



Hypertonic saline or mannitol for treating elevated intracranial pressure in traumatic brain injury: a meta-analysis of randomized controlled trials

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Abstract

Hyperosmolar therapy is regarded as the mainstay for treatment of elevated intracranial pressure (ICP) in traumatic brain injury (TBI). This still has been disputed as application of hypertonic saline (HS) or mannitol for treating patients with severe TBI. Thus, this meta-analysis was performed to further compare the advantages and disadvantages of mannitol with HS for treating elevated ICP after TBI. We conducted a systematic search on PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Wan Fang Data, VIP Data, SinoMed, and China National Knowledge Infrastructure (CNKI) databases. Studies were included or not based on the quality assessment by the Jadad scale and selection criteria. Twelve RCTs with 438 patients were enrolled for the meta-analysis. The comparison of HS and mannitol indicated that they were close in field of improving function outcome (RR = 1.17, 95% CI 0.89 to 1.54, $p = 0.258$) and reducing intracranial pressure (MD = -0.16, 95% CI: -0.59 to 0.27, $p = 0.473$) and mortality (RR = 0.78, 95% CI 0.53 to 1.16, $p = 0.216$). The pooled relative risk of successful ICP control was 1.06 (95% CI: 1.00 to 1.13, $p = 0.044$), demonstrating that HS was more effective than mannitol in ICP management. Both serum sodium (WMD = 5.30, 95% CI: 4.37 to 6.22, $p < 0.001$) and osmolality (WMD = 3.03, 95% CI: 0.18 to 5.88, $p = 0.037$) were increased after injection of hypertonic saline. The results do not lend a specific recommendation to select hypertonic saline or mannitol as a first-line for the patients with elevated ICP caused by TBI. However, for the refractory intracranial hypertension, hypertonic saline seems to be preferred.

Keywords Intracranial hypertension · Intracranial pressure · Hypertonic saline · Mannitol · Traumatic brain injury · Meta-analysis

Introduction

Severe traumatic brain injury (TBI) remains a substantial public health problem worldwide. The global pooled incidence of TBI for all ages is up to 349 per 100,000 person-years [1] and possesses a high mortality rate [2, 3]. Characteristically, TBI

survivors suffer varying degrees of neurological disability [3, 4]. Intracranial pressure (ICP) is a major predictor of neurological deterioration in patients with TBI, with elevated ICP being associated with poor neurological outcome [5]. Hyperosmolar therapy is regarded as the mainstay for treating elevated ICP in TBI, whereas mannitol has long been the gold standard for controlling intracranial hypertension [6, 7]. Recently, many adverse effects of mannitol have been identified, such as acute renal failure, rebound ICP elevation, and hypovolemia [7–9]. As an alternative therapeutic approach, hypertonic saline (HS) has been used to treat patients with cerebral edema and elevated ICP. The views of previous meta-analyses tend to hold that HS is more effective than mannitol in reducing ICP, but the fourth edition of the Brain Trauma Foundation’s “Guidelines for the Management of Severe Traumatic Brain Injury” states that “there is insufficient evidence available from comparative studies to support a formal recommendation” and there is also lacking evidence to support the application of any specific hyperosmolar drug for patients with severe traumatic brain injury [10]. Thus, this

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meta-analysis further compares the strengths and weaknesses of mannitol versus hypertonic saline for treating elevated ICP resulting from TBI.

Materials and methods

Inclusion criteria

The following inclusion criteria were applied: (1) study: randomized controlled trials; (2) patients: 14 years and older who suffered from TBI with high ICP; (3) intervention: hypertonic saline and mannitol; (4) full text available.

Exclusion criteria

Studies met the following criteria were excluded: (1) animal studies, cohort studies, and case reports; (2) patients with liver and renal failure, cardiac dysfunction, or hypovolemic shock; (3) studies that either did not directly compare the effects on elevated ICP of hypertonic saline and mannitol or that did not provide primary outcome data; (4) low-quality literature (Jadad score ≤ 2).

Literature search

We performed a systematic search on PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Wan Fang Data, VIP Data, SinoMed, and China National Knowledge Infrastructure (CNKI) databases for relevant articles using the following text words or MeSH: “intracranial pressure,” “hypertonic saline,” and “mannitol,” and we also complemented the literature by searching clinicaltrials.gov and using the Related Articles function on PubMed. The search was completed on December 31st, 2017; then, two investigators independently reviewed the titles and abstracts of all studies and excluded those that did not conform to the eligibility criteria. Any disagreement was decided by a third investigator.

Data extraction

For each eligible study, the following were extracted: name of the first author, year of publication, country, patient demographic data, definition of ICP control, formulation, study design, main results of the study, and follow-up results. Primary outcomes were the maximum mean reduction in ICP in each group during treatment. Secondary outcomes contained maximal serum sodium, maximal serum osmolality, relative risk of successful ICP treatment, functional outcomes, and mortality.

Quality assessment

The Jadad scale was used to assess the quality of the RCTs [11]. This scale examines the following terms: (1) randomization (yes = 2, unclear = 1, no = 0); (2) double-blind (yes = 2, unclear = 1, no = 0); and (3) withdrawals and dropouts (described = 1, no = 0). The quality scale ranges from 0 to 5 points. A Jadad score ≤ 2 is considered as low quality and a score ≥ 3 indicates high quality [12].

