CME

Trauma Bleeding Management: The Concept of Goal-Directed Primary Care

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The early and aggressive high-volume administration of fresh frozen plasma, platelet concentrates, and red blood cells (RBCs), using ratio-driven massive transfusion protocols, has been adopted by many for the treatment of trauma-induced coagulopathy and hemorrhagic shock. However, the optimal ratio of RBC: fresh frozen plasma and RBC:platelet concentrate is still under investigation. In some European trauma centers, hemostatic agents such as fibrinogen concentrate, prothrombin complex concentrates, and antifibrinolytics are integral parts of goal-directed massive transfusion protocols. Both a ratio-driven coagulation therapy and a point-of-care–guided coagulation management based on coagulation factor concentrates aim for the same target—the rapid prevention and treatment of shock and coagulopathy to prevent death from traumatic hemorrhage. In this review, we compare the evidence relating to the effectiveness and safety of the ratio-driven and goal-directed approaches to trauma-induced coagulopathy to draw attention to the potential benefits and drawbacks associated with these management strategies. (Anesth Analg 2014;119:1064–73)

Severe trauma often results in uncontrolled, noncompressible diffuse microvascular bleeding, potentially leading to exsanguination;[1,2] importantly, approximately 40% of all trauma-related deaths are linked to pronounced coagulopathy.[3] Patient management strategies in cases of major bleeding prioritize attenuating the hemorrhage, the resuscitation of intravascular volume, and the early support of coagulation.[4] Recent experiences derived initially from military trauma-care providers suggest the administration of a ratio of fresh frozen plasma (FFP), platelet concentrate (PC), and red blood cells (RBCs) close to 1:1:1 reduces mortality in patients with major bleeding.[5–9] However, the evidence supporting this approach is not conclusive, and the optimal ratio of FFP:PC:RBCs is still under investigation.[10–16]

An alternative management strategy for the treatment of trauma-induced coagulopathy (TIC) has been developed after the emergence of viscoelastic point-of-care (POC) coagulation monitoring tools such as rotational thromboelastometry (ROTEM®; Tem International, Munich, Germany) and thrombelastography (TEG®; Haemonetics, Braintree, MA).[15,17–19] These tests offer the ability to rapidly assess the initiation processes of clot formation, clot strength, and clot stability.[20] The use of these rapid POC assessment techniques can facilitate the aim of an individualized coagulation therapy based on FFP, PC, RBCs, and hemostatic agents. In some European trauma centers, viscoelastic tests are used to guide an approach to hemostatic therapy in which coagulation factor concentrates are prominent.[18,21,22] This management strategy is in contrast to the ratio-driven concept, because such testing allows deficits in certain phases of the clotting process to be identified and specifically addressed. It is important to note that both strategies focus on the same therapeutic goals: the aggressive increase in hemostatic capacity via the administration of coagulation factors and platelets, and as a result, facilitating the rapid reversal of shock and endothelial dysfunction while supporting effective coagulation. Ultimately, the aims are a reduction in blood loss and an improvement in survival rates; these 2 treatment approaches are compared in this article. It is important to note that although more precise resuscitation is an appropriate aim for trauma physicians, the debate surrounding both the administration of the optimum ratio of blood products, or a targeted therapy based on rapid coagulation assessment, should not distract from the need to act quickly in cases of TIC; when resuscitation is necessary, "blind" protocol-guided transfusion is appropriate in the absence of diagnostic data.

HOW TO ASSESS TRAUMA-INDUCED COAGULOPATHY?

Standard Laboratory Tests

Routine coagulation tests, such as prothrombin time (PT), prothrombin index, International Normalized Ratio (INR), and/or activated partial thromboplastin time (aPTT) are used in most trauma centers worldwide to assess coagulopathy in trauma and to guide hemostatic therapy.[23] The value of these standard coagulation analyses in adequately reporting the complexities of trauma-associated coagulopathy has been challenged.[18,23,24] Because whole cells are removed by centrifugation before standard coagulation testing, the contribution to clotting from platelets, erythrocytes, and tissue factor–bearing cells, are not considered.[18] Standard tests do not provide any information regarding the strength or stability of clot formation; the important

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Accepted for publication August 20, 2012.

Supported by CSL Behring.

Conflicts of Interest: See Disclosures at the end of the article.

The article is part of the WCA Symposium (Buenos Aires 2012). A review on this topic has been published in the Scandinavian J Trauma Resuscitaion and Emerg Med.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0b013e318270a6f7

role of fibrinogen in mediating coagulation is also not recognized and the extent of any existing hyperfibrinolysis (a significant confounder of the coagulation process)[25–27] is not adequately assessed.[28] Moreover, extended lengths of time are required for clinical laboratories to process the results of such tests, with waits of between 78 (range, 62–103 minutes)[29] and 88 minutes (range, 29–295 minutes)[30] being reported. In short, standard coagulation tests are time consuming and were neither developed nor validated to diagnose the complex nature of TIC.[18]

A Role for Thromboelastometry and Thromboelastography in Identifying Acute Trauma Patients at Risk of Massive Transfusion?

