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Original Article

Comparing equiosmolar hypertonic saline and mannitol for achieving brain relaxation in elective craniotomy patients: A systematic review and meta-analysis

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Received: 17 December 2023
Accepted: 19 February 2024
Published: 05 April 2024

DOI
10.25259/SNI_994_2023

Quick Response Code:

ABSTRACT

Background: This study strives to provide a current and thorough assessment of the comparative efficacy and safety between equiosmolar quantities of hypertonic saline (HS) and mannitol in facilitating brain relaxation for patients undergoing elective craniotomies.

Methods: This systematic review and meta-analysis, following preferred reporting items for systematic reviews and meta-analyses guidelines, compared the efficacy and safety of equiosmolar concentrations of mannitol and HS in elective craniotomies. PubMed, Scopus, Cochrane Library, ScienceDirect, and Proquest databases were searched using keywords related to mannitol, HS, and craniotomy. Results were analyzed through a random-effects model using Mantel–Haenszel risk ratio and standard mean difference. $P < 0.05$ was considered significant.

Results: Thirteen randomized controlled trials encompassing 965 patients (516 in the HS group and 448 in the mannitol group) were analyzed. The quality of studies was moderate-to-high, and no significant publication bias was observed. The primary outcome, brain relaxation, favored HS over mannitol without significant heterogeneity. Mannitol was associated with increased urine output compared to HS, irrespective of dose, with high heterogeneity. HS was linked to significantly reduced fluid input, confirmed by subgroup analysis with lower heterogeneity. No significant difference was found in serum osmolality between the two agents. Serum sodium (Na^+) levels favored HS, whereas arterial blood Na^+ levels also favored HS despite considerable heterogeneity. Maximum mean arterial pressure was higher with HS, but it displayed significant heterogeneity. Maximum central venous pressure showed no significant difference between the two agents, with moderate heterogeneity.

Conclusion: HS appears more effective than mannitol in achieving brain relaxation, and it may offer advantages in fluid management and Na^+ balance. Clinicians should consider these findings when selecting hyperosmotic agents for neurosurgical procedures. Further research is needed to address heterogeneity in certain outcomes and guide clinical practice.

Keywords: Brain relaxation, Craniotomy, Hypertonic saline, Mannitol

INTRODUCTION

Cerebral relaxation is a crucial neuroprotective measure to mitigate local hypoperfusion and cerebral ischemia due to surgical compression following intracranial surgery; therefore, achieving a relaxed brain is a fundamental goal in neurosurgical anesthesia.[7] It allows for brain retraction, reducing the risk of retractor-induced ischemia. Various methods induce brain relaxation by managing intracranial volume, including brain tissue, cerebrospinal fluid (CSF), and blood.[19]

During a neurosurgical procedure, osmotherapy is routinely utilized to lower intracranial pressure (ICP) and the volume of brain tissue, for which hyperosmotic drugs such as mannitol and hypertonic saline (HS) are delivered before the opening of dura mater, reducing the risk of transdural herniation and associated neurological deterioration.[3]

Mannitol is the preferred hyperosmotic medication, offering both immediate and delayed reductions in ICP.[28] The immediate effect is attributed to increased plasma volume, reduced blood viscosity, enhanced cerebral blood flow, and cerebral vasoconstriction, which collectively slow down the production of CSF. Meanwhile, the osmotic effect of the delayed action further contributes to lowering ICP.[19,21,28] Nevertheless, it is important to note that the use of mannitol may also be associated with significant adverse effects, including renal failure, a rebound increase in ICP, and depletion of intravascular volume.[11]

Notably, in comparison to mannitol, HS exerts its impact by establishing an osmotic gradient, leading to brain tissue dehydration and cerebral vasoconstriction, ultimately reducing ICP. It has recently rekindled attention as an alternative therapy and has lately been employed in neurosurgical patients because of its additional positive effects that promote gas exchange and partial pressure of oxygen in the blood, including an increase in cardiac output, a decrease in extravascular lung capacity, and an increase in mean arterial pressure (MAP).[3,4,17,20]

Clinical research comparing the impact of HS and mannitol on ICP has indicated that HS is, at the very least, as effective as, if not more effective than, mannitol in addressing elevated ICP.[19,21] Some studies have even suggested that HS outperforms mannitol in terms of brain relaxation.[5,13,28] Furthermore, the dose and osmolarity of mannitol or HS utilized in these studies have varied, complicating the interpretation of their results. Hence, this study aims to offer an up-to-date and comprehensive evaluation of the relative effectiveness and safety of equiosmolar amounts of HS compared to mannitol in achieving brain relaxation among patients undergoing elective craniotomies. This analysis seeks to provide valuable guidance to clinicians, enabling them to make well-informed decisions regarding the use of these agents in neurosurgical practice.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards were followed for conducting this systematic review and meta-analysis.[16]

Search strategy

We searched extensively through a number of databases, including PubMed, Scopus, Cochrane Library, ScienceDirect, and Proquest, to find randomized controlled trials (RCTs) that contrasted the effects of mannitol and HS at equiosmolar concentrations on patients undergoing elective craniotomies. To get relevant results, In August 2023, we conducted a search using both Medical Subjects Headings phrases and specific keywords such as "mannitol," "hypertonic saline," "brain relaxation," "osmotherapy," "craniotomy," and "neurosurgery." No additional restrictions were applied to the search criteria.

