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REVIEW

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Equiosmolar doses of hypertonic saline versus mannitol for brain relaxation in patients undergoing elective craniotomies: an updated systematic review and meta-analysis

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Abstract

Background: Hypertonic saline and mannitol are hyperosmolar agents frequently used to lower ICP and relax the brain during surgeries. Several methods have been used to achieve a good and relaxed brain, such as hyperventilation, cerebrospinal fluid drainage, head position correction, and administration of hyperosmolar agents. Comparing equiosmolar doses between hypertonic saline and mannitol in patients undergoing elective craniotomies is important to further notice the differences in several outcomes. This study aims to compare the outcome of hypertonic saline versus mannitol on brain relaxation in patients undergoing elective craniotomy.

Results: 10 articles from 2007 to 2021 were included. Hypertonic saline is associated with better brain relaxation (OR = 1.84, 95% CI 1.31–2.59; $P = 0.001$) but significantly increase blood natrium level, both serum and arterial (MD = 3.03, 95% CI 1.70–4.36; $P = < 0.001$ and MD = 7.14, 95% CI 0.04–14.24; $P = < 0.001$, respectively). Mannitol was associated with increased fluid input and urine output (SMD = − 0.56, 95% CI − 0.98 to − 0.15; $P = < 0.001$ and SMD = − 0.96, 95% CI − 1.42 to − 0.50; $P = < 0.001$, respectively). Serum osmolality and hemodynamic parameters difference was insignificant.

Conclusions: Hypertonic saline is associated with significantly better brain relaxation score and increased blood sodium level without increase in urine. This may prove to be clinically significant in patients with electrolyte imbalance.

Keywords: Intraoperative brain relaxation, Hypertonic saline, Mannitol

Introduction

Cerebral relaxation is an important component of neuroanesthesia [1]. A good, relaxed brain improves surgical access and widens the surgical view for the surgeon [2]. It minimises retraction, reduces local hypoperfusion and cerebral ischemia, and, therefore, minimises the risk of complication and postoperative neurological deficit [1, 3]. Several methods have been used to achieve a good and relaxed brain, such as hyperventilation, cerebrospinal fluid drainage, head position correction, and administration of hyperosmolar agents [4]. Mannitol is the most popular hyperosmolar agent used for osmotherapy [5]. Hyperosmolar agents such as mannitol and hypertonic saline exert their effect via two mechanisms [6, 7]. Fast-acting effect through rheological effects, plasma expansion, and delayed effect through its osmotic action. This increases plasma osmolarity to shift fluid from the brain parenchyma into the intravascular space. Both solutions

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are routinely used in neurosurgery to treat intracranial hypertension. Mannitol is associated with various adverse events, such as hypovolemia, nephrotoxicity, and rebound phenomenon [8]. Hypertonic saline, due to its higher sodium content, is also associated with several adverse events, such as metabolic acidosis and central pontine myelinolysis (CPM) [9, 10]. There have been no reports of CPM after the use of HS in reducing ICP to date.

Several randomised controlled trials (RCTs) have been done, aiming to compare both solutions in their safety and efficacy. There were two meta-analyses initiated in 2015 and 2017 favouring hypertonic saline as the superior agent to reduce ICP and relax the brain. Since then, there have been 4 new RCTs conducted [5, 11–13]. We aimed to update the comparison of these solutions on their safety and efficacy in producing brain relaxation, along with their effect on fluid status, sodium content, and hemodynamic parameters.

Methods

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Search strategy

We searched Scopus, Cochrane Library databases, ScienceDirect, and Proquest for RCTs comparing equiosmolar doses of hypertonic saline versus mannitol for brain relaxation in patients undergoing elective craniotomies. We used Medical Subjects Headings (MESH) terms and keywords as follows: "mannitol," "hypertonic saline," "brain relaxation," "osmotherapy," "craniotomy," and "neurosurgery". No other restrictions were applied. The search commenced in early July 2022.

