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Thromboelastography with Platelet Mapping as an Alternative for the Platelet Function Assay-100 in Detecting Clopidogrel in Trauma Patients

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CONFLICTS OF INTEREST
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ABSTRACT

Objectives
Antiplatelet therapy is prevalent and can potentiate bleeding complications associated with trauma and surgery. Laboratory identification and quantification of the effect of antiplatelet medications has been difficult, with several assays, including the Platelet Function Assay [PFA]-100, yielding inconclusive results. The purpose of this study was to evaluate the effectiveness of thromboelastography with platelet mapping (TEG-PM) to identify the presence of antiplatelet medications and compare these results with the PFA-100.

Methods
All trauma patients with TEG-PM studies from September 2013 to September 2014 were retrospectively collected. The medical records were reviewed to determine home antiplatelet medications. Patients were then evaluated for concurrent PFA-100 tests to allow direct comparison of the studies.

Results
Twenty-one patients had both TEG-PM and PFA-100 test performed. In this set of patients, the sensitivity and specificity of the PFA for detecting antiplatelet medications was 50.0% and 61.9%, respectively; the TEG-PM had 88.9% sensitivity and 41.7% specificity for detecting aspirin and 100% sensitivity and 8.3% specificity for detecting clopidogrel.

Conclusion
Thromboelastography with platelet mapping was more sensitive for detecting both aspirin and clopidogrel than the PFA-100; the 100% sensitivity in detecting clopidogrel is key and indicates this may be a useful screening tool to rule out clopidogrel use in trauma patients. Interestingly, there is a very low specificity, which may be related to acute traumatic coagulopathy.

Keywords
Thromboelastography, Antiplatelet, Trauma, Acute traumatic coagulopathy

INTRODUCTİON

Acute Traumatic Coagulopathy (ATC) is a well-known entity in the severely-injured trauma patient and is a source of significant morbidity and mortality. Defined by activation of the coagulation cascade, ATC is mediated through activated protein C (APC), in the setting of local endothelial trauma, hypoperfusion, acidemia and inflammation[1–4]. Approximately one-third of the population taking antiplatelet medications, further increasing the risk to trauma patients[5]. Due to the prevalent use of antiplatelet medications, many trauma patients present with chemical coagulopathy from medications such as aspirin or clopidogrel. This chemical coagulopathy potentiates the already morbid ATC; as a result, the initial resuscitation and management of these patients requires additional assessment and interventions[5–8].

Previously, we reported our experience with the Platelet Function Assay-100™ (PFA-100, Dade Behring, Deerfield, IL) identifying clopidogrel use in traumatic brain injury (TBI) and stroke patients with a sensitivity and specificity of 48.6% and 74.8%, respectively[9]. With its low sensitivity, we determined it was an unreliable tool for detecting clopidogrel use in this patient population. We hypothesized that thromboelastography with platelet mapping (TEG-PM) may be more effective in identifying clopidogrel use in trauma patients.

Our institution has transitioned to using TEG-PM (Haeomoscope Corporation, Niles, IL, USA) in the acute evaluation of ATC. In this present study, we performed a retrospective analysis of all level one trauma patients during this transition period for whom we obtained both a PFA-100™ and TEG-PM. We aimed to evaluate the effectiveness of TEG-PM in identifying antiplatelet medications in trauma patients and compare these results with the PFA-100™. We hypothesized that TEG-PM has greater sensitivity, specificity and discriminatory power of positive and negative predictive values than the PFA-100™ in trauma patients taking the antiplatelet agents aspirin or clopidogrel.

METHODS

Following Institutional Review Board approval, we retrospectively reviewed all patients with TEG-PM studies from September 2013 to September 2014. Records were reviewed to determine admission diagnoses and home antiplatelet medications. Patients were divided into trauma and non-trauma groups. Those patients with diagnoses of intracranial masses were excluded from this study. Trauma patients were then evaluated for concurrent PFA-100™ tests to allow direct comparison of the results with TEG-PM. The overall sensitivity and specificity of the PFA-100™ was evaluated for detecting any antiplatelet agents (i.e. aspirin and clopidogrel). The sensitivity and specificity of TEG-PM were determined via 2x2 contingency tables for identifying aspirin and clopidogrel using arachidonic acid (AA) and adenosine diphosphate (ADP) inhibition, respectively.

