Goal-directed platelet transfusions correct platelet dysfunction and may improve survival in patients with severe traumatic brain injury

Elisa Furay, MD, Mitch Daley, PharmD, Pedro G. Teixeira, MD, Thomas B. Coopwood, MD, Jayson D. Aydelotte, MD, Natalia Malesa, PharmD, Christian Tellinghuisen, PharmD, Sadia Ali, MPH, Lawrence H. Brown, PhD, *and* **Carlos V.R. Brown, MD***, Austin, Texas*

BACKGROUND: Platelet dysfunction, defined as adenosine diphosphate inhibition greater than 60% on thromboelastogram, is an independent predictor of increased mortality in patients with severe traumatic brain injury (TBI). We changed our practice to transfuse platelets for all patients with severe TBI and platelet dysfunction. We hypothesized that platelet transfusions would correct platelet dysfunction and improve mortality in patients with severe TBI.

METHODS: This retrospective review included adult trauma patients admitted to our Level I trauma center from July 2015 to October 2016 with severe TBI (head Abbreviated Injury Scale score ≥ 3) who presented with platelet dysfunction and subsequently received a platelet transfusion. Serial thromboelastograms were obtained to characterize the impact of platelet transfusion on clot strength. Subsequently, the platelet transfusion group was compared to a group of historical controls with severe TBI patients and platelet dysfunction who did not receive platelet transfusion.

RESULTS: A total of 35 patients with severe TBI presented with platelet dysfunction. Following platelet transfusion clot strength improved as represented by decreased K time, increased α angle, maximum amplitude, and G-value, as well as correction of adenosine diphosphate inhibition. When comparing to 51 historic controls with severe TBI and platelet dysfunction, the 35 study patients who received a platelet transfusion had a lower mortality (9% vs. 35%; $p = 0.005$). In stepwise logistic regression, platelet transfusion was independently associated with decreased mortality (odds ratio, 0.23; 95% confidence interval, 0.06–0.92; $p = 0.038$).

CONCLUSION: In patients with severe TBI and platelet dysfunction, platelet transfusions correct platelet inhibition and may be associated with decreased mortality. (*J Trauma Acute Care Surg.* 2018;85: 881–887.

LEVEL OF EVIDENCE: Therapeutic, level II.

KEY WORDS: Platelet dysfunction; TBI; TEG; Platelet transfusion.

Traumatic brain injury (TBI) remains a major cause of mortality in the United States accounting for approximately 30% of all injury related deaths.[1,2] Coagulopathy is commonly identified in patients with TBI.[3,4] In a recent systematic review, incidences of coagulopathy were reported as high as 33% in all TBI patients and up to 60% in patients with severe TBI.[5] The degree of coagulopathy has been shown to be directly related to the severity of injury and its presence is a poor prognosticator in patients with TBI.[3,6–8] Traumatic brain injury patients with evidence of coagulopathy on admission have up to a nine times greater risk of mortality than those with no coagulopathy.[3,5,7,9–11]

The mechanism behind the coagulation disorders associated with TBI is complex and not fully understood.[3,5,11–13] Some authors hypothesize that increased tissue factor release, disseminated intravascular coagulation, platelet dysfunction, and activation of protein C pathways[12,14–16] all contribute to the coagulopathy associated with TBIs. Castellino et al.[13] suggested that the brain injury leads to elevated tissue factor release by the blood brain barrier leading to overwhelming activation of the extrinsic coagulation cascade and ultimately excess stimulation of thrombin. This significant thrombin activation then causes an increase in platelet activation ultimately leading to the platelets with decreased hemostatic abilities.[13] Adenosine diphosphate (ADP) and arachidonic acid (AA) pathways play a critical role in the initiation, activation and aggregation of platelets during coagulation and both have been implicated as possible contributors to coagulopathy of trauma and coagulopathy associated with traumatic brain injuries.[13,16–19]

Diagnosing coagulopathy historically has been achieved through conventional assays, such as international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen level, and platelet count.[20] Using these assays, studies have shown that thrombocytopenia is associated with increased risk of TBI progression and, when severe, is associated with a nine times greater risk of death.[21,22] Platelet dysfunction contributes significantly to coagulopathy and conventional assays are unable to evaluate this.[3,13,16,22–25] The identification of platelet dysfunction requires a more dynamic laboratory test such as thromboelastography with platelet mapping (TEG-PM) or other

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From the Department of Surgery and Perioperative Care, Dell Medical School, Austin, Texas. lphia, Pennsylvania (J.C.).

