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Platelet dysfunction on thromboelastogram is associated with severity of blunt traumatic brain injury

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ABSTRACT

Background: Platelet dysfunction associated with isolated traumatic brain injury (TBI) can be measured using thromboelastography-platelet mapping (TEG-PM). We hypothesized that platelet dysfunction can be detected after blunt TBI, and the degree of dysfunction is associated with increased TBI severity and in-hospital mortality.
Methods: This was a retrospective review of adult trauma patients admitted to a single level 1 trauma center from August 2013 to March 2015 who suffered isolated severe blunt TBI. Subjects were included if they received a TEG-PM within 24 h from injury, and excluded if on preinjury antiplatelet medications.
Results: 119 subjects were analyzed. Severe TBI subjects (AIS-head 5) had ADPi 18.4 points higher than moderate TBI subjects (AIS-head 3) ($p = 0.001$). Platelet dysfunction was not associated with TBI progression. ADPi significantly predicted mortality (OR 1.033; 95% CI 1.005–1.061, $p = 0.02$).
Conclusion: Platelet dysfunction occurs immediately after isolated blunt TBI, is more pronounced with increasing TBI severity, and is associated with higher odds of in-hospital mortality. Further investigation is needed to determine whether this is a marker of disease severity or a therapeutic target.

Background

Acute traumatic coagulopathy is common after severe trauma and is associated with increased mortality,[1] underscoring the importance of screening for coagulopathy early in the care of the trauma patient. The incidence of coagulopathy associated with traumatic brain injury (TBI) varies widely (10–90%) due to differing definitions of coagulopathy, severity of brain injury and study design, and carries an increased odds of death from 3-9.6.[2] Platelet dysfunction has been identified in patients with multiple injuries as well as those with isolated TBI, characterized by adenosine diphosphate pathway inhibition (ADPi) as high as 86%.[3–7]

The complex pathophysiology behind coagulopathy after isolated TBI remains incompletely understood and proposed mechanisms are varied.[8–10] Many hypothesize that brain tissue factor (TF) is released from the injured brain parenchyma and gains systemic access from disruptions in the blood brain barrier, leading to activation of the extrinsic coagulation cascade and subsequent factor and platelet depletion.[7–9] This consumptive coagulopathy renders the platelet in a refractory state and may be represented by dysfunction in both adenosine diphosphate (ADP) and arachidonic acid (AA) pathways.[7,8] The ADP pathway is critical to activation and aggregation of platelets,[11] and inhibition is a likely mechanism for platelet dysfunction observed in the setting of trauma.[3,5]

Early recognition of platelet dysfunction is challenging with conventional coagulation tests (CCTs) alone, as they do not provide insight into the complexities of coagulopathy.[8,12] A platelet count of $<100{,}000/mm^3$ has been associated with a nine-fold risk in mortality after TBI;[13] however, bleeding and progression of hemorrhage can be present with a normal platelet count,[14,15] suggesting its limited clinical utility. Dynamic hemostatic assays, such as thromboelastography (TEG) and platelet mapping (TEG-PM), measure the viscoelastic clot properties of whole blood and evaluate platelet function by directly measuring inhibition in both AA and ADP pathways.[10] Recent literature has sparked a trend toward increased reliance on TEG given its clinical superiority to CCTs in their ability to predict important clinical outcomes in massive hemorrhage and

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trauma patients.[16,17] Furthermore, many groups have acknowledged the utility of TEG-PM in identifying early platelet dysfunction in TBI patients.[18–21]

When our institution adopted the TEG-PM assay, we sought to evaluate our experience with its routine use in isolated TBI patients. We hypothesized that platelet dysfunction can be detected soon after injury using TEG-PM, and that the degree of dysfunction is associated with increased TBI severity as well as in-hospital mortality. We also aimed to investigate the impact of platelet dysfunction on progression of intracranial hemorrhage.

Methods

This study was a retrospective review of adult trauma patients admitted to a single level 1 ACS verified trauma center from August 2013 to March 2015 who suffered isolated blunt TBI. To define isolated TBI, subjects were included if they had a head abbreviated injury scale (AIS-head) score ≥3 and an AIS score in any other body region of ≤2. Subjects were eligible if at least one TEG-PM assay was drawn within 24 h of injury. We identified subjects by cross-matching the institutional trauma database registry with those who met the above criteria. Exclusion criteria included: age <18 years, pregnant, prisoner, chronic antiplatelet therapy, platelet transfusion prior to first lab draw. This study was approved by the Intermountain Central Institutional Review Board.

