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REVIEW

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Hypertonic saline in ICU setting: what is its position? A systematic review and empirical analysis

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Abstract

Background: Fluid overload has been linked to poor outcomes in the critically ill in recent years, with multiple studies showing an increase in mortality in the overall intensive care unit population. Although the administration of hypertonic saline has increased in recent years, few publications involving its use in intensive care unit have been published to date. The aim of this systematic review is to compare hypertonic and isotonic saline solutions and assess the current evidence to determine whether hypertonic saline can be used in the intensive care unit to treat critically ill or injured patients.

Main body: The PRISMA protocol was applied to conduct the search, which generated 622 possible trials. Only four papers were chosen and included in our study after duplicates and studies that did not fulfill our inclusion criteria, and outcomes were removed. The primary outcome was mortality, with the length of time spent in intensive care and in the hospital as secondary outcomes, and patients assessed in the intensive care unit ranged from 3 to 55, according to our revision. There were three to 24 trials in all, and not all of them used mortality or intensive care unit stay as an endpoint. The concentration of HS used in the intervention group ranged from 1.4 to 30%, while not all studies used isotonic saline solution as a control group.

Conclusions: Despite the limited scientific evidence, there seems to be support for the administration/use of hypertonic saline in the intensive care unit setting, in highly selected circumstance. Although hypertonic saline may have favorable therapeutic effects, no effect on mortality has been demonstrated. Patients suffering from a traumatic brain injury evidence suggests that hypertonic saline can effectively lower intracranial pressure, and there is a new trend supporting the use of hypertonic sodium solutions in these situations. Our updated review shows that studies still have a lot of variability, and that more controlled research are needed.

Keywords: Critically ill, Hypertonic saline, Intensive care unit, Time in intensive care unit, Mortality, Traumatic brain injury, Intracranial pressure

Background

Clinical evidence

Fluid excess is linked to poor outcomes in critically ill patients, according to a growing body of evidence (Kim et al. 2017; Lee et al. 2015; Corcoran et al. 2012).

In patients suffering from volume overload, studies have shown an increase in mortality in the overall intensive care unit (ICU) population (Garzotto et al. 2016), patients with sepsis (Chen et al. 2016), kidney failure (Haase-Fielitz et al. 2017), post-surgery (Kulemann et al. 2013), an increase in ICU-acquired infections (Corcoran et al. 2012), more postoperative complications (Haase-Fielitz et al. 2017), and a longer ICU and hospital stay (Mitchell et al. 2015; Magee and Zbrozek 2013). Exacerbation of the components of the "death triad" or "bloody vicious

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cycle" (acidosis, hypothermia, and coagulopathy) is one of the primary ways through which crystalloids can contribute to poor outcome (Cotton et al. 2006). Fluid excess should therefore be avoided, and fluid administration should be kept to a minimum. The paradoxical impact of fast fluid administration is intriguing. They may promote the release of atrial natriuretic peptide (NT-proBNP), which can cause vasodilation and initiate diuresis, lowering sensitivity to vasoconstrictors and attenuating the effect of volume load during elective cesarean delivery (Teoh et al. 2014). In this context, a useful approach is to consider intravenous fluids as drugs, including specific pharmacokinetic and pharmacodynamics properties, whose positive effects are inconstant, and which carries a significant risk of adverse effects (Hoorn 2017; Cecconi et al. 2015; Severs et al. 2015).

In a different approach, hypertonic fluid is used instead of isotonic fluid. Hypertonic saline (HS) is a term used to describe solutions with higher sodium and chloride molar contents. Hypertonic fluids cause an osmotic gradient across the vascular space, pulling fluid into the vessels from the interstitial and intracellular compartment (Tyagi et al. 2007). Hypertonic fluids have been shown to increase cardiac output, decrease tissue and endothelium edema, improve microcirculation and blood viscosity (Rocha e Silva 2014; Frithiof et al. 2007; Rocha-e-Silva and Poli de Figueiredo 2005), and regulate the inflammatory response (Lu et al. 2007;Angle et al. 2000). Such changes have clinical implications, such as a reduction in the total volume of fluid required for resuscitation and a lower susceptibility to sepsis in hemorrhagic shock patients. Several of these researches, which are outside the scope of this review, have focused on hypertonic solutions with additional colloids.

