ISSN: 3152-8686

Vol3; Issue3, May 2026

JOURNAL OF
TAZEEZ FOR PUBLIC HEALTH
AN OFFICIAL JOURNAL OF SAUDI HEALTH PROMOTION AND EDUCATION ASSOCIATION

Systematic review

Efficacy and safety of hypertonic saline versus mannitol in the acute management of traumatic brain injury in the emergency department: a systematic review

Mazi Mohammed Alanazi[1], Jumana Safwan Gassem[2], Amjad Ahmed Alharthi[3]

1. Saudi and Jordanian Board Emergency Medicine, Emergency Department, Head of Emergency Research Unit, First Health Cluster, Riyadh, Saudi Arabia
2. Saudi Board Emergency Medicine Resident Program, Emergency Department, Security Forces Hospital, Makkah, Saudi Arabia
3. Saudi Board Emergency Medicine Resident Program, Emergency Department, King Abdullah Medical City, Makkah, Saudi Arabia

---

Abstract

Background: Hypertonic saline (HTS) and mannitol are used widely for raised intracranial pressure (ICP) after traumatic brain injury (TBI), but the preferred agent remains uncertain. This systematic review evaluated the efficacy and safety in acute TBI management. **Methods:** This review followed PRISMA principles. PubMed, Embase, Scopus, and Web of Science were searched for original studies comparing HTS or related hyperosmolar sodium solutions with mannitol in TBI. Eligible designs included randomized trials, prospective studies, retrospective cohorts, case-control studies, and multicenter observational studies. Outcomes included ICP reduction, cerebral perfusion pressure, neurological outcome, mortality, treatment failure, and adverse effects. **Results:** Thirteen original studies were included, most enrolled severe TBI patients with raised ICP. Both agents reduced ICP. Several studies reported physiological advantages with HTS, including lower ICP burden, improved cerebral perfusion pressure, better brain tissue oxygenation, faster target achievement, or lower treatment failure. Studies using similar osmotic burdens found comparable short-term ICP reduction. HTS increased serum sodium or osmolality in some studies, and mannitol was associated with greater urine output. **Conclusion:** HTS had physiological advantages, and the included studies does not prove better clinical outcome than mannitol.

Keywords: Traumatic brain injury; Hypertonic saline; Mannitol; Intracranial pressure; Cerebral perfusion pressure; Osmotherapy; Emergency care.

Published: May 31th, 2026

https://doi.org/10.65759/skyq2a03

Introduction

Traumatic brain injury (TBI) is a major global health problem and it’s an important cause of death, disability, and long-term neurological impairment in all age groups. More than 50 million TBIs occur worldwide each year, and the condition creates a great burden for patients, families, health systems, and economies [1]. Global burden estimates show that TBI accounted for 27.08 million new cases and 55.50 million prevalent cases in 2016 [2]. 69 million individuals sustain TBI annually, with a high proportional burden in low- and middle-income countries [3].

The clinical consequences of TBI are driven by the primary mechanical insult and secondary brain injury processes that evolve after trauma. Secondary injury includes cerebral edema, impaired cerebral perfusion, ischemia, hypoxia, and increased intracranial pressure [1]. Intracranial hypertension is important because the brain is enclosed within the fixed cranial vault, and progressive swelling reduce cerebral blood flow or cause life-threatening tissue shifts [1].

Hyperosmolar therapy is commonly used to reduce ICP in patients with severe TBI. Mannitol has historically been used for this purpose because it creates an osmotic gradient, reduces brain water, and improve blood rheology [4]. Hypertonic saline (HTS) is an alternative therapy because it increases serum osmolality, shifts water from brain tissue into the intravascular space, and support hemodynamic stability and cerebral perfusion [5]. Current neurocritical-care guidance indicate that hyperosmolar therapy reduces ICP or cerebral edema in TBI [5].

