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PRECISION MEDICINE: CLINICAL TOLERANCE TO HYPERFIBRINOLYSIS DIFFERS BY SHOCK AND INJURY SEVERITY

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Abstract

The definition of hyperfibrinolysis based on thrombelastogram LY30 measurements should vary with trauma patient characteristics, i.e., as anatomic injury or shock severity increase, the ability to tolerate even mild degrees of fibrinolysis is markedly reduced. This trend is independent of institutional practice patterns. The management of hyperfibrinolysis, particularly with anti-fibrinolytics administration, should be interpreted in the context of injury severity/shock and managed on an individual patient basis.

Introduction:

Hyperfibrinolysis (HF) is a highly lethal phenotype of trauma-induced coagulopathy (TIC) characterized by accelerated fibrin breakdown causing increased clot dissolution and reduced hemostasis.[1] It is postulated to be due to a pathological upregulation of the normal fibrinolysis system responsible for maintaining vascular patency, driven by overwhelming endothelial tissue plasminogen activator (tPA) release, and a reduction in circulating plasminogen activator inhibitor-1 (PAI-1) during shock.[2] Clinically, HF manifests as diffuse bleeding, often from uninvolved sites, and is an independent predictor for massive transfusion[3] and early death from exsanguination, with a mortality greater than 40%.[3,4] Using viscoelastic assays (VCA) such as thrombelastography (TEG), HF can be measured by an elevated clot lysis 30 minutes after maximum clot strength (LY30).

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While TEG has the ability to quantify the level of fibrinolysis occurring in a trauma patient, the pathologic LY30 threshold remains a source of debate. Various studies in healthy volunteers and trauma patients[3,5] have set a wide range of LY30 thresholds. Indeed, our group was, to our knowledge, the first to publish that an LY30 threshold of 3% was the critical value for initiation of antifibrinolytics in severely injured patients.[6] On a subsequent study, we observed that a higher LY30 level of 7.6% was associated with adverse outcomes.[7] Recently, a European study of TIC noted that for rapid TEG detection of HF, there was an increase in mortality and in red blood cell (RBC) transfusions at LY30 values greater than 10%.[5] We also noted that these studies had substantial differences in median injury severity scores (ISS) (30 vs 16 vs 13) and degrees of shock. Thus, we conducted a multicenter study to determine whether hyperfibrinolysis LY30 thresholds were dependent on levels of injury severity and shock, and whether these thresholds were independent of institutional practice patterns. We hypothesized that the variability seen in LY30 thresholds was due to differences in injury severity and shock. Specifically, there would be an increase in clinically tolerable levels of hyperfibrinolysis with lower injury severity and magnitude of shock.

Methods:

Patient Population:

We analyzed prospectively collected data of patients at risk for trauma-induced coagulation admitted between 2010 and 2017 to three urban, level 1 trauma centers in three different states, under individually approved IRB approved protocols.[8,9] Trauma patients (age≥18 years) meeting criteria for the highest level of trauma team activation at each institution, who received at least 1 unit of red blood cells (RBC) within 10 hours of admission were included. Patients taking anticoagulant medication including warfarin or direct factor inhibitors were excluded.

Outcome:

The study's outcome was massive transfusion (MT), defined as >10 RBC units or death (to minimize survivor bias, i.e., patients who died before having the "opportunity" to receive 10 RBC units) within 6 hours postinjury.

Thrombelastography Assays:

Blood was collected in 3.5ml tubes containing 3.2% citrate as the patient arrived in the emergency department (ED) and analyzed using the TEG 500 Thrombelastography Hemostasis Analyzer (Haemonetics Corp., Niles, IL, USA). The following indices were obtained from the tracings of the rapid-TEG: reaction time (R-time min.), angle (°), maximum amplitude (MA [mm]), and lysis 30 min after MA (LY30 [%]).

Statistical Analysis:

Three strata were defined based on ISS (<26, 26–50, >50) and shock severity (systolic blood pressure [SBP] upon admission: >90, 60–90, <60 mmHg). The hyperfibrinolysis cutoffs were defined as the optimal predictive cutoffs for MT or death in the first 6 hours. These were stratified by ISS and SBP stratum for each institution. A generalized linear model accounting for intra-facility clustering was used to derive the relative risk (RR) for MT

associated with hyperfibrinolysis as measured by rapid TEG LY30. The cutoffs were derived using the Youden Index (maximum of [sensitivity + specificity −1]) and receiver-operating characteristics (ROC) curve analysis. Categorical variables were compared using Chi-square or Fisher Exact tests. Continuous variables were compared using the Mann-Whitney-U test. Tests were two-tailed with significance declared at $p<0.05$. Analyses were conducted using SAS vs 9.4 (SAS Institute, Cary, NC, USA).