Statistical analysis

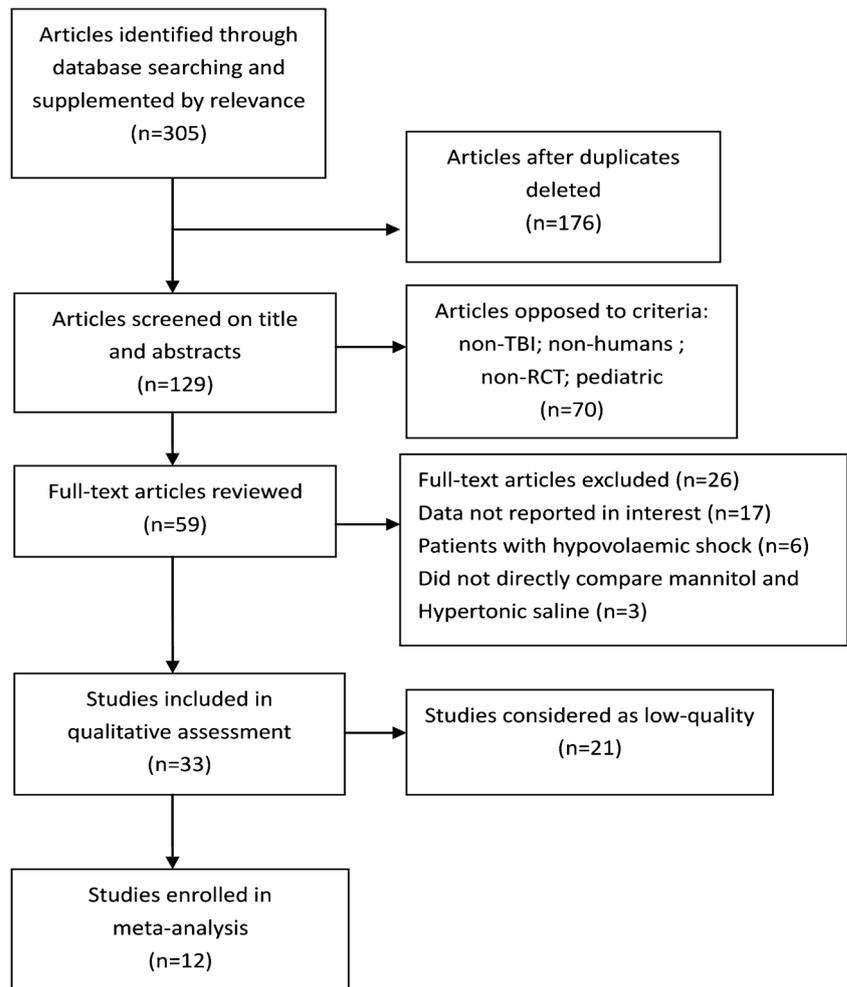
All data were analyzed using STATA 12.0 software. Statistical heterogeneity among studies was assessed by Cochran’s Q and Higgins’ I^2 . A p value < 0.1 or $I^2 > 50\%$ was considered to indicate significant heterogeneity [13]. The random-effect model was applied if heterogeneity was substantial. Otherwise, the fixed-effect model was used. Measurement data were expressed as weighted mean differences (WMD) and enumeration data as RRs with 95% CIs, and statistical significance was prespecified as a two-sided $p < 0.05$. Sensitivity analysis was performed for the primary outcomes by using the leave-one-out method and examining the influence of each specific study on the pooled results [14]. Publication bias was inspected using a funnel plot and Egger’s test.

Results

Characteristics of the included studies

There were 305 papers initially identified, of which 272 papers were excluded, leaving 33 articles for quality assessment using the Jadad scale. After evaluation, 21 articles were determined to be of low quality (Jadad score ≤ 2) and were excluded, leaving 12 studies for the meta-analysis (Fig. 1).

A total of 438 patients were recruited in the 12 studies. Trial sample size ranged from 9 to 132 individuals, but only one trial included more than 100 patients [15]. Among all of the included RCTs, five studies were crossover studies [16–20]. In three studies, multifarious neurosurgical patients were recruited, with only 33 out of 61 patients suffering from traumatic brain injury, and the others sustaining cerebral hemorrhage, stroke, or subarachnoid hemorrhage [16, 21, 22]. One study designed two groups of trials which compared mannitol with two different consistence of HS, and these two trials were, respectively, enrolled for analysis (Table 1) [19]. The methodological quality scores of the included studies are listed in Table 2.

Fig. 1 Flow diagram of study selection

Reduction of intracranial pressure

Of the 12 RCTs, 11 studies provided data on intracranial pressure change at baseline and after treatment [15–25]. The value for maximal change was extracted from the mannitol and HS groups for analysis. A fixed-effect model was applied on the basis of low statistical heterogeneity ($I^2 = 30.4\%$, $p = 0.149$). The pooled mean difference (MD) of maximal ICP reduction, comparing HS to mannitol, was -0.16 (95% CI: -0.59 to 0.27 , $p = 0.473$), indicating that there was no difference on the efficacy of ICP reduction between the two drugs (Fig. 2).

Control of intracranial pressure

Eight studies reported data on treatment times of increased ICP [16, 17, 19–22, 24–26]. The pooled relative risk of successful control of raised ICP was 1.06 (95% CI: 1.00 to 1.13, $p = 0.044$), with minimal heterogeneity across studies ($I^2 = 0\%$, $p = 0.456$). The pooled results demonstrated that HS was more effective than mannitol in ICP management (Fig. 3).

Serum sodium and serum osmolality

Seven studies provided data on serum sodium within 6 h after hyperosmolar therapy [16, 17, 19, 20, 22, 23, 26]. The results suggested that HS significantly increases the concentration of serum sodium when compared to mannitol (WMD: 5.30, 95% CI: 4.37 to 6.22, $p < 0.001$), which was associated with moderate heterogeneity ($I^2 = 38.4\%$, $p = 0.123$) (Fig. 4). Five studies reported data for serum osmolality [16, 17, 20, 21, 26]. The pooled mean difference was 3.03 (95% CI: 0.18 to 5.88, $p = 0.037$), indicating that HS could also significantly increase serum osmolality (Fig. 5).

