

Hypertonic Solutions in Traumatic Brain Injury: A Systematic Review and Meta-Analysis

Abstract

This study aims to evaluate the efficacy of hypertonic saline versus crystalloids (normal Saline/lactated Ringers) in improving clinical outcome in patients with traumatic brain injury (TBI). Electronic databases and grey literature (unpublished articles) were searched under different MeSH terms from 1990 to present. Randomized control trials, case-control studies and prospective cohort studies on decompressive craniectomy in TBI (>18-year-old). Clinical outcome measures included Glasgow Coma Outcome Scale (GCOS), Extended GCOS, and mortality. Data were extracted to Review Manager Software. A total of 115 articles that met the inclusion criteria were retrieved and analyzed. Ultimately, five studies were included in our meta-analysis, which revealed that patients with TBI who had hypertonic saline had no statistically significant likelihood of having a good outcome at discharge or 6 months than those who had crystalloid (odds ratio [OR]: 0.01; 95% confidence interval (CI): 0.03–0.05; $P = 0.65$). The relative risk (RR) of mortality in hypertonic saline versus the crystalloid at discharge or 6-month is RR: 0.80; 95% CI: 0.64–0.99; $P = 0.04$. The subgroup analysis showed that the group who had hypertonic solution significantly decreases the number of interventions versus the crystalloid group OR: 0.53; 95% CI: 0.48–0.59; $P < 0.00001$ and also reduces the length of intensive care unit stay (OR: 0.46; 95% CI: 0.21–1.01; $P = 0.05$). Hypertonic saline decreases the financial burden, but neither impacts the clinical outcome nor reduces the mortality. However, further clinical trials are required to prove if hypertonic saline has any role in improving the clinical and neurological status of patients with TBI versus the normal saline/lactated Ringers.

Keywords: Clinical outcome, hypertonic saline, traumatic brain injury

Introduction

Although osmotherapy along with other conventional treatment options, such as sedation, analgesia, head elevation, neuromuscular paralysis, and ventriculostomy, are the first line treatment in the management of patients with moderate-to-severe traumatic brain injury (TBI).^[1-9] Osmotherapy remains a controversial measure due to effects of osmotic agents being complex as well as the relatively nonselective in nature. As they may cause alteration in the volume of both damaged and undamaged brain parenchyma, and can exert widespread effects on the systemic circulation, besides the dynamics of cerebrospinal fluid (CSF).^[10]

Various osmotic agents such as glycerol, urea, sorbitol, mannitol, and hypertonic saline have been formulated. They play an indispensable role in decreasing

intracranial pressure by establishing a strong trans endothelial osmotic gradient, thus causing shrinkage through the water shifting outside the brain's tissue into the intravascular compartment.^[11-13] Urea is effective but with systemic side effects such as gastrointestinal complications (nausea, vomiting, and diarrhea), hemoglobinuria, and even rebound intracranial hypertension.^[13] Whereas, sorbitol and glycerol are associated with a significant increase in the blood glucose level which could be harmful to the traumatized brain.^[13] Mannitol is recommended by the European Brain Injury Consortium and Brain Trauma Foundation, but it causes hypotension especially in the hypovolemic state, rebound increase in intracranial pressure^[2,13,14] along with renal toxicity due to increase in the serum osmolality.^[15,16]

Weed and McKibben *et al.*,^[17] 1919 first described the hypertonic saline therapy in the TBI. It has osmotic, rheologic, and metabolic characteristics.^[18] The osmotic

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property exists because of the sodium as it has a high reflection coefficient, thus low permeability across the blood–brain barrier.^[18,19] The rheological effect is due to its property to reduce the blood viscosity by alteration in the red blood cell deformity.^[12,18,20,21] This prompts compensatory vasoconstriction to maintain the cerebral blood flow and thus reduces the cerebral blood volume and intracranial pressure.^[12,22] Although the data for pharmacokinetics of hypertonic saline are lacking, as per Lazaridis *et al.*^[18] it displays a similar onset as that of mannitol by effecting the intracranial pressure, begins within minutes, peaks between 15 and 120 min, and lasts up to 4–6 h.^[23]

In severe TBI, it is desirable to improve the hypovolemia and hypotension by adequate resuscitation to prevent secondary brain damage.^[24] Severe TBI patient with hypotension must have rapid active resuscitation with fluid, taking in care to prevent the excessive hydrostatic capillary pressure and prevent elevation of raised intracranial pressure. Therefore, lactated Ringers, which is slightly hypotonic, is considered the fluid of choice^[25] as a maintenance fluid for volume deficit, also keeps the intravenous line open so as to administer medications.^[26,27] Hypertonic saline has advantages in patients with brain injury, as it is positive inotropic and chronotropic and require less volume at lower capillary hydrostatic pressure.^[28-30]

The safety and efficacy of different variations in the dosage regimens of hypertonic saline in TBI have not been established since available data are limited due to small phase IIa-IIb randomized controlled trials (RCTs) or small case–control studies. Our group did perform the first meta-analysis on the efficacy and safety of different types of hypertonic saline in the management of patients with TBI.