Demographic variables, laboratory tests, emergency department (ED) Glasgow Coma Scale (GCS) score and systolic blood pressure (SBP), TBI lesion type, AIS scores and injury severity score (ISS), length of stay, discharge disposition, and mortality were abstracted from the registry. Subjects with moderate TBI (AIS-head 3) were compared to subjects with severe TBI (AIS-head 4 and 5).

At the time of the study, it was routine for all highest level (level I) trauma patients to receive a TEG-PM assay as part of the laboratory panel in the ED. In patients who did not meet level I activation criteria, TEG-PM was ordered at the discretion of the trauma provider. Similarly, platelet transfusion or desmopressin (DDAVP) was ordered on a case by case basis. No standardized goal-directed treatment guideline for platelet dysfunction using TEG-PM was in place at the time.

For TEG testing, citrated whole blood plus kaolin as an activator was analyzed using the Haemonetics TEG 5000 Thrombelastograph Analyzer (Haemonetics Corp. Braintree, MA). To evaluate platelet function, the TEG-PM assay was used to measure the reactivity of the platelet to arachidonic acid (AA) and adenosine diphosphate (ADP) activators.

At our institution, repeat computed tomography (CT) imaging is performed within 12–24 h, with variation relying on lesion type and clinical exam. We defined progression of TBI as an increase in size of existing hemorrhage, development of a new lesion or progression of cerebral edema based on radiology reports which were reviewed by study personnel. Neurosurgical intervention was defined as any invasive procedure including intracranial pressure monitoring device placement, craniotomy or craniectomy.

Descriptive data is reported as either percent, mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. Relationships between platelet dysfunction (ADPi) and covariates were examined using correlation and multiple regression. Covariates with correlation p-values ≤0.10 were entered into a multiple regression with ADPi as the outcome variable. We used hierarchical regression modeling where the covariate with the lowest correlation p-value was entered first, followed by the variable with the second lowest p-value, and so on. Covariates with significant R-squared change statistic were retained while those without significant R-squared change statistics were removed from the model. Next, we investigated relationships between TBI progression (yes vs. no) and the covariates using bivariate correlation followed by binary logistic regression. Covariates with p-values ≤ 0.10 were entered into a binary logistic regression with TBI progression as the outcome variable. One-by-one we removed covariates with the highest p-values and re-ran the model after each removal until only significant covariates remained. We explored relationships between hospital mortality and covariates using the same approach. Receiver Operating Characteristic (ROC) analysis was used to explore the ability of different ADPi thresholds to predict mortality, specifically 60%, 70%, and 80% thresholds. We computed the area under the curve, sensitivity and specificity for each. Finally, we used Wilcoxon signed-rank tests to evaluate the effect of platelet transfusion on platelet function as measured by MA, ADPi, and AAi.

Results

119 subjects met inclusion criteria over the study period and were included in the analysis. Demographics of the entire study cohort are presented in Table 1. Nearly half (47.9%) of patients suffered the highest TBI severity (AIS-head 5). CCTs and TEG values were within normal limits, with the exception of TEG-PM results which included an elevated AAi (38.5%) and ADPi (57.3%). 20.2% patients were anticoagulated on either warfarin or a direct oral anticoagulant, which did not have an association with AIS-head, ADPi, TBI progression, hospital LOS or mortality. When comparing subjects based on TBI severity, the only significantly different laboratory variable was ADPi (moderate group 47.4% versus severe

Table 1
Baseline characteristics.

