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Hematoma Enlargement Among Patients with Traumatic Brain Injury: Analysis of a Prospective Multicenter Clinical Trial

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Abstract

Observational studies suggest that hematomas continue to enlarge during hospitalization in patients with traumatic brain injury (TBI). There is limited data regarding factors associated with hematoma enlargement and on whether hematoma enlargement contributes directly to death and disability in patients with TBI.

We analyzed data collected as part of the Resuscitation Outcomes Consortium Hypertonic Saline and TBI Study. Hematoma enlargement was ascertained and collected as a predefined safety endpoint. We evaluated the effect of hematoma enlargement on the risk of death and disability at 6 months based on the Extended Glasgow Outcome Scale (GOSE) (dichotomized as >4 or ≤4) using stepwise logistic regression analysis. We adjusted for age (continuous variable), admission GCS score (dichotomized at >5 and ≤5), and computed tomography (CT) scan classification (Marshall grades entered as a categorical variable).

Of the 1200 patients with severe TBI analyzed, 238 (19.8%) patients were reported to have hematoma enlargement as an adverse event. The proportion of patients who reached favorable outcome at 6 months was significantly lower (defined by GOSE of >4) among patients with hematoma enlargement (29.0% vs. 40.1%, p<.0001). The proportion of patients who died within 6 months was significantly higher among patients with hematoma enlargement (31.9% vs. 20.7%, p<.0001). After adjusting for age, admission GCS score, and initial injury score, the odds of favorable outcome was lower in patients with hematoma enlargement (odds ratio 0.7, 95% confidence interval [CI]; 0.5–0.97).

Our results suggest that hematoma enlargement may be a direct contributor to death and disability in patients with TBI at 6 months. Future clinical trials must continue to evaluate new therapeutic interventions aimed at reducing hematoma enlargement with a favorable risk benefit ratio in patients with TBI.

Keywords

traumatic brain injury; hematoma enlargement; extended Glasgow Outcome Scale; hypertonic saline; mortality

Background

Observational studies have suggested that intracranial hemorrhage continues to enlarge in almost 30–42% of patients with traumatic brain injury (TBI) [1–3]. The risk of hematoma enlargement is higher in patients who are studied early after occurrence of TBI [3]. In an observational study, hematoma enlargement was observed in 51% of the 63 patients with initial computed tomography (CT) scan performed within 4 hours of TBI [4]. Identification of factors associated with, or predictive of, hematoma enlargement in patients with TBI may be important to identify a group of patients who are high risk, and in whom the risk benefit ratio of new therapeutic strategies may be acceptable. Hematoma enlargement appears to be associated with a high rate of neurological deterioration in patients with TBI [5,6]. In a study of 171 patients, 54 (32%) suffered progressive brain injury

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due to enlargement of intracranial hemorrhages [7]. However, previous studies have been unable to conclusively determine whether hematoma enlargement contributes directly to death and disability or is a manifestation of severe TBI[3,7] and thus not an appropriate therapeutic target.

We performed this study to address some of the aforementioned issues regarding hematoma enlargement in a prospectively studied cohort of patients with TBI.

Methods

We analyzed data collected as part of the Resuscitation Outcomes Consortium Hypertonic Saline (ROC HS) Trial Shock Study and Traumatic Brain Injury (TBI) Study. The details regarding the trial have been published previously [8]. Briefly, a multicenter, double-blind, randomized, placebo-controlled clinical trial involving 114 North American emergency medical services agencies, within the ROC, was conducted between May 2006 and May 2009. The study sought to determine whether prehospital administration of 7.5% hypertonic saline/dextran, compared to current standard therapy with normal saline, as an initial resuscitation fluid, affects survival following traumatic injury with hypovolemic shock or severe TBI as manifested by a prehospital Glasgow coma score (GCS) of 8 or less. The study was terminated by the data and safety monitoring board after randomization of 1331 patients, having met prespecified futility criteria. We included the TBI cohort in our analysis, which included patients with blunt trauma, prehospital GCS score ≤ 8, and age ≥15 years or weight ≥50kg. Patients with TBI, who met the criteria for hypovolemic shock, were included in the shock cohort. Patients were randomized to a single dose 7.5% saline in 6% Dextran-70 (250cc), 7.5% saline (no dextran) (250cc), or crystalloid (250cc) as the initial fluid for prehospital resuscitation. In an effort to minimize variability in the subsequent care of trauma patients, all sites agreed to encourage the implementation of resuscitation and critical care management guidelines, which included clinical protocol for trauma resuscitation, transfusion guidelines, intensive care unit (ICU) insulin infusion/blood glucose control, sedation/analgesia protocol for mechanical ventilation, mechanical ventilation protocol, venous thromboembolism prophylaxis, protocol for ventilator associated pneumonia, and management of severe TBI.