Eligibility and selection criteria

Two reviewers searched and independently screened the journals. Criteria of inclusion include the following: (1) studies have to be Randomised Controlled Trials (RCTs); (2) Equiosmolar doses of hypertonic saline versus mannitol have to be used; (3) Patients undergoing elective craniotomy surgeries of all brain pathologies; (4) reporting relevant outcomes; (5) written in English; (5) full text is available.

Two authors extracted the data needed independently. Disagreements were resolved through discussion. One author assessed the risk of bias using Cochrane risk of bias through Review Manager [15]. Another author rated the quality of evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) through the GRADEpro GDT Web app [16, 17]. Risk of bias table and a summary of findings with GRADE recommendation were generated.

Data synthesis and analysis

The primary outcome observed is the results of brain relaxation. Brain relaxation was assessed using a 4-point scale (perfectly relaxed, satisfactory relaxed, firm brain, bulging brain) or a 3-point scale (tight, appropriate, and soft). We categorised "perfectly relaxed," "satisfactory relaxed," "appropriate," and "soft" as good brain relaxation and generated dichotomous results. The outcome was assessed using the odds ratio (OR) with 95% confidence intervals (CI). Secondary outcomes were as follows: total urine output and fluid input were assessed using standardised mean difference (SMD) with 95% CI, serum sodium, arterial sodium, plasma osmolality, max mean arterial pressure (MAP) and max central venous pressure (CVP) were assessed using mean difference (MD) with 95% CI. Subgroup analyses were conducted on total urine output according to the different doses used.

A P value of <0.05 is considered statistically significant, and 95% confidence intervals were used. Sensitivity analyses were commenced by removing suspicious studies to find the source of heterogeneity. Heterogeneity was assessed using I2 and P value for Chi-square. Publication bias was analysed using a visual inspection of the funnel plot. A random-effects model was used in outcomes with high heterogeneity, presented by an I2 value of $>50\%$. We used Review Manager version 5.4 to process our meta-analysis and generate forest plots.

Results

Trial characteristics

A total of 181 Articles were identified initially. 12 duplicate studies were removed. 13 studies were included after screening the title and abstract. 11 full-text studies were thoroughly reviewed. The final 10 RCTs that were published from 2007 to 2021 were included in the study, as represented in Fig. 1. A total of 745 patients were included, consisting of 371 (49.7%) males and 374 (50.2%) females. Of the 745 patients, 373 (50%) were allocated in the HS group, while 372 (49.9%) were allocated in the mannitol group.

Risk of bias assessment and quality of evidence

The risk of bias assessment results is shown in Fig. 2. All studies included had an overall moderate risk of bias. Of the 10 studies included, 6 studies defined random sequence generation using computer-generated randomization or computerized random number generation and were deemed a low risk of bias [2, 5, 11, 13, 18, 19]. 4 of the studies did not define the sequence generation and were deemed the unclear risk of bias

