

Effect of Continuous Hypertonic Saline Infusion on Clinical Outcomes in Patients with Traumatic Brain Injury: A Retrospective Causal Analysis

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Keywords: Traumatic brain injury, Hypertonic saline, Clinical outcome, Marginal Structure Cox Model, Causal analysis

Posted Date: August 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-805195/v1>

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Abstract

Purpose: Intracranial pressure (ICP) control has long been recognized as an important requirement for traumatic brain injury (TBI) patients. Nevertheless, the long-term effect of hypertonic saline (HTS) remains unknown. The aim of this study was to elucidate the effect on clinical outcomes in TBI patients admitted to intensive care unit (ICU) settings.

Methods: We retrospectively identified moderate to severe TBI patients from two public databases named Medical Information Mart for the Intensive Care (MIMIC)-IV and eICU Collaborative Research Database (eICU-CRD). A marginal structural Cox model (MSCM) was used, with time-dependent variates designed to reflect exposure over time during the ICU stay. A trajectory modeling, based on intracranial pressure evolution pattern, allowed identification of subgroups.

Results: Overall, in our cohort of 1955 eligible patients, 130 (6.65%) received HTS. MSCM indicated that the HTS was significantly associated with better Glasgow coma score [(GCS): hazard ratio (HR) 1.19, 95% confidence interval (95% CI) 1.01-1.40, $p = 0.041$], higher infection complications [eg. urinary tract infection (HR 1.88, 95% CI 1.26-2.81, $p = 0.002$)], and increased ICU LOS (HR 2.02, 95% CI 1.71-2.40, $p < 0.001$). A protective effect from GCS by the HTS was found in the subgroup with medium and low ICP.

Conclusion: Our study revealed no significant difference in the all-cause mortality rates between patients receiving HTS or not. Increased occurrence rates of infection and electrolyte imbalance were inevitable outcomes caused by continuous HTS infusion. Although the study suggested the slight beneficial effects including better neurological outcome, the results warrant further validation.

Introduction

Traumatic brain injury (TBI), a severe condition observed in trauma patients, is estimated to jeopardize 69 million individuals in 2019 worldwide, possessing a high mortality rate[1]. And it is reported that nearly 33% of patients with TBI die in hospital[2]. Thanks to prompt surgical and medical management, the mortality has steadily reduced in the past few decades, however, the incomplete recovery still contributes to TBI survivors with varying degrees of neurological disability, specifically, adverse sequelae and changes in quality of life[3–5].

Intracranial pressure (ICP) represents a major predictor of neurological deterioration in patients with TBI, with elevated ICP being associated with poor neurological outcome[6]. Hypertonic saline (HTS) is regarded as the mainstay for treatment of elevated ICP in TBI. HTS agent might exert an early effect on ICP by decreasing blood viscosity and hematocrit, improving cerebral blood flow (CBF), and oxygen delivery, which in turn reduce cerebral blood volume (CBV) and ICP[7]. Thus, there may be a role for HTS administration to avoid progressive cerebral edema, subsequent neurological deterioration and secondary cognitive disorder.

However, there are concerns that HTS use may trigger acute kidney injury (AKI), hypernatremia and hyperchloremia, which, further, were independently associated with in-hospital mortality in patients with moderate–severe TBI (msTBI)[8, 9]. And the fourth edition of the Brain Trauma Foundation’s Guidelines states that there is insufficient evidence to support the application of any specific hyperosmolar drug for patients with msTBI[10]. Other guidelines do not elucidate the direct effect on clinical outcome associated with the use of HTS or just are based on low-quality evidence[11, 12]. Furthermore, the predominance of literature focused on severe TBI, whereas milder forms of TBI remain unclear.

In particular, the role of HTS administration in patients with msTBI, defined as Glasgow Coma Score (GCS) < 12 remains uncertain, with physiologic studies showing benefit and clinical studies suggesting harm[13, 14]. Although one retrospective study incorporated HTS as the time-dependent variable by conventional Cox analysis, its credibility was limited by residual confounding, inappropriate accounting for dynamic interaction between time-varying treatment and confounders[15].

It is noted that these publications were limited by the single hospital sampling, limited variables, insufficient statistic power, and a lack of effective control for time-varying confounders. In fact, the treatment with HTS, a long-term dynamic variable that changes over time, depends on sodium and chloride. However, there are concerns that performing a randomized controlled trial (RCT) may not be ethical, thus, we emulated an analysis of a hypothetical trial through the use of observational longitudinal data to achieve causal inference. Thus, this present article aimed to investigate the causal effect of HTS on the clinical outcomes in TBI patients from two large intensive care unit (ICU) databases. Additionally, with an aim to explore the heterogeneity of the data, a trajectory modeling based on longitudinal/dynamic ICP evolution pattern during ICU stay was achieved.

Methods

Data source and ethics approval

A longitudinal, multi-center, retrospective study of TBI patients from two sizeable critical care databases, the Medical Information Mart for Intensive Care (MIMIC)-IV version 1.0[16] and eICU Collaborative Research Database (eICU-CRD) version 1.2[17] was conducted. In brief, the MIMIC-IV database, an updated version of MIMIC-III, incorporated comprehensive, de-identified data of patients admitted to the ICUs at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, between 2008 and 2019, containing data from 383220 distinct admissions (single center). The other database, eICU-CRD, was a multicenter, freely available, sizeable database with de-identified high granularity health data associated for over 200,000 admissions to ICUs across the United States between 2014 and 2015. One author (CP) has obtained access to both databases and was responsible for data extraction (Certification number: 41657645). Since the study was an analysis of the anonymized publicly available databases with pre-existing institutional review board (IRB) approval from the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC), informed consent was also waived. The study was

reported accordance to the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement[18].

