Hypertonic saline (HTS) versus standard (isotonic) fluid therapy for traumatic brain injuries : a systematic review

Lourens, A. & Botha, JC.

DOI 10.1016/j.afjem.2014.03.003
ISSN 2211-419X

Publisher: Elsevier

African Journal of Emergency Medicine (2014) 4, 188–194

African Federation for Emergency Medicine

African Journal of Emergency Medicine

www.afjem.com
www.sciencedirect.com

CLINICAL REVIEW

Hypertonic saline (HTS) versus standard (isotonic) fluid therapy for traumatic brain injuries: a systematic review

Solution saline hypertonique (HS) ou thérapie de réhydratation (isotonique) standard dans le traitement des traumatismes crâniens: revue systématique

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Received 8 January 2014; revised 21 March 2014; accepted 30 March 2014; available online 9 June 2014

Traumatic Brain Injury (TBI) is one of the foremost causes of mortality secondary to trauma. Poorer outcomes are associated with secondary insults, after the initial brain injury occurred. The management goal of TBI is to prevent or minimise the effects of secondary brain injuries. The primary objective of this systematic review/meta-analysis was to assess the effects of Hypertonic Saline (HTS) compared to Standard Fluid Therapy (SFT) in the treatment and resuscitation of TBI patients. We searched CENTRAL, MEDLINE (from 1966), EBSCOhost, Scopus, ScienceDirect, Proquest Medical Library and EMBASE (from 1980) in May 2010 and updated searches in February 2011. Data were assessed and extracted by two independent authors. Risk ratios (RR) with a 95% confidence interval (CI) were used as the effect measure. The review included three RCTs (1184 participants) of which two were of high to moderate quality (1005 participants). HTS was not found to be associated with a reduction in mortality (3 RCTs, 1184 participants, RR 0.91, 95%CI 0.76 to 1.09) and morbidity in TBI patients. No significant improvement in haemodynamical stability was found whereas insufficient data were available to indicate a reduction in the intracranial pressure (ICP). In the HTS group, cerebral perfusion pressure (CPP) (MD 3.83 mmHg, 95%CI 1.08 to 6.57) and serum sodium level (MD 8 mEq/L, 95%CI 7.47 to 8.53) were higher. Existing studies show no indication that HTS, in comparison to SFT, reduces mortality or morbidity after the occurrence of TBI. Against this backdrop, some uncertainties still exist in terms of the use of different concentrations and volumes of HTS, the timing of administration as well as the benefit in specific injury profiles. As a result, formulating conclusive recommendations is complex.

Les traumatismes crâniens (TC) constituent l'une des causes les plus importantes de mortalité consécutive à un traumatisme. Les échecs thérapeutiques sont associés à des lésions secondaires, suite à la première lésion cérébrale. Le but de la HS en termes de gestion est de prévenir ou de minimiser les effets des lésions cérébrales secondaires. Le principal objectif de cette revue systématique/méta-analyse était d'évaluer les effets de la solution saline hypertonique (HS) par rapport à la thérapie de réhydratation standard (TRS) dans le traitement et la réanimation des patients souffrant de traumatismes cérébraux. Nous avons effectué des recherches dans les bases de données CENTRAL, MEDLINE (à partir de 1966), EBSCOhost, Scopus, ScienceDirect, Proquest Medical Library et EMBASE (à partir de 1980) en mai 2010 et avons mis nos recherches à jour en février 2011. Les données ont été évaluées et extraites par deux auteurs indépendants. Des rapports de risque (RR) avec un intervalle de confiance (IC) à 95% ont été utilisés comme mesure de l'effet. La revue incluait trois ECR (1 184 participants), dont deux étaient de qualité bonne à moyenne (1 005 participants). La revue n'a pas permis de révéler que la HS était associée à une réduction de la mortalité (trois ECR, 1 184 participants, RR 0,91 à un IC à 95% compris entre 0,76 et 1,09) et de la morbidité chez les patients victimes de traumatismes cérébraux. Aucune amélioration significative de la stabilité hémodynamique n'a été notée, et les données permettant d'indiquer une réduction de la pression intracrânienne (PIC) étaient insuffisantes. Dans le groupe HS, la pression de perfusion cérébrale (PPC) (DM 3,83 mmHg, IC à 95% compris entre 1,08 et 6,57) et les taux de sodium sérique (DM 8 mEq/L, IC à 95% compris entre 7,47 et 8,53) étaient plus élevés. Les études existantes n'indiquaient aucunement que la HS, par comparaison à la TRS, permettait de réduire la mortalité ou la morbidité suite à un traumatisme cérébral. Dans un tel contexte, des incertitudes subsistent quant à l'utilisation de différentes concentrations et volumes de HS, au moment de l'administration, ainsi qu'aux bénéfices possibles dans des profils de lésions spécifiques. Par conséquent, la formulation de recommandations conclusives s'avère complexe.

