The Utility of Thromboelastography for Predicting The Risk of Progression of Intracranial Hemorrhage in Traumatic Brain Injury Patients

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Traumatic brain injury (TBI) is a leading cause of death and disability in the United States.¹ Intracranial hemorrhage, including intraparenchymal (IPH), intraventricular (IVH), subarachnoid (SAH), and subdural (SDH) or epidural (EDH) hemorrhage, is a significant contributor to death and disability after TBI. In up to 50% of patients, traumatic intracranial hemorrhage (TICH) is observed to increase in size early after injury.^{2,3} Progression of TICH has been associated with an increased need for surgical intervention and is independently associated with 5-fold increased mortality.^{4,5}

The presence of a TICH frequently is associated with systemic alterations in coagulation.^{6,7} However, routine coagulation assays such as international normalized ratio (INR), prothrombin time (PTT), fibrinogen, and platelet count do not consistently reflect functional coagulopathy.⁸ In fact, up to 50% of patients with progression of TICH have been shown to exhibit normal routine coagulation tests.⁹ In contrast, thromboelastography (TEG), a point-of-care viscoelastic assay of whole blood, provides a kinetic assessment of coagulation and clot formation, reflecting the contribution of clotting factors, platelets, and red blood cells.¹⁰ TEG is increasingly being used clinically to

more accurately characterize coagulopathy in many aspects of patient care, including trauma, transplant, and cardiac surgery.^{11,12} However, limited data exist regarding the utility of TEG in TBI.^{13,14} Here we examined whether TEG values obtained near the time of admission predict the risk of progression of TICH, need for neurosurgical procedure, and mortality.

METHODS

We performed a prospective observational study of patients with TBI who received a TEG at admission and at 6 h postadmission. The study was conducted at Oregon Health & Science University (OHSU), an urban level 1 trauma center, from October 2011 to December 2014. Patient data were included, if they were diagnosed with TBI and intracranial hemorrhage on admission head computed tomography (CT). Patients were excluded for any of the following: red blood cell transfusion during the first 6 h after admission, recombinant factor VIIa administered during resuscitation, history of clopidogrel or warfarin use within 30 d of injury, known coagulation disorder, pregnancy, or age <15 yr. Demographic, physiological, laboratory, and outcome data were obtained from the electronic medical record and the state trauma registry. Using methodology published in the manufacturer's insert for the TEG 5000 machine, a non-citrated kaolin-activated TEG (TEG, Haemoscope, Niles, Illinois) was performed using 1 mL of whole blood. This was performed as soon as possible after admission and 6 h later. The TEG parameters analyzed are shown in Figure.

CT head was performed as soon as possible after admission, at approximately 6 h after admission (per institutional trauma protocol), and thereafter when clinically indicated as determined by the trauma and neurosurgical providers. Volumes of SDH, EDH, and IPH were measured using the previously validated ABC/2 method.¹⁵ Progression of TICH was defined as >30% increase in total hemorrhage volume, or a new lesion, or by official radiology interpretation in the case of SAH. Patients receiving neurosurgical evacuation of TICH were considered to have progression. Descriptive statistics were calculated for the data

ABBREVIATIONS: AIS, abbreviated injury scale score; **aPTT**, activated partial thromboplastin time; **CT**, computed tomography; **EDH**, epidural hemorrhage; **GCS**, Glasgow coma scale score; **INR**, international normalized ratio; **IPH**, intraparenchymal hemorrhage; **IRB**, Institutional Review Board; **ISS**, injury severity score; **IV**, intravenous; **IVH**, intraventricular hemorrhage; **NIH**, National Institutes of Health; **OHSU**, Oregon Health & Science University; **PTT**, partial thromboplastin time; **SAH**, subarachnoid hemorrhage; **SDH**, subdural hemorrhage; **TBI**, traumatic brain injury; **TEG**, thromboelastography; **TICH**, traumatic intracranial hemorrhage