Address for reprints: Elisa J. Furay, MD, Dell Seton Medical Center at the University of Texas Attn: General Surgery 1500 Red River St., Austin, Texas 78701; email: Efuray@ascension.org.

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viscoelastic assays. These tools allow for the analysis of kinetics and stability of clot formation.[3] The addition of platelet function tests, such as platelet mapping, allows for the diagnosis of platelet dysfunction by directly analyzing platelet responses to ADP and AA in the absence of thrombin generation.[23,26] The use of these assays is being widely investigated for use in trauma patients, and a recent Cochrane review suggests that these tools may reduce overall mortality when used to guide transfusion and may reduce the need for blood products.[27]

Previous studies in cardiology and cardiothoracic surgery found that ADP inhibition greater than 60% in patients taking antiplatelet medications was associated with bleeding complications during cardiac surgery.[28] Using this literature as a foundation our institution conducted a retrospective review and found increased mortality was associated with ADP dysfunction (inhibition ≥60% on TEG-PM) in patients with severe TBI.[17] As a result of that study, we changed our practice to transfuse platelets in all patients with severe TBI associated with platelet dysfunction (Fig. 1). In this study, we hypothesized that platelet transfusions would correct platelet dysfunction and improve mortality in patients with severe TBI.

METHODS

This was a retrospective study of all adult blunt trauma patients who sustained an intracranial hemorrhage and were admitted to our ACS-verified Level I trauma center from July 2015 to October 2016. Patients were included if they sustained a severe TBI (defined as head Abbreviated Injury Scale [AIS] score ≥3) and displayed platelet dysfunction (defined as ≥60% inhibition on the ADP platelet pathway) as measured by TEG-PM drawn at admission to the intensive care unit. Per our institutional practice patients with severe TBI and platelet dysfunction are transfused a unit of apheresis platelets to reverse inhibition. If platelet inhibition persists on repeat TEG, after this first round of transfusion, the patient then receives a second round of platelet transfusion (Fig. 1). Study patients with severe TBI and platelet inhibition who received a platelet transfusion (PTL group) were compared to a group of historic controls (February 2011 to October 2013) with severe TBI and platelet inhibition who did not receive a platelet transfusion (no PTL group). Patients were excluded if they received a transfusion of platelets or plasma prior to initial TEG-PM. Data was abstracted from our trauma registry and review of the electronic medical record.

Data collection included patient demographics, admission physiology, Injury Severity Score (ISS), head AIS, prothrombin time (PT), INR, PTT, platelet count, and preinjury antiplatelet therapy. TEG-specific variables included split point (SP), R time (R), K time (K), alpha angle (angle), maximum amplitude (MA), G value (G), estimated percent lysis (EPL), and platelet assay variables including ADP and AA inhibition. The primary outcomes were correction of ADP inhibition and mortality. Secondary outcomes included correction of other TEG parameters and thromboembolic complications.

Baseline characteristics and outcomes data were analyzed using χ^2 with Yates correction for categorical variables and unpaired Student's *t* test or Wilcoxan rank-sum test for continuous parametric and non-parametric data, respectively. A generalized linear model procedure was used to compare serial TEG parameters following platelet transfusions. Values are reported as mean ± standard deviation or raw percentages. An a priori alpha value of 0.05 was identified for statistical significance. Forward, stepwise logistic regression analysis was used to evaluate the impact of platelet transfusion on in-hospital mortality. If a variable was identified