African relevance

- Traumatic Brain Injuries is a public health burden.
- High global and Africa rate of Traumatic Brain Injuries.
- High rate of inter-personal violent, motor vehicle accidents as well as alcohol and drug abuse leading to high rates of TBI in the Southern Africa and African regions.
- Burden of Traumatic Brain Injuries on family units.

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Peer review under responsibility of African Federation for Emergency Medicine.

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Introduction

Traumatic Brain Injury (TBI) is the leading cause of injury-related deaths and disability in children and young adults, worldwide.[1] Nearly 50% of all deaths related to injury are

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http://dx.doi.org/10.1016/j.afjem.2014.03.003

attributed to TBI.[1] TBI is a critical public health problem,[2–5] resulting in substantial burdens to individuals, families and communities.[1,5] Bryan-Hancock and Harrison 2010 estimate the global TBI incidence at 200 per 100,000 people annually. South Africa has an incidence of 1.5 to 3.5 times the global rate.[6] The United States has an annual TBI related death rate of approximately 53,000.[3] Motor vehicle accidents, falls and interpersonal violence are the most common causes.[1,3,7]

Various studies have indicated that TBI is associated with poorer outcomes when aggravated by secondary brain injury,[8] therefore treating TBI requires a multifaceted approach. The initial injury, primary brain injury, occurs as a result of external mechanical forces causing damage to the scalp, cranium and intracranial contents. Secondary brain injury is defined as an additional insult to the brain that occurs hours to days after the initial injury and is particularly detrimental to patient outcomes. It can originate from causes related to intracranial (haematoma, swelling, infection) and extra cranial (hypoglycaemia, hypotension, hyperthermia, hypoxia) factors.[9]

The intervention of interest in this review, Hypertonic Saline (HTS), refers to osmotic solution with a sodium chloride concentration greater than found in normal human physiology. HTS has a variety of clinical effects, but in TBI its administration aims to prevent and/or treat the effects of secondary brain injury.[7]

During hypovolaemic shock, HTS is useful due to its ability to expand the plasma volume by drawing fluids from the extravascular spaces into the intravascular space.[10]HTS prevents, controls and/or decreases intracranial pressure (ICP) through this osmotic effect, drawing fluids from the oedematous brain tissue, which in turn reduce brain volume.[11]Apart from improving haemodynamic status and decreasing ICP, HTS also shows favourable vasoregulatory, immunomodulatory and neurochemical effects.[7,11,12]

The Cochrane review by Bunn 2008 focused on fluid resuscitation with the objective to establish whether HTS decreases the mortality of critically ill patients with hypovolaemia (with and without TBI).[13] It includes 14 RCTs and found insufficient data to make conclusions. As explained HTS may benefit TBI patients, however this remains inconclusive. This review examined the effect of HTS compared to SFT in TBI, irrespective of hypovolaemia and also contains outcomes not considered by Bunn 2008.[13] It adds to existing literature and examined available data in the anticipation to make informed decisions on the treatment of TBI.[7,14] Our objective was to assess the effects of HTS compared to SFT in the treatment and resuscitation of patients with TBI.

Methods

Criteria for considering studies for the review

RCTs of adult and paediatric patients with severe blunt TBI (GCS < 9/15) who received HTS compared to SFT [Ringers Lactate (RL) or Normal Saline (NS)] were included. The primary outcomes were mortality, morbidity and haemodynamic stability. Secondary outcomes were ICP, CPP, adverse events secondary to HTS, serum sodium levels and economical implications of both therapies.

