also searched.

Results: Seven articles were included. The degree brain of relaxation was comparable across the two groups with slight tendency toward HS (RR = 1.13, 95% CI 0.99–1.29; $P = 0.08$). Mannitol was associated with significantly higher urine output (standardized mean difference [SMD] = −1.33, 95% CI −1.56–−1.10; $P < 0.001$). Na^+ levels were higher in HS group (SMD = 1.47, 95% CI 0.86–2.09; $P < 0.001$). Mannitol was associated with non-significant decrease in CVP and increase fluid input (SMD = 0.42, 95% CI 0.00–0.85 and SMD = −0.18, 95% CI −0.37–0.02, respectively).

Conclusion: Both HS and mannitol are associated with satisfactory brain relaxation with a non-statistically significant tendency for HS to achieve better relaxation scores with mannitol resulting in higher urine output while HS with higher Na^+ levels.

Keywords: Brain relaxation, Hypertonic saline, Mannitol

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.[6] 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.[8,19,21]

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.[1,10,12,13,16,22] 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.[10] 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.[13] 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.[5]

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.[20,22]

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 I^2 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.[18] 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.[1,3,10,12,16,17,22] 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

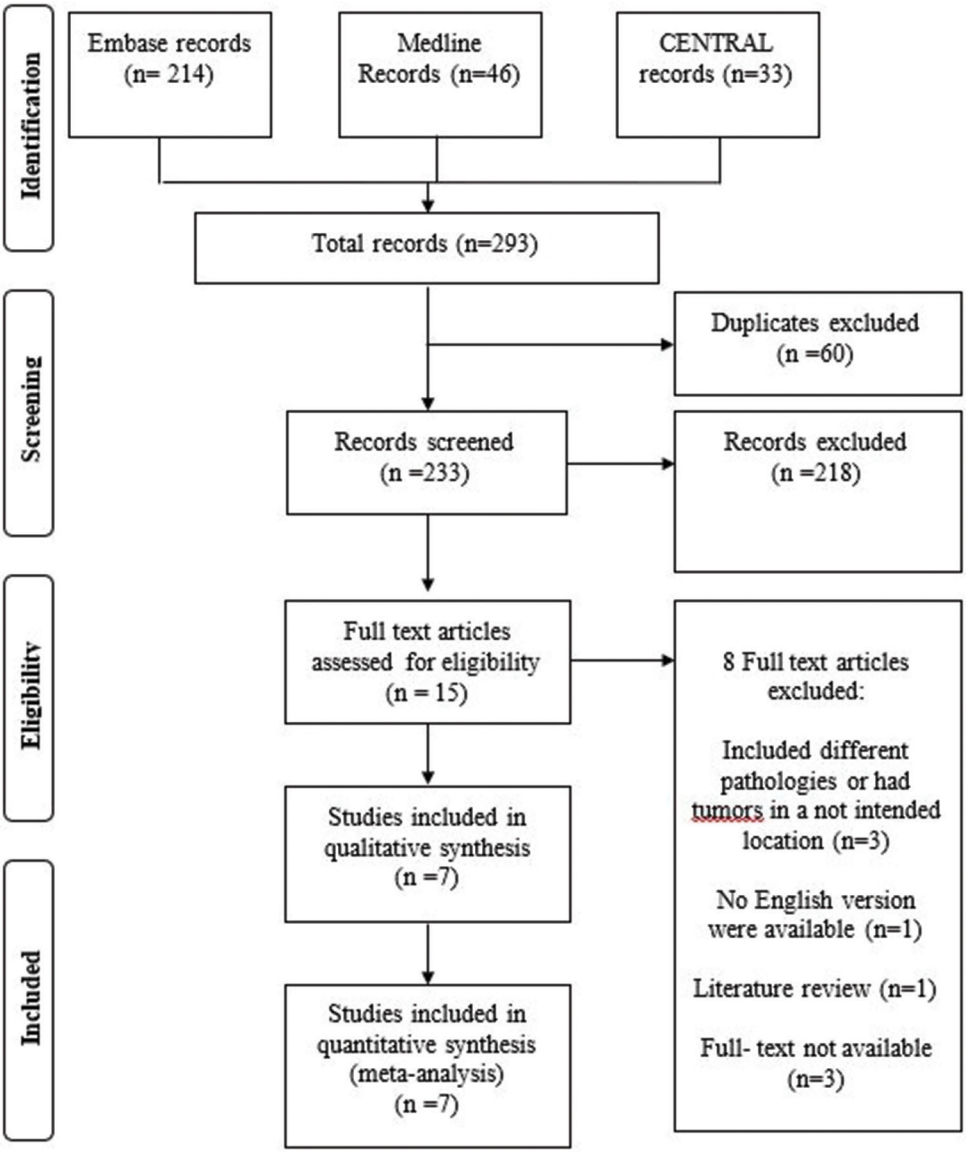

Figure 1: Flow diagram.

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; I^2 =7%) [Figure 3]. The result of the funnel plot for brain relaxation outcome was symmetrical [Supplementary B].

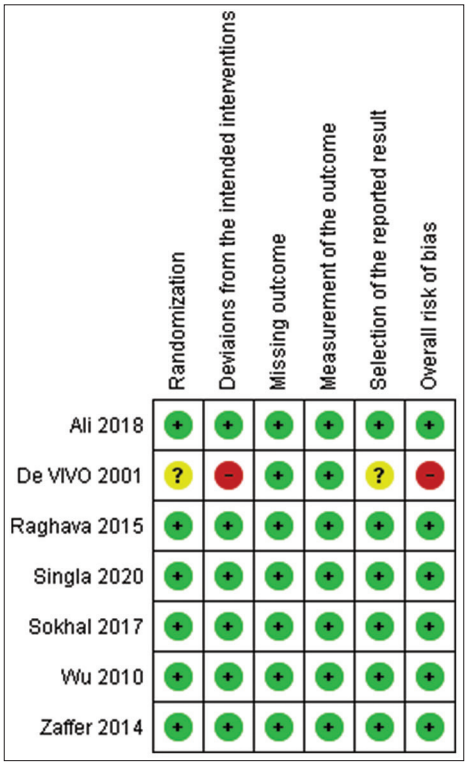

Figure 2: Risk of bias assessment.

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.[1,3,6,10,12,16,22] Thus, our meta-analysis only included two studies with a sample size of 89 participants.

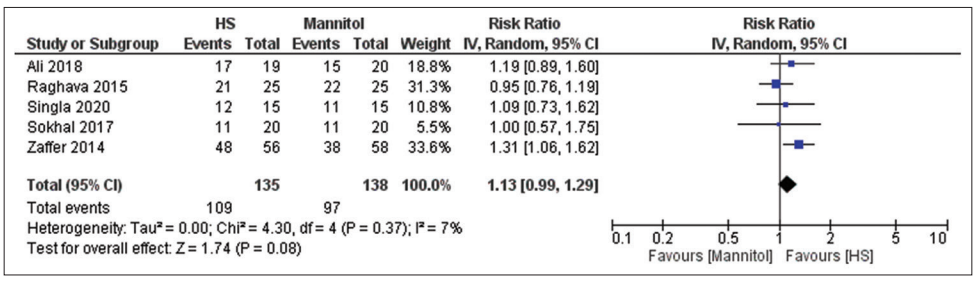

Figure 3: Brian relaxation forest plot.

Table 1: Characteristic of patients included in the studies.