Study selection and eligibility criteria

Two reviewers (AS and IM) conducted an independent search and screening of journals. The inclusion criteria for our study were as follows: (1) Only RCTs were considered; (2) studies had to involve the use of equal osmolar amounts of HS as compared to mannitol; (3) participants should be patients undergoing elective craniotomies for a range of brain conditions; (4) the studies needed to report relevant outcomes; (5) the documentation had to be in English; and (6) the full text of the studies had to be accessible.

Data extraction and quality assessment

Two authors (MAS and MSM) separately gathered the required data, and any discrepancies were resolved through discussion and the involvement of a third review author (BSR). Two investigators (BSR and MAO) individually evaluated the study quality and bias risk of each research study. They used the Cochrane Risk of Bias tool specifically for RCT.[10] In cases of differing assessments, they resolved any disagreements through consensus or sought the input of a third investigator (MSM).

Data analysis

Examining the effects of brain relaxation was the main focus of our observation. The degree of brain relaxation was measured using a 4-point scale that went from "perfectly relaxed" to "bulging brain" or a 3-point scale that included "tight," "appropriate," and "soft." We used judgments of "perfectly relaxed," "satisfactory relaxed," "appropriate," and "soft" as markers of good brain relaxation to produce binary results. To evaluate this main outcome, the odds ratio and associated 95% confidence intervals (CIs) were used.

The secondary outcomes we took into account included the following: Total urine output and fluid intake were assessed using standardized mean difference (MD) with a 95% CI; serum sodium (na), arterial sodium, plasma osmolality, maximum MAP, and maximum central venous pressure (CVP) were assessed using MD with a 95% CI. To further investigate the relationship between total urine production and various dosage levels, we also performed subgroup analyses.

A significance level of $P < 0.05$ was considered statistically significant, and the analysis incorporated 95% CIs. Sensitivity analyses were initiated by excluding potentially questionable studies to identify sources of heterogeneity, which was gauged using I^2 and the *P*-value derived from the Chi-square test; for outcomes displaying considerable heterogeneity, characterized by an I^2 value surpassing 50%, a random-effects model was employed. The meta-analysis and generation of forest plots were performed using Review Manager version 5.4. In addition, potential publication bias was assessed through a visual inspection of the funnel plot.

RESULTS

Literature search results study characteristics

We initially found a total of 253 articles. We examined the titles and abstracts of the remaining papers and included 21 studies after deleting 33 duplicate research. We carefully examined 18 full-text studies. Out of them, our study incorporated the most recent 13 RCTs that were published between 2007 and 2023, as depicted in Figure 1. In total, 965 patients were part of the analysis, with 487 (51%) were being male and 468 (49%) female. Out of these 965 patients, 516 (54%) were assigned to the HS group, whereas 448 (46%) were assigned to the mannitol group, as illustrated in Table 1.

Quality assessment and publication bias

Figure 2 displays the findings of the risk of bias assessment. Overall, the studies were of moderate to high quality. The publication bias was assessed using a funnel plot. On visual assessment, the plot showed that the studies were scattered throughout, indicating non-significant bias [Figure 3].