Variables	Blunt TBI subjects N = 119
Age (years); mean (SD)	61 (31)
Female sex; n (%)	45 (37.8%)
Weight (kg); median (IQR)	75 (28)
ISS; median (IQR)	21 (15)
ED GCS; median (IQR)	14 (8)
ED SBP < 90 mmHg; n (%)	4 (3.4%)
Blunt mechanism; n (%)	
Ground level fall	76 (63.9%)
Other	43 (36.1%)
Level I activation; n (%)	52 (43.7%)
Time (min) from ED to first TEG result; median (IQR)	49 (105.5)
TEG r-time; median (IQR)	4.3 (1.6)
TEG angle; median (IQR)	69.8 (8)
TEG MA; median (IQR)	65.6 (8)
TEG-PM ADPi (%); median (IQR)	57.3 (44.3)
TEG-PM AAi (%); median (IQR)	38.5 (39.1)
Platelet count ED; median (IQR)	195 (97)
International normalized ratio ED; median (IQR)	1.2 (8.3)
Hemoglobin; median (IQR)	13.3 (2.8)
AIS-head score; n (%)	
3	41 (34.5%)
4	21 (17.6%)
5	57 (47.9%)
TBI type	
Subarachnoid	58 (48.7%)
Subdural	81 (68.1%)
Intraparenchymal	40 (33.6%)
Epidural	7 (5.9%)
Preinjury anticoagulation; n (%)	24 (20.2%)
Neurosurgical Procedure; n (%)	33 (27.7%)
Progression of TBI; n (%[out of n = 96])	35 (36.5%)
Discharge Disposition; n (%)	
Home	38 (31.9%)
Home Health	8 (6.7%)
Extended Care Facility	20 (16.8%)
Acute rehab	28 (23.5%)
Hospital LOS (days); median (IQR)	5 (41)
Hospital mortality; n (%)	25 (21%)

Table 2
Laboratory characteristics of moderate versus severe TBI on presentation.

Variables	AIS-Head 3, n = 41 (Moderate)	AIS-Head 4 + 5, n = 78 (Severe)	p-value
Time (min) from ED to first TEG result; median (IQR)	55 (149.8)	39.5 (94.8)	0.17
TEG r-time; median (IQR)	4.5 (2.3)	4.2 (1.5)	0.07
TEG angle; median (IQR)	68.7 (9.8)	70.0 (8.0)	0.30
TEG MA; median (IQR)	65.8 (7.4)	64.6 (9.5)	0.41
TEG-PM ADPi (%); median (IQR)	48.4 (32.0)	65.1 (51.6)	0.001
TEG-PM AAi (%); median (IQR)	34.8 (31.6)	41.5 (40.0)	0.10
Platelet count; median (IQR)	182.5 (100)	197.0 (98)	0.81
International normalized ratio; median (IQR)	1.1 (0.2)	1.2 (0.3)	0.44

group 65.1%, p = 0.001) (Table 2).

In associations tests with ADPi, the following variables had p-values ≤0.10: GCS, age, sex, IPH, and AAi. In the regression analysis, sex and AIS-head significantly predicted ADPi. On average, male ADPi values were 11.65 points higher than female (p = 0.02). ADPi values for AIS-head 4 + 5 subjects were 18 and 19 points higher (p = 0.008 and 0.001), respectively, than for patients with AIS-head 3.

96 patients underwent a repeat CT brain within 24 h from initial imaging (median time 581.5 [431.25] minutes), and were therefore included in the analysis regarding TBI progression. 36.5% patients were found to experience progression of TBI. Neither CCTs nor TEG-PM values correlated with TBI progression. TBI lesion type was the only variable associated with progression, most notably subarachnoid hemorrhage (OR 4.28, 95% CI 1.07–6.68, p = 0.04) followed by IPH (OR 2.68, 95% CI 1.68–10.93, p = 0.002).

Overall hospital mortality was 21%. When testing associations with mortality, the following variables had correlation p-values ≤0.10: ADPi, AIS-head, GCS, AAi, midline shift on CT, and age. These variables were included in a logistic regression with hospital mortality as the outcome variable. Severe TBI (AIS-head 5) was the strongest predictor of mortality (OR 18.73, 95% CI 1.92–182.83, p = 0.01). ADPi was also a significant predictor (OR 1.033, 95% CI 1.01–1.06, p = 0.02) (Table 3). Comparing ADPi thresholds for predicting in-hospital mortality, area under the curve for 60% was not significant (AUC 0.598, p = 0.134), while the areas for 70% (AUC 0.631, p = 0.045) and 80% (AUC 0.634, p = 0.041) were significant (Fig. 1, Table 4).

There were 13 patients who received a corrective intervention (3 subjects got DDAVP only, 10 subjects got platelet transfusion with or without DDAVP). There was significantly less inhibition in both ADP and AA pathways after the intervention; this was not observed for MA (Table 5).

Discussion

The purpose of this study was to investigate the prevalence of platelet dysfunction after isolated TBI and its relationship to TBI severity and mortality utilizing the TEG-PM assay to evaluate inhibition in both ADP and AA pathways. We analyzed 119 trauma patients and found platelet dysfunction to be present soon after injury, prior to substantial crystalloid or colloid administration. Furthermore, the degree of platelet dysfunction correlated with TBI severity, measured by AIS score and GCS, suggesting a dose-response relationship. Our study also suggests that platelet dysfunction may predict increased hospital mortality, although the mechanism is unclear. This exploratory investigation contributes important findings to the growing body of evidence that a relationship between isolated TBI and coagulopathy marked by platelet dysfunction, particularly in the ADP pathway, exists.[7,18–22]

Table 3
Logistic regression evaluating the effect of having platelet dysfunction on in-hospital mortality.

