Persistent Fibrinolysis Shutdown Is Associated with Increased Mortality in Severely Injured Trauma Patients

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BACKGROUND: Acute fibrinolysis shutdown is associated with early mortality after trauma; however, no previous studies have investigated the incidence of persistent fibrinolysis or its association with mortality. We tested the hypothesis that persistent fibrinolysis shutdown is associated with mortality in critically ill trauma patients.

STUDY DESIGN: Thromboelastography was performed on ICU admission in 181 adult trauma patients and at 1 week in a subset of 78 patients. Fibrinolysis shutdown was defined as LY30 $\leq$ 0.8% and was considered transient if resolved by 1 week postinjury or persistent if not. Logistic regression adjusted for age, sex, hemodynamics, and Injury Severity Score (ISS).

RESULTS: Median age was 52 years, 88% were male, and median ISS was 27, with 56% transient fibrinolysis shutdown, 44% persistent fibrinolysis shutdown and 12% mortality. Median LY30 was 0.23% (interquartile range [IQR] 0% to 1.20%) at admission and 0.10% (IQR 0% to 2.05%) at 1 week. Transient shutdown more often occurred after head injury ($p = 0.019$); persistent shutdown was more often associated with penetrating injury (29% vs 9%; $p = 0.020$), lower LY30 at ICU admission (0.10% vs 1.15%; $p < 0.0001$) and at 1 week (0% vs 1.68%; $p < 0.0001$), and higher mortality (21% vs 5%; $p = 0.036$). Persistent fibrinolysis shutdown was associated with admission LY30 (odds ratio [OR] 0.05; 95% CI 0.01 to 0.34; $p = 0.002$) and transfusion of packed RBCs (OR 0.81; 95% CI 0.68 to 0.97; $p = 0.021$) and platelets (OR 2.81; 95% CI 1.16 to 6.84; $p = 0.022$); moreover, it was an independent predictor of mortality (OR 8.48; 95% CI 1.35 to 53.18; $p = 0.022$).

CONCLUSIONS: Persistent fibrinolysis shutdown is associated with late mortality after trauma. A high index of suspicion should be maintained, especially in patients with penetrating injury, reduced LY30 on admission, and/or receiving blood product transfusion. Judicious use of tranexamic acid is advised in this cohort. (J Am Coll Surg 2017;224:575−582. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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The fibrinolysis pathway is an integral component of the coagulation cascade as it works to provide a balance between post-injury hemorrhage and thrombosis. Basic evidence of coagulation and fibrinolysis after trauma has been available for decades,[1-3] and was first recognized by John Hunter in 1794[4]; however, recent advances in the detection of post-injury coagulation abnormalities have highlighted significant knowledge gaps in our fundamental understanding of this problem. Current data indicate that trauma patients may develop either coagulopathy or hypercoagulability early after injury. The factors predisposing to one phenotype over the other require further investigation.

Acute traumatic coagulopathy develops in approximately 25% of severely injured patients and is associated

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Abbreviations and Acronyms

AIS = Abbreviated Injury Scale
AOR = adjusted odds ratio
GCS = Glasgow Coma Scale
ISS = Injury Severity Score
IQR = interquartile range
LY30 = clot lysis at 30 minutes after maximum amplitude
TEG = thromboelastography
tPA = tissue plasminogen activator

with a substantial risk of multisystem organ failure and a 4-fold higher risk of death.[5,6] Primary hyperfibrinolysis, an infrequent but highly lethal finding, plays a central role in acute traumatic coagulopathy and is likely mediated by an overwhelming release of tissue plasminogen activator after hemorrhagic shock.[7-15]