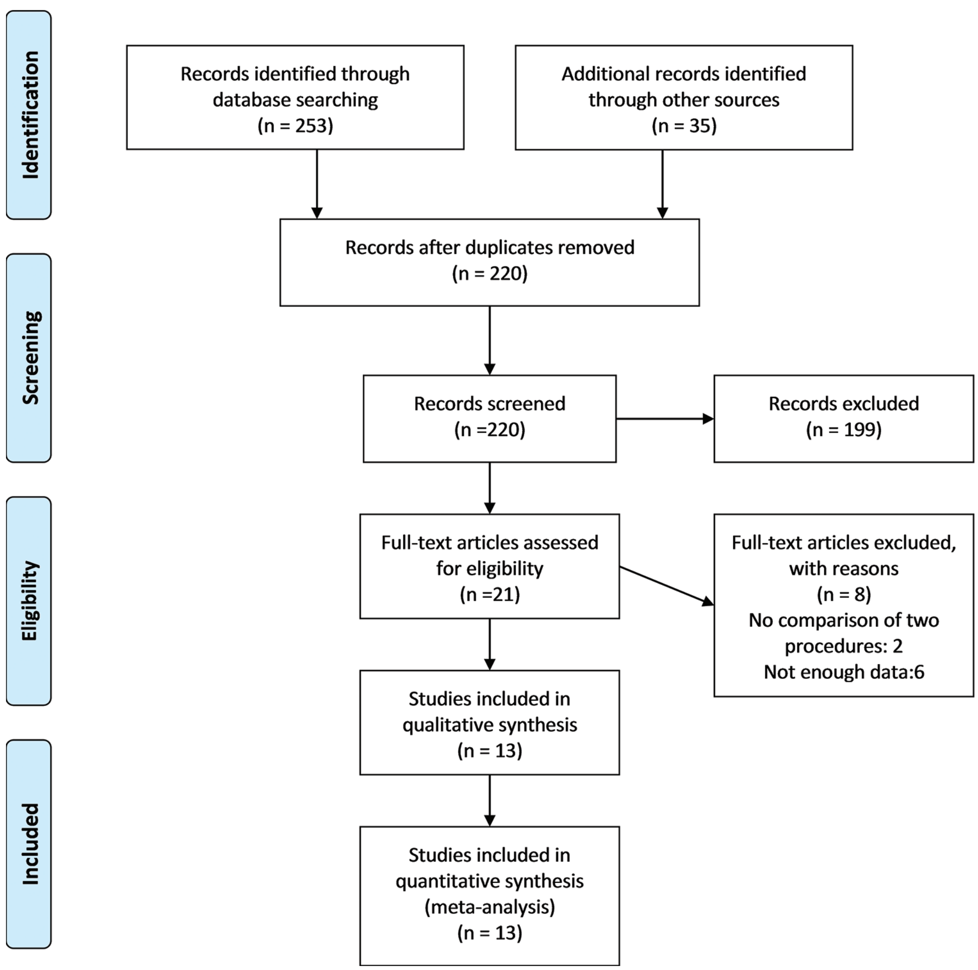

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses diagram.

Table 1: Baseline characteristics table.

Name of study	Type of Study	Year of Study	Country	Number of patients	Gender of patient		HS					Mannitol				
					Male	Female	No. of patients	Male/female *n* (%)	Mean age	Duration of surgery	ASA status (I/II/III)	No of patients	Male/female *n* (%)	Mean Age	Duration of surgery	ASA status (I/II/III)
Tsaousi *et al.*[27]	Prospective	2023	Greece	51	15	36	25	6/19	58.6±13.1	352±141 (min)	0/6/19	26	9/17	51.8±19.3	334±102 (min)	0/9/17
Hernández-Palazón *et al.*[8]	Prospective	2023	Spain	60	32	28	30	17/13	51 (40–65)	347±170 (min)	0/17/13	30	15/15	52 (40–65)	286±94 (min)	0/14/16
Bhatnagar *et al.*[3]	Prospective	2021	India	90	71	19	35	9/26	35	2.20±0.47	NA	26	6/20	35	2.17±0.41	NA
Barik *et al.*[2]	Prospective	2021	India	90	47	43	30	17 (56.7)/13 (43.3)	40.13	268.2 (min)	16/14	30	19 (63.3)/11 (36.7)	40.6	258.2 (min)	16/14
Singla *et al.*[24]	Prospective	2020	India	30	18	12	15	8/7	40.40±14.98	NA	10/5/0	15	10/5	46.33±12.29		13/2/0
Ali *et al.*[1]	Prospective	2018	Turkey	48	21	18	24	10 (52.6)/9 (47.4)	50.0±9.7	NA	14/5	24	11 (55)/9 (45)	46.4±10.0		15/5
Sokhal *et al.*[25]	Prospective	2017	India	40	25	15	20	14 (60)/6 (30)	40.8±13.9	7.15 (h)	0/16/4	20	11 (55)/9 (45)	38.25±11.0	7.44 (h)	0/19/1
Hernández-Palazón *et al.*[9]	Prospective	2017	Spain	40	22	18	20	9 (45)/11 (55)	48±13	NA	0/9/11	20	13 (65)/7 (35)	49±14	NA	0/8/12
Dostal *et al.*[5]	Prospective	2015	Czech Republic	74	30	44	36	16/20	52.1±13.1	248.5±79.1 (min)	0/30/6	38	14/24	53.5±13.0	295.9±123.8	0/28/10
Raghava *et al.*[19]	Prospective	2015	India	50	21	29	25	12/13	41.6±12.9		0/11/14	25	9/16	38.8±11.9		0/12/13
Malik *et al.*[13]	Prospective	2014	India	114	59	55	114	31/25	43.39	248±60.0	0/40/16	58	28/30	46.93	262±56.50	0/35/23
Wu *et al.*[28]	Prospective	2010	Taiwan	238	112	126	122	56/66	56	268 (150–656) min	0/26/96	116	56/60	54	257 (149–520) min	0/28/88
Rozet *et al.*[21]	Prospective	2007	America	40	14	25	20	8/12	49±13		0/7/10	20	7/13	48±11		0/6/10

HS: Hypertonic saline, ASA: American society of anesthesiologists, NA: Not applicable

