

# Hypertonic saline in severe traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials

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## ABSTRACT

**Objectives:** Hypertonic saline solutions are increasingly used to treat increased intracranial pressure following severe traumatic brain injury. However, whether hypertonic saline provides superior management of intracranial pressure and improves outcome is unclear. We thus conducted a systematic review to evaluate the effect of hypertonic saline in patients with severe traumatic brain injury.

**Methods:** Two researchers independently selected randomized controlled trials studying hypertonic saline in severe traumatic brain injury and collected data using a standardized abstraction form. No language restriction was applied. We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Scopus, Web of Science, and BIOSIS databases. We searched grey literature via OpenGrey and National Technical Information Service databases. We searched the references of included studies and relevant reviews for additional studies.

**Results:** Eleven studies (1,820 patients) were included. Hypertonic saline did not decrease mortality (risk ratio 0.96, 95% confidence interval [CI] 0.83 to 1.11,  $I^2 = 0\%$ ) or improve intracranial pressure control (weighted mean difference  $-1.25$  mm Hg, 95% CI  $-4.18$  to  $1.68$ ,  $I^2 = 78\%$ ) as compared to any other solutions. Only one study reported monitoring for adverse events with hypertonic saline, finding no significant differences between comparison groups.

**Conclusions:** We observed no mortality benefit or effect on the control of intracranial pressure with the use of hypertonic saline when compared to other solutions. Based on the current level of evidence pertaining to mortality or control of intracranial pressure, hypertonic saline could thus not be recommended as a first-line agent for managing patients with severe traumatic brain injury.

## RÉSUMÉ

**Objectifs:** Les solutés salés hypertoniques sont de plus en plus utilisés dans le traitement de l'élévation de la pression intracrânienne par suite d'une lésion cérébrale traumatique grave. Toutefois, on ne sait pas avec certitude si les solutés salés hypertoniques sont plus efficaces que d'autres traitements dans l'abaissement de la pression intracrânienne et s'ils donnent de meilleurs résultats. Les auteurs ont donc entrepris une revue systématique de la documentation afin d'évaluer l'effet des solutés salés hypertoniques chez les patients ayant subi une lésion cérébrale traumatique grave.

**Méthode:** Deux chercheurs ont sélectionné chacun de leur côté des essais comparatifs à répartition aléatoire portant sur l'utilisation du soluté salé hypertonique dans le traitement des lésions cérébrales traumatiques graves, et ont recueilli des données sur un formulaire normalisé de résumé analytique. Aucune restriction de langue n'a été appliquée. Des recherches ont été effectuées dans les bases de données Medline, Embase, Cochrane Central Register of Controlled Trials, Scopus, Web of Science et Biosis. Les auteurs ont également consulté la documentation parallèle en passant par les bases de données OpenGrey et National Technical Information Service. Enfin, les références bibliographiques fournies dans les études extraites et les revues pertinentes ont aussi servi à la recherche d'autres études.

**Résultats:** Onze études (1820 patients) ont été sélectionnées. Les solutés salés hypertoniques, comparativement à ceux d'autre type, n'ont pas eu pour effet de diminuer la mortalité (rapport des risques : 0,96; intervalle de confiance [IC] à 95 % : 0,83 à 1,11;  $I^2 = 0$  %) ou d'améliorer la normalisation de la pression intracrânienne (moyenne pondérée des différences :  $-1,25$  mm Hg; IC à 95 % :  $-4,18$  à  $1,68$ ;  $I^2 = 78$  %). Par ailleurs, les événements indésirables liés aux solutés salés hypertoniques ont fait l'objet de surveillance dans une seule

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étude, et aucune différence importante n'a été relevée entre les groupes comparés.

**Conclusions:** Les auteurs ont constaté que le soluté salé hypertonique n'était pas meilleur que les autres types de solution au regard de la mortalité ou de l'effet sur la normalisation de la pression intracrânienne. Compte tenu de l'état actuel des données probantes sur la mortalité ou la

normalisation de la pression intracrânienne, le soluté salé hypertonique ne saurait être recommandé comme produit de première intention dans le traitement des patients ayant subi une lésion cérébrale traumatique grave.