Alternatives to routine coagulation tests including viscoelastic coagulation monitors such as ROTEM and TEG are proving to be of increasing clinical value to trauma physicians. ROTEM and TEG devices measure the changes in clot formation in whole blood, accounting for the contributions to the clotting process of platelets, and tissue factor–bearing cells; this provides a more comprehensive analysis than conventional testing[21,29,31–33] that is, relative to plasma-based coagulation variables, more reflective of the in vivo coagulation status of the patient and, importantly, can be available within minutes.[29,34] It should be noted that the contribution to clotting mediated by endothelial cells (which remains largely unknown and underappreciated) is not assessed by either standard laboratory or viscoelastic tests of coagulation. However, whole blood tests do assess the role of any endothelial-derived factors that are present.

Both ROTEM and TEG provide the opportunity to discern between different potential causes of bleeding. A general picture of coagulation status, looking at both the intrinsic and extrinsic activation pathways can be assessed (e.g., impaired, normal, hypercoagulable); furthermore, the fibrin-dependent component of the clot and an assessment of hyperfibrinolysis is also possible. The functional properties of the assays used by ROTEM and TEG have been described in detail,[28,35] and an example of ROTEM traces observed during normal and impaired coagulation are shown in Figure 1.[18]

How Useful Is the Rapid Assessment of Coagulation Status in Patients with Major Bleeding?

A retrospective analysis of severely injured trauma patients (n = 44) presenting at a level 1 trauma center compared the results of conventional coagulation tests with rapid TEG (r-TEG). The use of r-TEG performed on noncitrated whole blood was an effective real-time measure of thrombostatic function, which could guide transfusion therapy and may result in reduced FFP administration compared with conventional testing.[20] The feasibility of using ROTEM to assess the coagulation status of patients requiring massive transfusion accurately was investigated prospectively in deployed military personnel.[36] ROTEM was shown to detect significantly more coagulation abnormalities than PT and aPTT, and its use was effective in both monitoring and guiding individualized therapy during massive transfusion.[36] It is important to note that further prospective study into the application of POC viscoelastic devices for real-time assessment of coagulation status in severely bleeding patients is required.

Early Identification of Patients At Risk for Massive Transfusion Is Crucial

It is of paramount importance for trauma-care providers to identify those patients at risk for massive transfusion early in the course of initial treatment for 2 reasons; first, it has been shown that a delay in the initiation of coagulation therapy is associated with a poor outcome when patients were massive bleeders.[10,12] Second, there is evidence that the use of high plasma:RBC ratios in patient groups who ultimately do not receive massive transfusion may not improve survival and can increase complication rates.[37–39]

Predictive scores were developed to assess the risk of the individual patient for massive transfusion. Most of these scores are based on both anatomical findings and rapidly