Although hypertonic fluids have a range of benefit, they also have a lot of drawbacks. Hypertonic saline solution can cause hypernatremia, hypokalemia, and hyperchloremia, as well as a rapid increase in plasma osmolality and electrolyte imbalances. These changes can cause catastrophic effects in susceptible patients, including arrhythmias, metabolic acidosis, and central pontine myelinolysis (White et al. 2006). Although rare, central pontine myelinolysis is thought to be more common when hyponatremia is treated too quickly, and prolonged starvation and drinking may also enhance the risk (Kumar et al. 2006). Furthermore, hypertonic saline solution might aggravate bleeding in patients with a non-tamponized injury (Bhardwaj and Ulatowski 2004). Traumatic brain injury (TBI) has increased in the USA in recent years, accounting for around 2.2% of all deaths in the USA (Taylor et al. 2017), and with a significant proportion of deaths across all age groups. In patients with head traumas, hypertonic solutions have been advocated as the fluid of choice (Walsh et al. 1991), since they may maintain cerebral perfusion pressure without producing brain swelling due to an increase in intracranial pressure. Hypertonic saline has similar effects on intracranial pressure (ICP) as mannitol; however, they may not last as long (Qureshi and Suarez 2000). Both mannitol and sodium have minimal blood-brain barrier penetration, which aids in maintaining the osmotic gradient between brain tissue and intravascular space (Grape and Ravussin 2012; Fink 2012;Vialet et al. 2003). Local vasodilation may be one of hypertonic saline's brain-protective characteristics, counteracting the vasospasm that occurs because of TBI (Shackford et al. 1994). Aside from its impact on intracranial pressure, hypertonic saline causes an increase in mean arterial pressure, which helps to maintain adequate cerebral perfusion pressure (Grape and Ravussin 2012). HS concentrations utilized in clinical trials range from 1.8 to 30% NaCl with variable osmoles loading in several investigations (Himmelseher 2007; Johnson and Criddle 2004). The values represent safety concerns, with concentrations above 10% being potentially dangerous due to possibly opening tight junctions in the blood-brain barrier (Suarez 2004).

Although there is now a lot of experimental information demonstrating hypertonic saline's hemodynamic and microvascular characteristics (Rocha e Silva 2014; Frithiof et al. 2007; Tyagi et al. 2007; Rocha-e-Silva and Poli de Figueiredo 2005), a Cochrane review has highlighted the lack of clinical evidence to support the routine use of hypertonic saline as a resuscitation fluid (Bunn et al. 2002) and clinical trials comparing hypertonic and isotonic solutions (Wu et al. 2017; Bulger et al. 2010; Bulger et al. 2008; Vassar et al. 1990) have yielded conflicting results. Finally, but certainly not least, what is the HS position?

This review looks at the available evidence to see if hypertonic saline can be used in the ICU to resuscitate critically ill or injured patients.

Main text

Eligibility

We prioritized systematic reviews and meta-analyses, followed by randomized controlled trials (RCTs) including adult ICU patients, with the primary goal of comparing the effects of hypertonic saline (HS) as a resuscitation fluid to conventional saline solutions. Trials in pediatric patients, pregnant women, studies comparing crystalloid versus other colloid solutions or hypertonic saline-colloid mixtures, studies investigating hypertonic solutions other than HS, trials comparing hypertonic saline versus other hypertonic solutions, and hypertonic saline for inhalation therapy or cystic fibrosis were all excluded. All papers were evaluated, but only those having a complete English

translation, or an English abstract, were considered for inclusion. The following are the exclusion criteria (see Table 1):