**Keywords:** hypertonic saline, traumatic brain injury, meta-analysis, outcome

## INTRODUCTION

Severe traumatic brain injury is common in Canada and is associated with a high morbidity and mortality rate.<sup>1,2</sup> Increased intracranial pressure, a frequent consequence of traumatic brain injury, is strongly associated with mortality in this patient population.<sup>3</sup> To control this increase in pressure, several interventions were proposed, including cerebrospinal fluid drainage,<sup>4</sup> barbiturate coma,<sup>5</sup> and decompressive craniectomy.<sup>4</sup> Hyperosmolar solutions are also widely used as a resuscitation technique to control intracranial pressure.<sup>5</sup>

Among hyperosmolar solutions, mannitol is the most frequently administered and is the solution recommended by clinical practice guidelines.<sup>5</sup> It is considered the gold standard for hyperosmolar therapy in the treatment of increased intracranial pressure.<sup>5,7,8</sup> However, concerns have been raised with regards to the diuretic properties of mannitol solutions, which may lead to volume depletion, hypotension, and secondary decrease in cerebral perfusion.<sup>8-10</sup> Indeed, patients with severe traumatic brain injury have both increased morbidity and mortality with the occurrence of hypotension.<sup>11</sup> Recently, hypertonic saline solutions have been suggested as the preferred solution in traumatic brain injury due to their volume repletion properties and their osmotic effect.<sup>6</sup> Hypertonic saline solutions are also considered an alternative in hypotensive trauma patients because of their volume expansion properties,<sup>12</sup> leading to their increased usage, when compared to mannitol, for the management of intracranial pressure.<sup>13-15</sup>

Six systematic reviews aiming to evaluate the effect of hypertonic saline in neurocritically ill patients have been published showing inconsistent results.<sup>16-21</sup> However, these systematic reviews have important methodological flaws, notably the inclusion of studies with different designs and search strategies with low sensitivity. Furthermore, these reviews did not include the most recent publications. We conducted a

systematic review of randomized controlled trials to investigate the clinical benefits and harm associated with the use of hypertonic saline when compared to any alternative solution in patients with severe traumatic brain injury.

## MATERIALS AND METHODS

### Search strategy

We developed a standardized protocol (not published) prior to conducting this systematic review and meta-analysis. We used a three-pronged strategy to identify randomized controlled trials investigating the use of hyperosmolar solutions in patients with traumatic brain injuries. Our sensitive search strategy was created by using both key words and Medical Subject Heading (MeSH) or Emtree terms; these were connected using Boolean operators. An information specialist collaborated on the development of our search strategy. We systematically searched electronic databases, including OVID MEDLINE, EMBASE, Cochrane Central Register of Controlled Studies, Scopus, Web of Science, and BIOSIS (from their inception to July 2014). The complete search strategy for OVID MEDLINE is presented in Appendix 1. We used OpenGrey and National Technical Information Service databases to search relevant grey literature. We examined the individual references of included studies and relevant narrative reviews to identify potentially missed studies. No language restriction was applied.

### Study selection

We i) selected randomized controlled trials of adults (ages 18 years and older) suffering from severe traumatic brain injury (Glasgow Coma Scale  $\leq 8$ ) and ii) assigned them randomly to receive either hypertonic saline or any other type of solution (e.g., mannitol,

normal saline) to treat an increased or suspected increased intracranial pressure. When case-mix populations were evaluated, studies enrolling more than 80% of eligible patients with traumatic brain injury and adult patients were included in the meta-analysis. Our primary outcomes were death and control of intracranial pressure, regardless of the primary outcome of the included studies. Our secondary outcomes included neurological outcomes at discharge, length of stay in the intensive care unit (ICU) and hospital, and the occurrence of adverse events (including plasmatic osmolality and natremia). We included studies presenting mortality and/or intracranial pressure data according to treatment groups.

Two independent reviewers (EBP, JFS) screened citations based on title and abstract. Studies were then evaluated according to the information found in the full publication. Discrepancies between reviewers were resolved by discussion and revision of the source material. When consensus could not be achieved, a third party arbitrator was consulted (AFT).

### **Risk of bias assessment**

The methodological quality was assessed using the Cochrane Collaboration's tool for assessing the risk of bias.<sup>22</sup> This six-item tool classifies studies as either having a low, high, or unclear risk of bias.

### **Data abstraction**

Two reviewers extracted data from the included studies independently using a standardized data extraction form developed by our research team. The form was piloted on three initial articles to confirm inter-rater agreement. When data were ambiguous or missing, the authors of the studies were contacted for clarification or additional data.