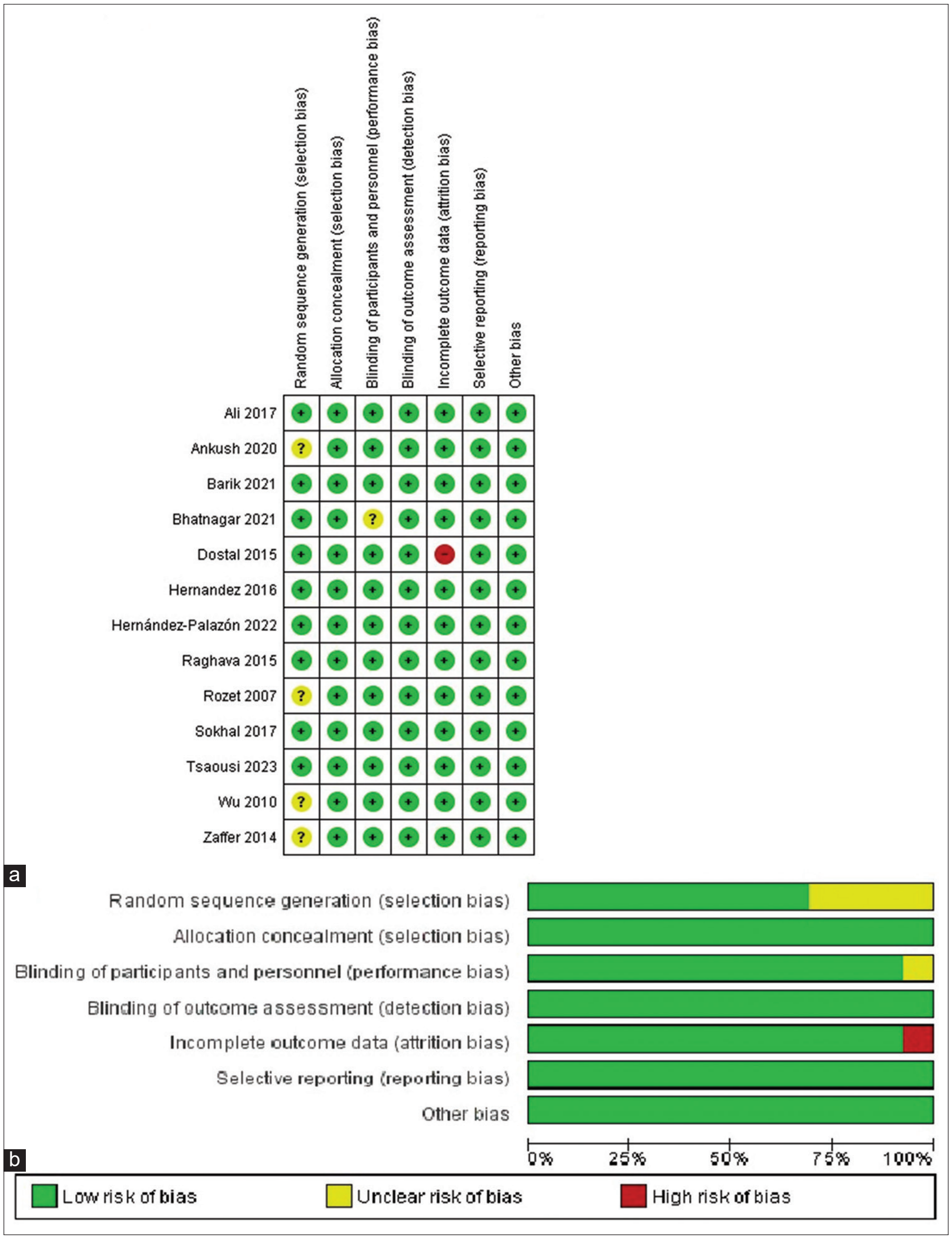

Figure 2: (a and b) Quality assessment.

Brain relaxation

In all 13 studies, this particular outcome was reported, involving a total of 936 patients. The results consistently show that HS is significantly more effective than mannitol in achieving improved brain relaxation scores. Notably, there was no notable variation observed in the outcomes across these studies [Figure 4].

Urine output

Out of the 13 studies, 9 of them provided data on urine output, involving a total of 726 patients. Mannitol was found to be linked to a noteworthy increase in total urine output when compared to HS. Due to the observed high heterogeneity, we conducted a sensitivity analysis to pinpoint the source of this variation. The subgroup analysis demonstrated that irrespective of the dosage administered, there was a substantial increase in urine output when using mannitol as opposed to HS [Figure 5].

Fluid input

Among the complete set of 13 studies, eight of them presented data on fluid input, encompassing a total of

687 patients. It was evident that HS was linked to notably reduced total fluid input when contrasted with mannitol. Due to the observed high heterogeneity, a subgroup analysis was conducted, which corroborated the previous findings but with significantly reduced heterogeneity [Figure 6].

