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## Review

# Prehospital fluid administration in patients with severe traumatic brain injury: A systematic review and meta-analysis

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## ABSTRACT

**Background:** Prehospital management of severe traumatic brain injury (TBI) focuses on preventing secondary brain injury. Therefore, hypotension should be prevented, or if present, should be promptly treated in order to maintain optimal cerebral perfusion pressure. Fluid resuscitation is a traditional mainstay in the prehospital treatment of hypotension, however, the choice of fluid type that is to be administered in the prehospital setting is the subject of an on-going debate. This systematic review and meta-analysis was therefore performed to assess the effect of different fluid types on outcome in patients with severe TBI.

**Methods:** PubMed, Embase and Web of Science were searched for articles up to March 2020. Studies comparing two or more prehospital administered fluid types with suspected or confirmed severe TBI were deemed eligible for inclusion. Studied outcomes were mortality and (extended) Glasgow Outcome Scale (GOS). The meta-analysis tested for differences in survival between hypertonic saline (HTS) and normotonic crystalloids (i.e. normal saline or Lactated Ringer's) and between hypertonic saline with dextran (HSD) and normotonic crystalloids. The systematic review is registered in the PROSPERO register with number CRD42020140423.

**Results:** This literature search yielded a total of 519 articles, of which 12 were included in the systematic review and 6 were included in the meta-analysis. Eleven studies found no statistically significant difference in survival between patients treated with different fluid types (e.g. normal saline and hypertonic saline). All studies assessing neurological outcome, measured through (extended) GOS, found no statistically significant difference between different fluid types. Meta-analysis showed no better survival for patients treated with HSD, when compared to normotonic crystalloids (overall RR 0.99, 95% CI 0.93–1.06). Moreover, HTS compared to normotonic crystalloids does not result in a better survival (overall RR 1.04, 95% CI 0.97–1.12).

**Conclusions:** This systematic review and meta-analysis did not demonstrate a survival or neurological benefit for one specific fluid type administered in the prehospital setting.

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## Introduction

Severe traumatic brain injury (TBI) is a major cause of death among younger individuals [1] and a leading cause of disability [2–8]. It is therefore apparent that TBI has a substantial impact on public health, emphasizing the need for optimal treatment strategies. The prehospital phase is of great significance in the management of TBI, as this is the earliest opportunity for healthcare

providers to initiate treatment and prevent secondary brain injury. However, due to lack of robust scientific evidence, uncertainty regarding optimal treatment in the prehospital setting remains. Current prehospital guidelines are mostly based on expert opinion, rather than on scientific evidence [9, 10].

Early management of traumatic brain injury focuses on treating factors known to provoke secondary brain injury, such as hypotension, hypoxia and edema formation [11–14]. In particular, hypotension remarkably worsens the outcome after traumatic brain injury [15]. Therefore, hypotension should ideally be prevented or promptly treated in order to maintain optimal cerebral perfusion pressure. Fluid resuscitation is the most common approach to treat

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**List of abbreviations**

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
TBI	Traumatic Brain Injury
GCS	Glasgow Coma Scale
H-AIS	Head Abbreviated Injury Score
GOS	Glasgow Outcome Scale (GOS)
GOSe	Extended Glasgow Outcome Scale
HTS	Hypertonic Saline
HSD	Hypertonic Saline with Dextran
LR	Lactated Ringer's
NS	Normal Saline

hypotension in the prehospital setting. However, the choice of fluids that is to be administered is the subject of an on-going debate. While isotonic crystalloids are conventionally used, a variety of fluids are available to treat patients with TBI in the prehospital setting. Prehospital guidelines state that patients in need of fluid resuscitation should be treated with isotonic fluids and that hypertonic fluids are a "treatment option" for traumatic brain injury [16].

Crystalloids, such as normal saline or Lactated Ringer's solution, are salt solutions containing small molecules that can freely move between intravascular and interstitial space [17]. Hypertonic saline causes fluid to shift from the interstitial space to the intravascular space through osmosis, which may result in a decrease of cerebral edema. Colloids, such as dextran, hydroxyethyl starch (HES) or albumin, consist of larger molecules and are assumed to stay in the intravascular compartment for a longer time and thus achieve prolonged intravascular volume replacement compared to crystalloids [18]. However, there is no evidence of a beneficial effect of colloids in the treatment of traumatic brain injury and their use is mostly limited to the hospital setting [19, 20].

Clearly, uncertainty regarding the type of fluids used in the prehospital setting remains. Therefore, we performed a systematic review and meta-analysis on available literature to assess the effect of different prehospital fluid therapies on outcome in patients with severe traumatic brain injury [21, 22].

**Methods***Protocol and registration*

This study was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline [23, 24]. The search strategy, study selection, bias assessment and data extraction were defined a priori and the protocol was registered in the PROSPERO register (International Prospective Register of Systematic Reviews) with number CRD42020140423.

*Eligibility criteria*

Articles deemed eligible for inclusion were randomized controlled trials or observational studies comparing two or more prehospital administered fluid types in patients with suspected or confirmed severe TBI. In line with previous literature, severe TBI was defined as either a prehospital or admission Glasgow Coma Scale (GCS) <9 combined with a trauma, or a Head Abbreviated Injury Score (H-AIS)  $\geq 3$  [25]. Studies reporting the outcomes mortality, Glasgow Outcome Scale (GOS) and Extended Glasgow Outcome Scale (GOSe) were eligible for inclusion. Animal studies were

excluded. Studies assessing other patient populations were considered appropriate when it was possible to extract the data of the TBI population.

Articles eligible for meta-analysis were randomized controlled trials (irrespective of the score on the Cochrane Collaboration's tool) or observational studies with a Newcastle Ottawa Score of  $\geq 6$  stars and 2 awarded stars for comparability.

