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REPORTS OF ORIGINAL INVESTIGATIONS

The effect of continuous hypertonic saline infusion and hypernatremia on mortality in patients with severe traumatic brain injury: a retrospective cohort study

Effet d'une perfusion saline hypertonique continue et de l'hypernatrémie sur la mortalité de patients souffrant d'un traumatisme cérébral grave: une étude de cohorte rétrospective

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Abstract

Purpose *Hypertonic saline (HTS) is used to control intracranial pressure (ICP) in patients with traumatic brain injury (TBI); however, in prior studies, the resultant hypernatremia has been associated with increased mortality. We aimed to study the effect of HTS on ICP and mortality in patients with severe TBI.*

Methods *We performed a retrospective cohort study of 231 patients with severe TBI (Glasgow Coma Scale [GCS] ≤ 8) admitted to two neurotrauma units from 2006-2012. We recorded daily HTS, ICP, and serum sodium (Na) concentration. We used Cox proportional regression modelling for hospital mortality and incorporated the following time-dependent variables: use of HTS, hypernatremia, and desmopressin administration.*

Results *The mean [standard deviation (SD)] age of patients was 34 (17) and the median (interquartile range [IQR]) GCS was 6 [3-8]. Hypertonic saline was administered as a continuous infusion in 124 of 231 (54%) patients over 788 of 2,968 (27%) patient-days. Hypernatremia (Na > 145 mmol·L^{-1}) developed in 151 of 231 (65%) patients over 717 of 2,968 (24%) patients-days. In patients who developed hypernatremia, the median [IQR] Na was 146 [142-147] mmol·L^{-1}. Overall hospital mortality was 26% (59 of 231 patients). After adjusting for baseline covariates, neither HTS (hazard ratio [HR], 1.07; 95% confidence interval [CI], 0.56 to 2.05; P = 0.84) nor hypernatremia (HR, 1.31; 95% CI, 0.68 to 2.55; P = 0.42) was associated with hospital mortality. There was no effect modification by either HTS or hypernatremia on each another. Patients who received HTS observed a significant decrease in ICP during their ICU stay compared with those who did not receive HTS (4 mmHg; 95% CI, 2 to 6; P < 0.001 vs 2 mmHg; 95% CI, −1 to 5; P = 0.14).*

Conclusions *Hypertonic saline and hypernatremia are not associated with hospital mortality in patients with severe TBI.*

Résumé

Objectif *Une solution saline hypertonique (HTS) est utilisée pour contrôler la pression intracrânienne (PIC) chez les patients ayant subi un traumatisme cérébral (TC); toutefois, dans des études précédentes, l'hypernatrémie*

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découlant de ce traitement a été associée à une augmentation de la mortalité. Notre objectif était d'étudier l'effet de la HTS sur la PIC et la mortalité de patients souffrant d'un TC grave.

Méthode *Nous avons réalisé une étude de cohorte rétrospective portant sur 231 patients souffrant d'un TC grave (Échelle de coma de Glasgow [GCS] ≤ 8) admis dans deux unités de neurotrauma entre 2006 et 2012. Nous avons enregistré les données quotidiennes de HTS, de PIC et de concentration de sodium (Na) sérique. Nous avons utilisé des modèles de régression proportionnelle de Cox pour mesurer la mortalité hospitalière et incorporé les variables en fonction du temps suivantes : utilisation de HTS, hypernatrémie et administration de desmopressine.*

Résultats *L'âge [écart type (ÉT)] moyen des patients était de 34 (17) ans et le score médian sur le GCS (écart interquartile [ÉIQ]) était de 6 [3-8]. La solution saline hypertonique a été administrée sous forme de perfusion continue chez 124 patients sur 231 (54 %) au cours de 788 jours-patient sur 2968 (27 %). Une hypernatrémie (Na > 145 mmol·L^{-1}) est apparue chez 151 patients sur 231 (65 %) au cours de 717 jours-patient sur 2968 (24 %). Chez les patients ayant manifesté une hypernatrémie, le niveau médian [ÉIQ] de Na était de 146 [142-147] mmol·L^{-1}. La mortalité hospitalière globale était de 26 % (59 des 231 patients). Après ajustement pour tenir compte des covariables de base, ni la HTS (rapport de risque [RR], 1,07; intervalle de confiance [IC] 95 %, 0,56 à 2,05; P = 0,84) ni l'hypernatrémie (RR, 1,31; IC 95 %, 0,68 à 2,55; P = 0,42) n'ont montré d'association avec la mortalité hospitalière. Il n'y a eu aucune indication que la HTS modifie l'effet sur l'hypernatrémie ou vice versa. Les patients ayant reçu une HTS ont observé une réduction significative de leur PIC pendant leur séjour aux soins intensifs comparativement à ceux n'en ayant pas reçu (4 mmHg; IC 95 %, 2 à 6; P < 0,001 vs 2 mmHg; IC 95 %, −1 à 5; P = 0,14).*