overall and by progression. Secondary outcomes were mortality and receipt of neurosurgical procedure. Neurosurgical procedure was defined as craniotomy, craniectomy, ventriculostomy, or intracranial pressure monitor. Regression analysis was used to determine whether TEG values predict outcomes. Two sensitivity analyses were performed, examining the change between admission and 6 h TEG, and TEG values dichotomized as normal vs abnormal. The following reference ranges were used, per OHSU laboratory reference ranges for standard coagulation laboratories and per the TEG manufacturer's reference ranges for all TEG parameters: platelet count 150 to 400 K/mm³, INR 0.9 to 1.2, activated partial thromboplastin time (aPTT) 26 to 36 s, fibrinogen 200 to 450 mg/dL, K 1 to 3 min, R time 4 to 9 min, α -angle 59° to 74°, MA 55 to 74 mm, LY30 0% to 8%. Data analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina). Significance was set at $P < .05$. This study was approved by the OHSU Institutional Review Board (IRB). An initial waiver of consent was granted by the IRB, given the necessity for timely enrollment, with daily attempts made by the research team to obtain consent. Informed consent was sought from the patient or patient's legally authorized representative as soon they were available and able to provide informed

consent. In the event that no legally authorized representative was identified and patient unable to provide consent, a waiver of consent was applied.

RESULTS

There were 169 patients that met inclusion criteria. Patient characteristics are described in Table 1. The majority of subjects were male (118/169; 70%). Progressors had significantly lower admission Glasgow Coma Scale score (GCS), higher Abbreviated Injury Scale score (AIS) Head and Neck, and more frequent receipt of blood product transfusion either preadmission or on admission. In addition, progressors had a significantly higher median age (56.2 vs 51.3), lower median platelet count (201 vs 238), and higher median INR (0.99 vs 0.95). Compared with nonprogressors, progressors had a higher incidence of receipt of neurosurgical procedure (34% vs 14%, $P = .004$), as well

TABLE 1. Patient Demographic and Physiological Covariates by Outcome

	No progression	Progression	P value
Age ^a	51.3 (25.8-65.8)	56.2 (36.3-73.5)	.03
ISS ^a	17 (10-26)	26 (17-30)	<.01
Admission GCS (%)			
3 to 8	9 (12.3%)	25 (27.5%)	<.01
9 to 12	2 (2.7%)	8 (8.8%)	
13 to 15	62 (84.9%)	58 (63.7%)	
Admission systolic blood pressure ^a	146 (131-164)	148 (130-164)	.88
Admission platelets (K/mm ³) ^a	238 (187-267)	201 (159-257)	.05
Admission INR ^a	0.95 (0.89-1.03)	0.99 (0.94-1.14)	<.01
Admission aPTT (seconds) ^a	25.6 (23.1-28.1)	25.7 (24-28.1)	.90
Admission fibrinogen (mg/dL) ^a	305.5 (256-367)	287 (237-367)	.44
Admission sodium (mmol/L) ^a	140 (139-142)	140 (137-141)	.10
Male gender, n (%)	48 (65.8%)	70 (76.9%)	.26
Prehospital and admission fluids, n (%)			
None	37 (50.7%)	42 (46.2%)	.58
LR only	6 (8.2%)	9 (9.9%)	
NS only	28 (38.4%)	31 (34.1%)	
Other fluids	2 (2.7%)	9 (9.9%)	
Prehospital or admission blood product transfusion, n (%)	2 (2.7%)	15 (16.5%)	.01
Aspirin in week prior to admit, n (%)			
No	63 (86.3%)	67 (73.6%)	.16
Yes	9 (12.3%)	23 (25.3%)	
Unknown	1 (1.4%)	1 (1.1%)	
AIS head and neck ^a	4 (3-4)	4 (4-5)	<.01
AIS face ^a	1 (0-2)	2 (0-2)	.07
AIS chest ^a	2 (0-3)	3 (0-3)	.24
AIS abdomen ^a	0 (0-2)	0 (0-0)	.94
AIS extremity ^a	2 (0-3)	2 (0-3)	.37
AIS external ^a	1 (1-1)	1 (1-1)	.76
Intubation status (%)			
Never intubated	52 (71.2%)	46 (50.5%)	.11
Intubated in hospital	13 (17.8%)	25 (27.5%)	
Intubated in field	8 (11.0%)	20 (22.0%)	

Wilcoxon 2-sample tests were used for all continuous data; Chi-square test of association for categorical data (except for prehospital aspirin use for which Fisher's exact test was used).

