Journal of Taibah University Medical Sciences (2024) 19(5), 961–973

Taibah University

Journal of Taibah University Medical Sciences

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Review Article

Hypertonic saline achieves superior brain relaxation in tumor craniotomy: An updated systematic-network meta-analysis

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Received 31 March 2024; revised 27 July 2024; accepted 7 September 2024; Available online 19 September 2024

الملخص

أهداف البحث: يتطلب بضع القحف لورم الدماغ استرخاء الدماغ، ويتم ذلك عن طريق تقليل الضغط داخل الجمجمة. العلاج الأسموي بفرط الأسمولية هو تقنية يمكن استخدامها لتقليل الضغط داخل القزحية. تهدف هذه الدراسة إلى تحديث الدراسات السابقة لتقييم فعالية وسلامة استخدام المحلول الملحي مفرط التوتر مقارنة بالمانيتول في خفض الضغط داخل الجمجمة لدى مرضى الأورام الدماغية البالغين الخاضعين لجراحة فتح الجمجمة.

طرق البحث: تم إجراء بحث منهجي في خمس قواعد بيانات من عام 2013 إلى ديسمبر 2023 لتحديد التجارب العشوائية المضبوطة التي تقارن المحلول الملحي مفرط التوتر بالمانيتول. تم إجراء التحليل التلوي التقليدي، والتحليل البايزي، وتحليل التسلسل التجريبي، وتقييم جودة التجارب.

النتائج: شملت الدراسة 11 تجربة عشوائية مضبوطة بمجموع 593 مشاركا. ارتبط المحلول الملحي مفرط التوتر بتحسن كبير في استرخاء الدماغ، وانخفاض كبير في إنتاج البول، وانخفاض كبير في مدخلات السوائل. كما ارتبط بارتفاع كبير في متوسط ضغط الدم الشرياني ومستوى الصوديوم في البلازما. لم يكن هناك فرق كبير في ضغط الإرواء الدماغي بين المجموعتين. أظهر التحليل البايزي تفوق المحلول الملحي مفرط التوتر بتركيز 3% بجرعة 5 مل/كجم في تحقيق استرخاء الدماغ.

الاستنتاجات: المحلول الملحي مفرط التوتر متفوق على المانيتول في تحقيق استرخاء الدماغ الأمثل، والحفاظ على تدفق الدم المستقر، وتقليل التأثيرات المدرة للبول. ومع ذلك، من المهم ملاحظة أن استخدامه قد يؤدي إلى زيادة مستويات الصوديوم في البلازما. الجرعة الموصى بها لتحقيق استرخاء الدماغ هي المحلول الملحي مفرط التوتر بتركيز 3% بجرعة 5 مل لكل كجم من وزن الجسم.

الكلمات المفتاحية: استرخاء الدماغ؛ فتح الجمجمة؛ ورم الدماغ؛ المحلول الملحي مفرط التوتر؛ الضغط داخل الجمجمة؛ المانيتول

Abstract

Background: Brain tumor craniotomy requires relaxation of the brain through decreasing the intracranial pressure (ICP). Osmo-hyperosmolar therapy can be used to lower the ICP.

Objectives: This study was aimed at updating previous studies to determine the effects and safety of using hypertonic saline (HTS) and mannitol to decrease ICP in adult patients with brain tumors undergoing craniotomy.

Methods: To identify randomized controlled trials (RCTs) comparing HTS vs mannitol, we performed a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, by examining records from 2013 to December of 2023 in five databases. The primary outcome was brain relaxation, and the secondary outcomes were cerebral perfusion pressure (CPP), urine output (UO), fluid input, mean arterial pressure (MAP), and plasma sodium. Conventional meta-analysis,

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Peer review under responsibility of Taibah University.

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Bayesian meta-insight analysis, trial-sequential analysis, and trial quality assessment were conducted.

Results: Eleven RCTs involving 593 participants were included in the meta-analysis. Use of HTS, compared with mannitol, was associated with significantly greater brain relaxation, and significantly lower UO and fluid input. HTS was also significantly associated with elevated MAP. Plasma sodium was significantly higher in the HTS group than the mannitol group. No significant difference in CPP was observed between groups. Trial sequential analysis indicated true significance for the brain relaxation outcomes. Bayesian analysis demonstrated the superiority of 3% HTS at 5 ml/kg in achieving brain relaxation, followed by 3% HTS at 5.3 ml/kg and 20% mannitol at 5 ml/kg.

Conclusions: HTS is superior to mannitol in achieving optimal brain relaxation, maintaining stable blood flow, and minimizing diuretic effects. However, use of HTS during tumor craniotomy procedures can increase plasma sodium levels. The optimal dose for achieving brain relaxation appears to be 3% HTS at 5 ml/kg body weight.

Keywords: Brain relaxation; Craniotomy; Craniotomy tumor; Hypertonic saline; Intracranial pressure; Mannitol

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Introduction

Neuroanesthesia in craniotomy for brain tumors requires adequate control of intracranial pressure (ICP) and optimal cerebral perfusion to prevent iatrogenic injury (i.e., hypoperfusion or ischemia) intraoperatively.[1–5] The many parameters used for decreasing ICP intraoperatively include brain relaxation, which can be assessed with the Brain Relaxation Score. Although not identical, ICP and brain relaxation are conceptually similar. Brain relaxation can be achieved through a pharmacological or non-pharmacological approach, according to the patient's clinical condition. Widely used techniques to induce brain relaxation include positioning; airway patency; and respiratory control to avoid hypo- or hypercarbia and hypoxia; maintenance of hemodynamic stability to produce optimal cerebral perfusion; drainage of cerebrospinal fluid; or the use of hyperosmolar therapy such as hypertonic saline (HTS) or mannitol.[6,7]

HTS and mannitol are frequently used to lower ICP during craniotomy procedures, because of their rheologic effects. However, the optimal choice for hyperosmolar therapy remains unclear, because each solution is associated with different adverse effects. For example, mannitol is associated with adverse effects including nephrotoxicity, hypovolemia, and rebound effects. In contrast, HTS is associated with events such as plasma hypernatremia, metabolic acidosis, and pontine demyelination.[8–10] A recent meta-analysis including patients with traumatic brain injury has reported that HTS is more efficacious than mannitol in lowering ICP.[11] Other studies have reported the safety and efficacy of HTS and mannitol in achieving brain relaxation during brain tumor surgery, and have shown no significant differences in brain relaxation during brain tumor craniotomy.[12–19] Given the conflicting results regarding the optimal hyperosmolar therapy for brain relaxation in brain tumor surgery, we sought to compare these solutions' efficacy and safety in producing brain relaxation in brain tumor surgery. We conducted a network meta-analysis of data from recent studies to determine the direct and indirect effects of the two solutions on several outcomes. Additionally, we assessed variables including cerebral perfusion pressure (CPP), mean arterial pressure (MAP), intraoperative fluid status, electrolyte changes, and urine output (UO).

Materials and Methods

This systematic review and network meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The study protocol for this review was registered with PROSPERO (www.crd.york.ac.uk; CRD42024498614).

Search strategy

We conducted a literature search of records from 2013 until December 2023 in databases including Scopus, PubMed, Cochrane Trial Library, ScienceDirect, and EBSCO. We used Boolean operators with Medical Subject Heading (MESH) terms and the following keywords: "mannitol," "hypertonic saline," "brain relaxation," "intracranial pressure," "craniotomy," and "tumors." A search of references in previously published systematic reviews was also conducted to identify additional studies. A detailed description of the search strategy is provided in Table 1.