Conclusion *La solution saline hypertonique et l'hypernatrémie ne sont pas associées à la mortalité hospitalière chez les patients souffrant de TC grave.*

Cerebral edema is common following traumatic brain injury (TBI) and occurs from a variety of mechanisms, including disruption of endothelial tight junctions of the blood-brain barrier, increased permeability to serum sodium (Na) and potassium (K), parenchymal uptake of osmotically active solutes, energy depletion following sodium-potassium adenosine triphosphatase (Na/K-ATPase) failure, and cerebral ischemia.[1,2] When intracranial compliance is limited, any increase in volume (e.g., cerebral edema or contusion) can lead to a precipitous rise in intracranial pressure (ICP), resulting in impaired cerebral blood flow and secondary ischemia.[1,3] The duration and magnitude of elevated ICP consistently portends worse neurologic outcomes following TBI.[4-6] As such, treatment of elevated ICP remains a cornerstone in the management of severe TBI, with the Brain Trauma Foundation recommending keeping ICP below 20 mmHg.[7]

Clinicians use osmotherapy (hypertonic saline or mannitol) to help lower ICP. Owing to its high osmolarity, intravenous administration of hypertonic saline (HTS) leads to egress of water from the brain interstitium to the intravascular space, thereby reducing cerebral edema and lowering ICP.[8,9] When administered as an intravenous bolus, HTS reduces ICP by 25-45%[10,11] and augments brain tissue oxygen delivery.[12,13] Alternatively, HTS may be administered as a continuous infusion, targeting hypernatremia, to achieve long-term control of ICP.[14,15] Nevertheless, sustained hypernatremia may be deleterious by exacerbating cerebral edema, particularly in areas where the blood-brain barrier is disrupted.[16] Furthermore, hypernatremia itself is a known risk factor for mortality in critically ill patients,[17,18] including those with TBI.[12,19,20] Commentators have expressed concerns regarding the use of HTS as a continuous infusion citing the lack of clinical evidence and the potential for harm.[21-23] Overall, there appears to be conflicting data concerning the use of HTS, with physiologic studies showing benefit and clinical studies suggesting harm. Given this equipoise, we performed a retrospective cohort study in patients with severe TBI to examine the association between a continuous HTS infusion strategy to maintain hypernatremia in TBI patients and hospital mortality.

Methods

We performed a two-centre retrospective cohort study in keeping with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[24] The University of British Columbia and hospital clinical research ethics boards approved the protocol and waived the requirement for written informed consent (H12-02502).

Study population and hospitals

We defined our cohort as all patients admitted to the intensive care units (ICU) at Vancouver General Hospital (31 beds) and Royal Columbian Hospital (16 beds) during April 2006 to May 2012 with a diagnosis of severe TBI, as defined by a post-resuscitation Glasgow Coma Score (GCS) of ≤ 8, and with ICP monitoring.

Affiliated with the University of British Columbia, both ICUs are closed mixed medical-surgical ICUs that run on an approximate 1:1.2 nurse-to-patient ratio. Both units are

staffed by fellowship-trained subspecialty critical care medicine consultants with specialty residents and house staff in attendance.

Data collection

Data were recorded in an electronic database using Microsoft Access 2013® and subsequently exported to Microsoft Excel 2013® (Redmond, WA, USA). Demographic data consisted of age, sex, and injury details (date, time, and location). We also collected the following baseline data: pupillary abnormalities, pre-hospital hypoxia ($SpO_2 < 92\%$) or hypotension (systolic blood pressure < 90 mmHg), mechanism of injury, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Rotterdam computed tomography (CT) head score.[25] The following daily ICU management data were collected: medication use (desmopressin, vasopressors, neuromuscular blockers, barbiturates), volume (total millilitres) of intravenous fluids per day (crystalloids, colloids, red blood cells, and mannitol), 8 AM ICP, 8 AM GCS, 8 AM mean arterial pressure, presence of external ventricular drain, and use of therapeutic hypothermia. Data on surgical procedures (type, date) were also collected. We collected total volume and percentage of HTS administered each day. We also collected daily Na values. We obtained the following outcome data from the ICU database: intensive care and hospital days, duration (in days) of mechanical ventilation, and both intensive care and hospital mortality.

