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The incidence and magnitude of fibrinolytic activation in trauma patients: a rebuttal

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Trauma-induced coagulopathy (TIC) has been recognized as a potential preventable cause of mortality in 40% [1] of civilian deaths and 80% of military casualties [2]. Recent studies indicate that fibrinolysis may be a significant component of TIC in the most severely injured patients [3] and the CRASH2 study [4] has stimulated worldwide interest in this arena. Although treatment is available to prevent plasmin-induced hyperfibrinolysis in the forms of aminocaproic acid and tranexamic acid, it is important to confirm the diagnosis of systematic hyperfibrinolysis before subjecting a patient to a potentially thrombogenic agent. Raza *et al.* [5] have questioned the validity of thrombelastometry (ROTEM) to identify pathologic fibrinolysis in injured patients, but we respectfully caution that their conclusions may be misleading owing to a number of reasons.

The gold standard, first developed in 1959, for evaluating fibrinolysis is the euglobulin lysis time (ELT) [6,7]. However, this time-consuming procedure is impractical for evaluation of the acutely injured patient. ROTEM and thrombelastography (TEG) have been used in elective cardiac surgical and liver transplant patients for decades for point-of-care detection of pathologic fibrinolysis [8,9]. Although present manufacturer recommendations for TEG and ROTEM assessment of fibrinolysis have been established in healthy individuals, these assays have not been validated in the trauma population. For example, Haemonetics has arbitrarily set their detection threshold for hyperfibrinolysis in their TEG instrument as a lysis of < 7.5% at 30 min (LY30) after achievement of the maximum amplitude [10]. But analysis of patients with severe trauma requiring a massive transfusion, at our urban Level I

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Addendum

C. R. Ramos: Primary Author, critical writing and revising, analysis and interpretation of data, final approval; E. E. Moore: Concept and design, analysis and interpretation of data, critical writing and revising, final approval; M. L. Manco-Johnson: Critical writing and revising, analysis and interpretation of data, final approval; C. C. Silliman: Critical writing and revising, final approval; M. C. Chapman: Critical writing and revising, final approval; A. Banerjee: Concept and design, analysis and interpretation of data, final approval.

Trauma Center, revealed that > 3% lysis at 30 min by TEG was associated with an increase in mortality, 70 vs. 18.5%, $P = 0.002$, compared with lysis < 3% (Chapman MC, Moore EE, Ramos CR. Fibrinolysis above 3% is the critical value for initiation of anti-fibrinolytic therapy. *J Trauma* 2013 [In press]). Furthermore, we have documented a much lower TEG detection threshold for lysis with ELT (Ramos CR, Moore EE, Chapman MC. Defining post-injury hyperfibrinolysis with thrombelastography: technology in evolution. *Shock Society* 2013 [abst]). Presumably a similar issue exists for the ROTEM threshold for the detection of hyperfibrinolysis.

Raza *et al.*[5] defined severe fibrinolysis based upon a ROTEM maximal lysis of > 15% compared with the moderate group with a maximal lysis < 15%. Both had plasmin–antiplasmin complex levels > 1500 $\mu\text{g L}^{-1}$. The moderate and severe groups both had significant biomarkers of enzymatic fibrinolysis, including decreased antiplasmin and fibrinogen as well as increased D-dimer and TPA. A third group with elevated ROTEM lysis but normal levels of PAP complexes is noted to additionally differ from both the moderate and severe hyperfibrinolysis groups in having no changes in these biomarkers of hyperfibrinolysis. The TEM lysis only group did not differ from the normal group except in having lower D-dimer and prothrombin fragments 1+2, which are opposite to the expected direction of change.

Furthermore, ROTEM has developed an assay in which aprotinin is added *in vitro* to the patient samples to inhibit the serine protease plasmin. This confirms plasmin-mediated clot dissociation by comparing the maximum lysis of a native sample (EXTEM) to the maximum lysis of a treated sample (APTEM). A potential explanation of the TEM lysis only group, using EXTEM, is (i) this small group ($n = 8$) did not have hyperfibrinolysis and (ii) the maximal lysis > 15% produced on ROTEM is alternatively reflecting platelet retraction or a non-enzymatic change in fibroelastic character of the formed clot, as has been previously reported in healthy individuals [11,12]. Such alternative causes for the observed 'hyperfibrinolysis' is also consistent with the low mean injury severity score for this group [2–9]. We expect that in patients with normal biomarkers of fibrinolysis, as in this TEM lysis only group, the EXTEM and APTEM maximal lysis would not be different. Thus, it would be interesting to determine if there was a correlation between elevated PAP levels and the difference in maximal lysis between EXTEM and APTEM in all groups.

Finally, the massive elevations in PAP could be an artifact because the samples were not drawn into aprotinin and this has been previously described as a cause of falsely elevated PAP complexes [13–15]. Thus, an alternative explanation of the results of Raza *et al.* is (i) increased mortality occurs in patients with elevated fibrinolysis confirmed by plasma biomarkers and (ii) the group with negative biomarkers of proteolytic fibrinolysis are manifesting non-fibrinolytic changes in fibro-elastic clot characteristics.

In summary, we agree further studies are required to determine both TEG and ROTEM thresholds for pathologic fibrinolysis in the trauma population, and this should be systematically validated by ELT.

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