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Comparison of Equimolar Doses of Mannitol and Hypertonic Saline for the Treatment of Elevated Intracranial Pressure After Traumatic Brain Injury

A Systematic Review and Meta-Analysis

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Abstract: The purpose of this meta-analysis was to compare the effectiveness of mannitol and hypertonic saline for reducing intracranial pressure (ICP) after traumatic brain injury (TBI).

PubMed, Cochrane, Embase, and ISI Web of Knowledge databases were searched until July 3, 2014 using the terms intracranial hypertension, mannitol, and hypertonic saline. Randomized controlled trials and 2-arm prospective studies in which elevated ICP was present after TBI treated with mannitol or hypertonic saline were included. The primary outcome was the change of ICP from baseline to termination of the infusion, while the secondary outcomes were change from baseline to 30, 60, and 120 minutes after terminating the infusion and change of osmolarity from baseline to termination.

A total 7 studies with 169 patients were included. The mean age of patients receiving mannitol ranged from 30.8 to 47 years, and for patients receiving hypertonic saline ranged from 35 to 47 years. A pooled difference in means = −1.69 (95% confidence interval [CI]: −2.95 to −0.44, $P = 0.008$) indicated that hypertonic saline reduced ICP more effectively than mannitol when compared from the baseline value to the last measurement after treatment. At 30 minutes after intervention, there was no difference in the mean ICP change between the groups, whereas at 60 minutes after intervention (pooled difference in means = −2.58, 95% CI: −4.37 to −0.80, $P = .005$) and 120 min after intervention (pooled difference in means = −4.04, 95% CI: −6.75 to −1.32, $P = .004$) hypertonic saline resulted in a significantly greater decrease in ICP. The pooled difference in means = 1.84 (95% CI: −1.64 to 5.31, $P = .301$) indicated no difference in serum osmolarity between patients treated with hypertonic saline or mannitol.

Hypertonic saline is more effective than mannitol for reducing ICP in cases of TBI.

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Abbreviations: CI = confidence interval, GCS = Glasgow Coma Score, HES = hydroxyethyl starch, ICP = intracranial pressure, RCT = randomized controlled trial, TBI = traumatic brain injury.

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INTRODUCTION

Cerebral edema and elevated intracranial pressure (ICP) are cardinal manifestations of severe brain injury in cases of traumatic brain injury (TBI), stroke (ischemic and hemorrhagic), aneurysmal subarachnoid hemorrhage, infection, and neoplasms.[1] An elevated ICP can result in life-threatening compromised cerebral circulation and brainstem compression, and is the most common cause of death in patients with severe TBI.[2,3] Hyperosmolar therapy is used to treat cerebral edema and elevated ICP, and hypertonic saline and mannitol are 2 of the commonly used agents.[4] In brief, the osmotic agents create an osmotic gradient across an intact blood–brain barrier and thus draw water from the cerebral interstitium into the vascular space.[5,6] The volume decrease in the brain reduces the ICP.

Mannitol is effective at reducing ICP, and has been used for decades in the treatment of TBI. However, it may precipitate acute renal failure if serum osmolarity exceeds 320 mOsm/L, and there are concerns of elevated serum concentrations of mannitol and rebound intracranial hypertension.[5] Concerns with the use of mannitol have led to interest in other agents. Hypertonic saline appears to be safe, and elevations of serum sodium with the use of hypertonic saline have not been associated with significant neurologic, cardiac, or renal injury.[5,7,8] Prior meta-analyses have suggested that hypertonic saline is more effective than mannitol at reducing ICP, but have been limited by the small number and size of included trials.[9,10]

Thus, the purpose of this meta-analysis was to compare the effectiveness of mannitol and hypertonic saline for reducing ICP after TBI.

MATERIALS AND METHODS

Literature Search Strategy

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.[11] PubMed, Cochrane, Embase, and ISI Web of Knowledge databases were searched until July 3, 2014 using combinations of the search terms: intracranial hypertension, mannitol, and hypertonic saline. The approval by an institutional review board is not required for this study because human subjects were not studied.

Selection Criteria and Data Extraction

Inclusion criteria were randomized controlled trial (RCT), 2-arm prospective or retrospective study; patients sustained TBI; elevated ICP; and treatment consisted of hypertonic saline or mannitol. Cohort studies, letters, comments, editorials, case reports, proceedings, and personal communications were excluded. In addition, studies that did not include patients with TBI (eg, studies that only included patients with stroke or brain tumor), those that studied pediatric patients, and those that did

not provide quantitative data with respect to the primary outcome were also excluded.

