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Multiplate and TEG Platelet Mapping in a Population of Severely Injured Trauma Patients

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Abstract

Objectives—The objectives of this study were to compare Thromboelastography Platelet Mapping (TEG PM) to impedance aggregometry (Multiplate) in a single trauma population and relate their results clinically.

Background—Platelet function as measured by thromboelastography and impedance aggregometry demonstrate significant reductions in platelet function following traumatic injury. However, there is no study comparing these devices and correlation between them is unknown.

Methods—TEG PM and Multiplate were performed in Level 1 trauma patients at their initial Emergency Department presentation. Within-device repeatability and between-device associations were determined using correlation analyses. Demographic variables, Injury Severity Score (ISS), blood product transfusion, laboratory test results, and mortality were recorded.

Results—Ninety-two patients were enrolled. Within-device repeatability was high for TEG PM and Multiplate for arachidonic acid (AA) and adenosine diphosphate (ADP) activation pathways. When comparing TEG PM to Multiplate, results correlated weakly for the ADP pathway (Spearman's $\rho=0.11$, $p=0.44$) and moderately in the AA pathway (Spearman's $\rho=0.56$, $p<0.0001$). TEG PM was predictive of blood product transfusion and correlated with elevated base deficit while Multiplate was only predictive of mortality.

Conclusions—TEG PM and Multiplate intra-device variability was low, but the two point of care devices measuring platelet function correlate poorly with each other in the injured trauma patient. Each device also had different clinical associations.

Introduction

Platelet function in trauma patients is clinically relevant because it is a vital component of hemostatic potential. Clinical measures of platelet function in cardiovascular and hepatic surgery are well established, however investigation regarding its use in trauma is limited (Jacoby *et al.* 2001). Light transmission aggregometry (LTA) has classically been used to

determine platelet function associated with inherited or acquired bleeding disorders. However, use of this technique is limited at the point of care because it requires significant sample processing (Ramsey *et al.* 2016).

Recently other point of care platelet function devices have been introduced to measure platelet function in trauma. Initial studies employing these devices have demonstrated significant reductions in platelet function that persist for days following traumatic injury. These reductions in function are observed in the presence of a normal platelet count, vary with the type of injury and may occur with even minor injuries (Sirajuddin *et al.* 2016). Platelet dysfunction in patients with traumatic injuries has been associated with decreases in hemostatic potential (Wohlauer *et al.* 2012), increased need for blood product transfusions (Stein *et al.* 2017), and poor outcomes. The point of care means employed to determine platelet function are viscoelastometry and impedance aggregometry. Both methods have been validated and approved by the US Food and Drug Administration based on comparison to LTA by demonstrating close agreement with LTA.

The use of point of care platelet function tests to direct hemostatic therapy after trauma is emerging. However, there is no study directly comparing the two available devices to assess their concordance. There is a significant lack of knowledge regarding if these two approaches to platelet function testing give similar results, or can be used interchangeably. In the present study, we compare thromboelastography platelet mapping (TEG PM) and impedance aggregometry (Mutiplate) to determine the amount of agreement between these two point of care platelet function devices.

Methods

Human Subjects

This prospective observational study was performed at Memorial Herman Hospital within the Texas Medical Center, Houston Texas, USA. Institutional Review Board approval was obtained prior to initiating the study (HSC-GEN-12-0059). Patients meeting the highest level of trauma team activation were included into the study from June 2016 to September 2016. Patients were excluded from the study if they were younger than 16 years, pregnant, prisoners, enrolled in other studies, or declined to give consent. Presence of antiplatelet medications or NSAIDS were not an exclusion criteria for this study. Patients from whom we could not obtain an admission blood draw were excluded from analysis. Consent was obtained from the patient or a legally authorized representative within 72 h of admission. A waiver of consent was obtained for those patients discharged or who died within 24 h. In the remaining cases in which consent could not be obtained, the patient was excluded from the study, and their blood samples were destroyed.

Blood samples from trauma subjects were drawn with the initial sample approximately 10 minutes after arrival to the hospital. 20 mL of blood was drawn via venipuncture into vacutainer tubes containing 3.2% citrate or heparin and inverted to insure proper anticoagulation. Platelet function was assessed using TEG PM and MP within one hour after sample collection. Samples from different subjects were also run in single devices in duplicate. Patient vital signs, injury mechanism, injury severity score, laboratory data and

demographics were also recorded. After review of medications, no subjects in this study were noted to take antiplatelet medications or NSAIDS.