Despite frequent clinical use, the preferred hyperosmolar agent still debated. Previous clinical studies compared different concentrations of HTS with different doses of mannitol [6]. Some studies found that HTS produce faster or greater ICP reduction and better cerebral perfusion effects, and other studies show no significant difference between the two agents [7]. Pediatric studies are also uncertain, as recent multicenter data found no clear survival or functional outcome advantage of 3% HTS over 20% mannitol in children with moderate to severe TBI [8].

This is clinically relevant in emergency and acute-care settings, where rapid selection of an osmotic agent affects ICP control, cerebral perfusion, fluid balance, electrolyte safety, and subsequent neurocritical-care management. Differences in drug concentration, route of administration, renal effects, serum sodium changes, and patient-specific conditions such as hypovolemia or renal impairment influence bedside decision-making. In this study we aimed to systematically review the original comparative studies to analyze the efficacy and safety of HTS versus mannitol in the acute management of TBI.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach. The review was designed to evaluate the efficacy and safety of HTS compared with mannitol in the acute management of TBI. The research question was structured using the PICO framework. The population included adult or pediatric patients with TBI. The intervention was HTS or a related hyperosmolar sodium solution used for ICP control. The comparator was mannitol. The outcomes of interest included intracranial pressure reduction, cerebral perfusion pressure, brain oxygenation, neurological outcome, mortality, treatment failure, and reported adverse effects.

A systematic literature search was performed using four electronic databases: PubMed, Embase, Scopus, and Web of Science. The search focused on original studies evaluating HTS or hyperosmolar sodium therapy versus mannitol in TBI. Search terms included combinations of terms related to traumatic brain injury, head injury, intracranial pressure, intracranial hypertension, hypertonic saline, sodium chloride, sodium lactate, mannitol, osmotherapy, emergency care, trauma care, intensive care, and neurocritical care. Boolean operators were used to combine the search terms. The reference lists of relevant articles were checked to identify eligible original studies. Duplicate records were removed before screening.

Studies were eligible for inclusion if they were original human research articles comparing hypertonic saline, hypertonic sodium chloride, or another hyperosmolar sodium solution with mannitol in patients with traumatic brain injury. Randomized controlled trials, prospective studies, retrospective cohort studies, case-control studies, and multicenter observational studies were considered eligible. Studies were included if they reported one relevant efficacy or safety outcome (intracranial pressure response, cerebral perfusion pressure, neurological outcome, mortality, treatment failure, serum sodium or osmolality changes, renal effects, urine output, or other adverse events). Review articles, systematic reviews, meta-analyses, editorials, letters, animal studies, laboratory studies, case reports, conference abstracts without sufficient data, and studies not comparing hypertonic saline or hyperosmolar sodium therapy with mannitol were excluded.

Titles and abstracts retrieved from the database search were screened for relevance. Articles that were uncertain were assessed using full-text review. Final inclusion was based on the predefined eligibility criteria. Only original articles directly relevant to the review question were included in the qualitative synthesis. When a study included a hyperosmolar sodium solution other than sodium chloride, it was retained only if it compared that agent with mannitol in TBI.

Data were extracted into tables, and extracted variables included author, year, country or setting, study design, population characteristics, sample size, intervention, comparator, dosing strategy, outcomes assessed, main efficacy findings, safety findings, and authors' conclusions. The included studies were summarized narratively because of differences in study design, population age group, HTS concentration, mannitol dose, outcome definitions, and follow-up duration. The analysis focused on patterns of ICP control, cerebral perfusion effects, mortality, neurological outcomes, and adverse effects across studies.

Results

Thirteen original studies met the inclusion criteria and were included in the qualitative synthesis. The included studies consisted of prospective randomized studies, open-label randomized trials, alternating-treatment studies, retrospective cohorts, case-control analyses, and prospective multicenter observational cohorts. Most studies enrolled patients with severe TBI and increased ICP.

The clinical setting was ICU, neurocritical care, trauma center, or pediatric ICU after acute TBI.

