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Original Article

Hypertonic saline administration and complex traumatic brain injury outcomes: a retrospective study

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Abstract: Although hypertonic saline (HTS) decreases intracranial pressure (ICP) with traumatic brain injury (TBI), its effects on survival and post-discharge neurologic function are less certain. We assessed the impact of HTS administration on TBI outcomes and hypothesized that favorable outcomes would be associated with larger amounts of 3% saline. This is a retrospective study of consecutive-patients with the following criteria: blunt trauma, age 18-70 years, intracranial hemorrhage, Glasgow Coma Scale score (GCS) 3-12, and mechanical ventilation ≥ 5 days. The need for craniotomy or craniectomy denoted surgical decompression patients. Amounts of HTS were during the first-5 trauma center days. Traits for the 112 patients during 2012-2016 were as follows: GCS, 6.8 ± 3.2; subdural hematoma, 71.4%; cerebral contusion, 31.3%, ICP device, 47.3%; surgical decompression, 51.8%; ventilator days, 14.8 ± 6.7; trauma center mortality, 13.4%; and no commands at 3 months 35.5%. In surgically decompressed patients, trauma center mortality was greater with ≤ 8.0 mEq/kg sodium (38.9%) than with > 8.0 mEq/kg (7.5%; P = 0.0037). In surgically decompressed patients, following commands at 3 months was greater with ≥ 1400 mEq sodium (76.9%) than with < 1400 mEq (50.0%; *P* = 0.0489). For trauma center surviving non-decompression patients with no ICP device, those following commands at 3 months received more sodium (513 ± 784 mEq) than individuals not following commands (82 ± 144 mEq; *P* = 0.0142). For patients with a GCS 5-8, following commands at 3 months was greater with ≥ 1350 mEq sodium (92.3%) than with < 1350 mEq (60.0%; *P* = 0.0214). In patients with subdural hematoma or cerebral contusion, following commands at 3 months was greater with ≥ 1400 mEq sodium (84.2%) than with < 1400 mEq (61.8%; *P* = 0.0333). Patients with ICP > 20 mmHg for ≤ 10 hours (mean hours 2.0) received more sodium (16.5 ± 11.5 mEq/kg) when compared to ICP elevation for ≥ 11 hours (mean hours 34) (9.4 ± 6.3 mEq/kg; *P* = 0.0139). These observations demonstrate that hypertonic saline administration in patients with complex traumatic brain injury is associated with 1) mitigation of intracranial hypertension, 2) trauma center survival, and 3) following commands at 3 months post-injury.

Keywords: Saline solution, hypertonic, intracranial pressure, brain injuries, traumatic

Introduction

Of the 10 studies that investigated the efficacy of hypertonic saline (HTS) for managing intracranial hypertension from 2000 to 2016, seven involved intermittent bolus HTS dosing [1-7] and three assessed continuous HTS administration [8-10]. Of the studies assessing intermittent bolus administration, three demonstrated that HTS was more effective than mannitol in lowering intracranial pressure (ICP) [2-4] and two showed that HTS and mannitol had comparable efficacy [5, 6]. Of the two investigations of an intermittent bolus without a mannitol control group, one provided data that showed efficacy [1], while the other found HTS to be ineffective [7]. All three studies investigating continuous infusion concluded that HTS was effective in reducing ICP when intracranial hypertension was documented; however, a mannitol comparison group was not included [8-10]. For patients with intracranial hypertension who received intermittent HTS boluses, one study found that 3-6 month post-discharge neurologic function was better with HTS than with mannitol [4], while two investigations found no difference [2, 5]. Of the studies involving continuous HTS infusion (no mannitol comparison group), one demonstrated no reduction in hospital mortality [9], and one showed no de-

crease in 6 month neurologic function [10]. Continued interest in this topic is supported by the numerous meta-analyses regarding HTS infusion published over the past few years [11-15].

These investigations do not address traumatic brain injured patient outcomes for those without intracranial hypertension. Apropos, a recent publication described the elements of a study that will investigate the use of continuous HTS infusion in patients with traumatic brain injury (TBI) [16]. The intent of this study is to assess not only efficacy for ICP management in those with intracranial hypertension, but also to evaluate 3 month and 6 month neurologic outcomes for patients with and without intracranial hypertension, stratified according to use or non-use of continuous HTS infusion.

For several years the Trauma/Critical Care Services at our institution has commonly administered bolus and continuous infusion 3% saline to select patients with TBI. Therefore, the current investigators were motivated to assess the potential impact of 3% saline administration on TBI outcomes. We hypothesized that patients receiving larger amounts of HTS would have better associations with desirable outcomes than those with no or lesser amounts of HTS administration.

Materials and methods

This retrospective study assessed consecutive patients during 2012-2016. Inclusion criteria were blunt trauma, age 18-70 years, intracranial hemorrhage with head Abbreviated Injury Scale scores ≥ 2, Glasgow Coma Scale (GCS) score 3-12, and mechanical ventilation ≥ 5 days. Mechanisms of injury, age, sex, head Abbreviated Injury Scale scores, ventilator days, body weight, Injury Severity Score values, and trauma center death or survival was obtained from the trauma registry. The initial GCS values were principally obtained from the Epic System electronic medical record (EMR) trauma service History and Physical Examination documentation and represented the findings at the time of trauma center arrival. Because a few patients underwent pre-hospital tracheal intubation and sedation, the initial GCS value was assigned using pre-hospital documentation records. For an additional small number of patients who had neurologic deterioration during the first-24 hours after trauma center arrival, the examination findings at that time were used to determine the initial GCS.