Eligibility and selection criteria

We screened the titles and abstracts of the results of the data search to determine eligibility. Studies included in this systematic review were full-text articles reporting randomized controlled trials (RCTs) in English meeting the following "PICO" inclusion criteria: (P) adult patients who underwent craniotomy for brain tumors; (I) use of 3% HTS, with various doses and preparations; (C) use of mannitol in various doses and preparations; and (O) primary outcome of brain relaxation. The secondary outcomes assessed were CPP, MAP, intraoperative volume status (i.e., UO and intraoperative fluid input), and plasma sodium concentration.

Data extraction and quality assessment

Three authors (KT, LBB, and CJS) were involved in study selection and full-text review. Data extraction was performed independently and in duplicate by two reviewers (CJS and LBB). The data extracted from full-text articles included author, year, study design, demographic characteristics (i.e., age, sex, and number of participants), American Society of Anesthesiologists (ASA) physical status, doses and concentrations of HTS and mannitol, tumor size (cc), and midline shift (mm).

Brain relaxation is determined according to the relationship between the volume of the intracranial contents and the

capacity of the intracranial space.[5] Brain relaxation is considered adequate if the volume of intracranial contents is equal to or less than the capacity of the intracranial space, and is considered inadequate if the volume surpasses this capacity.[5] Assessment of brain relaxation can be both subjective and objective. During craniotomy, when a patient is anesthetized, subjective tactile and visual evaluation of brain tissue is performed before and after the dura mater is opened.[5] A four-point scale is used to grade brain relaxation as follows: completely relaxed, satisfactorily relaxed, firm, or bulging. Subdural pressure, objectively measured when the cranium is opened while the dura is closed, can serve as an indicator of brain relaxation.[5]

Risk of bias assessment was performed independently by two reviewers (CJS and LBB), and any discrepancies were resolved by a third reviewer (KT or DYB). Risk of bias was assessed with the revised Cochrane risk of bias tool (RoB 2.0).[21,22] A table of RoB results with a summary of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria was compiled. Because brain relaxation is generally assessed subjectively by neurosurgeons and anesthesiologists, substantial potential for bias exists. To minimize bias, assessments should ideally be performed by the same individual blinded to the intervention measures. Alternatively, using subdural pressure measurements as an objective method can decrease bias. Although this method is simple, minimally invasive, and reliable, it is not routinely used in neurosurgery.

Data synthesis

Data synthesis and analysis were performed in Meta-Insight and Review Manager (RevMan) version 5.4. The primary outcome of this study was brain relaxation. The degree of brain relaxation was classified at the opening of the dura according to a four-point scale (brain relaxation score: 1, very relaxed; 2, satisfactorily relaxed; 3, brain assertive; and 4, brain prominent).[5,23] We categorized scores of 1 or 2 as good brain relaxation (good BRS) and scores of 3 or 4 as bad brain relaxation (bad BRS). Secondary outcomes included in this study were CPP, fluid status (i.e., UO and intraoperative fluid input), and plasma sodium concentration, which are presented as continuous data.

Because of potential differences in craniotomies for brain tumors and heterogeneity across studies, we used random-effect models. Dichotomous data were analyzed with risk ratios (RRs) and 95% confidence intervals (CIs) by using inverse variance. Continuous data including CPP, and plasma sodium concentration were evaluated with mean differences (MDs) and 95% CIs by using the inverse variance. Standardized mean differences (SMDs) and 95% CIs were used to estimate the intraoperative fluid input effect sizes. Sensitivity analysis was performed by omitting each study individually, to explore the reliability of the effect size. Heterogeneity across studies was calculated with Higgins' I^2 statistics.

Subgroup analysis was performed if the heterogeneity was high ($I^2 > 40\%$). Publication bias was analyzed through visual inspection of funnel plots if more than ten studies were included in each synthesis. Trial sequential analysis (TSA) was performed in TSA software (version 0.9.5.10 Beta, Copenhagen Trial Unit, Copenhagen, Denmark), to decrease the risk of type I and II error in the effect size. We also performed a Bayesian network meta-analysis to assess the direct effects on producing good BRS, comparing HTS with mannitol, as well as indirectly comparing different HTS doses.

Results

We identified 174 articles from five databases, and three additional articles in searches of the citations therein. A total of 11 RCTs published between January 2013 and December

Table 1: Search strategy.

Database	Keywords	Filter	Result
PubMed	**(mannitol AND "hypertonic saline") AND (craniotomy OR "craniotomy tumor") AND ("brain relaxation" OR ICP)** Filters: **Randomized Controlled Trial** ((("mannitol" [MeSH Terms] OR "mannitol" [All Fields] OR "mannitols" [All Fields]) AND "hypertonic saline" [All Fields] AND ("craniotomy" [MeSH Terms] OR "craniotomy" [All Fields] OR "craniotomies" [All Fields] OR "craniotomy tumor" [All Fields]) AND ("brain relaxation" [All Fields] OR "ICP" [All Fields])) AND (randomizedcontrolledtrial [Filter])	**Years: 2013–2023**	**10**
Cochrane **TRIAL**	#1 **(mannitol AND "hypertonic saline")** #2 **(craniotomy OR "craniotomy tumor")** #3 **("brain relaxation" OR ICP)** #4 #**1 AND** #2 **AND** #3	**Years: 2013–2023**	24
EBSCO CINAHL	**S1** (mannitol AND "hypertonic saline") **S2** (craniotomy OR "craniotomy tumor") **S3** ("brain relaxation" OR ICP) **S4 S1** AND S**2** AND S**3**	**Years: 2012–2023**	24
Science Direct	(mannitol AND "hypertonic saline") AND (craniotomy OR "craniotomy tumor") AND ("brain relaxation" OR ICP)	**Years: 2013–2023**	36
Scopus	(TITLE-ABS-KEY (mannitol AND "hypertonic saline") **AND** TITLE-ABS-KEY (craniotomy OR "craniotomy tumor") AND TITLE-ABS-KEY ("brain relaxation" OR ICP)	**Years: 2013–2023**	27

2023 were included in this systematic review (Figure 1). This study included 666 participants, comprising 278 men (41.74%) and 388 women (58.25%). Of the 666 patients (one study did not report samples by sex), 294 were in the HTS group, and 299 were in the mannitol group (Table 2).

The results of the risk of bias analysis are shown in Figure 2. Two studies had unclear risk of bias. All studies included in this review conducted random sequence generation through computer-generated randomization or computerized random number generation, and were considered to have low risk of bias.[16–19,24–27] Two studies showed deviations from the intended intervention,[16,19] and six RCTs did not report some of the desired data.[15,18,19,24,25,27]

The GRADE profile evidence produced in this review was compiled by using the GRADE pro-GDT web application and a summary of the findings (Table 3). The quality of evidence ranged from very low to moderate. The brain relaxation outcomes had moderate quality, whereas the MAP, UO, and electrolyte outcomes had low quality. The ICP, CPP, HR, and glucose outcomes had very low quality.