^aValues for which median (IQR) are represented.

Bold values indicate statistically significant findings ($P < 0.05$).

as a higher rate of mortality (11% vs 1%, $P = .04$). Other demographic, physiological, and laboratory characteristics were not different between groups.

The most common type of hemorrhage observed was SAH (77%), followed by SDH (56%), IPH (41%), and EDH (8%). Fifty-nine percent of patients had multiple types of TICH. Overall, 56% of subjects were found to have progression of their TICH during the first 48 h following admission, 25% required a neurosurgical procedure, and overall mortality was 6%. The incidence of more than 1 type of TICH differed significantly between progressors and nonprogressors (Table 2). Progressors had a higher incidence of IPH (59% vs 16%), SDH (71% vs 33%), and SAH (89% vs 69%) than nonprogressors.

There was no difference in admission TEG values or change in TEG values between admission and 6 h postadmission based on progression, receipt of neurosurgical procedure, or survival status (Table 3). Regression analyses, controlling for prehospital aspirin use, receipt of intravenous (IV) fluids, and blood product transfusion (either prehospital or at the time of admission), showed that admission TEG values did not predict progression of hemorrhage (Table 4). In analyzing the odds of needing a neurosurgical procedure, we controlled for age, admission Injury Severity Score (ISS), prehospital and admission IV fluid administration, AIS Head and Neck, and admission GCS, and found that admission TEG did not predict the need for neurosurgical procedure (Table 5). When examining the change in TEG values between admission and 6 h, for every 1% increase in

TABLE 2. Incidence of TICH Types for Nonprogressors and Progressors

	No progression n (%)	Progression n (%)	P value
IPH	16 (21.9%)	54 (59.3%)	<.01
EDH	4 (5.5%)	9 (9.9%)	.46
SDH	24 (32.9%)	65 (71.4%)	<.01
IVH	5 (6.8%)	12 (13.2%)	.34
SAH	50 (68.5%)	81 (89.0%)	<.01
Multiple hemorrhage types	22 (30.1%)	77 (84.6%)	<.01

Bold values indicate statistically significant findings ($P < 0.05$).

LY30, the need for neurosurgical procedure increased by 17% (Table 5). While no difference was observed in admission TEG between survivors vs nonsurvivors (Table 6), sensitivity analysis demonstrated that patients with an abnormal K time were 4.7 times more likely to die than those with a normal K time. Given the small number of events for this outcome, we were unable to control for patient covariates in the regression analysis.

DISCUSSION

While overall management after trauma focuses on resuscitation, stabilization, and evaluation of multisystem organ injury, management of TBI primarily focuses on minimizing secondary brain injury. This primarily involves optimization of risk factors thought to contribute to progression of hemorrhage, minimizing cerebral edema, and assessing the need for surgical evacuation of a mass lesion or decompression. Multiple characteristics, including increasing age, male sex,³ low level of consciousness on admission,¹⁶ and volume of intracranial hematoma¹⁷ have been shown to predict poor outcome after TICH. The presence of coagulopathy has also been linked to the progression of TICH as well as increased morbidity and mortality.^{6,7,18} Coagulopathy after TBI has been shown to include abnormalities of

TABLE 4. The Odds of Progression of TICH by TEG Values

	OR (95% CI)	P value
Admission TEG value		
R	0.98 (0.75-1.27)	.86
K	1.05 (0.68-1.63)	.83
Alpha angle	1.01 (0.95-1.07)	.77
Maximum amplitude	1.00 (0.94-1.06)	.92
LY30	0.93 (0.80-1.08)	.34
Change in TEG		
R	1.02 (0.89-1.16)	.83
K	0.90 (0.44-1.83)	.76
Alpha angle	0.97 (0.91-1.03)	.28
Maximum amplitude	1.01 (0.93-1.10)	.76
LY30	1.04 (0.93-1.16)	.50
Admission TEG (normal vs abnormal)		
R	0.90 (0.42-1.93)	.78
K	0.62 (0.15-2.61)	.51
Alpha angle	0.44 (0.16-1.18)	.10
Maximum amplitude	0.75 (0.23-2.46)	.64
LY30	0.68 (0.07-6.20)	.73