*Information sources and search strategy*

PubMed, Embase and Web of Science were searched without restrictions. This search was last updated in March 2020. The following search was used in PubMed: ((*"saline solution, hypertonic"*[MeSH Terms] OR (*"saline"*[All Fields] AND *"solution"*[All Fields] AND *"hypertonic"*[All Fields]) OR *"hypertonic saline solution"*[All Fields] OR (*"hypertonic"*[All Fields] AND *"saline"*[All Fields]) OR *"hypertonic saline"*[All Fields] OR *"saline solution"*[All Fields]) OR (*"Mannitol"*[All fields] OR *"Mannitol"*[Mesh]) OR (*"Fluid therapy"*[Mesh] OR *"Fluid therapy"*[All fields]) AND (*"brain injuries"*[Mesh] OR *"brain injuries"*[All Fields] OR (*"brain"*[All Fields] AND *"injuries"*[All Fields]) OR (*"head"*[All Fields] AND (*"injuries"*[All Fields] OR *"trauma"*[All Fields])) OR (*"traumatic"*[All Fields] AND *"brain"*[All Fields] AND *"injury"*[All Fields]) OR *"traumatic brain injury"*[All Fields] OR *"head injury"*[All Fields] OR *"head trauma"*[All Fields]) AND (*"emergency medical services"*[Mesh] OR *"prehospital"*[All Fields])). For EMBASE and Web of Science, the search terms were adapted correspondingly. Additionally, reference lists of relevant articles were screened for eligible articles.

*Study selection*

Publications were evaluated for eligibility by screening the abstracts of the identified studies, which was done independently by two investigators (SMB, SFB). When relevance could not be determined based on title or abstract, the full text article was retrieved. Disagreements on eligibility were solved by discussion (SMB, SFB) or by contacting a third reviewer (PS).

*Data extraction*

One of the authors (SFB) extracted the data using a standardized data collection sheet, which was checked for accuracy by a second author (SMB). The following data was extracted from the included studies: [1] study characteristics: study design, sample size, inclusion and exclusion criteria, time period, location of study; [2] patient characteristics: age, gender, injury severity; [3] type of fluids administered; [4] outcome variables.

*Assessment of study quality and risk of bias*

Two of the authors (SMB and SFB) independently assessed the quality of the included studies and in case of a disagreement, a third reviewer (PS) was consulted. The Newcastle-Ottawa scale was used to assess the risk of bias of cohort studies [26]. This scale assigns a total of nine stars per study for selection of participants, comparability of cohorts and assessment of outcome. For randomized controlled trials (RCT), the Cochrane Collaboration's tool for assessing risk of bias was used [27].

*Data synthesis and statistical analysis*

A meta-analysis was performed to test for differences in survival at hospital discharge (or at 28 days when survival at hospital discharge was not reported) between patients who received hypertonic saline (HTS) versus normotonic crystalloids (i.e. normal saline or Lactated Ringer's), and for differences in survival between

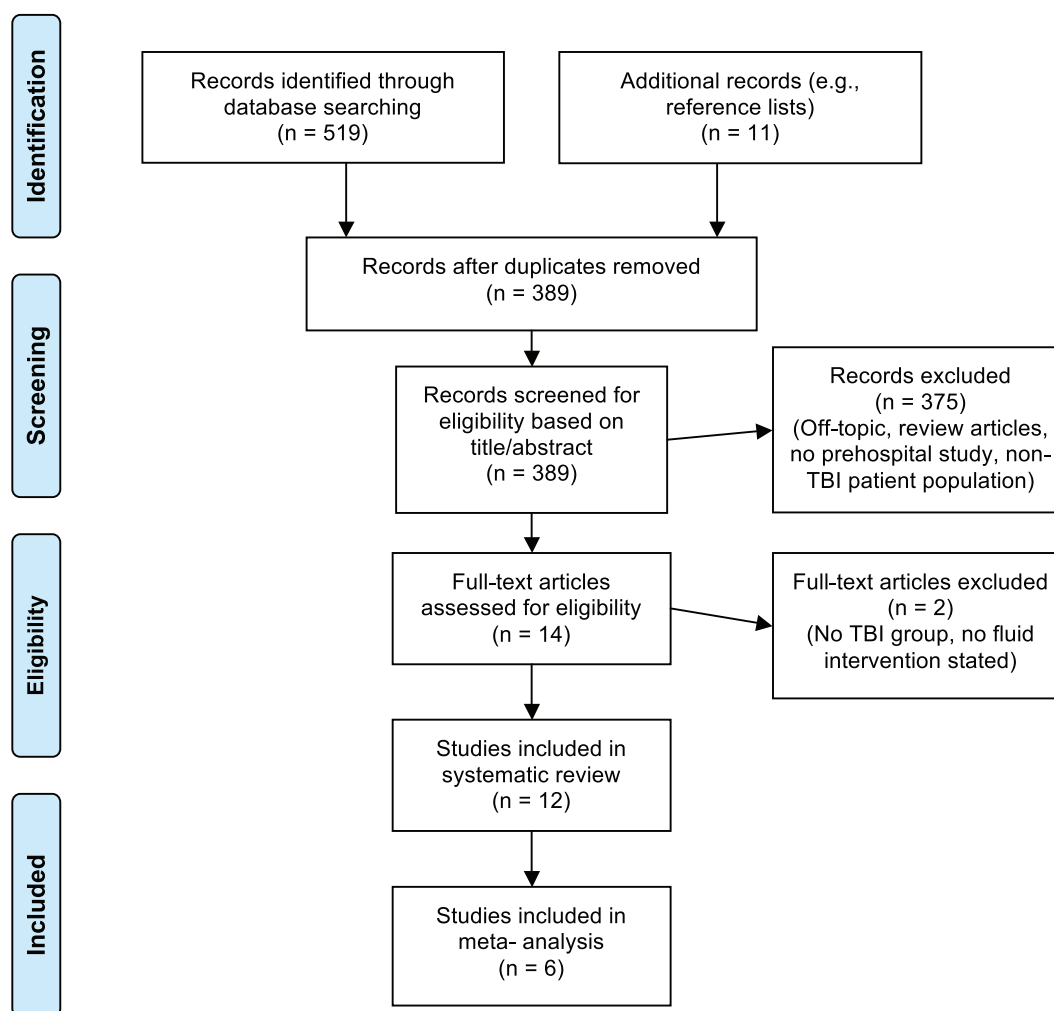


Fig. 1. PRISMA flow diagram.

hypertonic saline with dextran (HSD) and normotonic crystalloids. There were no eligible studies on HES or mannitol compared to other fluids. A random effects meta-analysis was performed with STATA 13.0 (StataCorp, Texas). As a sensitivity analysis, to gauge the potential influence of lower-quality studies on the results, we re-performed the meta-analysis while excluding RCTs with a high risk of bias in any domain as well as observational studies. Testing for publication bias with funnel plots and Egger's test was planned, but was not possible due to the limited number of studies.