The included studies compared different concentrations and regimens of HTS or hyperosmolar sodium solutions against mannitol. HTS concentrations included 3%, 7.5%, 7.45%, 15%, and 23.4% sodium chloride. One study compared sodium lactate with mannitol and was retained as a related hyperosmolar sodium-solution comparator. Mannitol was most commonly given as 20% mannitol, although some studies used 25% mannitol or weight-based mannitol dosing.

HTS and mannitol were effective in reducing ICP in patients with TBI. Vialet et al. found that 7.5% HTS was associated with fewer and shorter refractory intracranial hypertension episodes and a lower treatment failure rate than 20% mannitol. Francony et al. and Sakellaridis et al. didn’t find statistically significant difference between mannitol and HTS in the magnitude of ICP reduction when similar osmotic burdens were used. Cottenceau et al. found that both mannitol and HTS decrease intracranial pressure, although HTS produced a stronger and sustained effect on cerebral perfusion.

Several studies found physiological advantages of HTS. Oddo et al. found improved brain tissue oxygenation, lower intracranial pressure, and higher cerebral perfusion pressure after HTS in patients with refractory intracranial hypertension. Mangat et al. 2015 found that HTS was associated with lower cumulative and daily intracranial pressure burdens than mannitol. Mangat et al. 2020 [9] reported that HTS was associated with a lower combined burden of high intracranial pressure and low cerebral perfusion pressure. Patil and Gupta found that all agents reduced intracranial pressure, but 3% HTS produced the greatest reduction and the shortest time to target intracranial pressure.

The CENTER-TBI study found similar ICU mortality and 6-month outcomes between mannitol-preference and HTS-preference strategies. In pediatric TBI, Kumar et al. [10] found no significant difference in intracranial pressure reduction or 6-month outcome between 3% HTS and mannitol. Chong et al. [8] found no significant difference in mortality or functional outcomes between children treated with 3% HTS and those treated with 20% mannitol. Tatro et al. [6] found no significant difference between 23.4% sodium chloride and mannitol in intracranial pressure reduction at 30, 60, or 120 minutes.

HTS was associated with increased serum sodium, chloride, and osmolality in some studies, while mannitol was associated with greater urine output. Serious comparative safety differences were not consistently reported. The included studies indicate that HTS offer physiological advantages in selected patients, mainly for refractory intracranial hypertension or impaired cerebral perfusion. Characteristics of the included studies and main findings were presented in Table 1 & 2 respectively.

Table 1. Characteristics of the included studies

Study	Country and setting	Design	Population	Sample size	Intervention	Comparator	Outcomes
Vialet et al., 2003 [11]	France; university hospital trauma center	Prospective randomized study	Severe head trauma with refractory intracranial hypertension	20	7.5% HTS, 2 mL/kg	20% mannitol, 2 mL/kg	Number and duration of intracranial hypertension episodes, treatment failure, CPP, safety
Francony et al., 2008 [12]	France; two ICUs in a university hospital	Parallel randomized controlled trial	Severe brain injury with sustained ICP >20 mmHg; mainly TBI, with small stroke subgroup	20	7.45% HTS, 100 mL	20% mannitol, 231 mL	ICP reduction, CPP, middle cerebral artery flow velocities, brain tissue oxygenation, urine output, serum osmolality
Ichai et al., 2009 [13]	France; adult ICU	Prospective open randomized study	Isolated severe TBI with intracranial hypertension	34	Hyperosmolar sodium lactate, 1.5 mL/kg	20% mannitol, 1.5 mL/kg	ICP reduction, treatment success, 1-year Glasgow Outcome Score
Oddo et al., 2009 [14]	USA; neurointensive care unit	Retrospective analysis from prospective observational database	Severe TBI with refractory intracranial hypertension and PbtO2 monitoring	12 patients; 42 treatment episodes	7.5% HTS, 250 mL	25% mannitol, 0.75 g/kg	Brain tissue oxygenation, ICP, CPP, cardiac output
Cottenceau et al., 2011 [15]	France and Israel; two university ICUs	Prospective randomized study	Severe TBI with increased ICP	47	7.5% HTS, 2 mL/kg	20% mannitol, 4 mL/kg	ICP, CPP, cerebral blood flow, cerebral metabolism, serum sodium, hematocrit, 6-month GOS
Sakellaridis et al., 2011 [16]	Greece; hospital ICUs/neurosurgery setting	Alternating-treatment clinical study	Severe head injury	29 patients; 199 hypertensive events	15% HTS, 0.42 mL/kg	20% mannitol, 2 mL/kg	Extent of ICP reduction and duration of effect