Mortality

Data on mortality was available in six studies [15, 21, 23–26]. There was no evidence of heterogeneity among the six studies ($I^2 = 0\%$, $p = 0.957$). The pooled relative risk of mortality was 0.78 (95% CI 0.53 to 1.16, $p = 0.216$), indicating that HS had no clear advantage in reducing mortality (Fig. 6).

Table 1 Characteristics of included studies

Study	Country	Design	Patients	Group	Number of patients	Sex (M/F)	Age	GCS at admission	Baseline ICP (mmHg)	Definition of ICP control	Formulation	Dose
Vialet et al. 2003	France	RCT	TBI (<i>n</i> = 20)	M	10	4/6	30.8 (19)	5.4 (2.8)	NA	< 25 mmHg	20%, 2 ml/kg	2.3 mOsm/kg
Battison et al. 2005	UK	RCT	TBI (<i>n</i> = 6)	HS	10	5/5	35 (18)	4.1 (1.6)	NA	< 18 mmHg	7.5%, 2 ml/kg	4.8 mOsm/kg
		Crossover	SAH (<i>n</i> = 3)	M	9	NA	NA	NA	24.0 (18.8, 25.9) ^a 22.0 (20.1, 26.3) ^a	< 18 mmHg	20%, 200 ml 7.5% saline and 6% dextran-70, 100 ml	249 mOsm 250 mOsm
Harujunyan et al. 2005	Germany	RCT	TBI (<i>n</i> = 10)	M	15	8/7	47 (16)	5.8 (1.4)	23 (19, 30) ^b	< 15 mmHg	15%	NA
			Stroke (<i>n</i> = 7) SAH (<i>n</i> = 9) ICH (<i>n</i> = 4) Other (<i>n</i> = 2)	NaCl/HES	17	9/8	47 (16)	6 (1.3)	22 (19, 31) ^b	< 15 mmHg	7.2% NaCl/HES 200/0.5	NA NA
Mao et al. 2007	China	RCT	TBI (<i>n</i> = 14)	M	NA	NA	36.3 (3.8)	(3.8) ^b	NA	< 20 mmHg	20%, 250 ml	311 mOsm
Francony et al. 2008	France	Crossover	TBI (<i>n</i> = 17)	HS	NA	NA	NA	NA	NA	> 20% below baseline	3%, 300 ml	308 mOsm
		RCT	ICH (<i>n</i> = 2) Stroke (<i>n</i> = 1)	M	10	7/3	43 (11)	8 (2)	31 (6)	> 20% below baseline	20%, 231 ml	255 mOsm
Cottenceau et al. 2011	France	RCT	TBI (<i>n</i> = 47)	HS	10	9/1	37 (16)	7 (2)	27 (3)	< 20 mmHg	7.45%, 100 ml	255 mOsm
		RCT	TBI (<i>n</i> = 29)	M	25	NA	36.1 (16.8)	7 (5.8) ^c	16.3 (9.3)	< 20 mmHg	20%, 4 ml/kg	4.6 mOsm/kg
Sakellariadis et al. 2011	Greece	RCT	TBI (<i>n</i> = 29)	HS	22	NA	42.7 (19.9)	5 (4.7) ^c	17.9 (9.9)	< 20 mmHg	7.5%, 2 ml/kg	4.8 mOsm/kg
		Crossover	TBI (<i>n</i> = 16)	M	NA	NA	36 (14.82) ^b	5.4, GCS < 8	NA	< 20 mmHg	20%, 2 ml/kg	2.3 mOsm/kg
Yan et al. 2013	China	RCT	TBI (<i>n</i> = 16)	HS	NA	NA	43.5 (30.52) ^b	6.25 (1.65)	NA	< 25 mmHg	15%, 0.42 ml/kg 20%, 250 ml	2.02 mOsm/kg 275 mOsm
		Crossover	TBI (<i>n</i> = 16)	M	11/5	NA	NA	NA	NA	< 25 mmHg	3%, 300 ml	308 mOsm
Huang et al. 2014	China	RCT	TBI (<i>n</i> = 33)	HS	NA	NA	36.5 (16.5)	5.3, GCS < 8	NA	< 20 mmHg	20%, 250 ml	288 mOsm
		Crossover	TBI (<i>n</i> = 48)	M	24	17/7	32.8 (19.72) ^b	NA	21.69 (6.93)	< 15 mmHg	7.5%, 120 ml	275 mOsm
Qin et al. 2016	China	RCT	TBI (<i>n</i> = 38)	HS	24	18/6	32.6 (18.72) ^b	NA	22.30 (3.61)	< 15 mmHg	20%, 250 ml	498 mOsm
		RCT	TBI (<i>n</i> = 38)	M	20	18/2	31 (13)	5 (3–7) ^a	NA	< 20 mmHg	3%, 250 ml	410 mOsm
Jagannatha et al. 2016	India	RCT	TBI (<i>n</i> = 38)	HS	18	16/2	27 (8)	4 (3–7) ^a	NA	< 20 mmHg	20%, 2.5 ml/kg	2.88 mOsm/kg
		RCT	TBI (<i>n</i> = 132)	M	67	41/26	41.28 (8.46)	5.84 (1.07)	NA	< 20 mmHg	3%, 2.5 ml/kg	2.4 mOsm/kg
Du et al. 2017	China	RCT	TBI (<i>n</i> = 132)	HS	65	35/30	38.82 (9.93)	5.54 (1.39)	NA	< 20 mmHg	20%, 5.0 ml/kg 3%, 5.4 ml/kg	5.75 mOsm/kg 5.19 mOsm/kg