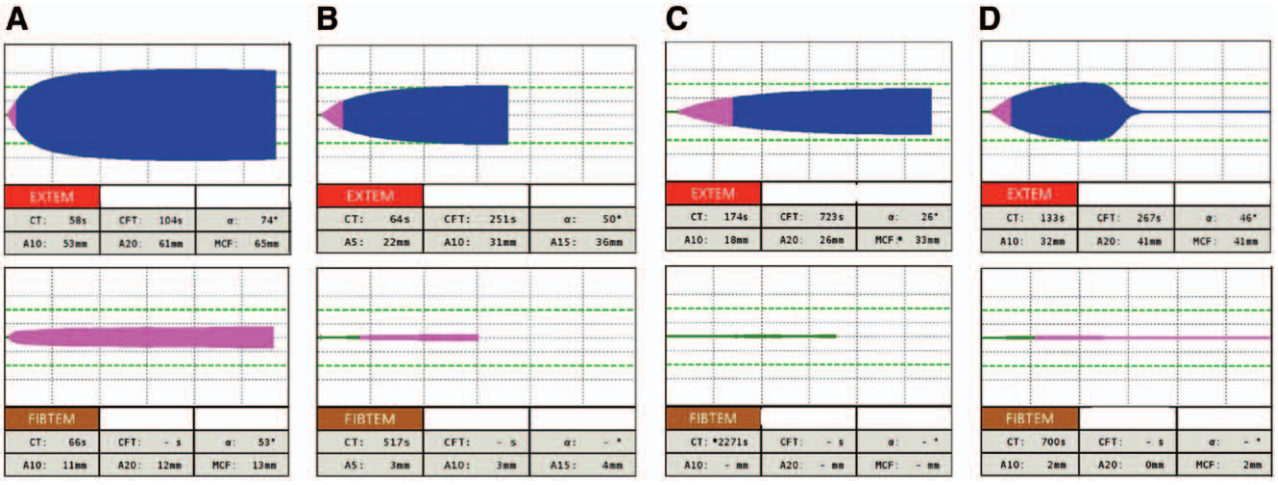

Figure 1. An example of ROTEM (EXTEM and FIBTEM) traces observed during normal, impaired, and hyperfibrinolytic coagulation states.[18] A, Normal test result. B, Reduced MCF in EXTEM and FIBTEM, normal CT, prolonged CFT. C, Severe coagulopathy: delayed initiation of coagulation (prolonged CT), low CFT, and MCF; no measurable FIBTEM. E, Hyperfibrinolysis: complete breakdown of the clot, very low FIBTEM. CT = coagulation time; CFT = clot formation time; MCF = maximum clot firmness.

available laboratory data, such as hemoglobin and base deficit.[40–44] Massive transfusion scores were mostly developed from retrospective data sets, and few were prospectively validated.[45,46]

How Can Early Coagulation Therapy Be Achieved in Trauma Patients with Major Bleeding?

Ratio-Driven Volume Resuscitation

To both overcome insufficiencies in therapy, and improve the hemostatic capacity of the bleeding patient, the adoption of the "damage-control resuscitation" concept has led to the introduction of massive transfusion protocols (MTPs) in recent years,[47–49] with experience from both military and civilian studies leading to a reappraisal of treatment protocols in bleeding trauma victims. This approach proposes the early and aggressive transfusion of FFP and PCs to replace both circulating volume, depleted clotting factors, and platelets.[50] Geeraedts et al.[51] suggested that the majority of trauma patients who died because of exsanguination within the first 24 hours after admission (82%) received insufficient amounts of FFP and PCs. These data were confirmed by Gonzalez et al.[52] who found that trauma patients were coagulopathic on admission to the intensive care unit (ICU) due to inadequate pre-ICU coagulation therapy. INR and aPTT were prolonged at ICU admission (INR, 1.6 ± 0.1; aPTT, 36 ± 2 seconds) and did not fully normalize by the end of day 1 in the ICU.[52]

High Ratio of FFP:RBC

Hirshberg et al.[53] developed a computer model where they showed that to sufficiently correct coagulopathy in major bleeding, FFP treatment has to be started early with a necessary ratio of FFP:RBC of 2:3.

This mathematical model was confirmed by Borgman et al.[5] who performed a retrospective review of patients receiving massive transfusion (≥10 units RBCs in 24 hours) at a military trauma center. When patient groups receiving a median plasma:RBCs ratio of 1:8, 1:2.5, and 1:1.4 were compared, the overall mortality rates observed were 65%, 34%, and 19% ($P < 0.001$), respectively. The increased survival rate was associated with decreased death from hemorrhage,[5] findings which were supported by similar results in a retrospective study of civilian patients.[7]

In addition to any resulting improvements in hemostatic capacity, other potential beneficial effects of plasma transfusion have been suggested. Johansson et al.[54] identified that high levels of circulating syndectan–1, a marker of endothelial glycocalyx degradation, was associated with increased mortality. Experimental studies in rats have suggested a potential role for plasma in protecting the endothelial glycocalyx after hemorrhagic shock compared with a crystalloid-based fluid therapy,[55] as well as improving endothelial cell function and hemodynamic stability.[56]

Although many published studies have supported a high FFP:RBC transfusion ratio,[5,7–9,57–60] limitations to these observations have been identified,[10,12] and a consensus within the literature remains to be established.[48,49,61] The evidence currently available is either retrospective or nonrandomized; consequently, results from these studies can only be hypothesis generating.[12,15,47,49,62,63]

Advantages and Limitations of the Ratio-Driven Concept

Survivor Bias

There are limitations to the ratio-driven concept. A survivor bias can skew the data in observational studies, whereby an artificially high number of patients with a poor prognosis have the potential to be included in the low plasma ratio cohorts, because such patients died before more plasma units could be transfused.[12] Moreover, there is the possibility of selection bias also, whereby physicians expended more resources, including plasma transfusions, on those patients most likely to survive. It should also be considered that the decision to cease coagulation therapy in severely injured patients with no chance of survival can often occur after RBC transfusion, but before FFP and other allogeneic administration. As such, reported FFP:RBC ratios will be significantly lower in this subsection of patients. Attempts to mitigate these sources of bias include performing time covariant analysis,[64] as well as the exclusion from retrospective data sets of patients who died within 1 to 2 hours. Both methods produce data that show an association of high ratio transfusion with improved survival; however, the sources of bias cannot be completely excluded. A recent analysis of 26 studies relating to blood ratios in trauma concluded that, because of the difficulties presented in trying to exclude survivor bias, the available evidence relating to higher ratios of FFP:RBC are inconclusive, and prospective trials are required.[10]