Participant selection

Inclusion criteria were patients with msTBI. People with an age of less than 16 years old, ICU stays less than 48 h, osmotherapy use prior to ICU admission, cervical spinal cord injury, and bolus injection were excluded from the study. Moreover, for patients with ICU admissions more than once, only data of the first ICU admission of the first hospitalization were included in the analysis.

Data collection

In this study, the data were extracted from MIMIC-IV and eICU-CRD including age, gender, race, weight, body mass index (BMI), admission type, smoking history. Coexisting disorders were also collected based on the recorded International Classification of Diseases (ICD)-9 and ICD-10 codes. Then, the Charlson comorbidity index (CCI) was calculated from its component variables. Lastly, we extracted data containing laboratory parameters, injury details, multiple scoring systems, medication use, ICU interventions, and neurosurgical interventions on the first day of ICU admission. Laboratory variables of HTS, sodium and chloride were measured during the entire ICU stay. For patients with multiple measurements, the minimum daily value of serum sodium and chloride was included in the analysis owing to the fact that it was related to the greatest severity of illness.

Primary and secondary outcomes

The primary outcomes were all-cause mortality, GCS value on the day of discharge. Secondary outcomes incorporated AKI, infection complications [Urinary tract infection (UTI), pneumonia, sepsis], electrolyte imbalance (defined as hyperchloremia, hypernatremia), ICU length of stay (LOS) and hospital LOS. Then, a trajectory modelling based on ICP evolution pattern during ICU stay was established.

Statistical analysis

Values were presented as the means with standard deviations (if normal) or medians with interquartile ranges (IQR) (if non-normal) for continuous variables, and total numbers with percentages for categorical variables. Proportions were compared using χ^2 test or Fisher exact tests while continuous variables were compared using the t test or Wilcoxon rank sum test, as appropriate.

Marginal structure Cox model (MSCM)

In this study, HTS, a time-dependent variable, was dichotomized as “any dose of HTS exposure versus none” on a daily basis. The daily use of HTS was predicted by both time-fixed covariates and time-varying confounders including sodium and chloride to facilitate casual interference. In the first step, the probability of receiving HTS at each follow-up day was estimated by both time-fixed and time-varying covariates, and then inverse probability of treatment weighting (IPTW) was calculated. In the second step, covariates were balanced across the population to attempt to emulate RCT at the time of the HTS

exposure period[19]. Then, a causal estimate of the treatment's effect on the study outcome was estimated. Details of MSCM can be seen at electronic supplemental material (ESM).

Grouped based trajectory modeling

Group-based trajectory modeling (GBTM) is an established analytical technique used to identify hourly ICP clusters following a similar progression of changes over time on a given variable[20]. Details on GBTM are also reported in the ESM.

Sensitivity Analysis

To increase the robustness of our findings, pre specified subgroup analyses stratified by age, gender, BMI, ICP, blood sodium level, blood chloride level, severity of injury, CCI and injury severity score (ISS) were performed. Moreover, the patterns assumed missing to be completely at random, so multiple imputation approach was used to iterate the original data (ESM table S1)[21]. Ultimately, unmeasured confounding may bias the estimates from this observation study, thus, the E-value was also computed to further evaluate the robustness of the findings[22, 23]. The E-value indicated how strongly an unmeasured confounder would have to be associated with both the HTS use and the outcomes of interest to reduce the observed effect to the null, conditional on the measured covariates.

Statistical significance was considered to be at two-sided $p < 0.05$. All analyses were performed with R version 4.0.2 (<http://www.R-project.org>) and STATA (version 16.0; Stata Corporation, College Station, TX, USA).

Results

Study cohort

Initially, the search identified 382278 adult ICU admissions from the MIMIC- IV database and 200859 ones from the eICU-CRD database, respectively. Of these, 10542 were diagnosed with TBI. According to the exclusion criteria, 1955 patients were finally included in the study cohort. Of this cohort, 130 patients were treated with HTS, while the remaining patients not (Fig. 1). The baseline characteristics of the HTS and non-HTS groups are described in Table 1 and ESM table S2. Patients in the HTS group were likely to be younger [55.00 (IQR 29.00–69.00) vs. 63.00 (IQR 44.00–79.00) years, $p < 0.001$], Asian (3.85% vs. 1.70%, $p < 0.001$), have smoking history (30.77% vs. 20.71%, $p = 0.010$), lower CCI [2.00 (IQR 0.00-4.75) vs. 4.00 (IQR 1.00-5.00); $p = 0.019$] than the non-HTS group. On the first day of ICU admission, HTS group showed lower sodium [137.25 (IQR 133.07-141.23) vs. 139.00 (IQR 136.67–141.70) mmol/L; $p = 0.005$], lower creatinine [70.72 (IQR 61.88–88.40) vs. 79.56 (IQR 61.88–97.24) mmol/L; $p = 0.018$], lower BUN [13.00 (IQR 10.00–17.00) vs. 15.00 (IQR 11.00-21.30) mg/dL, $p < 0.001$], more severe TBI (70.77% vs. 61.15%, $p = 0.037$), less subarachnoid hemorrhage and cranial extradural hematoma [(11.54% vs. 24.33%, $p = 0.001$), (0.00% vs. 2.90%, $p = 0.046$)], more cerebral contusion (15.38% vs. 8.99%, $p = 0.024$), more unintentional falls, motor vehicle crashes, and firearm injuries [(48.46% vs. 27.84%, $p < 0.001$), (40.77% vs. 26.36%, $p = 0.001$), (2.31% vs. 0.22%, $p = 0.008$)] than the non-HTS group. In general, patients in the HTS