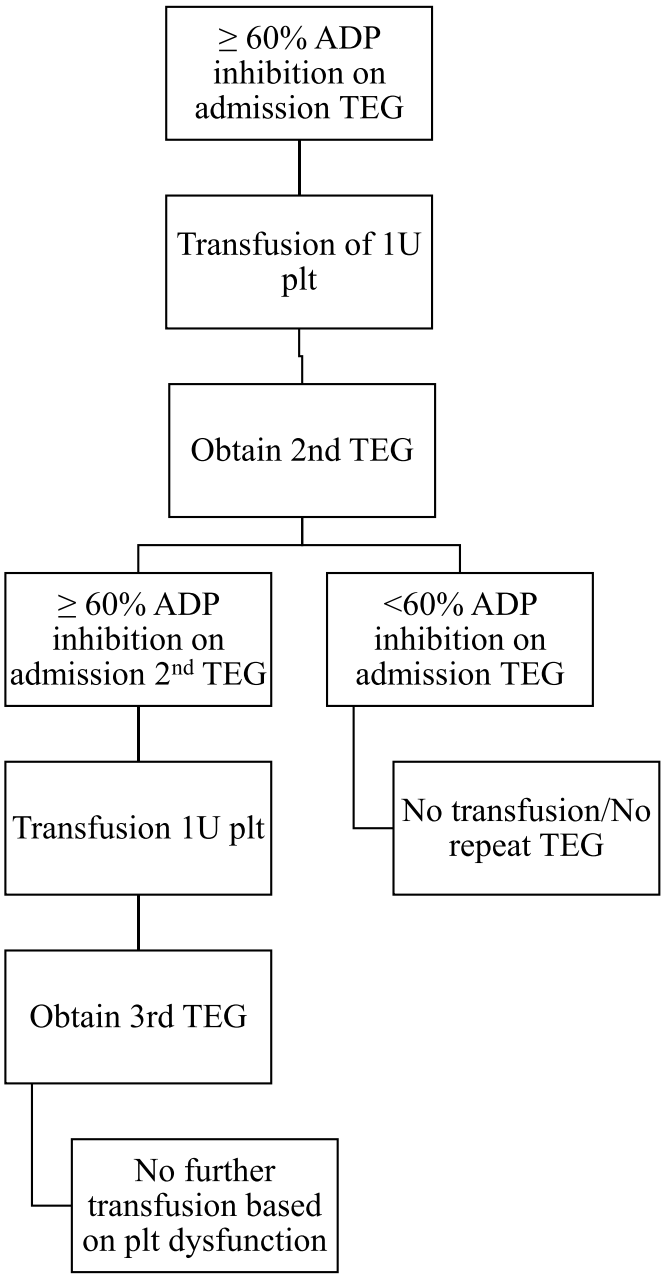

Figure 1. Algorithm for treatment of platelet dysfunction in TBI patients diagnosed on TEG. Algorithm for platelet transfusion. In patients with TBI with admission TEG showing ADP inhibition of 60% or greater, they would be transfused 1 unit of platelets. The TEG would be repeated and if ADP inhibition had corrected to less than 60% no further transfusions based on TEG would occur. If on the second TEG there was continued ADP inhibition of 60% or greater, then another round of platelet transfusion would occur. The third TEG was obtained to evaluate response but no further treatment would occur based on the third TEG.

TABLE 1. Serial TEG Variables Following Platelet Transfusion

TEG Variables, Mean ± SD	Baseline TEG, n = 35	Second TEG, n = 35	Third TEG, n = 16	*p* value
SP, min	3.9 ± 1.2	3.8 ± 0.81	3.8 ± 0.73	0.92
Reaction time (*r*), min	4.3 ± 1.4	4.2 ± 0.87	4.1 ± 0.80	0.80
K, min	1.6 ± .75	1.1 ± 0.22	.92 ± 0.14	< 0.01
Angle (α), degrees	68.5 ± 6.9	73.7 ± 2.9	76.3 ± 2.5	< 0.01
MA, mm	63.03 ± 6.8	67.8 ± 4.1	71.4 ± 4.4	< 0.01
G value, dynes/cm^2	8.9 ± 2.4	10.8 ± 2	12.9 ± 3.1	< 0.01
EPL, %	2.4 ± 3.9	2.3 ± 2.7	6.8 ± 6.03	< 0.01
Adenosine diphosphate inhibition, %	88.6 ± 12.6	69.4 ± 22.1	58.8 ± 24.5	< 0.01
AA inhibition, %	40.3 ± 32.6	30 ± 28.4	25.4 ± 29.06	0.19

Baseline TEG was obtained on admission to the ICU. Second TEG was obtained following one round of platelet transfusion in the entire study cohort. Third TEG was obtained following an additional round of platelet transfusion in the subset of patients who did not have ADP inhibition correct below 60% initially.

