Inhibition of platelet function is common following even minor injury

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BACKGROUND: Hemorrhage remains the leading cause of preventable death following injury. Whereas significant attention has been paid to the coagulation cascade, there are fewer studies evaluating platelet dysfunction following injury. Thrombelastogram platelet mapping (TEG-PM) allows for the measurement of maximal potential clot strength and clot strength selectively caused by arachidonic acid and adenosine disphosphate receptors on the platelet. The purpose of this study was to determine the incidence and magnitude of receptor-specific platelet dysfunction following injury in patients who are not otherwise pharmacologically anticoagulated.

METHODS: A retrospective study of adult trauma patients evaluated at a Level I trauma center from August 2013 to September 2014 was conducted. Platelet function was assessed using TEG-PM. Patients on any anticoagulant or antiplatelet medication were excluded. Patients were divided into those with and without radiographically evident traumatic brain injury (TBI). Demographic variables, Injury Severity Score (ISS), injury pattern, laboratory test results, and mortality were abstracted. Statistical comparisons were made using the Student's *t* test or Mann-Whitney U-test.

RESULTS: The study includes 459 patients, 92% following blunt injury. Median ISS was 5. Patients with TBI (n = 102) were significantly older (median age, 54 years vs. 35 years), were more severely injured (median ISS, 10 vs. 4), had a longer stay and higher mortality (9% vs. 0.3%). Maximal potential clot strength was normal in all cohorts, but the arachidonic acid and adenosine diphosphate pathways were significantly inhibited (30% ± 26% and 58% ± 27%, respectively). There was no correlation between TEG-PM values and ISS, length of stay, or mortality. There was no difference in the TBI cohort. There were no significant differences in TEG-PM parameters in those with an ISS greater than 14. There was no significant change in TEG-PM following platelet transfusion.

CONCLUSION: Marked platelet inhibition is common following minor injury. Whereas the clinical significance of this finding remains unknown, the results of this study should be factored in the overall resuscitative strategy. (*J Trauma Acute Care Surg.* 2016;81: 328–332.

LEVEL OF EVIDENCE: Prognostic/epidemiogic study, level III.

KEY WORDS: Thrombocytopathy; platelet dysfunction; coagulopathy; trauma; platelet inhibition.

The top two leading causes of death following trauma are brain injury and hemorrhage, with hemorrhage accounting for the leading cause of preventable death.[1,2] A significant amount of attention has been paid to describing factors and treatment modalities related to the acute coagulopathy of trauma; however, the majority of these studies concentrate on the coagulation cascade primarily. Less attention has been focused on the role of platelet dysfunction in trauma-related hemorrhage.

Historically, there have not been readily available, reproducible tests to assess platelet function.[3] Platelet count has little correlation with clotting ability.[4,5] Although there are now several modalities that can be used to assess platelet function, viscoelastography, including thrombelastography (TEG), provides the only modality to quantitatively assess both the humoral as well as cellular components of hemostasis simultaneously using a whole-blood sample. Specifically, TEG-platelet mapping (TEG-PM) allows for the measurement of maximal potential clot strength (MA) resulting from the contributions of both fibrin and platelets as well as clot strength selectively caused by stimulation of the arachidonic acid (MA-AA) and adenosine disphosphate (MA-ADP) platelet receptors. The TEG also computes the percent inhibition of each biochemical pathway, percent inhibition-AA, and percent inhibition-ADP, by comparing the MA-AA and MA-ADP with the overall MA. The MA-AA and MA-ADP are inversely proportional to their respective percent inhibitions.

Whereas the few available studies on platelet dysfunction following injury have been on severely injured patients, defined as those with an Injury Severity Score (ISS) at least 15 or those requiring emergency blood transfusion,[6–9] there are no studies on the incidence of platelet dysfunction and outcome in patients with lower ISS or in those with and without traumatic brain injury (TBI). The purpose of this study was to determine the incidence and magnitude of receptor-specific platelet dysfunction following injury in patients who are not otherwise pharmacologically anticoagulated. We hypothesize that platelet dysfunction is common following even minor injury and that there are no differences in the degree of dysfunction in those with and without TBI or those with mild or severe injury.