Serum osmolality

Out of all the studies, only four of them provided information on this particular outcome, involving a total of 215 participants. The data did not reveal any significant distinction in serum osmolality when comparing the use of mannitol and HS in elective craniotomies. To pinpoint the origin of the high heterogeneity observed, a sensitivity analysis was conducted, further confirming that there is no disparity in serum osmolality between mannitol and HS [Figure 7].

Serum Na^+

In the analysis, data from a subset of five out of 13 studies were considered, encompassing a total of 253 sampled patients. The findings suggest that HS exhibited favorable outcomes for brain relaxation in comparison to mannitol. Notably, there was no noteworthy evidence of significant heterogeneity among the included studies [Figure 8].

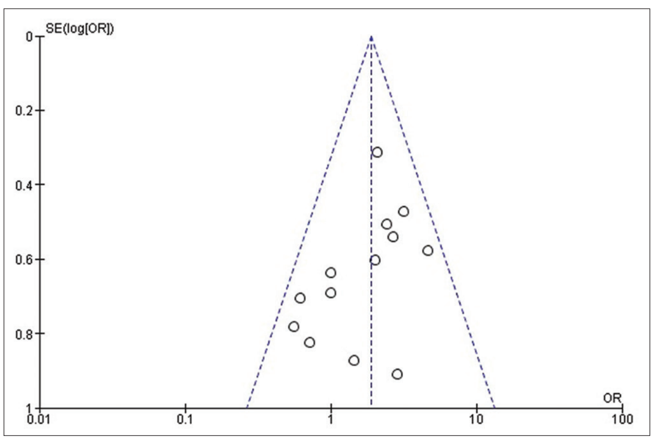

Figure 3: Funnel plot between hypertonic saline and mannitol for brain relaxation. SE: Standard error, OR: Odds ratio.

Arterial blood Na^+ levels

Out of the studies analyzed, only five studies provided data on the outcome, involving a combined sample size of 439 patients. Mannitol exhibited notably lower relaxation scores compared to HS, even in the presence of considerable heterogeneity across the studies [Figure 9].

Max MAP

In the analysis, data from a subset of five out of the 13 studies were considered, encompassing a total of 253 sampled patients. The findings suggest that HS exhibited favorable outcomes for brain relaxation in comparison to mannitol. Notably, there was evidence of significant heterogeneity among the included studies [Figure 10].

Max CVP

Among the set of 13 included studies, seven studies provided data on the outcome related to maximum CVP, involving a collective sample size of 374 patients. No significant outcomes were identified for either HS or mannitol. To better understand the source of observed high heterogeneity, a sensitivity analysis was conducted, which reaffirmed a slightly more favorable score associated with HS, accompanied by a moderate level of heterogeneity [Figure 11].

DISCUSSION

This meta-analysis is an update on Theodorus' previous meta-analysis in 2022.[12] We incorporated 3 RCTS that have been published since the initiation of the last meta-analysis.[3,8,27] Our results indicate that HS leads to a notable improvement in inducing greater brain relaxation in comparison to

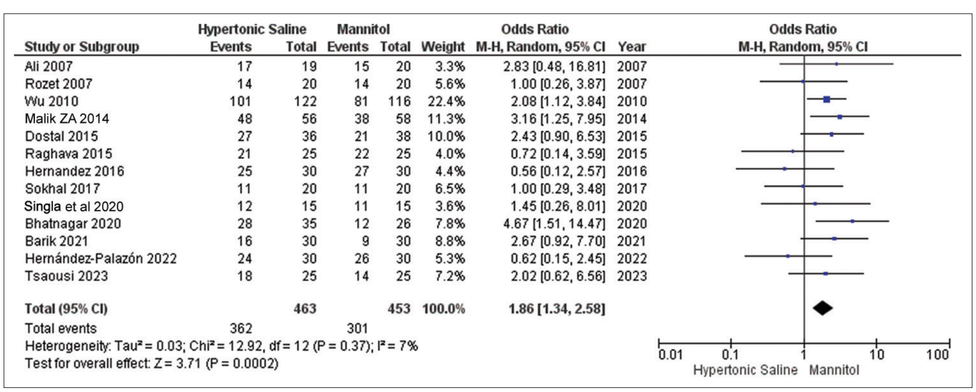

Figure 4: Brain relaxation, M-H: Mantel-Haenszel, CI: Confidence interval.