	Odds Ratio	95% Confidence Interval	p-value
Outcome: Hospital Mortality			
Age	1.05	(1.01, 1.09)	0.02
AIS-head 5	18.726	(1.92, 182.83)	0.01
ADP inhibition	1.033	(1.01, 1.06)	0.02
GCS in ED	0.723	(0.61, 0.85)	<0.001
Ground level fall (ref: other)	8.92	(1.30, 61.34)	0.03

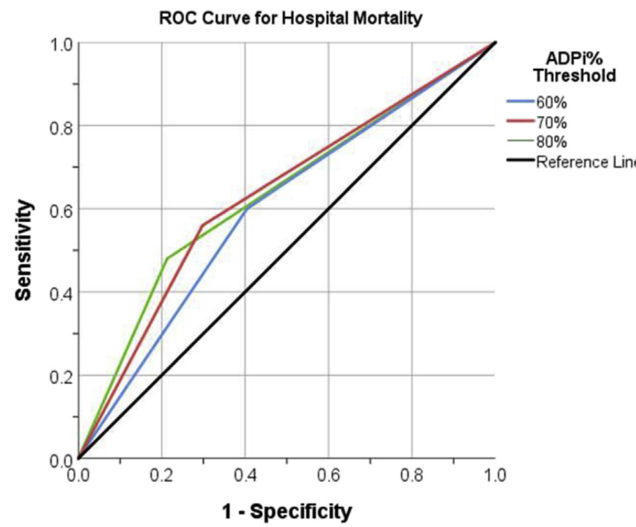

Fig. 1. ROC analysis evaluating ADPi thresholds on in-hospital mortality.

Table 4
ROC results for predicting mortality using ADP% thresholds.

ADPi	AUC	P-value	Sensitivity	1-Specificity
60%	0.598	0.134	60%	40%
70%	0.631	0.045	56%	30%
80%	0.634	0.041	48%	21%

It is important to note this association between TBI severity and platelet dysfunction exists despite both normal conventional coagulation tests (CCTs) and maximum amplitude (MA) on TEG, questioning the clinical utility of CCTs and TEG without the use of platelet mapping. When comparing patients based on TBI severity in our analysis, ADP inhibition (ADPi) was the only significantly different marker of coagulation. This is similar to other groups who have found that while both percent ADPi and AAi are acutely elevated in the TBI patient,[7,19] ADPi appears to better correlate with injury severity and contribute to platelet dysfunction.[4,6]

Platelet dysfunction of isolated TBI occurs in the absence of multiple injuries or systemic shock. Both animal and human subjects with isolated TBI and no systemic shock have been found to

Table 5
Platelet function before and after platelet transfusion and/or DDAVP.

TEG-PM parameter	Pre-intervention, n = 13 (median [IQR])	Post-intervention, n = 13 (median [IQR])	p-value
MA (mm)	61.3 (9.6)	64 (4)	0.33
ADP inhibition (%)	94.7 (34.5)	50.5 (21)	0.003
AA inhibition (%)	53 (39.3)	30.9 (20.9)	0.004

have significant platelet dysfunction by ADPi compared to healthy controls.[7,19] Lee et al. found no difference between TBI-associated coagulopathy and that caused by similar injury severity to other body regions, concluding that TBI is associated with a similar but not more profound coagulopathy.[21] One group found that patients with minor injuries including TBI exhibited platelet dysfunction in both pathways (AAi 30% and ADPi 58%).[20] This look at minorly injured patients delivers a unique perspective suggesting that, while there may be an association between severity of TBI and platelet dysfunction, severe injury is not necessarily needed to render platelets dysfunctional on TEG-PM.