Author	Study design	Age		Sex		Number of patients		Pre-operative GCS score		ASA	
		HS	Mannitol	HS	Mannitol	HS	Mannitol	HS	Mannitol	HS	Mannitol
Raghava *et al.* 2015	RCT	41.6±12.9	38.8±11.9	M (*n*=12); F (*n*=13)	M (*n*=9); F (*n*=16)	*n*=25	*n*=25	NR	NR	II (*n*=11), III (*n*=14)	II (*n*=12), III (*n*=13)
Ali *et al.* 2018	RCT	50.0±9.7	46.4±10.0	M (*n*=10); F (*n*=9)	M (*n*=11); F (*n*=9)	*n*=19	*n*=20	14.3±0.8	14.1±0.9	II (*n*=14), III (*n*=5)	II (*n*=15), III (*n*=5)
Sokhal *et al.* 2017	RCT	40.8±13.9	38.25±11.04 (22–60)	M (*n*=14); F (*n*=6)	M (*n*=11); F (*n*=9)	*n*=20	*n*=20	4.4±0.68	4.55±0.76	II (*n*=16), III (*n*=4)	II (*n*=19), III (*n*=1)
Zaffer *et al.* 2014	RCT	43.39±13.6	46.93±12.1	M (*n*=31); F (*n*=25)	M (*n*=28); F (*n*=30)	*n*=56	*n*=58	NR	NR	II (*n*=40), III (*n*=16)	II (*n*=35), III (*n*=23)
De Vivo *et al.* 2001	RCT	58 years (range 17–75)	58 years (range 17–75)	M (*n*=13); F (*n*=17)	M (*n*=13); F (*n*=17)	*n*=10	*n*=10	15	15	NR	NR
Wu *et al.* 2010	RCT	Median 56 (18–80)	54 (18–80)	M (*n*=56); F (*n*=66)	M (*n*=56); F (*n*=60)	*n*=122	*n*=116	NR	NR	II (*n*=26), III (*n*=96)	II (*n*=28), III (*n*=88)
Singla *et al.* 2020	RCT	40.40 (±14.98)	46.33 (±12.29)	M (*n*=8); Female (*n*=7)	Male (*n*=10); Female (*n*=5)	*n*=15	*n*=15	NR	NR	I (*n*=10), II (*n*=5), III (*n*=0)	I (*n*=13), II (*n*=2), III (*n*=0)

Author	Study design	Dose		Groups		Infusion method	Peri-operative complication		Post-operative complication	
		HS	Mannitol	HS	Mannitol	Both	HS	Mannitol	HS	Mannitol
Raghava *et al.* 2015	RCT	5 ml/kg	5 ml/kg	3%	20%	Central line	NR	NR	NR	NR
Ali *et al.* 2018	RCT	5 ml/kg	5 ml/kg	3%	20%	NR	NR	NR	NR	NR
Sokhal *et al.* 2017	RCT	5.35 ml/kg	5 ml/kg	3%	20%	Central line	Hypotension (*n*=0), pulmonary edema (*n*=0), decreased urine output (*n*=1), Paresis (*n*=2), Deep Vein Thrombosis (*n*=2), seizure (*n*=1), Pneumocephalus (*n*=1), Hematoma (*n*=0)	Hypotension (*n*=2), pulmonary edema (*n*=1), decreased urine output (*n*=0), Paresis (*n*=2), Deep Vein Thrombosis (*n*=0), seizure (*n*=3), Pneumocephalus (*n*=1), Hematoma (*n*=1)	Nausea, vomiting, headache, disorientation, restlessness, convulsion, weakness of limbs, and aphasia	

Table 1: *(Continued)*.