Outcome measures

- Primary outcomes: mortality
- Secondary outcomes: the amount of time spent in intensive care as well as the total average time spent in the hospital

Electronic searches Ovid

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, PubMed and PubMed Central (PMC) (National Library of Medicine), and OVID (medical research platform) CINAHL for this updated review. Controlled clinical trials, RCTs, systematic reviews, and meta-analyses were the only publication types we considered. The comprehensive search took place from January to July 2019 and was updated through January 2021. We used a search and bibliographical arrangement program due to the large number of databases and publications available. We selected Zotero software, which is a tool for finding, organizing, and analyzing articles (Duong 2010). We also looked for ongoing trials on trial registries such as clinicaltrials.gov, controlled-trials.com, and ifpma.org/clinicaltrials.

Search methods for identification of studies

The first query, the population query, had the headings and terms "Intensive Care Unit" OR "Intensive Critical Care" OR "Critical Care" OR "Critical Care" OR "Critically Ill" OR "Critical Illness." The second query, exposure query, was formed of following headings and terms: "saline solution, hypertonic" OR "hypertonic saline" OR "Hypertonic Solutions, Saline" OR "Saline Hypertonic Solutions" OR "Solutions, Saline hypertonic" OR "Saline Solutions, Hypertonic" OR "Sodium Chloride Solution, Hypertonic" OR "Hypertonic Saline Solutions" OR "Solutions, Hypertonic Saline." The third query, the outcome query, was composed of the following headings and terms: "mortality in ICU" OR "survival in ICU," and "time in ICU." Additionally, reference lists of possibly relevant reports and reviews were examined to find other research that fit the criteria.

Data collection and analysis/selection of studies/authors contributions

The study's design and data collection were done by all the authors. Two authors (EPD) (LD) scanned titles and abstracts founded during the initial search to remove duplicates and irrelevant research, as well as trials that fulfilled our inclusion criteria. With the intervention of a third adjudicator (MAD), any conflicts were resolved by consensus. To identify potentially overlooked studies, we searched at the individual references of included studies as well as relevant narrative reviews. We required the study to be conducted in ICU, and we also required the study to report death, intensive care survival status, and hospital stay duration. Ethics committee approval was not required as no patients were involved in this review. All the included studies were subjectively and independently assessed for risk of biases (Table 2) by two authors (MD, EPD) using the bias domain described in PRISMA

Table 1 Exclusions criteria

Exclusions criteria
1. Text articles
Unreported findings
It`s irrelevant
Size of sample
Identical research
2. Compared to other hypertonic solutions, as colloid
3. Other illnesses (coeliac or cystic fibrosis diseases)
4. Not remaining in the intensive care unit
5. Miscellaneous
6. Compared to other medications and isotonic fluids other than 0.9% saline
7. Treatment of hyponatremia
8. Prehospital/preoperative/perioperative treatment
9. Other therapies
10. In volunteers

Table 2 Assessment of risk of bias of all included studies

Author	Sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Selective reporting bias	Other bias
Pfortmueller and Schefold (2017)	Unclear	Unclear	Unclear	Unclear	+	Unclear	+
Berger-Pelletier et al. (2016)	−	−	−	−	−	−	−
Strandvik (2009)	Unclear	Unclear	+	Unclear	+	−	+
Bunn et al. (2004)	−	−	−	−	−	−	−

statement for reporting systematic reviews and meta-analyses (Page et al. 2021). The studies were assigned a judgment of "high," "low," or "unclear" risk of bias across the following domains: sequence generation, allocation concealment, performance bias, detection bias, attrition bias, selective reporting bias, and other bias.

Statistical analysis

Because of the heterogeneity of the body of literature and the inability to investigate the rigor of findings, a meta-analysis was not done. Given the low reported incidence of mortality or serious morbidity in the trials studied, estimating sample size is difficult. Due to it, we felt to be inappropriate to pool them and to apply statistical analysis. This review is registered in PROSPERO with registry number: 245748.