Traumatic brain injury management

Both hospitals use TBI management protocols based on the Brain Trauma Foundation Guidelines.[7] The head-of-bed elevation is maintained at $\geq 30°$, and all ICP monitoring is performed using external ventricular drains (EVDs) (Medtronic, Inc. Minneapolis, MN, USA). If the ICP increases to > 20 mmHg for more than five minutes, the EVD is opened to allow drainage of cerebrospinal fluid. Three percent HTS is administered as a continuous infusion at both sites, whereas administration of HTS as bolus therapy is not standard practice. Osmolar therapy, therapeutic hypothermia, neuromuscular blocking drugs, and barbiturates are used at the discretion of the attending physician.

Statistical analysis

All analyses, including plots, were done in R (R Project for Statistical Computing, http://www.r-project.org). All reported *P* values were two-tailed and a complete case analysis was performed. Descriptions of normally distributed data, non-normally distributed data, and categorical data were stratified by HTS use and performed using mean (standard deviation [SD]), median (interquartile range [IQR]), and proportion (percent), respectively. Normality of data was assessed using the Shapiro-Wilk test. Univariable comparisons of continuous variables were performed using Student's *t* tests for normally distributed data and Mann-Whitney U test for non-normally distributed data where appropriate. The sample size was one of convenience and designed to ensure stability around our point estimates of a multivariable model. Assuming an expected mortality of 20-25%[26] and approximately seven to eight events per covariate[27] with a final model of approximately eight covariates, a sample size of approximately 250 patients would be required. The degree of missing data is presented when applicable.

Generation of time-dependent variables and extrapolation of data

The HTS infusion was modelled as a time-dependent indicator variable. To avoid the possibility that HTS administration might be interpreted as a marker of TBI severity rather than as a predictor of mortality, the coding of the variable was changed from 0 to 1 starting from the day on which HTS was first administered. The use of desmopressin was also expressed as a time-varying variable and coded in a similar manner. The presence of hypernatremia on each day was also modelled as a time-dependent indicator variable. Daily hypernatremia was defined as daily Na >145 mmol·L^{-1}. The daily Na level is a single daily determination that was measured at 8 AM every day during the14-day ICU period. The daily use of HTS and desmopressin as well as daily Na levels were measured and recorded only during the first 14-day ICU period. The status of these variables were not known after discharge from the ICU. To account for these variables beyond this period, we extrapolated the data such that the subsequent values for these variables took on those of the final day of the ICU period. Multicollinearity was assessed by calculating the variance inflation factor for all predictor variables in the final multivariable model. All variables had a variance inflation factor below 2, indicating an absence of multicollinearity.

Survival analysis

For all survival analyses, hospital mortality was the main outcome. Using univariable and multivariable Cox proportional-hazard regression models, we explored the relationship between HTS and hospital mortality. To account for baseline risk of death, known determinants of

outcome in patients with TBI were selected *a priori* to be included as covariates in the eventual multivariable model. These included age, Rotterdam CT score (interval continuous variable), APACHE II score, abnormal pupil reactivity (one or both eyes), admission motor GCS, admission hypotension (systolic blood pressure < 90 mmHg), and site of admission. The use of desmopressin was also included as a time-varying covariate to adjust for potential confounding due to diabetes insipidus, which may be associated with a higher risk of death. Censoring was done at the time of discharge for patients who did not experience death during the hospital stay.

Linearity of continuous variables was tested using residual-based plots. Deviations from proportional assumptions were examined using the method proposed by Grambsch and Therneau, which is based on Schoenfeld residuals. The Efron method was used to handle tied failures. The *P* values, profile likelihood for point estimates, and 95% confidence intervals (CI) were calculated using the likelihood ratio test.

To assess the association between HTS-induced hypernatremia and hospital mortality, we examined whether the association between HTS and mortality was modified by hypernatremia and whether the association between hypernatremia and mortality was altered by HTS. In two separate analyses, HTS and hypernatremia were chosen as stratum variables, and a stratified Cox proportional-hazard model with an interaction between HTS and hypernatremia was fitted in each instance.