Our study aims to evaluate whether hypertonic saline has any role in improving the clinical outcome in comparison with the normal saline and lactated Ringers in TBI. Our *a priori* hypothesis is that hypertonic saline plays an important role in improving the clinical functional outcome and decreasing mortality in TBI by decreasing the intracranial pressure. We hypothesize that hypertonic saline is safe and effective and should be taken into account in the design of future RCTs.

Methods

Search strategy

We developed our research question: Does hypertonic saline (2%, 3%, or 7.5%) has any role in improving the clinical outcome as compared to the normal saline/lactated Ringers in TBI and based on that the following PICO question was developed:

Population

Patients with TBI due to motor vehicle injury, blows, fall, and penetrating head injury.

Intervention

Hypertonic solution (saline/acetate solution) with any dosage regimen (2%, 3%, or 7.5%).

Control

Normal saline/lactated Ringer's Solution.

Outcome

Good outcome and mortality at discharge or 6 months, number of interventions (frequency of hyperventilation, sedation, mannitol, and CSF drainage) and length of stay in the intensive care unit (ICU).

We applied stringent inclusion criteria. The following study's types were selected: RCTs, case–control studies, prospective cohort study, and retrospective study with two groups (intervention/control) and populations with TBI who were able to get hypertonic solution. Retrospective (without groups), case series and case report studies were excluded from our systematic review.

We used the following MeSH headings: Brain injury, traumatic or saline, hypertonic or normal saline. We did not define any limitation in language. Articles published between 1990 and the present were searched. Two reviewers MS and NF completed all the review process.

The following databases were reviewed: The Cochrane Library, Medline, Embase, and Pub Med. In addition, we reviewed the following gray literature: Unpublished abstracts from Europeans and American Neurological conferences over the last 10 years to determine whether there were any abstracts in the field of osmotherapy in TBI.

A total of 364 articles were retrieved based on the MeSH headings mentioned above. Then, the titles of articles were reviewed, and the duplicates were deleted. The titles and abstracts of the studies identified by the literature search were screened for eligibility based on the inclusion criteria mentioned above. Manuscripts that met the inclusion criteria were obtained illustrated in Figure 1.

The reviewer was not blind to the author's name and institutions, journals of publication, or study results.

Data extraction and management

Demographic information, detailed methods, intervention, and outcomes were abstracted from the manuscripts chosen for the review and recorded on the special data form.

The data form included the following:

1. Methods, design, method of randomization, setting of the treatment, number of interventions, mortality, and survival ratio
2. Population: Sample size, inclusion and exclusion criteria, age, and gender
3. Intervention: Type of hypertonic solution, dose of hypertonic solution

4. Control: Patients with normal saline or lactated Ringers
5. Outcome: Time of outcome, measurement, reported poor and good outcome, mortality and survival ratio.

Outcome measures: Following outcomes were selected for our meta-analysis:

1. Functional Outcomes: Glasgow Coma Outcome Scale Extended (GOSE) 0–8: Outcomes were dichotomized to good (5–8) or poor (1–4) at discharge or 6 months and 12 months, and GCOS at discharge or 6 months good outcome (4–5) and unfavorable outcome (1–3)
2. Mortality defined as the number of deaths in a particular population per unit of time.

Assessment of risk of bias in included studies

To avoid publication bias, we reviewed the abstracts from the European and American TBI meetings, looking at the unpublished trials, and contacted to experts to determine if negative trials have been carried out and unpublished.

Measures of intervention effect

Intervention efficacy was determined by the good clinical outcome and relative mortality risk ratio.

In order for the hypertonic saline to be effective in improving the clinical outcome, we required the threshold of distribution between two groups to be clinically and statistically significant ($P < 0.05$).

The risk ratio was determined for mortality in the pooled analysis whereas the Odds Ratio (OR) was used for analysis of good outcome, subgroup mortality analysis, length of stay in the ICU, and number of required interventions between two groups.

Subgroup analysis and investigation of heterogeneity

The following subgroup analysis was performed:

1. Subgroup analysis based on the mortality risk among types of hypertonic saline versus normal saline/lactated Ringer’s solution
2. Subgroup analysis based on the length of stay in ICU and number of interventions required in intervention compared to the control group.

Statistical analysis

Statistical analyses were performed using Review Manager program version 5 that is provided by the Cochrane Library. This software is used for performing meta-analysis and presenting the results graphically as per Cochrane Reviews. The data from each individual study were extracted and put in the review manager software to perform a pooled meta-analysis.