Data extracted from studies that met the inclusion criteria were the name of the first author, year of publication, study design, demographic data of patients, Glasgow Coma Score (GCS), the presence of intracranial hypertension and level, osmolarity, dosage, formulation, and administration of mannitol and hypertonic saline, and outcomes. Data extraction was performed by two independent reviewers, and a third reviewer was consulted for any uncertainties.

Quality Assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)[12] by 2 reviewers.

Outcome Measures and Data Analysis

The primary outcome was the mean change of ICP from baseline to the last measurement after terminating the infusion between patients treated with mannitol and hypertonic saline. The secondary outcomes were mean change of ICP from baseline to 30, 60, and 120 minutes after terminating the infusion, and the mean change of osmolarity from baseline to the last measurement after terminating the infusion between patients treated with mannitol and hypertonic saline. If data were not presented as mean and standard deviation, median, range, and the size of the sample were used to estimate the mean and variance.[13] If median and interquartile range (IQR) were reported, it was assumed that the median of the outcome variable was equal to the mean response and the width of the interquartile range was approximately 1.35 standard deviations.[12] The difference in means with 95% confidence intervals (CIs) were calculated for each individual study and for the pooled estimates.

A χ^2-based test of homogeneity was performed using Cochran Q statistic and I^2. I^2 indicates the percentage of the total variability in effect estimates among trials due to heterogeneity rather than chance. Random-effects models of analysis were used if heterogeneity was detected ($I^2 > 50\%$). Otherwise, fixed-effects models were used. Pooled effects were calculated, and a 2-sided P value $<.05$ was considered to indicate statistical significance. Sensitivity analysis was carried out for the primary outcome using the leave-one-out approach. Publication bias was assessed by constructing funnel plots for the primary outcome and by Egger test.[14] The absence of publication bias is indicated by the data points forming a symmetric funnel-shaped distribution, and a 1-tailed significance level $P > .05$ (Egger's test). All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Literature Search

A flow diagram of study selection is shown in Figure 1. After initially identifying 260 articles, 244 were excluded and the full texts of 16 were reviewed. Subsequently, 9 studies were excluded, and 7 studies[15–21] were included in the systematic review and meta-analysis (Table 1).

Study Characteristics

Characteristics of the 7 studies are summarized in Table 1, and outcomes are summarized in Tables 2 and 3. A total of 169 patients were included in the 7 studies, and the mean age of patients who received mannitol ranged from 30.8 to 47 years, and for patients who received hypertonic saline ranged from 35 to 47 years.

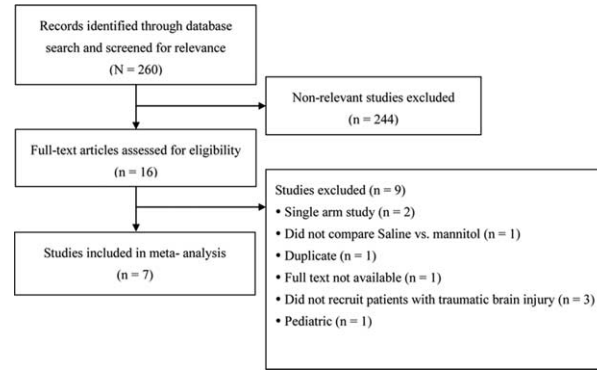


FIGURE 1. Flow diagram of study selection.

Intracranial Pressure

Six[15–20] of the 7 studies provided complete data with respect to ICP change from baseline to the last measurement after termination of the infusion, and were included in the meta-analysis. There was no evidence of heterogeneity (Q statistic = 7.10, $I^2 = 29.57\%$, $P = .213$); therefore, a fixed-effects model of analysis was used. The pooled difference in means = −1.69 (95% CI: −2.95 to −0.44, $P = 0.008$) indicated that hypertonic saline reduced ICP more effectively than mannitol (Figure 2A).

Four studies[15,17–19] provided complete ICP data at baseline and 30 minutes after intervention. There was no evidence of heterogeneity (Q statistic = 0.44, $I^2 = 0\%$, $P = .932$); therefore, a fixed-effects model was used. The pooled difference in means = −0.87 (95% CI: −2.57 to 0.83, $P = .316$) indicated no difference in mean change of ICP between patients treated with mannitol and hypertonic saline (Figure 2A).