group were less critically ill than the non-HTS group [sepsis related organ failure assessment (SOFA): 5.00 (IQR 4.00–7.00) vs. 6.00 (IQR 4.00–8.00); $p = 0.037$]. With regard to treatment, patients treated with HTS were more likely to receive barbiturates (3.08% vs. 0.33%, $p = 0.003$), hypothermia (1.54% vs. 0.11%, $p = 0.024$), craniectomy (10.00% vs. 1.59%, $p < 0.001$), simultaneously, with lower ICP [9.00 (IQR 9.00, 17.00) vs. 29.00 (IQR 19.00–40.00), $p < 0.001$].

Table 1
Baseline characteristic of the included TBI patients stratified by continuous HTS use

Variables	ALL (n = 1955)	HTS (n = 130)	Non-HTS (n = 1825)	P Value
Demographics				
Median age (IQR), y	62.00 (43.00, 79.00)	55.00 (29.00, 69.00)	63.00 (44.00, 79.00)	< 0.001
Male, n (%)	1294 (66.22)	92 (70.77)	1202 (65.90)	0.299
Race, n (%)				< 0.001
Black	138 (7.06)	6 (4.62)	132 (7.23)	
White	1341 (68.59)	63 (48.46)	1278 (70.03)	
Hispanic	70 (3.58)	4 (3.08)	66 (3.62)	
Asian	36 (1.84)	5 (3.85)	31 (1.70)	
Others	370 (18.93)	52 (40.00)	318 (17.42)	
Weight, kg	76.45 (64.60, 90.00)	75.35 (64.75, 90.98)	76.60 (64.60, 90.00)	0.990
BMI (IQR), kg/m ²	25.90 (22.80, 30.00)	25.30 (22.50, 30.70)	25.90 (22.90, 29.90)	0.866
Smoking history	418 (21.38)	40 (30.77)	378 (20.71)	0.010
CCI, median (IQR)	3.00 (1.00, 5.00)	2.00 (0.00, 4.75)	4.00 (1.00, 5.00)	0.019
Electrolyte				
Sodium, mmol/L	139.00 (136.50, 141.70)	137.25 (133.07, 141.23)	139.00 (136.67, 141.70)	0.005
Chloride, mmol/L	106.00 (102.00, 110.00)	104.50 (100.75, 109.00)	106.00 (102.00, 110.00)	0.158
Potassium, mmol/L	3.90 (3.60, 4.20)	3.80 (3.60, 4.10)	3.90 (3.60, 4.20)	0.600
Plasma osmolality, Osm/kg.H ₂ O	302.00 (292.00, 312.00)	304.50 (295.00, 314.00)	300.50 (291.00, 312.00)	0.191
Renal function				

TBI traumatic brain injury, HTS hypertonic saline, IQR interquartile range, BMI body mass index, AIDS Acquired Immune Deficiency Syndrome

CCI Charlson comorbidity index, BUN blood urea nitrogen, GCS glasgow coma score, SOFA sepsis related organ failure assessment, APSIII acute physiology score III, ISS injury severity score, ICU intensive care unit, ICP intracranial pressure

Variables	ALL (n = 1955)	HTS (n = 130)	Non-HTS (n = 1825)	P Value
Creatinine, µmol/L	79.56 (61.88, 97.24)	70.72 (61.88, 88.40)	79.56 (61.88, 97.24)	0.018
BUN, mg/dL	15.00 (11.00, 21.00)	13.00 (10.00,17.00)	15.00 (11.00, 21.30)	< 0.001
Renal replacement therapy, n (%)	49 (2.51)	2 (1.54)	47 (2.58)	0.769
TBI severity				0.037
Moderate TBI (GCS 9–12)	747 (38.21)	38 (29.23)	709 (38.85)	
Severe TBI (GCS < = 8)	1208 (61.79)	92 (70.77)	1116 (61.15)	
Type of injury, n (%)				
Subarachnoid hemorrhage	459 (23.48)	15 (11.54)	444 (24.33)	0.001
Cranial extradural hematoma	53 (2.71)	0 (0.00)	53 (2.90)	0.046
Cerebral contusion	184 (9.41)	20 (15.38)	164 (8.99)	0.024
Mechanism of injury, n (%)				
Unintentional falls	571 (29.21)	63 (48.46)	508 (27.84)	< 0.001
Motor vehicle crashes	534 (27.31)	53 (40.77)	481 (26.36)	0.001
Firearm injuries	7 (0.36)	3 (2.31)	4 (0.22)	0.008
Scoring systems				
SOFA	6.00 (4.00, 8.00)	5.00 (4.00, 7.00)	6.00 (4.00, 8.00)	0.037
APSIII	55.00 (40.00, 74.00)	55.00 (41.75, 74.00)	55.00 (40.00, 74.00)	0.647
ISS				0.282
>= 15	1199 (61.33)	86 (66.15)	1113 (60.99)	
< 15	756 (38.67)	44 (33.85)	712 (39.01)	
TBI traumatic brain injury, HTS hypertonic saline, IQR interquartile range, BMI body mass index, AIDS Acquired Immune Deficiency Syndrome				
CCI Charlson comorbidity index, BUN blood urea nitrogen, GCS glasgow coma score, SOFA sepsis related organ failure assessment, APSIII acute physiology score III, ISS injury severity score, ICU intensive care unit, ICP intracranial pressure				