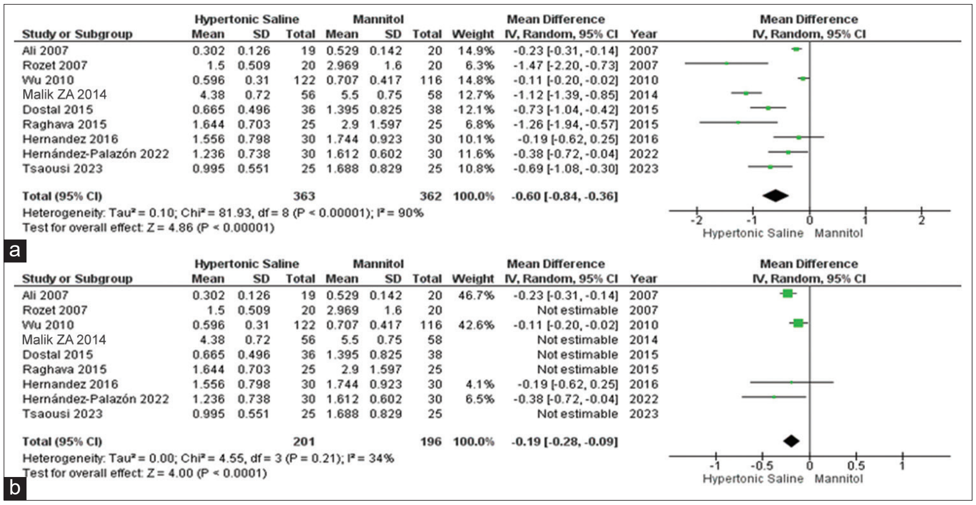

Figure 5: (a) Urine output (b) sensitivity analysis. SE: Standard error, CI: Confidence interval.

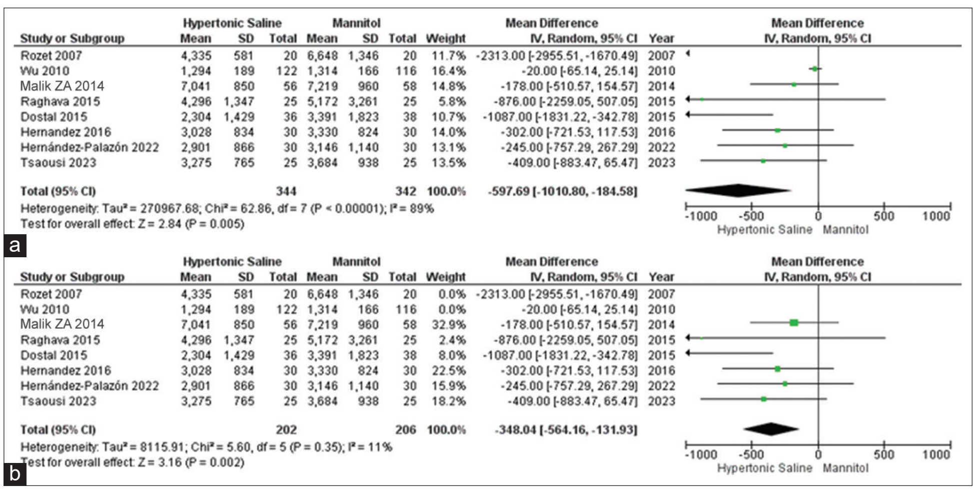

Figure 6: (a) Fluid input (b) sensitivity analysis. SE: Standard error, CI: Confidence interval.

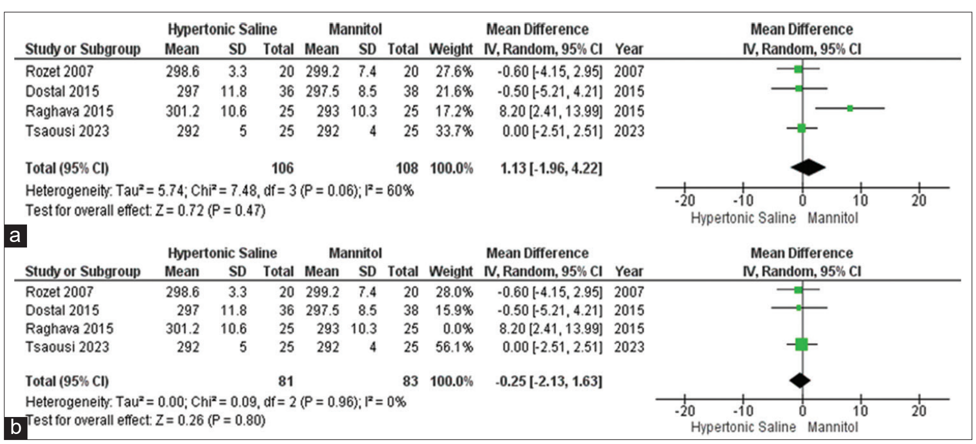

Figure 7: (a) Serum osmolality (b) sensitivity analysis. SE: Standard error, CI: Confidence interval.

mannitol. We also observed a substantial decrease in overall urine production and fluid intake, with serum osmolality remaining unchanged. In addition, there was a significant rise in both serum and arterial Na^+ levels within the HS

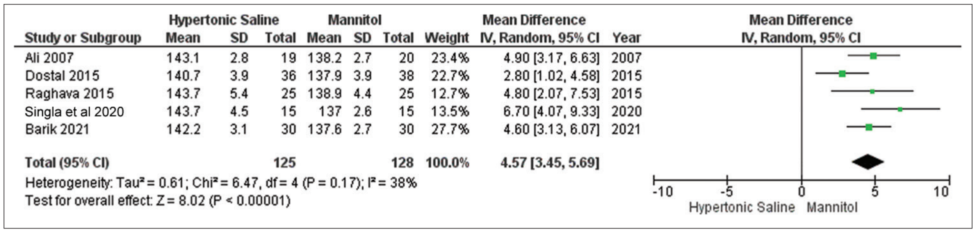

Figure 8: Serum Na^+. SE: Standard error, CI: Confidence interval.