Study	Country and setting	Design	Population	Sample size	Intervention	Comparator	Outcomes
			Severe TBI with raised ICP episodes				
Mangat et al., 2015 [17]	USA; New York State TBI-trac database	Retrospective matched cohort	Severe TBI with intracranial hypertension treated with only one hyperosmolar agent	25 HTS matched to 25 mannitol	Mostly 3% HTS bolus; one patient received 23.4% HTS	20% mannitol	Cumulative ICP burden, daily ICP burden, ICU days, ICP monitoring days, 2-week mortality
Kumar et al., 2019 [10]	India; tertiary neurosurgical ICU	Prospective open-label randomized controlled trial	Children ≤16 years with severe TBI and raised ICP	30	3% HTS, 2.5 mL/kg	20% mannitol, 2.5 mL/kg	Mean ICP reduction, 6-month Glasgow Outcome Scale
Patil and Gupta, 2019 [7]	India; neurosurgical department	Prospective randomized controlled study	Adults with isolated severe TBI and sustained ICP >20 mmHg	120	3% HTS	20% mannitol; third arm received 10% mannitol + 10% glycerol	ICP reduction, CPP, MAP, GCS change, serum sodium, serum osmolality, hematocrit
Mangat et al., 2020 [9]	USA; New York State TBI-trac database	Case-control study using prospectively collected data	Severe TBI patients treated with only one hyperosmolar agent	25 HTS matched to 25 mannitol; sensitivity analysis 24 HTS matched to 48 mannitol	HTS bolus therapy	Mannitol	Combined high ICP and low CPP burden, ICP/CPP burden duration, 2-week mortality
Tatro et al., 2021 [6]	USA; single tertiary academic medical center	Single-center retrospective cohort	TBI patients ≥16 years on severe TBI pathway with ICP monitor or EVD	31 patients; 162 doses	23.4% sodium chloride, 30 mL	Mannitol, 0.5 g/kg	Absolute ICP reduction at 30, 60, and 120 minutes; time to next elevated ICP
van Veen et al., 2023 [18]	Europe and Israel; CENTER-TBI multicenter cohort	Prospective multicenter comparative effectiveness cohort	TBI patients aged ≥16 years admitted to ICU and treated with mannitol and/or HTS	502 treated with mannitol or HTS from 2056 assessed	HTS-first or HTS-preference strategy	Mannitol-first or mannitol-preference strategy	ICU mortality, 6-month GOSE, patient determinants of agent choice

Study	Country and setting	Design	Population	Sample size	Intervention	Comparator	Outcomes
Chong et al., 2025 [8]	Asia, Latin America, and Europe; 28 pediatric ICUs	Prospective multicenter observational cohort	Children <18 years with moderate to severe TBI	445	3% HTS	20% mannitol	Mortality, discharge PCPC, 3-month GOS-E-Peds, functional outcomes