M mannitol, HS hypertonic saline, SAH subarachnoid hemorrhage, HSD hypertonic saline and dextran, RCT randomized controlled trial, NA not available continuous measures are expressed as mean (SD)

^a Which are expressed as median (interquartile range)

^b Which are expressed as mean (range)

^c Which are expressed as median (median with lower and upper 95% confidence limit of median)

Table 2 Quality score of included trials

Study	Randomization	Double-blind	Withdrawals and dropouts	Jadad score
Vialet et al. 2003	1	1	1	3
Battison et al. 2005	2	1	1	4
Harutjunyan et al. 2005	2	0	1	3
Mao et al. 2007	2	0	1	3
Francony et al. 2008	2	0	1	3
Cottenceau et al. 2011	2	0	1	3
Sakellaridis et al. 2011	2	2	1	5
Yan et al. 2013	2	0	1	3
Huang et al. 2014	2	1	1	4
Qin et al. 2016	2	0	1	3
Jagannatha et al. 2016	2	0	1	3
Du et al. 2017	2	0	1	3

Neurological functional outcome

For the outcome of neurological function, as assessed by the Glasgow outcome scale, data was reported in five included studies [15, 23–26]. A good neurological outcome was defined as having a scale ranging from 4 to 5. The pooled results indicated that there was no significant difference between the groups of hypertonic

saline and mannitol (RR = 1.17, 95%CI 0.89 to 1.54, $p = 0.258$), with low heterogeneity across studies ($I^2 = 30.3%$, $p = 0.220$) (Fig. 7).

Sensitivity analysis

Sensitivity analysis was performed for the primary outcomes. The remained pooled results were not significantly altered by

Fig. 2 Forest plot of a fixed-effect model comparing hypertonic saline with mannitol on maximal reduction of intracranial pressure. A/B represent different trials of the study

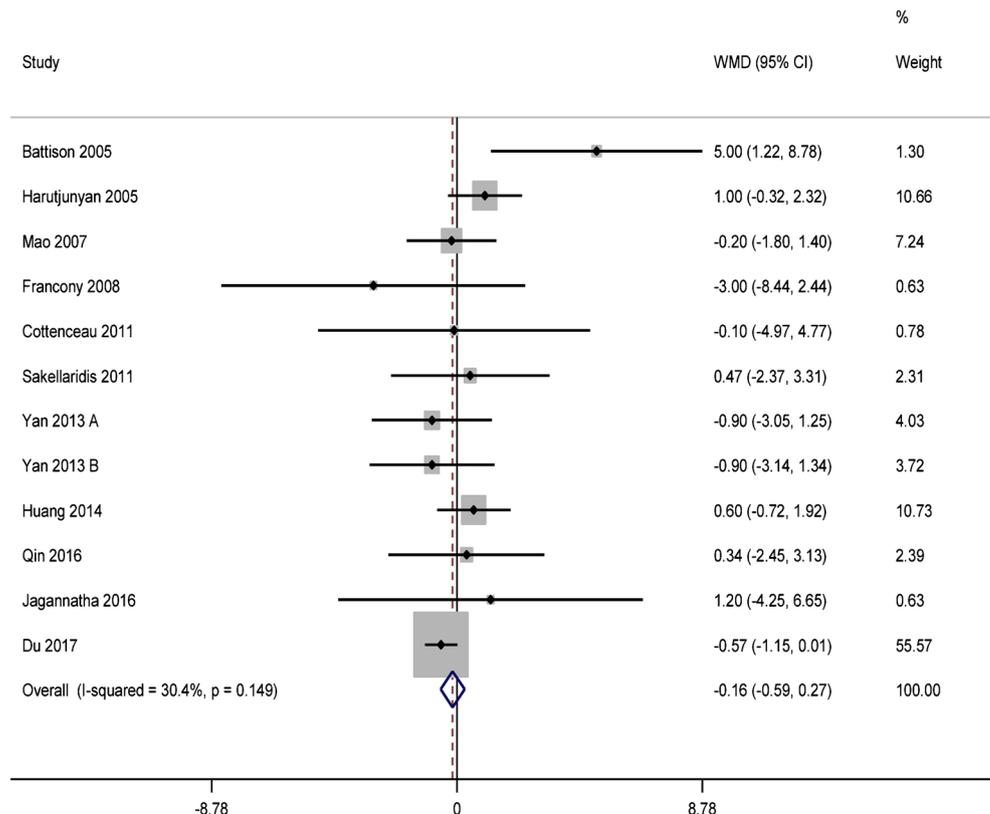
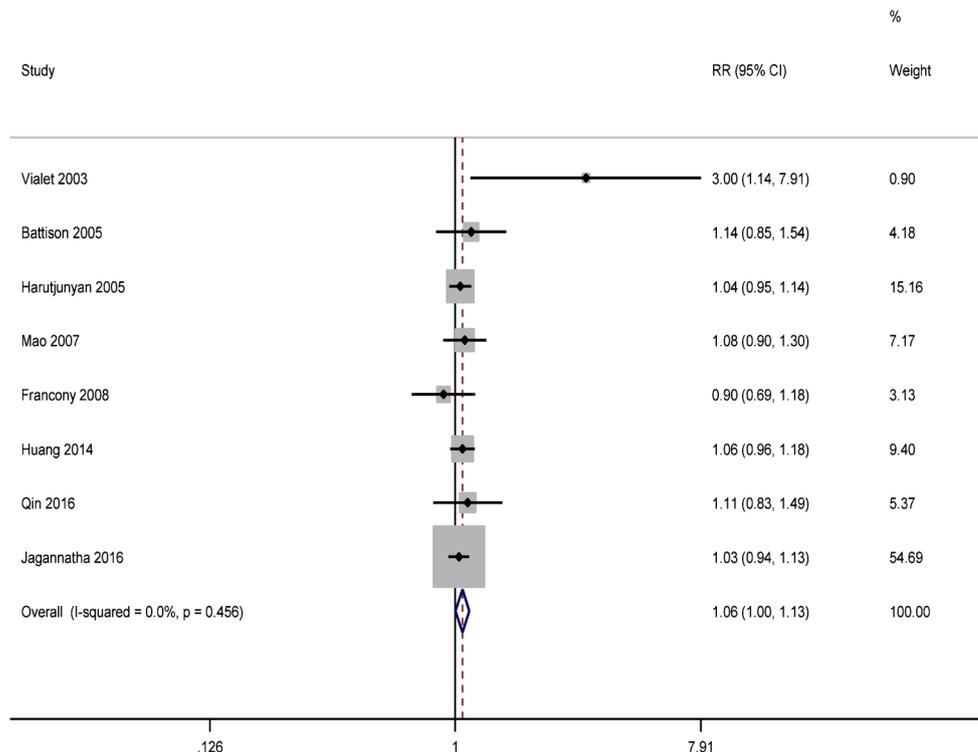


