Platelet adenosine diphosphate receptor inhibition provides no advantage in predicting need for platelet transfusion or massive transfusion

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Background. *Thrombelastography platelet mapping is a useful assay to assess antiplatelet therapy. Inhibited response to the adenosine diphosphate receptor on platelets occurs early after injury, but recent work suggests this alteration occurs even with minor trauma. However, the utility of thrombelastography platelet mapping, specifically the percent of adenosine diphosphate receptor inhibition, in predicting outcomes and guiding platelet transfusion in trauma-induced coagulopathy remains unknown We assessed the role of percent of adenosine diphosphate-inhibition in predicting survival, requirement for massive transfusion or platelet transfusion in patients at risk for trauma-induced coagulopathy.*
Methods. *Thrombelastography platelet mapping was assessed in 303 trauma activation patients from 2014–2016 and in 89 healthy volunteers. Percent of adenosine diphosphate-inhibition is presented as median and interquartile range. We compared the area under the receiver operating characteristic curve of percent of adenosine diphosphate-inhibition, platelet count, and rapid thrombelastography maximum amplitude for in-hospital mortality, massive transfusion (>10 red blood cells or death/6 hours), and platelet transfusion (>0 platelet units or death/6 hour).*
Results. *Overall, 35 (11.5%) patient died, 27 (8.9%) required massive transfusion and 46, platelet transfusions (15.2%). Median percent of adenosine diphosphate-inhibition was 42.5% (interquartile range: 22.4–69.1%), compared with 4.3 % (interquartile range: 0–13.5%) in healthy volunteers ($P < .0001$). Patients that died, had a massive transfusion, or platelet transfusion had higher percent of adenosine diphosphate-inhibition than those that did not ($P < .05$ for all). However, percent of adenosine diphosphate-inhibition did not add significantly to the predictive performance of maximum amplitude or platelet count for any of the 3 outcomes, after adjustment for confounders. Subgroup analyses by severe traumatic brain injury, severe injury and requirement of red blood cells showed similar results.*
Conclusion. *Adenosine diphosphate receptor inhibition did not add predictive value to predicting mortality, massive transfusion, or platelet transfusion. Thus, the role of thrombelastography platelet mapping as a solitary tool to guide platelet transfusions in trauma requires continued refinement. (Surgery 2017;■:■-■.)*

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Uncontrolled hemorrhage is the leading causes of preventable death from trauma and occurs predominantly within 2 hours of injury.[1] An endogenous trauma-induced coagulopathy (TIC) is the driving mechanism and, if present at admission, is associated with a 4-fold increase in mortality.[2] TIC is a multifocal process attributed to reduced thrombin generation, fibrinogen depletion, platelet dysfunction, and systemic fibrinolysis.[3-5] Consequently, early blood component administration is now standard in patients at risk for TIC.[5] However, the optimal composition of blood components remains debated. A large multicenter randomized controlled trial, Pragmatic Randomized Optimal Platelet and Plasma Ratios, indicated no survival benefit of empiric immediate platelet transfusion.[6]

Our recent goal-directed resuscitation trial based on viscoelastic assays indicated a 50% reduction in mortality, but current thrombelastography (TEG) and thromboelastometry assays do not include a measurement specific for platelet transfusion.[7] Although these devices are capable of measuring platelet receptor inhibition to monitor antiplatelet therapy,[8] their role in guiding platelets transfusions for TIC remains unclear. The present TEG platelet mapping (TEG-PM) assays represent the responses to arachidonic acid (AA), which serves as substrate for cyclooxygenase dependent thromboxane A2 that binds to the thromboxane (TP) receptor, or adenosine diphosphate (ADP), which binds to platelet P2Y1 and P2Y12 receptors.[9] ADP is released from the dense granules of platelets. Simplistically, the inner core of a blood clot (primary hemostasis) is composed of activated platelets in an environment abundant in thrombin and fibrin; whereas, platelet released TXA2 and ADP are thought to be important in the formation of the subsequent outer core of less active platelets.[9,10]

Our previous work has shown that inhibited platelet response to AA after trauma is nonspecific.[3] Consequently, our group and others have focused on the ADP response in TEG-PM to determine its role in guiding platelet transfusion.[3,11] Although inhibited platelet response to ADP after injury has been suggested to represent an exhausted platelet, recent work does not support this concept.[12] Specifically, trauma patients maintain their dense granules even in the presence of ADP receptor inhibition contradicting the theory of platelet granule exhaustion as the etiology for platelet dysfunction.[12] Furthermore, other studies have documented a significant inhibited response to ADP after minor trauma, suggesting receptor status may be a biomarker of injury rather than a mediator of TIC.[13] Therefore, we propose to assess the role of platelet ADP receptor dysfunction, measured by TEG-PM mapping in predicting mortality, requirement of massive transfusion and platelet transfusion among patients at risk for TIC.

METHODS

Study design. This is an analysis of prospectively collected data from our Trauma Activation Protocol from 2014 to 2016 database (TAP database), which includes patients who met criteria for the highest level of trauma team activation at Denver Health Medical Center, an American College of Surgeons verified and Colorado state certified Level 1 trauma center affiliated with the University of Colorado Denver. The Colorado Multiple Institutional Review Board approved all studies included in the TAP database. We did not exclude patients who were taking medications affecting coagulation or platelet function, as this information is rarely available or reliable upon admission.

Clinical data were collected by trained research professional assistants and included: age, sex, mechanism, body mass index, new injury severity score, field and hospital arrival systolic blood pressure, heart rate, Glasgow Coma Scale, international normalized ratio, partial thromboplastin time, fibrinogen, base deficit, as well as number of units of blood products transfused (red blood cells [RBCs]), fresh frozen plasma [FFP], platelets, cryoprecipitate) and volume of crystalloid infused. Severe traumatic brain injury (TBI) was defined as abbreviated injury scale [AIS]-head $\geq$3.

Outcome variables: The outcomes of this study were: 1) in-hospital death within 28 days postinjury; 2) massive transfusion, defined as >10 units of RBCs or death within 6 hours[3-6]; and 3) platelet transfusion: defined as platelet transfusion or death within 6 hours of injury. The death criterion was added to both massive transfusion and platelet transfusion to minimize survivor bias (ie, nonsurvivors did not have the "opportunity" to receive transfusions).

Main effect variables: the main effects in this study were: 1) % ADP INH; 2) platelet count; 3) rapid thrombelastography (rTEG) MA. All these variables were obtained within 1 hour after injury.

The protocol for massive transfusion of blood products has been described previously and includes initial empiric initial transfusion of FFP:RBC 1:2[14] followed by a standardized rTEG guided hemostatic resuscitation.[15] Transfusion was triggered if the patient was perceived to have ongoing blood loss and had the after TEG-derive parameters; FFP for activated clotting time (ACT) >128, cryoprecipitate for angle <65, platelets for maximum amplitude (MA) <55 and, tranexamic