This initial data, including demographics, mechanism of injury, prehospital and emergency department (ED) hemodynamic variables, time to definitive care, mode of transport, injury severity score (ISS), the presence of TBI, and total fluids in the first 12 hours were collected prospectively as patient care progressed. Data collection was based on a daily review of the medical records and results of diagnostic studies. All in-hospital electrolyte levels in the first 24 hours were tracked. Information regarding the initial resuscitation of the patient, intracranial pressure (ICP) monitoring and management, neurologic assessment based on the GCS, and adherence to the clinical care guidelines was collected. Serum sodium values upon admission and every 8 hours for the first 24 hours were collected for all patients requiring ICU admission. Any sodium value >160 mEq/L requiring therapeutic intervention, any seizure activity associated with hypernatremia, and any sodium values > 160 mEq/L without intervention, were considered serious adverse events. Total fluid and blood products required in the first 24 hours and coagulation parameters on admission were recorded for all patients. For patients with TBI, the results of the first three head CT scans obtained within the first week after injury were collected. ICP and cerebral perfusion pressure (CPP) at the time of ICP monitor placement, total hours of ICP >25 mmHg and CPP <60 mmHg (measured in increments of 15 minutes), and total amount of mannitol administered in 12-hour period of time for the first 48 hours after injury were also collected. The time interval between TBI onset and CT scan was estimated as the sum of time intervals between 911 call and ED admission and between ED admission and CT scan.

Certain adverse events were collected as safety endpoints, which included evidence of increased intracranial hemorrhage on head CT scan. All members of the trauma team were instructed as to recognize the possible adverse events prior to initiation of the trial and were instructed to immediately report any suspected adverse event to the investigators using an emergency contact number. Any expeditable serious and life-threatening adverse event was reported to the Food and Drug Administration (FDA), Institutional Review Board (IRB), and chairperson of the Data Monitoring Committee (DMC) within 72 hours by telephone, and by a written report, submitted within 7 days. All nonlife-threatening unexpected serious adverse events were reported in writing within 15 days. The main outcome measure was six-month neurologic outcome based on the Extended Glasgow Outcome Scale (GOSE) (dichotomized as >4 or ≤4) obtained by telephone survey. Additional neurological outcomes included disability rating score (DRS) (at discharge and 6 months), and 28-day and 6-month survival.

We performed all analyses using the IBM SPSS 20 statistical software (IBM Corp., Armonk, NY). Means and frequencies were compared using one-way analysis of variance and the [chi] [2] method, respectively. We evaluated the association of hematoma enlargement with the patients' demographic and clinical and laboratory characteristics. Baseline variables of interest included age, race, gender, initial systolic blood pressure (BP), admission GCS, baseline hemoglobin level, platelet count, fibrinogen levels, and sodium levels. These variables were dichotomized based on either median values (e.g., GCS score, serum sodium) or normal ranges (e.g., baseline hemoglobin) to identify clinically meaningful cutoff values for defining association.

We evaluated the effect of hematoma enlargement on the risk of death and disability at 6 months based on GOSE (dichotomized as >4 or ≤4) [9] using stepwise logistic regression analysis. We adjusted for age (continuous variable), admission GCS score (dichotomized at >5 and ≤5), and CT scan classification (Marshall grades II, III, and mass lesion entered as a categorical variable) [10–12]. Because our study cohort also included polytrauma patients, we adjusted for ISS (dichotomized at >26 and ≤26) in the model [13–15]. A second multivariate analysis was performed using death within 6 months as the dependent variable and the model was adjusted for the same potential confounding factors as mentioned above. A p value below 0.05 was defined as an entry criterion in each of the stepwise regressions. A p value below 0.05 was considered significant.