Transfusion Volume

The physiological concentrations of plasma proteins present in standard FFP and solvent/detergent plasma necessitate high transfusion volumes to sufficiently increase coagulation factor activity.[65] Chowdary et al.[66] measured the recovery of coagulation factors after the transfusion of 12.2 mL/kg compared with 33.5 mL/kg, showing that only high-volume plasma transfusion induced increases in the concentrations of factors to or above target levels. Thus, a formula-driven strategy requires immediate access to large volumes of universal donor FFP. Thawing before transfusion is required for FFP, which is time consuming and can potentially delay necessary and immediate coagulation therapy. To overcome this hindrance, some centers instigate the prethawing of FFP in ready-to-administer transfusion packages;[47] however, a universal implementation of this strategy beyond busy trauma centers would potentially result in wasted plasma, its overuse, or both.[67] Lyophilized plasma, which is available immediately, could address these logistical problems.[68,69]

Timing of Intervention

It is becoming increasingly evident that effective treatment of TIC requires early intervention to improve the hemostatic capacity of exsanguinating patients. Snyder et al.[70] report a mean time of 93 minutes until first FFP transfusion, compared with 18 minutes for RBCs. This lag in FFP administration can distort the true ratio of administered blood products. Because the time between FFP and RBC transfusion can vary so widely, it is difficult to state definitively the true ratio of products transfused. As such, the transfusion of FFP and RBC units within a 30-minute

period is proposed for a 1:1 ratio to be considered an accurate reflection of the clinical reality. This limitation has been highlighted by de Biasi et al.[71] reporting a significant relationship between the by-hour mortality rate and the observed plasma deficit status within the first 2 hours of volume resuscitation. Furthermore, Riskin et al.[72] reviewed data on trauma patients requiring massive transfusion (≥10 units RBCs) before and after the implementation of an MTP. The FFP:RBC ratios were identical in both observation periods (1:1.8 and 1:1.8; $P = 0.97$), but the mean time to administration of the first FFP decreased from 254 to 169 minutes ($P = 0.04$). Despite the unchanged ratio of blood products, mortality decreased from 45% to 19% ($P = 0.02$), suggesting a time-dependent variable and underscoring that the early transfusion intervention might be vital.[72] It should be highlighted that the introduction of MTPs that use prethawed plasma products have now been reported, allowing the administration of the first blood product within as little as 3 minutes (range, 0–23 minutes).[47] However, in this study, the storage of prethawed FFP in the blood bank was only allowed for up to 72 hours, raising the possibility for the wastage of this valuable resource using this approach. Moreover, preclinical data have indicated that administration of human plasma stored for 5 days resulted in significantly decreased survival compared with freshly thawed plasma in a rat model of acute hemorrhage after hepatic injury ($P = 0.03$).[73]

Potential Adverse Events

High-volume transfusions are associated with a risk of complications. In patients without massive bleeding, FFP transfusion is associated with both acute respiratory distress syndrome (ARDS) and acute lung injury (ALI).[12,37,65,74,75] A dose-dependent relationship between FFP administration and ARDS has been observed.[74] It is important to note that, as previously discussed, massive transfusion that includes FFP has been shown in several studies to improve survival, irrespective of the associated complications. However, in nonmassively transfused patients (<10 U packed RBC within 12 hours of admission) FFP transfusion was associated with large increases in complications, particularly ARDS, with no concomitant improvement in survival.[37] The prospective analysis of patients admitted to the ICU at a combat support hospital found an independent relationship between the amount of FFP transfused and the onset of ALI.[76] A separate study found the incidence of multiple organ failure in massively transfused trauma patients was associated with early FFP administration.[38] As such, the need for carefully chosen transfusion triggers for FFP administration is clear.[37,38]

Platelet Administration

The role of platelet transfusion in the management of TIC is currently unclear. Improved survival in patients receiving high platelet:RBC ratios have been reported[8]; however, the reported improvements in survival associated with platelet transfusion are subject to survival and selection biases similar to those seen with FFP,[15] and the efficacy of platelet transfusion in a predetermined ratio is not established. The before and after comparison of an MTP published by Dirks et al.[47] showed a significant increase in platelet concentrate transfusion with no improvement in survival rate, while similar results were observed by Simmons et al.[49] who reported that the introduction of new clinical practice guidelines forcing early platelet transfusion resulted in no survival benefit. As such, there is the potential for wasting valuable and expensive resources risk to patients being exposed to potential complications (e.g., ALI and pathogen transmission) unnecessarily. The authors believe this treatment option should not be routine.