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PATIENTS AND METHODS

A retrospective study of adult trauma patients evaluated at a Level I trauma center from August 2013 to September 2014 was conducted. Patients who underwent TEG-PM testing at the discretion of the trauma surgeon, based on clinical index of suspicion for hemorrhage, were enrolled in the study. Patients on anticoagulant and antiplatelet agents, those whose anticoagulation status was not known, and those who were not initially evaluated as trauma team activations were excluded. Patients were divided into those with and without TBI and also divided based on ISS. TBI was defined as presence of intracranial hemorrhage of any sort on initial noncontrast computed tomographic scan of the brain. Platelet transfusion was ordered at the discretion of the attending surgeon based on the presence and/or severity of TBI or other potential sources of hemorrhage as well as the TEG-PM results; no protocol was used to standardize indications for platelet transfusion.

Demographic variables, injury severity (ISS), injury pattern, laboratory test results, length of stay (LOS), and mortality were abstracted. Standard laboratory tests did not include either a blood gas or lactate level. Patients with an ISS greater than or equal to 15 were also compared with those with an ISS less than 15. Patients were also grouped into tertiles based on the degree of AA and ADP platelet receptor inhibition. Statistical comparisons were made using the Student's *t* test or Mann-Whitney U-test for comparison of the two cohorts and the Kruskal-Wallis or χ^2 test for comparison of three or more cohorts as appropriate. Statistical significance was defined as $p < 0.05$. Paired testing was used to compare TEG-PM results before and after platelet transfusion. There were no missing data points.

Blood for TEG-PM was obtained from patients immediately upon arrival to the trauma center and analyzed immediately along with other standard blood tests ordered by the trauma team. Citrated, whole-blood samples were analyzed using a Model 5000 Thrombelastrograph Analyzer (Haemonetics Corp., Braintree, MA). Kaolin was added as a catalyst to all specimens. Standard TEG-PM indices were analyzed and recorded as previously described.[6] Repeat TEG-PM testing following platelet transfusion was ordered at the discretion of the attending trauma surgeon. When requested, this follow-up test was ordered immediately following transfusion.

TABLE 1. Patient Demographics

	Overall Cohort (n = 459)	TBI (n = 102)	No TBI (n = 357)	*p**
Age, median (25th–75th IQR), y	38 (27–56)	54 (34–86)	35 (26–51)	<0.0001
Male, %	70	70	71	0.91
ISS median (25th–75th IQR)	5 (2–9)	10 (5–17)	4 (1–5)	<0.0001
ICU days, median (25th–75th IQR)	0 (0–0)	1 (0–2)	0 (0–0)	<0.0001
LOS, median (25th–75th IQR)	1 (0–2)	1 (1–4)	1 (0–1)	<0.0001
Mortality, %	2.2	8.8	0.3	<0.0001

*p value refers to comparison between the TBI and no TBI group.

TABLE 2. Platelet Count and Function

Test	Overall Cohort, n = 459 (Mean ± SD)	TBI, n = 102 (Mean ± SD)	No TBI, n = 357 (Mean ± SD)	*p**
Platelet count	230 ± 65	215 ± 67	234 ± 64	0.01
MA, mm	63 ± 6	64 ± 7	63 ± 6	0.74
MA-AA, mm	47 ± 16	46 ± 15	47 ± 16	0.54
MA-ADP, mm	32 ± 17	32 ± 16	32 ± 17	0.9
Percent inhibition AA	30 ± 26	32 ± 25	30 ± 26	0.17
Percent inhibition ADP	58 ± 27	59 ± 27	58 ± 27	0.58

*Comparison between TBI and no TBI cohort.