Results

Of the total of 1224 patients with severe TBI recruited in the trials, 1200 were analyzed. Patients who died en route (n = 4) and those who died on arrival to the ED (n = 54) were excluded. The mean age (± standard deviation [SD]) of the study cohort was 39±18 years and the median GCS score was 3 (range 3). There were 238 (19.8%) patients who were reported to have hematoma enlargement as an adverse event. The mean (95% confidence interval [CI]) estimated time interval between TBI onset and CT scan was 114 minutes (95% CI: 100–127) and 130 minutes (95% CI: 116–144) in patients with and without hematoma enlargement (p value = 0.26), respectively.

The mean age (±SD) of patients who had hematoma enlargement was similar in patients who underwent hematoma enlargement compared with those who did not have enlargement (39±17 vs. 39±18 years, p = 0.9). There were no differences between the two groups in regards to gender and race/ethnicity. The mean initial systolic BP was higher in patients with hematoma enlargement than those without hematoma enlargement (146±30 vs. 140±30, p = 0.01). The proportion of patients with admission GCS score ≤5 was higher among patients who underwent hematoma enlargement. The ISS was significantly higher among those who underwent hematoma enlargement. The proportion of patients with ISS score >26 was significantly higher among those with hematoma enlargement. There was a trend for mean fibrinogen levels to be lower among those who underwent hematoma enlargement. There was no difference in proportion of patients randomized to hypertonic saline with or without dextran in patients who had hematoma enlargement compared with those who did not have hematoma enlargement. The proportion of patients with diffuse injury types II and III, and mass lesions on initial CT scans were higher among patients who underwent hematoma enlargement.

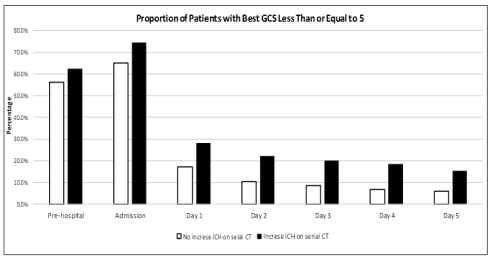

Figure 1. The proportion of surviving patients with Glasgow Coma Scale (Gcs) score of ≤5 in severe Tbi patients with and without hematoma expansion expressed on a daily basis.

The proportion of patients with best GCS ≤5 continued to be higher among patients with hematoma enlargement on Days 2 through 5 (Fig. 1). The requirements for ICP monitoring, ventriculostomy, and craniotomy were higher among patients with hematoma enlargement, which was evident within the first 12 hours. The hours of time spent with ICP>25 mm Hg, CPP<60 mmHg, and the proportion of patients with serum sodium >145 mmol/L within the first 12 hours was not different between patients who underwent hematoma enlargement compared with those who did not have enlargement. The mean amount of mannitol used (g/kg) in the first 12 hours was higher among those who underwent hematoma enlargement. A significantly higher proportion of

Table 1. The association of hematoma enlargement with the patients' demographic, and clinical and laboratory characteristics in patients with severe Tbi