First, the hypertonic saline, and good and poor outcomes, and mortality were computed across the different crystalloid used in the different studies were analyzed. The adjusted Wald method, which provides the best coverage

for binomial confidence interval (CI) when samples are <150 , was used for computation of 95% CI. Statistical comparisons between groups were performed using the Chi-square test and Fisher’s exact test as appropriate. The OR for experimental hypertonic Saline versus crystalloid associated with good and poor outcome were calculated in all individual studies with available data comparing the various outcomes among different studies. The OR from separate studies were combined by the fixed-effects meta-analysis according to the Mantel–Haenszel method, which is also valid for paired OR. Heterogeneity between studies was assessed by the Breslow-Day Chi-square test and I2 statistic.^[31] The I2 statistic describes the percentage of total variation across studies that are attributable to heterogeneity rather than chance. Compared with the classical Breslow-Day Chi-square test, its interpretation is more intuitive, and the value does not depend on the number of studies. There is no simple categorization of values of I2, although values $>75\%$ are usually considered as meaning high heterogeneity.

Results

Description of studies

A total of 364 articles were reviewed from the above-mentioned electronic literature. Reviewing the grey literature did not add any abstracts. A total of 115 studies were retrieved and analyzed. In total, 110 articles were excluded, and 5 articles were added met the inclusion criteria, and included in our meta-analysis. The baseline characteristics and the outcome of the RCTs, case–control, prospective cohort study, and retrospective study are summarized in Tables 1-4.

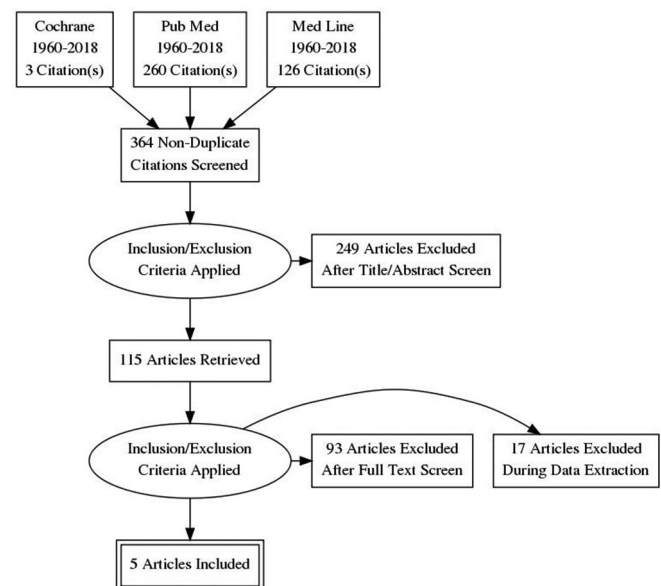


Figure 1: Database search

Table 1: Baseline characteristics: Demographic variables

Study	Type of study	Total number of patients (n)	Intervention (treatment/control)	Initial GCS	Maintenance fluid	Study period	Age	Gender	Inclusion criteria	Exclusion criteria
Simma et al., 1998 ^[32]	Open Randomized Prospective Study	35: 3 excluded	32: Group 1: Hypertonic saline (Na: 131 mmmol/L, 277 mOsm/L)-15 Group 2: Lactated Ringers-17	<8	1200 ml/m ²	72 h	Group 1: 88±43 Group 2: 88±42	Group 1: 7 (46) male Group 2: 9 (52) male	GCS<8 Age<16 years	Not available
Qureshi et al., 1999 ^[33]	Retrospective Study	82	Group 1: 2% or 3% saline/acetate-36 Group 2: 0.9% saline-46	<8	75-150 ml/h	72±85 h	Group 1: 37.8±19.1 Group 2: 40.5±19.1	Group 1: 32 (89)-Male Group 2: 36 (78)-Male	1. Severe Head Injury (GCS<8)	Polytrauma patients not admitted in the neurointensive care unit
Shackford et al., 1998 ^[34]	Prospective Randomized Study	34	Group 1: 1.6% hyper tonic saline-18 Group 2: Lactated Ringer's solution-16	<and equal to 7	15 ml/kg	5 days	Group 1: 1:33±15 Group 2: 2:31±11	Group 1: 1:17-male; 1-female Group 2: 10-male; 6-female	Age greater than 18 years Blunt injury Within 12 h of admission	Not available
Cooper et al., 2004 ^[35]	Double Blind Randomized Trial	229	Group 1: 7.5% saline-114 Group 2: Ringers lactate-115	<9	10 ml/kg	Prehospital	Group 1: 1:38±19 Group 2: 2:37±19	Group 1: 1:75-male Group 2: 2:37-male	Coma due to blunt head trauma GCS<9 SBP<100 mmHg	Penetrating trauma Younger than 18 years No IV access Serious premorbid condition
Bulger et al., 2010 ^[36]	Multicenter 3-group double-blind Randomized Trial	1331	Group 1: 359-saline/6% dextran 70 Group 2: 355%-7.5% saline Group 3: 582%-0.9% saline	<8	250 ml bolus	Out-of-hospital	Group 1: 1:38.5±18.6 Group 2: 2:38.6±17.3 Group 3: 39.5±19.2	Group 1: 1:273-male Group 2: 2:277-male Group 3: 426-male	Age 15 years and older Blunt trauma	Hemorrhagic shock

GCS – Glasgow Coma Scale; SBP – Systolic blood pressure; CT – Computed tomography; IV – Intravenous

Risk of bias in the included studies

None of the prospective cohort trials followed adequate sequence generation (computer generation), and few had the allocation of treatment concealed. Just one article has double-blinded RCT. This is understandable in this type of prospective cohort study, in which procedure is evaluated,

and it could be difficult to blind the investigator or the patient to procedure allocation. However, blindness could have been achieved for functional outcome, and this was not the case in any of the studies except one.