RESULTS

There were 459 patients enrolled, 70% of whom were male. Mechanism of injury was blunt in 92%. The median (25th–75th interquartile range [IQR]) age and ISS in the overall cohort were 38 years (27–56 years) and 5 (2–9), respectively (Table 1). TBI was noted in 102 patients. Brain-injured patients were significantly older (median, 54 years [34–86] vs. 35 years [26–51], $p < 0.0001$) and more severely injured (median ISS, 10 [IQR, 5–17] vs. 4 [IQR, 1–5], $p < 0.0001$) than those without TBI. Two percent of the overall cohort died. Mortality was significantly higher in the TBI cohort than in the non-TBI cohort. Similarly, both intensive care unit (ICU) and overall LOS were significantly higher in the TBI cohort than in the non-TBI cohort, although the absolute difference in median LOS was only 1 day.

MA was normal in all cohorts, but MA-AA and MA-ADP were significantly reduced (Table 2). As expected based on the MA-AA and MA-ADP, the percent inhibition AA and ADP were also significantly elevated. There was no difference in mean MA, MA-AA, or MA-ADP in those with and without TBI. There was no relationship noted between the MA-AA or MA-ADP and ISS, LOS, or mortality.

To determine if there was a difference between those with minor and major injury, we compared the results in those with an ISS greater than or equal to 15 with those with lesser injury (Table 3). The median ISS (25th–75th IQR) in the two

TABLE 3. Characteristics of Patients With an ISS Equal to or Greater than 15, n = 54

Variable	ISS ≥ 15 Group	ISS < 15 Group	*p*
ISS, median (25th–75th IQR)	21 (17–22.5)	4 (1–5.5)	<0.0001
Age, median (25th–75th IQR), y	43 (23–65)	38 (27–54)	0.324
Male, %	70	70	0.970
Platelet count (mean ± SD)	227 ± 80	230 ± 63	0.755
MA, mm	63 ± 7	63 ± 6	0.523
MA-AA, mm	44 ± 16	47 ± 16	0.111
MA-ADP, mm	28 ± 17	32 ± 17	0.070
Percent inhibition AA	35 ± 26	30 ± 26	0.188
Percent inhibition ADP	65 ± 28	57 ± 27	0.04

TABLE 4. Platelet Function Before/After Platelet Transfusion

	Before Platelet Transfusion, n = 16 (Mean ± SD)	After Platelet Transfusion, n = 16 (Mean ± SD)	*p*
MA, mm	62 ± 7	62 ± 7	0.6
MA-AA, mm	43 ± 13	52 ± 13	0.07
MA-ADP, mm	24 ± 16	31 ± 19	0.18
Percent inhibition AA	36 ± 19	22 ± 18	0.06
Percent inhibition ADP	76 ± 24	64 ± 32	0.16

subgroups were 21 (17–23) and 4 (1–6), respectively. There was no difference in median age or percentage of patients who were male. There was no difference in MA, MA-AA, and MA-ADP between this group and those with an ISS of less than 15. Although there was no statistical difference in percent inhibition AA between the two groups, there was a statistically significant 8% greater degree of inhibition in the ADP pathway in those with an ISS of greater than 14 ($p = 0.04$).

A total of 28 patients in the overall cohort received a platelet transfusion, 18 in the TBI group and 10 in the non-TBI group. The mean number of single-donor platelets transfused was 2 ± 1 U in the TBI group and 2 ± 2 U in the non-TBI group. A follow-up TEG-PM was obtained on 16 patients. As noted in Table 4, there was no statistically significant change in any parameter. Although the change in MA-AA (12 mm) and percent inhibition AA (14%) approached significance, statistical analysis is very limited because of the small sample size. Nevertheless, the follow-up TEG-PM still revealed a significant degree of inhibition in this pathway. The MA-AA remained almost 20 mm less than the overall MA, and the percent inhibition remained 22% following platelet transfusion. The degree of inhibition in the ADP pathway was also markedly elevated both before and after platelet transfusion.

Patients were evaluated based on the degree of inhibition in the AA and ADP pathways (Tables 5 and 6). A higher number of male patients were found to have between 33% and 66% inhibition in the AA pathway, whereas a significantly higher number of male patients were more than 66% inhibited in the ADP pathway. There was no clinically meaningful change in the median ISS among the tertiles. There was also no statistically or clinically significant difference in ICU LOS or mortality based on the degree of inhibition in either pathway.