Fig. 3 Forest plot of a fixed-effect model comparing relative risk of successful ICP treatment between hypertonic saline and mannitol



excluding each study in turn, indicating that our results were stabilized and credible (Fig. 8). In addition, when the weakest study was excluded [15], the statistical heterogeneity among the studies was decreased (I^2 decreased from 30.4 to 12.4%, $p = 0.326$) (Fig. 9).

Publication bias

A funnel plot and Egger’s test were performed to estimate the publication bias. Visual symmetrical distribution of the funnel plot and data from the Egger’s test

Fig. 4 Forest plot of a fixed-effect model comparing hypertonic saline with mannitol on the maximal concentration of serum sodium after injection. A/B represent different trials of the study

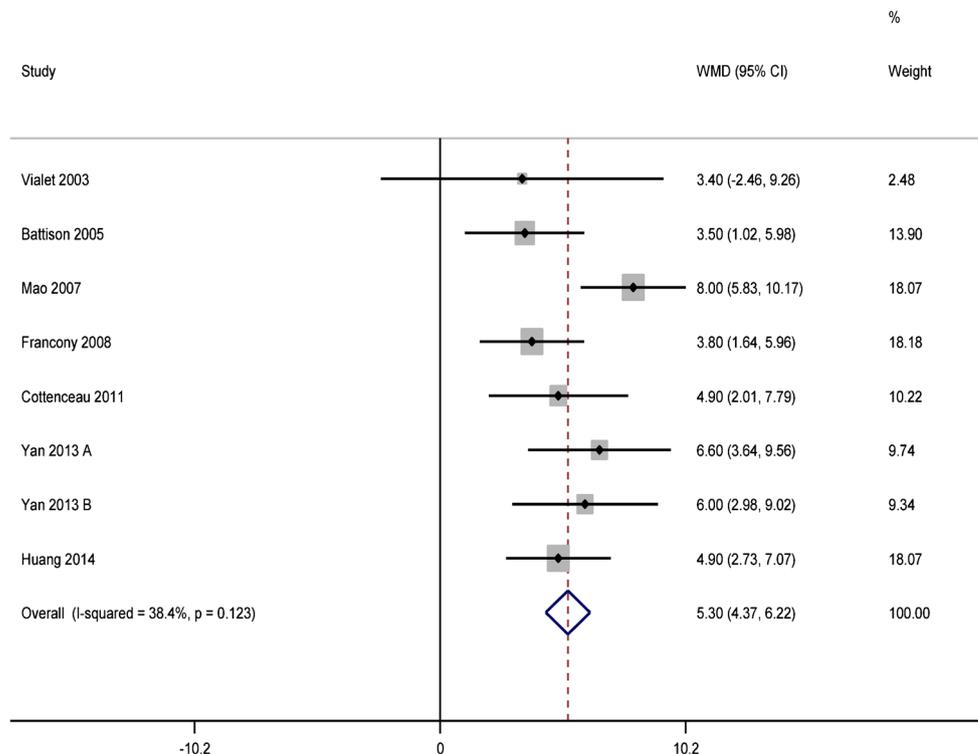
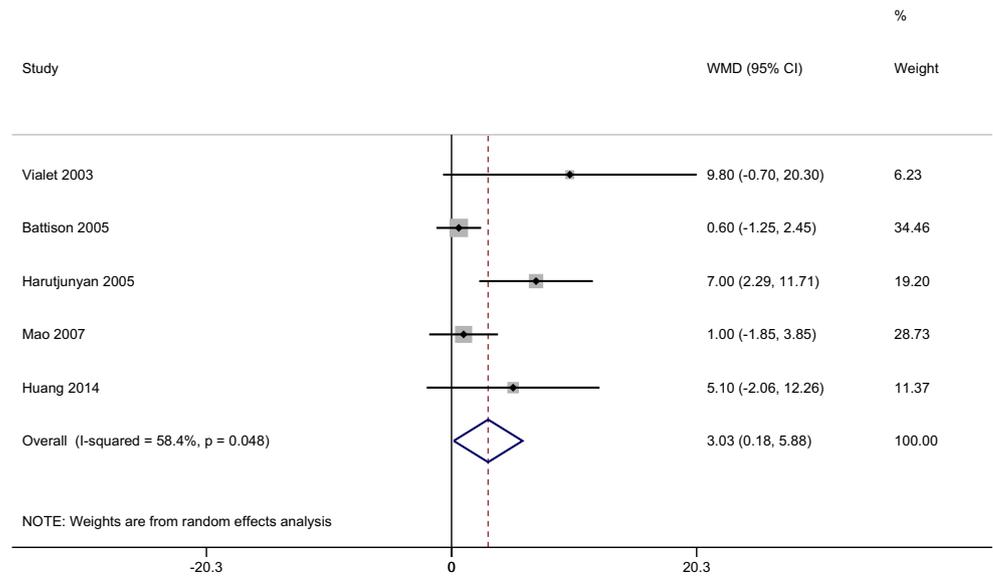