Platelet Function Assay-100 (PFA-100)

The PFA-100 is a coagulation device that can detect platelet dysfunction due to aspirin and ADP inhibition[10]. It has historically been used to serve as a guide for managing coagulopathy in TBI and stroke patients. The test is initially performed with the Collagen/Epinephrine (Col/Epi) membrane. A normal Col/Epi closure time rules out platelet dysfunction; if prolonged, the Col/ADP test will be performed. A normal Col/ADP test indicates platelet dysfunction that is most likely aspirin-induced. If both tests are prolonged, this indicates platelet dysfunction related to medications other than aspirin, such as clopidogrel. If a patient had positive Col/Epi result with documented aspirin use, this was considered a positive test with a positive antiplatelet in the contingency table; this same patient would then have a Col/ADP analysis that would be documented in a similar manner. If a patient had a negative Col/Epi result, the presence or absence of an antiplatelet medication would be documented; however, a Col/ADP analysis would not be performed and therefore not documented in the contingency table for that patient.

Thromboelastography with Platelet Mapping (TEG-PM)

Thromboelastography with platelet mapping (TEG-PM, Haeomoscope Corporation, Niles, IL, USA) offers both numerical and graphical representations of the ex vivo rate and strength of clot formation and lysis. Reaction time (R, minutes) quantifies the progress of the clotting cascade from initiation to the start of fibrin formation. Kinetics (K, minutes) is the time since clot initiation to the maximum rate of fibrin formation. Alpha (α, degrees) is the slope or rate of fibrin formation towards a stable clot. Maximum Amplitude (MA, mm) quantifies the strength of the platelet-fibrin clot. Percent Lysis at 30 minutes (LY30, percent) is the percentage of the clot that has been lysed at 30 minutes since clot initiation. With the addition of platelet mapping one can assess the percentage of inhibition in both AA and ADP pathways. This test was initially designed to monitor antiplatelet

therapy. Aspirin exerts its antiplatelet effects via the AA pathway and clopidogrel acts via the ADP pathway. With TEG-PM, one can then assess the percentage of inhibition in both AA and ADP pathways from antiplatelet agents; significant inhibition is defined as greater than 20% in this study which is the threshold established by the company. Many normal controls can have some platelet inhibition caused by supplements, foods, or even alcohol, and typically is minimal and not clinically significant, but measurable[11]. Samples were collected in EDTA tubes and flow was performed same day. If a sample was collected at night, the sample was stored in the fridge and performed the next day. This is standard and routine practice for all our flow cytometry specimens.

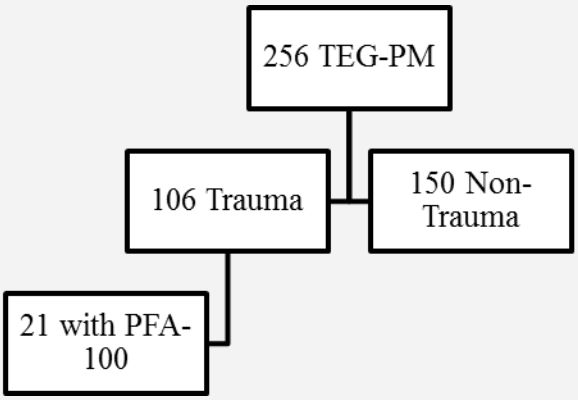

Figure S4. Study population breakdown with TEG-PM and PFA -100™ studies performed from September 2013 – September 2014.

Table 1. Contingency tables for TEG-PM in 106 trauma patients. Five patients were taking antiplatelet agents and were excluded from the ADP contingency table (101 patients).

TEG-PM: AA inhibition	(+) ASA	(-) ASA	Total	Measures
(+) test	38	34	72	PPV 52.8%
(-) test	14	20	34	NPV 58.8%
Total	52	54		
Measures	Sensitivity	Specificity 37%		

TEG-PM: ADP inhibition	(+) Clopidogrel	(-) Clopidogrel	Total	Measures
(+) test	22	69	91	PPV 24.2%
(-) test	0	10	10	NPV 100%
Total	22	79		
Measures	Sensitivity	Specificity 12.7%		

RESULTS

A total of 256 TEG-PM studies were performed in a 12-month period (Figure 1). One hundred six patients had traumatic injuries—in this subset of patients, TEG-PM with AA inhibition (TEG-PM: AA) identified aspirin with a sensitivity of 73.1%, a specificity of 37% and positive and negative predictive values of 52.8% and 58.8%, respectively. Five of the 106 patients were taking antiplatelet agents and were excluded from the contingency table. In those 101 patients, TEG-PM with ADP inhibition (TEG-PM: ADP) had a sensitivity of 100%, a specificity of 12.7% and positive and negative predictive values of 24.2% and 100%, respectively (Table 1).

Table 2. Contingency table for PFA-100™.

PFA-100	(+) an-	(-) antiplatelet	Total	Measures
(+) test	6	8	14	PPV
(-) test	6	13	19	NPV
Total	12	21		
Measures	Sensitivity 50.0%	Specificity 61.9%		

Table 3. Contingency table for TEG-PM in 21 trauma patients with both PFA-100 and TEG-PM studies.