Thromboelastography

All TEG PM assays were run on a Thromboelastograph 5000 (Hemoscope Corporation, Niles IL) by trained on-call research personnel. TEG PM can detect various anti-platelet drugs including aspirin and clopidogrel by independently measuring contribution of the adenosine diphosphate (ADP) and thromboxane (TxA2) platelet activation pathways to clot formation. The primary assay metric is the maximal amplitude (MA), a measurement of clot stiffness that is mostly associated with fibrin and platelet contributions. Measuring percent activation of either platelet pathway requires 4 channels of TEG tracings – 1.) kaolin induced TEG to measure the maximal clot formation in response to thrombin (MA_{THROMBIN}), 2.) reptilase and activated FXIII (activator F) to polymerize and crosslink fibrin without platelet activation to measure the isolated fibrin component (MA_{FIBRIN}), and activator F plus either 3.) ADP (MA_{ADP}) or 4.) arachidonic acid (AA) (MA_{AA}) induced TEG to measure the pathway-dependent contribution of platelets to clot formation (Bochsen *et al.* 2007). MA from each channel is recorded and using the following formula, percentage of platelet activation for a given platelet activation pathway is calculated:

$$\% \text{ Platelet Activation} = \frac{MA_{AA \text{ or } ADP} - MA_{FIBRIN}}{MA_{THROMBIN} - MA_{FIBRIN}} * 100 \%$$

For MA_{THROMBIN}, 340 µL of citrated blood mixed with kaolin is added to 20 µL of 0.2 M CaCl₂. For MA_{FIBRIN}, 360 µL of heparinized blood is added to 10 µL of activator F. For MA_{ADP} or MA_{AA}, 360 µL of heparinized blood is added to 10 µL of activator F plus either 10 µL of the ADP or AA agonist. The addition of ADP or AA to agonist F reflects the contribution of the P2Y1 and P2Y12 receptors or COX-1 receptor, respectively. Single assays were run for all enrolled patients and single device duplicates were run for selected patients. Each TEG PM assay takes approximately one hour and fifteen minutes to complete.

Impedance Aggregometry Using Multiplate

Platelet aggregation was measured in parallel using impedance aggregometry in whole blood. Assays were run using Multiplate (Verum Diagnostica GmbH, Munich, Germany). This method measures platelet function by agonist-induced platelet aggregation onto two electrodes submerged in a stirred blood sample. The resulting increased electrical resistance (impedance) between the electrodes from platelet adherence is measured as an indicator of the ability of platelets to adhere to surfaces and to each other. Four different agonists were used – ADP (20 µL 6.5 µM, receptor pathway P2Y12), thrombin receptor activating peptide-6 (TRAP, 20 µL 32 µM, PAR receptor pathway), Arachidonic Acid, (AA, 20 µL 0.5 mM, COX-1 pathway) and Ristocetin (RISTO, 50 µL 0.8 mg/ml, GPIb-IX-V receptor pathway). For this study, only ADP and AA agonists are presented because TEG PM only has corresponding ADP and AA channels. To perform this assay, 300 µL of whole blood is added to the electrode cartridge and diluted 1:1 with sodium chloride or calcium chloride. A magnetic stir-bar insures rapid mixing of blood and agonist throughout the measurement and

electrode impedance is measured continuously for 6 minutes, giving an impedance curve for each sample. Values are recorded as area under the impedance curve (AUC). Cut off values stated by the manufacturer for Multiplate ADP test is 57 – 113 AUC and the AA test is 71 – 115. Single assays were run for all enrolled patients and single device duplicates were run for selected patients. Each MP assay takes 10 minutes to complete.

Replicate Subjects

Forty different subjects, twenty for each device, were recruited under the above protocol to run the replicate assays.

Trauma Subjects

Fifty-two subjects different from those for device replicates were recruited under the above protocol for testing with both the TEG MP and MP devices.

Statistics

Statistical analysis was performed using Stata 14.2 (College Station, TX). Shapiro-Wilk analysis was used to determine normality of continuous data. For normally distributed data, Pearson's correlation was used to correlate device results, otherwise Spearman's rank correlation coefficient was used. Other data are expressed as mean and standard deviation if normally distributed, otherwise they are expressed as the median and interquartile range (IQR). To determine differences between clinical outcomes, a t-test was used for normally distributed data and the Mann-Whitney U-test was used for data that was significantly skewed. Significance was set to $p < 0.05$ for all analysis.