Cardiothoracic literature evaluating surgical patients on antiplatelet therapy suggests that ADPi ≥60% is associated with increased bleeding risk.[23,24] Evaluating the clinical relevance of this threshold in TBI patients is a recent area of interest.[22,25–26] Daley et al. found that TBI patients with platelet dysfunction, defined by ADPi ≥60%, were more likely to die in the hospital than those without (OR 6.2, 95% CI 1.2–33; 32% vs 8%, $p < 0.01$).[24] This was an evaluation of multi-system trauma patients, about one quarter of whom suffered severe chest injuries, which may confound the relationship between TBI and platelet dysfunction. We did not find the commonly used ADPi threshold of 60% to be a meaningful cutoff; rather, 70% was the better predictor of in-hospital mortality. While recent literature may support defining ADPi ≥60% as a therapeutic target, evidence is inconsistent and dysfunctional platelets with ADPi near this cutoff appear to be present even after minor injury, a population who rarely experience progression of hemorrhage or related complications. Further investigation into the clinical relevance of platelet dysfunction and utility of a threshold to guide intervention strategies is needed.

Quantifying the degree of platelet dysfunction in TBI patients is an enticing endpoint for goal-oriented correction; however, no validated transfusion protocols exist.[27] The literature has largely targeted platelet transfusion in patients on prehospital antiplatelet therapy. Some groups have found that TBI patients on prehospital antiplatelet therapy experience no difference in clinical outcomes with platelet transfusion.[28,29] On the contrary, Jehan et al. evaluated isolated TBI patients on preinjury P2Y12 inhibitors and found platelet transfusion to be protective with a decreased incidence of TBI progression, neurosurgical intervention and mortality.[30] In massive transfusion, improved survival has been noted in TBI patients who received higher ratios of platelets to packed red blood cells.[31] Furay et al. assessed their protocol for platelet transfusion in severe TBI patients with an ADPi ≥60% in 35 patients. Compared to a historical control, platelet transfusion protected against mortality (OR 0.23, 95% CI 0.06–0.92, $p = 0.04$).[25] Another group transfused TBI patients with an ADPi ≥60% and found a lower mortality rate in those who received platelets if ADPi corrected to below the threshold of 60% (22.2% vs 56.4%) than if it failed to correct.[26] Our analysis also demonstrated correction of platelet dysfunction by ADPi far below 60% in the 13 patients who received a platelet transfusion and/or DDAVP. Small sample sizes limit the aforementioned studies, including our own, highlighting the need for further investigation into whether or not correction of platelet inhibition improves outcomes in TBI patients.

One of our aims was to explore the effect of platelet dysfunction on the important outcome of early TBI progression. Coagulopathy has been identified in 55% of patients with TBI progression, compared to just 9% in those without.[32] Variability exists regarding the best predictors of TBI progression.[14,32–33] Thrombocytopenia may predict TBI progression, but thresholds vary.[33–34] TEG parameters may better predict progression of TBI than CCTs,[35] but most recent studies evaluating platelet inhibition have not addressed TBI progression specifically. Using rapid-TEG, Folkerson et al. looked at TBI progression and found higher incidence of coagulopathy in the TBI progression group, but this was not significant (61% vs 50%, $p = 0.089$).[15] In our study population, we failed to identify a significant association between platelet dysfunction on TEG-PM and progression of hemorrhage. The most meaningful predictor of TBI progression was intracranial lesion type, which is consistent with other findings[14]. We do acknowledge that defining TBI progression using radiographic findings only may be not always be clinically significant. Furthermore, whether or not platelet inhibition contributes to progression of hemorrhage due to poor hemostatic competence or rather is a marker of initial injury severity with associated expected increased risk for progression and death remains unclear.

Several limitations of this study can be attributed to the constraints of a retrospective, single cohort and single center design, as well as a small sample size. Without a treatment guideline, TEG-PM utilization was left to the discretion of the trauma provider in many subjects contributing to selection bias. However, nearly half underwent routine TEG-PM testing as a level I activation, thereby reducing such bias. While we did find significant improvement in platelet inhibition after transfusion in the subgroup analysis, our study was not designed to assess the effect of an intervention on platelet inhibition. We are unable to address any mechanisms underlying our findings to better interpret why platelet inhibition occurs after injury or how it may impact mortality.

Conclusion

Platelet dysfunction, measured by inhibition in the ADP pathway using TEG-PM, occurs immediately after isolated blunt injury to the brain and appears to be more profound with increasing severity of injury. Presence of platelet dysfunction is associated with in-hospital mortality, although the explanation behind this remains incompletely understood. Further investigation is needed to determine whether TBI-induced coagulopathy marked by platelet dysfunction is simply a marker of disease severity or is a clinically meaningful target warranting therapeutic intervention.

Conflicts of interest

None of the authors have anything to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.09.024.