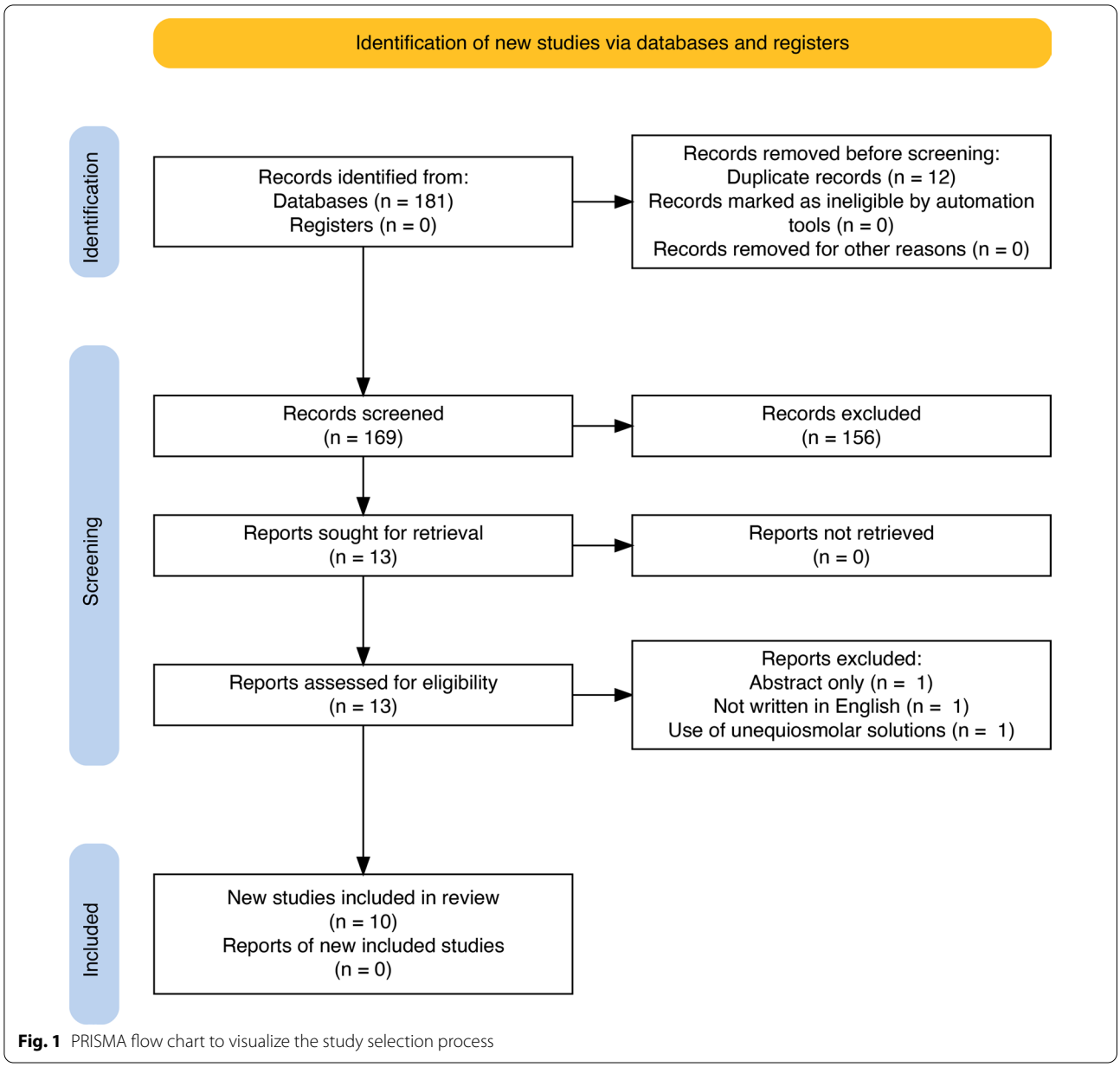

Fig. 1 PRISMA flow chart to visualize the study selection process

[12, 20–22]. One of the studies was rated with a high risk of bias in the domain of incomplete outcome data due to it having an unequal number of patients in each group with no explanation [18].

The GRADE evidence profile was generated using the GRADEproGDT web app, and the summary of findings alongside can be found in Table 1. Quality of evidence ranges from very low to moderate; moderate for brain relaxation, total urine output, serum sodium, and fluid input; low for arterial sodium and max CVP; very low for serum osmolality and max MAP. We downgraded the outcomes for "risk of bias," "inconsistency," and "imprecision."

Brain relaxation

All 10 studies reported this outcome with a total sample size of 735 patients.[2, 5, 11–13, 18–22]. We used a fixed-effects model for this outcome. The outcome favours HS to achieve a better brain relaxation score when compared to mannitol with a significant relationship. There was no significant heterogeneity observed.