Variables	ALL (n = 1955)	HTS (n = 130)	Non-HTS (n = 1825)	P Value
Medication use				
Vasopressin	104 (5.32)	9 (6.92)	95 (5.21)	0.522
Barbiturates	10 (0.51)	4 (3.08)	6 (0.33)	0.003
ICU interventions				
Maximum ICP, mmHg	9.00 (9.00, 25.00)	9.00 (9.00, 17.00)	29.00 (19.00, 40.00)	< 0.001
Hypothermia	4 (0.20)	2 (1.54)	2 (0.11)	0.024
Hyperventilation	1831 (93.66)	121 (93.08)	1710 (93.70)	0.924
Neurosurgical interventions				
Craniectomy	42 (2.15)	13 (10.00)	29 (1.59)	< 0.001
Ventriculostomy	66 (3.38)	2 (1.54)	64 (3.51)	0.316
TBI traumatic brain injury, HTS hypertonic saline, IQR interquartile range, BMI body mass index, AIDS Acquired Immune Deficiency Syndrome				
CCI Charlson comorbidity index, BUN blood urea nitrogen, GCS glasgow coma score, SOFA sepsis related organ failure assessment, APSIII acute physiology score III, ISS injury severity score, ICU intensive care unit, ICP intracranial pressure				

Marginal structural cox model

As expected, the first step in fitting MSCM indicated that sodium (HR for each 3 mmol/L decrease 0.80; 95% CI 0.75–0.95; $p = 0.017$), chloride (HR for each 1 mmol/L decrease 0.94; 95% CI 0.91–0.97; $p < 0.001$) were important predictors of continuous HTS infusion (ESM table S3). Other independent predictors included age, unintentional falls, motor vehicle crashes, GCS and ISS. Weights distribution plot for the IPTW is shown in Fig. 2. By adjusting for both baseline and time-varying covariates, the association between HTS and clinical outcomes was investigated in the MSCM. Interestingly, it has to be noted that continuous HTS infusion was associated with better neurological outcomes (GCS: HR 1.19; 95% CI 1.01–1.40; $p = 0.041$). Similarly, with respect to secondary outcomes, the study identified significant effect of HTS on urinary tract infection (HR 1.88; 95% CI 1.26–2.81; $p = 0.002$), sepsis (HR 2.66; 95% CI 2.21–3.22; $p < 0.001$), hyperchloremia (HR 4.53; 95% CI 3.78–5.44; $p < 0.001$), hyponatremia (HR 3.66; 95% CI 2.50–5.38; $p < 0.001$). Also, MSCM results showed that HTS was associated with significantly increased ICU LOS (HR 2.02; 95% CI 1.71–2.40; $p < 0.001$), hospital LOS (HR 1.77; 95% CI 1.44–2.20; $p < 0.001$) in the overall msTBI patients (Table 2). In the entire cohort, continuous infusion of HTS was not associated with 30-day mortality (HR 0.93; 95% CI 0.64–1.79; $p = 0.786$), nonetheless, the subgroup sensitivity analysis

indicated that the increased mortality was found in the obesity group (BMI: ≥ 30 vs < 30 kg/m², HR 1.13, 95% CI 0.87–1.47, p for interaction = 0.019) (ESM Fig. 1).

Table 2
Impact of HTS on clinical outcomes by a marginal structural cox model

Outcomes	Model 1		Model 2	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Primary outcomes				
All-cause mortality (30 days)	0.83 (0.48, 1.36)	0.477	0.93 (0.64, 1.79)	0.786
GCS value on the day of discharge	2.08 (1.16, 4.16)	0.012	1.19 (1.01, 1.40)	0.041
Secondary outcomes				
AKI	0.70 (0.36, 1.24)	0.232	0.64 (0.34, 1.19)	0.159
Infection complications				
Urinary tract infection	1.93 (1.24, 2.94)	0.004	1.88 (1.26, 2.81)	0.002
Pneumonia	1.08 (0.57, 1.89)	0.805	1.25 (0.66, 2.38)	0.488
Sepsis	5.08 (3.38, 7.86)	< 0.001	2.66 (2.21, 3.22)	< 0.001
Electrolyte imbalance				
Hyperchloremia	8.06 (5.41, 12.3)	< 0.001	4.53 (3.78, 5.44)	< 0.001
Hypernatremia	3.81 (2.48, 5.73)	< 0.001	3.66 (2.50, 5.38)	< 0.001
ICU LOS, days, median (IQR) (6)	4.11 (2.63, 6.74)	< 0.001	2.02 (1.71, 2.40)	< 0.001
Hospital LOS, days, median (IQR) (13)	2.70 (1.83, 4.06)	< 0.001	1.77 (1.44, 2.20)	< 0.001
Model 1 (unadjusted model): unadjusted, Model 2 (Marginal structural model): adjusted for baseline and time-varying covariables				
HTS hypertonic saline, HR hazard ratio, CI confidence interval, ICU intensive care unit, LOS length of stay, IQR interquartile range				
AKI acute kidney injury, DVT deep venous thrombosis, GCS glasgow coma scale, ICP intracranial pressure, MV mechanical ventilation				

E values for the observed estimates of association between HTS and in-hospital outcomes are shown in the ESM Table S4, for instance, the E-value for GCS value was 1.66, with a lower confidence limit of 1.11, showing that unmeasured confounders were unlikely to explain the entirety of the treatment effect.