Brain relaxation

A total of 11 RCTs with a total sample of 593 patients reported brain relaxation outcomes.[13,14,27,15–19,24–26] Pooled analysis indicated that HTS was associated with a significant tendency toward good BRS outcomes ($p = 0.007$; $I^2 = 43\%$). To identify sources of heterogeneity, we performed subgroup analyses according to dose (with doses >5 ml/kg BW considered high). In pooled statistical data, this effect was significant in the low-dose HTS subgroup (<5 ml/kg BW) compared with the high-dose HTS subgroup (RR 1.40; 95% CI 1.13–1.74; $p = 0.002$; Figure 3). The overall effect persisted after sensitivity analysis after omission of each study individually (Figure 4).

Cerebral perfusion pressure

The outcomes of CPP were reported by two studies.[18,25] No significant difference in CPP was observed, although a tendency toward higher CPP was found with HTS use (MD 3.06; 95% CI −0.90 to 7.02; $p = 0.13$). No heterogeneity was found across studies ($I^2 = 0\%$, Figure 5).

Mean arterial pressure

Hemodynamic status was evaluated according to the MAP, which was reported in seven studies.[15–18,24–26] Our data synthesis indicated a non-significant difference in MAP between HTS and mannitol ($I^2 = 78\%$). Subgroup analysis showed significantly higher MAP in the high-dose HTS group (MD 3.58; 95% CI 0.74–6.42; $p = 0.01$; Figure 6). In sensitivity analysis, omission of a study by Wirawijaya et al.[17] resulted in significantly higher MAP in the HTS group than the mannitol group (Figure 7).

Plasma sodium concentration

Plasma sodium concentrations were reported in seven studies.[14–17,24–26] Higher sodium concentrations were observed in the HTS group, and the heterogeneity was significant ($I^2 = 89\%$). Subgroup analysis revealed significantly higher plasma sodium concentrations in both high-dose (MD 5.29; 95% CI 2.28–8.30; $p < 0.001$) and low-dose (MD 4.44; 95% CI 0.76–8.11; $p < 0.001$, Figure 8)

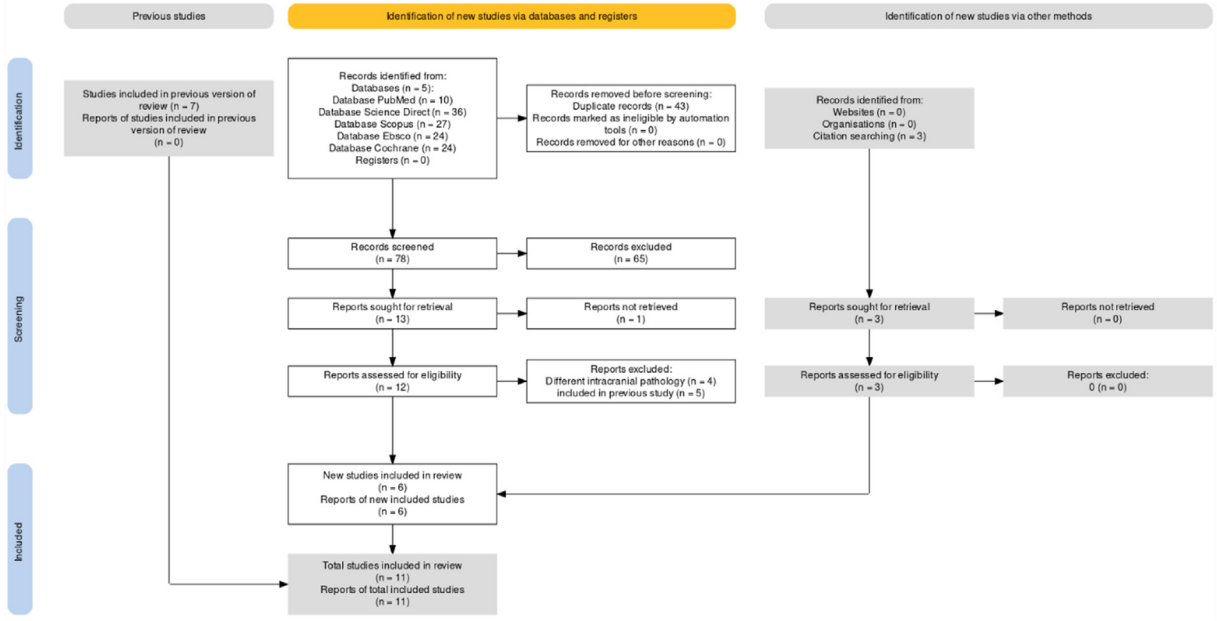

Figure 1: PRISMA flowchart.

Table 2: Characteristics of patients included in the studies.

Author	Study design	Age		Sex		Number of participants		ASA PS		Dose		Concentration		Tumor size (cc)		Midline shift (mm)	
		HTS	Mannitol	HTS	Mannitol	HTS	Mannitol	HTS	Mannitol	HTS	Mannitol	HTS	Mannitol	HTS	Mannitol	HTS	Mannitol
Barik, 2021	RCT	40.13 ± 13.2	40.60 ± 13.2	M (n = 17); F (n = 13)	M (n = 19); F (n = 11)	30	30			5.3 ml/kg	5 ml/kg	3%	20%	104.43 (63.8)	108.75 (69.7)	NR	NR
Ali, 2018	RCT	50.0 ± 9.7	46.4 ± 10.0	M (n = 10); F (n = 9)	M (n = 11); F (n = 9)	19	20	II (n = 14); III (n = 5)	II (n = 15); III (n = 5)	5 ml/kg	5 ml/kg	3%	20%	58.9 ± 33.4	53.4 ± 26.5	NR	NR
Dostal, 2015	RCT	52.1 ± 13.1	53.5 ± 13.0	M (n = 16); F (n = 20)	M (n = 14); F (n = 24)	36	38	II (n = 30); III (n = 6)	II (n = 28); III (n = 10)	3.75 ml/kg	3.75 ml/kg	3.2%	20%	NR	NR	7.7 ± 3.2	8.4 ± 3.5
Palazon, 2023	RCT	51 (6.25)	53 (6.25)	M (n = 17); F (n = 13)	M (n = 15); F (n = 15)	30	30	II (n = 17); III (n = 13)	II (n = 14); III (n = 6)	5 ml/kg	5 ml/kg	3%	20%	69.7 ± 48.7	56.6 ± 29.8	9.1 ± 3.7	8.3 ± 3.6
Singla, 2020	RCT	40.40 ± 14.98	46.33 ± 12.29	M (n = 8); F (n = 7)	M (n = 10); F (n = 5)	15	15	I (n = 10); II (n = 5); III (n = 0)	I (n = 13); II (n = 2); III (n = 0)	5 ml/kg	5 ml/kg	3%	20%	79.25 ± 86.08	114.95 ± 128.59	NR	NR
Raghava, 2015	RCT	41.6 ± 12.9	38.8 ± 11.9	M (n = 12); F (n = 13)	M (n = 9); F (n = 16)	25	25	II (n = 11); III (n = 14)	II (n = 13); III (n = 12)	5 ml/kg	5 ml/kg	3%	20%	NR	NR	NR	NR
Zaffer, 2014	RCT	43.39 ± 13.6	46.93 ± 12.1	M (n = 31); F (n = 25)	M (n = 28); F (n = 30)	56	58	II (n = 40); III (n = 16)	II (n = 35); III (n = 23)	5 ml/kg	5 ml/kg	3%	20%	NR	NR	NR	NR
Sokhal, 2017	RCT	40.8 ± 13.9	38.25 ± 11.04	M (n = 14); F (n = 6)	M (n = 11); F (n = 93)	20	20	II (n = 16); III (n = 4)	II (n = 19); III (n = 1)	5.35 ml/kg	5 ml/kg	3%	20%	146.7 ± 110.1	120.4 ± 111.42	6.4 ± 4.43	6.05 ± 6.08
Amin, 2015	RCT	NR	NR	NR	NR	20	20	NR	NR	5 ml/kg	5 ml/kg	3%	20%	NR	NR	NR	NR
Wirawijaya, 2018	RCT	44.61 ± 9.421	39.53 ± 9.896	M (n = 1); F (n = 12)	M (n = 2); F (n = 11)	13	13	NR	NR	2.5 ml/kg	2.5 ml/kg	3%	20%	NR	NR	NR	NR
Samir, 2021	RCT	57.4 ± 8.7	51.2 ± 10.8	M (n = 16); F (n = 14)	M (n = 19); F (n = 11)	30	30	II (n = 23); III (n = 7)	II (n = 24); III (n = 6)	3.2 ml/kg	3.2 ml/kg	3%	20%	NR	NR	NR	NR