## Results

### Study selection

In total, 519 articles were obtained through the database search. Additionally, 11 articles were found through reference lists. After removing duplicates, a total of 389 articles were screened for eligibility based on title and abstract. After excluding 375 articles (off-topic, review articles, no prehospital study, no TBI population), 14 full text articles were assessed for eligibility. Full text screening resulted in the exclusion of 2 articles. The final systematic review therefore yielded a total of 12 articles [28-39]. A total of 6 studies were included in the meta-analysis. Fig. 1 presents the PRISMA flow diagram.

### Study characteristics

The 12 included studies reported data from 3253 patients. Five studies were performed in the United States, four in Canada, one in the United States and Canada, one in Australia and one in Austria. Ten studies were randomized controlled trials, one study was a retrospective cohort and one study was a prospective observational trial (Table 1). Eleven studies compared hypertonic saline with or without dextran to a normotonic crystalloid, and one study compared the two crystalloids Lactated Ringer's and normal saline to each other. No studies compared other colloids (e.g., HES) or mannitol to other types of fluids.

### Patient characteristics

The patients included had a median or mean age of around 36 to 46 years and were mostly male (60–86.4%). In accordance with our inclusion criteria, patients were severely injured (head AIS, ISS) (Table 2). One study explicitly reported their study population as being isolated TBI [36], meaning that patients were excluded if they suffered from life threatening injury in organs other than the brain.

### Risk of bias

Quality assessment by the Newcastle Ottawa Scale of the two cohort studies revealed one star [32] and six stars [39]. The

**Table 1**  
Study characteristics.

First author (year)	Study design	Study period	Region	Inclusion criteria	Exclusion criteria	Total sample size
Vassar (1991)	RCT	1986–1990	California, USA	Systolic BP $\leq$ 100 mmHg, palpable peripheral pulse or sinus complex on ECG, age $\geq$ 18y <b>Subgroup</b> severe TBI (head AIS $\geq$ 4)	Pregnancy, severe hepatic, renal, cardiac or neurologic disease	53
Vassar (1993) [29]	RCT	1990–1991	California, USA	Injured patients with systolic BP $<$ 90 mmHg <b>Subgroup</b> severe TBI (head AIS $\geq$ 4)	Asystolic, undergoing CPR, lacked sinus complex on ECG, age $<$ 18y, $>$ 2 h after injury, pregnant, history of seizures or a bleeding disorder, pre-excising hepatic, cardiac, renal disease, bun, no iv access.	72
Vassar (1993) [30]	RCT	1988–1991	California, USA	Trauma patients with systolic BP $<$ 90 mmHg <b>Subgroup</b> severe TBI (head AIS $\geq$ 4)		27
Cooper (2004)	RCT	1998–2002	Melbourne, Australia	TBI and GCS $<$ 9, hypotensive (systolic BP $<$ 100 mmHg)	Penetrating trauma, $<$ 18y, pregnant, no iv access, serious pre-morbid disease on a medical identification bracelet, peripheral edema, scoop and run, absent sinus rhythm or cardiac arrest	229
Lenartova (2007)	Retrospective cohort of description paper	NR	Vienna, Austria	Severe TBI, GCS $<$ 9 after resuscitation or GCS $<$ 9 within 48 h of injury <b>Subgroup</b> hypertonic saline	Died at scene, during transport to hospital or immediately after admission	396
Bulger (2008)	<del>RCT</del>	2003–2005	USA	Blunt trauma, at least 1 prehospital systolic BP $<$ 90 mmHg, age $>$ 17y <b>Subgroup</b> blunt head injuries (head AIS $>$ 2)	Ongoing CPR, isolated penetrating trauma, pregnancy, receipt of $>$ 2000 mL crystalloid.	78
Baker (2009)	RCT	2004–2006	Toronto, Canada	Coma or loss of consciousness due to isolated blunt head trauma and/or a GCS $<$ 9	Primary penetrating injury, previous intravenous therapy $>$ 50 mL, a time interval between arrival at scene and intravenous access exceeding 4 h, age $<$ 16y, presumed pregnant, amputation or burn, absent vital signs prior to randomization	64
Bulger (2010)	RCT	2006–2009	USA, Canada	Blunt trauma, GCS $<$ 9, systolic BP $>$ 70 or 71–90 with heart rate $>$ 108 (did not meet criteria for hypovolemic shock), age $\geq$ 15y	Suspected pregnancy, out of hospital CPR, administration of $>$ 2000 mL of crystalloid or any amount of colloid/blood products prior to enrollment, severe hypothermia, drowning, asphyxia, burns $>$ 20% body surface, isolated penetrating injury, no iv access, $>$ 4 h between receipt of dispatch call to study intervention, prisoner status, interfacility transfer.	1282
Rhind (2010)	RCT	NR	Toronto, Canada	Blunt head trauma with loss of consciousness and/or GCS $<$ 9	Primary penetrating injury, suffered severe life-threatening injury organs other than the brain, received previous fluid therapy $>$ 50 mL, time interval between arrival at scene and vascular access $>$ 4 h, age $<$ 16y, pregnant, vital signs absent prior to randomization.	65
Morrison (2011)	Feasibility study of RCT	NR	Toronto, Canada	Blunt trauma with GCS $<$ 9 and $\geq$ 16y	Known pregnancy, primary injury penetrating, vital signs absent before randomization, previous iv therapy $>$ 50 mL, time interval between arrival at scene and iv access $>$ 4 h, amputation above wrist or ankle, any burn, suspected hypothermia, asphyxia, fall from height	113
Junger (2013)	A priori subgroup analysis of larger RCT	2006–2009 (NR in this study, subgroup of Bulger (2010))	Seattle and Toronto, USA and Canada	Head trauma and GCS $<$ 9	Signs of hemorrhagic shock, age $<$ 15y, pregnant, received iv fluid therapy $>$ 1000 mL, $>$ 4 h after injury, pre-hospital CPR, severe hypothermia, drowning, asphyxia, burns $>$ 20%, isolated penetrating head injury, inability iv access, prisoner.	103
Rowell (2016)	Prospective observational	2009–2010	Texas, USA	Patients who required highest level activation at a level 1 trauma center, received 1 or more units of red blood cells (RBC) within 6 h of hospital admission. Patients with TBI (head AIS $\geq$ 3) and without TBI (head AIS $\leq$ 2) compared.	Age $<$ 16y, transfer from another hospital, pregnancy, $>$ 20% burn injury, inhalation injury, incarceration, death within 30 min of hospital admission, receiving small volume of prehospital fluid ( $<$ 200 mL), minor injuries (ISS $<$ 9), received both NS and LR, received any other type of fluid or blood products.	791