Trajectory modeling analysis

According to the trajectory modeling, five subgroups of patients with distinct ICP evolution pattern during their ICU stay were identified (Fig. 3). The ICP patterns of the different subgroups can be seen as follows:

Group 1: persistently high ICP subgroup: 83 (IQR, 40–90), Group 2: low ICP subgroup: 8 (IQR, 5–13), Group 3: medium ICP subgroup: 15 (IQR, 12–18), Group 4: high ICP subgroup: 23 (IQR, 19–29), Group 5: relatively high ICP subgroup: 32 (IQR, 21–48). Detailed information of HTS infusion and main outcomes among subgroups are shown in the ESM table S5.

With regard to the percentage of HTS infusion, the difference between the five subgroups was not statistically significant. In contrast, there were fewer death events and better neurological outcomes in the subgroup with the low and medium ICP level. Owing to the fact that 92% patients were in the group 2 and 3, thus, the further subgroup analyses were conducted in these two subgroups. Continuous infusion of HTS was not associated with a lower risk of death for the medium and low ICP subgroup [(HR 0.54; 95% CI 0.08–2.13; $p = 0.525$), (HR 1.67; 95% CI 0.47–5.30; $p = 0.411$)]. However, HTS infusion was associated with increased GCS in these two groups [(HR 4.02; 95% CI 1.02–29.1; $p = 0.046$), (HR 4.77; 95% CI 1.19–35.0; $p = 0.025$)] (ESM table S6).

Discussion

To the best of our knowledge, this is the first, multicenter, longitudinal study indicating the effect of continuous HTS infusion on in-hospital outcome among msTBI patients while addressing simultaneously the time-varying nature of this type of exposure. We found that the utility of HTS was not independently associated with mortality, but with better neurological outcomes, increased infection complications, DVT, hyperchloremia, hypernatremia, LOS, and sedation duration. By characterizing the ICP trajectories of patients, we also identified that HTS was associated with better neurological outcome in the medium and low ICP subgroups.

Of note, cerebral edema develops from several pathologic mechanisms following TBI, leading to cerebral herniation and a rapid worsening of prognosis[24, 25]. Nevertheless, the availability of neurosurgical interventions in most medical facilities is limited, means of inducing a hyperosmolar environment including HTS are currently proposed[26]. Accordingly, the effects of HTS on TBI patients need to be further explored.

As expected, in this passage, both hypernatremia and hyperchloremia are both causes and results of HTS. Similarly, previous studies have also concluded that if not properly controlled, continuous infusion of HTS may bring hypernatremia and hyperchloremia, accompanied by the increased in-hospital mortality[27, 28].

Moreover, in this study, continuous HTS infusion did significantly improve neurological outcome as assessed by the GCS value on the day of discharge. Relatively more severe TBI (moderate: 747 vs severe: 1208) patients have increased the power to indicate the impact of HTS owing to the fact that the risk of intracranial hypertension or brain edema is higher in this population[29]. The precise regulatory mechanism remains to be further elucidated. Perhaps, the efficacy of HS in brain edema resulting from TBI was closely associated with the downregulation of aquaporin-4 (AQP4), the restoration of brain blood

barrier (BBB) integrity and the suppression of inflammatory factors including Interleukin (IL-1 β), tumor necrosis factor (TNF- α), NF- κ B[30].

Furthermore, our study provided evidence that continuous HTS infusion was not significantly associated with mortality. It is worth noting that our passage was able to elucidate that the mortality described was related to an underlying medical condition itself, not other confounders, including hypernatremia or hyperchloremia. Congruently, a 2021 COBI RCT published in JAMA found that there was no significant difference in 6-month mortality between the HTS group and control group[31]. Likewise, Tan SK et al[15] found that HTS was not associated with hospital mortality in patients with severe TBI. Yet one systematic review concluded that HTS was associated with a reduction of in-ICU mortality[32]. Given the heterogeneity of the included population, we planned a subgroup analysis to account for this possibility. Specifically, restricting the analysis to the subgroup of obesity patients did demonstrate a higher mortality. In this regard, studies conducted by Brown CV et al, Chabok SY et al had similar results to ours[33, 34]. Further, this adverse effect seems to be due to age, lower admission blood pressure, and more associated chest injury, rather than a direct result of the obese state, however, this speculation needs further validation[33].

In addition, our findings added additional evidence to previous studies suggesting that continuous HTS infusion did not result in increased AKI, suggesting no harm to the kidney[35, 36]. An important factor may be that, in ICU, patients were kept in euvolemia or mild hypervolemia, despite supraphysiologic serum sodium and serum osmolarity.

Nevertheless, a concerning finding was the association between continuous HTS infusion and increased infection and LOS. Previous clinical trials concerning continuous HTS infusion and infection were limited with mixed results; some reported increased infection[35] while others did not[37, 38]. Physiologically, high sodium levels have demonstrated suppressive effects on leukocyte activation and could theoretically impair the immune system, resulting in higher infection rates[39]. As hypothesized, previous studies have suggested that increased LOS may be due to multiple complications, especially, hypernatremia and infection. Further studies might be needed to confirm the above assumptions.