No disclosures were made regarding the funding for these studies.

Table 2: Baseline characteristics: Outcome variables

Study trial	Initial GCS	Initial ICP (mmHg)	Initial serum sodium (mmol/L)	Initial osmolality (mOsm/kg)	Target values ICP	Target values Na+	Target values CPP	Clinical outcome
Simma <i>et al.</i> , 1998 ^[32]	Group 1: 5.5±1.4	Group 1: 9±5	Group 1: 138.2±2.5	Group 1: 282±11	Less and equal to 15 mmHg	145-150 mmol/L	<45 mmHg infants <±50 mmHg children	Primary Correlation between ICP and serum Na+ CPP and serum Na+ concentration
	Group 2: 5.8±1.6	Group 2: 13±8	Group 2: 137.5±2.2	Group 2: 283±12				Secondary Number of interventions to keep ICP within normal limits Additional changes in fluid volume Clinical outcome variables
Qureshi <i>et al.</i> , 1999 ^[33]	Group 1: 6.4±3.7	Group 1: 19 (53)	Group 1: 138.8±5.7	Not available	Less and equal to 20 mmHg	145-155 mmol/L	>70 mmHg	Glasgow Coma Outcome Scale at 6 months
	Group 2: 6.0±3.3	Group 2: 26 (57)	Group 2: 138.2±5.0	Not available				Intensive care unit stay (days) Hospital stay (days)
Shackford <i>et al.</i> , 1998 ^[34]	Group 1: 4.7±0.7	Group 1: 16±2	Not available	Not available	Less and equal to 20 mmHg	>155 meq/L	MAP>90 mmHg	ICP CPP Number of Interventions required during stay in the hospital
	Group 2: 6.7±0.7	Group 2: 11±2	Not available	Not available				Primary outcome GOSE at 3 and 6 months
Cooper <i>et al.</i> , 2004 ^[35]	Group 1: 3 (3-6)	Not available	Group 1: 149±3.7	Not available	Not available	Not available	>70 mmHg	Secondary outcome Serum Na + and BP ICP CPP GOSE at 3 months Hospital mortality
	Group 2: 3 (3-5)	Not available	Group 2: 141±3.6	Not available	Not available	Not available	>70 mmHg	Primary outcome GOSE at 3 and 6 months
Bulger <i>et al.</i> , 2010 ^[36]	Group 1: 5.0±1.0	Group 1: 17.9±17.0	Group 1: 146.1±5.1	Not available	<25 mmHg	145-150 meq/L	>60 mmHg	Primary GOSE at 6 months DRS at 6 months
	Group 2: 4.9±2.3	Group 2: 15.1±13.3	Group 2: 147±5.1	Not available				Secondary 28 days survival Survival and hospital discharge ICP Intervention required to manage the ICP Blood required within the first 24 h 28 days ARDS free survival
	Group 3: 5.0±2.1	Group 3: 18.6±14.5	Group 3: 139.1±3.6	Not available				

GCS – Glasgow Coma Scale; ICP – Intracranial pressure; CPP – Cerebral perfusion pressure; GOSE – Glasgow Outcome Scale extended; DRS – Disability rating scale; ARDS – Acute respiratory distress syndrome

Effects of interventions

The pooled meta-analysis of all five studies (treatment arm 1107 and control arm 975) revealed the following:

Five studies have reported the mortality rate in their results.^[32-36] The RR of mortality at discharge or 6-month is 0.80; 95% CI: 0.64–0.99; *P* = 0.04. Hence, the mortality rate is reduced with the hypertonic solutions as compared to the crystalloid as shown in Figure 2 Panel A.

There is no statistically significant difference in the good clinical outcome at discharge to 3 months between

hypertonic solutions and crystalloids (normal saline and Ringer’s Lactate) (OR of favorable clinical outcome at discharge to 6-month: 0.01; 95% CI: 0.03–0.05; *P* = 0.65). Hence, there does not exist any comparative difference in the clinical outcome between the hypertonic solutions and the control arm as indicated in Figure 2 Panel B.