Fig. 5 Forest plot of a random-effect model comparing hypertonic saline with mannitol on the maximal serum osmolality after injection



($p = 0.256$) jointly suggested an absence of publication bias (Figs. 10 and 11).

Discussion

In this review, we evaluated hypertonic saline and mannitol from six aspects: intracranial pressure reduction, intracranial pressure control, serum sodium, serum osmolality, mortality, and neurological function outcome. A comparison of the two drugs indicates that they are close in ability to improve function and decrease

mortality. These results are in line with the viewpoint of Burgess et al. and Berger et al. [27, 28].

Regarding reduction of intracranial pressure, there appears to be no significant advantage of one specific hypertonic agent. Reviewing the prior research, four studies showed, as does ours, that there is no statistically significant difference in the ability to reduce intracranial pressure between HS and mannitol [27–30]. By comparing different time nodes of treatment, two other studies concluded that greater ICP-lowering effects are obtained from hypertonic saline [31, 32]. However, in these two studies, the different duration times of mannitol and hypertonic saline and the disparate maximum

Fig. 6 Forest plot of a fixed-effect model comparing relative risk of reducing mortality between hypertonic saline and mannitol

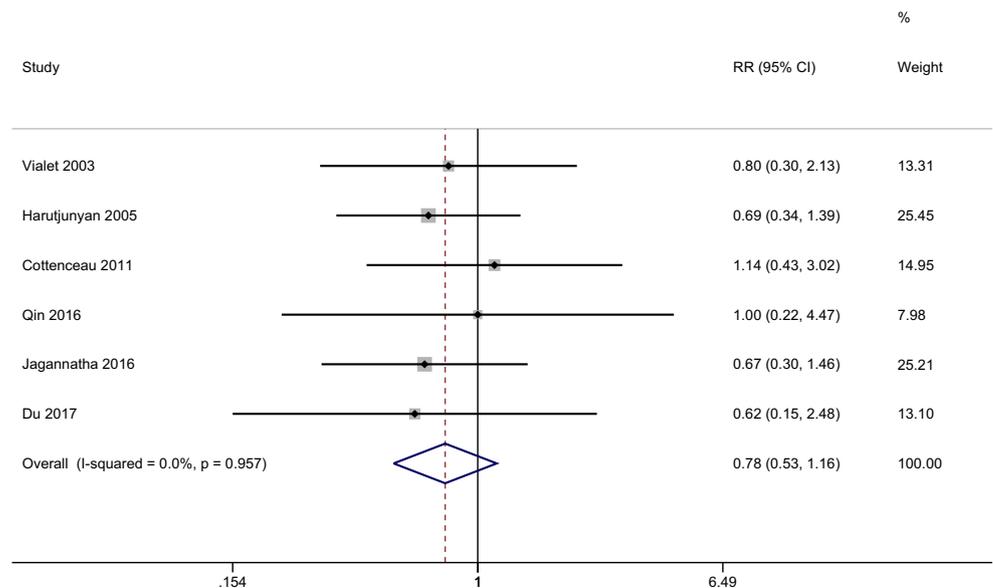
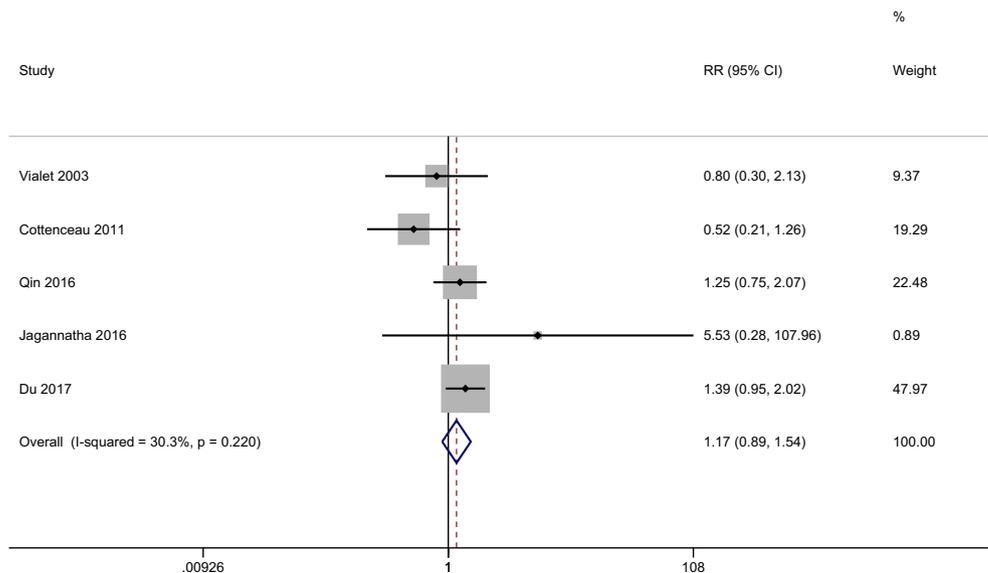


Fig. 7 Forest plot of a fixed-effect model comparing hypertonic saline and mannitol on improving function outcome



ICP reduction times may have biased the results [33, 34]. Another two systematic reviews used different inclusion criteria from ours, and both favored hypertonic saline over mannitol [33, 35]. Nevertheless, those results were also limited by inclusion of various study designs and diverse study populations. By contrast, our meta-analysis followed a more meticulous set of exclusion criteria, and specifically enrolled studies on traumatic brain injury.