Goal-Directed, POC-Guided Hemostatic Therapy in Trauma

The increased sensitivity and range of testing capabilities provided by modern viscoelastic coagulation monitors (ROTEM and TEG), coupled with the increased awareness of physicians of such techniques means that an alternative modern theragnostic approach toward the early assessment and management of TIC is now a possibility.[18,77] A theragnostic management strategy relies on real-time monitoring of coagulation status to guide the targeted supplementation of hemostatic agents. Such a methodology allows for a feedback loop to be established, whereby the treatment is responsive to patient physiology and rapidly addresses the hemostatic needs of the individual.[18] This approach is in stark contrast to the formulaic ratio-driven approach.

Improving and Maintaining Clot Quality During TIC

The primary focus of goal-directed coagulation therapy is the maintenance, or restoration, of clot strength. Reductions in clot firmness reported by viscoelastic tests have been shown to be predictive of increases in bleeding rates, requirements for blood product transfusion, and mortality.[32,78–81] Further retrospective analysis of the coagulation profiles of severely bleeding trauma patients at admission showed that abnormal clot firmness results measured using ROTEM, as well as hemoglobin levels at or below 10 g/dL, reliably predicted the requirement for massive transfusion.[82] An example of a goal-directed POC treatment algorithm used at the authors' institute (AUVA Trauma Hospital, Salzburg, Austria)[18] demonstrates the key coagulation variables that are measured, and the respective treatment approaches, when treating TIC with this approach (Fig. 2).

Hyperfibrinolysis

Hyperfibrinolysis is a key consideration in patients with severe shock and major tissue trauma.[1,26,83,84] Early primary fibrinolysis was detected in 34% of trauma-related admissions (determined by r-TEG) and was associated with massive transfusion requirements, coagulopathy, and hemorrhage-related death.[25] Hyperfibrinolysis was also found to be a predictor of poor survival, being associated with high mortality rates.[26] Tranexamic acid (TXA) is a synthetic lysine derivative that inhibits fibrinolysis by blocking the lysine binding sites of plasminogen.[85,86] TXA administration reduced the risk of death caused by bleeding in trauma patients significantly compared with placebo ($n = 10{,}060$ vs $n = 10{,}067$, respectively) during the recent Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage study (4.9% vs 5.7%, respectively; relative risk, 0.85; 95% confidence interval, 0.76–0.96; $P = 0.0077$).[86] As such, the use of TXA should be considered for the