The presence of an epidural hematoma, subdural hematoma, cerebral contusion, subarachnoid hemorrhage, cerebral hematoma, and intraventricular hemorrhage in each patient was determined according to the documentation in the radiologists' reports. The first-author evaluated all axial and coronal slices of each patient's computed tomography (CT) scan to calculate a brain CT score. A single-point was assigned for each of the three following findings: midline shift ≥ 3 mm, lateral ventricular compression (asymmetry), and basal cistern compression with a combined potential range of 0-3. ICP device insertion or performance of a craniotomy or craniectomy was obtained from neurosurgical operative records. For the patients who had an ICP device inserted, EMR intensive care unit flow sheets were reviewed and the number of hours when the ICP was > 20 mmHg was recorded for the first 96 hours.

The status of following commands at trauma center discharge was obtained from the EMR discharge summary and pre-discharge progress notes. The documentation of following commands at 3 months was obtained from the EMR which typically included hospital readmissions, office visits, and clinic appointments. For a few patients, deaths were discovered by using Internet obituary documentation. The EMR medication administration records were reviewed to document the amounts of 3% sodium chloride (milliequivalents [mEq] sodium) and mannitol (grams) administered to each patient during the first 5 days following trauma center arrival. The admission base deficit and day 5 serum sodium concentration were obtained from the EMR.

HTS administration was at the discretion of each neurosurgeon and intensivist. The amounts of HTS (first 5 day mEq sodium administration) were variably dichotomized and assessed for associations with outcomes (trauma center mortality, 3 month command status, and intracranial hypertension). Specifically, various cut points or threshold values were selected and ranged from < 515 versus ≥ 515 mEq sodium up to and including < 1600 versus ≥ 1600 mEq sodium. For each cut point, a dichotomous outcome and two categorical HTS groups existed and were assessed using 2 × 2 contingency analyses. A beneficial relationship was consid-

Table 1. Characteristics of study patients

Total Patients	112	Cerebral Hematoma	25 (22.3%)
Age	45.3 ± 14.2	Brain CT Score	2.3 ± 0.9
Male Sex	91 (81.3%)	ICP Device	53 (47.3%)
Body Weight (kg)	82.8 ± 19.5	Surgical Decompression	58 (51.8%)
Initial Glasgow Coma Score	6.8 ± 3.2	Injury Severity Score	28.5 ± 4.5
Epidural Hematoma	8 (7.1%)	Admission Base Deficit	-5.4 ± 4.5
Subdural Hematoma	80 (71.4%)	Ventilator Days	14.8 ± 6.7
Cerebral Contusion	35 (31.3%)	Trauma Center Mortality	15 (13.4%)
Subarachnoid Hemorrhage	62 (55.4%)	No Commands at 3 Months	39 (35.5%)

CT, computed tomography; ICP, intracranial pressure; subarachnoid hemorrhage includes intraventricular hemorrhage.

ered present when the *p*-value was significant and the risk ratio was greater than 1.0 [17-19].

As a Level I trauma center, care providers adhered to Brain Trauma Foundation guidelines. One of the three co-author neurosurgeons was directly involved in the care of each study patient. ICP monitoring was at the discretion of the neurosurgeon.

Statistical analysis

Data were entered into a Microsoft Excel® 2010 spreadsheet (Microsoft Corp., Redmond, WA) and imported into SAS System for Windows, release 9.2 (SAS Institute Inc., Cary, NC) for statistical analyses. For the continuous variable cohort data, mean and standard deviation are used. The Cochran-Mantel-Haenszel test was used to analyze the significance of a 2 × 3 contingency table. A t-test was used to compare interval data for two independent groups. The Wilcoxon rank sum test was used to compare ordinal data for two independent groups (e.g., GCS and brain CT scores). Analysis of variance was used to compare interval data means for more than two independent groups (e.g., age, admission base deficit, and HTS [mEq sodium]). The Kruskal-Wallis test was used to compare ordinal data means for more than two independent groups (e.g., GCS score, brain CT score, and Injury Severity Score). Bonferroni t-tests were used to analyze continuous data for intergroup significance when more than two groups were assessed. The Cohen d statistic was used to assess the magnitude of difference between the mean and standard deviation of two groups with the following difference interpretations: small, 0.2; medium, 0.5; large, 0.8; and very large ≥ 1.2. Multivariate logistic regression analysis was used to assess the significance of independent variables relative to a dichotomous dependent variable. We assessed 2 × 2 contingency tables for significance using the Exact Mid-*P* in Epi Info™ 7.0.9.7, a program developed by the Centers for Disease Control and Prevention. The epidemiological statisticians who designed the system specifically state that the Exact Mid-*P* is the preferred test (page 103 of the Epi Info™ manual) [20, 21]. Others also advocate the Exact Mid-*P* for 2 × 2 table analysis, especially when sample sizes are relatively small or data are unbalanced [22-24]. The level of significance was considered $P < 0.05$.

Results

Patient traits

Characteristics of the 112 patients with TBI are shown in **Table 1**. Mechanisms of injury were as follows: fall, 44 patients (39.3%); motor vehicular crash, 34 patients (30.4%); motorcycle crash, 25 patients (22.3%); pedestrian struck, 6 patients (5.4%); assault, 2 patients (1.8%); and other, 1 patient (0.9%).