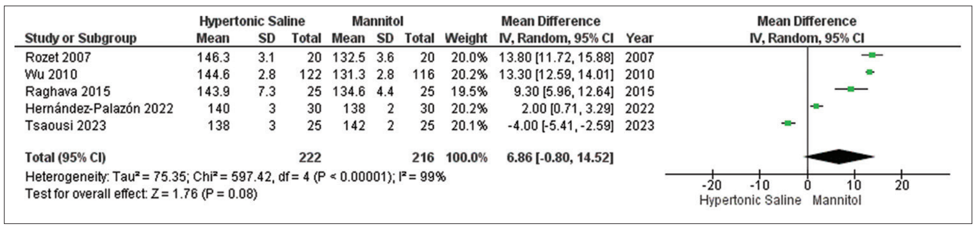

Figure 9: Arterial blood Na^+ level. SE: Standard error, CI: Confidence interval.

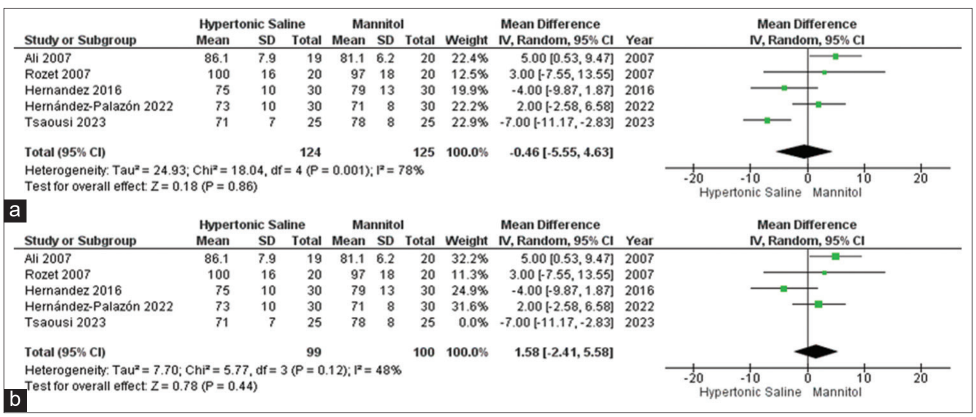

Figure 10: (a) Max mean arterial pressure (b) sensitivity analysis. SE: Standard error, CI: Confidence interval.

group compared to the mannitol group. These findings were consistent with the previous results by Theodorus.

However, the three new studies, we included revealed that the max MAP and max CVP were higher for HS as compared to mannitol.[3,8,27] The results for increased max MAP were also in line with Joacil's findings in his 2010 research.[4] This is different from the previous study by Theodorus, where they found no difference in max MAP as well as max CVP between the two solutions.[12]

Our meta-analysis revealed that HS is linked to a notably higher brain relaxation score in comparison to mannitol which is in line with the result of the previous meta-analysis.[6,12,22]

Just like mannitol, its primary mode of action involves generating an osmotic gradient across the blood-brain barrier (BBB), leading to a shift in cerebral fluid and a reduction in ICP and cerebral swelling.[3] The "reflection coefficient" (RC) of the hyperosmolar solute, which establishes the relative impermeability of an intact BBB to the solute, affects its efficacy. A solute with an RC of 1 is completely impermeable, and one with an RC of 0 is optimally porous. Because HS has a higher RC compared to mannitol (1.0 vs 0.9), indicating lower permeability through the BBB, there is a reduced likelihood of ICP increasing on its discontinuation.[28] Nevertheless, given that the majority of conditions necessitating osmotic therapy are linked to BBB disruption, this distinction may hold little significance. Enhancing blood rheology, lowering CSF production, and having anti-inflammatory properties are some of the other therapeutic effects of HS that help lower ICP and promote better brain relaxation.[2] Mishra *et al.*[15] and Wu *et al.*[28] conducted studies comparing the effects of 3% HS and 20% mannitol on patients undergoing surgery for supratentorial brain tumors that also found better brain relaxation with HS than mannitol.