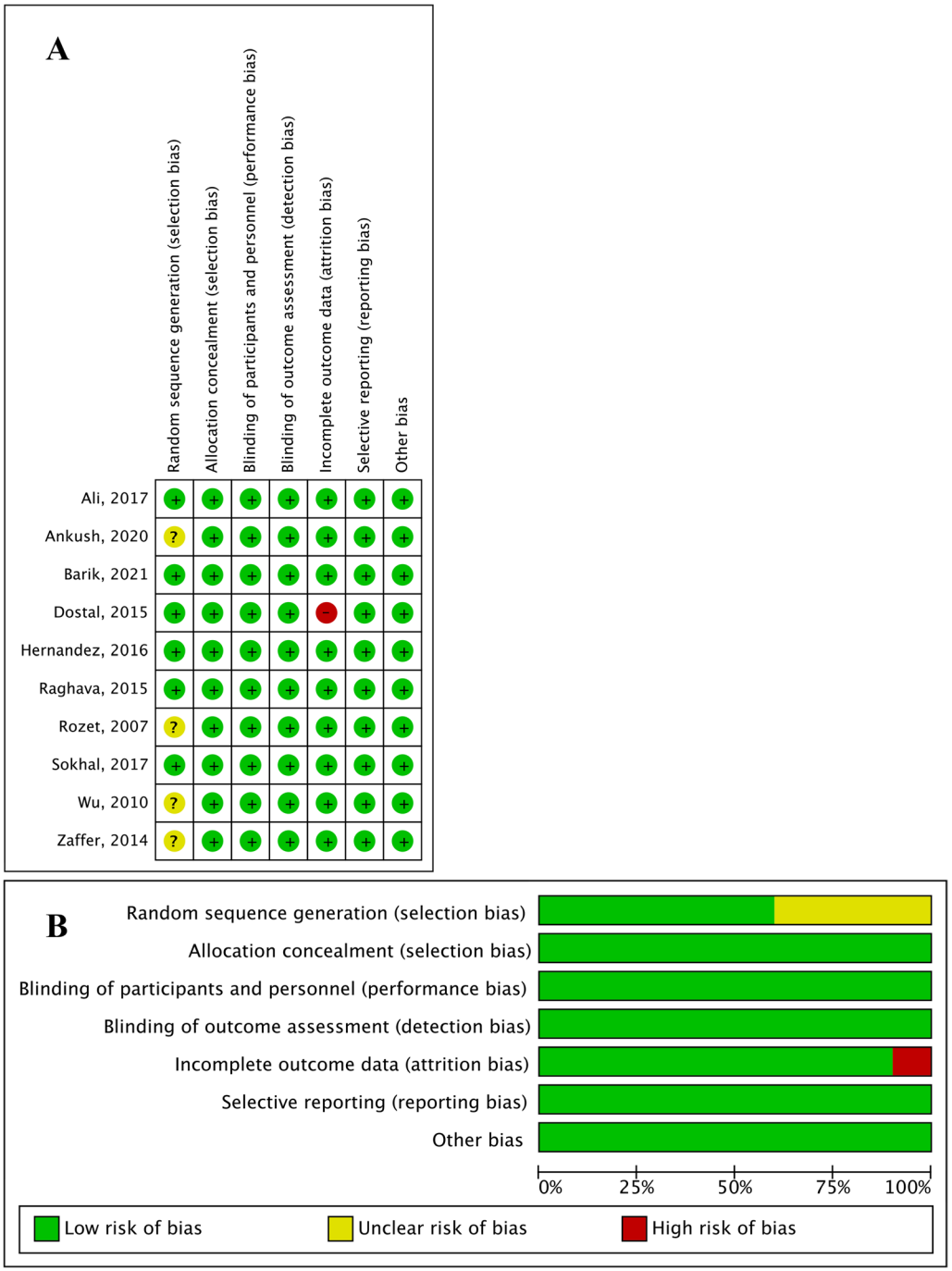

Fig. 2 **A** Risk of bias assessment; + indicates a low risk of bias; − indicates high risk of bias; ? indicate an unclear risk of bias. **B** Risk of bias graph, presented as percentages

Total urine output

Data on urine output were reported on 7 studies with a total sample size of 615 patients [2, 11, 18–22]. We chose to use standardized means difference with 95% CIs as the pooled statistic. The heterogeneity was high, and a random-effects model was used for this outcome. Mannitol is associated with significantly increased total urine output when compared with HS.