OR, odds ratio; CI, confidence interval.

both coagulation and fibrinolysis.¹⁹ Some investigators assert that injured neural tissue releases tissue thromboplastin that enters the circulation and activates the extrinsic coagulation pathway to produce a fibrin clot, leading to disseminated intravascular coagulation, platelet depletion, and hyperfibrinolysis.⁶ Others have proposed that alterations in the Protein C pathway brought on by early hypoperfusion lead to early coagulopathy in TBI patients.²⁰ Thus, no clear consensus exists regarding the underlying mechanism(s) involved.

Given these phenomena and their known association with progression of TICH, current standard of care supports serial examination of coagulation testing, including INR, PTT, and platelet count.²¹ Though the shortcomings of these standard coagulation tests are well known, they are still used routinely

TABLE 3. Median Admission TEG Values Based on Progression, Mortality, and Need for Neurosurgical Procedure. There Were no Significant Differences in Median Admission TEG Values Between Groups for Each Clinical Outcome

	Progression		Mortality		Neurosurgical procedures	
	No progression (n = 73)	Progression (n = 91)	Alive (n = 158)	Dead (n = 11)	No procedures (n = 127)	1 or more procedures (n = 42)
TEG values: median (IQR)						
R (min)	4.4 (3.2-5.15)	4.2 (3.6-5)	4.3 (3.35-5.1)	4.6 (3.9-5.2)	4.3 (3.4-5.1)	4.3 (3.2-5)
K (min)	1.3 (1.2-1.65)	1.4 (1.2-1.8)	1.35 (1.2-1.8)	1.85 (1.6-2)	1.3 (1.2-1.7)	1.6 (1.2-1.8)
Alpha angle (degrees)	70.3 (66-73.3)	70.65 (65.8-73)	70.6 (66.35-73.05)	64.9 (62.9-68.4)	70.8 (66.6-73.4)	68.4 (64.3-72)
MA (mm)	68.05 (65-71.55)	67.9 (63.20-71.5)	68.15 (63.65-71.6)	65.2 (62.6-71.6)	68.7 (64.4-71.7)	66.3 (62.6-70.8)
LY30 (%)	0.6 (0-1.9)	0.3 (0-1.1)	0.5 (0-1.4)	0 (0-0.3)	0.6 (0-1.6)	0.2 (0-1)

TABLE 5. The Odds of Neurosurgical Procedure by TEG Values

	OR (95% CI)	P value
Admission TEG value		
R	1.08 (0.79-1.49)	.62
K	1.01 (0.52-1.95)	.98
Alpha angle	0.99 (0.93-1.07)	.83
Maximum amplitude	0.99 (0.93-1.06)	.74
LY30	0.83 (0.62-1.11)	.20
Change in TEG		
R	1.25 (0.96-1.63)	.10
K	1.86 (0.71-4.88)	.21
Alpha angle	0.95 (0.88-1.02)	.15
Maximum amplitude	0.98 (0.90-1.08)	.73
LY30	1.17 (1.01-1.36)	.04
Admission TEG (normal vs abnormal)		
R	1.08 (0.46-2.55)	.87
K	2.11 (0.49-9.16)	.32
Alpha angle	2.31 (0.80-6.71)	.12
Maximum amplitude	2.59 (0.78-8.55)	.12
LY30	**	

OR, odds ratio; CI, confidence interval.