To further explore the association of HTS on in-hospital outcomes and provide an insight into the mechanisms by which ICP level produces this effect, we characterized the ICP trajectories and estimated the impact of ICP burden on outcomes. Indeed, the heterogeneity of the included population in terms of ICP evolution pattern was evidenced. Although case mixes were different from one subgroup to the others, a protective effect was found in the low and medium ICP subgroups, which was consistent with the result of MSCM, adding the robustness to our findings.

The strength of our study lied in a population-based longitudinal cohort from multi-center in US, a high-quality data with granular temporal detail, a homogeneous population, accordingly, ensuring the robustness, reliability, generalizability of the findings. Apart from this, to estimate the causal effect of HTS administration on in-hospital outcome, we employed MSCM, which helped align results from an observational study with those of actual randomized controlled trials. Moreover, by implementing

multiple imputation to missing data, the analysis gave a relatively robust conclusion to reduce the estimation bias and improve validity. Unmeasured confounders were also treated by E-Value. When compelling randomized trials are not yet forthcoming, it is incrementally valuable that credible evidence for the effect of the HTS in TBI patients was supplied in our study.

This study had several limitations, consistent with those inherent to many large administrative database studies. First, based on electronic records of routine clinical practice, missing data and outliers were common. Second, we did not have data on functional outcomes after discharge, which was arguably an important indicator in this study. Second, as a retrospective study, unmeasured confounding was inevitable. Thus, to quantify the potential implications of it, E-Value sensitivity analysis was used, which demonstrated that the results obtained would be different only if we had omitted the major covariates, which was often not the case in our study. Third, instead of outcome adjudication, our outcomes were defined by ICD-9 and ICD-10 diagnosis codes. Incorrect codes or misclassification bias inevitably exist, so the codes we used were all verified by previous articles[40, 41].

Conclusions

In this cohort study which enabled a less bias estimation by causal inference methods, we found that HTS was not associated with reduced mortality but with better neurological outcome, accompanied by increased infection, and LOS in msTBI patients. Despite careful methodology involving MSM and trajectory modeling were employed, well-designed, prospective, multicenter simulation studies or RCTs are needed to further clarify the impact of HTS on clinical outcomes.

Abbreviations

TBI

traumatic brain injury; ICP:intracranial pressure; HTS:hypertonic saline; CBF:cerebral blood flow; CBV:cerebral blood volume; AKI:acute kidney injury; msTBI:moderate–severe traumatic brain injury; GCS:Glasgow Coma Score; RCT:randomized controlled trial; ICU:intensive care unit; MIMIC-IV:medical Information Mart for Intensive Care; eICU-CRD:eICU Collaborative Research Database; IRB:institutional review board; MIT:massachusetts Institute of Technology; BIDMC:beth Israel Deaconess Medical Center; RECORD:reporting of studies Conducted using Observational Routinely collected health Data; BMI:body mass index; ICD:International Classification of Diseases; CCI:charlson comorbidity index; LOS:length of stay; UTI:Urinary tract infection; DVT:deep venous thrombosis; MV:mechanical ventilation; MSCM:Marginal structure Cox model; IPTW:inverse probability of treatment weighting; ESM:electronic supplemental material; GBTM:group-based trajectory modeling; ISS:injury severity score; IQR:interquartile range; SOFA:sepsis related organ failure assessment; AQP4:aquaporin-4; BBB:brain blood barrier; IL-1 β :interleukin; TNF- α :tumor necrosis factor

Declarations

Funding: This study received the following funding: The San Hang Program of the Second Military Medical University; Three-Year Action Plan for Strengthening Public Health System in Shanghai (2020-2022) Key Discipline Construction Project (NO: GWV-10.1-XK05).

Conflicts of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and material: All data were derived from these two public databases.

Code availability: The codes in the study are available upon reasonable request from the corresponding Author (ZJ).

Authors' contributions:

FY, CZ, and LB collected, analyzed and interpreted the data regarding the tracheostomy in trauma patients. CP designed the study, and was a major contributor in writing the manuscript. JY performed the statistical analysis. LP, WL, and ZJ participated in the revision of the draft. All authors read and approved the final manuscript.

Ethics approval: Not applicable.

Consent to participate: applicable.

Consent for publication: applicable.