Table 2. Main findings of the included studies

Study	Main findings	Clinical outcome findings
Vialet et al., 2003 [11]	7.5% HTS reduced the number and duration of refractory intracranial hypertension episodes more than 20% mannitol. Treatment failure was lower with HTS.	Mortality and neurologic outcome did not significantly differ between groups.
Francony et al., 2008 [12]	Equimolar 20% mannitol and 7.45% HTS produced similar sustained ICP reduction over 120 minutes.	Mannitol caused greater urine output; HTS increased sodium and chloride. No major PbtO2 difference was observed.
Ichai et al., 2009 [13]	Sodium lactate produced greater and more prolonged ICP reduction than mannitol and had a higher treatment-success rate.	The authors reported better long-term GOS in the sodium lactate group.
Oddo et al., 2009 [14]	HTS was associated with lower ICP and higher CPP than mannitol in refractory episodes.	HTS increased brain tissue oxygenation, while mannitol did not show a significant PbtO2 increase.
Cottenceau et al., 2011 [15]	HTS and mannitol reduced ICP; HTS had a stronger and longer cerebral perfusion effect.	No significant difference in neurological outcome at 6 months; cerebral metabolic rates were not improved by either agent.
Sakellaridis et al., 2011 [16]	Mean ICP decrease was similar: 7.96 mmHg with mannitol vs 8.43 mmHg with HTS. Duration of effect was also similar.	One electrolyte complication occurred after each treatment.
Mangat et al., 2015 [17]	HTS reduced cumulative ICP burden and daily ICP burden compared with mannitol.	ICU days were lower in the HTS group; 2-week mortality was lower numerically but not statistically significant.
Kumar et al., 2019 [10]	Mean ICP reduction did not differ significantly between mannitol and 3% HTS in pediatric severe TBI.	Death or vegetative survival was not significantly different between groups.
Patil and Gupta, 2019 [7]	All three agents reduced ICP below 15 mmHg. The largest ICP reduction, shortest time to ICP target, and greatest CPP/MAP changes were observed with 3% HTS.	Serum sodium and osmolarity increased most after HTS. No clear neurological outcome benefit over mannitol was shown.

Study	Main findings	Clinical outcome findings
Mangat et al., 2020 [9]	HTS was associated with lower combined burden of high ICP and low CPP than mannitol in matched comparisons.	The analysis focused mainly on ICP/CPP burden; observational design limits causal certainty.
Tatro et al., 2021 [6]	No significant difference in absolute ICP reduction at 30, 60, or 120 minutes between 23.4% sodium chloride and mannitol.	No difference in time to next elevated ICP. Patient-specific selection was recommended.
van Veen et al., 2023 [18]	ICU mortality and 6-month outcomes were similar between mannitol-preference and HTS-preference strategies.	Choice of hyperosmolar agent was driven more by center practice than patient characteristics.
Chong et al., 2025 [8]	In children with moderate to severe TBI, HTS was not associated with lower mortality or better functional outcome than mannitol after adjustment.	Mortality was 7.1% with HTS and 11.0% with mannitol, but the difference was not statistically significant.

Discussion

This systematic review found that HTS and mannitol were effective for reducing raised ICP in patients with TBI, with no significant advance of one agent for mortality or functional recovery. This is consistent with previous comparative literature, where they reduced ICP with the magnitude and duration of benefit differ in studies because of differences in HTS concentration, mannitol dose, osmotic load, timing of administration, and outcome definitions [19]. The absence of a uniform clinical advantage is important because hyperosmolar therapy is selected rapidly during acute TBI care [20].

The physiological results of our review indicate that HTS have advantages in selected patients, mainly where cerebral perfusion pressure, prolonged intracranial pressure control, or systemic hemodynamics are important. Shi et al. reported that 3% HTS and 20% mannitol reduced ICP [21]. Schwimmbeck et al. found no significant difference in mortality or favorable neurological outcome and reported lower ICP at 90–120 minutes and higher cerebral perfusion pressure after HTS compared with mannitol [20].

Miyoshi et al. reviewed randomized trials in prehospital, emergency department, and ICU settings and the included trials were all conducted in ICUs, which limit direct data for emergency department practice [22]. Their study showed no significant difference in all-cause mortality between HTS and mannitol, and the certainty of evidence was rated very low for all outcomes [22]. A Cochrane review by Chen et al. found no significant difference in the effect of HTS compared to mannitol in efficacy or safety for long-term management of acute TBI [23].