SP, spllit point; K, clot formation time; EPL, estimated percent lysis.

as significant in univariate analysis, using a *p* value less than 0.2, variables were subsequently included in a multivariate regression analysis. This study was approved by our local institutional review board.

RESULTS

There were 35 patients with severe TBI and platelet dysfunction who received a platelet transfusion and were admitted during the study period. After platelet transfusion the PTL group had correction of the majority of TEG variables including K time, alpha angle, MA, G, and ADP inhibition (Table 1, Fig. 2). However, there was no change in split point, R time, or AA inhibition and there was an increase in EPL. Following one round of platelet transfusion 54% of patients had correction of their ADP inhibition to <60%. Patients who did not achieve goal following the first round continued to show improved ADP inhibition with a second round of platelet transfusion, with 26% completely correcting after two rounds of treatment. Only 20% of patients did not achieve complete correction of ADP inhibition following two rounds of platelet transfusions.

When the 35 patients in the PTL group were compared to 51 control patients (Table 2) the PTL group patients were younger (42 ± 19 years old vs. 63 ± 18 years old, $p < 0.0001$) and more often Caucasian (94% vs. 78%, $p = 0.04$), but there was no difference in male gender (75% vs. 75%, $p = 0.55$). When comparing the PTL group to the no PTL group there was no difference in admission heart rate (104 ± 31 vs. 95 ± 25, p = 0.14), hypotension (11% vs. 10%, $p = 0.80$), Glasgow Coma Scale (GCS) score (9 ± 6 vs. 11 ± 5, $p = 0.20$), ISS (23 ± 9 vs. 28 ± 13, $p = 0.05$), or head AIS (4.1 ± 0.8 vs. 4.3 ± 0.8, $p = 0.52$). We used AIS scores of ≥3 to compare other injuries on admission. No significant differences between cohorts were found. When comparing traditional coagulation parameters, there was no difference in PT (11.9 ± 2.03 seconds vs. 13.8 ± 5.1 seconds, $p = 0.046$), INR (1.04 ± 0.18 vs. 1.2 ± 0.51, $p = 0.07$), PTT (28.8 ± 5.5 seconds vs. 31.6 ± 11.5 seconds, $p = 0.22$), platelet count (222 ± 59 vs. 186 ± 64, $p = 0.06$), or rate of preinjury antiplatelet therapy (11.4% vs. 29%, $p = 0.06$). When comparing blood products received during admission the no PTL group had significantly more fresh frozen plasma (3.3 ± 8.7 units vs. 0.11 ± 0.47 units $p = 0.04$) and PRBC (4.2 ± 8.4 units, vs. 1.1 ± 2.5 units, $p = 0.04$). The PTL group received significantly more platelets (1.7 ± 3.5 units, vs. 3 ± 1.3 units $p = 0.04$).

The PTL group had a lower mortality (9% vs. 35%, $p = 0.005$). There was no difference in cause of death between groups ($p = 0.96$). The causes of death in each group included TBI (no PTL-11, PTL-2) comfort care (no PTL-4, PTL-1) cardiopulmonary arrest (no PTL-1), multisystem organ failure (no PTL-1), and sepsis (no PTL-1). Using logistic regression to adjust for differences between groups, platelet transfusion was independently associated with survival (odds ratio = 0.23, 95% confidence interval: 0.06–0.92, $p = 0.04$, Hosmer and Lemeshow Goodness-of-Fit Test p = 0.26). In order to further control for age and ISS we matched the two cohorts for age ± 5 years and ISS of <16, 16–25, and > 25. The matched groups were similar for age (48 ± 19 vs. 49 ± 19, $p = 0.85$) and ISS (23 ± 8 vs. 28 ± 16, $p = 0.20$) and the platelet transfusion group still had a lower mortality (17% vs. 33%, $p = 0.44$), but this did not achieve statistical significance due to the smaller sample size (n = 18) in each group. No patient experienced a deep vein thrombosis or myocardial infarction in either group. Only one patient developed a pulmonary embolism, that person was in the no platelet transfusion cohort.