### **Data synthesis**

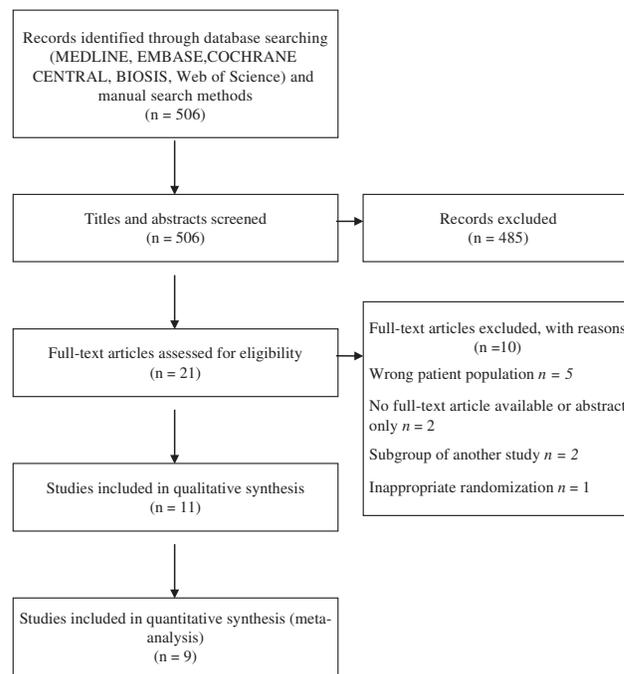
We used the Cochrane Review Manager software (Version 5.1.6 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) to pool individual studies. To determine the effect of hypertonic saline solutions on mortality, outcomes were pooled using the DerSimonian and Laird method with Mantel-Haenszel random effect models. We expressed summary effect measures for mortality using risk ratio (RR) with 95% confidence intervals (95% CIs). An RR of less than one

suggests a decrease in mortality in the hypertonic saline solution group. The inverse variance method was used to assess the impact of the intervention on the control of intracranial pressure. The effect measure was expressed as weighted mean differences (WMDs) with 95% CI. In order to assess the largest potential effect of hypertonic saline solution, we used the lowest mean intracranial pressure measured at least 120 minutes after the administration of the solution.

We assessed the presence of statistical heterogeneity using the  $I^2$  index.<sup>23</sup> We planned a priori to investigate potential sources of heterogeneity and explore the robustness of the findings by conducting subgroup and sensitivity analyses based on care setting (prehospital setting v. ICU setting); intervention (dose regimen) and comparative agent (mannitol v. isotonic fluids); and risk of bias (low v. high risk). We visually explored potential publication bias for each outcome using funnel plots.<sup>24</sup>

## **RESULTS**

Of the 506 records identified, 485 were excluded based on title or abstracts (Figure 1); 21 articles were considered for full-text analyses, of which 13 met our selection criteria. Two of the retrieved studies<sup>25,26</sup> were subgroup studies of a larger trial,<sup>27</sup> which was already eligible for inclusion, leaving 11 included studies.



**Figure 1.** Flow diagram of studies.

Two studies met our inclusion criteria, but no data on mortality or intracranial pressure could be extracted from the publications, and we could not obtain additional data after contacting the authors.<sup>28,29</sup> These studies were thus not included in our pooled analyses.

### Study characteristics

A total of 1,820 patients were enrolled in the 11 included studies.<sup>27-37</sup> All studies were published in English. Of the 11 studies, only 3 included more than 100 patients<sup>27,31,32</sup> (Table 1). All studies specified adult population; however, three studies defined adult population as 16 years of age and older,<sup>27,30,33</sup> and one study as 15 years of age and older.<sup>31</sup> One study randomized intracranial hypertension episodes, instead of randomizing patients.<sup>30</sup> In one study, three patients (0.01% of our total population) with stroke were also included, which represented less than 15% of that study's patient population.<sup>34</sup>

Three comparators were identified: hyperosmolar solution (mannitol or sodium bicarbonate),<sup>28,33-35,37</sup> iso-osmolar solution (normal saline or ringer's lactate),<sup>27,31,32</sup> and hypo-osmolar solution<sup>36</sup> (see Table 1).

### Risk of bias assessment

In general, allocation concealment was respected in most studies (63%),<sup>27,30-35</sup> and the randomization method was specified in slightly more than half of them (54%).<sup>27,31-33,35,36</sup> In six studies (63%), the research staff, patients, and medical staff were not blinded to the intervention studied.<sup>27,28,30,33,34,37</sup> The information regarding blinding was missing in three studies (27%).<sup>29,35,36</sup> In one study (9%), an additional source of bias was identified<sup>36</sup>: the study treatment and control groups were not comparable because the baseline Glasgow Coma Scale score was lower in the hypertonic saline solution group.