The mechanistic findings explain why HTS is better in physiological outcomes. HTS increase serum osmolality and intravascular volume, which reduce cerebral edema and support cerebral perfusion pressure, whereas mannitol can cause osmotic diuresis and limited by dehydration, hypotension, renal effects, or rebound intracranial pressure in some patients [19]. Oddo et al. found improved brain tissue oxygenation, lower ICP, and higher cerebral perfusion pressure after 7.5% HTS in severe

TBI with refractory intracranial hypertension [14]. Ichai et al. found that sodium lactate produced a prolonged ICP reduction than mannitol [13].

Our findings indicate individualized selection rather than universal preference for either agent. HTS is reasonable when hypovolemia, hyponatremia, low cerebral perfusion pressure, or refractory intracranial hypertension is present. Future studies should use standardized dosing, clearly defined emergency and neurocritical-care settings, consistent neurological outcomes, and systematic adverse-event reporting to determine whether short-term physiological advantages translate into patient-centered benefit.

Conclusion

Our systematic review found that HTS and mannitol are effective for reducing raised ICP after TBI. HTS is better in physiological outcomes in some studies, including lower ICP burden, improved cerebral perfusion pressure, better brain oxygenation, and faster target achievement. These benefits did not translate into superiority in mortality or functional outcomes. Safety findings were reported, with HTS affecting sodium or osmolality and mannitol mainly increasing diuresis. Treatment choice should be individualized according to hemodynamics, serum sodium, renal status, clinical urgency, injury severity, setting, and available monitoring resources.

References

1] Maas AIR, Menon DK, David Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017;16:987–1048. https://doi.org/10.1016/S1474-4422(17)30371-X.

[2] James SL, Bannick MS, Montjoy-Venning WC, Lucchesi LR, Dandona L, Dandona R, et al. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:56–87. https://doi.org/10.1016/S1474-4422(18)30415-0.

[3] Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg 2019;130:1080–97. https://doi.org/10.3171/2017.10.JNS17352.

[4] Wakai A, Mccabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database of Systematic Reviews 2013;2013. https://doi.org/10.1002/14651858.CD001049.pub5.

[5] Cook AM, Morgan Jones G, Hawryluk GWJ, Mailloux P, McLaughlin D, Papangelou A, et al. Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients. Neurocrit Care 2020;32:647–66. https://doi.org/10.1007/s12028-020-00959-7.

[6] Tatro HA, McMillen JC, Hamilton LA, Rowe AS. 23.4% Sodium Chloride Versus Mannitol for the Reduction of Intracranial Pressure in Patients With Traumatic Brain Injury: A Single-Center Retrospective Cohort Study. Annals of Pharmacotherapy 2021;55:988–94. https://doi.org/10.1177/1060028020982379.

7] Patil H, Gupta R. A Comparative Study of Bolus Dose of Hypertonic Saline, Mannitol, and Mannitol Plus Glycerol Combination in Patients with Severe Traumatic Brain Injury. World Neurosurg 2019;125:e221–8. https://doi.org/10.1016/j.wneu.2019.01.051.

8] Chong SL, Zhu Y, Wang Q, Caporal P, Roa JD, Chamorro FIP, et al. Clinical Outcomes of Hypertonic Saline vs Mannitol Treatment among Children with Traumatic Brain Injury. JAMA Netw Open 2025;8. https://doi.org/10.1001/jamanetworkopen.2025.0438.

9] Mangat HS, Wu X, Gerber LM, Schwarz JT, Fakhar M, Murthy SB, et al. Hypertonic Saline is Superior to Mannitol for the Combined Effect on Intracranial Pressure and Cerebral Perfusion Pressure Burdens in Patients with Severe Traumatic Brain Injury. Clin Neurosurg 2020;86:221–30. https://doi.org/10.1093/neuros/nyz046.

10] Kumar SA, Devi BI, Reddy M, Shukla D. Comparison of equiosmolar dose of hyperosmolar agents in reducing intracranial pressure-a randomized control study in pediatric traumatic brain injury. Child's Nervous System 2019;35:999–1005. https://doi.org/10.1007/s00381-019-04121-3.