Relationship between HTS and ICP

To explore the relationship between HTS and ICP, linear mixed models (with patients included as a random effect) adjusted for baseline risk of death were constructed for both HTS and non-HTS groups. The within-subject (random effects) and between-subject (fixed effects) relationships between HTS use and ICP were determined by maximizing the restricted maximum likelihood. The Wald test was used to assess the overall change in ICP over the first 14-day ICU period for the two groups.

Results

The initial database search revealed 250 patients. Nineteen patients who sustained a penetrating TBI were excluded, leaving 231 patients included in the final analysis. The baseline characteristics of the cohort are summarized in Table 1. The majority of the patients were male (78%), the mean (SD) age was 34 (17) yr, and the median [IQR] total GCS at admission was 6 [3-8]. The clinical interventions and outcomes for the study population are presented in Table 2.

Hypernatremia and HTS use during the ICU period

Hypernatremia developed in 151 of 231 (65%) patients over 717 of 2,968 (24%) patients-days. In patients who developed hypernatremia, the median [IQR] Na was 146 [42-147] $mmol \cdot L^{-1}$. Hypertonic saline was used in 124 of 231 (54%) patients at least once over 788 of 2,968 (27%) patient-days. Hypertonic saline was used for a median [IQR] of 13 [10-13] days. Figure 1 displays the raw data regarding the daily Na recorded during the patients' ICU period and the use of HTS. There was a significant association between HTS use and hypernatremia, with 82% of patients who received HTS developing hypernatremia compared with 46% of patients who did not receive HTS. Desmopressin was administered in 33 of 231 (14%) patients over 261 of 2,968 (9%) patient-days.

Effect of HTS on ICP

Figure 2 shows the result from mixed-model analyses, which examined the effect of HTS on ICP over the 14-day ICU period. Patients who received HTS had a higher admission ICP than patients who did not. Over the course of the 14-day ICU period, patients who received HTS experienced a significant decrease in ICP (estimated ICP decrease from mixed-model analysis, 4 mmHg; 95% CI, 2 to 6; $P < 0.001$). There was no reduction in ICP in those patients who did not receive HTS (estimated ICP decrease, 2; 95% CI, -1 to 5; $P = 0.14$).

Relationship between hypernatremia, HTS use, and hospital mortality

The results of the Cox regression analyses are summarized in Table 3. The unadjusted univariable analyses show that the association between HTS use and hospital death was not statistically significant (hazard ratio (HR), 1.09; 95% CI, 0.62 to 1.91; $P = 0.76$). In the multivariable analyses, the adjustment for baseline risks, hypernatremia, and use of desmopressin decreased the estimated relative increase in mortality with use of HTS, but the association remained insignificant (HR, 1.07; 95% CI, 0.56 to 2.05; $P = 0.84$). Hypernatremia was not associated with a statistically significant increase in hospital mortality even after adjusting for baseline risks, HTS, and desmopressin (HR, 1.31; 95% CI, 0.68 to 2.55; $P = 0.42$). Use of desmopressin was associated with an increased rate of hospital mortality (HR, 4.27; 95% CI, 2.00 to 9.11; $P < 0.001$) in the final multivariable model. Finally, we wanted to determine if hypernatremia with the use of HTS was associated with mortality (in contrast to hypernatremia that occurred without the use of HTS). Multivariable stratified Cox regression, which included hypernatremia status as a

Table 1 Baseline characteristics of cohort

	Total Cohort (n = 231)	HTS (n = 124)	No HTS (n = 107)	P value (HTS *vs* no HTS)
Age in yr, mean (SD)	34 (17)	31 (14)	40 (19)	<0.001
Female sex, n (%)	50 (22)	25 (20)	25 (23)	0.69
Median APACHE II [IQR]	19 [12-23]	18 [11-23]	19 [13.5-23]	0.35
Admission hypotension, n (%)	41 (18)	20 (16)	21 (20)	0.60
Admission hypoxemia, n (%)	29 (13)	16 (13)	13 (12)	0.99
Glasgow Coma Scale				
Median total score [IQR]	6 [3-8]	5 [3-8.25]	6 [4-8]	0.44
Median motor score [IQR]	3 [1-5]	3 [1-5]	4 [1-5]	0.65
At least 1 pupil non-reactive, n (%)	103 (45)	50 (40)	53 (50)	0.20
Mechanism of injury, n (%)				
Motor vehicle or motorcycle accident	82 (35)	40 (32)	42 (39)	0.83
Accidental fall	70 (30)	40 (32)	30 (28)	0.23
Pedestrian or cyclist struck	50 (22)	29 (23)	21 (20)	0.26
Other	24 (10)	12 (10)	12 (11)	0.99
Missing	5 (2)	3 (2)	2 (2)	0.65
Rotterdam score, median [IQR]	3 [2-4]	3 [3-4]	3 [2-4]	0.11
First ICP measured, median [IQR]	12 [6-17]	13 [9-20]	10 [4-15]	0.03
First serum sodium, median [IQR]	139 [138-142]	139 [138-142]	140 [137-142]	0.66
Hospital A, n (%)	126 (55)	61 (49)	65 (61)	0.08
Hospital B, n (%)	105 (45)	63 (51)	42 (39)	0.10