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Figures

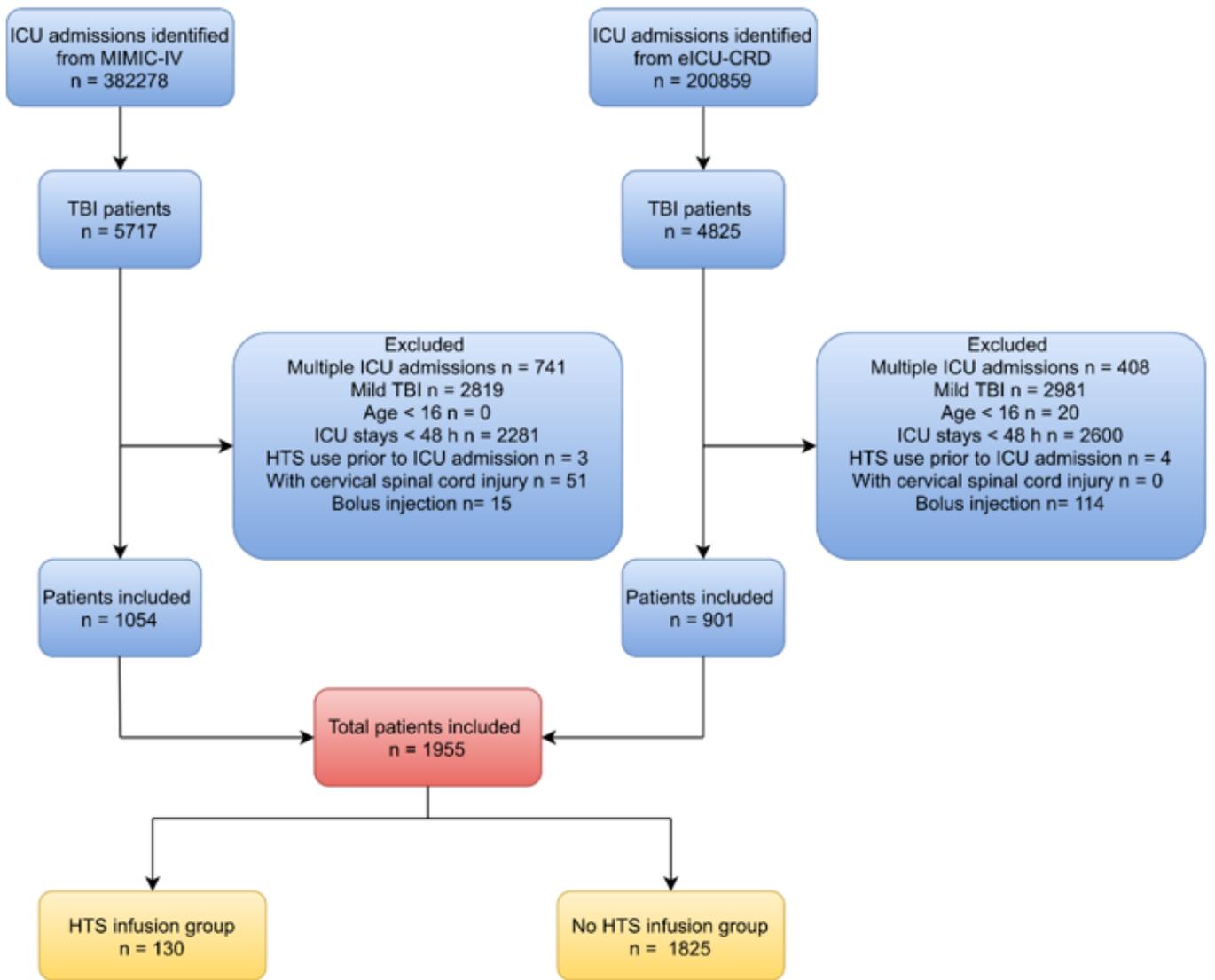


Figure 1

Flowchart of eligible participants. ICU intensive care unit, TBI traumatic brain injury, HTS hypertonic saline