RCT: randomized controlled trial.

BP: blood pressure.

(s)TBI: (severe) traumatic brain injury.

H-(AIS): (head) abbreviated injury scale.

GCS: Glasgow Coma Scale.

CPR: cardiopulmonary resuscitation.

ISS: Injury Severity Scale.

NS: normal saline.

LR: Lactated Ringer's.

NR: not reported.

**Table 2**  
Patient and injury characteristics.

First author (year)	Intervention(s) and control groups (n)	Age (mean (SD))	Male gender (n (%))	Initial GCS (median (IQR))	ISS (median (IQR))	Head-AIS (median (IQR))
Vassar (1991)	<b>Subgroup</b> of head-AIS $\geq 4$ 06/1986: 7.5% HTS in 4.2% dextran (HSD); 03/1988: 7.5% HTS in 6% dextran (HSD) [28] Lactated Ringer's (LR) [25]	NR*	NR	NR*	NR*	NR
Vassar (1993) [29]	<b>Subgroup</b> of head-AIS $\geq 4$ Lactated Ringer's (LR) [16] 7.5% hypertonic saline (HTS) [19] 7.5% HTS + 6% dextran (HSD6%) [14] 7.5% HTS + 12% dextran (HSD12%) [23]	NR*	NR*	NR*	NR*	NR*
Vassar (1993) [30]	<b>Subgroup</b> of head-AIS $\geq 4$ Normal saline (NS) [6] 7.5% hypertonic saline (HTS) [8] 7.5% HTS + 6% dextran (HSD) [13] 7.5% hypertonic saline (HTS) (114) Lactated Ringer's (LR) (115)	NR*	NR	NR*	NR*	NR
Cooper (2004)	7.5% hypertonic saline (HTS) (114) Lactated Ringer's (LR) (115)	38 (19 SD) 37 (19 SD)	75 (66%) 76 (66%)	4 (IQR 3–7) 4 (IQR 3–7)	38 (IQR 28–48) 38 (IQR 29–45)	4 (IQR 4–5) 4 (IQR 3–5)
Lenartova (2007)	<b>Subgroup</b> hypertonic saline No HTS (375) HTS [21]	NR	NR	NR	NR	NR
Bulger (2008)	<b>Subgroup</b> blunt head injuries (head AIS $>2$ ) 7.5% HTS + 6% dextran (HSD) [44] Lactated Ringer's (LR) [34]	NR	NR	NR	NR	NR
Baker (2009)	7.5% HTS + 6% dextran (HSD) [31]	42.5 (20.9 SD)	18 (60%)	Mean 5.2 (2.1 SD)	Mean 36.2 (15.7 SD)	NR
	Normal saline (NS) [33]	42.3 (20.7 SD)	23 (71%)	Mean 5.8 (3.0 SD)	Mean 31.5 (11.7 SD)	NR
Bulger (2010)	7.5% HTS + 6% dextran (HSD) (359)	38.5 (18.6 SD)	273 (76.3%)	Mean (SD) 5.0 (2.0)	Mean (SD) 26.9 (15.9)	Mean (SD) 3.3 (1.9)
	7.5% hypertonic saline (HTS) (341)	38.6 (17.3 SD)	277 (81.2%)	4.9 (2.3)	26.2 (15.3)	3.3 (1.8)
	Normal saline (NS) (582)	39.5 (19.2 SD)	426 (73.3%)	5.0 (2.1)	26.1 (15.6)	3.3 (1.8)
Rhind (2010)	7.5% HTS + 6% dextran (HSD) [30]	41.8 (17.4 SD)	19 (63.3%)	Mean (SD) 5.6 (2.8)	Mean (SD) 34.9 (9.5)	NR
	Normal saline (NS) [35]	42.8 (18.8 SD)	25 (71.4%)	5.9 (2.6)	31.7 (14.6)	NR
Morrison (2011)	HTS + dextran (HSD) [50]	46 (21 SD)	(60%)	NR	Mean (SD) 31 [17] 32 [15]	NR
	Normal saline (NS) [56]	43 (21 SD)	(75%)		25.5 (17.5–35)	4.1 (1.0)
Junger (2013)	7.5% hypertonic saline (HTS) [22]	39.1 (17.7 SD)	19 (86.4%)	5.0 [3–7]	29 [17–38]	4.0 (1.2)
	7.5% HTS + 6% dextran (HSD) [22]	37.2 (21.0 SD)	13 (59.1%)	5.5 [3–7]	29 [16–35]	3.8 (1.2)
	Normal saline (NS) [39]	36.2 (19.1 SD)	29 (74.4%)	5.0 [3–7]		
Rowell (2016)	TBI (head AIS $\geq 3$ ) Lactated Ringer's (LR) [52] Normal saline (NS) (256)	45.2 (20.8 SD) 42.8 (18.4 SD)	(65.4%) (71.9%)	NR NR	42 [32–57] 34 [26–43]	5 [4–5] 4 [3–5]

TBI: traumatic brain injury.

(H-)AIS: (head) abbreviated injury scale.

NS: normal saline.

LR: Lactated Ringer's solution.

HTS: hypertonic saline.

HSD: hypertonic saline with dextran.

NR: not reported.

SD: standard deviation.

IQR: interquartile range.

\* Only reported for total cohort, not for subgroup.