DISCUSSION

In our current study, we looked at 35 patients with severe TBI who underwent platelet transfusion based on platelet dysfunction diagnosed on TEG-PM and compared these to 51 historical controls who did not receive platelet transfusion to treat platelet dysfunction seen on TEG-PM. Platelet transfusion led to a correction of platelet dysfunction as measured by TEG-PM and well as an overall improvement of TEG parameters and clot strength. In addition, we were able to identify a survival benefit in severe TBI patients with platelet dysfunction who were treated with platelets. However, we recognize that our groups are different which may have contributed to our outcomes. We attempted to control for these differences using a logistic regression and a matched analysis but we concede that strong conclusions cannot be made regarding mortality differences seen in our two cohorts. To our knowledge, no previous studies have investigated TBI outcomes based on treatment of platelet dysfunction seen on TEG-PM.

Castellino et al. were the first to identify ADP receptor inhibition as an early finding in both patients and rats with TBIs.[13] They showed a median ADP pathway inhibition of 64.5%, compared with 15.5% in the healthy controls ($p < 0.0001$). When stratified based on severity of TBI, the severe (GCS score ≤ 8) cohort showed a median ADP inhibition of 93% compared with 57% in the mild-to-moderate (GCS score > 8) cohort ($p = 0.0014$). These results quantitatively identified that TBI patients manifest platelet dysfunction in the form of ADP inhibition and that this platelet dysfunction is related to the severity of injury.

These finding were later supported by a study performed by Davis et al. and another by Sirajuddin et al.[29] Davis et al. found a correlation between ADP receptor inhibition and the severity of brain injury.[23] They compared healthy controls with TBI