Four studies[17–20] provided complete ICP data at baseline and 60 minutes after intervention. There was no evidence of heterogeneity (Q statistic = 2.50, $I^2 = 0\%$, $P = .475$); therefore, a fixed-effects model was used. The pooled difference in means = −2.58 (95% CI: −4.37 to −0.80, $P = .005$) indicated that hypertonic saline resulted in a significantly greater decrease in ICP than mannitol (Figure 2A).

Three studies[15,17,18] provided complete ICP data at baseline and 120 minutes after intervention. There was no evidence of heterogeneity (Q statistic = 2.40, $I^2 = 16.5\%$, $P = .302$); therefore, a fixed-effects model was used. The pooled difference in means = −4.04 (95% CI: −6.75 to −1.32, $P = .004$) indicated that hypertonic saline resulted in a significantly greater decrease in ICP than mannitol (Figure 2A).

Osmolarity

Three studies[19–21] provided complete numerical data with respect to osmolarity. There was no evidence of heterogeneity among the 3 studies (Q statistic = 1.02, $I^2 = 0\%$, $P = .599$); therefore, a fixed-effect model of analysis was used. The pooled difference in means = 1.84 (95% CI: −1.64 to 5.31, $P = .301$) indicated no difference in serum osmolarity between patients treated with hypertonic saline or mannitol (Figure 2B).

TABLE 1. Basic Characteristics of the Included Studies

Reference	Study Design	Patients	Intervention	Route of Administration	Formulation	Number of Patients	Age (y)	Male (%)	GCS at Admission	Episodes of Intracranial Hypertension
Cottenceau (2011)[15]	RCT	Severe traumatic brain injury	Mannitol	IV	Equiosmolar infusions of 20% (4 mL/kg), delivered intravenously within 20 min	25	36.1	NA	7	NA
			Hypertonic saline	IV	Equiosmolar infusions of 7.5% (2 mL/kg), delivered intravenously within 20 min	22	42.7	NA	5	NA
Sakellaridis (2011)[16]	RCT	Severe brain injury	Mannitol	Infusion	20%, 2 mL/kg, infused over 20 min	29	36*	NA	5.4	199
			Hypertonic saline	Bolus	15%, 0.42 mL/kg, administered as a bolus via a central venous catheter			NA		
Oddo (2009)[17]	Retrospective	Severe traumatic brain injury	Mannitol	Infusion	25%, 0.75 g/kg (412 mOsm/dose) infused over 20 min	12	36	75%	3	28
			Hypertonic saline	Infusion	7.5%, 250 mL (641 mOsm/dose) infused over 30 min					14
Francony (2008)[18]	RCT	Severe brain injury	Mannitol	Infusion	20%, 231 mL, (1100 mOsm/L; 255 mOsm/dose) infused in 20 min	10	43	70%	8	NA
			Hypertonic saline	Infusion	7.45%, 100 mL, (2548 mOsm/L; 255 mOsm/dose) infused in 20 min	10	37	90%	7	NA
Harutjunyan (2005)[19]	RCT	Severe neuronal damage	Mannitol	Infusion	15%	15	47	53%	5.8	53
			NaCl/HES	Infusion	7.2% NaCl/HES 200/0.5	17	47	53%	6	57
Battison (2005)[20]	RCT	Brain injury	Mannitol	Infusion	20%, 200 mL (1245 mOsm/kg; 249 mOsm/dose) infused over 5 min	9	NA	NA	NA	NA
			Hypertonic saline and dextran	Infusion	7.5% saline and 6% dextran-70, 100 mL (2498 mOsm/kg; 250 mOsm/dose) infused over 5 min		NA	NA	NA	NA
Vialet (2003)[21]	RCT	Head trauma and persistent coma	Mannitol	Infusion	20%, 2 mL/kg (1160 mOsm/kg/H_2O) infused in 20 min	10	30.8	40%	NA	13.3/d
			Hypertonic saline	Infusion	7.5%, 2 mL/kg (2400 mOsm/kg/H_2O) infused in 20 min	10	35.0	50%	NA	6.9/d

GCS = Glasgow Coma Score, HES = hydroxyethyl starch, IV = intravenous, NA = not available, RCT = randomized controlled trial.