**Table 3**  
Quality assessment.

First author (year)	Newcastle Ottawa Scale									Cochrane Risk of Bias Tool							Meta analysis
	1	2	3	4	5	6	7	8	9	A	B	C	D	E	F	G	
Vassar (1991)										Low	Low	Low	High	Low	Unclear	Low	No <sup>1</sup>
Vassar (1993) [29]										Low	Low	Unclear	Low	Low	Unclear	Low	No <sup>1</sup>
Vassar (1993) [30]										High	Low	Unclear	Low	Low	Low	Low	No <sup>1</sup>
Cooper (2004)										Low	Low	Low	Low	Low	Low	Low	Yes
Lenartova (2007)	-	-	*	*	-	-	-	-	-								No <sup>2</sup>
Bulger (2008)										Low	Low	Low	Low	Low	Low	High	No <sup>3</sup>
Baker (2009)										Low	Low	Low	Low	Low	Low	Unclear <sup>4</sup>	Yes
Bulger (2010)										Unclear <sup>5</sup>	Low	Low	Low	Low	Low	Low	Yes
Rhind (2010)										Unclear	Unclear	Low	Low	High <sup>6</sup>	High <sup>6</sup>	Low	Yes <sup>7</sup>
Morrison (2011)										Low	Low	Low	High <sup>8</sup>	High	High	High	Yes <sup>7</sup>
Junger (2013)										Unclear <sup>9</sup>	Low	Low	Low	Low	Unclear	Low	Yes
Rowell (2016)	-	-	*	*	*	*	*	*	-								No <sup>10</sup>

1. No patient characteristics reported of these subgroups.

2. "HTS" vs "no HTS" compared, not stated what "no HTS" is.

3. Survival rates not reported.

4. Not stated if patients were excluded (and why).

5. Labeling issue at onset study, randomization scheme was initially biased toward enrolling more patients into the NS group.

6. Not blinded.

7. High risk of bias, however, we performed a sensitivity analysis by re-performing the meta-analysis and excluding these two RCTs (see meta-analysis).

8. Feasibility study.

9. Nothing stated about randomization, however, groups comparable.

10. LR vs NS, not hypertonic saline.

Newcastle Ottawa Scale:

Selection: 1. Representativeness of the exposed cohort.

2. Selection of the non-exposed cohort.

3. Ascertainment of exposure.

4. Demonstration that outcome of interest was not present at start of study.

Comparability: 5. Comparability of cohorts on the basis of the design or analysis: most important factor.

6. Comparability of cohorts on the basis of the design or analysis: additional factors.

Outcome: 7. Assessment of outcome.

8. Was follow-up long enough for outcomes to occur?

9. Adequacy of follow up of cohorts.

Cochrane Risk of Bias Tool:

A. Random sequence generation.

B. Allocation concealment.

C. Selective outcome reporting.

D. Other sources of bias.

E. Blinding of participants and personnel.

F. Blinding of outcome assessment.

G. Incomplete outcome data.

Cochrane Risk of Bias Tool for the included RCTs revealed varying quality of the included studies. Table 3 shows an overview of the quality assessment.

### Results of individual studies

Our main outcome of interest was survival. Seven studies reported survival at hospital discharge. Four studies reported survival at 28 or 30 days and two studies reported survival at 3 or 6 months. Eleven studies assessing survival found no statistically significant difference in survival between patients treated with different fluid types, such as normal saline and hypertonic saline with or without dextran. One study compared the two crystalloids Lactated Ringer's and normal saline to each other. In that study by Rowell et al. (2016), treatment with Lactated Ringer's was associated with higher 30-day mortality compared with normal saline [39].

Five studies assessed the Extended Glasgow Outcome Score (GOSe). All three studies assessing GOSe as a primary outcome measure did not find a statistically significant difference in patients treated with different fluid types. A total of three studies assessed the Glasgow Outcome Score (GOS), all of which found no statistically significant difference between different fluid types. Table 4 presents the outcome measures of the individual studies.

### Meta-analysis

After excluding lower quality studies (observational studies with a Newcastle Ottawa Score of <6 stars and <2 awarded stars for comparability), 2 meta-analyses were performed. The meta-analysis of 5 studies comparing treatment with hypertonic saline with dextran (HSD) to crystalloid fluids (normal saline in all studies) [34–38] does not show a better survival rate for one specific fluid type (overall RR 0.99, 95% CI 0.93–1.06) (Fig. 2). The meta-analysis of 3 studies comparing hypertonic saline (HTS) with crystalloids (normal saline in two studies and Lactated Ringer's in one study) [31, 35, 38] does also not show a better survival rate for either of the groups (overall RR 1.04, 95% CI 0.97–1.12) (Fig. 3). The sensitivity analysis excluding two randomized controlled trials with high risk of bias provided virtually identical results (data not shown).

### Discussion

#### Summary of evidence

This systematic review and meta-analysis was performed to assess the effect of different prehospital fluid therapies on outcome in patients with severe traumatic brain injury. The included studies did not demonstrate a survival or neurological benefit for one certain fluid type.