Author	Study design	Dose		Groups		Infusion method	Peri-operative complication		Post-operative complication	
		HS	Mannitol	HS	Mannitol	Both	HS	Mannitol	HS	Mannitol
Zaffer *et al.* 2014	RCT	5 ml/kg	5 ml/kg	3%	20%	Central line	NR	NR	NR	NR
De Vivo *et al.* 2001	RCT	3.5 ml/kg	0.5 g/kg	3%	18%	IV Bolus (Central line)	NR	NR	NR	NR
Wu *et al.* 2010	RCT	160 ml	150 ml	3%	20%	Central line and infusion pump	NR	NR	NR	NR
Singla *et al.* 2020	RCT	5 ml/kg	5 ml/kg	3%	20%	Central line	NR	NR	NR	NR

ASA: American Society of Anesthesiologists, GCS: Glasgow Coma Scale, NR: Not reported, HS: Hypertonic Saline, M: Male, F: Female

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.[10,12,22] 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.[3,12,16] 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

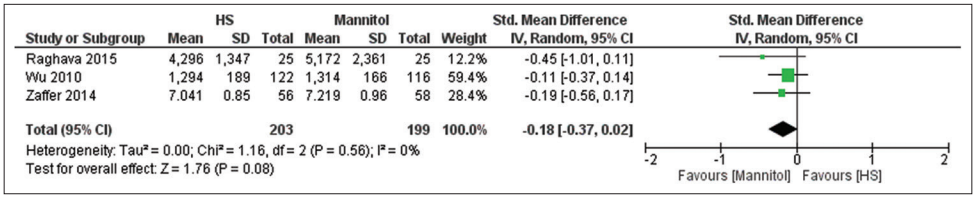

Figure 4: Perioperative fluid input forest plot.

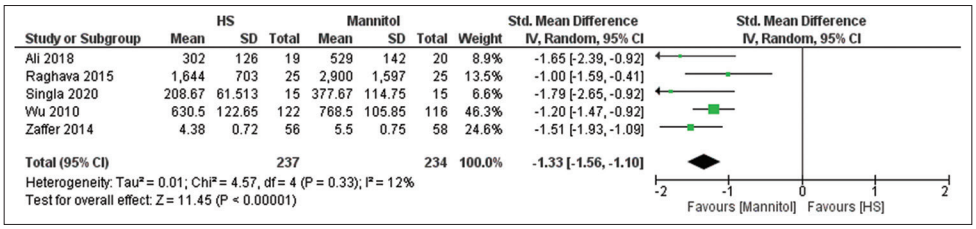

Figure 5: Urine output forest plot.

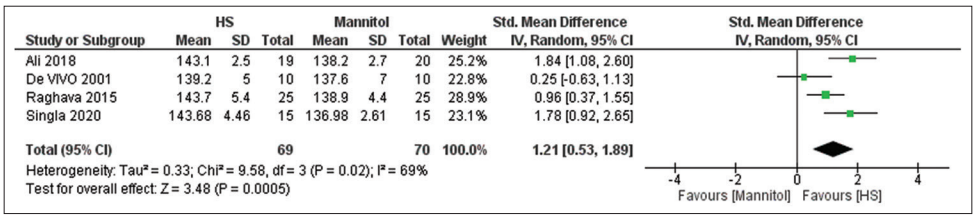

Figure 6: Serum Na^+ levels forest plot.

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.[11] 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.[5,15] 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. However, this study was on patients with TBI, and there was no mentioning of equiosmolar doses of HS and mannitol.[14] Another study done by Shao *et al*. showed that HS significantly reduces intra-operative ICP in patients undergoing neurosurgical procedures with different brain pathologies.[15] 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.[8,23]

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.[2] Singla *et al*. suggested that the increase in Na^+ levels in HS will return to normal within

48 h.[16] 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^+.[13]

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.[3,16] 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.[4]