TABLE 2. ICP Data of the Included Studies

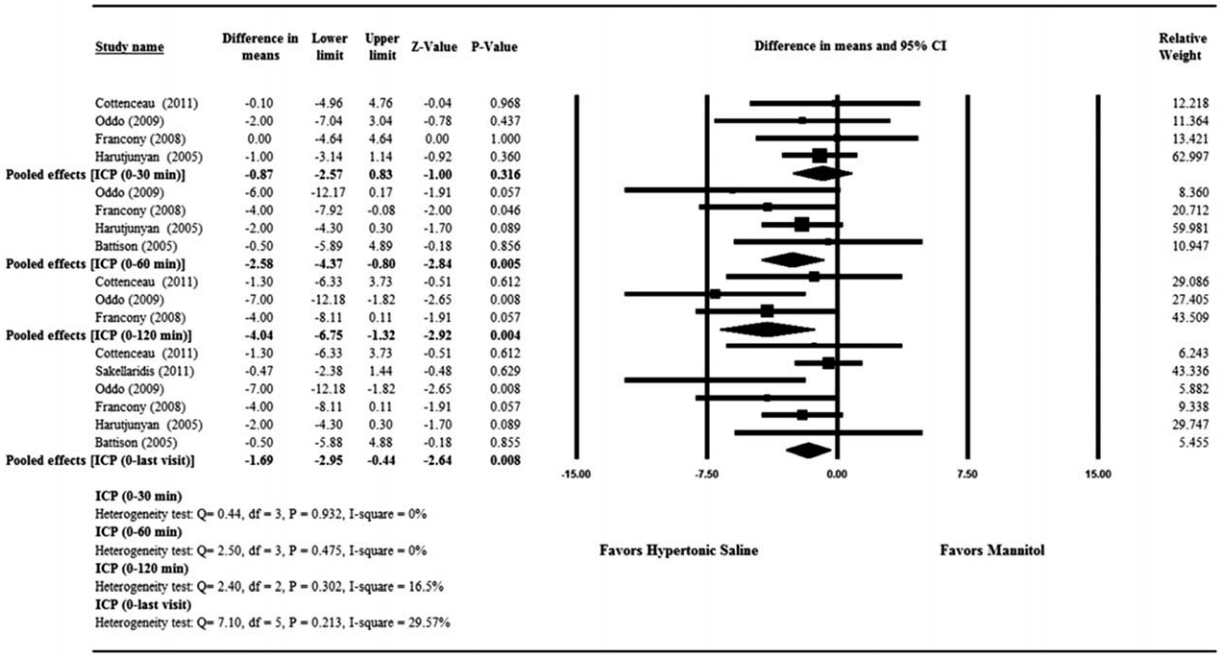
		ICP (mm Hg)				
Reference	**Intervention**	**Initial**	**30 min**	**60 min**	**120 min**	**Mean Difference From Baseline at Last Measurement**
Cottenceau (2011)[15]	Mannitol	16.3 (9.3)	10.5 (6.8)	NA	13.6 (7.5)	−1.3 (2.57)‡
	Hypertonic saline	17.9 (9.9)	12.2 (6.1)	NA	13.9 (7.8)	
Sakellaridis (2011)[16]	Mannitol	NA	NA	NA	NA	−7.96 (5.79)
	Hypertonic saline	NA	NA	NA	NA	−8.43 (6.65)
Oddo (2009)[17]	Mannitol	29 (8)	21 (8)	23 (12)	24 (9)	−7 (2.64)‡
	Hypertonic saline	27 (8)	17 (7)	15 (6)	15 (5)	
Francony (2008)[18]	Mannitol	31 (6)	18 (7)	19 (5)	21 (5)	−4 (2.10)‡
	Hypertonic saline	27 (3)	16 (4)	19 (3)	21 (4)	
Harutjunyan (2005)[19]	Mannitol	23 (19, 30)*	12 (6, 19)*	14 (7, 20)*	NA	−2 (1.18)‡
	NaCl/HES	22 (19, 31)*	10 (6, 14)*	11 (5, 18)*	NA	
Battison (2005)[20]	Mannitol	24.0 (18.8, 25.9)†	NA	12.5 (9.75, 20.5)†	NA	−0.5 (2.75)‡
	Hypertonic saline and dextran	22.0 (20.1, 26.3)†	NA	8.0 (6.5, 12.0)†	NA	
Vialet (2003)[21]	Mannitol	NA	NA	NA	NA	NA
	Hypertonic saline solution	NA	NA	NA	NA	

Data are presented as mean (standard deviation) unless otherwise stated. HES = hydroxyethyl starch, ICP = intracranial pressure, NA = not available.
* Data are presented as mean (range).
† Data are presented as median (interquartile range).
‡ Data are presented as mean (standard errors).