	Patients without hematoma enlargement	Patients with hematoma enlargement	*p*-value
Overall number (%)	962	238	
Age, mean±SD	39±18	39±17	0.9
Gender			
Men	738(76.7)	176(73.9)	
Women	224(23.3)	62(26.1)	0.4
Race/ethnicity			
Asian	27(2.8)	9(3.8)	
African American	93(9.7)	12 (5.0)	
White	489(50.8)	114(47.9)	
Other	12(1.2)	3(1.3)	
Hispanic or Latino	19 (2.0)	7(2.9)	0.2
Randomization group			
Hypertonic saline/dextran	279(29.0)	56(23.5)	
Hypertonic saline	260(27.0)	60(25.2)	
Normal saline	423(44.0)	122(51.3)	0.1
Out-of-hospital GCS (median, range)	5±2	4±2	0.4
Out-of-hospital GCS >5	421(43.8)	11(4.6)	
Out-of-hospital GCS ≤5	399(41.5)	149(62.6)	0.08
ISS, (median, range)	24±16	33±12	<.0001
ISS >26	368(38.3)	151(63.4)	
ISS ≤26	575(59.8)	85(35.7)	<.0001
Marshall Score, first head CT scan			
Diffuse injury I	366(38.0)	6(2.5)	
Diffuse injury II	319(33.2)	114(47.9)	
Diffuse injury III	101(10.5)	44(18.5)	
Diffuse injury IV	31(3.2)	12(5.0)	
Mass lesion	132(13.7)	59(24.8)	
Others	12(1.2)	3(1.3)	<0.0001
Out-of-hospital advanced airway	573(59.6)	151(63.4)	0.3
Time from dispatch call to fluid administration, min (mean±SD)	35.0±23.6	34.7±22.5	0.9
Total out-of-hospital time, min (mean±SD)	57.1±29.4	54.8±27.3	0.3
Out-of-hospital fluids, L (mean±SD)	0.8±0.6	0.8+0.7	0.7

Abbreviations: CT, computed tomography; GCS, Glasgow Coma Score; ISS, Injury Severity Score; L, liters; min, minutes; Range for GCS, 3 through 15; range for ISS, 0 through 75; SD, Standard deviation

patients required mannitol, additional hypertonic saline, and hyperventilation within the first 5 days among patients who underwent hematoma enlargement. The amount of fresh frozen plasma, cryoprecipitate, and platelets transfused were higher among patients who underwent hematoma enlargement. There were significantly higher rates of in-hospital adverse events, including pneumonias, urinary tract infections, and overall nosocomial infections, in patients who underwent hematoma enlargement. The total ICU days and hospital days were significantly higher, and ventilator free days were significantly lower among patients with hematoma enlargement.

The proportions of patients in DRS categories of moderately severe/severe/extremely severe or vegetative/extreme vegetative/dead were significantly higher among patients with hematoma enlargement compared with those without enlargement at both 1 month and 6 months. The proportion of patients who reached favorable outcome at 6 months was significantly lower (defined by GOSE of >4) among patients with hematoma enlargement (29.0% vs. 40.1%, p <.0001). The proportion of patients who died within 6 months was significantly higher among patients with hematoma enlargement (31.9% vs. 20.7%, p<.0001). After adjusting for age, admission GCS score, and initial trauma score, the odds of favorable outcome was lower in patients with hematoma enlargement (odds ratio [OR] 0.7, 95% CI; 0.5–0.97). After adjusting for age, admission GCS score, and initial trauma score, the odds of 6 month survival was not significantly lower in patients with hematoma enlargement (OR 0.9, 95% CI; 0.6–1.2).

Discussion

In our cohort of severe patients with TBI, hematoma enlargement was observed in 20% of the patients who survived prehospital resuscitation. The proportions of patients in DRS categories of severe, vegetative and dead were significantly higher among patients with hematoma enlargement at both 1 month and 6 months. The rate of favorable outcomes and survival at 6 months was significantly lower among patients who underwent hematoma enlargement. It is possible that hematoma enlargement was a manifestation of severe TBI and higher rates of death and disability are related to severity of initial TBI. In such circumstances, preventing, or ameliorating, hematoma enlargement is unlikely to reduce the death and disability associated with TBI. We

Table 2. The association of hematoma enlargement with in-hospital physiological parameters, therapeutic interventions, and adverse events in patients with severe TBI.