Only two studies^[33,36] compared the hypertonic solution versus the normal saline. Bulger *et al.*^[36] used two different types of hypertonic saline; 7.5% hypertonic saline and hypertonic saline/acetate. There is no statistical significance

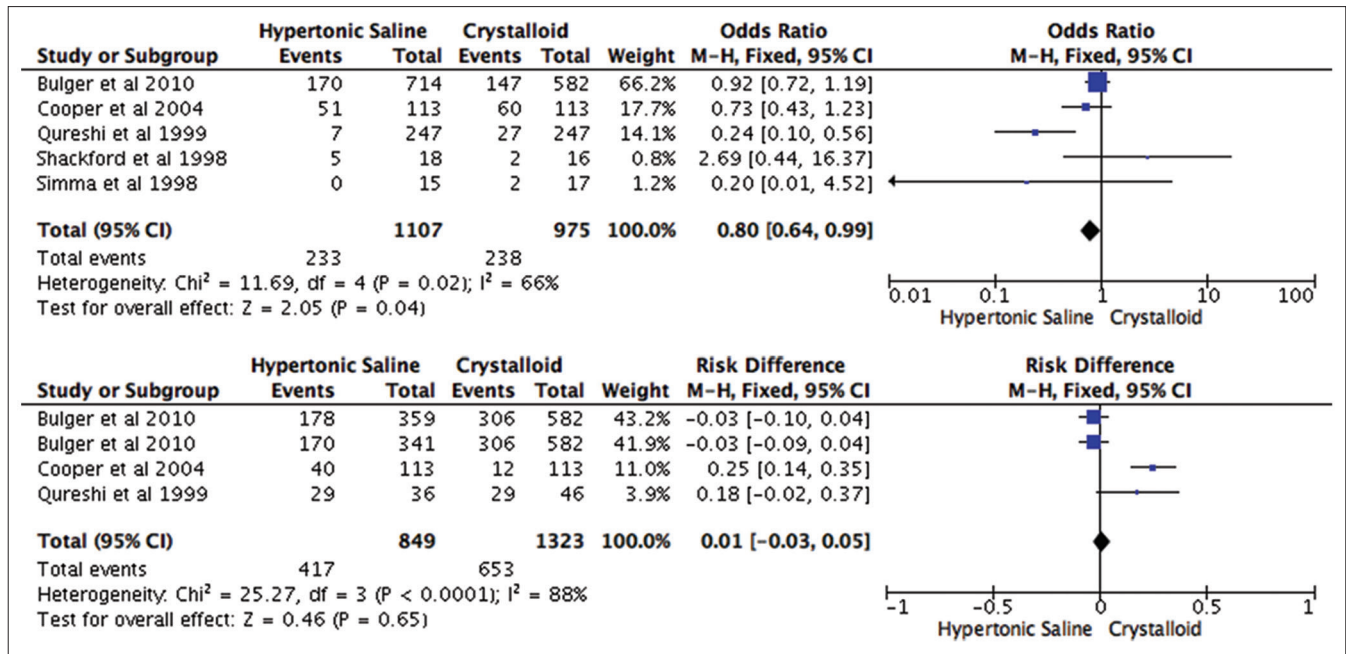


Figure 2: Panel A: relative risk of mortality in hypertonic solutions versus crystalloids. Panel B: Good Clinical Outcome in hypertonic solutions versus crystalloids in traumatic brain injury Panel (a) and (b): Pooled meta-analysis

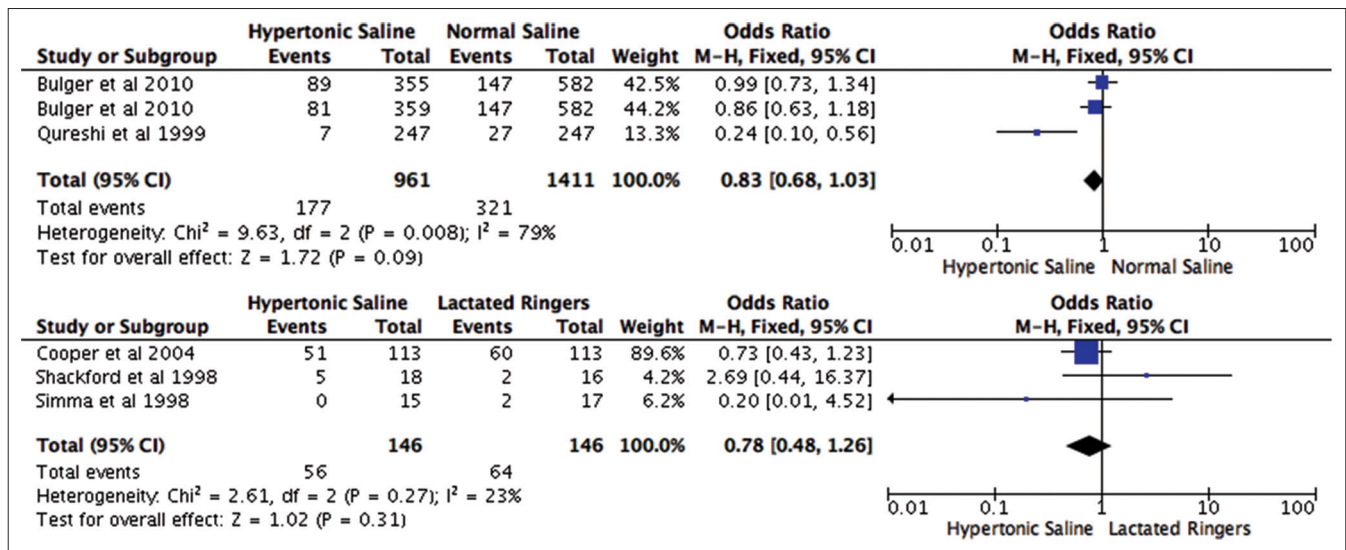


Figure 3: Panel A: Subgroup analysis comparing relative risk of mortality in hypertonic solutions versus the normal saline. Panel B: Relative risk of mortality in hypertonic saline versus lactated Ringers

difference in the mortality rate between the two groups. The OR of mortality at discharge or 6 months; 0.83; 95% CI: 0.68–1.03; P = 0.09 [Figure 3 Panel A].