APACHE = Acute Physiology and Chronic Health Evaluation; HTS = hypertonic saline; ICP = intracranial pressure; IQR = interquartile range; SD = standard deviation

Table 2 Clinical interventions and outcomes stratified by HTS

	Total Cohort (n = 231)	HTS (n = 124)	No HTS (n = 107)	P value
Hypernatremia, n (%)	151 (65)	102 (82)	49 (46)	<0.001
Median days of hypernatremia [IQR]	2 [0-5]	4 [1-7]	0 [0-2]	<0.001
DDAVP (i.e., desmopressin) use, n (%)	33 (14)	24 (19)	9 (8)	0.03
Median days of desmopressin [IQR]	0 [0-0]	0 [0-0]	0 [0-0]	0.02
Jugular bulb use, n (%)	53 (23)	37 (30)	16 (15)	<0.001
EVD use, n (%)	225 (97)	123 (99)	102 (95)	0.10
Median days of EVD [IQR]	7 [4-12]	9 [6-13]	5 [3-8]	<0.001
Median days of mechanical ventilation [IQR]	10 [4-15]	13 [8-17]	6 [3-12]	<0.001
Craniotomy performed, n (%)	104 (45)	56 (45)	48 (45)	1.00
Craniectomy performed, n (%)	45 (19)	34 (27)	11 (10)	0.01
Mannitol use, n (%)	83 (36)	63 (51)	20 (19)	<0.001
Neuromuscular blocker use, n (%)	76 (33)	57 (46)	19 (18)	<0.001
Barbiturate use, n (%)	5 (5)	8 (6)	3 (3)	0.32
Median ICU days [IQR]	12 [5-17]	15 [10-20]	8 [4-13]	<0.001
Hospital mortality, n (%)	59 (26)	28 (23)	31 (29)	0.34

APACHE = Acute Physiology and Chronic Health Evaluation; EVD = external ventricular drain; HTS = hypertonic saline; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation

stratum variable and a fitted interaction between HTS and hypernatremia, showed that, among hypernatremic patients, the association between use of HTS and death was not statistically significant (HR, 0.77; 95% CI, 0.09 to 6.31; P = 0.53). A second multivariable regression, this time using the use of HTS as a stratum variable and a fitted

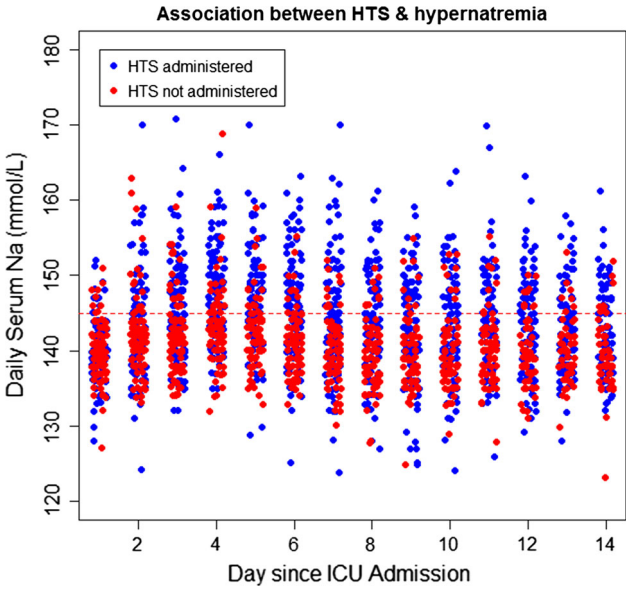

Fig. 1 Daily measured at 8 AM during the intensive care unit (ICU) stay. Serum sodium values measured when continuous hypertonic saline (HTS) was administered and when HTS was not administered are represented by blue dots and red dots, respectively. A horizontal dashed line is drawn at 145 mmol·L^{-1}, i.e., the cut-off level for hypernatremia. Hypertonic saline was associated with higher serum sodium levels ($P < 0.001$)

interaction between HTS and hypernatremia, revealed that, among patients who received HTS, hypernatremia was not associated with increased mortality (HR, 1.53; 95% CI, 0.16 to 14.66; $P = 0.79$). This shows that the relationship between hypernatremia and death was not modified by HTS.