TEG-PM: AA Inhibition	(+) ASA	(-) ASA	Total	Measures
(+) test	8	7	15	PPV 53.3%
(-) test	1	5	6	NPV 83.3%
Total	9	12		
Measures	Sensi-tivity	Specificity 41.7%		

TEG-PM: AA Inhibition	(+) ASA	(-) ASA	Total	Measures
(+) test	9	11	20	PPV 45.0%
(-) test	0	1	1	NPV 100%
Total	9	12		
Measures	Sensi-tivity 100%	Specificity 8.3%		

Twenty-one of the 106 trauma patients had both a TEG-PM and PFA-100™ test performed. Their average age was 72.5 years and included 13 males and 8 females. In this subset of patients, the PFA-100™ identified any antiplatelet use with a sensitivity of 50%, a specificity of 61.9% and positive and negative predictive values of 42.9% and 68.4% (Table 2). In identifying aspirin use in this combined group, TEG-PM: AA had an 88.9% sensitivity, a 41.7% specificity and positive and negative predictive values of 53.3% and 83.3%, respectively

(Table 3). In identifying clopidogrel use, TEG-PM: ADP inhibition had a sensitivity of 100%, a specificity of 8.3% and positive and negative predictive values of 45% and 100%, respectively (Table 3).

DISCUSSION

Our retrospective study comparing TEG-PM and PFA-100™ in trauma patients demonstrated the superior discriminatory capability of TEG-PM in ruling out use of either aspirin or clopidogrel with higher sensitivity and higher negative predictive values than the PFA-100™. The TEG-PM was less effective at ruling in the use of these antiplatelet agents, as demonstrated by its poor specificity and lower positive predictive values. These results imply that a negative TEG-PM for AA inhibition has an 83.3% success rate in ruling out aspirin use but a positive result only has a 53.3% success rate in ruling it in. Likewise, a negative TEG-PM for ADP inhibition has a 100% success rate in ruling out clopidogrel use but a positive result only has a 45% success rate in ruling it in. As a result, TEG-PM may be a useful screening tool to eliminate or reduce the likelihood of aspirin or clopidogrel contributing to ATC in a trauma patient. This may affect a clinician's decision to transfuse platelets, however, Briggs and colleagues determined in a prospective study that platelet transfusion did not improve trauma-induced platelet dysfunction like it did aspirin-induced dysfunction[12].

The low specificity of the TEG-PM suggests the possibility of other unknown processes in trauma patients that inhibit platelet AA and ADP receptors without aspirin or clopidogrel use. Platelet dysfunction in trauma is one arm of acute traumatic coagulopathy. Cohen and colleagues identified clinically significant platelet dysfunction—resulting in greater than 10-fold higher early mortality—after trauma in the presence of normal platelet count and standard clotting studies[13]. Additional studies reiterate the significance of patients presenting with ATC—they have a mortality approaching 50%, require more blood transfusions and have a significantly higher morbidity; however, the mechanism of this platelet dysfunction is largely unknown[14,15]. Traumatic brain injury is hypothesized as a cause, while some presume platelets become "exhausted"[16,17]. Future studies of platelet function in trauma patients compared to healthy controls may isolate this phenomenon.

LIMITATIONS

Our analysis was based on a retrospective single-institution study with a small sample size. It excluded non-trauma patients which could certainly broaden the appeal of subsequent results. The hypothesis was based on our clinical observation of TEG-PM results on our trauma patients in the context of antiplatelet use.

CONCLUSION

Thromboelastography with platelet mapping was more sensitive for detecting both aspirin and clopidogrel than the PFA-100 in the same set of patients. The high sensitivity of the TEG-PM for detecting clopidogrel was also seen. A 100% negative predictive value of the TEG-PM: ADP inhibition is noteworthy and suggests that this may be a useful screening tool in the acute evaluation and management of trauma patients to rule out platelet inhibition due to clopidogrel. Unexpectedly high levels of ADP inhibition are seen in trauma patients despite no known antiplatelet medication use. This is possibly attributable to acute traumatic coagulopathy; the etiology and clinical significance of the hematologic abnormalities seen in these patients warrants further investigation.

ABBREVIATIONS

AA—arachidonic acid , ADP—adenosine diphosphate, APC—activated protein C, ASA—aspirin , ATC—acute traumatic coagulopathy, Col/ADP—collagen/adenosine diphosphate, Col/Epi—collagen/epinephrine, PFA-100—platelet function assay-100, TBI—traumatic brain injury, TEG-PM—thromboelastography with platelet mapping, TEG-PM: AA—thromboelastography with platelet mapping with AA inhibition, TEG-PM: ADP—thromboelastography with platelet mapping with ADP inhibition

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