TABLE 3. Osmolarity and Mortality Reported in the Included Studies

		Osmolarity (mOsm/kg)			
Reference	**Intervention**	**Before**	**After**	**Mean Difference From Baseline at Last Measurement**	**Mortality**
Cottenceau (2011)[15]	Mannitol	NA	NA	NA	NA
	Hypertonic saline	NA	NA	NA	NA
Sakellaridis (2011)[16]	Mannitol	NA	NA	NA	7 (24%)
	Hypertonic saline	NA	NA	NA	
Oddo (2009)[17]	Mannitol	NA	NA	NA	4 (33%)
	Hypertonic saline	NA	NA	NA	
Francony (2008)[18]	Mannitol	296 (11)	NA	+1% (1%)	NA
	Hypertonic saline	292 (13)	NA	+2% (1%)	NA
Harutjunyan (2005)[19]	Mannitol	286 (270, 315)*	295 (278, 327)*		9 (60.0%)
	NaCl/HES	284 (273, 300)*	300 (284, 319)*		7 (41.2%)
Battison (2005)[20]	Mannitol	307.3 (300.3, 315.9)†	309.3 (300.5, 320.3)†		NA
	Hypertonic saline and dextran	308.3 (297.9, 319.6)†	309.8 (301.1, 322.0)†		NA
Vialet (2003)[21]	Mannitol	NA	296 (10)	1.3 (4.7)	NA
	Hypertonic saline solution	NA	314 (16)	4.7 (8.2)	NA

Data are presented as mean (standard deviation) unless otherwise stated. NA = not available.
* Data are presented as mean (range).
† Data are presented as median (interquartile range).



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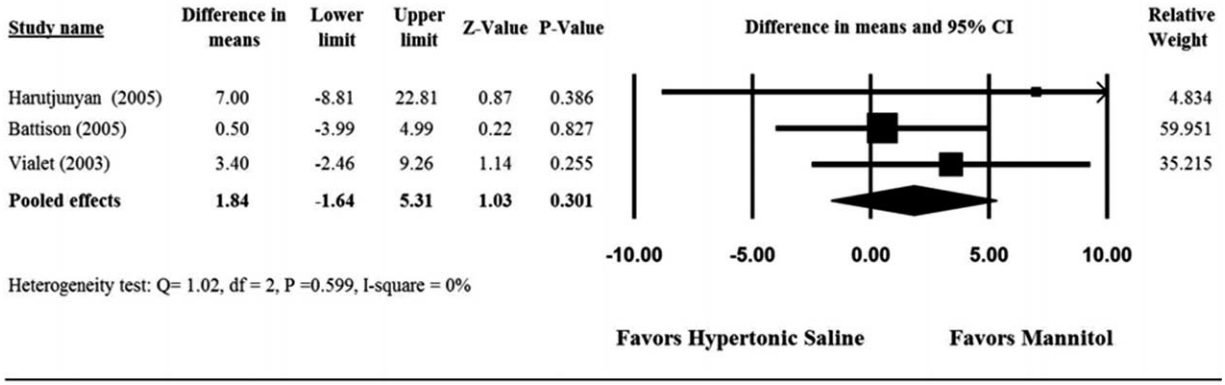

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FIGURE 2. Forest plots of meta-analysis results. (A) Intracranial pressure at different time points. (B) Osmolarity.

Sensitivity Analysis and Publication Bias

Sensitivity analyses using the leave-one-out approach indicated the direction and magnitude of the combined estimates did not change markedly with the exclusion of individual studies, indicating that the meta-analysis had good reliability (Figure 3).

Funnel plot symmetry (Figure 4) and Egger's test ($t = 1.395$, 1-tailed, $P = 0.118$) indicated that there was no publication bias with respect to the mean change of ICP from baseline to last measurement after terminating the infusion between patients treated with hypertonic saline and those treated with mannitol.

Quality Assessment

Results of the quality assessment of the 6 RCTs are shown in Table 4. The 6 studies exhibited an unclear or high risk of bias with regard to performance bias and detection bias, and only 1 study clearly indicated that an intention-to-treat analysis was performed.