11] Vialet R, Albanèse J, Thomachot L, Antonini F, Bourgouin A, Alliez B, et al. Isovolume hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. Crit Care Med 2003;31:1683–7. https://doi.org/10.1097/01.CCM.0000063268.91710.DF.

[12] Francony G, Fauvage B, Falcon D, Canet C, Dilou H, Lavagne P, et al. Equimolar doses of mannitol and hypertonic saline in the treatment of increased intracranial pressure. Crit Care Med 2008;36:795–800. https://doi.org/10.1097/CCM.0B013E3181643B41.

[13] Ichai C, Armando G, Orban JC, Berthier F, Rami L, Samat-Long C, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med 2009;35:471–9. https://doi.org/10.1007/s00134-008-1283-5.

[14] Oddo M, Levine JM, Frangos S, Carrera E, Maloney-Wilensky E, Pascual JL, et al. Effect of mannitol and hypertonic saline on cerebral oxygenation in patients with severe traumatic brain injury and refractory intracranial hypertension. J Neurol Neurosurg Psychiatry 2009;80:916–20. https://doi.org/10.1136/jnnp.2008.156596.

[15] Cottenceau V, Masson F, Mahamid E, Petit L, Shik V, Sztark F, et al. Comparison of effects of equiosmolar doses of mannitol and hypertonic saline on cerebral blood flow and metabolism in traumatic brain injury. J Neurotrauma 2011;28:2003–12. https://doi.org/10.1089/neu.2011.1929.

[16] Sakellaridis N, Pavlou E, Karatzas S, Chroni D, Vlachos K, Chatzopoulos K, et al. Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries Clinical article. J Neurosurg 2011;114:545–8. https://doi.org/10.3171/2010.5.JNS091685.

[17] Mangat HS, Chiu YL, Gerber LM, Alimi M, Ghajar J, Härtl R. Hypertonic saline reduces cumulative and daily intracranial pressure burdens after severe

traumatic brain injury. J Neurosurg 2015;122:202–10. https://doi.org/10.3171/2014.10.JNS132545.

18] Van Veen E, Nieboer D, Kompanje EJO, Citerio G, Stocchetti N, Gommers D, et al. Comparative Effectiveness of Mannitol Versus Hypertonic Saline in Patients With Traumatic Brain Injury: A CENTER-TBI Study. J Neurotrauma 2023;40:1352–65. https://doi.org/10.1089/neu.2022.0465.

19] Boone MD, Oren-Grinberg A, Robinson TM, Chen CC, Kasper EM. Mannitol or hypertonic saline in the setting of traumatic brain injury: What have we learned? Surg Neurol Int 2015;6. https://doi.org/10.4103/2152-7806.170248.

20] Schwimmbeck F, Voellger B, Chappell D, Eberhart L. Hypertonic saline versus mannitol for traumatic brain injury: A systematic review and meta-analysis with trial sequential analysis. J Neurosurg Anesthesiol 2021;33:10–20. https://doi.org/10.1097/ANA.0000000000000644.

21] Shi J, Tan L, Ye J, Hu L, Das UN. Hypertonic saline and mannitol in patients with traumatic brain injury: A systematic and meta-analysis. Medicine (United States) 2020;99. https://doi.org/10.1097/MD.0000000000021655.

22] Miyoshi Y, Kondo Y, Suzuki H, Fukuda T, Yasuda H, Yokobori S, et al. Effects of hypertonic saline versus mannitol in patients with traumatic brain injury in prehospital, emergency department, and intensive care unit settings: A systematic review and meta-analysis. J Intensive Care 2020;8. https://doi.org/10.1186/s40560-020-00476-x.

23] Chen H, Song Z, Dennis JA. Hypertonic saline versus other intracranial pressure–lowering agents for people with acute traumatic brain injury. Emergencias 2021;33:218–9. https://doi.org/10.1002/14651858.CD010904.pub3.