Onset of Coagulation Function Recovery Is Delayed in Severely Injured Trauma Patients with Venous Thromboembolism

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BACKGROUND: Altered coagulation function after trauma can contribute to development of venous thromboembolism (VTE). Severe trauma impairs coagulation function, but the trajectory for recovery is not known. We hypothesized that enhanced, early recovery of coagulation function increases VTE risk in severely injured trauma patients.

STUDY DESIGN: Secondary analysis was performed on data from the Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial, excluding patients who died within 24 hours or were on pre-injury anticoagulants. Patient characteristics, adverse outcomes, and parameters of platelet function and coagulation (thromboelastography) were compared from admission to 72 hours between VTE ($n = 83$) and non-VTE ($n = 475$) patients. A p value < 0.05 indicates significance.

RESULTS: Despite similar patient demographics, VTE patients exhibited hypercoagulable thromboelastography parameters and enhanced platelet function at admission ($p < 0.05$). Both groups exhibited hypocoagulable thromboelastography parameters, platelet dysfunction, and suppressed clot lysis (low clot lysis at 30 minutes) 2 hours after admission ($p < 0.05$). The VTE patients exhibited delayed coagulation recovery (a significant change compared with 2 hours) of K-value (48 vs 24 hours), α-angle (no recovery), maximum amplitude (24 vs 12 hours), and clot lysis at 30 minutes (48 vs 12 hours). Platelet function recovery mediated by arachidonic acid (72 vs 4 hours), ADP (72 vs 12 hours), and collagen (48 vs 12 hours) was delayed in VTE patients. The VTE patients had lower mortality (4% vs 13%; $p < 0.05$), but fewer hospital-free days (0 days [interquartile range 0 to 8 days] vs 10 days [interquartile range 0 to 20 days]; $p < 0.05$) and higher complication rates ($p < 0.05$).

CONCLUSIONS: Recovery from platelet dysfunction and coagulopathy after severe trauma were delayed in VTE patients. Suppressed clot lysis and compensatory mechanisms associated with altered coagulation that can potentiate VTE formation require additional investigation. (J Am Coll Surg 2017;225:42–51. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Members of the PROPPR Study Group and Clinical Sites are listed in the Appendix.

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Abbreviations and Acronyms

DVT = deep vein thrombosis
GCS = Glasgow Coma Scale
IQR = interquartile range
LY30 = clot lysis at 30 minutes
MA = maximum amplitude
OR = odds ratio
PE = pulmonary embolism
PROPPR = Pragmatic Randomized Optimal Platelet and Plasma Ratio
TEG = thromboelastography
TRAP = thrombin receptor activator peptide
VTE = venous thromboembolism

The prevention of venous thromboembolism (VTE) after traumatic injury is an ongoing challenge. Venous thromboembolism occurs in as many as 25% of trauma patients with pharmacologic prophylaxis,[1] and 58% in nonprophylaxed patients,[2] and is associated with an increased risk of morbidity and mortality.[3,4] As defined by Virchow's triad, the core factors that contribute to thrombosis are static blood flow, endothelial injury, and hypercoagulability.[5] Therefore, indices of hypercoagulability, such as enhanced thrombin formation, hypercoagulable thromboelastography (TEG) parameters,[1,6,7] platelet levels,[8] enhanced platelet function,[9] and fibrinogen activity,[10] have all been identified as key clinical risk factors for VTE formation after trauma.

The rationale for targeting enhanced coagulation and platelet formation pathways to prevent VTE formation appears to be contradictory during severe traumatic hemorrhage, for the combined effect of injury and hemorrhage induces development of acute traumatic coagulopathy.[11] Acute traumatic coagulopathy is primarily mediated by the hypocoagulable effects of the activated protein C pathway, although enhanced fibrinolysis,[12] platelet dysfunction,[13-15] and other hypocoagulable pathways independent of activated protein C[12] also contribute to this coagulopathic state. Despite this phenomenon, VTE development is still prevalent in this patient population. Recent findings from the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, which enrolled 680 severely injured hemorrhaging patients predicted to receive a massive transfusion, showed that 15% of patients had a thrombotic event (deep vein thrombosis [DVT] or pulmonary embolism [PE]) over the duration of the study.[16]

Although the mediators of VTE development after severe hemorrhage are not known, the recovery process from acute traumatic coagulopathy might be a contributing factor. Using platelet aggregometry, Kutcher and colleagues[13] showed that multiple platelet function pathways are initially inhibited by trauma, but are then slowly restored over time. However, platelet function restoration has not been evaluated specifically after severe traumatic hemorrhage, or in patients who had a VTE develop. Because hypercoagulability enhances VTE development, we hypothesize that an early onset of recovery from coagulopathy or platelet dysfunction after traumatic hemorrhage enhances coagulation, serving as a precursor for VTE development. By using the PROPPR database to target a population of patients who would exhibit acute traumatic coagulopathy and impaired platelet function, we performed a secondary analysis of prospectively collected data to characterize the trajectory of coagulation and platelet function over time in severely injured trauma patients with and without VTE.

METHODS

The PROPPR trial randomized 680 severely injured trauma patients from 12 Level I trauma centers to receive either 1:1:1 or 1:1:2 ratios of plasma to platelets to RBCs. The eligibility criteria for the PROPPR trial have been described previously.[16] For this analysis, patients were dichotomized into either the non-VTE or VTE group. The VTE group was defined as patients who had a DVT or PE (asymptomatic or symptomatic) develop. Deep vein thrombosis was diagnosed with duplex ultrasound. Pulmonary embolism was diagnosed by CT angiogram, pulmonary angiogram, or ventilation perfusion scan. However, screening and diagnosis of thromboembolic events were not standardized in PROPPR. To remove patients who did not live long enough for a VTE to develop, patients who died within 24 hours were excluded from the analysis. To remove the bias for VTE prevention, patients prescribed anticoagulants before admission (ie warfarin, clopidogrel, aspirin, thrombin inhibitors, or other) were also excluded.

Admission patient characteristics, including age, BMI, and sex (percent male), were compared between VTE and non-VTE patients. Injury profile characteristics, such as mechanism of injury (blunt vs penetrating), Injury Severity Score, Glasgow Coma Scale score (GCS), and injury types associated with VTE, including chest trauma, long bone fracture, pelvic fracture, pulmonary contusion, spinal cord injury, spine fracture, and venous injury, were also compared between groups. Clinical outcomes (hospital-free days, ICU-free days, ventilator-free days, acute lung injury, ARDS, acute kidney injury, systemic inflammatory response syndrome, infection, sepsis, multiple organ failure, death), total