The most common disorder of coagulation after injury, however, is hypercoagulability.[16-18] The incidence of hypercoagulability detected on viscoelastic testing is greater than 50% on admission[16] and as high as 90% at 1 week post-injury.[17,18] Hypofibrinolysis, or fibrinolysis shutdown,[12,19] is an integral component of postinjury hypercoagulability. Groups from Denver and Houston have demonstrated that fibrinolysis shutdown is the most prevalent phenotype in the spectrum of post-injury fibrinolysis, which also includes hyperfibrinolysis and physiologic fibrinolysis.[12,15] This phenotype is seen in up to 65% of severely injured trauma patients within 12 hours of hospital admission and is associated with delayed mortality from multisystem organ failure via a mechanism involving direct tissue injury rather than hemorrhagic shock.[12,14,15]

Postinjury fibrinolysis shutdown is presumed to persist for several days after initial resuscitation, but no previous studies have identified the incidence of persistent fibrinolysis shutdown after trauma. This information has important implications for critically ill patients at risk for bleeding and venous thromboembolism. Therefore, the purpose of this study was to describe the incidence of persistent fibrinolysis shutdown after trauma and its associated outcomes. We hypothesized that persistent fibrinolysis shutdown after trauma is common and is associated with higher in-hospital mortality in patients admitted to the ICU.

METHODS

Study design and setting

This prospective observational study was approved by the IRBs of the University of Miami Miller School of Medicine and Jackson Memorial Hospital. Inclusion criteria were critically ill adult trauma patients who underwent viscoelastic testing with thromboelastography (TEG) on admission to the trauma ICU, from August 2011 to January 2015, at an American College of Surgeons verified level I trauma center. Exclusion criteria were patients with burn injury, and/or those who were incarcerated, pregnant, or received tranexamic acid before baseline TEG. There were 1,273 patients screened during the study period; 422 were deemed high-risk severely injured patients[20] and 181 had TEG samples drawn.

We have previously described the kaolin TEG method.[17,18] Briefly, 6 mL of whole blood was drawn into 2 citrated vacuum-sealed tubes on admission to the ICU and weekly thereafter. Samples were analyzed in duplicate on a TEG 5000 Thromboelastograph Hemostasis Analyzer System (Haemonetics Corporation). The initial TEG drawn on ICU admission was considered the baseline.

Study variables

Patient demographics and injury characteristics included age; sex; Injury Severity Score (ISS); Abbreviated Injury Scale (AIS) for the head, chest, and abdomen/pelvis; mechanism of injury; admission pH, base deficit, systolic blood pressure, Glasgow Coma Scale (GCS) score; and clot lysis at 30 minutes after the maximum amplitude (LY30).

Fibrinolysis phenotypes were stratified according to Moore and colleagues.[12,15] Fibrinolysis shutdown was defined as LY30 $\leq$ 0.8%; physiologic fibrinolysis was defined as LY30 between 0.8% and 3%; and hyperfibrinolysis was defined as LY30 $>$ 3%.[12,15] Transient fibrinolysis shutdown was defined as fibrinolysis shutdown that was present on admission to the ICU and resolved by week 1; persistent fibrinolysis shutdown was defined as fibrinolysis shutdown present on ICU admission and at week 1. Blood product use (including packed red blood cells, plasma, platelets, and cryoprecipitate) was collected retrospectively for each ICU day. Outcomes variables included ICU and hospital lengths of stay and in-hospital mortality.

Statistical analysis

All statistical analyses were performed using SPSS Statistics, version 22.0 (IBM Corp). Continuous variables are presented as median (interquartile range) and were compared using the Kruskal-Wallis test or the Mann-Whitney U test, as appropriate. Categorical variables are expressed as frequency (percent) and were compared using the chi-square test or Fisher's exact test, as appropriate. Logistic regression was used to identify independent predictors of persistent fibrinolysis shutdown and to identify its effect on mortality, controlling for ISS, sex, GCS, admission systolic blood pressure, mechanism of injury, base deficit, and age. Adjusted odds ratios (AOR) and the area under the receiver operator curve are provided with their respective 95% confidence intervals. Kaplan-Meier curves are reported for