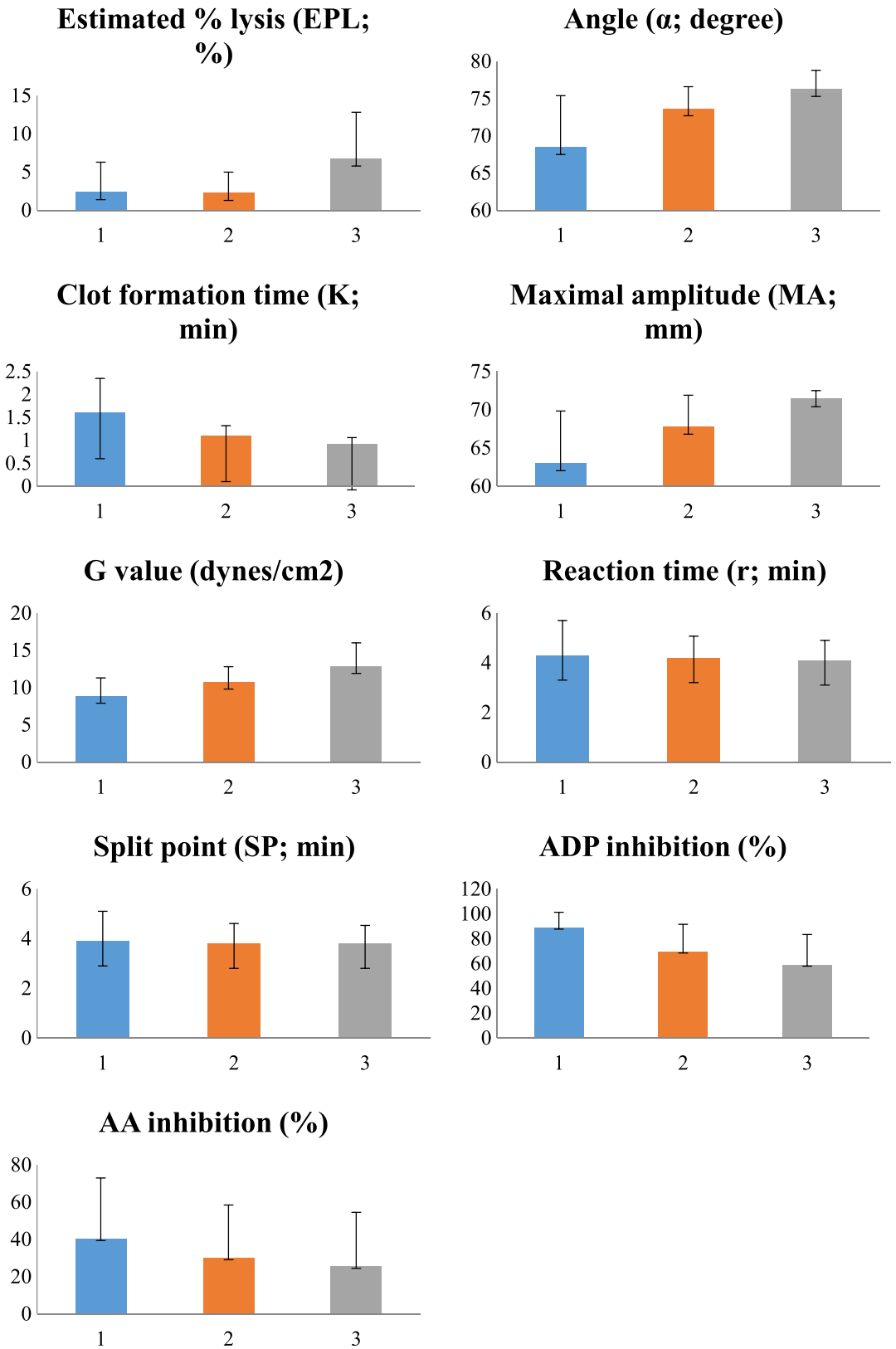

Figure 2. Graphic representation of serial TEG variables following platelet transfusion. Graphic representation of the values shown in Table 1.

TABLE 2. Demographic comparison by cohort

	Whole Population (N = 86)	Platelet Transfusion N = 35	No Platelet Transfusion N = 51	*p* value
Age	55 ± 21	42 ± 19	63 ± 18	**< .0001**
Male	77%	80%	75%	**.55**
White	85%	94%	78%	**.04**
ED Respiratory Rate	17 ± 11	16 ± 10	18 ± 11	**.44**
ED Systolic Blood Pressure	141 ± 36	143 ± 37	139 ± 36	**.62**
ED Pulse	99 ± 28	104 ± 31	95 ± 25	**.14**
ED GCS	10 ± 28	9 ± 6	11 ± 5	**.20**
AIS Head	4.2 ± .78	4.1 ± .77	4.3 ± .80	**.52**
% AIS Head ≥ 3	100%	100%	100%	
AIS Face	.58 ± .99	.74 ± 1.1	.47 ± .92	**.21**
% AIS Face ≥ 3	4%	3%	4%	**.99**
AIS Chest	1.2 ± 1.6	.91 ± 1.3	1.4 ± 1.7	**.16**
% AIS Chest ≥ 3	27%	14%	35%	**.03**
AIS Abdomen	.56 ± 1.2	.14 ± .49	.84 ± 1.4	**.005**
% AIS Abdomen ≥ 3	12%	0%	20%	**.005**
AIS Extremities	.86 ± 1.2	.77 ± 1.1	.92 ± 1.2	**.57**
% AIS Extremities ≥ 3	15%	11%	18%	**.43**
AIS External	.66 ± .59	.86 ± .60	.53 ± .54	**.01**
% AIS External ≥ 3	0	0	0	
ISS	26 ± 12	23 ± 9	28 ± 13	**.05**
Mortality	24%	9%	35%	**.005**
Hospital days	12 ± 14	15 ± 18	9 ± 11	**.06**
ICU days	7 ± 10	8 ± 13	5 ± 6	**.13**
Ventilation days	4 ± 5	3 ± 5	4 ± 5	**.70**
Craniotomy/Craniectomy	14%	20%	10%	**.48**
ICP monitor	5%	3%	6%	**.60**
Laparotomy	3%	0%	6%	**.23**
Thoracotomy	0	0	0	
PT (seconds)	13.05 ± 4.2	11.9 ± 2.03	13.8 ± 5.1	**.046**
INR	1.1 ± .42	1.04 ± .18	1.2 ± .51	**.07**
PTT (seconds)	30.6 ± 9.8	28.8 ± 5.5	31.6 ± 11.5	**.22**
Platelet Count (x10^9/L)	229 ± 67	264 ± 65	205 ± 57	**< .0001**
Pre Injury Antiplatelet Therapy	23%	11%	29%	**0.06**
FFP given (units)	2 ± 6.9	.11 ± .47	3.3 ± 8.7	**0.04**
PRBC given (units)	2.9 ± 6.8	1.1 ± 2.5	4.2 ± 8.4	**0.04**
Platelets given (units)	2.2 ± 2.9	3 ± 1.3	1.7 ± 3.5	**0.04**