DISCUSSION

Clot formation involves a highly complex series of interactions between the cellular and humoral factors of the clotting cascade.[5,10] Studies on severely injured and hemorrhaging patients suggest that both coagulopathy and mortality are reduced following empiric platelet transfusion.[11–13] However, these studies do not address the underlying cause(s) of platelet dysfunction that may account for this observed effect. Moreover, there are no large studies that address the incidence of platelet dysfunction following minor-to-moderate injury.

TEG-PM offers a means to assess both maximal potential clot strength, the MA, as well as clot strength related specifically to the stimulation of the AA and ADP receptors on the platelet. Aspirin exerts its effects by inhibition of AA-mediated platelet function, and clopidogrel functions by inhibiting ADP-dependent platelet degranulation. Because kaolin, a potent prothrombotic catalyst, is added to the specimen before analysis, the MA represents maximal clot strength and may differ from true in vivo clotting ability. However, kaolin is also present in the AA- and ADP-specific assays. Thus, there should not be a difference among the MA, MA-AA, and MA-ADP in patients who are not otherwise pharmacologically anticoagulated.

Based on studies suggesting that coagulopathy occurs early following injury and that platelet transfusion may improve mortality outcome, we implemented TEG-PM testing to assess for the presence and clinical relevance of platelet dysfunction following injury. Our study found that a significant number of patients have marked inhibition of both the AA- and ADP-mediated platelet activation pathways irrespective of the severity of injury. Conversely, a recent study comparing normal volunteers with severely injured patients found that the mean percent inhibition in the ADP and AA pathways in the volunteers was 4% and 0.5%, respectively.[6] The study also found a marked degree of platelet inhibition in the severely injured cohort, whose mean ISS was 19. In comparison, the mean ISS in our cohort was 7, a severity score that much more closely resembles noninjured patients. The mean ISS of patients in the National Trauma Data Bank from 2010 to 2011 is 9, suggesting that our study population is broadly similar to the patient populations of other trauma centers nationwide. We further found that while platelet transfusion may improve platelet function via AA receptor–mediated pathways, it has little, if any, impact on ADP receptor–mediated pathways.

The role of the platelet in the well-known causal relationship between TBI and coagulopathy is still being defined.[14,15] Most studies on this topic use an animal model of TBI or a multisystem injury model in the human or involve mainly severe TBI patients. That our study did not find any difference in the degree of platelet inhibition between the TBI and non-TBI cohorts may be related to the low acuity of most of our TBI patients. Our subgroup analysis of patients with severe injuries

TABLE 5. Patient Characteristics Based on the Degree of Inhibition in the AA Pathway and Outcomes

Variable	1–33% Inhibition, n = 310	33.1–66% Inhibition, n = 98	66.1–100% Inhibition, n = 51	*p*
Age, median (25th–75th IQR), y	38 (27–54)	43 (25–60)	39 (27–59)	0.242
Male, %	67	80	69	0.062
ISS, median (25th–75th IQR)	5 (1–9)	5 (2–9)	5 (2–10)	0.062
TBI present	22	24	20	0.905
ICU days, median (25th–75th IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.587
Mortality, %	1	3	6	0.203

TABLE 6. Patient Characteristics Based on the Degree of Inhibition in the ADP Pathway and Outcomes

Variable	1–33% Inhibition, n = 101	33.1–66% Inhibition, n = 176	66.1–100% Inhibition, n = 182	*p*
Age, median (25th–75th IQR), y	47 (33–60)	37 (26–55)	35 (25–53)	0.001
Male, %	57	68	79	0.001
ISS, median (25th–75th IQR)	4 (1–9)	5 (2–10)	4 (1–9)	0.064
TBI present	21	37	44	0.716
ICU days, median (25th–75th IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.017
Mortality, %	0	1	4	0.101

showed a slightly higher degree of inhibition of the ADP-mediated platelet pathway, but because of the small number of patients within this subgroup, statistical significance could not be reliably measured. However, based on previous trials, we feel that it is very likely that those with severe TBI have even more platelet dysfunction than the patients with mild TBI included in our study, a trend which is suggested by our data.