The initial GCS score distribution was as follows: 3-4, 38 patients (33.9%); 5-8, 38 patients (33.9%); and 9-12, 36 patients (32.1%). Patients dying in the trauma center had a lower initial GCS score (4.8 ± 2.2) than survivors (7.1 ± 3.3; $P = 0.0130$; Cohen d = 0.8). The cohort who did not follow commands at 3 months had a lower initial GCS score (5.3 ± 2.7) when contrasted with those following commands (7.6 ± 3.2; $P = 0.0006$; Cohen d = 0.8). Proportions of brain deformations on a brain CT scan were as follows: midline shift, 81 patients (72.3%); ventricular compression, 77 patients (68.8%); basal cistern compression, 98 patients (87.5%); and all three deformations, 63 patients (56.3%). The brain CT score was higher in patients who underwent surgical decompression (2.8 ± 0.5)

Table 2. Traits according to neurosurgical interventions

	Surgical Decompression	No Decompression With ICP Device	No Decompression No ICP Device	
Total Patients	58 (51.9%)	14 (12.8%)	40 (35.7%)	*P* value
Initial GCS Score	6.0 ± 3.0	6.5 ± 2.9	8.3 ± 3.4	0.0138
Brain CT Score	2.8 ± 0.5	1.6 ± 0.9	1.8 ± 1.0	< 0.0001
Epidural Hematoma	6 (10.3%)	0 (0%)	2 (5.0%)	0.2820
Subdural Hematoma	49 (84.5%)	4 (28.6%)	27 (67.5%)	0.0388
Cerebral Contusion	17 (29.3%)	5 (35.7%)	13 (32.5%)	0.7204
Subarachnoid Hemorrhage	30 (51.7%)	12 (85.7%)	20 (50.0%)	0.9941
Cerebral Hematoma	11 (19.0%)	3 (21.4%)	11 (27.5%)	0.3246
Age (years)	45.0 ± 13.4	43.8 ± 15.2	46.4 ± 15.2	0.8123
Injury Severity Score	28.4 ± 7.7	32.1 ± 9.2	27.3 ± 10.2	0.3847
Admission Base Deficit	-5.2 ± 4.4	-6.2 ± 4.5	-5.3 ± 4.6	0.7616
5-day mEq Na^+ HTS	955 ± 605	1385 ± 954	538 ± 747	0.0004
mEq Na^+ = 0	6 (10.3%)	1 (7.1%)	19 (47.5%)	< 0.0001
Trauma Center Mortality	10 (17.2%)	2 (14.3%)	3 (7.5%)	0.1690
Commands at 3 Months	32 (56.1%)	6 (42.9%)	33 (84.6%)	0.0065

ICP, intracranial pressure; GCS, Glasgow Coma Scale, CT, computed tomography; mEq, milliequivalents; Na^+, sodium; HTS, hypertonic saline.

than in those without surgery (1.7 ± 1.0; $P < 0.0001$). Results of multivariate logistic regression analysis demonstrated that surgical decompression was independently associated with an increasing brain CT score ($P < 0.0001$) and decreasing initial GCS score ($P = 0.0179$). The brain CT score was higher in patients with a subdural hematoma (2.5 ± 0.9) than in those without (1.8 ± 0.9; $P = 0.0001$) and it was lower in individuals with subarachnoid hemorrhage (2.1 ± 1.0) than in those without (2.6 ± 0.7; $P = 0.0065$). Results of multivariate logistic regression analysis demonstrated that the brain CT score was independently associated with subdural hematoma ($P = 0.0010$) and subarachnoid hemorrhage ($P = 0.0252$).

Categorizations of neurosurgical intervention

Analysis of the data demonstrated that 3 clinical neurosurgical groups could be delineated based on neurosurgical interventions (surgical decompression and ICP monitor insertion) with variations in initial GCS scores, brain CT scores, proportions of subdural hematoma, amounts of HTS, and proportions following commands at 3 months (**Table 2**). The 3 clinical neurosurgical intervention groups were surgical decompression, non-decompression with an ICP device, and non-decompression with no ICP device. The initial GCS score was lower for the surgical decompression group than for the non-decompression with no ICP device cohort ($P < 0.05$). The brain CT score was higher for the surgical decompression group than for the other two cohorts ($P < 0.05$). The proportions of subdural hematoma differed for all the possible two-group comparisons ($P < 0.05$). Lower amounts of HTS were given to the non-decompression with no ICP device group than to the other two cohorts ($P < 0.05$); however, the amounts of HTS were not different for the surgical decompression group and the non-decompression with an ICP device cohort ($P > 0.05$). A higher proportion of following commands at 3 months was found for the non-decompression with no ICP device group than for the other two cohorts ($P < 0.05$); however, the proportions were not different for the surgical decompression group and the non-decompression with an ICP device cohort ($P > 0.05$).