Identification of studies for inclusion

Potentially eligible RCTs were identified by comprehensive searches (Table 1a–c: data supplement, available online) of the following electronic databases (May 2010): Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 1966), EBSCOhost (Academic Search Premier, Africa-wide: NiPAD and Cinahl), Scopus, ScienceDirect, Proquest Medical Library and EMBASE (from 1980). Searches were updated in February 2011 (excluding EMBASE) and not limited by year or language of publication. Reference lists of included RCTs were reviewed for eligible publications and first authors contacted to identify ongoing or unpublished RCTs. Conference and congress proceedings: International Trauma Conference 2009, 4th International Hokkaido Trauma Conference 2010 and 8th World Congress on Trauma, Shock, Inflammation and Sepsis were searched (June 2010) for relevant abstracts. The South African National Trials Registry, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform were searched to identify relevant protocols and ongoing RCTs in June 2010 and updated in Feb 2011.

Selecting eligible studies and data extraction

Following de-duplication, titles were reviewed for relevance. Abstracts of the study titles deemed relevant were reviewed for eligibility using the pre-specified eligibility criteria. Full text reports were retrieved and study eligibility judged by two independent reviewers. Data of included studies were captured independently on a data extraction form. Disagreements were resolved through discussion.

Risk of bias in included studies

The risk of bias within included studies was assessed independently using The Cochrane Collaboration Risk of Bias tool. This tool judges RCTs as high, low or unclear risk of bias in the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete data, selective reporting and other possible sources of bias. Primary authors of included RCTs were contacted to clarify information (Table 3: data supplement, available online).

Data analysis

RevMan 5.1 software (2011) was used to perform meta-analyses. For dichotomous outcomes, RR and 95%CI were calculated and where appropriate, the Mantel–Haenszel method of meta-analysis was used. For continuous outcomes, mean difference (MD) and 95%CI and where appropriate the Inverse Variance method of meta-analysis was used. Heterogeneity was assessed using a Chi^2 test with a P value of 0.10 used for statistical significance and quantified using the I^2 statistic. With no significant evidence of heterogeneity ($I^2 < 40\%$) a fixed-effects model of analysis was used, alternatively a random-effect model was appropriate. When meta-analysis was inappropriate, the results were interpreted and presented without an overall statistic.

If present, and depending on the number of studies included, heterogeneity was to be explored through the

following subgroup analyses: age, haemodynamic stability, concentration of HTS and setting as well as a sensitivity analysis, between the fixed and random-effects models conducted.

Results

Results of the search

The search identified 306 potential titles. Twenty of the identified titles were selected as possibly relevant and full text articles retrieved for eligibility assessment. Of these, fourteen were excluded and three included (Figure 1). The three remaining titles included a duplicate RCT, an additional abstract of included RCTs and a protocol.[15–17]

Included studies

Bulger 2010,[18] is one of two double-blinded RCTs (Table 2) conducted concurrently with the same intervention but two different patient cohorts, hypovolaemic shock and TBI. The TBI cohort received either 7.5% HTS in 6% Dextran-70 250 ml, 7.5% HTS 250 ml and 0.9% NS 250 ml, all administered as a one-time IV bolus in the pre-hospital setting. A total of 1331 participants were randomised however in the HTS/dextran and HTS groups, 14 patients and 21 patients in the NS group did not receive treatment as intended. Three hundred and fifty-nine patients received HTS/dextran (373 randomised), 341 received HTS (355 randomised) and 582 received NS (603 randomised). Data from the HTS/dextran cohort were not included in the meta-analysis. The primary outcome was six month neurologic status based on the Extended Glasgow Outcome Score (GOSE).