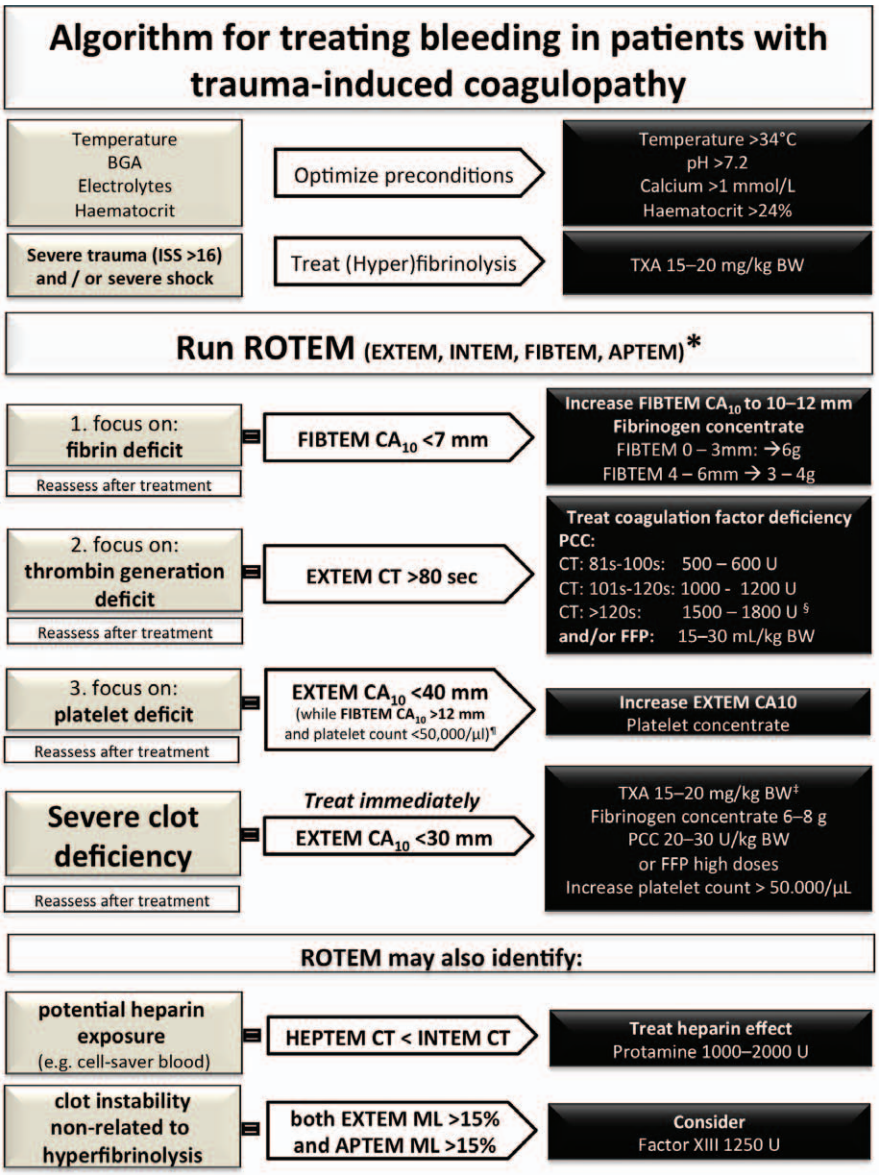

Figure 2. ROTEM-guided treatment algorithm: managing trauma-induced coagulopathy and diffuse microvascular bleeding (AUVA Trauma Hospital, Salzburg, Austria).[18] The algorithm is the standard operating procedure for ROTEM-guided hemostatic therapy on admission of trauma patients to the emergency room. Hemostatic agents suggested for use in clinics where coagulation factor concentrates are not available. *For patients who are unconscious or known to be taking platelet inhibitor medication, Multiplate tests (adenosine diphosphate [ADP] test, arachidonic acid [ASPI] test, and thrombin receptor activating peptide-6 [TRAP] test) are also performed. §If decreased ATIII is suspected or known, consider coadministration of ATIII. †Any major improvement in extrinsicaly activated test plus aprotinin (APTEM) parameters compared with corresponding EXTEM parameters may be interpreted as a sign of hyperfibrinolysis. ‡Only for patients not receiving TXA at an earlier stage of the algorithm. Traumatic brain injury: platelet count 80,000 to100,000/µL. Normal values: EXTEM/APTEM coagulation time (CT): 38 to 79 seconds; EXTEM/APTEM clot amplitude at 10 minutes (CA10): 43 to 65 mm; EXTEM/APTEM maximum lysis (ML) < 15%; FIBTEM CA10: 7 to 23 mm; intrinsically activated test (INTEM) CT: 100 to 240 seconds. CA10 = clot amplitude at 10 minutes; BGA = blood gas analysis; BW = body weight; Ca = calcium; CT = clotting time; FFP = fresh frozen plasma; ISS = injury severity score; MAPTECF = maximum clot firmness; ML = maximum lysis; PCC = prothrombin complex concentrate; TXA = tranexamic acid.

treatment of severely bleeding trauma patients. In contrast to the patients included in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage study, a recent study of the military application of TXA in trauma emergency resuscitation analyzed data from cohorts where all patients were operated on and received RBC transfusion.[87] The military application of TXA in trauma emergency resuscitation study showed that overall mortality rates were 6.5% lower in the TXA group compared with the non-TXA group ($P = 0.03$), whereas the difference in mortality rates was even greater in patients receiving massive transfusion (14.4% vs 28.1%, respectively; $P = 0.004$).[87] Figure 3 shows an example of severe hyperfibrinolysis.

Fibrinogen Supplementation

There is increasing evidence that fibrinogen supplementation is helpful in major bleeding and during the management of TIC.[88,89] Hippalla et al.[90] observed that fibrinogen was the first coagulation factor to reach a critically low concentration in cases of blood loss, whereas a recent study showed fibrinogen deficiency (<100 mg/dL) was the initial abnormality of coagulation in almost all trauma patients who developed coagulopathy.[91] The maximum clot strength (measured by ROTEM) is a result of the interaction of activated platelets, fibrin, and aFXIII.[35] As such, an improvement of the maximum amplitude of the clot in severe bleeding patients can be achieved by administration of sufficient amounts of fibrinogen.[34] Current European guidelines now recommend supplementation of fibrinogen when plasma concentrations are in the critical range 1.5 g/L to 2.0 g/L.[92]

When considering the ratio of fibrinogen to RBCs administered to military trauma patients receiving massive transfusion, Stinger et al.[93] reported that an increased total amount of fibrinogen administered was independently associated with improved survival rates. However, it is important to note that patients included in this study receiving higher ratios of fibrinogen:RBCs also received