	Patients without hematoma enlargement	Patients with hematoma enlargement	P-value
Overall number (%)	962	238	
Admission physiology			
Admission systolic blood pressure, mmHg (mean±SD)	140 ± 30	146 ± 30	0.01
Admission systolic blood pressure ≤140 mmHg	499(51.9)	106(44.5)	
Admission systolic blood pressure >140 mmHg	463(48.1)	132(55.5)	0.04
Admission systolic blood pressure ≤90 mmHg	49(5.1)	9(3.8)	0.4
Admission GCS (median, range)	3 ± 4	3 ± 3	0.002
Admission GCS >5	334(34.7)	61(25.6)	
Admission GCS ≤5	625(65.0)	177(74.4)	0.007
Hemoglobin g/dL (mean±SD)	12.8 ± 2.2	12.6 ± 2.2	0.4
Admission INR (mean±SD)	1.2 ± 0.5	1.2 ± 0.4	0.6
Admission serum sodium, mEq/L (mean±SD)	143 ± 5.8	142 ± 6.1	0.05
Serum sodium >145 mEq/L			
At 0–4 h	361(37.5)	82(34.5)	0.3
At 4–12 h	222(23.1)	76(31.9)	0.1
At 12–24 h	173(18.0)	72(30.3)	0.01
First ED platelet count (mean±SD)	237660 ± 72316	236770 ± 70542	0.9
First ED fibrinogen level, mg/dL (mean±SD)	227.4 ± 102.6	205.5 ± 72.8	0.06
Neurologic monitoring			
ICP monitored	207(21.5)	146(61.3)	<.0001
Initial ICP, mmHg (mean±SD)	16±15	19±14	0.1
Initial ICP ≥25 mmHg	32(3.3)	31(13.0)	
Initial ICP <25 mmHg	152(15.8)	97(40.8)	0.1
Highest ICP in the first 12h, mmHg (mean±SD)	23±19	27±18	0.05
Highest ICP ≥25 mmHg in first 12 h	64(6.7)	63(26.5)	
Highest ICP <25 mmHg in first 12 h	139(14.4)	82(34.5)	0.02
Hours with ICP >25 mmHg in the first 12 h (mean±SD)	0.9 ± 2.6	1.3 ± 2.8	0.1
Initial CPP, mmHg (mean ± SD)	73.9 ± 22.3	72.2 ± 20.3	0.5
Initial CPP ≥60 mmHg	142(14.8)	82(34.5)	
Initial CPP <60 mmHg	35(3.6)	28(11.8)	0.3
Hours with CPP <60 mmHg in first 12h (mean±SD)	1.6 ± 3.0	1.8 ± 3.1	0.5
Interventions for intracranial hypertension			
Total mannitol in first 12 h, g/kg (mean(95%CI))	5.5(2.4–8.6)	12.4(7.5–17.4)	0.01
Mannitol in first 5 d	152(15.8)	99(41.6)	<.0001
Additional hypertonic fluids in first 5d	82(8.5)	54(23.9)	<.0001
Hyperventilation			
First 24 h	10(1.0)	13(5.5)	<.0001
First 5 d	15(1.6)	13(5.5)	<.0001
Ventriculostomy			
First 24 h	75(7.8)	73(30.7)	<.0001
First 5 d	80(8.3)	80(33.6)	<.0001
Craniotomy			
First 24 h	83(8.6)	71(29.8)	<.0001
First 5 d	88(9.1)	79(33.2)	<.0001
In hospital management			
Intubated in ED	280(29.1)	91(38.2)	0.006
FFP (mL) given (mean(95%CI))	217.7(177.8-257.6)	416.0 (295.7-536.4)	<.0001
Cryoprecipitate (mL) given (mean(95%CI))	8.0 (5.0-11.0)	18.2(7.4-29.0)	0.01
Platelets (mL) given (mean(95%CI))	39.9(27.0-52.7)	96.9(58.0-135.7)	0.001
Total Fluids in First 24hrs, L (mean±SD)	6.5±5.4	8.2±5.7	<.0001
Adverse events			
≥1 Nosocomial infections	235(24.4)	101(42.4)	<.0001
Pneumonia	168(17.5)	73(30.7)	<.0001
Bloodstream infection	44(4.6)	19(8.0)	0.05
Urinary tract infection	66(6.9)	27(11.3)	0.04
Wound infection	19(2.0)	13(5.5)	0.005
Hypernatremia (sodium >160 mEq/L) requiring intervention	25(2.6)	12(5.0)	0.05
Seizures in first 24 h	18(1.9)	1(0.4)	0.1