**Table 4**  
Outcome measures.

First author (year)	Main outcome	Survival (n (%)), time of assessment (significance)	GOSe (median (IQR)*), time of assessment (significance)	GOS (median (IQR)*), time of assessment (significance)	LOHS (days, median (IQR)* (significance)	Other outcome measures	Author's conclusions
Vassar (1991)	Median systolic blood pressure	HSD: 9 (32%) LR: 4 (16%) At hospital discharge ( <i>p</i> = 0.068)	NR	NR	NR	NR for sTBI subgroup	Tendencies toward improving survival in sTBI
Vassar (1993) [29]	Blood pressure response, survival	LR: 2 (13%) HS: 5 (26%) HSD6%: 2 (14%) HSD12%: 5 (22%) At hospital discharge (not sign.)	NR	NR	NR	NR for sTBI subgroup	No difference in fluid type on survival
Vassar (1993) [30]	NR	NS: 1 (17%) HTS: 3 (38%) HSD: 3 (23%) At hospital discharge (not sign.)	NR	NR	NR	NR for sTBI subgroup	No sign. differences in overall actuarial survival
Cooper (2004)	GOSe $\geq 5$	HTS: 93 (82%) LR: 97 (84%) At hospital arrival ( <i>p</i> = 0.58) HTS: 63 (55%) LR: 57 (50%) At hospital discharge ( <i>p</i> = 0.32) HTS: 63 (55%) LR: 55 (48%) At 3 months ( <i>p</i> = 0.26) HTS: 62 (55%) LR: 53 (47%) At 6 months ( <i>p</i> = 0.23)	HTS: 5 (3–6) LR: 5 (5–6) At 6 months ( <i>p</i> = 0.45) GOSe $\geq 5$ : RR 0.99 (95% CI 0.76–1.30, <i>p</i> = 0.96)	HTS: 4 (3–4) LR: 4 (3–4) At 3 months ( <i>p</i> = 0.64) HTS: 4 (4–4) LR: 4 (3–4) At 6 months ( <i>p</i> = 0.43)	HTS: 12 (0.5–27) LR: 11 (0.5–23) ( <i>p</i> = 0.52)	Days on ventilator: HTS: 3.8 (IQR 0.5–11), LR: 3.0 (0.5–8.1), <i>p</i> = 0.39. First ICP: HTS: 10 (IQR 6–17), LR: 15 (8.5–22), <i>p</i> = 0.08	Small trend toward greater survival for HTS, neurological outcomes almost identical at 6 months
Lenartova (2007)	NR	Mortality HTS: 38.1% No HTS: 31.5% ICU (not sign.) Mortality HTS: 38.1% No HTS: 37.1% At 90 days (not sign.)	NR	NR	NR	O/E ratio: HTS: 0.79 No HTS: 1.02	HTS no benefits, however outcomes better than expected for HTS
Bulger (2008)	Survival without ARDS	NR	NR	NR	NR	NR for sTBI subgroup	No significant advantage of HSD
Baker (2009)	NR	HSD: 25 (80.7%) NS: 29 (87.9%) At hospital discharge (or 30 days) ( <i>p</i> = 0.82)	<i>Mean (SD)</i> HSD: 4.6 (2.3) NS: 4.4 (2.2) At hospital discharge (or 30 days) ( <i>p</i> = 0.86)	<i>Mean (SD)</i> HSD: 3.3 (1.4) NS: 3.3 (1.4) At hospital discharge ( <i>p</i> = 0.87)	<i>Mean (SD)</i> HSD: 14.6 (15.1) NS: 15.2 (16.6) ( <i>p</i> = 0.87)	HSD associated with reduction in serum biomarkers (S100B, NSE, MBP), correlated with better outcome DRS (mean (SD)): HSD: 3.0 (4.3) NS: 3.9 (4.6)	No statistically sign. differences in outcome

(continued on next page)

Table 4 (continued)

First author (year)	Main outcome	Survival (n (%)), time of assessment (significance)	GOS <sub>e</sub> (median (IQR)*), time of assessment (significance)	GOS (median (IQR)*), time of assessment (significance)	LOHS (days, median (IQR)*) (significance)	Other outcome measures	Author's conclusions
Bulger (2010)	GOS <sub>e</sub> at 6 months	HSD: 263 (74.3%) HTS: 255 (75.7%) NS: 432 (75.1%) At 28 days ( $p = 0.88$ ) HSD: 265 (74.4%) HTS: 258 (75.9%) NS: 427 (74.3%) At discharge hospital ( $p = 0.85$ )	HSD: GOS <sub>e</sub> $\leq 4$ : HSD vs NS difference 2.2% HTS: GOS <sub>e</sub> $\leq 4$ : HTS vs NS difference 2.9% At 6 months (HSD vs NS: 95%CI $-4.5$ – $9.0$ , $p = 0.67$ ; HTS vs NS: 95%CI $-4.0$ – $9.7$ , $p = 0.67$ )	NR	NR	DRS: no (sign.) differences between groups	HTD or HTS, compared with NS, did not result in superior 6-month neurologic outcome or survival
Rhind (2010)	Inflammatory/coagulation cascades	Mortality HSD: 4 (13.3%) NS: 6 (17.1%) NR ( $p = 0.67$ )	NR	Mean (SD) HSD: 3.7 (1.3) NS: 3.5 (1.5) At 30 days ( $p = 0.81$ )	Mean (SD) HSD: 14.1 (13.6) NS: 14.7 (12.5) ( $p = 0.90$ )	HSD: role in attenuating pro-inflammatory mediators (such as TNF- $\alpha$ , IL-10)	HSD may improve secondary brain injury by attenuating pro-inflammatory mediators
Morrison (2011)	Survival at 30 days	HSD: 34 (68%) NS: 41 (72%) At discharge hospital (NR) HSD: 35 (70%) NS 42 (74%) At 30 days (NR)	GOS <sub>e</sub> $\geq 4$ HSD: 20 (67%) NS: 26 (68%) At 30 days (NR)	NR	Mean (SD) HSD: 35 (37) NS: 35 (35) (NR)	–	Feasible to conduct a RCT, little evidence to support a trend toward superiority with HSD for survival or neurocognitive outcomes at 30 days
Junger (2013)	GOS <sub>e</sub> at 6 months	HTS: 18 (81.8%) HSD: 15 (68.2%) NS: 28 (71.8%) At 28 days (not sign.)	HTS: 3.5 (2–6) HSD: 3.5 (1–6) NS: 4.0 (1–6) At 6 months (not sign.)	NR	Mean (SD) HTS: 30.8 (22.8) HSD: 21.9 (27.8) NS: 28.7 (29.3) (not sign.)	HTS: makers PMN adhesion and degranulation lower than NS group. HSD/HTS inhibited PMN oxidative burst responses.	HTS can partially restore normal PMN activity, additional research needed for clinical outcome
Rowell (2016)	Mortality at 30 days	Mortality (unadjusted): LR: 50% NS: 28% Adjusted**: HR 1.78 (CI 1.04–3.04) At 30 days $p = 0.035$	NR	NR	NR	Fluid type no effect on biochemical or physiological parameters in both TBI and no-TBI group	TBI group: LR associated with higher adjusted 30-day mortality compared with NS. No difference in no-TBI group.