Results

The PRISMA protocol was used in the search approach, which yielded 622 potential articles (PRISMA flowchart given in Fig. 1 — appendix) (Liberati et al. 2009). Three-hundred sixty-three titles and abstracts were assessed for inclusion criteria after duplicates were removed. For various reasons (outside of our inclusion criteria), detailed review rejected 353 papers, resulting in the retrieval of 10 publications for full-text analysis. Six studies were eliminated following a thorough review because they did not meet the primary criteria. Only four studies (Pfortmueller and Schefold 2017; Berger-Pelleiter et al. 2016; Strandvik 2009; Bunn et al. 2004) met the pre-specified inclusion criteria and were included in this review (Table 3) and reviewed in detail.

The concentration of HS in the intervention group ranged from 1.4 to 30%; while not all studies used isotonic saline solution as a control group, it ranged from 12 to 80%. The number of patients in the ICU ranged from 3 (12%) to 55 (100%). Only one study (Strandvik 2009) was undertaken exclusively in ICU patients. The outcome measured ranged from three trials (Pfortmueller and Schefold 2017; Bunn et al. 2004) and four trials (Berger-Pelleiter et al. 2016) to 24 trials (Strandvik 2009) (Table 3).

Pfortmueller and Schefold (2017) conducted a systematic review of adult ICU patients with clinically heterogenous patients. Following their revision, they found that 25 papers satisfied the predetermined inclusion criterion. Only three articles (Duchesne et al. 2012; Parrinello et al. 2011; Ramires et al. 1992) evaluated patients in ICUs with mortality as an endpoint; the rest did not match the primary inclusion criteria. However, two studies (Duchesne et al. 2012; Ramires et al. 1992) were a prospective review, and another (Parrinello et al. 2011) included furosemide as an adjuvant in the groups. The conclusion of Pfortmueller and Schefold (2017) is that in carefully selected critically ill patients, the use of hypertonic saline may have therapeutic benefits.

In their final analyses, Berger-Pelleiter et al. (2016) included eleven trials in their randomized study. Eight (72%) of the studies were conducted in an ICU setting, and only four of the studies reported mortality as a result. Two studies use 0.9% NaCl as a control group and hypertonic saline-dextran (HSD) as an intervention group, both of which are prehospital trials conducted outside of the ICU. Based on the current level of evidence in the areas of mortality and intracranial pressure control, they conclude that "hypertonic saline could thus not be recommended as a first-line agent for managing patients with severe traumatic brain injury."

Strandvik (2009) looked at two types of ICU patients: those in shock (29 trials) and those with intracranial hypertension (26 trials). Forty-one (74%) trials were removed from the total because they compared HS to fluids other than 0.9% NaCl, and twenty-four (43%) of the studies reveal death as a result, four (7%) of which are child studies. The conclusion of Strandvik (2009) is that hypertonic saline solutions are effective at lowering intracranial pressure and restoring blood pressure in hemorrhagic shock but not in other forms of shock. They also reported no benefit from HS in terms of survival or prognosis.

Bunn et al. (2004) identified eighteen randomized studies with the aim to determine whether HS lowers mortality in patients with hypovolemia and head trauma, ten (56%) of which were done in the intensive care unit. They concluded that the review does not give enough data to