Two studies (18%) were deemed to have a low risk of bias, having respected all but one criteria<sup>31,32</sup> (Table 2). Due to the limited number of studies, it was not possible to undertake a sensitivity analysis according to the risk of bias.

### Data synthesis

#### Mortality

Four studies presented data on mortality.<sup>27,31,32,37</sup> One study used mannitol as a comparator.<sup>37</sup> Our meta-analysis

showed that hypertonic saline was not associated with a significant reduction in mortality rate ( $k = 4$ ;  $n = 1,638$ ; RR 0.96; 95% CI 0.83 to 1.11;  $I^2 = 0\%$ ) (Figure 2). Sensitivity analysis with studies comparing hypertonic saline solutions to isotonic solutions only yielded to similar results ( $k = 3$ ;  $n = 1,618$ ; RR 0.96; 95% CI 0.83 to 1.11;  $I^2 = 0\%$ ).

#### Intracranial pressure

Data on intracranial pressure managed with hypertonic saline solutions were available in six studies.<sup>30,31,33-36</sup> We pooled data on the best (lowest) mean intracranial pressure measurement from each study in order to capture the intervention with the greatest effect (see Table 1). We did not observe a significant better control of intracranial pressure with the use of hypertonic saline as compared with other solutions ( $k = 6$ ,  $n = 532$ , WMD  $-0.39$ , 95% CI  $-3.78$  to  $2.99$ ,  $I^2 = 79\%$ ) (Figure 3). Excluding the study that included three patients with stroke<sup>34</sup> did not modify these results ( $k = 5$ ,  $n = 512$ , WMD  $-0.27$ , 95% CI  $-4.41$  to  $3.60$ ), nor did removing the studies that included patients <18 years old<sup>30,31,33</sup> (*post hoc analyses*). When we only considered studies performed in an ICU setting, we obtained similar results ( $k = 4$ ,  $n = 159$ , WMD  $-0.94$ , 95% CI  $-5.46$  to  $3.58$ ,  $I^2 = 80\%$ ). Finally, the sensitivity analysis of studies using mannitol as control was also non-significant ( $k = 3$ ,  $n = 125$ , WMD  $-1.72$ , 95% CI  $-6.71$  to  $3.27$ ,  $I^2 = 83\%$ ) (Figure 3).

As for our aforementioned secondary outcomes—namely neurological outcomes at ICU or hospital discharge, length of stay in the ICU and hospital—less than three studies reported these outcomes, and a meta-analysis was not performed.

#### Functional outcomes

Two studies reported data on neurological outcome measured using the Glasgow Outcome Scale extended in 85% (1087/1282)<sup>31</sup> and 31% (33/107) of the patients,<sup>27</sup> at 6 and 4 months respectively. Pooled estimates using imputed data for one study<sup>31</sup> showed no difference between groups (RR 1.12, 95% CI 0.92 to 1.36,  $I^2 = 52\%$ ). Data on the modified Rankin Scale were also collected in these two studies but could not be pooled due to the type of measures of central tendency used (median in one study).<sup>27</sup> No effect of the intervention based on the modified Rankin Scale was observed in both studies. The Functional Independence Measure and the Cerebral Performance Category Scale