GOS<sub>e</sub>: extended Glasgow Outcome Score.

GOS: Glasgow Outcome Score.

LOHS: length of hospital stay.

NS: normal saline.

LR: Lactated Ringer's solution.

HTS: hypertonic saline.

HSD: hypertonic saline with dextran.

(s)TBI: severe traumatic brain injury.

ICP: intracranial pressure.

ICU: intensive care unit.

O/E ratio: ratio of observed mortality (at 90 days)/expected mortality predicted by TRISS.

ARDS: acute respiratory distress syndrome.

DRS: disability rating scale.

PMN: polymorphonuclear leukocytes.

NR: not reported.

IQR: interquartile range.

SD: standard deviation.

CI: confidence interval.

HR: hazard ratio.

\* Median (IQR) unless otherwise stated.

\*\* Adjusted for fluid type, fluid volume, ISS, head AIS, extremity AIS, age, prehospital intubation status, hospital site.



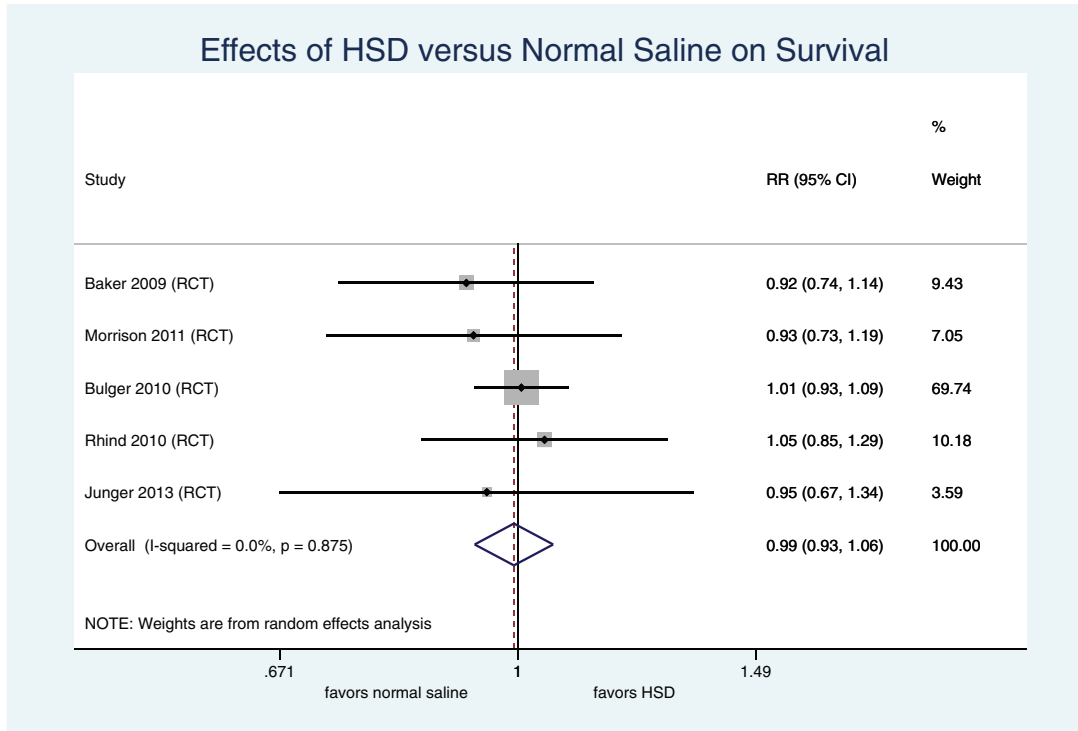


Fig. 2. Meta-analysis.

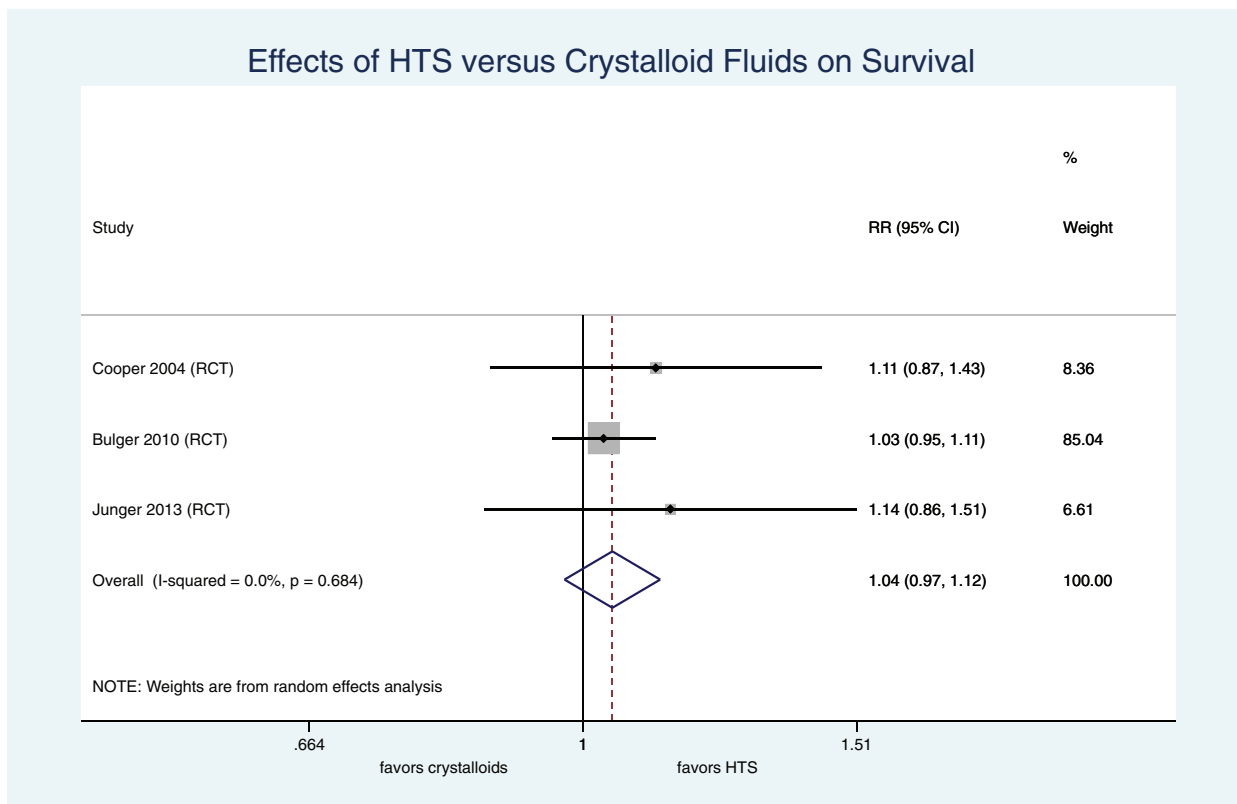


Fig. 3. Meta-analysis.