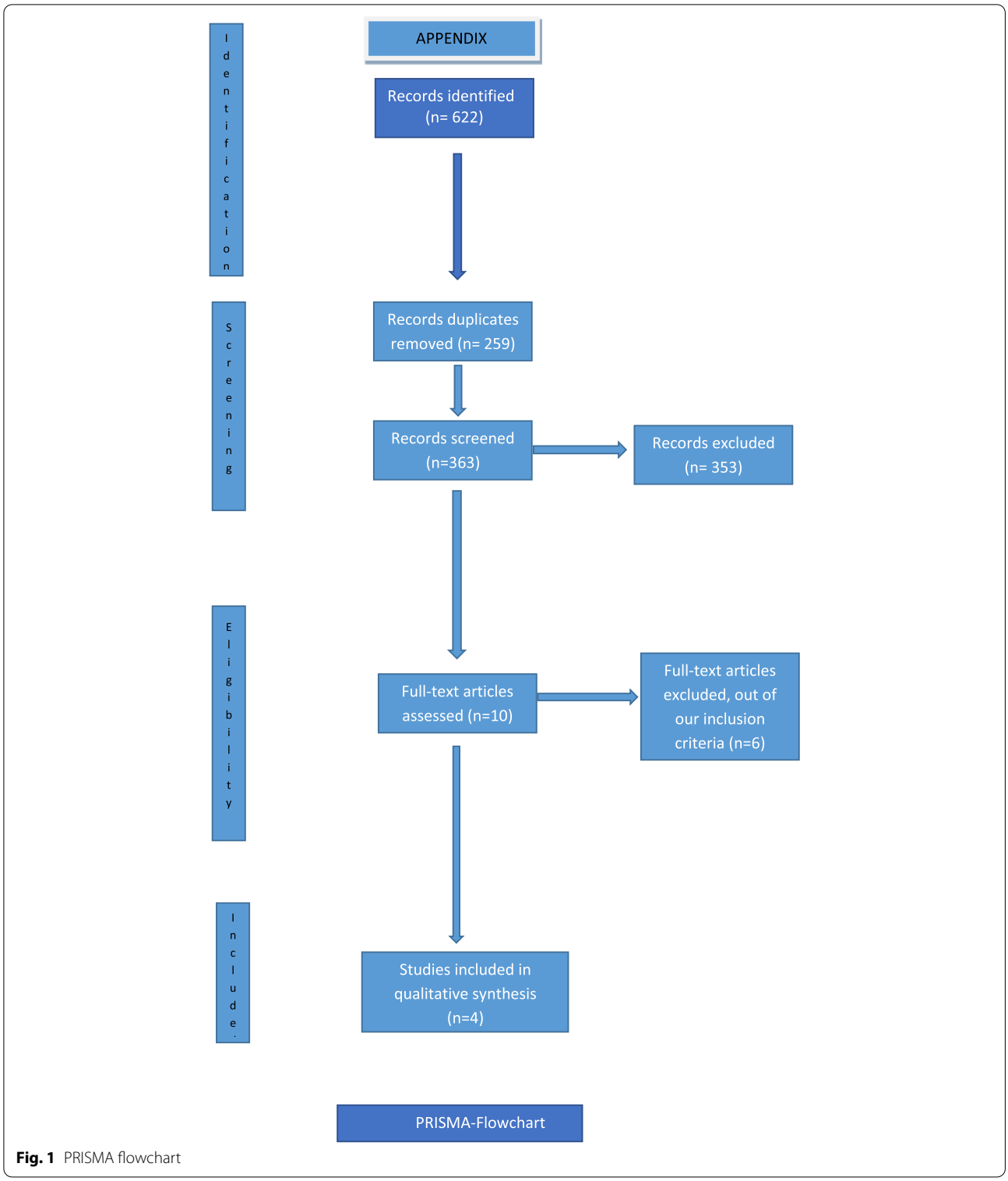

Fig. 1 PRISMA flowchart

be able to say whether hypertonic solution is better than isotonic and near isotonic crystalloid for the resuscitation of patients with trauma or burns or those undergoing surgery.