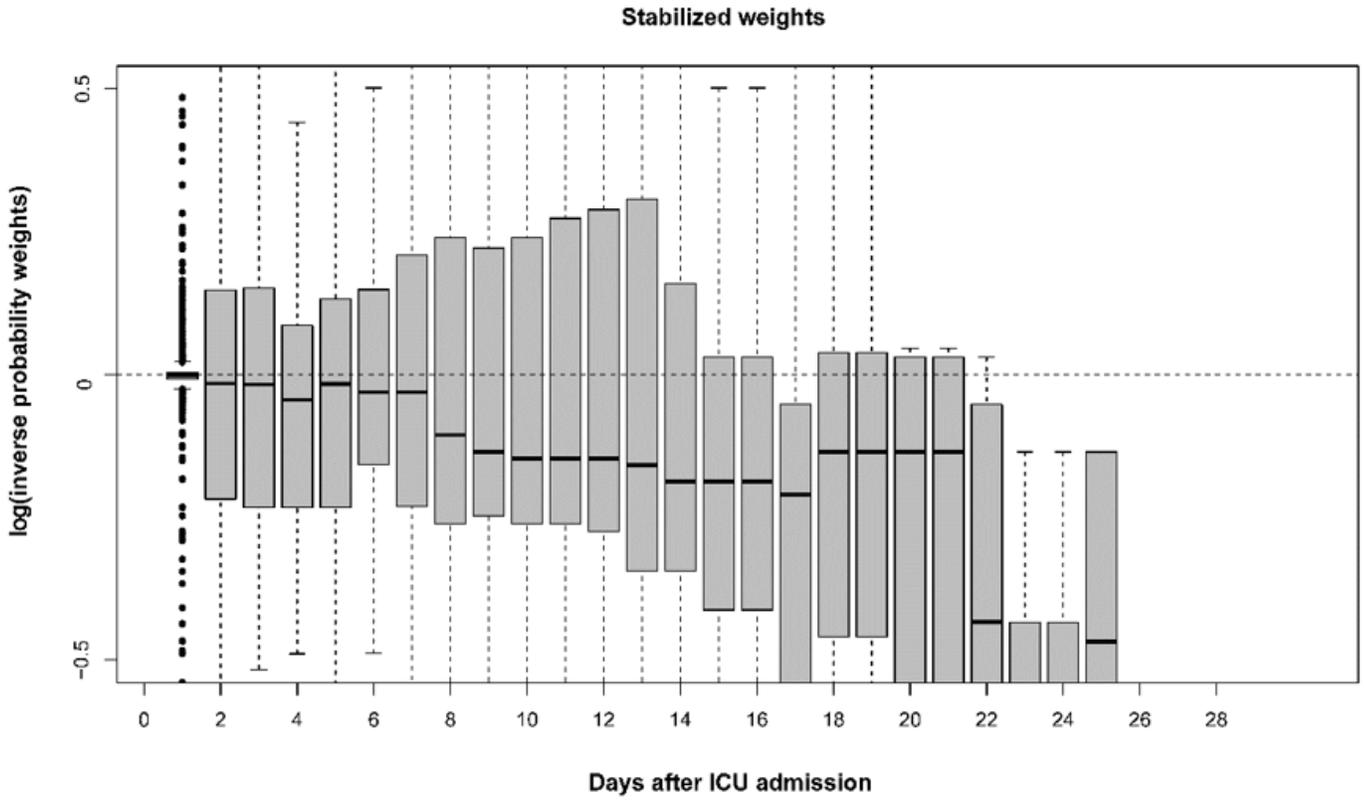


Figure 2

Weights distribution plot for the inverse probability weights that were used to adjust for confounding. ICU intensive care unit

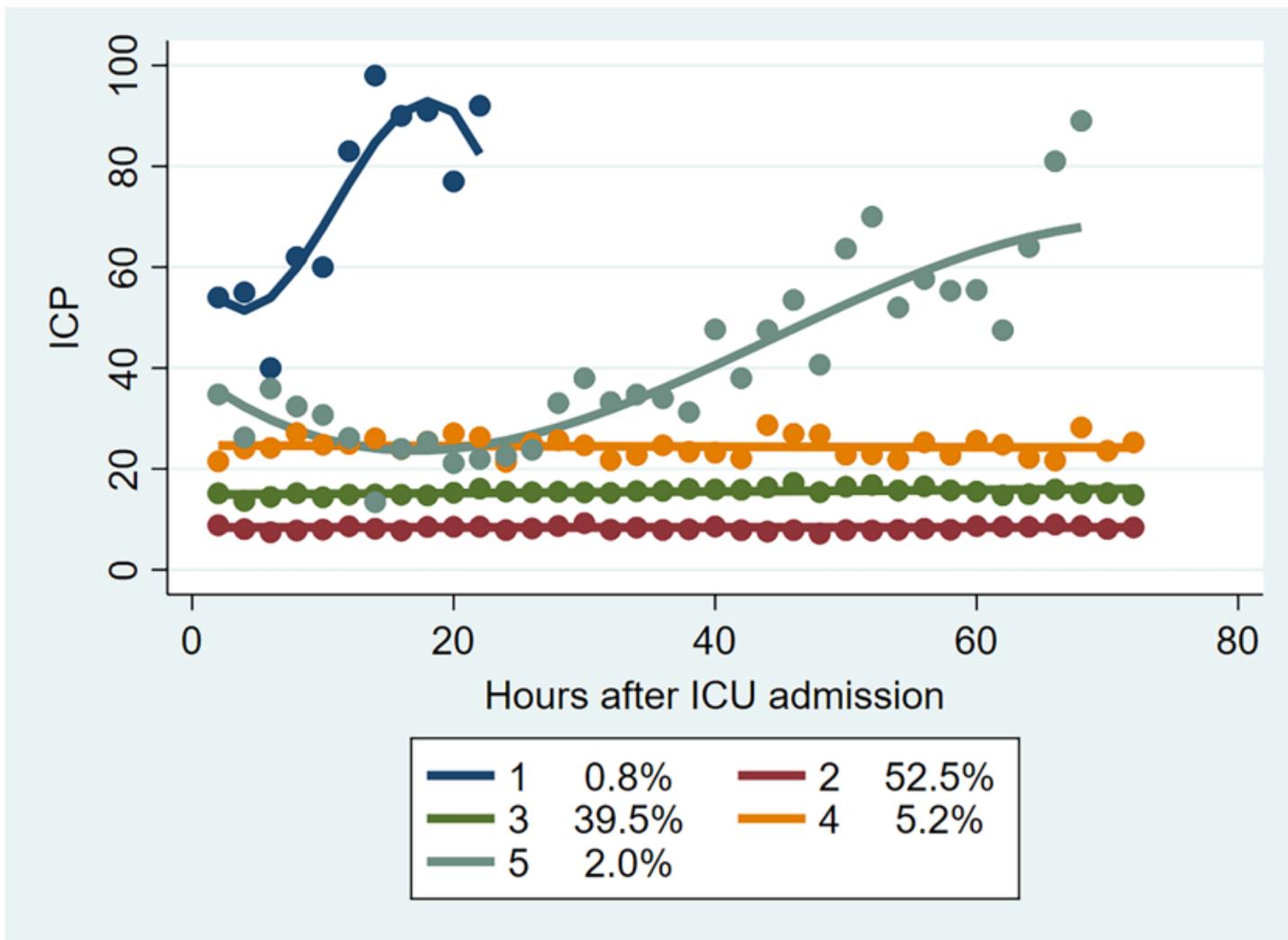


Figure 3

ICP evolution pattern among the five subgroups defined thanks to the trajectory modeling. ICP intracranial pressure, ICU intensive care unit

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