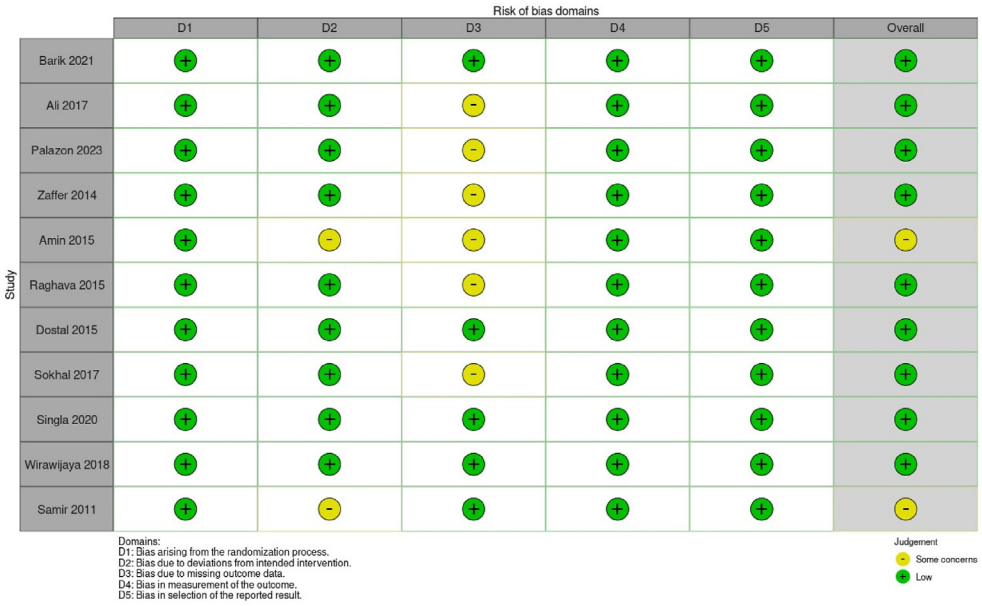

Figure 2: Risk of bias assessment.

Table 3: GRADE scoring to assess participants' details for each outcome, including quality of evidence.

Outcome	No. participants (Studies)	Certainty of evidence (GRADE)	Relative effect (95% Cl)	Anticipated absolute effects	
				Assumed risk	
				Mannitol	Risk Difference with HTS
Good BRS	593 (11 RCTs)	⊕⊕⊕O Moderate[a]	**RR 1.21** (1.05 −1.38)	**630 per 1000**	**132 more per 1000** (31 more to 239 more)
MAP	305 (7 RCTs)	⊕⊕OO Low[a,b]	—	Mean MAP: **76.48** mmHg	MD **3.59 mmHg higher** (0.35 lower to 7.54 higher)
Urine Output	396 (7 RCTs)	⊕⊕OO Low[a,d]	—	—	SMD **1.52 lower** (2.13 lower to 0.92 lower)
Serum Sodium	340 (7 RCTs)	⊕⊕OO Low[a,b]	—	Mean serum sodium: **136.6** mmol/L	MD **4.91 mmol/L higher** (2.77 higher to 7.05 higher)
Fluid Input	348 (5 RCTs)	⊕⊕OO Low[a,b]	—	—	SMD **0.75 lower** (1.42 lower to 0.08 lower)
Cerebral Perfusion Pressure (CPP)	79 (2 RCTs)	⊕OOO Very Low[c,e]	—	Mean cerebral perfusion pressure (CPP): **70.65** mmHg	MD **3.06 mmHg higher** (0.9 lower to 7.02 higher)

BRS: Brain Relaxation Score, MAP: Mean Arterial Pressure, HR: Heart Rate, $PaCO_2$: Carbon Dioxide, Arterial.
*Statistically significant, $p < 0.05$.
[a] Multiple unclear risk of bias on random sequence generation.
[b] Substantial heterogeneity among studies.
[c] Considerable heterogeneity among studies.
[d] Moderate heterogeneity among studies.
[e] Fewer than ten studies present, study size of fewer than 50 or 1000 patients in total.

groups. The overall effect persisted in a sensitivity analysis omitting each study individually (Figure 9).

Urine output and intraoperative fluid input

UO was reported in six studies, which showed significant heterogeneity ($I^2 = 84\%$). The pooled SMD indicated significantly lower UO in HTS (SMD −1.52; 95% CI −2.13, −0.92; $p < 0.00001$; Figure 10), and this finding was consistent in both subgroups. Sensitivity analysis showed consistent results after omission of one study at a time (Figure 11).

Five studies[14–16,19,27] reported intraoperative fluid input, and significant heterogeneity was observed across studies ($I^2 = 88\%$). The pooled SMD demonstrated that use of HTS was associated with diminished intraoperative fluid input (SMD −0.75; 95% CI −1.42, −0.08; $p = 0.03$; Figure 12). Subgroup analysis indicated no significant difference between groups. Sensitivity analysis showed a