Day 5 serum sodium concentration

The amounts of HTS administration over the first five trauma center days were as follows: < 515 mEq sodium, 39 patients (34.8%); 515-1030 mEq sodium, 30 patients (25.8%); 1031-1545 mEq sodium, 25 patients (22.3%); and > 1545 mEq sodium, 18 patients (16.1%). For the 112 patients, the day 5 serum sodium was 146.6 ± 7.3 with a range of 125-159 mEq/L. The day 5 serum sodium level was greater in those receiving ≥ 515 mEq sodium (148 ± 6.7

Table 3. Trauma center mortality and HTS administration in patients with surgical decompression

Hypertonic Saline	≤ 8.0 mEq Na^+/kg	> 8.0 mEq Na^+/kg	
Total Patients	18	40	
Brain CT Score	2.9 ± 0.3	2.8 ± 0.5	*P* = 0.3197
Trauma Center Death	7 (38.9%)	3 (7.5%)	*P* = 0.0037
			Risk Ratio = 5.2
			(1.5-17.8)
mEq Na^+	297 ± 271	1250 ± 463	*P* < 0.0001
			Cohen d = 2.5
mEq Na^+ per kg	3.4 ± 3.1	15.4 ± 5.9	*P* < 0.0001
			Cohen d = 2.6

HTS, hypertonic saline; mEq, milliequivalents; Na^+, sodium; kg, kilograms of body weight; CT, computed tomography.

mEq/L) than in those receiving < 515 mEq sodium (143 ± 7.2 mEq/L; *P* = 0.0001; Cohen d = 0.7). Trauma center mortality was insignificantly higher for the 17 patients with day 5 serum sodium ≥ 155 mEq/L (23.5%) than for those with day 5 serum sodium level < 155 mEq/L (11.6%; *P* = 0.1100). Results of multivariate logistic regression analysis demonstrated that trauma center mortality was associated with a decreasing initial GCS score (*P* = 0.0206), but not related to day 5 serum sodium level ≥ 155 mEq/L (*P* = 0.3667). Failure to follow commands at 3 months was insignificantly higher for the 17 patients with day 5 serum sodium ≥ 155 mEq/L (52.9%) than for those with day 5 serum sodium level < 155 mEq/L (32.3%; *P* = 0.0600). Results of multivariate logistic regression analysis showed that failure to follow commands at 3 months was associated with a decreasing initial GCS score (*P* = 0.0008), but not related to the day 5 serum sodium level ≥ 155 mEq/L (*P* = 0.2597).

Patients with surgical decompression

Of the patients with surgical decompression, 44 (75.9%) had a craniectomy and 14 (24.1%) underwent a craniotomy. A comparison of the 2 groups showed similar initial GCS scores (*P* = 0.7211), brain CT scores (*P* = 0.8517), proportions of trauma center death (*P* = 0.7368), and ability to follow commands at trauma center discharge (*P* = 0.2853). Because of these similarities, the patients with craniectomy and craniotomy were considered a single group, surgical decompression.

Proportions of trauma center mortality and HTS administration for the patients with surgical decompression are displayed in **Table 3**. Substantially larger amounts of HTS were associated with a reduced proportion of trauma center mortality, despite similar brain CT scores. Results of multivariate logistic regression analysis demonstrated that trauma center death was independently associated with ≤ 8.0 mEq sodium/kg body weight administration (*P* = 0.0043) and a decreasing initial GCS score (*P* = 0.0240), but not with amounts of mannitol (*P* = 0.6976).

The proportions of following commands at 3 months for the patients with surgical decompression are displayed in **Table 4**. Substantially larger amounts of HTS were associated with an increased proportion for following commands, although brain CT and GCS scores and amounts of mannitol were similar.

Non-decompression patients with no ICP device

For the patients without decompression and no ICP device, an analysis of the trauma center survivors showed that the amounts of mEq of sodium were greater for those following commands at 3 months (513 ± 784) than for patients not following commands (82 ± 144; *p* = 0.0142; Cohen d = 0.8). The initial GCS score was similar for those following commands at 3 months (8.5 ± 3.3) compared to patients not following commands (7.0 ± 4.0; *P* = 0.5521; Cohen d = 0.4; effect size = 0.20). The brain CT score was comparable for those following commands at 3 months (1.9 ± 1.0) compared to patients not following commands (1.7 ± 1.2; *P* = 0.7279; Cohen d = 0.2; effect size = 0.09). The amount of mannitol was similar for those following commands at 3months (9.5 ± 26.4 g) compared to patients not following commands (25.0 ± 43.3 g; *P* = 0.3587; Cohen d = 0.4; effect size = 0.21).

Non-decompression patients with an ICP device

Compared to the non-decompression with no ICP device patients, the non-decompression patients with an ICP device had a lower initial

Table 4. Three-month following command status and HTS administration in patients with surgical decompression

Hypertonic Saline	< 1400 mEq Na^+	≥ 1400 mEq Na^+	
Total Patients	44 (77.2%)	13 (22.8%)	
Initial GCS Score	5.9 ± 3.0	6.1 ± 2.6	*P* = 0.8357
Brain CT Score	2.8 ± 0.5	2.8 ± 0.4	*P* = 0.7496
Amount of Mannitol (g)	30.8 ± 58.3	42.7 ± 58.9	*P* = 0.5209
Followed Commands at 3 Months	22 (50.0%)	10 (76.9%)	*P* = 0.0489
			Risk Ratio = 1.5
			(1.01-2.3)
mEq Na^+	710 ± 425	1803 ± 272	*P* < 0.0001
			Cohen d = 3.1
mEq Na^+ per kg body weight	8.9 ± 5.7	21.4 ± 5.0	*P* < 0.0001
			Cohen d = 2.3

HTS, hypertonic saline; mEq, milliequivalents; Na^+, sodium; GCS, Glasgow Coma Scale; CT, computed tomography; kg, kilograms; g, grams.