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.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ali A, Tetik A, Sabanci PA, Altun D, Sivrikoz N, Abdullah T, *et al*. Comparison of 3% hypertonic saline and 20% mannitol for reducing intracranial pressure in patients undergoing supratentorial brain tumor surgery: A randomized, double-blind clinical trial. J Neurosurg Anesthesiol 2018;30:171-8.
2. Berl T, Robertson G. Pathophysiology of Water Metabolism. Philadelphia, PA: Saunders; 2000.
3. De Vivo P, Del Gaudio A, Ciritella P, Puopolo M, Chiarotti F, Mastronardi E. Hypertonic saline solution: A safe alternative to mannitol 18% in neurosurgery. Minerva Anestesiol 2001;67:603-11.
4. Dostal P, Dostalova V, Schreiberova J, Tyll T, Habalova J, Cerny V, *et al*. A comparison of equivolume, equiosmolar solutions of hypertonic saline and mannitol for brain relaxation in patients undergoing elective intracranial tumor surgery: A randomized clinical trial. J Neurosurg Anesthesiol 2015;27:51-6.
5. Fang J, Yang Y, Wang W, Liu Y, An T, Zou M, *et al*. Comparison of equiosmolar hypertonic saline and mannitol for brain relaxation during craniotomies: A meta-analysis of randomized controlled trials. Neurosurg Rev 2018;41:945-56.
6. Hans P, Bonhomme V. Why we still use intravenous drugs as the basic regimen for neurosurgical anaesthesia. Curr Opin Anaesthesiol 2006;19:498-503.
7. Hernández-Palazón J, Fuentes-García D, Doménech-Asensi P, Piqueras-Pérez C, Falcón-Araña L, Burguillos-López S. A comparison of equivolume, equiosmolar solutions of hypertonic saline and mannitol for brain relaxation during elective supratentorial craniotomy. Br J Neurosurg 2016;30:70-5.
8. Hinson HE, Stein D, Sheth KN. Hypertonic saline and mannitol therapy in critical care neurology. J Intensive Care Med 2013;28:3-11.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009;151:W65-94.
10. Malik ZA, Mir SA, Naqash IA, Sofi KP, Wani AA. A prospective, randomized, double blind study to compare the effects of equiosmolar solutions of 3% hypertonic saline and 20% mannitol on reduction of brain-bulk during elective craniotomy for supratentorial brain tumor resection. Anesth Essays Res 2014;8:388-92.
11. Ogden AT, Mayer SA, Connolly ES Jr. Hyperosmolar agents in neurosurgical practice: The evolving role of hypertonic saline. Neurosurgery 2005;57:207-15.
12. Raghava A, Bidkar PU, Prakash MV, Hemavathy B. Comparison of equiosmolar concentrations of hypertonic saline and mannitol for intraoperative lax brain in patients undergoing craniotomy. Surg Neurol Int 2015;6:73.
13. Rozet I, Tontisirin N, Muangman S, Vavilala MS, Souter MJ,

Lee LA, *et al*. Effect of equiosmolar solutions of mannitol versus hypertonic saline on intraoperative brain relaxation and electrolyte balance. Anesthesiology 2007;107:697-704.
14. Schwimmbeck F, Voellger B, Chappell D, Eberhart L. Hypertonic saline versus mannitol for traumatic brain injury: A systematic review and meta-analysis with trial sequential analysis. J Neurosurg Anesthesiol 2021;33:10-20.
15. Shao L, Hong F, Zou Y, Hao X, Hou H, Tian M. Hypertonic saline for brain relaxation and intracranial pressure in patients undergoing neurosurgical procedures: A meta-analysis of randomized controlled trials. PLoS One 2015;10:e0117314.
16. Singla A, Mathew PJ, Jangra K, Gupta SK, Soni SL. A comparison of hypertonic saline and mannitol on intraoperative brain relaxation in patients with raised intracranial pressure during supratentorial tumors resection: A randomized control trial. Neurol India 2020;68:141-5.
17. Sokhal N, Rath GP, Chaturvedi A, Singh M, Dash HH. Comparison of 20% mannitol and 3% hypertonic saline on intracranial pressure and systemic hemodynamics. J Clin Neurosci 2017;42:148-54.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al*. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
19. Tenny S, Patel R, Thorell W. Mannitol. Treasure Island, FL: StatPearls Publishing; 2021.
20. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
21. Witherspoon B, Ashby NE. The use of mannitol and hypertonic saline therapies in patients with elevated intracranial pressure: A review of the evidence. Nurs Clin North Am 2017;52:249-60.
22. Wu CT, Chen LC, Kuo CP, Ju DT, Borel CO, Cherng CH, *et al*. A comparison of 3% hypertonic saline and mannitol for brain relaxation during elective supratentorial brain tumor surgery. Anesth Analg 2010;110:903-7.
23. Ziai WC, Toung TJ, Bhardwaj A. Hypertonic saline: First-line therapy for cerebral edema? J Neurol Sci 2007;261:157-66.