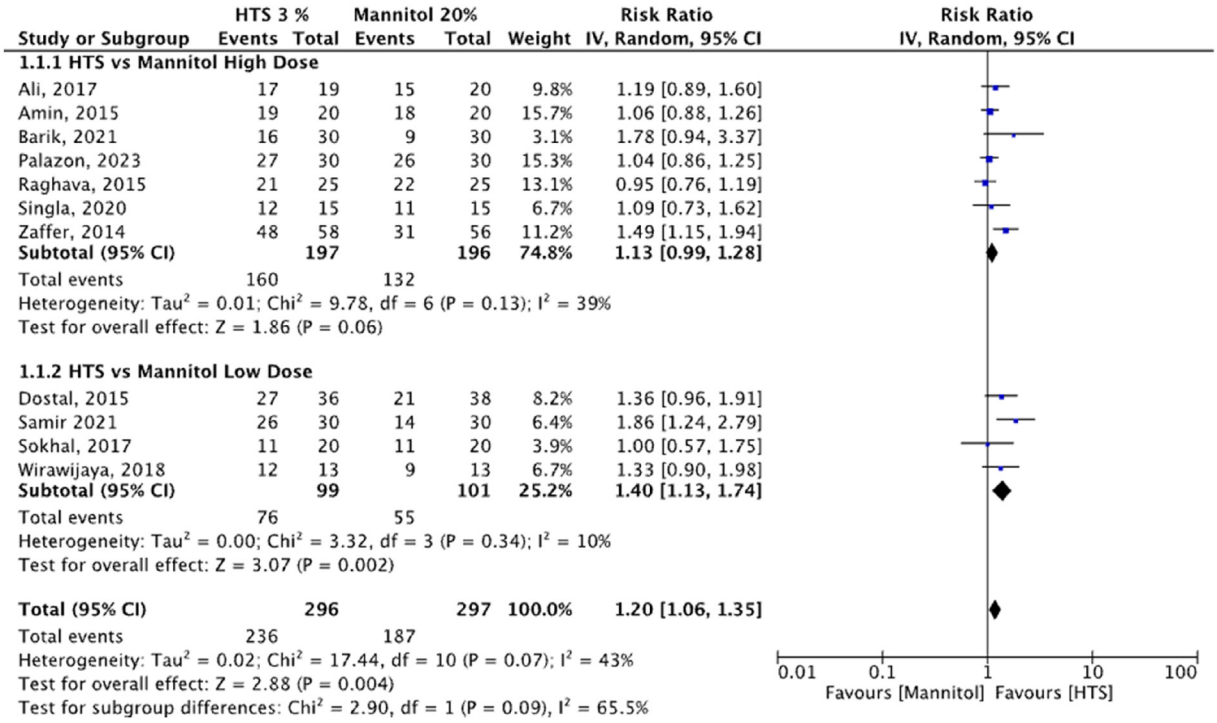

Figure 3: Forest plot of effects of HTS vs mannitol on good BRS outcomes.

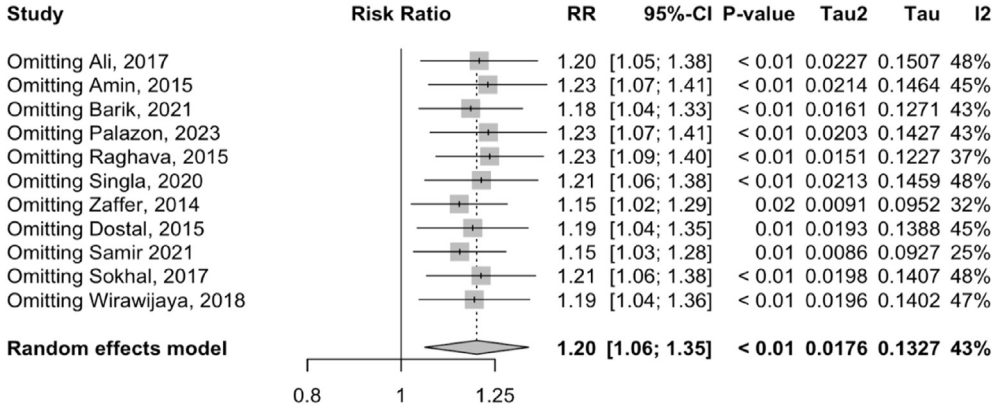

Figure 4: Sensitivity analysis of good BRS.

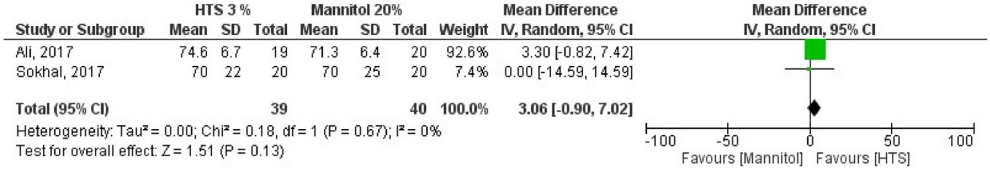

Figure 5: Forest plot of effects of HTS vs mannitol on CPP outcomes.

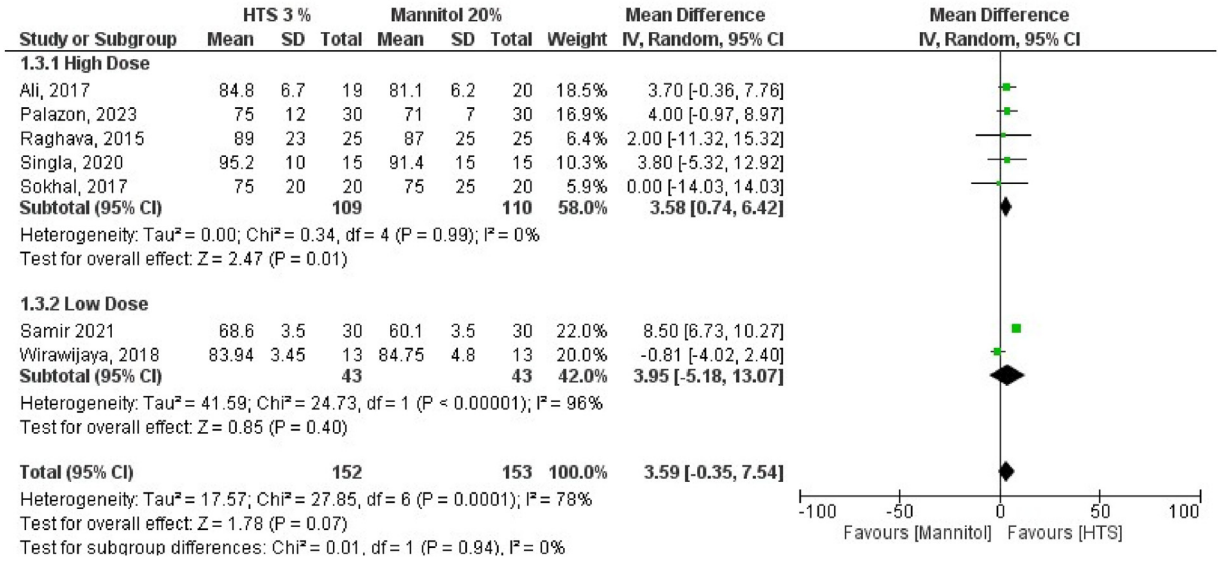

Figure 6: Forest plot of effects of HTS vs mannitol on MAP outcomes.

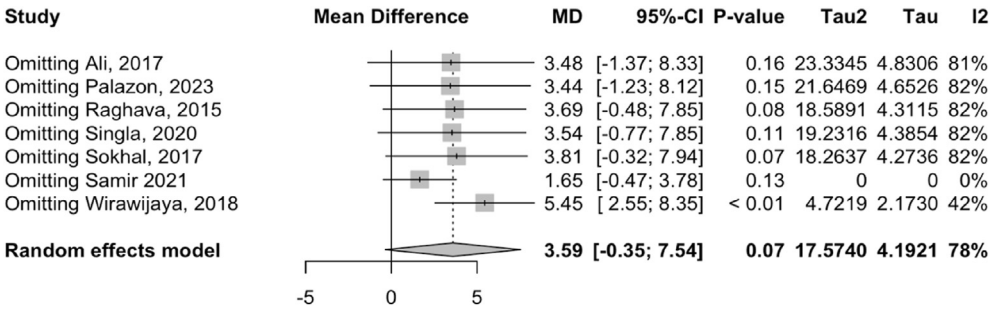

Figure 7: Sensitivity analysis of MAP.