Cooper 2004,[15,19] a double-blinded RCT (Table 2), compared 250 ml 7.5% HTS and 250 ml RL. TBI patients with a GCS < 9 and SBP < 100 mmHg were eligible and randomised to receive either of the study fluids in addition to standard intravenous resuscitation. Of 229 patients, 114 received HTS with one patient withdrawing consent, and 115 received RL with two withdrawing consent. Primary outcomes were

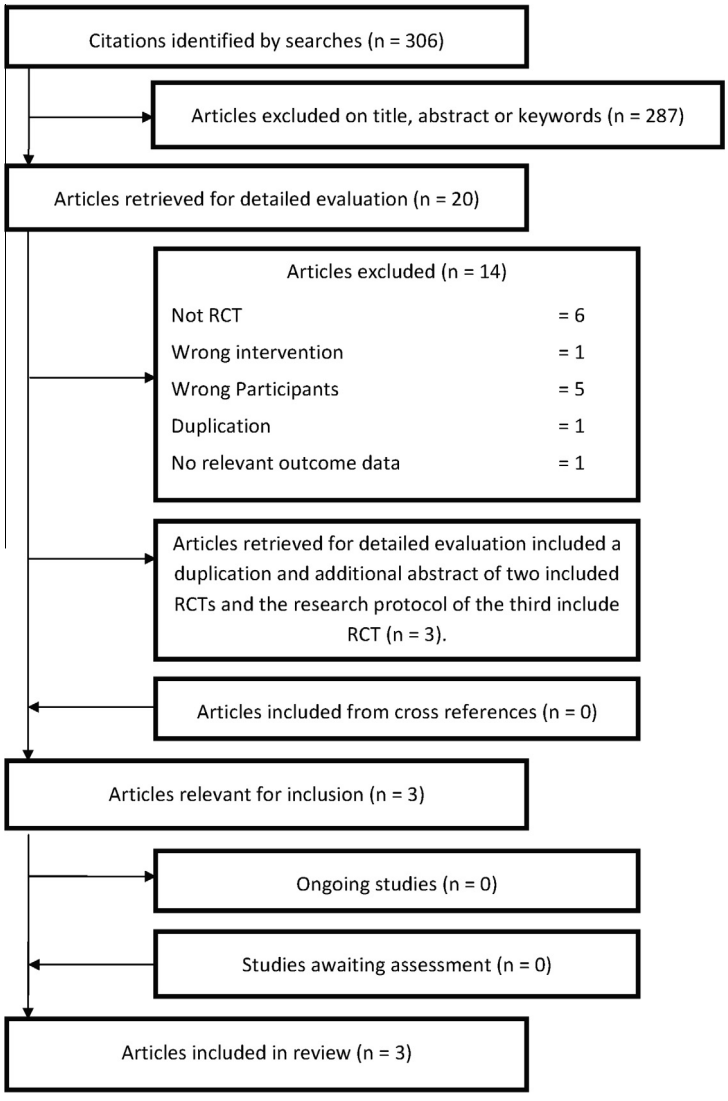

Figure 1 Flow diagram of study selection. RCT, randomised controlled trial.

Table 2 Included studies.