**Table 1. Characteristics of included studies**

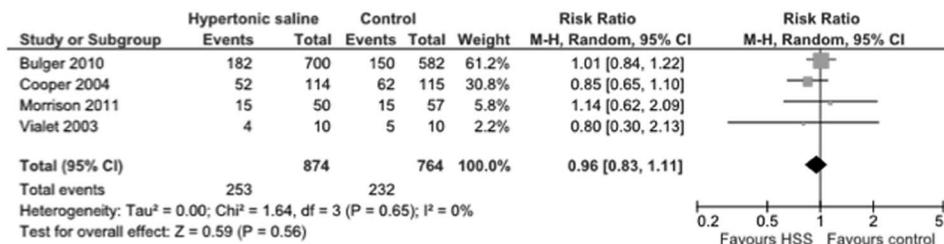
Studies	n	HSS group (n)	HSS	Control group (n)	Control	Study setting	Intervention	Mortality (n)	ICP monitoring
Shackford et al., 1998	34	18	1.6%	16	0.45% NS	ICU	Infusion as needed during hemodynamic instability	N/A	Daily mean and numbers of high ICP episodes per day
Vialet et al., 2003	20	10	7.5%	10	20% mannitol	ICU	2 mL/kg bolus in 20 min during high ICP episode during 7 days	At 90 days: HSS n = 4 Control n = 5	Numbers of high ICP episodes per day
Cooper et al., 2004	229	114	7.5%	115	RL	Prehospital	Single 250 mL bolus	At 6 months: HSS n = 52 Control n = 62	Median ICP at arrival in ICU
Francony et al., 2008	20	10	7.45%	10	20% mannitol	ICU	1 bolus during high ICP episode	N/A	Mean ICP at 120 min
Ichai et al., 2009	34	17	Hypertonic lactate solution	17	20% mannitol	ICU	1 bolus during high ICP episode	N/A	Mean ICP at 240 min
Bulger et al., 2010	1282	359/341	7.5%, 7.5% HSS + dextran	582	0.9% NS	Prehospital	Single 250 mL bolus	At 28 days: HSS n = 186 Control n = 150	Mean ICP at arrival in ICU
Bourdeaux et al., 2011	11(20)*	10	5%	10	8.4% sodium bicarbonate	ICU	Bolus of solution during high ICP episode	N/A	Mean ICP every 20 min and 360 min
Cottenceau et al., 2011	47	22	7.5%	25	20% mannitol	ICU	Bolus as needed to decrease ICP < 15 mmHg	N/A	Mean ICP at 30 and 120 min
Morrison et al., 2011	106	50	7.5% HSS + dextran	56	0.9% NS	Prehospital	Single 250 mL bolus	At 30 days: HSS n = 16 Control n = 16	N/A
Sakellaridis et al., 2011	29	N/A	15%	N/A	20% mannitol	ICU	1 bolus during high ICP episode	N/A	Mean decrease in ICP
Scaffani et al., 2012	8	N/A	23.4%	N/A	20% mannitol	ICU	1 bolus during high ICP episode	N/A	Mean ICP at 60 min

\*Including both TBI and non-TBI patients.

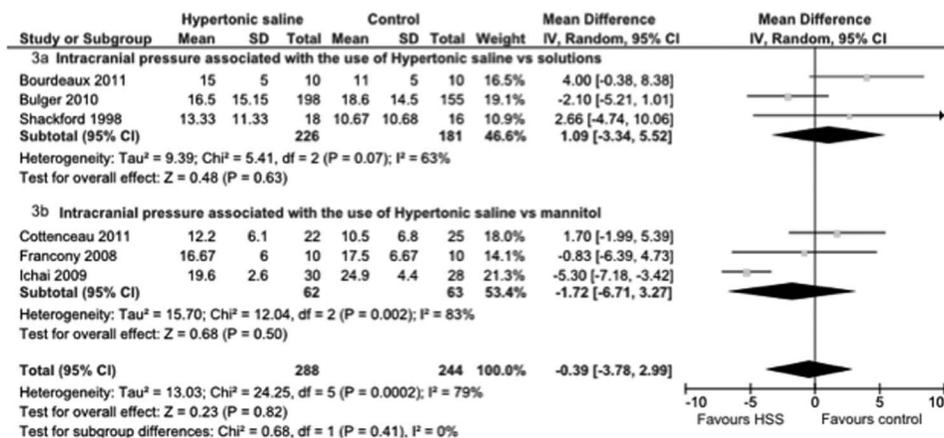
HSS = hypertonic saline solution; ICP = intracranial pressure; ICU = intensive care unit.

**Table 2. Risk of bias assessment**

Studies	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other source of bias
Shackford et al., 1998	Low	Unclear	Unclear	Unclear	High	Low	High
Vialet et al., 2003	Unclear	Unclear	High	Low	High	Low	None
Cooper et al., 2004	Low	Low	Low	Low	Low	High	None
Francony et al., 2008	Unclear	Low	High	Unclear	High	Low	None
Ichai et al., 2009	Low	Low	Unclear	Unclear	Low	Low	None
Bulger et al., 2010	Low	Low	Low	Low	Low	High	None
Bourdeaux et al., 2011	High	Low	High	Low	High	Low	None
Cottenceau et al., 2011	Low	Low	High	High	High	Low	None
Morrison et al., 2011	Low	Low	High	High	High	High	None
Sakellaridis et al., 2011	High	High	High	High	High	Low	None
Scalfani et al., 2012	High	Unclear	Unclear	Low	High	High	None



**Figure 2.** Mortality associated with the use of hypertonic saline.



**Figure 3.** Intracranial pressure associated with the use of hypertonic saline.

were also provided in one study<sup>27</sup> without showing clinical and statistical difference between groups.