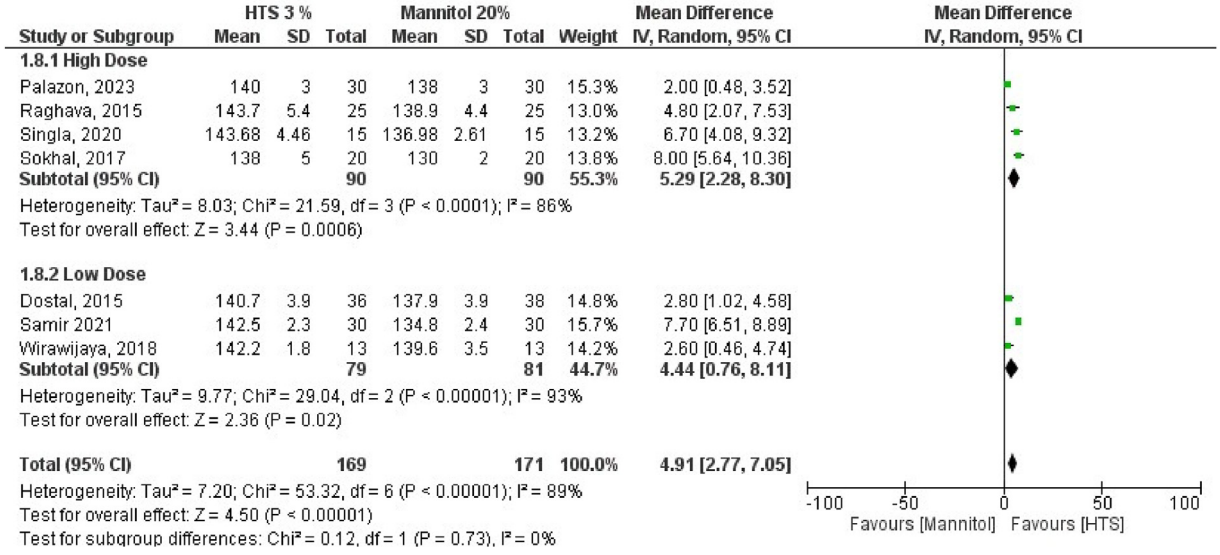

Figure 8: Forest plot of effects of HTS vs mannitol on plasma sodium concentration outcomes.

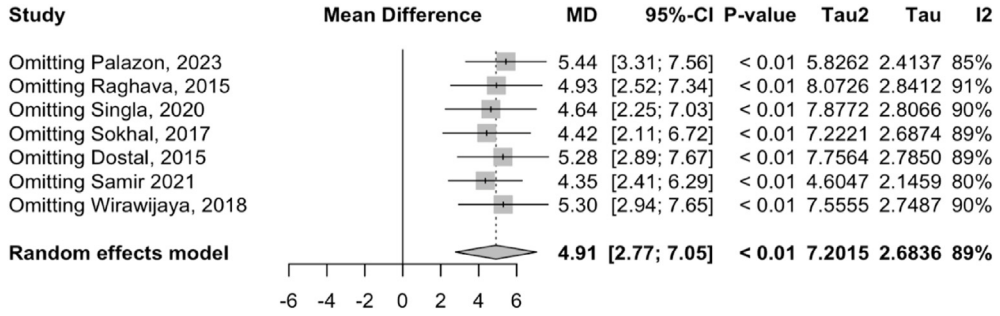

Figure 9: Sensitivity analysis of plasma sodium concentration.

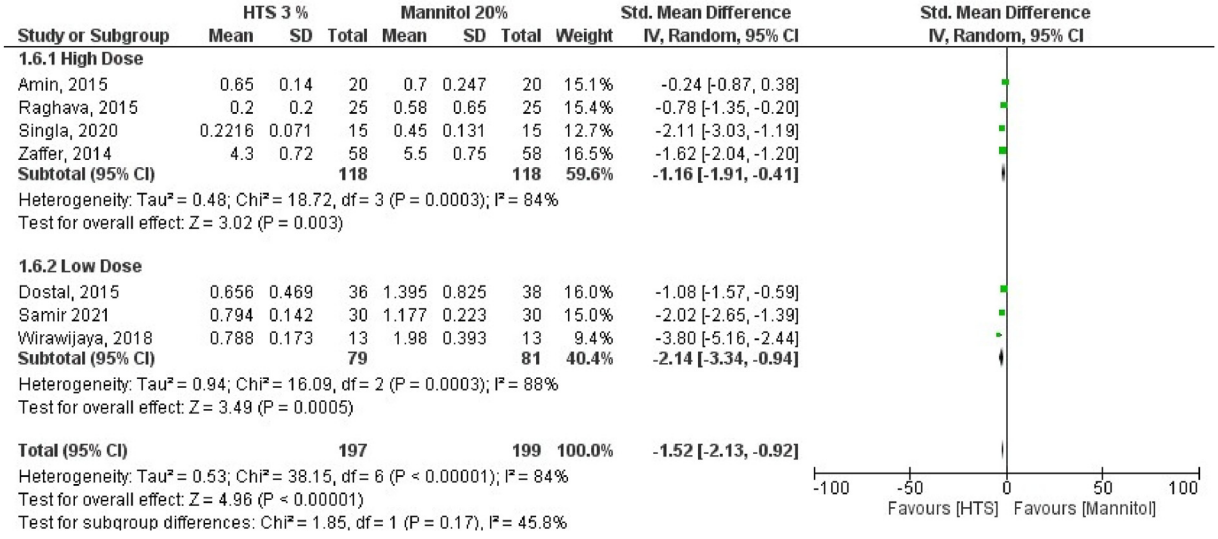

Figure 10: Forest plot of effects of HTS vs mannitol on urine output outcomes.

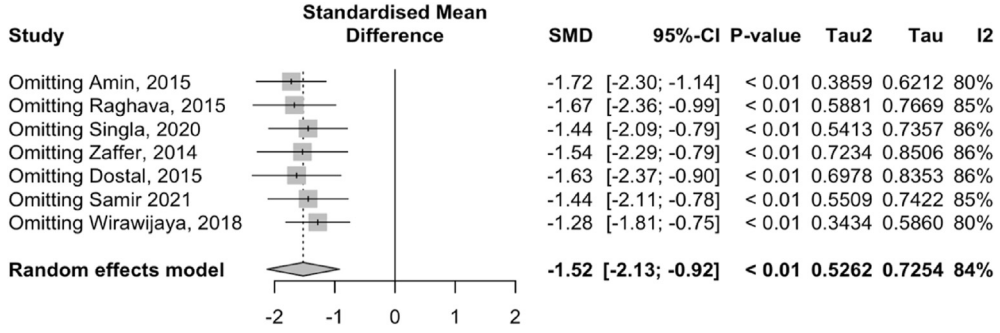

Figure 11: Sensitivity analysis of urine output.

non-significant difference in intraoperative fluid input after omission of the study by Dostal et al.[14] (Figure 13).

Trial sequential analysis

TSA was performed to decrease the risk of type I and II error. Because of the small sample sizes in the included studies, we used TSA to evaluate the accuracy of effect size in relation to the study sample size. TSA was conducted for only brain relaxation, the primary study outcome. Our analysis demonstrated that the good BRS outcome crossed both the conventional and trial sequencing monitoring boundaries for benefit, thus suggesting true significant results. The required information size (RIS) for the study's primary outcome was met (Figure 14).