Regarding the mortality rate in comparison with the lactated Ringers, there is no statistical significance difference in the mortality rate between the two groups. OR of mortality rate in hypertonic solution versus lactated Ringers is 0.78; 95% CI: 0.48–1.26; P = 0.31 [Figure 3 Panel B].

Four studies^[32-34,36] indicate the number of interventions during treatment. Interventions mean the use of

hyperventilation, sedation, mannitol, analgesia, and CSF drainage. The number of interventions required with hypertonic saline is reduced significantly compared to the normal saline. The OR of number of interventions is 0.53 95% CI: 0.48–0.59; P < 0.00001 [Figure 4].

Two studies^[32,33] indicated that the stay in the ICU is reduced with the hypertonic solution compared to the crystalloid. The OR of ICU stay is 0.46 95% CI: 0.21–1.01; P = 0.05 [Figure 5].

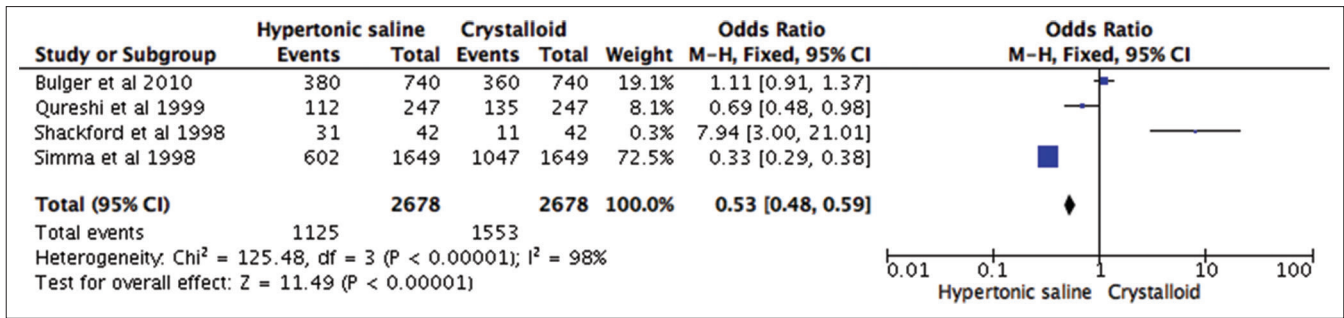


Figure 4: Subgroup analysis comparing number of interventions in hypertonic saline versus crystalloids. Interventions means the use of hyperventilation, sedation, mannitol, analgesia, and cerebrospinal fluid drainage

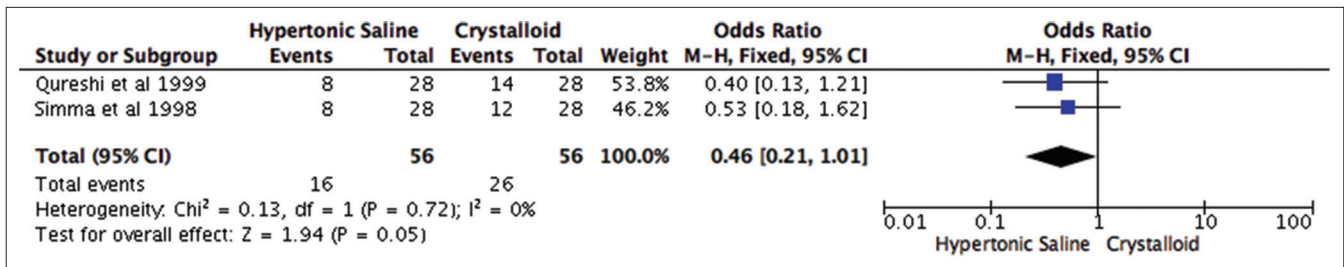


Figure 5: Subgroup analysis comparing the stay in intensive care unit in hypertonic saline versus crystalloid group

Discussion

Our study is the first to evaluate whether hypertonic saline has any role in improving the clinical outcome and mortality among patients with TBI. Our meta-analysis revealed that hypertonic saline has no statistically significant difference in improving the clinical outcome and reducing the mortality in patients with TBI. However, because of the several limitations in the clinical studies (lack of adequate sequence generation, blindness in randomized and clinical follow-up, and the small sample size in all of the studies), future double-blinded RCT with large sample size is needed to prove the concept of this novel intervention. In addition, more evidence is required regarding different types of hypertonic saline correlating with decrease in the intracranial pressure, thus improving the clinical and functional outcome.