Change of the intracranial pressure is correlated with cerebral blood flow, cerebral perfusion pressure, cerebrospinal fluid circulation, and so on. It can also be used as an important prognosticator of patients with TBI [5]. The ICP treatment threshold has changed over time as new evidence appeared, getting more precise and stronger. The fourth edition Guidelines for the Management of Severe Traumatic Brain Injury recommended ICP > 22 mmHg as a treating ICP threshold,

Fig. 8 A sensitivity analysis of the maximal reduction on intracranial pressure. A/B represent different trials of the study

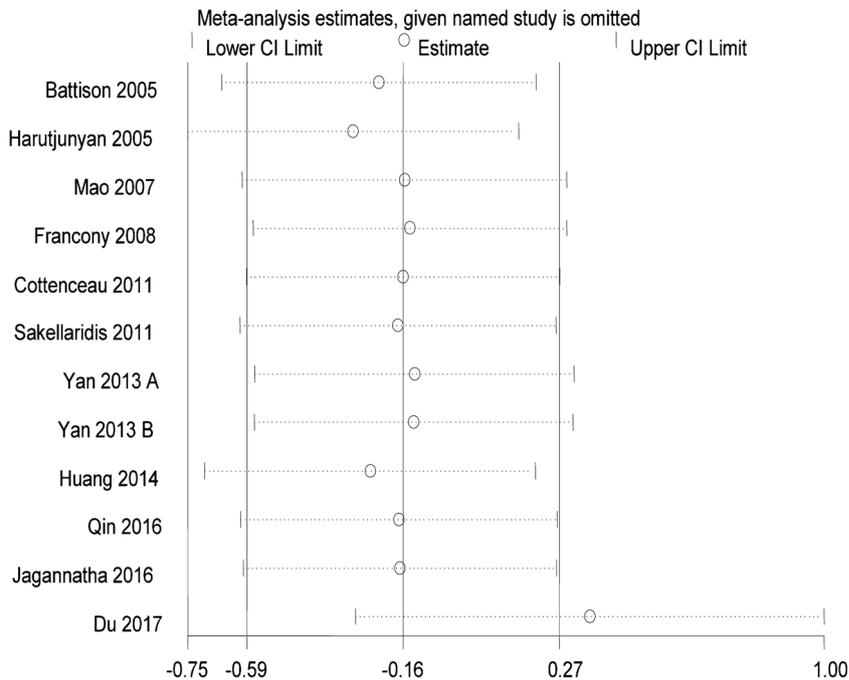
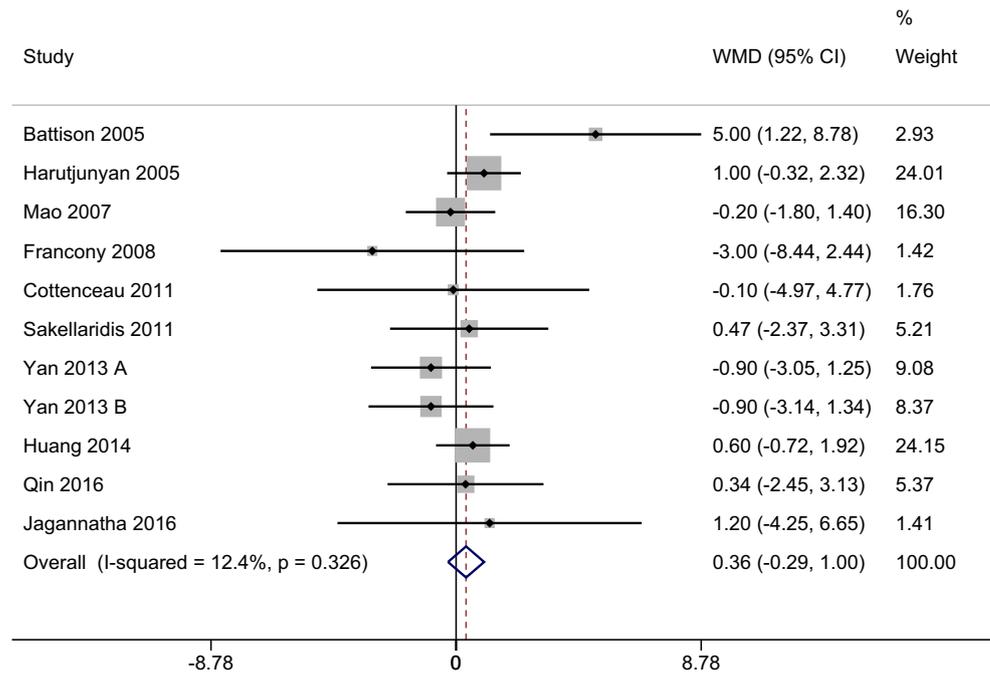


Fig. 9 Forest plot of a fixed-effect model comparing hypertonic saline with mannitol on maximal reduction of intracranial pressure after excluding the weakest study. A/B represent different trials of the study



because values above this level would increase mortality [10]. In this meta-analysis, there are no differences in improving function and decreasing mortality between using hypertonic saline and mannitol. It could be partly due to the fact that most studies previously did not set this numeric as the ICP treatment threshold. Of course, further research is needed to prove the assumption.

