Goal-directed hemostatic resuscitation for trauma induced coagulopathy: Maintaining homeostasis

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A century ago, Walter B. Cannon, after studying battlefield casualties, concluded “… shock is a lack of homeostasis and without homeostasis the patient does not survive.” This statement is particularly relevant to the management of trauma-induced coagulopathy (TIC). Today in both military and civilian scenarios, acute hemorrhage and its sequelae are the leading cause of preventable death. Trauma-induced coagulopathy is the culmination of endogenous responses to hemorrhagic shock and tissue injury and has been attributed variably to activated protein C deactivation of clotting factors V and VIII, autoheparinization, tissue injury and has been attributed variably to activated protein C deactivation of clotting factors V and VIII, autoheparinization from glycocalyx degradation, fibrinogen depletion, platelet dysfunction, disseminated intravascular coagulation, and dysregulated fibrinolysis. The contribution of fibrinolysis to TIC was unappreciated until the advent of whole blood viscoelastic assays, that is, thrombelastography (TEG) (Haemonetics, Niles, IL) and thromboelastometry (ROTEM, TEM Systems, Munich) to guide blood component transfusion. The dominant mechanisms responsible for impaired clot formation (platelet activation, thrombin generation, fibrin crosslinking) are distinct from those regulatory clot degradation (fibrinolysis).

Moreover, there are a multitude of additional factors implicated in impaired clot formation (Fig. 1) and dysregulated clot degradation (Fig. 2). Recently, we have identified nine phenotypes of post-injury fibrinolysis based on clot lysis at 30 minutes by TEG, further stratified by tissue plasminogen activator challenge TEG. Collectively, the regulatory factors and events involved in clot formation and degradation result in an array of TIC phenotypes that may be encountered in the severely injured patient (Fig. 3). These phenotypes are determined by the magnitude of shock and tissue injury pattern, further modified by resuscitation and ongoing blood loss. The challenge is to match blood component therapy with these TIC phenotypes while achieving mechanical control of bleeding.

GOAL-DIRECTED MANAGEMENT OF TIC

While 10 units of red blood cells (RBC) within the first 6 hours is the best predictor of mortality due to acute blood loss, most deaths occur within the first 2 hours. Consequently, a number of formulas, based on early clinical measurements, have been promoted to identify the patient at risk for massive transfusions. These formulas appear reliable based on receiver operator characteristic analyses, but the positive predictive values are typically less than 50%, due to the relatively low incidence of massive transfusion among seriously injured patients.

Irrespective of the method used, the key question is how to manage the patient at high risk for life-threatening hemorrhage. The basic approaches are fixed ratio-based blood products or goal-directed blood components based on assessment of coagulations function (Fig. 4). The current preemptive strategy is the so-called 1:1:1, representing one unit of plasma, one donor unit of platelets and one unit of RBCs. This ratio is based on the military proposal of replacing the equivalent of whole blood loss for life-threatening hemorrhage. While conceptually attractive, the storage, release, consumption, and necessity for this specific balance of blood components raise questions as to whether 1:1:1 is the optimal resuscitation strategy for all seriously injured patients. The only randomized prospective study to test this concept has been the Pragmatic, Randomized Optimal Platelet and Plasma Ratios Trial. This was reported to be a comparison of 1:1:1 to 1:1:2 (plasma, platelets, RBC). In reality, however, for the first six units of RBC, it was 1:1:1 versus 1:0:2 as no platelets were administered until the second round of six units of RBC. This was due to the fact that one unit of apheresis platelets equals 6 units of single whole blood derived platelets, which could not be divided practically. Despite the lack of platelets until >6 RBC units, there was no difference in the primary endpoints of 24-hour and 30-day mortalities. In a cohort study, the Ben Taub group reported improved survival following TEG-guided blood component therapy compared to 1:1:1; survival was associated with a reduction in platelet transfusion.