The findings from this meta-analysis indicated that HS was linked to elevated plasma Na^+ levels and exhibited a comparatively reduced diuretic efficacy when contrasted with mannitol proven by reduced urine output. Elevated

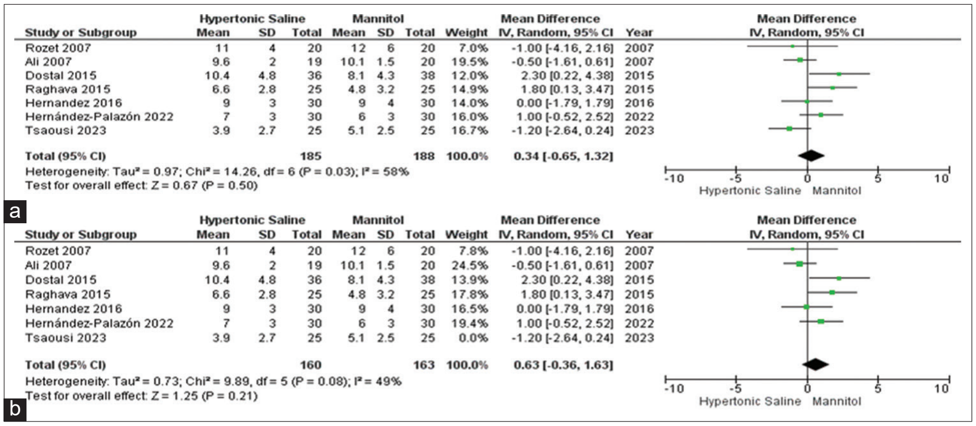

Figure 11: (a) Max central venous pressure (b) sensitivity analysis. SE: Standard error, CI: Confidence interval.

serum Na^+ levels trigger the production of antidiuretic hormones, resulting in absorption of free water by the kidneys resulting in lower urine output by HS.[28] As a widely accepted concept, effectively managing fluids during surgery is essential for preserving the equilibrium of bodily fluids and ensuring stable cardiovascular function during neurosurgical procedures. Reduced urinary excretion with HS indicates a decreased need for fluid administration during surgery, as demonstrated in our meta-analysis results, which highlight that HS is linked to lower intraoperative fluid requirements. Conversely, mannitol leads to an initial reduction in serum Na^+ levels, followed by a gradual rise as water dilutes serum electrolytes over time.[6] This hyponatremia in patients treated with mannitol can be attributed to alterations in osmolarity and the initial movement of fluid into the intravascular space driven by the osmotic gradient, leading to hemodilution. Increased mannitol dosages were associated with a dose-dependent elevation in osmolarity, likely leading to a corresponding dose-dependent reduction in brain water content.[26]

The potent diuretic effect of mannitol can lead to hypovolemia, an undesirable condition during neurosurgical procedures for which surgeons should be aware. In addition to this, Rozet *et al*. concluded higher serum lactate levels as a result of diuresis in patients treated with mannitol.[21] In summary, HS can demonstrate enhanced hemodynamic stability when compared to mannitol. However, surgeons must exercise caution due to the potential for hypernatremia associated with the clinical application of HS.

Based on multiple previous meta-analyses, the most frequently observed adverse outcomes are related to these electrolyte imbalances, such as hypernatremia, which can prove to be significant in patients with electrolyte abnormalities.[18] However, a substantial body of prior research indicates that hypernatremia resulting from HS infusion is temporary, with serum Na^+ levels typically returning to normal by the study's conclusion, particularly after a single infusion.[14,18,23] This finding aligns with the absence of severe adverse events associated with hypernatremia in the trials included in the study.

Incorporating three new studies into our analysis showed that HS consistently raised both maximum MAP and maximum CVP compared to mannitol. This is particularly valuable in elective craniotomies, where maintaining adequate cerebral perfusion pressure (CPP) is crucial. Higher MAP levels achieved with HS can help maintain the desired CPP range, reducing the risk of cerebral ischemia during surgery. In addition, HS has a greater propensity to increase CVP when compared to mannitol. While an elevated CVP can be beneficial in specific situations, such as managing ICP in patients with intracranial hypertension, it may present challenges in patients with compromised cardiac function. On the other hand, mannitol demonstrated a relatively minor impact on CVP, which could be advantageous in cases prioritizing the avoidance of fluid overload and excessive CVP elevation.[2] Although, it is worth noting that our analysis revealed substantial variability among the included studies.

CONCLUSION

Our updated systematic review and meta-analysis indicate that equiosmolar doses of HS outperform mannitol in terms of brain relaxation in patients undergoing elective craniotomies. However, the selection of the osmotic agent should be based on the patient's clinical condition, safety considerations, and surgical objectives. Further research and long-term studies are needed to refine our understanding of the comparative effectiveness of these osmotic agents and their impact on patient outcomes in neurosurgery.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Rangwala BS, Noor T, Shakil A, Mustafa M, Shafique M, Manan S, *et al*. Comparing equiosmolar hypertonic saline and mannitol for achieving brain relaxation in elective craniotomy patients: A systematic review and meta-analysis. Surg Neurol Int. 2024;15:116. doi: 10.25259/SNI_994_2023