Table 5. Initial Glasgow Coma Scale score 5-8 command status at 3 months post-injury and HTS administration

Hypertonic Saline	< 1350 mEq Na^+	≥ 1350 mEq Na^+	
Total Patients	25 (65.8%)	13 (34.2%)	
Initial Glasgow Coma Scale Score	6.5 ± 1.2	6.6 ± 0.8	*P* = 0.8473
Brain CT Score	2.4 ± 1.0	2.4 ± 0.9	*P* = 0.9858
Followed Commands at 3 Months	15 (60.0%)	12 (92.3%)	
No Commands at 3 Months	10 (40.0%)	1 (7.7%)	*P* = 0.0214
			Risk Ratio = 1.5
			(1.1-2.2)
mEq Na^+	554 ± 448	1766 ± 468	*P* < 0.0001
			Cohen d = 2.7
mEq Na^+ per kg body weight	7.0 ± 5.8	23.4 ± 9.7	*P* < 0.0001
			Cohen d = 2.1

HTS, hypertonic saline; mEq, milliequivalents; Na^+, sodium; CT, computed tomography; kg, kilograms.

GCS score and lower proportion of following commands at 3 months (**Table 2**). Following an additional investigation of the EMR for the 14 non-decompression patients with an ICP device, a vehicular or motorcycle crash was the mechanism of injury in 12 (85.7%), brainstem dysfunction (decerebrate posturing, conjugate eye deviation, or abnormal pupillary function) at trauma center arrival was found in 7 (50.0%), intraventricular or subarachnoid hemorrhage was identified on brain CT scan in 12 (85.7%), and an ICP > 20 mmHg for < 10 hours during the first 96 hours was found in 11 (78.6%). Similar amounts of mEq sodium/kg body weight were administered to the patients dying in the trauma center (20.6 ± 5.7) compared to the survivors (19.4 ± 18.0; *P* = 0.9323) and those not following commands at 3 months (22.0 ± 16.3) compared to the cohort following commands (16.4 ± 18.2; *P* = 0.5537).

Patients with an initial GCS score 5-8

All 38 patients with an initial GCS score 5-8 were able to be categorized with an ability or inability to follow commands at 3 months (**Table 5**). Substantially larger amounts of HTS were associated with an increased proportion for following commands, despite similar brain CT and GCS scores. Results of multivariate logistic regression analysis demonstrated that following commands at 3 months was independently associated with ≥ 1350 mEq sodium administration (*P* = 0.0470), but not with initial GCS score (*P* = 0.7239), brain CT score (*P* = 0.4478), or amount of mannitol (*P* = 0.4014).

Subdural hematoma or cerebral contusion patients

Of the 110 patients who were able to be categorized with an ability or inability to follow commands at 3 months, 95 (86.4%) had a subdural hematoma or cerebral contusion (**Table 6**). Of those patients, substantially larger amounts of HTS were associated with an increased proportion for following commands, despite similar brain CT and GCS scores and amounts of mannitol. In the subdural hematoma or cerebral contusion group, results of multivariate logistic regression analysis demonstrated that follow-

Table 6. Subdural hematoma or cerebral contusion patients' command status at 3 months post-injury and HTS administration

Hypertonic Saline	< 1400 mEq Na^+	≥ 1400 mEq Na^+	
Total Patients	76 (80.0%)	19 (20.0%)	
Initial Glasgow Coma Scale Score	6.8 ± 3.3	6.1 ± 2.2	*P* = 0.4740
Brain CT Score	2.3 ± 0.9	2.6 ± 0.7	*P* = 0.3024
Amount of Mannitol (g)	21.1 ± 46.0	39.7 ± 57.9	*P* = 0.1384
Followed Commands at 3 Months	47 (61.8%)	16 (84.2%)	
No Commands at 3 Months	29 (38.2%)	3 (15.8%)	*P* = 0.0333
			Risk Ratio = 1.4
			(1.05-1.8)
mEq Na^+	558 ± 471	1840 ± 390	*P* < 0.0001
			Cohen d = 3.0
mEq Na^+ per kg body weight	7.0 ± 6.2	22.9 ± 7.9	*P* < 0.0001
			Cohen d = 2.2

HTS, hypertonic saline; mEq, milliequivalents; Na^+, sodium; CT, computed tomography; kg, kilograms; g, grams.

Table 7. Proportions of intracranial hypertension in patients with ICP device and HTS administration

Hours of ICP > 20 mmHg	≤ 10 Hours	≥ 11 Hours	
Total Patients	39 (79.6%)	10 (20.4%)	
Mean Hours	2.0 ± 2.9	34.0 ± 24.4	*P* = 0.0025
			Cohen d = 1.8
Brain CT Score	2.4 ± 0.9	2.7 ± 0.5	*P* = 0.4978
Initial Glasgow Coma Scale Score	6.0 ± 2.8	7.2 ± 3.2	*P* = 0.2957
Amount of Mannitol (g)	41.3 ± 58.2	74.3 ± 90.0	*P* = 0.2940
mEq Na^+ per kg body weight	16.5 ± 11.5	9.4 ± 6.3	*P* = 0.0139
			Cohen d = 0.8
≥ 515 mEq Na^+	36 (92.3%)	6 (60.0%)	*P* = 0.0134
			Risk Ratio = 1.5
			(0.9-2.6)

HTS, hypertonic saline; ICP, intracranial pressure; CT, computed tomography; mEq, milliequivalents; Na^+, sodium; kg, kilograms; g, grams; Hours of ICP > 20 mmHg is the number relative to the first 96 hours following trauma center arrival.

ing commands at 3 months was independently associated with ≥ 1400 mEq sodium (*P* = 0.0421) and an increasing initial GCS score (*P* = 0.0007).