Network meta-analysis

Of the 11 included RCTs, the doses and concentrations differed in both the HTS and mannitol groups. We included three RCTs[13,25,27] in a network meta-analysis, using the Bayesian meta-insight application to perform indirect

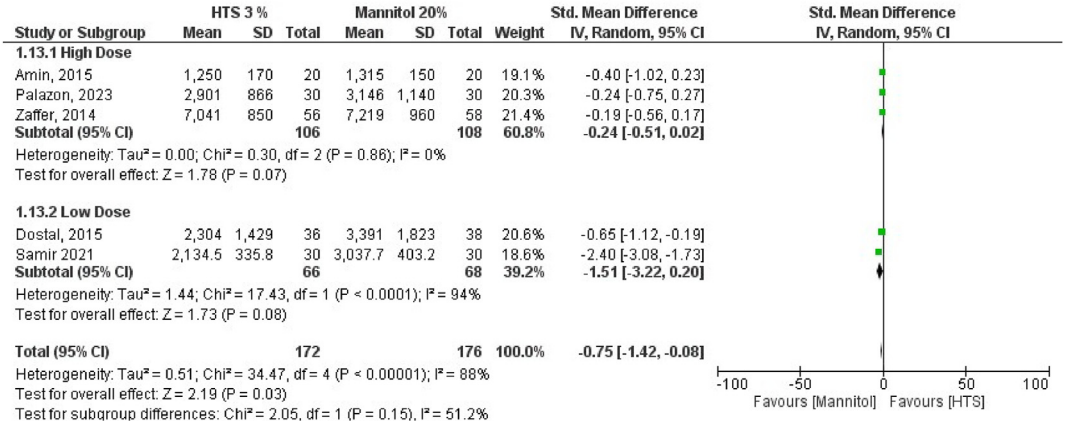

Figure 12: Forest plot of effects of HTS vs mannitol on intraoperative fluid input outcomes.

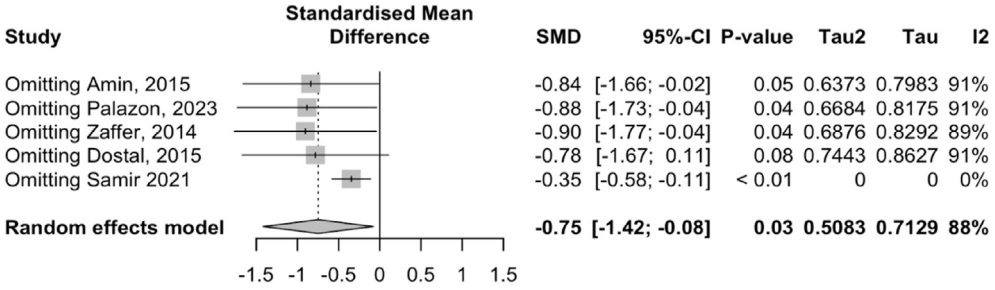

Figure 13: Sensitivity analysis of intraoperative fluid input.

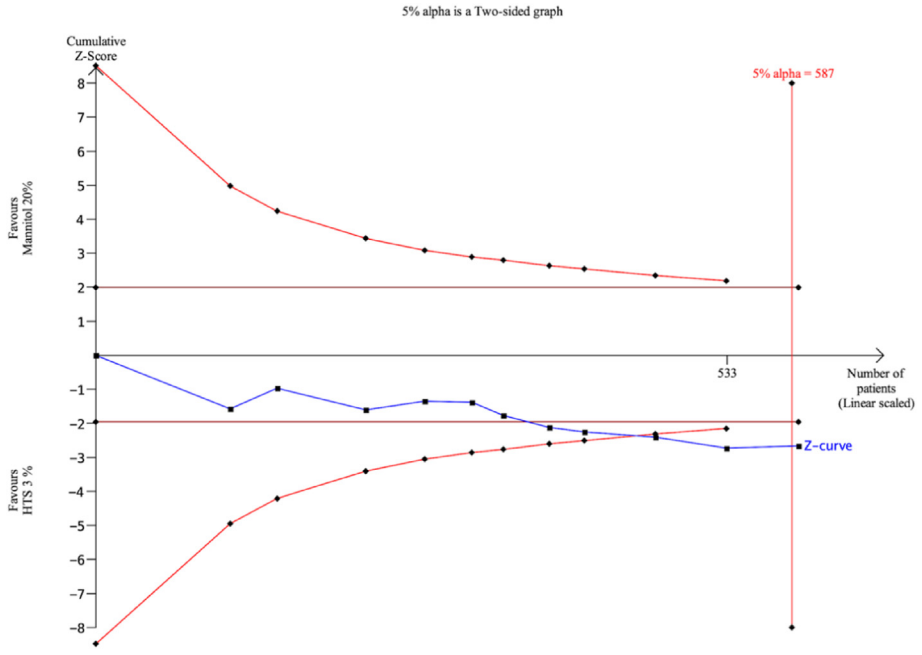

Figure 14: TSA of trials included in analysis of good BRS showed an RIS of 587, according to proportions of control and intervention groups of 63% and 80%, respectively, with a diversity of 62%, $\alpha = 0.05\%$, and $1\text{-}\beta = 80\%$. The Z-curve crossed both the conventional boundary and trial sequencing monitoring boundary for benefit, thus suggesting a significant result.

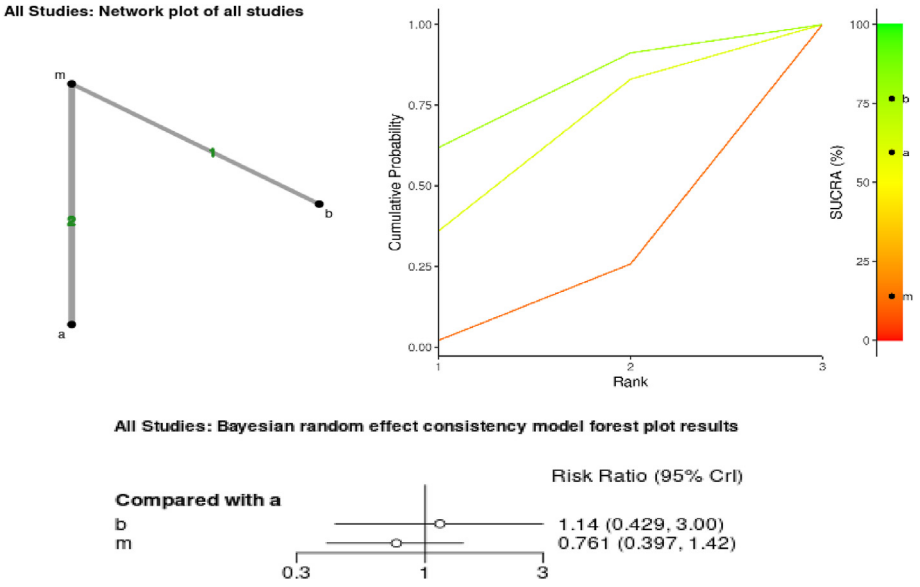

Figure 15: Bayesian network meta-analysis. Network analysis study (A) illustrating a comparison of 3% HTS doses of 5.3 ml/kg BW (a) vs 5 ml/kg BW (b) against a 20% mannitol dose of 5 ml/kg BW (m). In all studies, the ranking (B) shows the best brain relaxation in group (a), followed by groups (b) and (m). C shows a forest plot comparing groups (b) and (m) to group (a). Group (b) achieved 1.14 times better brain relaxation than group (a). Group (m) did not achieve a higher proportion of good BRS outcomes than group (a).

comparisons (indirect effects) between HTS at two doses (3% HTS doses of 5.3 ml/kg BW and 5 ml/kg BW) in producing good brain relaxation, as well as a direct comparison between HTS at these two doses and mannitol, in producing good BRS outcomes.