Bulger 2010[18]	*Description*
Methods	Double blind, 3 groups RCT conducted in 114 North American emergency medical services agencies over a 6-month follow-up period
Participants	Patients eligible for the TBI cohort had to be 15 years of age and older, GCS Score of 8 or less, sustained blunt mechanism of injury and ineligibility for enrolment into haemorrhagic shock cohort. The haemorrhagic shock cohort included patients with a systolic blood pressure (SBP) of 70 mmHg or 71 mmHg to 90 mmHg with an associated heart rate of $\geqslant$108 per minute (Total participants: 1331)
Intervention	(1) 7.5% HTS in 6% Dextran-70 250 ml dose given as a one-time IV bolus in the pre-hospital setting (373 participants) (2) 7.5% HTS 250 ml dose given as a one-time IV bolus in the pre-hospital setting (355 participants) (3) Comparator: 0.9% NS 250 ml dose given as a one-time IV bolus in the pre-hospital setting (603 participants)
Outcomes	Primary Outcome Measures: 6 Month Neurologic status based on the GOSE Additional assessments of neurological outcomes: GOSE at discharge and 1 month after discharge and DRS at discharge, 1 month after discharge and 6 months after the injury Secondary Outcome Measures: Survival to discharge, 28 day survival, ICP, interventions required to manage intracranial hypertension, fluid and blood requirements in the first 24 h, physiologic parameters of organ dysfunction, 28 day ARDS-free survival, Multiple Organ Dysfunction Score and Nosocomial infections
Cooper 2004[19]	*Description*
Methods	Double Blinded RCT conducted in Melbourne, Australia over a 6 month follow-up period
Participants	TBI Patients with GCS of $<$9 and SBP of $<$100 mmHg (Total participants: 229) Exclusion criteria: Penetrating trauma, younger than 18 years, were pregnant, had no IV access, had a serious premorbid disease on a medical identification bracelet, had peripheral oedema, were in close proximity to receiving hospital (scoop and run), had absent sinus rhythm, or cardiac arrest
Intervention	(1) 250 ml of 7.5% HTS (114 participants) (2) 250 ml of RL solution (115 participants) as a rapid once off infusion in addition to standard IV resuscitation fluids
Outcomes	Primary outcomes – Functional neurological outcomes – survival to hospital discharge, survival at 3 and 6 months, GOS and GOSE score at 3 and 6 months Secondary outcomes: First ICP and CPP, Duration of elevated ICP and inadequate CPP, worst oxygenation (lowest PaO2 / FiO2 ratio) and duration of inotropic support and mechanical ventilation. Functional independence measure (measure physical and cognitive independence) and Rancho Los Amigos score (Measure cognitive function)
Simma 1998[20]	*Description*
Methods	RCT conducted in Zurich, Switzerland followed up until hospital discharge
Participants	Consecutive children (younger than 16 years) with severe traumatic brain injuries (GCS $<$ 8/15) admitted to ICU of the children's Hospital of Zurich (Total participant: 32)
Intervention	(1) HTS (sodium 268 mmol/L, 598 mOsm/L) (15 participants) (2) RL solution over 72 h period (17 participants)
Outcomes	Primary Outcomes: (1) Correlation between ICP and Serum sodium concentration for both groups. (2) Correlation between CPP and serum sodium concentration for both groups Secondary Outcomes: (1) Number of interventions to keep ICP within normal limits (2) Additional changes in fluid volumes (3) Clinical outcome variables (Days in ICU, Days of mechanical ventilation, survival rate and number of patients with predefined complications)

functional neurological outcomes in terms of survival to hospital discharge, survival at three and six months, GOS and GOSE score at three and six months.

Simma 1998,[16,20] a RCT of consecutive children with severe TBI, admitted to ICU (Table 2). Of the 32 participants, seventeen were randomised to receive RL and fifteen to receive HTS over a 72-h period. The primary outcomes aimed to correlate, ICP and serum sodium concentration as well as CPP and serum sodium concentration for both groups.

Risk of bias of included studies

Allocation sequence generation was adequate in two RCTs and unclear in the third.[18–20] Cooper 2004 incorporated block randomisation stratified by ambulance and hospital.[19] Bulger 2010 used a randomly generated numeric code. Simma 1998 omitted to clarify the sequence generation, merely stated that randomisation occurred.[20]

Allocation concealment and blinding were adequate for two RCTs,[18,19] whereas allocation concealment was not reported and blinding impossible in the third.[20] The RCTs incorporating blinding used identical intravenous bags, and paramedics, clinicians, patients and the study coordinator were blinded to treatment allocation.[18,19]

Bulger 2010 addressed missing data for the primary outcome six-month neurologic outcome through multiple hot deck imputations.[18] Cooper 2004 had same missing data, but it appeared to be consistent across the two groups and modified intention-to-treat analyses were conducted.[19] Simma 1998 had no missing data.[20]

Bulger 2010 is free from selective reporting, due to the fact that pre-specified outcomes in the study protocol were reported.[17] The study protocols of Cooper 2004 and Simma 1998 were not available.[19,20] Bulger 2010 was stopped in 2009 by the Data and Safety Monitoring Board, because the futility boundary was crossed.[18] The remaining RCTs seemed to be free from other sources of bias.[19,20]

Primary outcomes of interventions

A meta-analysis was conducted for mortality at hospital discharge however the comparison (3 RCTs; 1184 patients; RR 0.91, 95%CI 0.76 to 1.09) (Figure 2) presented no statistically significant difference. No heterogeneity ($Chi^2 = 0.96$, $P = 0.62$; $I^2 = 0\%$) was found and the fixed effect model was used. In addition, RCT by Cooper 2004 (229 patients) reported no statistically significant difference between mortality at three months (RR 0.87, 95%CI 0.67 to 1.14) and six months (RR 0.72, 95%CI 0.43 to 1.21).[19]