Abbreviations: CI, confidence interval; CPP, cerebral perfusion pressure; d, days; ED, emergency department; FFP, fresh frozen plasma; GCS, Glasgow Coma Score; h, hours; ICP, intracranial pressure; INR, International normalization ratio; SD, standard deviation

performed multivariate analysis to adjust for known predictors, such as age, admission GCS score, admission ISS, and CT scan findings. Hematoma enlargement reduced the odds of favorable outcomes at 6 months, independent of the known predictors of 6-month outcome in patients with TBI. Therefore, it appears that hematoma enlargement directly contributes to death and disability among patients with TBI. Our ability to conclusively demonstrate the relationship between hematoma enlargement and 6-month outcome is related to the large sample size and high compliance with the 6-month follow-up assessment. Previous smaller studies have supported our conclusions. Oertel et al.,[3] in a study of 142 patients with TBI, reported that 17% of patients

Table 3. The association of hematoma enlargement with outcome measures in patients with severe TBI.

	Patients without hematoma enlargement	Patients with hematoma enlargement	P-value
Overall number (%)	962	238	
Outcome			
6-month GOSE ≤4	410(42.6)	147(61.8)	
6-month GOSE >4	386(40.1)	69(29.0)	<.0001
DRS categories of disability - 1 month			
0–1 (none/mild)	109(11.3)	16 (6.7)	
2–6 (partial/moderate)	172(17.9)	50(21.0)	
7–21(moderately severe/severe/extremely severe)	41(4.3)	13(5.5)	
22–30 (vegetative/extreme vegetative/dead)	199(20.7)	75(31.5)	0.02
DRS categories of disability - 6 month			
0–1 (none/mild)	304(31.6)	47(19.7)	
2–6 (partial/moderate)	221(23.0)	67(28.2)	
7–21 (moderately severe/severe/extremely severe)	63(6.5)	24(10.1)	
22–30 (vegetative/extreme vegetative/dead)	206(21.4)	78(32.8)	<.0001
28-day survival	779(81.0)	172(72.3)	0.002
6 month survival	763(79.3)	162(68.1)	<.0001
Ventilator-free days, (mean±SD)	19.4 ± 11.1	14.1 ± 10.6	<.0001
Total ICU days, (mean±SD)	7 ± 13	11 ± 10	<.0001
Total hospital days, (mean±SD)	16 ± 25	26 ± 27	<.0001

Abbreviations:; DRS, Disability Rating Score; GOSE, Extended Glasgow Outcome Score; ICU, intensive care unit; SD, standard deviation

with hematoma enlargement and 28% of patients without hematoma enlargement had a favorable neurological outcome at discharge (p = 0.13). Six-month follow-up data were obtained in only 51% of patients. At 6 months, a favorable neurological outcome was seen in 60% of patients with hematoma enlargement and in 70% of those without hematoma enlargement, respectively (p = 0.34). Narayan et al.,[4] in a study of 64 patients, reported that 7 of 35 (20%) TBI patients with hematoma expansion and 1 of 25 (4%) TBI patients without hematoma expansion died.

The most likely explanation is that the higher death and disability was due to secondary neurological injury among those who underwent hematoma enlargement. The proportion of patients with GCS score ≤5 remained greater over each successive day, postadmission, among those with hematoma enlargement. The requirement for mannitol, additional hypertonic saline, and hyperventilation was higher within the first 5 days among patients who underwent hematoma enlargement. Such observations suggest a higher rate of secondary neurological injury among those who underwent hematoma enlargement. The higher proportion of in-hospital adverse events such as nosocomial infections may have contributed to increasing the rate of death and disability among patients with hematoma enlargement. Our observations are similar to the study by Oertel et al.,[3] which reported that the proportion of patients with mean daily ICP > 20 mmHg was higher in those with hematoma enlargement compared with those without hematoma enlargement. Previous investigators also reported that patients who undergo hematoma enlargement have larger hemorrhages and a higher frequency of subdural hemorrhages and/or subarachnoid hemorrhages on initial CT scan [4,16]. This may further predispose such patients to the exaggerated detrimental effect of increase in intracranial mass effect, due to limited intracranial compliance.