Intracranial hypertension in patients with ICP device

For the 53 patients with an ICP device, ICP data were available from the EMR in 49 (92.5%). For the 39 patients with an ICP > 20 mmHg for ≤ 10 hours during the first 96 hours, the amounts of HTS were substantially more compared to those in the 10 patients with ICP > 20 mmHg for > 10 hours (**Table 7**). Results of multivariate logistic regression analysis demonstrated that ICP > 20 mmHg for ≤ 10 hours was independently associated with ≥ 515 mEq sodium (*P* = 0.0349), but not with the initial GCS score (*P* = 0.9686), brain CT score (*P* = 0.2732) or amount of mannitol (*P* = 0.1134).

Discussion

Complex TBI traits

Complex TBI is a reasonable clinically descriptive term for the study cohort when considering initial GCS values, the prevalence and diversity of intracranial hemorrhage, brain and ventricular deformations found on CT scans, frequent need for surgical decompression and ICP monitoring, duration of mechanical ventilation and substantial proportion of neurologic dysfunction at 3 months post-injury. The study inclusion requirement for ≥ 5 days of mechanical ventilation excluded the extremes of TBI severity; that is, patients who 1) proceeded to life support withdrawal within the first couple of days, 2) did not require tracheal intubation, and 3) could be extubated within a few days. The distribution of patients according to initial GCS values was similar for GCS score 3-4, 5-8, and 9-12 groups, thus providing a diverse array of neurologic dysfunction following traumatic injury. We found that the initial GCS score was associated with trauma center mortality and inability to follow commands at 3 months. Other investigators have also shown that the GCS score has an association with trauma center mortality [25, 26] and post-discharge

neurologic dysfunction and mortality [25, 27-30]. Nearly three-quarters of the study patients had a subdural hematoma, an intracranial pathology that has been associated with trauma center mortality [26], poor post-discharge neurologic function [27, 28], and the need for surgical decompression [31, 32]. Slightly more than half of the patients had subarachnoid hemorrhage, a CT finding that has also been linked to trauma center mortality [25, 26] and poor post-discharge neurologic function [25, 27, 30], possibly as a result of cerebral vasospasm or direct brainstem injury [33, 34].

The magnitude of intracranial pathology for the study patients was substantial, as demonstrated by the high proportions for midline shift, ventricular compression, and basal cistern compression. Other investigators have demonstrated the TBI clinical significance of midline shift [25, 27, 28], ventricular compression [35-37], and basal cistern compression [25, 27, 28]. The current study found that the brain CT score was higher in patients who underwent surgical decompression, a finding that was independent of the initial GCS values. We believe that these observations provide support for the validity of the CT score as a means for assessing the magnitude of intracranial hemorrhage, but recognize that other brain CT scoring systems have been more extensively investigated and proven valuable [27].

The inability to follow commands at 3 months in the study cohort with complex TBI was substantial, a finding documented by several other investigators [25, 27, 28]. The inability to follow commands at 3 months varied according to the categorization of neurosurgical intervention. Although other investigators have demonstrated that post-discharge neurologic function has an association with subdural hematoma [27, 28], subarachnoid hemorrhage [25, 27], intraventricular hemorrhage [27], brain parenchymal and ventricular deformation [25, 27, 28], GCS score [27, 28, 30], and pupillary dysfunction [27, 28, 30], we are not aware of an investigation separating patients according to neurosurgical interventions. The 2-week duration of mechanical ventilation demonstrated the acute morbidity and severity of illness for these patients with complex TBI and is similar to that documented for other cohorts with severe TBI [38, 39].

HTS in patients with surgical decompression

Among the three neurosurgical intervention groups, the patients with surgical decompression had the lowest initial GCS score, highest brain CT score and proportion of subdural hematoma, an intermediate amount of HTS, and an in-between proportion for not following commands at 3 months. Of the patients with surgical decompression, most had a craniectomy and the others underwent a craniotomy. A comparison of the two groups showed similar initial GCS scores, brain CT scores, proportions of trauma center death, and ability to follow commands at trauma center discharge. Because of these similarities, the patients with craniectomy and craniotomy were considered a single group, surgical decompression. While some investigators have demonstrated superior outcomes for craniectomy when compared to craniotomy [40], others have shown that post-procedural effects are similar [31].

For the patients with surgical decompression, trauma center mortality was higher for those receiving lesser amounts of HTS. At the designated cut point, the amounts of HTS were substantially different for the two groups. The similarity of brain CT score values for the two HTS cohorts and the independent association of the smaller HTS quantity with death, relative to the initial GCS and the amount of mannitol, diminish the likelihood that confounding factors accounted for the association of increased mortality with the lower amounts of HTS.