Platelets are known acute phase reactants. Injury, however minor, leads to inflammation with elaboration of chemotactic factors and resultant activation the inflammatory cascade inclusive of the platelet.[16] Platelet activation involves degranulation and release of ADP along with other factors that result in the elaboration of eicosanoids. Regeneration of these preformed granules can take up to 24 hours, resulting in transient platelet dysfunction and circulation of "exhausted" platelets.[17,18] As such, it is logical to assume that the degree of platelet dysfunction is directly proportional to the degree of tissue disruption or injury, an assumption that has been borne out in the literature.[19] Our study is unique in that it suggests that platelet exhaustion may also manifest following seemingly minor injury and, as such, may serve as one of the earliest abnormalities in the clotting cascade following injury.

Platelet inhibition alone may not be associated with a propensity toward hemorrhage or death. Thus, as with total platelet count and other conventional tests, platelet function needs to be considered in the appropriate clinical context. Other than the single study by Wohlauer et al.,[6] there are no studies to determine "normal values" for AA and ADP receptor inhibition in the general population, and this is the first study to compare these values following both minor and major injuries. Because of the lack of data establishing normal values for TEG-PM, the clinical relevance of the test panel cannot be ascertained. It is possible that our study has found an in vitro laboratory abnormality with limited clinical applicability. Further study in various populations including injured and noninjured but critically ill patients is needed to determine the baseline prevalence of platelet dysfunction and the propensity for hemorrhage related thereto. Minimally injured patients, such as those in our cohort, have very little risk of hemorrhage or death and thus generally do not require intervention. However, more severely injured patients, such as those described in previous studies, have a significantly higher risk of bleeding or dying and thus may benefit from platelet transfusion. Future studies with a larger data set involving changes in the TEG-PM metrics following platelet transfusion are needed to better elucidate the role of transfusion therapy following injury.

Despite the fact that this is one of the largest studies of platelet function performed in acutely injured patients and the only study to concentrate on minimally injured patients, it has several limitations that we acknowledge. First, it is a single-center, retrospective study with all of the limitations inherent therein. The decision to order a TEG-PM assay was made at the discretion of the trauma surgeon, thereby raising the possibility of a selection bias. Our study does not address mechanisms that underlie its findings, and future biochemical studies are needed to better elucidate reasons why the AA and ADP pathways are inhibited following injury. Very few patients had a TEG-PM following platelet transfusion. The lack of statistically significant difference in the TEG-PM parameters following platelet transfusion is likely caused by a small sample size, but this cannot be fully elucidated without a larger sample size. Lastly, although we intentionally excluded patients on any anticoagulants, we did not account for alterations in platelet function that may be related to dietary supplements or overall eating habits.[20]

CONCLUSION

In conclusion, using the data gathered from the large number of minimally injured patients in this study, we hope to direct clinicians' attention to the novel finding that marked platelet inhibition is common following even minor injury and should be considered in the overall resuscitative strategy. Further study is required to elucidate the clinical significance of this platelet inhibition and basic science–based studies are needed to elucidate mechanisms that may account for these findings. Until these studies are performed, TEG-PM alone cannot be used to guide decisions regarding platelet transfusion.

AUTHORSHIP

S.S. contributed in the data collection, statistical analysis, literature search, data interpretation, and drafting of the manuscript. C.V. contributed in the study design and drafting of the manuscript. L.D. contributed in the data interpretation and drafting of the manuscript. P.M. contributed in the critical revision. R.S. contributed in the data collection and interpretation. M.S. contributed in the critical revision. B.S. contributed in the study design, data collection, literature search, data interpretation, and drafting of the manuscript.

DISCLOSURE

B.S. received an honorarium from Haemonetics. The remaining authors do not have any conflicts of interest.

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