Neuronal signals processing and transmission are greatly dependent on the brain ionic and osmotic balance. Despite large fluctuations in the ionic and osmolality composition, the brain is able to possess a well-developed osmoregulatory mechanism to maintain the intracellular and extracellular ionic composition and volume within normal limits.^[37] The interstitial fluid (ISF) also called as intracellular fluid compartment surrounds cells of the nervous system. Blood-Brain Barrier separates it from plasma whereas it is separated from the CSF by the ependymal cells lining the ventricles and from the surface of the brain by pia mater. Both CSF and ISF appear to have a similar composition that differs from the plasma significantly. K⁺, HCO₃⁻, Ca²⁺, and glucose are higher whereas Mg²⁺, Cl⁻, and H⁺ are lower than those in CSF and ISF.^[37] As a result of increase in

osmolality, there is shrinkage of the brain as cell membranes are more permeable to water than electrolytes. “Idiogenic osmoles,” composed of inorganic ions and organic solutes, are accumulated to restore the brain volume to its normal level known as “Volume Regulatory Increase” in solutes.^[37]

Acute hypernatremia, defined as the development of Na⁺>145 mmol/l in 24–48 h. It results in the prompt reduction in the brain water content. However, the brain works as an osmometer by rapidly accumulating the solutes to stabilize its brain volume.^[38]

Acute (15–120 min) hypernatremia in rats showed the reduction in brain volume was proportional to the increase in plasma osmolality and get stabilized within 15–30 min. However, after 30 and 120 min, the brain water loss was only 35% of the predicted. In response to acute hyperosmotic stress, intracellular and extracellular water shift leads to variations in the electrolytes balance especially total brain Na⁺, Cl⁻ and K⁺. Within 15–30 min after the elevation of plasma osmolality as a result of acute hypernatremia, the brain loses water slowly and stabilizes at a new reduced volume.^[39,40]

Holliday *et al.*^[41] 1968 in a study of rats revealed that 3 h of hypernatremia Na⁺ >200 mmol/L leads to decrease in the water content of the brain by 14% and 34% increase in Na⁺, 60% increase in Cl⁻ and no change in K⁺.

Our meta-analysis findings are in line with the previous findings.^[32-36] In our meta-analysis, represents a further step in evaluating the efficacy of 7.5% hypertonic saline in improving the outcome by decreasing the mortality. However, it also indicates that there is no clinically

significant difference between the hypertonic saline and normal saline in reducing mortality. There are various kinds of hypertonic solution with different dose regimens as shown in Table 3.

The administration of mannitol increases the patient risk of renal toxicity and fluid accumulation in the brain

Table 3: Different concentrations of hypertonic solutions

	Sodium concentration (mmol/l)	Osmolality (mOsm/kg)
0.9% saline	154	308
Lactated Ringer's solution	130	275
1.7% saline	291	582
3% saline	513	1026
7.5% saline	1283	2566
10% saline	1712	3424
23.4% saline	4004	8008
29.2% saline	5000	10,000

parenchyma leading to worsening of cerebral edema. Therefore, Ware *et al.*^[42] 2005 found that the 23.4% sodium chloride and mannitol when administered for reduction in intracranial pressure have no significant difference between each other. However, the increased intracranial pressure (ICP) reduction for hypertonic saline lasted for 96 min whereas that of mannitol lasted for 59 min. There were no complications associated with hypertonic saline. Kerwin *et al.*^[43] 2009 conducted a study on 22-patients with severe TBI and found that 23.4% of HTS is more efficacious than mannitol in reducing ICP.

Suarez *et al.*^[44] 1998 evaluated the efficacy of intravenous bolus administration of 23.4% saline and found that there was a significant reduction in intracranial pressure and augmentation in the cerebral perfusion pressure in patients with refractory intracranial pressure in patients with intracranial disorders. Rockswold *et al.*^[45] 2009 found that 23.4% of hypertonic saline decreases the