A recent prospective randomized trial of platelet transfusion versus standard care after acute hemorrhagic stroke associated with antiplatelet therapy trial reported an adjusted odds ratio for mortality of 2.05 for patients given early empiric platelets. A small trial conducted in Canada comparing 1:1:1 to laboratory-guided blood component therapy showed that achieving 1:1:1 despite concerted efforts was only achieved in
57% of the patients; moreover, it resulted in increased plasma wastage. In summary, there is currently a lack of evidence to support empiric ratio-based blood product administration, including immediate platelet transfusion, for the seriously injured patient at risk for life-threatening hemorrhage.

The alternative approach is goal-directed blood component administration based on laboratory assessments of coagulation function (Fig. 4). Conventional laboratory testing consists of prothrombin time (PT) and partial thromboplastin time (PTT) with additional measures of platelet count, fibrinogen levels and D-dimers. The PT and PTT are plasma-based tests that were originally designed to evaluate anticoagulant therapy and hemophilia due to isolated clotting factor deficiencies. Prothrombin time assesses the extrinsic pathway, and is believed to represent the clotting activity of factor VII, whereas the PTT assesses the intrinsic pathway, reflecting the clotting activity of factors XI, IX, VIII. Both tests reflect the common pathway (factors X, V, and II). The PT, reported as the international normalized ratio (INR), has generally been used to define TIC, with thresholds values ranging from greater than 1.2 to greater than

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**Figure 1.** Impaired clot formation is driven by both hypoxia and tissue injury. Proposed mechanisms include the activation of protein C with subsequent deactivation of factors V and VIII, and the release of heparan sulfate from the endothelial glyocalyx.

**Figure 2.** Systemic hyperfibrinolysis is stimulated by hypoxia with endothelial release of TPA that activates plasminogen. Inhibited fibrinolysis (shutdown), on the other hand is promoted via the byproducts of tissue injury and activation of platelets releasing antifibrinolytic agents. TPA, tissue plasminogen activator.
1.5. Interestingly, however, seriously injured patients at risk for massive transfusion present with varied profiles of isolated prolongation of the INR, isolated elevated PTT, and a combination of abnormalities. A recent report from the San Francisco General group\(^{26}\) indicated prolonged INR (>1.3) in 9%, elevated PTT (>34 seconds) in 43%, and combined PT and PTT abnormalities in 48% among coagulopathic patients. In our recent analysis of patients requiring a massive transfusion (>10 RBC/first 6 hours), 2% had a prolonged INR (>1.3), 13% had an elevated PTT (>30 seconds), and 72% had combined abnormalities of INR and PTT. Of note, 13% had normal INR and PTT (manuscript in preparation). Perhaps, more concerning, in a preliminary study of 30 seriously injured patient in whom we measured clotting factors activity, greater than 40% of the variation in INR and PTT could not be explained by clotting factor deficiency. In summary, although modest prolongation in the INR or PTT is relatively sensitive in identifying the seriously injured patients at risk for TIC, they do not clearly indicate its cause(s), and consequently are weak guides for therapy. Moreover, platelet count is very insensitive for identifying the need for platelet transfusion. The vast majority of patients at risk for a massive transfusion present with what is currently considered a normal platelet count, that is, greater than 150,000/\(\mu\)L.\(^{22}\) Similarly, most patients with TIC appear to have adequate fibrinogen (>150 mg/dL) levels.\(^{22}\) Thus, platelet counts and fibrinogen levels add little to the initial management of most patients at risk for life-threatening hemorrhage.