To identify the source of heterogeneity, we performed a subgroup analysis based on the doses used. In the

Table 1 Detailed participants for each outcomes including their quality of evidence

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with mannitol	Risk difference with hypertonic saline
Brain Relaxation*	745 (10 RCTs)	⨁⨁⨁◯ Moderate[a]	OR 1.84 (1.31 to 2.59)	67 per 100	12 more per 100 (6 more to 17 more)
Total urine output*	615 (7 RCTs)	⨁⨁⨁◯ Moderate[b]	–	–	SMD 0.75 SD lower (0.92 lower to 0.22 lower)
Serum osmolality	164 (3 RCTs)	⨁◯◯◯ Very low[b,c]	–	The mean serum osmolality was 296.6 mOsm/L	MD 1.97 mOsm/L higher (3.05 lower to 7 higher)
Arterial sodium*	328 (3 RCTs)	⨁⨁◯◯ Low[b,c]	–	The mean arterial sodium was 132 mmol/L	MD 12.69 mmol/L higher (10.85 higher to 14.53 higher)
Serum sodium*	253 (5 RCTs)	⨁⨁⨁◯ Moderate[c]	–	The mean serum sodium was 138 mmol/L	MD 4.5 mmol/L higher (3.65 higher to 5.35 higher)
Fluid input*	576 (6 RCTs)	⨁⨁⨁◯ Moderate[b]	–	–	SMD 0.56 SD lower (0.98 lower to 0.15 lower)
Max MAP	139 (3 RCTs)	⨁◯◯◯ Very low[b,c]	–	The mean max MAP was 84.7 mmHg	MD 1.83 mmHg higher (1.54 lower to 5.2 higher)
Max CVP	263 (RCTs)	⨁⨁◯◯ Low[c,d]	–	The mean max CVP was 8.6 mmHg	MD 0.56 mmHg higher (0.68 lower to 1.8 higher)

CVP: central venous pressure; MAP: mean arterial pressure; MD: mean difference; SMD: standardised mean difference; SD: standard deviation; CI: confidence interval; OR: odd ratio

* Statistically significant, *P* value < 0.05

[a] Multiple unclear risk of bias on random sequence generation

[b] There is a significant level of heterogeneity among studies

[c] Small sample size

[d] There is a mild level of heterogeneity among studies

subgroup analyses, we found low heterogeneity in high doses and significant heterogeneity in low–moderate doses. The results of these subgroup analyses show a significant increase in total urine output when using mannitol in comparison with HS, regardless of the dose.

Fluid input

Among the studies, 6 studies reported this outcome [2, 18–22]. HS is associated with significantly less total fluid input when compared to mannitol. Heterogeneity was high, and a random-effects model was used.

Serum osmolality

Out of the 10 studies, only 3 studies reported this outcome [18–20]. The pooled data show no significant difference in serum osmolality between both solutions when used in elective craniotomies. High heterogeneity was observed, and a random-effects model was used.

Sodium level

Data on sodium level were observed in 7 studies with different modes of measurements. 4 of the studies measure serum sodium level [11–13, 18]. 2 of the studies measure arterial sodium level [11, 20]. 1 study reports both serum and arterial sodium level [19].

HS is associated with a significant increase in serum sodium level in comparison with mannitol with moderate heterogeneity. A fixed-effects model was used. HS is also associated with a significant increase in sodium level when measured through arterial blood samples. Heterogeneity was high, and a random-effects model was used.

Max MAP

Only 3 studies reported this outcome [2, 11, 20]. The pooled data show no significant difference in maximum MAP between the two groups. Heterogeneity was high, and a random-effects model was used.

Max CVP

Data on max CVP were observed on 5 studies [2, 11, 18–20]. No significant difference was found between the two solutions. Heterogeneity was high, and a random-effects model was used. Each analysis result was provided as a forest plot shown in Fig. 3.