Results:

Overall, 332, 893 and 922 patients from the three level 1 trauma centers were included (Table). Although statistically significant, the difference in median age between the three institutions was clinically irrelevant. Patients in Center 2 were more likely to suffer blunt injuries and in Center 1 had the highest median ISS and the lowest admission SBP. Fibrinolysis level (LY30) significantly predicted MT, both when the samples of all three centers were pooled (RR: 1.022; 95%CI:1.020–1.026; $p<0.0001$), as well as at the individual center level (Center 1 RR: 1.019; 95% CI: 1.012–1.027; $p<0.0001$; Center 2 RR: 1.024; 95%CI: 1.018–1.031, $p<0.0001$; Center 3: RR: 1.032; 95%CI: 1.025–1.040, $p<0.0001$).

As shown in the Table, at each institution, the LY30 optimal cutoff (Youden Index) for MT prediction decreased with worsening hypotension and increasing injury severity in every institution. Although the specific LY30 optimal cutoffs for the prediction of MT varied by center, all three centers observed the same decreased tolerance for fibrinolysis with higher levels of shock and/or injury severity.

Discussion:

The purpose of this study was to test the hypothesis that patients with less severe injuries would be able to tolerate high levels of hyperfibrinolysis (as measured by LY30) without adverse outcomes (massive transfusion), while more severely injured patients would be more sensitive and develop adverse outcomes at lower levels of hyperfibrinolysis. The findings confirmed our initial hypothesis, i.e., we found that the optimal LY30 threshold predictive for MT decreases with worsening hypotension and increasing Injury Severity Score, suggesting that anti-fibrinolytics should be initiated early in severely injured/hypotensive patients, while more latitude is allowed among those with less severe injuries and higher SBP.

VCA-guided hemostatic resuscitation has been shown in a randomized controlled trial to lead to a significantly improved survival in patients at risk for massive transfusion.[10] In addition, studies in civilian and military settings suggest that while anti-fibrinolytics may decrease mortality in traumatic hemorrhagic shock, they may also induced thrombotic complications.[4,11–14] Thus, it is important to define a hyperfibrinolysis threshold that achieves a good risk-benefit ratio. Rather than setting a strict threshold for HF for all patients, we recommend a more patient-centric approach, aligned with the modern trend towards personalized, precision medicine. More severely injured patients can only tolerate low levels of fibrinolysis, while conversely, a less severely injured patient with mild hypotension may tolerate higher levels of clot lysis.

Conclusion:

The definition of hyperfibrinolysis based on TEG-LY30 should be adapted to the characteristics of each trauma patient, i.e., as anatomic injury or shock severity increase, the ability to tolerate even mild degrees of fibrinolysis is markedly reduced. This trend is independent of institutional practice patterns. The management of hyperfibrinolysis should be interpreted in the context of injury severity/shock and managed on an individual patient basis.

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Table 1.

Patient Characteristics and Hyperfibrinolysis Cutoffs Predictive of Massive Transfusion at Three Level 1 Trauma Centers

Characteristics	***Center 1 N=332***	***Center 2 N=893***	***Center 3 N=922***	***P-value***
Age in years, Median (IQR)	35 (26–50)	37 (26–52)	36 (25–49)	0.03
ISS, Median (IQR)	26 (15–36)	22 (18–29)	13 (4–27)	<0.0001
Blunt Injury, N (%)	173 (52.1%)	689 (77.2%)	472 (51.2%)	<0.0001
Admission SBP (mmHg) Median (IQR)	93(76–120)	110 (90–130)	122 (100–140)	<0.0001
Massive Transfusion, N (%)	75 (22.6%)	108 (12.1%)	93 (10.1%)	<0.0001
In Hospital Mortality, N (%)	85 (25.6%)	92 (10.3%)	116 (12.6%)	<0.0001

Hyperfibrinolysis Cutoffs, LY30%			
All Patients	11.5	5.0	7.0
By Admission SBP, mmHg			
>90	13.9	5.1	8.7
70–90	7.7	2.9	7.0
<70	2.5	2.2	3.7
By Injury Severity Score			
<26	11.5	5.0	7.0
26–50	2.6	5.1	1.8
>50	2.5	1.0	1.9

ISS: Injury Severity Score; SBP: Systolic Blood Pressure; IQR: interquartile range