The alternative to conventional laboratory assessment of clotting functions is whole blood viscoelastic hemostatic assays (VHA). The currently US FDA approved methods are TEG and ROTEM.\(^{27,28}\) Unlike PT and PTT, which only measure the plasma-dependent enzymatic component of clotting, VHAs reflect thrombin generation, platelet activity, and fibrinogen crosslinking, providing a measurement of maximum clot strength and subsequent clot dissolution. Recognizing these advantages, coupled with the availability of improved equipment, has resulted in progressive adoption of VHAs for management of TIC, but there are few comparative studies between VHAs and conventional
coagulation tests. The Memorial Herman group reported superiority of TEG compared to PT and PTT in a large animal model\textsuperscript{29} and the Ben Taub group suggested advantages of TEG compared to 1:1:1 in a retrospective cohort study.\textsuperscript{23} We have had encouraging experience with both TEG and ROTEM in trauma management, but have done more work with TEG due to our institution’s preference. Based on an analysis of 160 healthy control patients in Denver and clinical investigations, we established transfusion thresholds for specific citrated rapid TEG measurements, that is, FFP plasma for an activated clotting time longer than 128 seconds, fibrinogen for an angle less than 65°, platelets for a maximum amplitude less than 55 mm, and antifibrinolytic (e.g., tranexamic acid [TXA]) for a lysis at 30 minutes greater than 5%.\textsuperscript{30} Over a 3-year period, patients at risk for massive transfusion were randomized to TEG versus conventional coagulation test–guided resuscitation. The overall results were a 50% improvement in survival when blood components were delivered based on TEG measurements (Fig. 5). These results are limited to a single institution; however, at this time, we are not aware of any additional prospective randomized trials comparing TEG (or ROTEM)-guided hemostatic resuscitation to conventional laboratory testing or to a fixed ratio 1:1:1 ratio. Nevertheless, the dramatic survival benefit we observed in the trial should serve as an impetus for wider adoption of VHA-based resuscitation, enabling more definitive and generalizable studies.

Based on our collective experience over the past decade, our current protocol for the resuscitation of the seriously injured patient is summarized in Figure 6. We believe the key to preventing life-threatening coagulopathy is rapid reversal of shock and preservation of microvascular circulation. Our first cooler of blood products consists of four units of RBC and two units of

**Goal-directed Hemostasis**

![Flowchart showing blood product ratios for resuscitation](image)

**Figure 5.** Kaplan-Meier estimates of survival by randomization group for patients analyzed as treated. Survival in the TEG guide group was significantly higher than the CCA group.\textsuperscript{31} Reproduced from reference 31 with permission from Wolters Kluwer Health, Inc. CCA, conventional coagulation assays.

**Figure 6.** Based on our ongoing studies, and those from others, we believe the priority in hemostatic resuscitation is minimizing the duration of shock and avoiding hemodilution with crystalloid. Goal-directed component therapy is initiated after the first two units of plasma and four units of RBCs.
Fibrinogen (FGB) is no longer administered because its availability of blood components also appears limited.35 Transport to a Level I trauma center where there is immediate availability of blood products is also compromised.36 Of course, we believe whole blood is the preferred mode of resuscitation before transfusion of platelets and cryoprecipitate. An exception to the TEG-directed protocol outlined above is the severely injured patient requiring helicopter transport (personal communication M.A. Schreiber, October 20, 2017) and seriously injured patients lacking hypersensitivity to tissue plasminogen activator.

The role of TXA in a mature trauma system with rapid transport to a Level I trauma center where there is immediate availability of blood components also appears limited.35–40 It is likely, however, that TXA is beneficial in a subpopulation of severely injured patients with a combination of poor clot strength and hyperfibrinolysis, as suggested by a recent reevaluation of the MATTERS trials.41 Ongoing analysis of military experience42 also suggests that TXA may be beneficial with inherent delays in transport of combat casualties to definitive facilities, or at an increased risk of venous thromboembolism. However, the subpopulation likely to benefit has yet to be defined. The majority of severely injured patients in the civilian setting arrive at the hospital in fibrinolysis shutdown,15–40 rendering them at risk of thrombosis if TXA is given. Currently, there are large multicenter randomized civilian trials designed to determine the role of prehospital TXA in traumatic brain injury (personal communication M.A. Schreiber, October 20, 2017) and seriously injured patient requiring helicopter transport (personal communication J.L. Sperry, October 20, 2017).

In summary, our collective experience, and that of a number of other investigators, indicates blood component transfusion in the seriously injured patients at risk for massive transfusions should be personalized and goal-directed, using TEG or ROTEM. The availability of new generation devices should enhance the feasibility of earlier testing and, ultimately, the proven benefit.

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The authors declare no conflicts of interest.

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