Description of whole population and each cohort regarding demographics, operative interventions, coagulation parameters, prehospital antiplatelet therapy, and blood products given.
ED; emergency department.
AIS; abbreviated injury scale.
ISS; injury severity score.
ICU; intensive care unit.
ICP; intracranial pressure.
PT; prothrombin time.
INR; international normalized ratio.
PTT; partial thromboplastin time.
FFP; fresh frozen plasma.
PRBC; packed red blood cells.

patients and found that TBI patients had significant decrease in ADP reactivity. After subdividing TBI patients based on injury severity they found that the more severe the injury the greater the ADP inhibition. Sirajuddin et al. performed a retrospective review of 459 adult trauma patients and assessed platelet function using TEG-PM in patients with and without radiographic evidence of TBI.[29] They found that both AA and ADP mediated platelet activation pathways are significantly inhibited (30% and 58%, respectively) in TBI patients regardless of severity of injury.

The aforementioned studies identify that patients with TBI have significant coagulopathy in the form of platelet dysfunction and that this dysfunction is related to severity. In a recent study from our institution we were able to expand on these studies and identify an increased mortality risk associated

with ADP inhibition of 60% or greater diagnosed by TEG-PM. We examined 90 patients diagnosed with TBI (head abbreviated injury score ≥ 3) who underwent TEG-PM within the first 24 hours of admission were included in this study. Patients were subdivided in ADP dysfunction (defined as inhibition ≥60%) vs. no ADP dysfunction on TEG-PM. Results showed that ADP dysfunction on TEG-PM was associated with higher in-hospital mortality rate (32 vs. 8%, $p < 0.01$).[17]

Literature investigating platelet transfusion for platelet dysfunction related to TBI is scarce. Brasel et al.[30] compared TBI patients with non-TBI patients who received massive transfusion and identified improved survival in TBI patients who received a higher ratio of platelets to packed red blood cells. Most literature on platelet transfusions in patients with TBI has focused on patients taking prehospital antiplatelet agents. A systematic review looking at prehospital antiplatelet agent use in patients with traumatic intracranial hemorrhage found that platelet transfusion was associated with increased in-hospital mortality.[31] In a prospective interventional trial Joseph et al.[32] transfused TBI patients with platelet dysfunction taking prehospital high dose aspirin with platelets. This study showed that platelet transfusion was not associated with improved platelet function. Washington et al. conducted a retrospective review looking at platelet transfusion versus no transfusion in isolated mild TBI patients taking prehospital antiplatelet agents. They found that when comparing those two groups there was no significant difference in progression of injury on head CT, neurologic decline, or Glasgow Outcome Scale at hospital discharge.[33] Our current study adds to the existing literature and found not only that platelet transfusion reverses platelet dysfunction measured by TEG-PM, but also that platelet transfusion may be associated with improved mortality in patients with severe TBI.

Several limitations of this study can be attributed to the inherent retrospective design. We relied on the accuracy and homogenous documentation practices in the medical chart and/or the trauma registry. TEG utilization was not an automated process and ordering of this test was subject to the physician discretion which may have influenced patient selection thus creating a bias. Another limitation was our small sample size and heterogeneous groups.

CONCLUSION

In patients with severe TBI and platelet dysfunction, platelet transfusions correct platelet dysfunction and may be associated with improved survival. Increased clot strength suggests platelet dysfunction may be a therapeutic target in severe TBI patients. Future prospective studies are needed to determine the specific benefit associated with the treatment of platelet dysfunction in TBI patients, as well as to develop validated treatment algorithms for this treatment.

AUTHORSHIP

E.F., M.J.D., C.V.R.B. participated in the literature review. E.F., M.J.D., P.G.T., T.B.C, J.D.A. C.V.R.B. participated in study design. E.F., M.J.D., P.G.T., T.B.C., J.D.A., N.M., C.T., L.H.B., C.V.R.B. participated in data collection. E.F., M.J.D., P.G.T., T.B.C., J.D.A., N.M., C.T., S.A., L.H.B., C.V.R.B. participated in data analysis. E.F., M.J.D., P.G.T., T.B.C., J.D.A., C.V.R.B. participated in data interpretation. E.F., M.J.D., C.V.R.B. participated in writing. E.F., M.J.D., C.V.R.B. participated in Critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

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