For the patients with surgical decompression, the proportion of those following commands at 3 months was higher for those receiving larger amounts of HTS. At the designated cut point, the amounts of HTS were substantially different for the two groups. The similarity of brain CT scores, initial GCS scores, and amounts of mannitol for the two HTS cohorts decrease the likelihood that confounding factors accounted for the association of increased ability to follow commands with the larger amounts of HTS.

HTS in non-decompression patients with no ICP device

Among the three neurosurgical intervention groups, the non-decompression patients with no ICP device had the highest initial GCS score, an intermediate brain CT score and proportion

of subdural hematoma, and the highest proportion for following commands at 3 months. The non-decompression patients with no ICP device had the least amount of HTS administration with nearly 50% receiving no HTS. For the trauma center survivors in the non-decompression patients with no ICP device, the amount of HTS was greater for those following commands at 3 months. The similarity of brain CT scores, initial GCS scores, and amounts of mannitol for the two HTS cohorts diminish the likelihood that confounding factors other than the larger amounts of HTS accounted for its association with the ability to follow commands.

HTS in non-decompression patients with an ICP device

Among the three neurosurgical intervention groups, the non-decompression patients with an ICP device had an intermediate initial GCS score, lowest brain CT score and proportion of subdural hematoma, the highest proportion of subarachnoid hemorrhage, greatest amount of HTS, and lowest proportion for following commands at 3 months. Following an additional investigation of the EMR for the 14 non-decompression patients with an ICP device, a vehicular or motorcycle crash was the mechanism of injury in 90%, brainstem dysfunction at trauma center arrival was found in 50%, intraventricular or subarachnoid hemorrhage was identified in 90%, and an ICP > 20 mmHg for < 10 hours during the first 96 hours was found in 80%. Other investigators have shown that post-discharge neurologic impairment is associated with clinical signs of brainstem dysfunction [27, 28, 41, 42], intraventricular hemorrhage [27], and subarachnoid hemorrhage [25, 27, 30].

The relatively low brain CT score, small proportion of intracranial hypertension, and comparatively low proportion of subdural hematoma in this group suggest that volumes of brain swelling and intracranial hemorrhage were less than that of the other two neurosurgical intervention groups. It seems likely that the presence of intracranial hypertension or manifestations of brainstem dysfunction might have been factors responsible for this group receiving the greatest amount of HTS. It is interesting that similar amounts of HTS were administered to the patients dying in the trauma center compared to the survivors and those not following commands at 3 months when contrasted with the cohort following commands. These observations suggest that the administration of HTS in this group was neither beneficial nor harmful and that outcomes were likely related to the underlying traumatic brain pathology. It is appealing to speculate that these patients likely had shearing or hemorrhagic injuries involving the brainstem, because clinical brainstem dysfunction, intraventricular hemorrhage, subarachnoid hemorrhage, and vehicular and motorcycle crash mechanisms were prevalent. Other experts cite evidence that primary brainstem injury is common in the presence of intraventricular hemorrhage, subarachnoid hemorrhage, signs of brainstem dysfunction, and TBI following vehicular crashes [33, 34].

Patients with initial GCS score 5-8

All 38 patients with initial GCS score 5-8 were able to be categorized with an ability or inability to follow commands at 3 months. Substantially larger amounts of HTS were associated with an increased proportion for following commands, despite similar brain CT and GCS scores. Results of multivariate logistic regression analysis demonstrated that following commands at 3 months was independently associated with ≥ 1350 mEq sodium administration, but not with initial GCS score, brain CT score, or amount of mannitol. At the designated cut point, the amounts of HTS were substantially different for the two groups. The similarity of brain CT score and initial GCS values for the two HTS cohorts and the independent association for following commands with the higher quantity of HTS, but the lack of effect for the initial GCS score, brain CT score, and mannitol administration diminish the likelihood that confounding factors accounted for the association of an increased proportion of following commands with the higher amounts of HTS.

Patients with subdural hematoma or cerebral contusion

Of the 110 patients who were able to be categorized with an ability or inability to follow commands at 3 months, 86% had a subdural hematoma or cerebral contusion. Of those patients, substantially larger amounts of HTS were associated with an increased proportion for following commands, despite similar brain CT and GCS scores and amounts of mannitol. In the subdural hematoma or cerebral contusion group, results of multivariate logistic regression analysis demonstrated that following com-

mands at 3 months was independently associated with ≥ 1400 mEq sodium administration and an increasing initial GCS score. Specifically, at the designated cut point, the amounts of HTS were substantially different for the two groups. The similarity of brain CT score and initial GCS values and amounts of mannitol administered in the two HTS cohorts decreases the likelihood that confounding factors accounted for the association of an increased proportion of following commands with the higher amounts of HTS. It seems relevant that other investigators have found cerebral edema to be a common occurrence with subdural hematomas [43-46] and cerebral contusions [33]. This is consistent with the notion that HTS administration may be of greatest benefit for those at risk for brain swelling.

Intracranial hypertension in patients with ICP device

For the patients with an ICP device, those with an ICP > 20 mmHg for ≤ 10 hours during the first 96 hours had amounts of HTS that were substantially greater than patients with ICP > 20 mmHg for > 10 hours. The brain CT and initial GCS values and the amounts of mannitol were similar for those without or with clinically significant intracranial hypertension. Results of multivariate logistic regression analysis demonstrated that ICP > 20 mmHg for ≤ 10 hours was independently associated with ≥ 515 mEq sodium administration, but not with the initial GCS score, brain CT score, or amount of mannitol administration. The similarity of the brain CT score, initial GCS score, and amounts of mannitol for the cohorts without and with clinically significant intracranial hypertension and the independent association of minimal intracranial hypertension with the higher quantity of HTS, but the lack of effect for the initial GCS score, brain CT score, and mannitol administration diminish the likelihood that confounding factors accounted for the association of less intracranial hypertension with the larger amounts of HTS. These observations are consistent with numerous other investigators who have demonstrated that HTS is effective in decreasing ICP [1-6, 8-10].