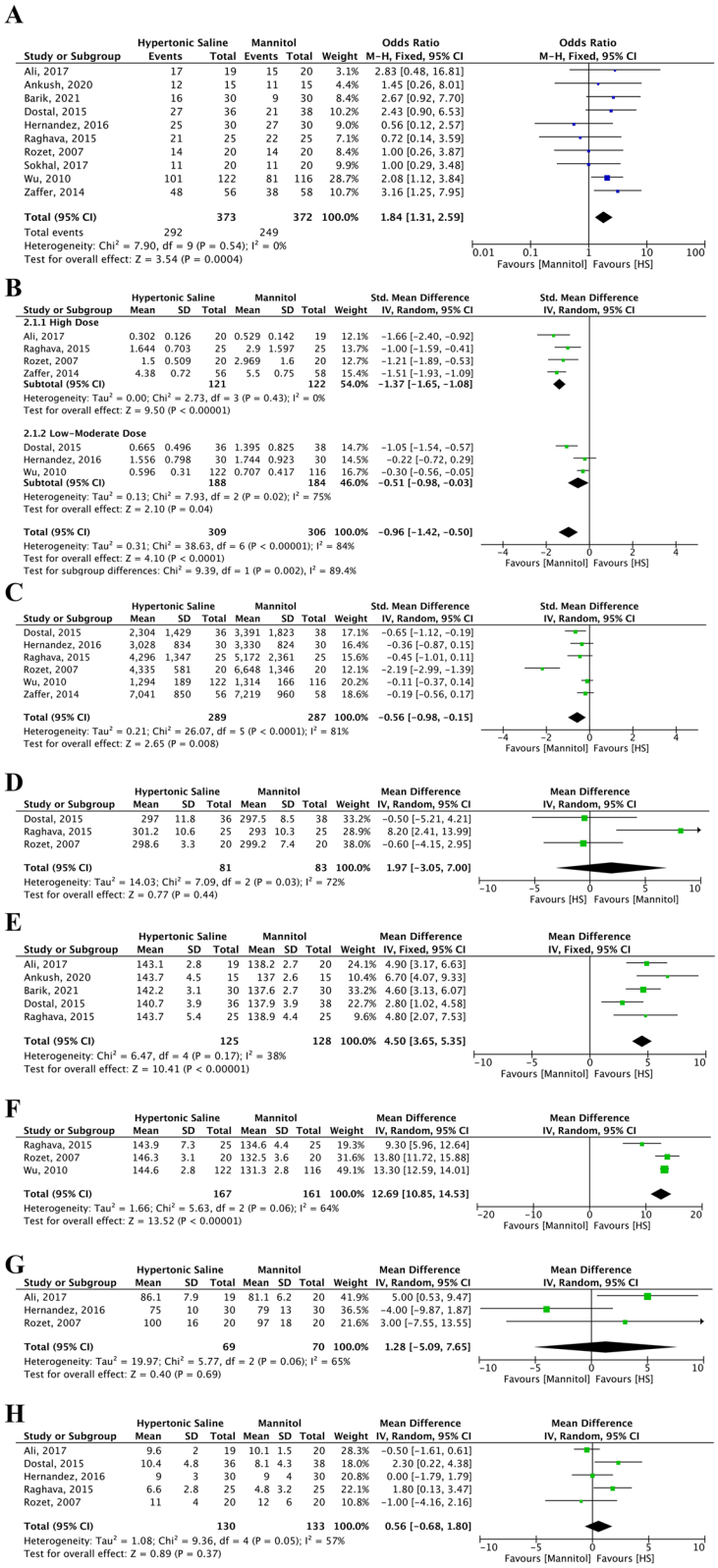

Fig. 3 **A** Brain relaxation, **B** urine output, **C** fluid input, **D** serum osmolality, **E** serum sodium level, **F** arterial blood sodium level, **G** max MAP, **H** max CVP

Discussion

This meta-analysis is an update on Shao's previous meta-analyses in 2015 and Fang in 2017 [23, 24]. We included 4 new RCTs that have been published, since the last meta-analysis was initiated to date. Our findings show that HS is associated with a significant increase in producing better brain relaxation compared to mannitol. This finding is in line with previous results by Shao and Fang. We also found significantly fewer total urine output and fluid input, no difference in serum osmolality, a significant increase in serum and arterial sodium, and no difference in max MAP in HS group when compared to mannitol. These findings are also consistent with previous studies [23, 24]. However, we added 1 new study and found no significant difference in maximum CVP between both solutions. This is different from a previous study by Fang, where they found a slightly greater reduction of CVP when compared with HS [24].