For the meta-analysis of mean initial GCS no statistically significant difference was found (2 RCTs; 955 patients; MD −0.12, 95%CI −0.40 to 0.20; $Chi^2 = 0.13$, $P = 0.72$; $I^2 = 0\%$) between the two groups. In addition, Cooper 2004 presented a median initial GCS of 4 and interquartile range (IQR) of 3 to 7 for both groups and concluded no statistically significant difference in the median and IQR for the GOSE for each group at three months ($p = 0.65$) and six months ($p = 0.45$).[19] The study further found no statistically significant difference between the two groups for the Rancho Los Amigos score and Functional independence score at three and six months. Bulger 2010 presented no statistically significant mean difference for 6 months GOSE $\leqslant 4$ for the HTS and NS group for the completer (MD 2.3, 95%CI −4.9 to 9.4) and imputed analysis (MD 2.9, 95%CI −4.0 to 9.7).[18] The DRS at discharge presented no statistically significant difference ($p = 0.84$) between the two groups.

Simma 1998 presented no SBP data before and after the administration of the two interventions.[20] Cooper 2004 presented a pre-enrolment median SBP of 80 mmHg and IQR of 38–90 mmHg for the HTS group (114 patients) and median SBP of 70 mmHg and IQR of 0–85 mmHg for the control group (115 patients).[19] The median SBP and IQR upon admission were 120 mmHg and 90–140 mmHg for the HTS group (109 patients) and 115 mmHg and 90–135 mmHg for the control group (107 patients). Bulger 2010 presented no SBP data before administration however the mean and standard deviation (SD) of SBP upon hospital admission were reported as 136.9 mmHg (mean) and 33.5 mmHg (SD) for the HTS group (341 patients).[18] The control group (582 patients) had a mean SBP of 139.1 mmHg and SD of 33.1 mmHg. No statistically significant difference between the mean SBP was found (1 RCT; 923 patients; MD −2.20 mmHg, 95%CI −6.66 to 2.26).

RCTs included no data on MAP. Bulger 2010 and Simma 1998 presented no data on pulse rates.[18,20] Cooper 2004 presented pre-enrolment mean pulse rate and SD of 100 BPM (beats per minute) and 33 BPM for the HTS group (108 patients). The mean pulse rate and SD of the control group (113 patients) were 100 BPM and 35 BPM, respectively.

Secondary outcomes of interventions

In Bulger 2010,[18] the ICP mean difference as measured after hospital admission was not statistically significant (248 patients; MD −3.50, 95%CI −7.04 to 0.04). Cooper 2004 reported the median and IQR of ICP for the two groups after admission to the ICU. The HTS group (37 patients) showed a median of 10 mmHg and IQR of 6–17 mmHg, whereas the control group (49 patients) had a median of 15 mmHg and IQR of 8.5–22 mmHg.[19] The study by Simma 1998 reported an inverse correlation between serum sodium and mean ICP in both the HTS group (15 patients, $r = -0.29$, $r^2 = 0.08$, $p < 0.001$) and the control group (17 patients, $r = -0.13$, $r^2 = 0.02$, $p < 0.03$).[20]However, there were no statistically significant differences in mean ICP and serum sodium between the two groups.

The meta-analysis for mean difference of CCP concluded a statistically significant difference (2 RCTs; 1005 patients; MD 3.83 mmHg, 95%CI 1.08 to 6.57) (Figure 3) indicating a lower CPP in the SFT group. No heterogeneity was found between studies ($Chi^2 = 0.00$, $P = 0.96$; $I^2 = 0\%$) and as a result a fixed-effect model was used. In addition, the study by Simma 1998 reported a statistically significant correlation between serum sodium and mean CPP in the HTS group (15 patients, $r = 0.2$, $r^2 = 0.04$, p 0.002), whereas the correlation for the control group was not statistically significant (17 patients, $r = -0.09$, $r^2 = 0.008$, NS).[20] Overall, there were no statistically significant differences in the correlation of serum sodium and CPP between the two groups.