HTS and hypernatremia

The amounts of HTS administered over the first 5 trauma center days varied substantially with a third receiving no HTS, a quarter receiving 1-2 L of 3% sodium chloride, and the other 40% over 2 L. For the entire cohort of patients, the day 5 serum sodium concentration was at the upper limit of normal. The day 5 serum sodium concentration was greater in those receiving 1 or more liters of 3% sodium chloride than in those receiving a lesser amount. Other investigators have also demonstrated that HTS administration in patients with TBI is associated with an increase in serum sodium concentration [1, 3, 8-10]. In the current study, hypernatremia (serum sodium concentration ≥ 155 mEq/L) was associated with an insignificantly higher trauma center mortality and inability to follow commands at 3 months. However, results of multivariate regression analysis demonstrated that these outcomes were associated with the initial GCS score, but not to hypernatremia. In a review of hypernatremia in severe TBI, Kolmodin, et al. were unable to find a convincing association between hypernatremia and intensive care unit or 14-day mortality [47].

HTS and TBI outcomes

As described in the Introduction, there is ample evidence that HTS is associated with a reduction in ICP for patients with intracranial hypertension. On the other hand, several experts, following reviews of the literature, have opined that there is little evidence to suggest that TBI outcomes are improved, harmed, or without effect when HTS is administered or hypernatremia is induced [16, 48-50]. Further, the 2016 guidelines by the Brain Trauma Foundation imply that there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe TBI [51]. The creators of the guidelines acknowledged that “more research is needed to inform more specific recommendations” [51]. The current investigation provides six analyses, which suggest that larger amounts of HTS are associated with desirable outcomes, when compared to lesser quantities. We enthusiastically await the results of the Roquilly 2017 trial to determine if their prospective design confirms our retrospective observations [16].

Dose titration of HTS

For the six analyses demonstrating clinically beneficial outcomes, the mean amounts of so-

dium in mEq administered to the cohorts receiving the larger amounts were 1250, 1803, 513, 1766, 1840, and 1320. The sum of these values divided by six is approximately 1400 mEq of sodium over the first 5 trauma center days. When administering HTS to patients with TBI at our institution, a common practice was to increase the serum sodium by 8 mEq per L over the subsequent 24-hour period. Using a formula similar to that described by Ropper, 8 mEq sodium × body weight (kg) × 60% was commonly used to compute the mEq of sodium to be administered during the 24-hour period [49]. Over a 4-day period, this would be approximately 1536 mEq of sodium in an 80-kg person and 1344 mEq in a 70-kg individual. Thus, the administration according to that practice is in harmony with the amounts seen in the analyses where valued outcome associations occurred. In the investigation by Ichai, et al., the mean amount of sodium administered was 1332 mEq for the HTS group, an observation that is in agreement with the current investigation [10].

The study proposal for the Roquilly 2017 trial provides an initial bolus and maintenance dosing regimen based on a current serum sodium level for the patients randomized to receive HTS [16]. We have estimated that an average patient would likely receive approximately 800 mEq of sodium over 48 hours or 1400 mEq over 96 hours. Obviously, this estimate involves substantial speculation, but the estimated amounts are similar to those observed in the current study. We expect that the Roquilly 2017 trial will likely explore dose-response relationships, because the HTS dosing patterns will be similar to the current investigation in that some patients will receive no HTS while others will receive varying amounts of HTS [16].

Limitations

The principal limitation to this investigation is that the study design is retrospective and that the patient cohort emanates from a single institution. Other investigations may produce different results if the design involves multiple institutions, is prospective, or assesses patients with dissimilar TBI characteristics. A prospective study is needed to provide an independent set of observations and determine if they are similar or disparate relative to the results presented in the current work.

Conclusions

The current investigation provides multiple analyses to indicate that beneficial outcomes have an association with the administration of larger amounts of HTS. That is, specific groups of patients with complex TBI had higher proportions of trauma center survival, intracranial hypertension containment, and ability to follow commands at 3 months, when given larger quantities of HTS. This suggests that certain TBI cohorts may benefit from HTS administration, while this strategy may be of minimal value for patients with other characteristics. We found no evidence that advanced hypernatremia was detrimental relative to adverse patient outcomes. The findings in the current investigation and the literature suggest that approximately 1000+ mEq sodium over 4-5 days may be necessary to demonstrate that HTS is associated with neurological outcomes; however, more research is needed. Although the current investigation has a retrospective study design, we believe that it is likely that the randomized control trial by Roquilly, et al. will produce similar results.

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Disclosure of conflict of interest

None.

Abbreviations

CT, computed tomography; EMR, electronic medical record; GCS, Glasgow Coma Scale; g, grams; HTS, hypertonic saline; ICP, intracranial pressure; kg, kilograms of body weight; mEq, milliequivalents; Na^+, sodium; TBI, traumatic brain injury.

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