During the review process, a *post hoc* sensitivity analysis was requested to include the administration of mannitol as a covariate in the final multivariable model (Table 3) for use of HTS and hospital mortality. In this *post hoc* analysis, mannitol administration was not associated with hospital mortality (HR, 1.13; 95% CI, 0.78 to 1.63; $P = 0.58$). Furthermore, there was no substantive change in the adjusted HTS point estimate. The adjusted HTS point estimate changed from 1.07 (95% CI, 0.56 to 2.05; $P = 0.84$) without mannitol in the final model to 1.05 (95% CI, 0.55 to 2.01; $P = 0.88$) with mannitol in the final model.

Discussion

In this two-centre retrospective cohort study of patients admitted with severe TBI, we found no association between either HTS administered as a continuous infusion or hypernatremia and hospital mortality. Furthermore, there was no differential effect of hypernatremia in those patients who received HTS *vs* those who did not. This suggests that there is no increased mortality conferred from HTS-induced hypernatremia. Finally, HTS as a continuous infusion was associated with a significant decrease in ICP during ICU admission.

There are multiple randomized and observational studies that examine continuous infusion HTS and ICP.[28-30] Nevertheless, the studies are small, with marked between-study heterogeneity in the patient population (adults *vs* pediatrics), type of brain injury (traumatic *vs* non-traumatic), concentration of HTS, and method of administration (continuous infusion *vs* bolus).[11,31] One randomized trial examined 32 patients with severe brain injuries (GCS < 8) from a variety of causes. Cerebral edema was present in these patients on CT scanning and their ICP was continuously monitored.[30] Once the ICP was > 20 mmHg for more than five minutes, patients were randomized to receive either 7.2% HTS in hydroxyethyl starch (200/0.5) or 15% mannitol until the ICP was reduced to < 15 mmHg. In those patients who received HTS, the mean (SD) ICP reduced to 15 (5) mmHg within a mean of six minutes. Another prospective study examined the effects of a continuous infusion of 3% HTS in children with medically refractory intracranial hypertension.[28] The HTS was used for a median of 7.6 days and increased Na with resultant decreased ICP. There was no comparator group (i.e., patients who did not receive HTS) in either of these two studies. This is in contrast to our study design where we were able to compare patients who received HTS with those who did not receive HTS.

Hypertonic saline may lead to hypernatremia, which is often the therapeutic endpoint for HTS administration.[32] Hypernatremia has itself been associated with elevated creatinine[33] and increased mortality[19,34-36] in patients with brain injury. In 4,296 patients admitted to a neurocritical care unit (only 17% patients had a TBI), results of a retrospective cohort study showed that a Na level > 160 mEq·L^{-1} was independently associated with an increased ICU mortality (odds ratio [OR], 4.8; 95% CI, 2.4 to 9.6). There was no increased mortality with mild (151-155 mEq·L^{-1}) or moderate (156-160 mEq·L^{-1}) hypernatremia. In their study, any single Na measurement > 160 mEq·L^{-1} would allocate the patient into the hypernatremia group. In contrast, we modelled both HTS and hypernatremia as time-dependent indicator variables, which allows for an individual's exposure status to vary by time. In another retrospective cohort study of 881 patients admitted with TBI, increasing degrees of hypernatremia were also associated with increased mortality.[35] Nevertheless, in contrast to our analysis, they did not consider diabetes insipidus in their modelling, which is a known strong predictor of mortality after TBI.[37] As an example, in their study, 145 of 167 (87%) patients who had a Na level of $\geq$ 160 mEq·L^{-1} died (OR, 29.3; 95% CI, 11.5 to 74.4).