**Other outcomes**

One study<sup>31</sup> looked at ventilator-free days, days alive out of the ICU, and days alive out-of-hospital without observing any benefit of the intervention.

**Adverse events**

All studies monitored osmolality and natremia. However, the monitoring was not standardized enough to allow a meta-analytic approach. Hypernatremia was observed in all studies, but no subsequent related adverse events were monitored except in one trial.<sup>31</sup> Nosocomial infections and seizures were evaluated, and no difference was observed. Renal insufficiency was noted in one study.<sup>36</sup>

### Publication bias

We performed a visual inspection of potential publication bias using funnel plots. We did not observe any obvious patterns. However, due to the small number of studies, we cannot exclude potential publication bias (see Appendix 2 for the studies on mortality and Appendix 3 for the studies on intracranial pressure).

## DISCUSSION

In our systematic review, we did not observe any clinically significant benefit with the use of hypertonic saline solutions compared to other resuscitation fluids for patients with severe traumatic brain injury. Indeed, we did not observe an effect of hypertonic saline solutions on mortality or on the control of increased intracranial pressure as compared to other solutions. Mortality data were mostly from studies conducted in prehospital settings with normal saline or ringer's lactate as the control solution. Our systematic review and meta-analysis is the largest overview on the clinical effect of hypertonic saline solution in the traumatic brain injury patient population.

Our findings support the conclusions from the most recent edition of the *Guidelines for the Management of Severe Traumatic Brain Injury: Hyperosmolar Therapy* (2007) by the Brain Trauma Foundation<sup>5</sup> and the 2008 *Advance Trauma Life Support (ATLS)*,<sup>38</sup> which states that the paucity of data precludes any recommendation for the use of hypertonic saline.

Six systematic reviews evaluating the effect of hypertonic saline in the treatment of increased intracranial pressure were previously published.<sup>16-21</sup> All reviews posed a different clinical question and used different inclusion criteria. One review, as with ours, concluded that hypertonic saline solution has no effect on mortality<sup>21</sup>; another study reporting on mortality suggested a decreased mortality with the use of hypertonic saline.<sup>16</sup> With regards to the five systematic reviews evaluating intracranial pressure management, they identified a reduction in intracranial pressure<sup>16-20</sup> associated with hypertonic saline solution, in contrast with our results. These discrepancies may be due to several factors. First, our study provides a more exhaustive review of the current evidence as compared to the previous reviews. Second, our inclusion criteria were different from previous reviews. Two reviews<sup>18,19</sup> included all study designs (retrospective, observational, randomized controlled trials). Four reviews<sup>17-20</sup>

included several neurosurgical pathologies beyond severe traumatic brain injury (e.g., tumor, stroke). By only including randomized controlled trials of patients with severe traumatic brain injury, we achieved less clinical heterogeneity. Consequently, our review presents a comprehensive targeted review of the evidence regarding the use of hypertonic saline for patients with traumatic brain injuries.

Nonetheless, our study has some important limitations. The risk of bias of the primary studies included in our systematic review, overall, was high. Only two studies were deemed to be at low risk of bias using the Cochrane Collaboration's tool for risk of bias assessment. Furthermore, the limited number of studies included the pooled analyses precluded or limited the performance of our planned sensitivity analyses. Consequently, several potential sources of heterogeneity and the rigor of certain findings could not be explored. Nonetheless, our systematic review followed a strict and concise protocol following the recommended methodological standards to conduct systematic reviews.<sup>39</sup> Our systematic review and meta-analysis is currently the largest overview on the clinical effect of hypertonic saline solution in traumatic brain injury.

## CONCLUSIONS

With consideration of quality of the studies included, we observed no mortality benefit or effect on the control of intracranial pressure with the use of hypertonic saline as compared to other solutions. However, only two studies were at low risk of bias. Thus, based on current level of evidence, hypertonic saline could not be recommended as a first-line agent for managing patients with severe traumatic brain injury.

### Key Messages

- The use of hypertonic saline solution did not decrease mortality or improve intracranial pressure when compared to other solutions for the care of patients with severe traumatic brain injury.
- Hypertonic saline solution cannot be recommended as a first line agent in the management of patients with traumatic brain injury.

## SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/cem.2016.12>

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**Competing interests:** None declared.

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