Discussion

We identified two systematic views where HS is superior to 0.9% NaCl (Pfortmueller and Schefold 2017; Strandvik 2009): one study where there is equality of effects

Table 3 Detailed studies

Randomized studies	Year	Records included	% HS ranking (1)	0.9% NaCl (2) (%)	ICU setting (%)	Outcomesmeasures (3)
Pfortmueller and Schefold	2017	25	1.4–7.5%	25/20 (0.8)	25/3 (0.12)	3
Berger-Pelleiter et al.	2016	11	1.6–23.4%	11/2 (0.18)	11/8 (0.72)	4
Strandvik	2009	55	1.7–30%	55/7 (0.12)	55/55 (1)	24
Bunn et al.	2004	18	7.5%	18/6 (0.33)	18/10 (0.56)	3

1, intervention group; 2, control group; 3, mortality/ICU stay

(Berger-Pelleiter et al. 2016) and one where it is not possible to prove any superiority or inferiority between the solutions for lack of evidence (Bunn et al. 2004). Regarding the diversity that the studies reveal, it is not possible to say that HS is superior to 0.9% NaCl for the resuscitation of patients in ICU. Our review indicates that, in highly selected circumstances, HS may offer some beneficial clinical effects, but that no effect on mortality has been demonstrated.

HS has been recommended as the fluid of choice in TCI as well (Qureshi and Suarez 2000). It can maintain cerebral perfusion pressure constant without creating brain edema or an increase in intracranial pressure (Shackford et al. 1998; Walsh et al. 1991), and most studies found no significant side effects or symptoms of osmotic demyelination syndrome (Blissitt 2012; Kumar et al. 2006). Since 2007, the section on hyperosmolar therapy in the Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury (Brain Trauma Foundation 2007) has included a discussion of both mannitol and HS. However, due to a lack of HS data, only evidence in favor of mannitol was classified. Since then, there has been more experience using HS in the therapy of elevated ICP and on mortality outcomes (Wu et al. 2017; Barbic et al. 2010). Our revision shows no survival benefit with the use of HS solutions, but the evidence is that HS and mannitol effectively lower ICP with a new trend favoring the use of hypertonic sodium solutions in patients with TBI (Mangat et al. 2020; Marko 2012;Hays et al. 2011;Wenham et al. 2008).

Limitation

During our analysis, we found that different clinical questions and inclusion criteria resulted in varied outcomes, and this issue has not been resolved due to the inconsistent results of clinical trials and systematic reviews. The discrepancies in outcomes could be attributed to a variety of factors, including patient populations, fluid types and amounts, and the comparator fluids' safety profile. As a result, various potential causes of heterogeneity as well as the statistical rigor of certain findings could not be investigated.

Conclusions

What is the HS position?

Despite the limited scientific evidence, there seems to be support for the administration/use of HS in the ICU setting, in highly selected circumstances. It is a well-known fact that none of the standard of care procedures used today has ever been put to the formal test of efficacy or safety, but the extensive empirical medical experience and expert opinion attached to their use warrant the view that they are generally effective and usually safe (Bajwa and Kalra 2013; Hinson et al. 2013; Hays et al. 2011;Wenham et al. 2008). HS may offer some beneficial clinical effects, but that no effect on mortality has been demonstrated. Our updated review demonstrates that studies still show great variability, and that there is a need for better and large controlled studies.

Abbreviations

ICU: Intensive care unit; NT-proBNP: Atrial natriuretic peptide; HS: Hypertonic saline; TBI: Traumatic brain injury; ICP: Intracranial pressure; RCTs: Randomized controlled trials; CENTRAL: Cochrane Central Register of Controlled Trials; PMC: PubMed Central; OVID CINAHL: Cumulative index to nursing and allied health literature, medical and nursing research platform; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HSD: Hypertonic saline-dextran.

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Authors' contributions

The authors read and approved the final manuscript. MD (conceptualization, data curation, investigation, supervision, validation, writing — original draft, writing — review & editing). ED (investigation, writing — original draft, writing — review & editing). LD (investigation, writing — original draft, writing— review & editing).

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Availability of data and materials

All the peer-reviewed publications and methods are mentioned with references.

Declarations

Ethics approval and consent to participate

Ethics committee approval was not required as no patients were involved in this review. No patients participated in this review, so consent for participation is not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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