Results

Repeatability for TEG Platelet Mapping (TEG PM) and MultiPlate (MP)

For each device, 20 patients were enrolled for replicate testing. Replicates in MP were concordant (Figure 1). Agreement between test 1 and test 2 was superior in the AA channel compared to the ADP channel. Mean ($\pm$ SD) AUC for the ADP replicates were 66 ($\pm$ 22) and AA replicates was 53 ($\pm$ 23). Replicates in TEG PM were also concordant (Figure 2). Median (IQR) percent platelet activation for the ADP replicates was 37% (9%, 57%) and AA replicates was 76% (44%, 90%).

Comparison of TEG Platelet Mapping to MultiPlate

There were 52 patients enrolled, 78% of which were male. Blunt injury was the mechanism of injury for 85% of patients and median injury severity (ISS) was severe 21.5 (10, 27). Demographic data are presented in Table 1. TEG PM correlated poorly with MP in the ADP channel and moderately in the AA channel (Figure 3). Median values for MP and TEG PM are shown in Table 2.

Clinical Correlation of TEG Platelet Mapping and Impedance Aggregometry

Forty-eight percent of patients received blood products within the first four hours after arrival to the hospital (packed red blood cells, plasma, platelets, or cryoprecipitate). TEG

PM was significantly lower in patients receiving any blood products within the first four hours after hospital arrival compared to those patients who did not for ADP (7% (1%, 35%) vs 54% (14%, 71%) platelet activation, Wilcoxon $p=0.0073$) and AA (73% (12%, 90%) vs 91% (80%, 96%) platelet activation, Wilcoxon $p=0.0376$). Mean (SD) MultiPlate values showed no such differences in either the ADP channel [AUC= 74 (6) vs 74 (5), $p=0.478$] or the AA channel [AUC= 56 (6) vs 63 (5), $p=0.21$].

The mortality rate in this cohort was 17% (Table 1). Multiplate values were significantly decreased in patients who died at any time during their hospital stay in the AA channel (AUC= 44 (7) vs 64 (4), $p=0.023$) but not in the ADP channel (AUC= 70 (7) vs 77 (4), $p=0.23$). There was no association with mortality using TEG PM in either the AA channel [60% (34%, 80%) vs 89% (74%, 94%) platelet activation, Wilcoxon $p=0.350$] or the ADP channel [13% (4%, 72%) vs 35% (8%, 64%) platelet activation, Wilcoxon $p=0.863$].

Base deficit (BD) ≥ 8 , an indicator of hemorrhagic shock, was present in 21% of patients. TEG PM was significantly decreased in patients with base deficit of 8 or greater in the ADP channel (7% (1%, 21%) vs 37% (10%, 67%) platelet activation, Wilcoxon $p=0.018$) but not the AA channel (71% (34%, 80%) vs 90% (74%, 96%) platelet activation, Wilcoxon $p=0.0730$). There was no difference in base deficit using Multiplate in the ADP channel [70 (30) vs 75 (28), $p=0.87$] or the AA channel [50 (25) vs 62 (29), $p=0.68$].

The median ISS in this population of trauma patients was 21.5 (10, 27). For patients with ISS ≥ 25 , there was no significant difference in platelet dysfunction in either device compared to the less injured cohort.

Discussion

In this study of platelet function in severely injured trauma patients, MP and TEG PM were compared using the ADP and AA channels. The devices have moderate correlation in the AA channel and no significant correlation in the ADP channel. Duplicate testing for each device demonstrated that both assays are repeatable.

Device discordance in trauma patients may exist because each device offers fundamentally different measurements of platelet function. Platelet-platelet aggregation after activation is mediated by increased surface membrane expression of the fibrinogen-binding integrin $\alpha\text{IIb}\beta 3$ in addition to conformational change of these integrins from a low-affinity to a high-affinity state. While further cytoskeletal rearrangement and activation accompanies these activation events, it is not required for aggregation to take place (Torti *et al.* 2000). On the contrary, full cytoskeletal activation and rearrangement is required to produce platelet-induced clot contraction, which is the process measured by TEG PM.

The inherent differences between platelet aggregation and cytoskeletal contraction are also highlighted by the different energetic processes required. Platelet aggregation, the primary signal in MP (Cardinal *et al.* 1980), is accompanied by an increase in platelet energy consumption in the form of ATP. Most of the increase in energy demand during aggregation is compensated for by increased glycolytic flux, without requiring platelet mitochondrial-derived oxidative phosphorylation (Ravi *et al.* 2015). Platelet-induced clot contraction,