Simma 1998,[20] reported no statistically significant difference ($p = 0.09$, Fisher's exact test) between the two groups for two or more complications (Table 4: data supplement, available online). However, there was a statistically significant difference in the development of Adult Respiratory Distress Syndrome (ARDS) between the two groups ($p = 0.01$, Fisher's exact test). Bulger 2010 reported a higher rate of nosocomial infections in the HTS group which they related to the higher rate of bloodstream and urinary tract infection.[18] The study concluded that there was no statistically significant difference in the adverse events between the groups (Table 4: data supplement, available online). Cooper 2004 presented no adverse event data.[19]

The meta-analysis for serum sodium levels concluded a statistically significant difference between the two groups (2 RCTs; 1125 patients; MD 8 mEq/L, 95%CI 7.47 to 8.53; $Chi^2 = 0.00$, $P = 1.00$; $I^2 = 0\%$) (Figure 4), indicating lower serum sodium levels for the SFT group. No heterogeneity was found between studies ($Chi^2 = 0.00$, $P = 1.00$; $I^2 = 0\%$) and as a result a fixed-effect model was used. RCTs included no data on financial implications of both therapies. No subgroup or sensitivity analyses were required as the heterogeneity (I^2) was 0% in all meta-analyses.

Discussion

This review included three RCTs (1184 patients) conducted in North America, Australia and Switzerland between 1992 and 2009. The administration of HTS in comparison to SFT for patients with TBI does not reduce mortality at hospital discharge (RR 0.91, 95%CI 0.76 to 1.09). Furthermore, HTS does not appear to reduce morbidity in terms of improving neurological status after TBI. There were no clear difference between HTS and SFT in terms of improving haemodynamical stability and insufficient data to indicate if ICP were considerably different. However, TBI patients receiving HTS had a higher CPP (MD 3.83 mmHg, 95%CI 1.08 to 6.57) and higher serum sodium levels (MD 8 mEq/L, 95%CI 7.47 to 8.53) than patients receiving SFT. Evidence suggests that low CPP is potentially detrimental to TBI patients however the most favourable CPP is less apparent. Cerebral auto-regulation may be disturbed by TBI and in order to avoid secondary

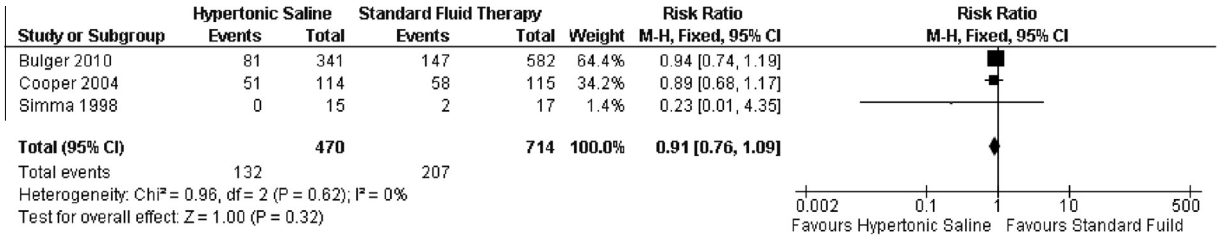

Figure 2 Forest plot – Mortality (at hospital discharge).

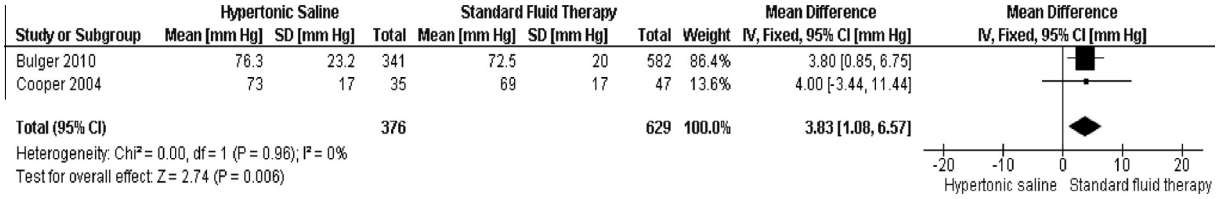

Figure 3 Forest plot – CPP, cerebral perfusion pressure (mmHg).