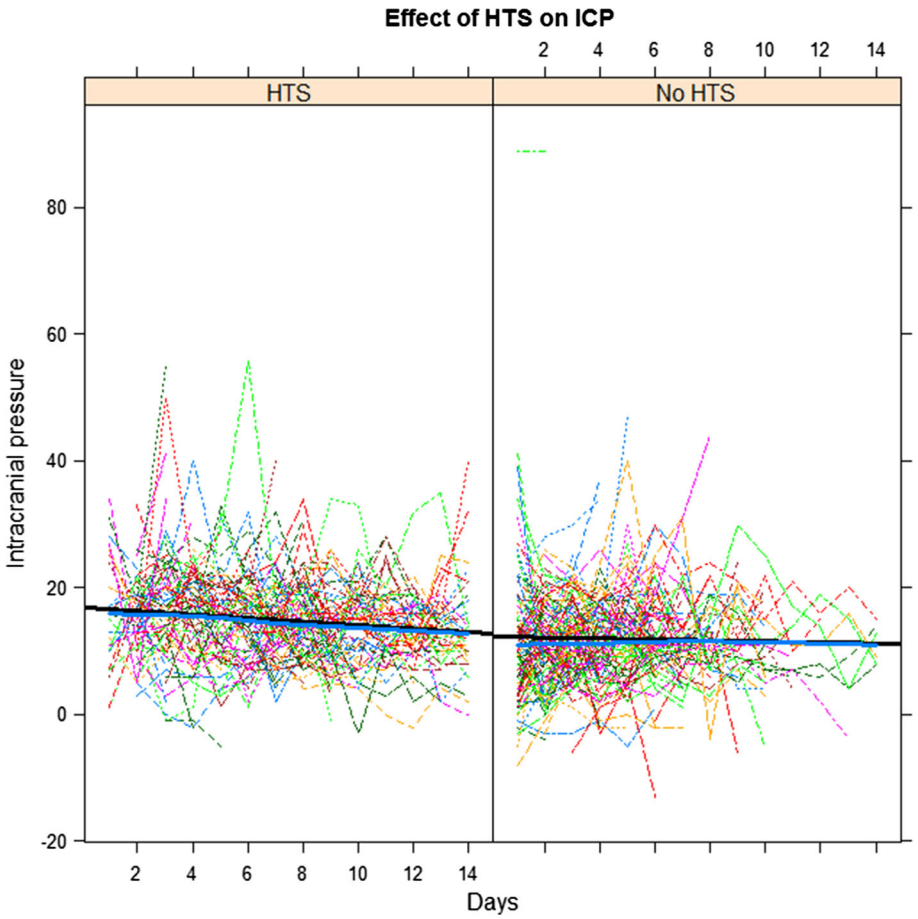

Fig. 2 A "spaghetti plot" of raw longitudinal data showing intracranial pressure (ICP) *vs* days during intensive care unit (ICU) stay for 231 patients, each having 0-14 observations over time (i.e., days during ICU stay). Patients were stratified according to the use of continuous hypertonic saline (HTS). The ICP values were measured at 8 AM daily during ICU stay. Thin dashed lines connect daily ICP values for an individual patient. The thick straight solid black line is the ordinary least squares regression line. The thick solid blue line is the ordinary least squares quadratic curve

Table 3 Univariable and multivariable Cox proportional hazards regression for the use of HTS and hypernatremia on hospital mortality

Predictor Variable	Unadjusted			Adjusted		
	HR	95% CI	*P* value	HR	95% CI	*P* value
HTS	1.09	0.62 to 1.91	0.76	1.07	0.56 to 2.05	0.84
Hypernatremia	1.35	0.87 to 2.09	0.12	1.31	0.68 to 2.55	0.42
Desmopressin	2.99	1.59 to 5.63	0.01	4.27	2.00 to 9.11	<0.001
Age per 1 year increase	1.03	1.02 to 1.04	<0.001	1.05	1.03 to 1.07	<0.001
Rotterdam CT score per 1 point increase	1.44	1.17 to 1.77	0.002	1.35	1.06 to 1.71	0.01
APACHE II score per 1 unit increase	1.06	1.02 to 1.10	0.01	1.05	1.01 to 1.10	0.02
Abnormal pupil reactivity	1.68	1.00 to 2.81	0.040	1.80	0.99 to 3.28	0.05
Admission hypotension	1.84	1.04 to 3.27	0.05	1.42	0.74 to 2.72	0.29
Admission to hospital B	1.39	0.84 to 2.32	0.09	1.28	0.60 to 2.73	0.53

APACHE = Acute Physiology and Chronic Health Evaluation; CT = computerized tomography; CI = confidence interval; HR = hazard ratio; HTS = hypertonic saline

Nevertheless, 84% of these patients had diabetes insipidus, which is likely a large contributor to the high mortality seen in the hypernatremia group.