The results of the direct comparison between HTS and mannitol indicated that good BRS was obtained in the HTS group. Indirect comparisons between different HTS doses indicated that good BRS was produced by HTS at a dose of 5 ml/kg. A SUCRA diagram further indicated that the three solutions achieved good BRS in the following order, from highest to lowest: 3% HTS at 5 ml/kg, 3% HTS at 5.3 ml/kg, and 20% mannitol at 5 ml/kg (Figure 15).

Discussion

This review was aimed at comparing the efficacy and safety of HTS and mannitol in intraoperative craniotomy of tumors, with a primary outcome of achievement of good brain relaxation. The use of HTS was found to produce significantly better brain relaxation than mannitol in this study, in contrast to previous studies.[12] Our meta-analysis suggested that the significantly higher rate of good BRS achieved with HTS supports use of this solution in brain tumor surgery. Taotsi et al., using 7.5% HTS at a dose of 2 ml/kg BW in supratentorial craniotomy, have reported that, in addition to good brain relaxation, HTS provides better cerebral oxygenation than mannitol.[28] Despite the non-significant difference in CPP in our findings, we observed a tendency toward an increase in CPP with HTS compared with mannitol. HTS also maintained better cerebral perfusion than mannitol in brain tumor surgery, thus potentially improving the brain tissue oxygenation essential for good patient outcomes and recovery.[29]

Regarding the safety of each hypertonic fluid, we assessed the risk of hypernatremia and hemodynamic instability across studies. Use of HTS was associated with a significant elevation in plasma sodium levels. High sodium levels may activate the hypothalamus to produce anti-diuretic hormone, thereby causing a net increase in fluid in the intravascular compartment.[30,31] Modest increases in sodium in HTS may increase serum osmolarity and lead to more effective brain-bulk decreases and subsequent ICP control with brain relaxation.[27] However, excessive increases in sodium levels with the risk of volume overload must considered with caution, because they may be detrimental to patients with prior cardiovascular morbidity.[32] We were unable to determine the baseline cardiovascular status in the included studies, although some studies included patients with ASA physical status grade III for brain surgery.[14,18,24,25,27]

Hypernatremia due to HTS administration has also been associated with an acute hyperosmolar state, thus prompting particular concern regarding osmotic demyelination pontine syndrome, which is associated with rapid correction of hyponatremia.[10,31,33] However, Singla et al., whose study was included in this review, have reported that hypernatremia during HTS therapy may resolve spontaneously to normal levels within 4–48 h, thus suggesting the safety of HTS use in brain surgery.[26]

The goal of administration of a hypertonic solution during brain surgery is to maintain brain relaxation without inappropriate intravascular fluid loss. The use of mannitol in tumor craniotomy has been reported to increase the need for intraoperative fluids. Mannitol also exerts more prominent diuretic effects than HTS; increased plasma sodium after HTS administration results in free fluid absorption by the kidneys. Whereas diuretic effects may be beneficial for ICP control, excessive hypovolemia may be detrimental after

brain injury, particularly in critically ill patients.[27,34] UO was also higher in the high-dose mannitol group. MAP was higher in the HTS group, in agreement with the higher risk of hypovolemia seen with mannitol administration. This finding correlated with the results of previous studies reporting the effects of mannitol on hydration status by increasing diuresis and intraoperative fluid requirements.[12]

An appropriate intravenous fluid dosage is also important in craniotomy. Through network meta-analysis, we assessed the direct and indirect effects of HTS vs mannitol in producing good brain relaxation outcomes. Our direct comparison between HTS and mannitol indicated better brain relaxation with HTS. Analysis of indirect effects revealed that, among the doses of HTS used to achieve good brain relaxation, 3% HTS at a dose of 5 ml/kg BW was optimal.

We recognize the importance of patients' baseline characteristics, such as cardiovascular status, in understanding the applicability of our findings to different patient populations. In the primary studies included in our analysis, detailed cardiovascular data were generally not reported. Exceptions included Ali et al., which noted 12 patients with hypertension and one with ischemic heart disease,[18] and Wirawijaya et al., which reported MAP values of 84.75 ± 3.453 in the mannitol group and 86.82 ± 4.177 in the HTS group.[17] The lack of comprehensive cardiovascular data are acknowledged as a limitation of our study.

This study has several additional limitations. First, significant heterogeneity was observed among the included studies, probably because of the varying doses and concentrations of HTS and mannitol used. Despite conducting subgroup analyses, we were unable to fully ascertain the sources of this heterogeneity, thus limiting the generalizability of our findings. Second, the assessment of brain relaxation relied primarily on subjective evaluations by neurosurgeons and anesthesiologists, thereby introducing a risk of bias. Although we recommend that assessments be performed by the same individual blinded to the intervention, inherent subjectivity remains a concern. Objective measures, such as subdural pressure, were not used consistently across studies, despite their potential to provide more reliable data. Additionally, the lack of detailed baseline cardiovascular characteristics in most primary studies limited our ability to fully assess the applicability of our results across different patient populations. Finally, although we conducted sensitivity analyses to measure the consistency of results, and performed TSA to decrease the risk of overestimation due to small sample sizes, these measures could not completely eliminate the limitations described above. These factors should be considered in interpreting the results of this meta-analysis.

Conclusion

This study was aimed at evaluating the efficacy and safety of HTS and mannitol in inducing brain relaxation during craniotomy surgery for brain tumors. Use of 3% HTS, compared with mannitol, was found to be associated with higher brain relaxation with adequate maintenance of hemodynamic stability, and minimization of diuretic effects. Increased sodium is observed after HTS administration and may resolve spontaneously. Network meta-analysis indicated that 3% HTS at 5 ml/kg BW was the optimal dose for achieving good brain relaxation during brain surgery.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

There are no ethical issues.

Authors contributions

KT conceived and designed the study, conducted research, provided research materials, collected and organized data, and drafted and finalized the article. LBB conducted research and collected data, drafted the article, and approved the final version of the article. CJS designed the study, analyzed and interpreted the data, drafted and revised the article, and approved the article's final version. EW analyzed and interpreted data, critically revised the article, and approved the final version of the article. DYB conceived and designed the study, and drafted and revised the article. TB conceived and designed the study, and drafted and revised the article. The authors confirm that all designated authors qualify for authorship and have verified the article for plagiarism. If plagiarism is detected, all authors will be held equally responsible and will bear any resulting sanctions imposed by the journal thereafter. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgments

None.

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How to cite this article: Tarimah K, Bramawangsa LB, Suhardi CJ, Wiyarta E, Bisri DY. Hypertonic saline achieves superior brain relaxation in tumor craniotomy: An updated systematic-network meta-analysis. J Taibah Univ Med Sc 2024;19(5):961–973.