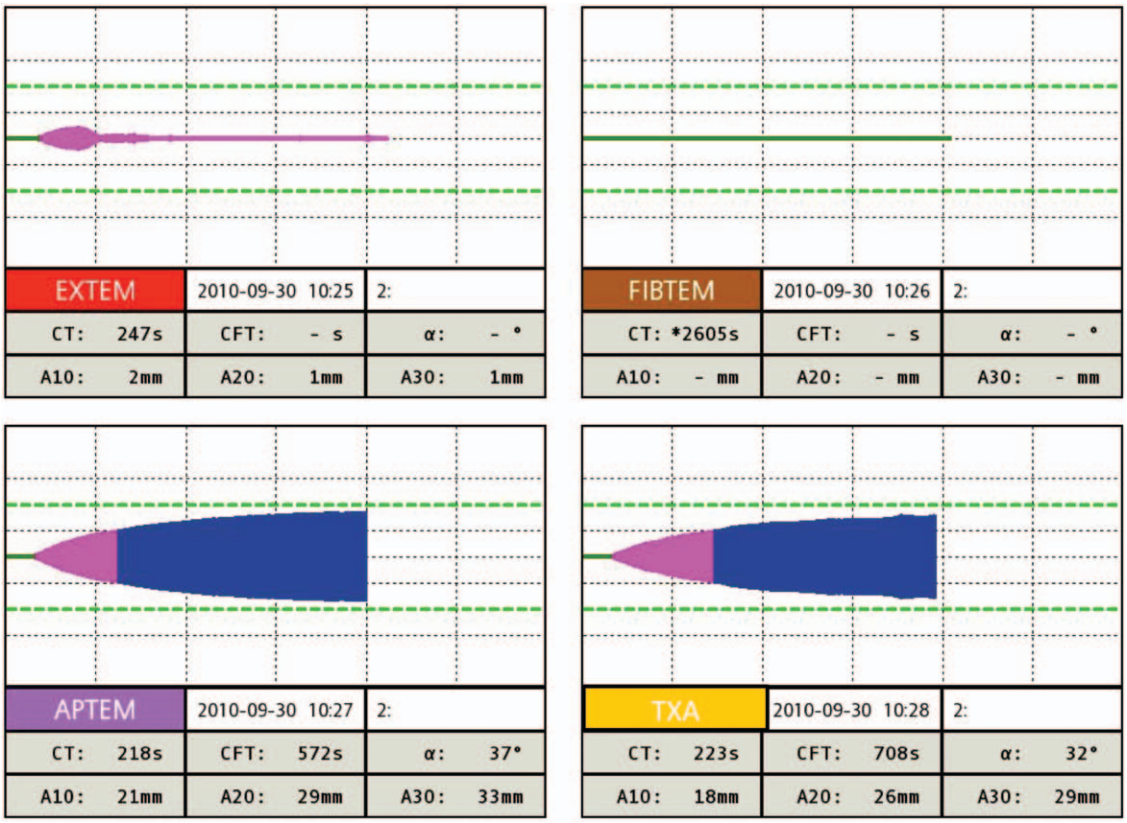

Figure 3. An example of severe hyperfibrinolysis. Note the fulminant breakdown of the clot within minutes in the EXTEM test. No clot formation in the FIBTEM test. When adding aprotinin (APTEM) or tranexamic acid (TXA), stable clot formation could be achieved.

more PCs, FFP, and cryoprecipitate, making the interpretation of the data difficult, especially given the central role of platelets in maintaining primary and secondary hemostasis.

Fibrinogen supplementation can be undertaken via the transfusion of large volumes of FFP, or the administration of either cryoprecipitate or fibrinogen concentrate. Cryoprecipitate has been used for the treatment of congenital fibrinogen deficiency and for intravascular volume resuscitation in trauma;[94] however, it has been withdrawn in many European countries because of significant safety concerns relating to its administration.[92] Fibrinogen concentrate can be easily and quickly reconstituted using sterile water or saline for administration without thawing or cross-matching,[88] allowing rapid and controlled dosing. Although used primarily in Europe, it should be noted that the administration of fibrinogen concentrate for the treatment of acquired bleeding is off-label in some countries including the United States. Consistent and high doses of fibrinogen can be delivered in small volumes, and in cases of urgent treatment of severe bleeding, delivery of 6 g in 1 to 2 minutes has been reported.[95] Clearly, given the physiological concentrations of fibrinogen present in FFP (2.0–2.7 g/L),[96,97] an equivalent approach is not feasible because it would involve the transfusion of approximately 2500 mL. It is possible to monitor improvements in clot formation and clot strength using POC testing regimes such as EXTEM, FIBTEM, which provide real-time information about the patient's coagulation status, and allow for guided dosing and administration. Thus, a theragnostic approach to fibrinogen supplementation is possible.