A retrospective single-centre study observed an increased risk of mortality associated with hypernatremia in patients with TBI (HR, 3.00; 95% CI, 1.34 to 6.51; *P* =

0.003),[19] although an underlying mechanism of adverse outcome has not been established. Subgroup analysis showed that the risk of hypernatremia was restricted to the group in which DDAVP (i.e., desmopressin) was not used (HR, 4.20; 95% CI, 1.62 to 10.17; $P = 0.004$). These results have led commentators to question the safety of continuous infusions of HTS to maintain constant hypernatremia in TBI patients.[23,38-40] Our study results stand in contrast with these results. The patients in their study were older than those in our study (52 *vs* 34 yr, respectively) and presented with a worse GCS motor score (1 *vs* 3, respectively). Furthermore, ICP monitoring was used ubiquitously in our study compared with 51 of 130 (39%) patients in their study. Importantly, our analytic plan differed substantially from their study, which considered hypernatremia as the explanatory variable and did not consider HTS administration.

The strength of our current study is ascertaining the effect sizes of both HTS and hypernatremia on hospital mortality and ICP. Given that hypernatremia is only one of several possible complications of continuous HTS therapy and that there may be other causes of hypernatremia besides HTS, both HTS and hypernatremia may present as independent risk factors for death in patients with severe TBI. By creating suitable time-dependent variables and performing appropriate Cox regressions, we were able to compute different hazard ratios for HTS and hypernatremia and study their relative effects on mortality over time separately. Additionally, mixed-model analyses allowed us to examine the effect of HTS on ICP longitudinally after adjusting for between-subject and within-subject variations. A distinguishing feature of the current study is its exploration of the effect modification of HTS and hypernatremia. Among those patients who received HTS, hypernatremia was not associated with increased mortality. Our results suggest that HTS will decrease ICP yet not confer increased risk of mortality from hypernatremia.

The results of our analyses should be interpreted in the context of several limitations. First, the study did not consider the concentration, dose, or duration of HTS as a hyperosmolar therapy. Second, as with any observational study, unmeasured or residual confounding may be another explanation for our results. This is particularly important as hypernatremia may develop through a variety of mechanisms in patients with TBI, including renal loss of water (diabetes insipidus, mannitol administration) or through administration of HTS.[41] Clinicians may avoid treating hypernatremia so as not to precipitate cerebral edema. Furthermore, physicians would likely administer HTS in patients who are more severely ill with higher ICPs. This can result in confounding by indication, where variables associated with outcomes in the study base are also associated with exposure variables.[42] In short, patients will develop hypernatremia for a variety of factors which themselves may increase mortality. Nevertheless, despite the risk of confounding by indication, hypernatremia was not associated with increased mortality. Another major limitation is the lack of data on HTS-induced complications other than hypernatremia. Hospital mortality was the only outcome variable used in our analyses, and given the low event rate, the study may be underpowered to observe differences in this outcome. Another important limitation is that we have only the daily ICP values, which limits the ability to make firm inference regarding the ICP-lowering effects of HTS. Additionally, we do not have data on functional outcomes, which is arguably more important in this population than mortality. Finally, being a two-centre study, generalizability is limited to hospitals with patients and practice patterns similar to our own.

Conclusion

Notwithstanding the aforementioned limitations, we observed that, in patients with severe TBI, neither HTS nor hypernatremia was associated with increased mortality on multivariable Cox regression. In addition, subgroup analysis found that HTS-induced hypernatremia was not associated with increased mortality. Finally, mixed-model analysis showed that a continuous HTS infusion was associated with a decrease in ICP.

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Author contributions *Donald Griesdale* was the principal investigator and responsible for the concept and design of the study. He had access to all the data and takes full responsibility for the integrity of the data and the accuracy of the data analysis. *Donald Griesdale, Sean Tan, Mypinder Sekhon, Lu Qiao, Jie Zou,* and *William Henderson* were involved in data interpretation and drafting the manuscript. *Sean Tan* performed the primary statistical analysis for the study. *Leif Kolmodin, Mypinder Sekhon,* and *William Henderson* were involved in the study design. *Leif Kolmodin* helped prepare and critically review the manuscript. *Leif Kolmodin, Mypinder Sekhon, Lu Qiao,* and *Jie Zou* were involved in the data collection.

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