DISCUSSION

The results of this meta-analysis indicate that hypertonic saline is more effective than mannitol for reducing ICP in the case of TBI, while serum osmolarity is not different after the 2 treatments.

A sustained ICP >20 mm Hg is considered intracranial hypertension, and is associated with decrease cerebral perfusion, brainstem herniation, and death.[6] Studies have shown that both mannitol[22–24] and hypertonic saline [1,25,26] are of value for reducing ICP; however, which is more effective remains a matter of debate.[4] Battison et al[20] performed a prospective, randomized, controlled, crossover trial of patients with an ICP >20 mm Hg and reported that hypertonic saline reduced ICP more effectively than mannitol. The study was limited,

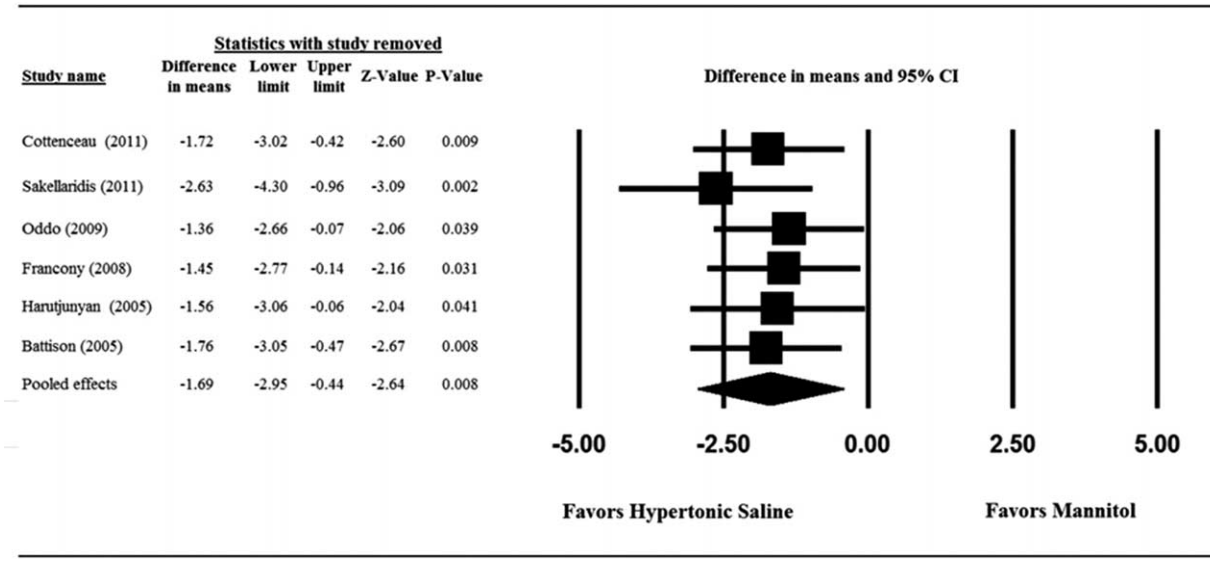

FIGURE 3. Sensitivity analysis for intracranial pressure.

however, in that it only included 9 patients. Harutjunyan et al[19] studied 32 neurosurgical patients and found that 7.2% NaCl/hydroxyethyl starch (HES) 200/0.5 was more effective at reducing increased ICP than 15% mannitol. Ichai et al[27] compared equally hyperosmolar and isovolumic mannitol or sodium lactate in the treatment of 34 patients with severe TBI and GCS $\leq$8 and found that the sodium lactate hyperosmolar treatment reduced ICP more effectively than mannitol and was associated with a better Glasgow Outcome Score. Animal models have also suggested that hypertonic saline is more effective at reducing cerebral edema and ICP than mannitol.[28,29]

Furthermore, Francony et al.[18] studied 20 patients with intracranial hypertension secondary to TBI in a parallel, RCT and found that a single equimolar infusion of 20% mannitol was as effective as 7.45% hypertonic saline in reducing ICP. Likewise, Sakellaridis et al[16] also found that hypertonic saline and mannitol were equally effective at reducing ICP.