Previous studies have not been able to identify consistent predictors of hematoma enlargement [2]. Patients who undergo early CT scan after TBI are more likely to undergo hematoma enlargement [1,3,4,7], although some studies including ours have not confirmed this observation [2]. We observed that GCS ≤5 and ISS ≤26, at admission, were associated with a higher rate of hematoma enlargement. The relationship between lower GCS and hematoma enlargement in patients with TBI was also identified by Chieregato et al [16]. Large size intraparenchymal hemorrhages, subdural hemorrhages, and/or subarachnoid hemorrhages on initial CT scan appear to be associated with a higher risk of hematoma enlargement [4,16]. We observed that the pattern of injury on initial CT scan (categorized by the Marshall classification) was associated with a risk of hematoma enlargement similar to a previous study [16]. Elevated international normalized ratio (INR) or D-dimer concentrations were associated with hematoma enlargement [7]. Similar to our study, other studies have not been able to demonstrate any relationship between laboratory measures of coagulopathy and hematoma enlargement [2]. However, patients who underwent hematoma enlargement in our study were more likely to receive fresh frozen plasma, cryoprecipitate, and platelet transfusions presumably to prevent further enlargement once CT scan evidence of hematoma enlargement was detected. Furthermore, we wanted to study the effect of hypertonic saline, which has become a commonly used agent in the treatment of severe TBI, [17–20] on hematoma enlargement. Hypertonic saline decreases platelet function, impairs the integrity of the plasma coagulation system, [21,22] and may increase the rate of hematoma

enlargement in patients with TBI. We did not observe any evidence to support that hypertonic saline bolus increases the risk of hematoma enlargement.

Our analysis has certain limitations that should be considered. The protocol for acquisition of serial CT scans was not specified and variation can be expected within institutions. Most likely, patients underwent CT scans subsequent to a neurological deterioration. Changes in serial CT scans may be detected in the absence of neurological deterioration [23]. However, previous studies have not found any abnormalities on serial CT scans, in the absence of neurological deterioration, that result in therapeutic decisionmaking [24,25]. Therefore, the rate of hematoma enlargement maybe underestimated in our analysis. Most of such undetected enlargements, however, are probably asymptomatic and do not require any therapeutic interventions. We did not use blinded or central interpretation of CT scans to identify hematoma enlargement and the ascertainment of hematoma enlargement was made by study investigators. Therefore, interobserver variation can be expected in identification of hematoma enlargement. The rates of hematoma enlargement have been higher in studies that use quantitative central analysis of CT scans in patients with TBI [4]. While each site in the trial was encouraged to implement resuscitation and critical care management guidelines, previous studies have found variance between institutions in compliance to such guidelines [26]. The effect of such variations on our results is undetermined, although a differential compliance based on presence or absence of hematoma enlargement is unlikely.

Recombinant activated factor VII (rFVIIa) may prevent hematoma enlargement in patients with TBI [27–29]. In a prospective study of rFVIIa in TBI patients with intracerebral hematoma, the rate of hematoma enlargement was lower in rFVIIa-treated patients compared with that seen in placebo-treated patients [29]. Therefore, the rate of hematoma enlargement can be reduced with therapeutic interventions in patients with TBI. The higher rate of thromboembolic events associated with rFVIIa prevented widespread use in patients with TBI [29,30]. The results from 35 randomized clinical trials observed that 401 (9%) of 4468 subjects suffered thromboembolic events (particularly arterial thromboembolic events) associated with rFVIIa [31]. Our results suggest that hematoma enlargement may be a direct contributor to death and disability in patients with TBI at both 1 and 6 months. Future clinical trials must continue to evaluate new therapeutic interventions aimed at reducing hematoma enlargement with a favorable risk benefit ratio in patients with TBI.

Authors' Disclosure Statement

No competing financial interests exist.

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