Improving Initiation of the Coagulation Process

It appears thrombin generation is not an acute problem in the very early stages of TIC. Dunbar and Chandler[98] reported on 15 trauma patients with PT >18 seconds or an INR >1.5, suggesting possible TIC. When thrombin generation was measured, it was found to be 3-fold higher compared with controls (P = 0.01). According to the TEG results of trauma patients (n = 65), the majority were hypercoagulable immediately after injury.[99] These data are in accordance with findings of Davenport et al.[29] who reported that TIC was mainly characterized by a reduction in maximum clot firmness rather than a prolonged ROTEM clotting time.

To increase thrombin generation, prothrombin complex concentrates (PCCs) and activated recombinant factor VII (rFVIIa) have been used as coagulation therapy during trauma-related bleeding.[21,100–102] However, randomized controlled studies did not reveal a survival benefit in trauma patients receiving rFVIIa.[100,101] Few studies have reported the use of PCC in trauma patients.[21,103,104] Although these reports have described a survival benefit associated with PCC administration, prospective trials are lacking. Because of the retrospective nature of the available study data, safety issues surrounding PCC were not adequately assessed. PCCs are potent procoagulants and, as such, the possibility

of associated thromboembolic event should be considered[92,104,105]; it is important to note that there are currently no robust safety data relating to PCC use in TIC. The coadministration of PCCs with antithrombotic factors such as antithrombin III has been suggested as a potential approach to minimize the risk of thromboembolism;[18] however, this is yet to be validated by prospective study.

To date, only initial results indicate the potential for goal-directed administration of clotting factor concentrates to reduce the requirement for allogeneic transfusion in the management of severe trauma-related bleeding, and prospective, randomized trials that interrogate this management strategy are necessary.

Advantages and Limitations of a Goal-Directed Approach Using Coagulation Factor Concentrates

The use of clotting factor concentrates for goal-directed coagulation management during trauma-related bleeding is a relatively new concept. Although there are significant potential benefits with this approach,[106–108] currently there is no consensus among physicians regarding this treatment strategy.[109,110] Care must be taken to consider the potential risks associated with this approach. A goal-directed approach that uses function measures of coagulation for factor concentrate administration may be able to avoid the adverse thrombotic events that have been reported with nonguided use of these agents.

The individualized theragnostic management of TIC holds many theoretical advantages over the ratio-driven approach. The formulaic administration of FFP and RBCs used by the latter of these strategies means that the undertransfusion and overtransfusion of some patients are inevitable. There is a clear need to avoid inappropriate transfusion levels, as too little will not effectively treat TIC whereas too much will increase the risk of ARDS, multiple organ failure, and ALI.[38,65,74,75,111]

CONCLUSIONS

It is clear that TIC management requires the early and aggressive replenishment of coagulation factors. When using high-volume plasma therapy, it is necessary to sufficiently increase hemostatic capacity of the patients, maintain circulating volume, and tissue oxygenation. Based on the available data, it is currently unknown which ratio of FFP:RBC is optimal to achieve this.

An individualized hemostatic treatment strategy based on viscoelastic test results is another promising concept for patients with severe trauma-related bleeding. It is still not clear whether this approach can improve outcomes while not increasing morbidity, nor is it clear what the optimal goal-directed algorithm in severe trauma patients should be. The availability of clotting factor concentrates is key to allow for the targeted supplementation of procoagulants. The administration of fibrinogen concentrate in cases of TIC can address the problems of early and critical fibrinogen depletion; this product holds significant timing and safety advantages over FFP transfusion for fibrinogen supplementation. The need for further prospective study of this technique is both clear and imperative.

DISCLOSURES

Name: Herbert Schöchl, MD.
Contribution: This author helped review and prepare the manuscript.
Attestation: Herbert Schöchl approved the final manuscript.
Conflicts of Interest: Herbert Schöchl has received study grants and honoraria as speaker from CSL Behring (manufacturer of fibrinogen concentrate and PCC) and Tem International (manufacturer of the ROTEM device).
Name: Christoph J. Schlimp, MD.
Contribution: This author helped review and prepare the manuscript.
Attestation: Christoph J. Schlimp approved the final manuscript.
Conflicts of Interest: The author has no conflicts of interest to declare.
This manuscript was handled by: Jerrold H. Levy, MD, FAHA.

ACKNOWLEDGMENTS

Editorial assistance was provided by John Timney of Fishawack Communications Ltd. during the preparation of this manuscript.

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