As for control of intracranial pressure, obvious advantages are embodied in the use of hypertonic saline,

which is consistent with previous findings. Eskandari et al., in a study that involved 11 adult TBI patients with intracranial hypertension, who received 14.6% HS injections after all other medical therapies failed, concluded that TBI patients with refractory intracranial hypertension can be treated safely and effectively by hypertonic saline [36]. Even so, concerns about the safety of hypertonic saline in clinical applications still persist. In the present study, there were significant increases in both serum sodium and osmolality after injection of hypertonic saline. Hyperosmolar states have been reported to cause damage, although no adverse events were recorded in the trials included here. Rapid changes in serum sodium have been considered as a causative factor for central pontine myelinolysis. Pietrini et al. indicated that the correction of abnormal serum sodium should be under 10 mEq/L, even upon acute onset hyponatremia [37]. A multicenter, retrospective cohort study by Erdman et al. suggested a positive link between severe hypernatremia and acute kidney injury (AKI), with a risk of AKI increasing dramatically when serum sodium exceeds 155 mmol/L [38]. We attempted to collect data on creatinine or urea nitrogen to assess the effect of hyperosmolality on renal function. Unfortunately, only two study reported detailed data on the indicator of creatinine or urea nitrogen [23, 24]. To better comprehend hyperosmolality's damage on body, serum sodium and serum osmolality should be noticed more often in subsequent research; the adverse events also ought to be

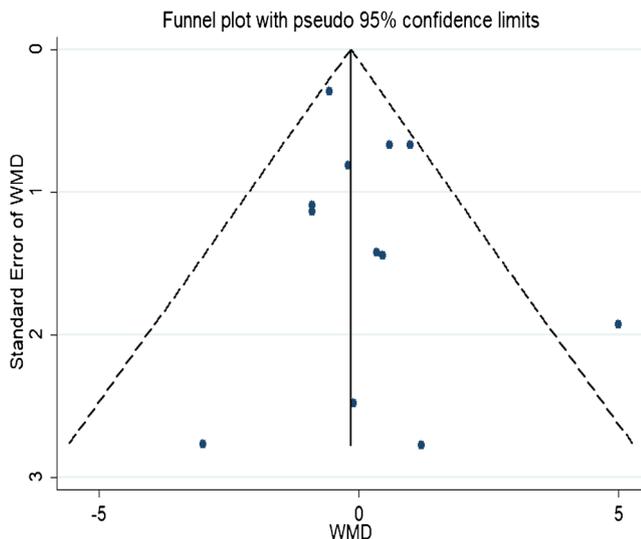
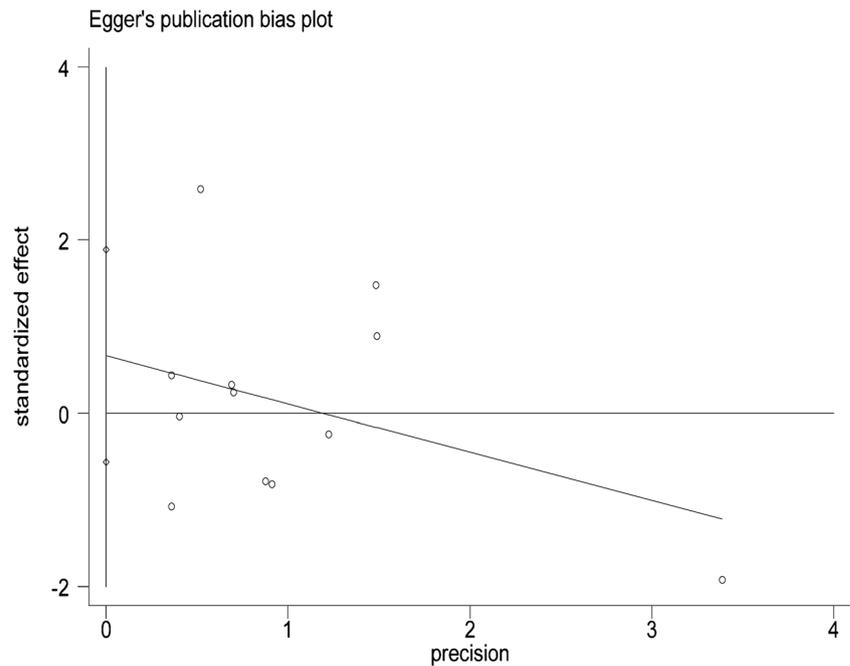


Fig. 10 Funnel plot for the publication bias test of studies provided data on maximal intracranial pressure reduction

Fig. 11 Egger's publication bias plot of studies provided data on maximal intracranial pressure reduction



listed on the report. In addition, more studies and further clinical trials are needed to determine the optimal concentration of hypertonic saline in treating traumatic intracranial hypertension.

This meta-analysis has several limitations. First, the included studies were limited both in sample size and quality. Second, although all included randomized controlled trials were aimed at comparing the efficacy, between hypertonic saline and mannitol, of reducing intracranial pressure, dosage and formulation of drug, time of treatment initiation, and definition of successful ICP treatment were heterogeneous. In addition, five cross-over controlled trials and three studies which included non-TBI neurosurgical patients were enrolled in this analysis. All of the above may lead to bias in our results.

Conclusion

In general, our results do not lend a specific recommendation to select hypertonic saline or mannitol as a first-line for the patients with elevated ICP caused by TBI. However, for refractory intracranial hypertension, use of hypertonic saline seems to be a priority.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical approval and informed consent Ethical approval was not required. All the studies contained in this article were in compliance with ethical standards and have been published online. All the presented data were anonymized and there is no risk of identification.

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