Bold values indicate statistically significant findings ($P < 0.05$).**This indicates that this could be modeled due to small number of patients ($n = 8$) with abnormal LY-30.

because of their universal availability. TEG, a whole blood viscoelastic assay, is a rapid and inexpensive point-of-care test used clinically in trauma, transplant, and cardiac surgery to evaluate coagulation^{11,12}; however, literature examining the utility of TEG in the setting of TICH is sparse.^{22,23} One study by Kunio et al²² showed that patients with TBI who were hypocoagulable based on a prolonged R time on admission TEG had worse clinical outcomes and increased incidence of neurosurgical intervention. Another retrospective study including patients with either acute intracranial hemorrhage or isolated TBI showed that hypocoagulability based on admission TEG was associated with worse 30-d clinical outcome.²³ To date, however, no study has examined whether TEG can be used to predict progression of TICH, need for neurosurgical procedure and mortality.

The goal of this study was to determine whether admission TEG can predict TICH progression and need for neurosurgical intervention. In addition to identifying potential targets for therapeutic intervention, this has the potential to risk-stratify patients and aid in patient disposition and resource utilization. Here we found that median admission TEG values do not significantly differ between progressors and nonprogressors, and do not appear to predict the risk of progression of TICH, need for neurosurgical procedure, or mortality. In addition to analyzing median admission TEG values, we also performed 2 sensitivity analyses to determine whether dichotomizing TEG values as normal vs abnormal and examining the change in TEG values between admission and 6 h would reveal differences between progressors and nonprogressors. Based on these sensitivity analyses, we

TABLE 6. The Odds of Mortality by TEG Values

	OR (95% CI)	P value
Admission TEG value		
R	1.11 (0.76-1.61)	.60
K	1.29 (0.69-2.42)	.42
Alpha angle	0.97 (0.91-1.03)	.25
Maximum amplitude	0.97 (0.91-1.04)	.38
LY30	0.97 (0.79-1.19)	.78
Change in TEG		
R	1.14 (0.88-1.48)	.33
K	1.10 (0.45-2.68)	.84
Alpha angle	0.99 (0.93-1.05)	.68
Maximum amplitude	0.97 (0.88-1.07)	.50
LY30	0.96 (0.85-1.09)	.53
Admission TEG (normal vs abnormal)		
R	0.60 (0.15-2.41)	.47
K	4.71 (1.09-20.44)	.04
Alpha angle	0.70 (0.14-3.44)	.66
Maximum amplitude	1.19 (0.24-5.94)	.83
LY30	2.35 (0.26-21.22)	.45

OR, odds ratio; CI, confidence interval.

Bold values indicate statistically significant findings ($P < 0.05$).

observed differences in clot formation as well as clot breakdown that predicted worse clinical outcomes. Specifically, we found that patients with an abnormal K time (clot formation) on admission had 4.7 times the odds of mortality compared to patients with normal K time. We also found that for every 1% increase in clot lysis at 30 min (LY30) between admission and 6 h, the odds of need for a neurosurgical procedure increased by 17%. Taken together, these results imply that patients with abnormal clot formation or increased rate of clot breakdown may have worse clinical outcomes.

Limitations

There are multiple limitations with this study. While TEG examines all phases of coagulation, it does not provide an independent assessment of platelet function. The addition of platelet function assays to this study may have provided more information to help explain the results observed related to LY30. Furthermore, we used the current reference ranges for TEG as supplied by the manufacturer. However, normative values for TEG in patients with TBI have not been established, which has the potential to mask clinically relevant differences that fall within the normal range of TEG values. Finally, while a number of covariates (admission sodium, aPTT, INR, fibrinogen, platelets, and aspirin use) were similar between progressors and nonprogressors, several clinically significant differences were observed between these groups (ISS, GCS, receipt of prehospital or admission blood products, distribution of hemorrhage type, and AIS Head and Neck). While it is not surprising that progressors were more injured, had a lower admission GCS, and were more

likely to have hemorrhage types associated with progression, we controlled for factors felt to be relevant to the clinical outcome studied in our regression models.

CONCLUSION

In conclusion, in this prospective observational study of patients with TBI and TICH, admission TEG values did not predict progression of TICH, need for neurosurgical procedure, or mortality. Sensitivity analyses suggest that alterations in clot formation and lysis may be associated with worse outcome; however, these findings warrant further study and we caution against relying on TEG to guide clinical decisions related to progression of TICH.

Disclosures

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