measured by TEG PM, also requires energy in the form of ATP. However, unlike aggregation, platelet contraction is sensitive to changes of oxidative phosphorylation (Holmsen *et al.* 1979). Also, platelet contraction in TEG PM occurs and is measured over the course of an hour while aggregation in MP is complete in 6 minutes. This infers that TEG PM would potentially be more sensitive to metabolic derangement in traumatic injury because it relies more on continued *in-vivo* oxidative energy production rather than the short term stored glycolytic energy used in aggregation (Verhoeven *et al.* 1986). Ultimately, TEG PM is more reflective of the total energetic potential of platelets. This concept has been proven with *in-vitro* testing. Verhoeven et al measured energy consumption during platelet aggregation and concluded that the increased energy consumption during aggregation does not change when the platelet actin-myosin contractile apparatus is inhibited with cytochalasin. Furthermore, aggregation was unaffected by cytochalasin (Verhoeven *et al.* 1986). However, eliminating the platelet contribution to clot strength in viscoelastic assays is commonly achieved by inhibiting the polymerization of actin using cytochalasin (Schlimp *et al.* 2014). Thus, platelet aggregation measured by MP and cellular contraction measured by TEG PM appear to be mediated by separate intracellular mechanical and energetic responses.

The *in-vitro* sample environment and physics governing the two devices is also vastly different. In MP, citrated whole blood is added to a heated cartridge with a rotating stir bar. After addition of whole blood, platelets initially form a monolayer over the silver-coated copper sensor wires. Platelets, leukocytes, and trapped red blood cells adhere to the platelet mon-layer in response to different agonists. This cellular aggregation increases the electrical resistance, or impedance, of the circuit which drives the device signal. TEG utilizes citrated-recalcified blood in a heated pin-and-cup device measuring resistance to shear as a clot adheres to both the pin-and-cup and coagulation progresses. The device signal depends upon two key players – 1) fibrin and 2) platelets. Fibrin formation marks the transition from liquid to gel, and drives the initial forces defining clot initiation, or R time, in a TEG curve. Platelets also contribute significantly via fibrin cross linking through glycoprotein IIb/IIIa and clot stiffening through contraction mediated by the platelet actin-myosin contractile apparatus. Previous estimations propose that platelets contribute 80% of total clot strength, with fibrin contributing the remaining 20% (Harr *et al.* 2013). This contribution is reflected primarily in the maximum amplitude (MA) metric in a TEG curve and is especially important in the Platelet Mapping assay. Shear on the assay sample in TEG is very low compared to MP, with the cup rotating no more than 5° every 10 seconds compared to a stir bar rotating up to 1,200 RPM. Assay metrics in TEG are determined by factors including thrombin production, fibrin polymerization, and platelet contraction. TEG Platelet Mapping attempts to isolate platelet function through the AA and ADP platelet activation pathways, and it records data during all phases of platelet function from aggregation to contraction. However, changes in fibrin polymerization may yet influence platelet-induced clot contraction in the assay and cannot be fully de-coupled from the measurement. The cumulative effect of the physical device differences in TEG PM and MP are a potentially discordant expression of platelet function. While these two independent tests of platelet function only moderately correlate in the AA channel, individually they detect platelet dysfunction of clinical importance. MP has been found to predict mortality in the setting of

trauma. Solomon et al reported significant increases in mortality related to platelet hypofunction in trauma patients as measured by ADP and thrombin receptor-activating pathway (TRAP) agonist pathways (Solomon *et al.* 2011). Kutcher et al found that platelet responsiveness to AA and collagen agonists in MP was predictive of both early and late mortality despite normal platelet count (Kutcher *et al.* 2012). Similarly, in the present study mortality was found to be associated with decreased platelet responsiveness in the AA channel on Multiplate. However, while platelet dysfunction measured by TEG PM was not associated with mortality, it was associated with clinical measures of physiologic derangement such as elevated base deficit and increased blood transfusion requirement, more likely reflecting the local metabolic state of the blood.

In agreement with our findings, Wohlaue et al demonstrated an association between significant decreases in TEG PM to ADP and both transfusion requirements within 6 hours after arrival and hemorrhagic shock as measured by BD > 8. Similarly, in the present study, the TEG PM ADP and AA channels were significantly lower in patients requiring blood product transfusion within 4 hours after arrival and BD > 8. However, our study differs from both Wohlaue and others in that there was no association between ISS and platelet dysfunction in the ADP channel (Wohlaue *et al.* 2012; Sirajuddin *et al.* 2016). Regardless, agreement between these two studies suggests TEG PM as a useful clinical adjunct in the early decision to administer blood products to trauma patients. TEG PM is potentially a superior indicator of hemorrhagic shock in trauma patients than MP.