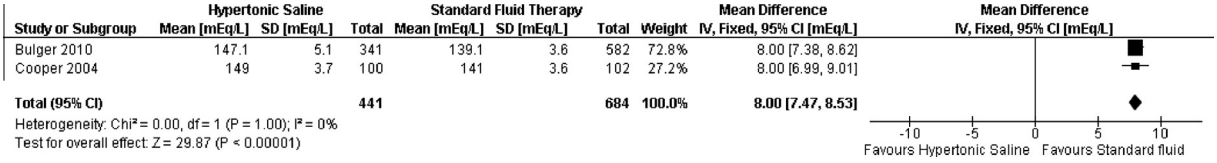

Figure 4 Forest plot – serum sodium level – admission (mEqL).

brain injury the maintenance of CPP is imperative.[21,22] A recent study conducted in 2012 concluded that hypernatremia in TBI patients admitted to Neurosurgical Intensive Care Units increases the odds of death.[23]

All RCTs in the review reported mortality or survival rate. The reporting of morbidity varied due to the use of different measurement tools amongst trials, and incomplete data on the restoration of haemodynamical stability. Data on secondary outcomes were more complete. Two RCTs presented data on adverse events,[18,20] both indicate no difference between treatment groups. No economic data were reported. Included RCTs did not assess different concentrations, volumes or time of HTS administration and therefore limiting the overall applicability of the findings. Although three RCTs were included in the review the majority of the data (97%) originated from the two high to moderate quality studies.[18,19]

In order to avoid publication bias, a comprehensive search of various databases, trial registries and conference proceedings was conducted, without language or publication time restrictions. Authors of included studies were contacted to identify ongoing or unpublished studies. Study selection and data extraction were done independently to avoid selection bias. The number of included studies was insufficient to assess publication bias with a funnel plot.

HTS has long been proposed to be beneficial in the management of TBI secondary to a variety of mechanisms of effect.[12,14] The basis for this data was from small observational studies or case reports.[14] The review by Bunn 2008 included two of the three RCTs included in this review.[13,19,20] The objective was to establish whether HTS decreases mortality in patients with hypovolaemia with and without head injuries. The review included trauma, surgery and burns patients. Although, the review details the possible benefits of HTS in TBI, the authors only conducted a meta-analysis on trauma with hypovolaemia, which showed no statistically significant difference in mortality. The analysis of poor outcomes in terms of GCS incorporated one RCT demonstrating no difference between the interventions.[19] Bunn 2008 mentioned the potential benefit of HTS in TBI but pointed to a lack of sufficient data to examine this benefit. The review included Cooper 2004 and Simma 1998,[13,19,20] however stated in discussion that only one small trial examined the effect of HTS amongst TBI patients.[20] The reason for not including Cooper 2004 to the TBI data was not provided.[19] Similar to Bunn 2008, the current review identifies a deficiency of sound evidence to support the use of HTS compared to SFT and indicates a need for further research.

The lack of evidence to indicate that HTS compared to SFT improve mortality and morbidity in TBI patient suggest that in low resource setting where HTS is not readily available or too costly, using SFT will not be significantly detrimental.

Conclusion

Existing research does not indicate that HTS contributes to a reduction in mortality or improve neurological outcomes following TBI. Nevertheless, the use of different concentrations, volumes and bolus versus continuous infusion of HTS as well as the timing of administration may present some clinical

significance. In addition, HTS may have some clinical importance in specific injury profiles.

These uncertainties make formulating irrefutable recommendations related to the use of HTS in TBI problematic and identify the areas lacking high quality data in need of further research. Research aimed to clarify these gaps in the knowledge may also be difficult to justify, as considerable patient cohorts may be required to recognise potentially small treatment effects.

Author contribution

Andrit Lourens Contribution: Conceiving, designing and coordinating the review, Designing search strategies and undertaking searches, Screening search results, Screening retrieved papers against eligibility criteria and extracting data, Data collection for the review, Writing to authors of papers for additional information, Providing additional data about papers, obtaining and screening data on unpublished studies, Data management for the review, entering data into RevMan, Analysis and interpreting of data, Writing the review.

Johanna Catharina Botha Contribution: Screening search results, Screening retrieved papers against eligibility criteria and extracting data, data collection for the review.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

Thanks to Dr. Taryn Young for assistance with the methodological soundness and scientific writing and Dr. Heinrich Lamprecht for clinical assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.afjem.2014.03.003.

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