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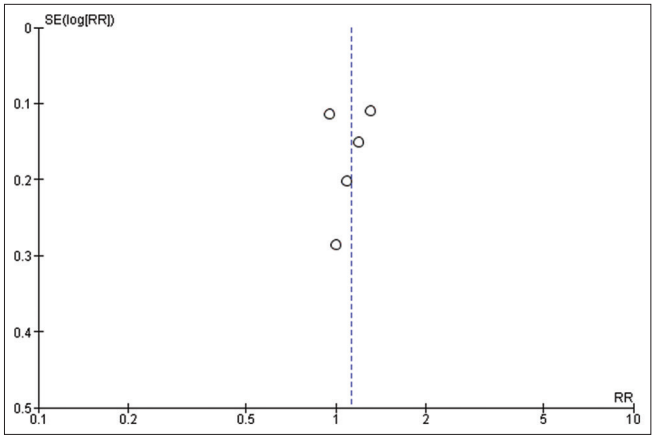
SUPPLEMENTARY

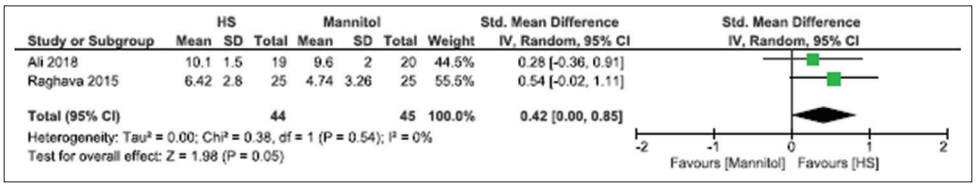
Supplementary A: Characteristics of included studies.

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/m^2), 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

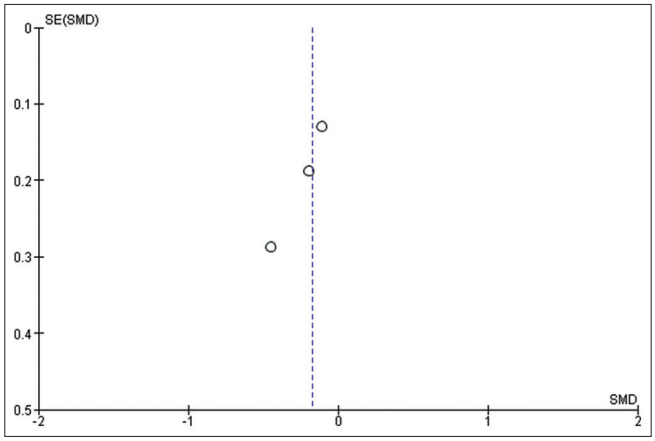
ASA: American Society of Anesthesiologists, GCS: Glasgow Coma Scale, NR: Not reported, HS: Hypertonic Saline