TEG PM is also useful in traumatic brain injury (TBI). Nekludov et al studied TEG PM in trauma patients and found low platelet responsiveness to AA was predictive of bleeding complications in patients with concomitant TBI, however this same association did not exist in trauma patients without TBI (Nekludov *et al.* 2007). Davis et al in a study of patients with TBI found that severity of traumatic brain injury and mortality was associated with low platelet responsiveness to ADP (Davis *et al.* 2013). The specificity of TEG PM for true platelet dysfunction in trauma is called into question however by Sirajuddin et al where marked platelet inhibition was found in minimally injured trauma patients (mean ISS = 7) (Sirajuddin *et al.* 2016).

An ideal test of platelet function in the trauma patient would isolate a platelet response reflective of patient physiology and would have high relevance to clinical bleeding management. Measuring platelet metabolism or function more specifically may help to fulfill these requirements. MP relies upon glycolysis and is predictive of mortality however it may be limited in its ability to guide management of hemorrhage. The present study and that by Wohlaue et al demonstrate that TEG PM, which relies more upon oxidative phosphorylation, correlates with the degree of hemorrhagic shock measured by base deficit and early transfusion requirements. This may make TEG PM a more useful POC measurement capable of informing early treatment decisions such as transfusion of platelet concentrates. However, TEG PM extrapolates the platelet contraction signal by subtracting the signal from fibrin formation. Thus, it remains an indirect is not a direct measure of platelet contraction. In the future, devices that could isolate and measure platelet contraction directly, such as those developed by Myers et al (Myers *et al.* 2017) and Feghhi et al (Feghhi

et al. 2016), could potentially remove the confounding influence of fibrin when seeking a pure test of platelet contractile function.

The limitations of this study include small sample size. While the present study was sufficiently powered, similar studies by Sirajuddin and Solomon included hundreds of patients. Additionally, measurements of platelet glycolytic and mitochondrial function run in parallel with the platelet function devices would have added significantly to this study. This data would allow correlation between clinically defined platelet function and platelet bioenergetics, and broaden the understanding of platelet dysfunction in trauma patients.

In summary, we have shown that platelet function measured by TEG PM and Multiplate in trauma patients correlate weakly with each other in the ADP channel and moderately in the AA channel. A potential reason for their discordance is that each signal is governed by different metabolic pathways and each device measures different platelet responses to activation. However, both devices individually are repeatable as duplicate variation in a single device is low. Also, clinical associations in this population of severely injured trauma patients were similar to previously published findings in both devices, except there is no association with indices of injury severity in either device.

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Figure 1.

Pearson correlations for duplicates in MP using the ADP and AA channel. Each point represents the assay value in Test 1 (x-axis) and Test 2 (y-axis). P value for all correlations is < 0.0001 .

Figure 2. Pearson correlations for duplicates in TEG PM using the ADP and AA channel. Each point represents the assay value in Test 1 (x-axis) and Test 2 (y-axis). P value for all correlations is < 0.0001 .

Figure 3.
Spearman's rank correlation coefficient comparing platelet function in TEG PM and MP.

Table 1

Demographic, vital sign, laboratory, and injury data on initial presentation to emergency department; also outcome data. Data are presented as mean and standard deviation or median and interquartile range. N, number of patients; ISS, Injury Severity Score; GCS, Glasgow Coma Score; LOS, length of stay; ICU, intensive care unit.

Patient Data (N = 52)	
Demographic Data	
Age (years)	40 (17)
Male (per-cent)	78.4%
Laboratory Data	
Base Deficit	4 (6, 1)
pH	7.29 (7.21, 7.36)
Vital Signs on Admission	
Systolic blood pressure (mmHg)	136 (107.5, 153)
Heart rate (beats/minute)	100 (81, 117)
Injury Data	
ISS	21.5 (10, 27)
GCS	11 (3, 14.5)
Outcome Data	
LOS (days)	11 (6, 20)
ICU (days)	4 (0, 8)
Mortality, n(per-cent)	9 (17%)

Table 2

Platelet function values on initial presentation to emergency department. Data are presented as median and interquartile range.

Platelet Function Data (N = 52)	
Platelet Count (1,000 platelets/ μ L)	243 (205, 287)
Multiplate	
ADPtest (normal range: 57–113 AUC)	76 (51, 95)
AAtest (normal range: 71–115 AUC)	61 (40, 76)
Thromboelastography Platelet Mapping	
%ADP Platelet Activation	33 (7, 63)
MA _{ADP} (normal range: 51–69 mm)	28 (8, 42)
%AA Platelet Activation	87 (58, 94)
MA _{AA} (normal range: 51–69 mm)	56 (39, 62)
MA _{THROMBIN} (normal range: 51–69 mm)	63 (60, 67)