Table 4: Clinical outcomes and results

Study trial	Na+ (mmol/kg/days)	ICP	Mechanical ventilation (days)	ICU stay (days)	Survival (%)	Total number of interventions to keep ICP within limit	GCS	GOS at 6 months	Mortality
Simma <i>et al.</i> , 1998 ^[32]	Group 1: 11.5±5.0 Group 2: 8.0±4.5	Not available	Group 1: 6.9±2.2 Group 2: 9.5±6.0	Group 1: 8.0±2.4 Group 2: 11.6±6.1	Group 1: 1: 15 (100)/15 Group 2: 15/17 (88)	Group 1: 602 Group 2: 1047	Not available	Not available	Group 1: 0/15 Group 2: 2/17
Qureshi <i>et al.</i> , 1999 ^[33]	Group 1: 18.9±5.7 Group 2: 10.4±2	Not available	Not available	Group 1: 8.2±7.5 Group 2: 13.5±16.6	Not available	Group 1: 112 Group 2: 135	GCS at 3 days: Greater and equal to 2 points and above Group 1: 8/36 Group 2: 21/46	GOS Good outcome HTS: 29/36 NS: 29/46 Poor outcome HTS: 6/36 NS: 7/46	Not available
Shackford <i>et al.</i> , 1998 ^[34]	Group 1: 144±0.6 Group 2: 138	Group 1: -9.1±3.6 Group 2: 2.5±3.3	Not available	Not available	Not available	Group 1: 31±4 Group 2: 11±3	GCS<8 Group 1: 29/18 Group 2: 13/16	Group 1: 2.7±0.2 Group 2: 2.5±0.2	Group 1: 5/18 Group 2: 2/16
Cooper <i>et al.</i> , 2004 ^[35]	Group 1: 148±4.3 Group 2: 143±4.8	Group 1: 10 (6-17) Group 2: 2: 15 (8.5-22)	Group 1: 3.8/110 Group 2: 3.0/110	Not available	Group 1: 62/113 Group 2: 53/113	Not available	Group 1: 15 (15-5)/114 Group 2: 15 (15-5)/115	Group 1: 4 (4-4) Group 2: 4 (3-4)	Group 1: 51/113 Group 2: 60/113
Bulger <i>et al.</i> , 2010 ^[36]	Group 1: 146.1±5.1 Group 2: 147±5.1 Group 3: 139.1±3.6	Group 1: 25.5±19.9 Group 2: 23.6±18.4 Group 3: 25.8±17.6	Not available	Not available	Group 1: 265/359 Group 2: 258/355 Group 3: 427/582	Group 1: 191 Group 2: 189 Group 3: 360	Not available	GOS-E at 6 months less and equal to 4 Group 1: 181/359 Group 2: 171/355 Group 3: 276/582	Group 1: 89/359 Group 2: 81/355 Group 3: 147/582

ICP – Intracranial pressure; ICU – Intensive care unit; GOS – Glasgow Outcome Scale; GOS-E – Glasgow Coma Extended Outcome Scale; GCS – Glasgow Coma Scale; HTS – Hypertonic saline; NS – Normal saline

intracranial pressure by mean of 8.3 mmHg ($P < 0.0001$) and there was improvement in brain tissue oxygenation by 3.1 mmHg ($P < 0.0001$) whereas the cerebral perfusion pressure increased by mean of 6 mmHg ($P < 0.0001$). The clinical outcome of the patient at 6 months' post-injury showed that 48% of favorable outcome while mortality was 28%. Paredes-Andrade *et al.*^[46] 2012 found that 23.4% hypertonic saline bolus was effective for the reduction of intracranial pressure in patients with severe TBI despite the presence of high serum and CSF osmolalities.

DeWitt *et al.*^[47] evaluated the effect of resuscitation with 3.0% NaCl, 0.9% NaCl, and 10% hydroxyl ethyl starch in cats subjected to fluid percussion injury and hemorrhagic hypotension. There were no significant differences in ICP, cerebral oxygenation, or cerebral blood flow at 60 and 120 min after the administration of fluid boluses. Weinstsabl *et al.*^[48] found that in 10 patients with TBI the ICP was decreased, and HS improved cerebral perfusion pressure in 7.5% hydroxyethyl starch. Fisher *et al.*^[49] compared the efficacy of 3% saline and 0.9% saline infusions on elevated ICP in pediatric patients with TBI. They found that mean ICP was lowered by a magnitude of 4 mm Hg for 2 h after infusion in the group that received 3% saline without changes in central venous pressure or renal function.

In addition, more evidence is required regarding the use of various kinds of hypertonic saline in patients with TBI and the role of different osmotherapies in improving the prognosis of patients with TBI.

Our study has several limitations. First, there is the possibility of selection and publication bias in our systematic review, since only two reviewers carried out this part of the process and he is part of the largest trial in this systematic review. He might, therefore, be more influenced by the positive trial results than by the negative ones. However, we tried to limit such bias by doing the following steps: A gray literature review, in which we reviewed the abstracts from several meetings to capture any RCT that was presented as an abstract but not published because of a negative result. Indeed, one abstract was found with a negative result, and it was included in the meta-analysis (this abstract was available in the electronic research record, however). Second, the lack of access to individual patient's data is one of the limitations. Third, there were few trials using different types of hypertonic solutions for the management of patients. Finally, our meta-analysis results cannot be generalized to all forms of TBI since we restricted mostly to moderate and severe TBI.

Conclusion

Our data point to a possible signal of reducing the financial burden by decreasing the number of interventions and length of ICU stay. However, there does not exist a significant difference in improving the clinical outcome and

reducing mortality in hypertonic solutions as compared to crystalloid in patients with TBI. Therefore, it is needed to design an RCT with less bias, and large sample size, for future comparing various concentrations of hypertonic solutions in patients with TBI.

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Conflicts of interest

There are no conflicts of interest.

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