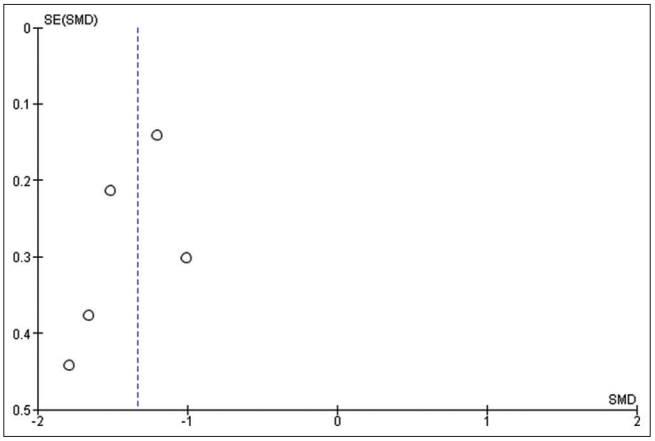
Supplementary B: Brain relaxation funnel plot.



Supplementary C: CVP forest plot.



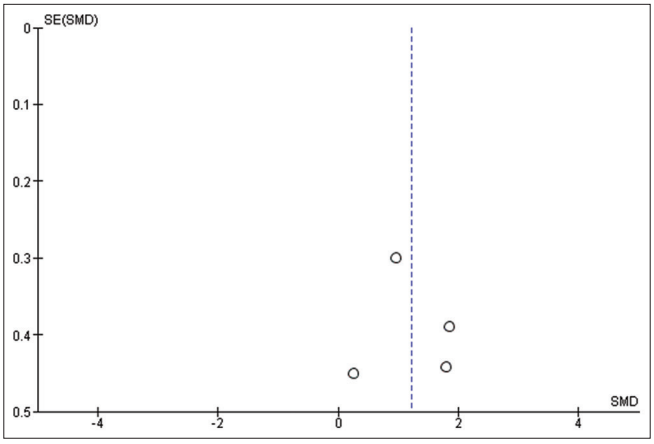
Supplementary D: Fluid input funnel plot.



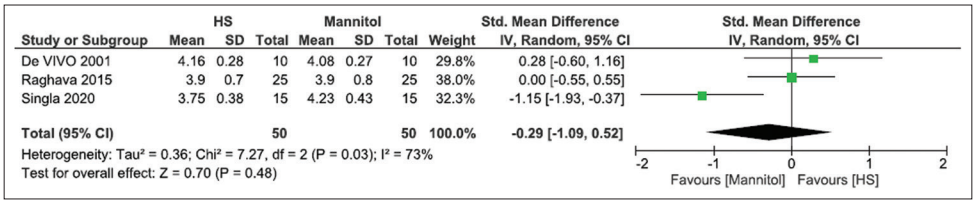
Supplementary E: Urine output funnel plot.

Supplementary F: Results after the sensitivity analysis.

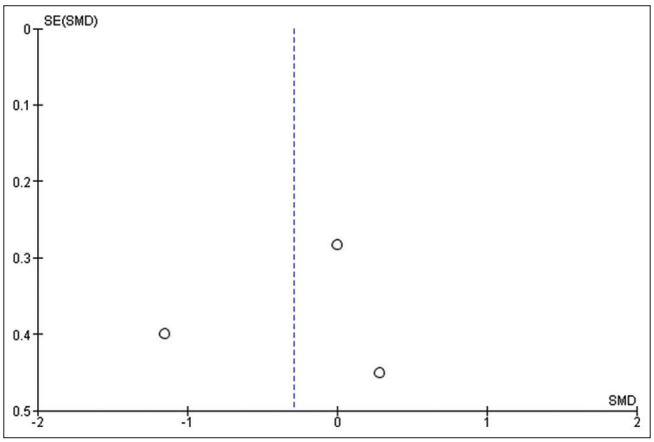
Outcomes	Number of studies	Number of patients	Standardized mean difference	95% CI	*P*-value	I^2
Na levels	3	119	1.47	0.86, 2.09	<0.001	53%
K levels	2	70	0.08	−0.39. 0.55	0.74	0%



Supplementary G: Na+ level funnel plot.



Supplementary H: Serum K+ levels forest plot.



Supplementary I: K+ level funnel plot.