### Strengths and limitations

This systematic review contains an extensive search strategy in three databases and was performed in accordance with pre-specified guidelines and recommendations of PRISMA [23, 24]. Search strategy, selection of studies, data extraction and quality assessment were double-checked for accuracy.

The quality assessment of the included studies shows varying quality. Only one of the ten RCTs shows low risk of bias in all domains in the Cochrane Risk of Bias Tool. One of the two cohort studies shows low risk of bias through the Newcastle Ottawa Scale. To present a complete overview of all the articles addressing this subject, we included all articles that met our inclusion criteria. However, to limit bias in the quantitative analysis, we performed a sensitivity analysis which excluded lower quality studies.

Due to expected clinical heterogeneity between studies, we had planned a random-effects meta-analysis to account for this heterogeneity. This analysis was performed on a limited number of studies, which can be problematic due to the limited precision in the estimate of the between-study variance, and it has been proposed that a fixed-effect analysis should then be performed instead [40]. However, as the estimated between study variance ( $\tau^2$ ) was 0 in our meta-analysis, the random-effects and fixed-effect meta-analysis give virtually identical results.

Our main outcome of interest was survival, because of its high clinical relevance. Even though most of the studies reported survival, the timing of measurement of survival varied between studies. Seven of the included studies reported survival at hospital discharge. Other studies reported mortality at 30 days, at hospital arrival and at 3 or 6 months. We chose mortality at hospital discharge for meta-analysis (or at 28 days when survival at hospital discharge was not reported) because this was the time point that was being assessed most often. Other outcomes, such as (Extended) Glasgow Outcome Scale, are of great relevance as well. However, we could not perform a meta-analysis of these results, because these outcomes were not consistently reported.

In our systematic review we were also interested in the use of mannitol in the prehospital setting. Only one study assessed the prehospital use of mannitol for TBI [41]. This very small study on 44 patients found no evidence for a difference in mortality between mannitol and normal saline. However, we did not include this study in our systematic review, as this study included patients with a GCS <12, as opposed to GCS <9.

We did not specifically review the quantity of the fluids as a detailed description of the type and quantity of “standard resuscitation fluids”, which were administered in addition to the fluids studied, was often lacking.

### Clinical implications

In the prehospital care of patients with severe traumatic brain injury, a single event of hypotension worsens outcome [15]. Therefore, hypotension should be prevented and optimal cerebral perfusion pressure should be maintained. Fluid resuscitation is regarded as an important therapy in the treatment of patients with TBI in the prehospital setting.

Various types of fluids are available for fluid resuscitation, with different pharmacological characteristics and with specific advantages and disadvantages. Traditionally, normotonic crystalloids are predominantly used in the prehospital setting. However, intravascular volume expansion is limited as only about 20% of the infused volume remains in the intravascular compartment [42]. Moreover, side effects such as edema and hyperchloremic acidosis (for normal saline) or electrolyte imbalances limit the usefulness for volume resuscitation. Hypertonic saline may be advantageous as it causes fluid to shift from the interstitial space to the intravas-

cular space through osmosis, which may result in a decrease of cerebral edema. Moreover, hypertonic saline may have an anti-inflammatory effect which reduces cerebral edema [43]. However, the hyperosmolarity may also lead to pulmonary edema and heart failure as a result of rapid volume expansion. Mannitol, an osmotic diuretic, is not useful for volume resuscitation but is yet regularly used in the prehospital setting to reduce intracranial pressure [44]. However, mannitol raises concerns with regard to its diuretic effect, which may cause hypotension and decrease cerebral perfusion [44-46]. In Emergency Departments and Intensive Care Units, mannitol, as well as hypertonic saline, are widely used to treat intracranial hypertension [45-58]. In the prehospital setting, however, no definitive guidelines regarding the treatment of suspected intracranial hypertension exist. Colloids, such as dextran, albumin or HES, should be effective for prehospital volume resuscitation, as the large molecules and oncotic pressure prevent rapid redistribution to the extravascular compartment, at least when the vasculature is intact. However, potential detrimental effects on coagulation, thrombocyte function or renal function raise concerns and may contribute to morbidity and mortality.

A previous review of Tan et al. published in 2011 found no evidence to support the use of hypertonic saline or colloid solutions over isotonic crystalloid solutions in patients with TBI in the prehospital setting [59]. Tan et al., however, did not perform a meta-analysis and a number of potentially relevant studies have been published in the meantime. We therefore re-evaluated the current evidence and also performed a quantitative data synthesis. Consistent with previous results from Tan et al., our meta-analysis showed no evidence for a higher survival in patients receiving hypertonic saline or hypertonic saline with dextran, when compared to normotonic crystalloids. Moreover, our qualitative analysis of functional outcome did not show evidence for a beneficial effect of any fluid. Hence, current data do not allow a recommendation on which type of fluid should be preferred for volume resuscitation in the prehospital setting for patients with severe TBI. Healthcare providers should thus individually balance the potential advantages and risks for each patient. More research is needed to further assess whether other fluid types, such as mannitol and HES, would confer benefit in this setting.

### Conclusions

For the treatment of patients with severe traumatic brain injury in the prehospital setting, this systematic review did not demonstrate a survival or neurological benefit for one particular fluid type. All but one study compared a hypertonic with an isotonic solution.

### Data availability

All relevant data are within the paper. Data in this systematic review are abstracted from previously published studies, which can be obtained from the respective publishers.

### Declaration of Competing Interest

The authors report no conflict of interest.

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