This study used the GRADE approach to assess the quality of evidence to provide an objective view of our certainty in the outcome. The evidence quality ranges from very low to moderate. We downgraded our evidence due to heterogeneity we cannot identify, small sample sizes, and a high risk of bias.

Our meta-analysis showed that HS is associated with a significantly better brain relaxation score when compared to mannitol. Hypertonic saline theoretically has a higher reflection coefficient of 1 when compared to mannitol (0.9). The higher reflection coefficient means that hypertonic saline is more impermeable to the biological membrane, our blood–brain barrier (BBB), and can exert a better osmotic driving force to draw out water from interstitial tissue to intravascular space [6, 7]. This also means that theoretically, HS will not cause rebound ICP increase, an adverse effect of long use of mannitol, as HS will not seep through the BBB and draw water to, instead of from the brain tissue [8]. This, however, only applies to an intact BBB. Brain tumours and other space-occupying lesions (SOLs) will cause peritumoral oedema and compromise BBB [25].

Significantly fewer urine output seen in HS might be explained by the high sodium value of hypertonic saline. A higher sodium value in HS might stimulate the hypothalamus to secrete an antidiuretic hormone, exerting its antidiuretic effect [6, 7]. The fewer urine output translates to less fluid needed to be administered intraoperatively, as we can see in this study, where HS is also associated with significantly fewer fluid input.

The high sodium content, however, might be a double-edged sword. Our study shows that HS is associated with significantly increased blood sodium levels, both by serum and arterial measurement. This may prove to be clinically significant in patients with electrolyte abnormalities. A study measuring sodium level in traumatic shock patients given hypertonic saline shows that all sodium levels return to baseline within 24 h, and most within 4 h [26]. One study by Ankush also shows sodium level return to baseline value in 48 h [12]. Safety concern regarding the use of HTS is centered around the consequences of an acute hyperosmolar state. Rapid correction of sodium in a previously hyponatremic patient may produce central pontine myelinolysis, otherwise known as osmotic demyelination syndrome (ODS) [6, 7, 9]. This condition is, however, best treated by prevention of rapid correction of sodium through good preoperative evaluation and blood electrolyte workup. There have been no reports of CPM after the use of HS in reducing ICP to date. Another concern is rapid initial blood volume expansion in patients with acute heart failure and pulmonary edema leading to acute worsening of respective diseases [6, 7]. This adverse effect is due to hyperosmolarity and affects both HTS and mannitol. This may be prevented with the addition of diuretics.

Our study had some limitations. First, the brain relaxation score is a subjective measurement and, therefore, is prone to bias and subjective views. Ideal and objective measurement is ICP values, but in our included studies, only two provided the measurement, albeit only in figures [5, 11]. Second, we cannot identify sources of heterogeneity in some outcomes. Third, small sample sizes and a small number of studies may limit the power of our study.

Conclusions

This study demonstrated that HS might have a greater effect on producing good brain relaxation when compared to mannitol in patients undergoing elective craniotomies under multiple brain pathologies. HS is associated with fewer total urine output and fluid input. However, HS is associated with increased blood sodium levels, and its use and safety in patients with electrolyte abnormalities warrant further investigation. Both solutions have no significant difference in serum osmolality or hemodynamic parameters. However, this study limitations requires further high-quality RCTs with an objective assessment of brain relaxation to confirm the findings.

Abbreviations

HS: Hypertonic saline; MAP: Mean arterial pressure; CVP: Central venous pressure; BBB: Blood–brain barrier; SOL: Space-occupying lesion.

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Not applicable.

Author contributions

TKPJ and GAR conceived the original idea of this research and proof outline. TKPJ wrote the manuscript with support, help and input from JJ, IGAAAY, and

JN. TKPJ and GAR collected and input the data. TKPJ with help from JJ, IGAAAY, and JN analysed the data. TKPJ, GAR, and JN also done the copyediting, proofreading and revised the final manuscript. All authors were involved in drafting the article or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Availability of data and materials
The data used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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