Scalfini et al[30] used positron emission tomography to measure cerebral blood flow in 8 patients with TBI and found that equimolar dose of 20% mannitol or 23.4% saline both lowered ICP and increased cerebral perfusion pressure. A study of 42 episodes of increased ICP in patients with severe TBI found that 7.5% saline significantly increased brain oxygenation and improved cerebral hemodynamics in patients refractory to prior mannitol treatment.[17] Other study showed that mannitol and hypertonic saline were both effective at reducing ICP in severe TBI patients, though neither improved cerebral metabolism.[15]

Two other meta-analyses have compared hypertonic saline and mannitol for reducing ICP. A 2011 study by Kamel et al[10]

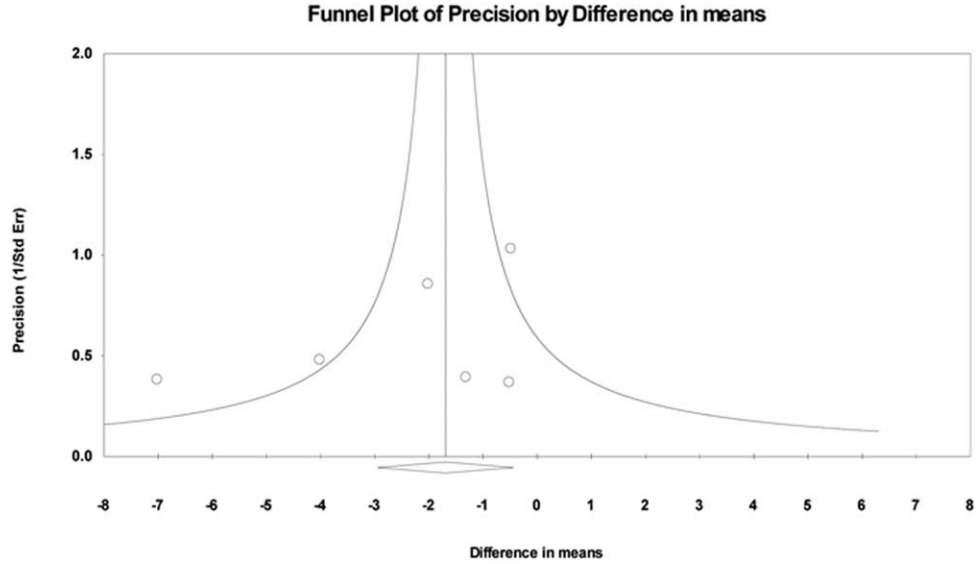

FIGURE 4. Funnel plot for publication bias of intracranial pressure.

TABLE 4. Quality Assessment of the Included Studies

Reference	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Did the Analysis Include an Intention-to-Treat Analysis?
Cottenceau (2011)[15]	Y	Y	NA	NA	Y	Y	NA
Sakellaridis (2011)[16]	Y	NA	N	N	Y	Y	NA
Francony (2008)[18]	Y	Y	N	N	Y	Y	Y
Harutjunyan (2005)[19]	Y	Y	NA	NA	Y	Y	NA
Battison (2005)[20]	Y	Y	N	N	Y	Y	NA
Vialet (2003)[21]	Y	NA	N	N	Y	Y	NA

N = high risk of bias, NA = unclear risk of bias, Y = low risk of bias.

included 5 trials with 112 patients and 184 episodes of elevated ICP found that the relative risk of ICP control was 1.16 (95% CI: 1.00−1.33), and the mean difference in ICP reduction was 2.0 mm Hg (95% CI: 1.6 to 5.7), both in favor of hypertonic saline over mannitol. A 2010 systematic review and meta-analysis by Mortazavi et al[9] included 36 studies (10 prospective RCTs, 1 prospective and nonrandomized trial, 15 prospective observational trials, and 10 retrospective studies), and concluded that hypertonic saline was more effective than mannitol at reducing ICP. The authors also pointed out that the analysis was limited by low patient numbers, limited RCTs, and inconsistent methods between studies.

There are limitations of this study that should be considered. First, the overall number of patients was relatively small, and while our purpose was to focus on patients with TBI some studies included patients with brain injury from causes other than trauma (eg, stroke). The concentrations, dosages, and infusion rates of mannitol and hypertonic saline varied between the studies. Adverse events related to the treatments were not analyzed, as they were reported in only 2 of the included studies. Examination of variables which can potentially affect ICP such as vasopressor use, blood pressure targets, and volume of fluids administered was not performed. Lastly, while the purpose of this study was to examine which treatment is more effective at reducing ICP it should be mentioned that successful control of ICP does not guarantee a good neurologic outcome.

CONCLUSIONS

The results of this study indicate that hypertonic saline is more effective than mannitol for reducing ICP in cases of TBI.

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