

# Trauma-Induced Coagulopathy and Massive Bleeding: Current Hemostatic Concepts and Treatment Strategies

Johannes Gratz<sup>1</sup> Daniel Oberladstätter<sup>2,3</sup> Herbert Schöch<sup>2,3</sup>

<sup>1</sup>Department of Anaesthesiology, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Austria

<sup>2</sup>Department of Anaesthesiology and Intensive Care, AUVA Trauma Centre, Salzburg, Austria

<sup>3</sup>Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Research Centre, Vienna, Austria

**Address for correspondence** Herbert Schöch, MD, AUVA Trauma Centre Salzburg, Austria and Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, AUVA Research Centre, Donaueschingenstrasse 13, Vienna 1200, Austria (e-mail: herbert.schoechl@auva.at).

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## Abstract

Hemorrhage after trauma remains a significant cause of preventable death. Trauma-induced coagulopathy (TIC) at the time of hospital admission is associated with an impaired outcome. Rather than a universal phenotype, TIC represents a complex hemostatic disorder, and standard coagulation tests are not designed to adequately reflect the complexity of TIC. Viscoelastic testing (VET) has gained increasing interest for the characterization of TIC because it provides a more comprehensive depiction of the coagulation process. Thus, VET has been established as a point-of-care-available hemostatic monitoring tool in many trauma centers. Damage-control resuscitation and early administration of tranexamic acid provide the basis for treating TIC. To improve survival, ratio-driven massive transfusion protocols favoring early and high-dose plasma transfusion have been implemented in many trauma centers around the world. Although plasma contains all coagulation factors and inhibitors, only high-volume plasma transfusion allows for adequate substitution of lacking coagulation proteins. However, high-volume plasma transfusion has been associated with several relevant risks. In some European trauma facilities, a more individualized hemostatic therapy concept has been implemented. The hemostatic profile of the bleeding patient is evaluated by VET. Subsequently, goal-directed hemostatic therapy is primarily based on coagulation factor concentrates such as fibrinogen concentrate or prothrombin complex concentrate. However, a clear difference in survival benefit between these two treatment strategies has not yet been shown. This concise review aims to summarize current evidence for different diagnostic and therapeutic strategies in patients with TIC.

## Keywords

- ▶ trauma-induced coagulopathy
- ▶ ratio-driven hemostatic therapy
- ▶ goal-directed coagulation therapy
- ▶ viscoelastic testing

## Zusammenfassung

Nach wie vor sind Blutungen die Ursache eines relevanten Anteils potentiell behandelbarer Todesfälle bei TraumapatientInnen. Das Auftreten einer trauma-induzierten Koagulopathie (TIC) bei Aufnahme ist mit einem schlechteren Outcome dieser PatientInnen assoziiert. TIC stellt eine komplexe Störung des Gerinnungssystems dar und wird durch Standardgerinnungstests nicht adäquat abgebildet. Aufgrund der umfassenderen Darstellung des Gerinnungsprozesses haben viskoelastische Tests (VET) an Bedeutung in der Charakterisierung von TIC gewonnen. VET werden daher

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**Schlüsselwörter**

- ▶ trauma-induzierte Koagulopathie
- ▶ verhältnismäßig gesteuerte hämostatische Therapie
- ▶ zielgerichtete Gerinnungstherapie
- ▶ viskoelastische Prüfung

zunehmend als bettseitig verfügbare gerinnungsspezifische Monitoringmöglichkeit verwendet. Die sogenannte “Damage-Control Resuscitation” sowie die frühzeitige Gabe von Tranexamsäure stellen die Basis der Behandlung von PatientInnen mit TIC dar. In der Hoffnung auf einen Überlebensvorteil haben viele Traumazentren weltweit Massivtransfusionsprotokolle eingeführt, welche eine frühzeitige und hochdosierte Transfusion von Plasma vorsehen. Plasma enthält alle Gerinnungsfaktoren sowie Gerinnungsinhibitoren; ein adäquater Ersatz der fehlenden Gerinnungsfaktoren bei blutenden PatientInnen kann jedoch nur durch Transfusion großer Volumina erreicht werden. Allerdings wurden für die Gabe großer Mengen an Plasmen relevante Risiken beschrieben. In einigen europäischen Traumazentren wird in diesem Zusammenhang zunehmend ein individualisiertes hämostatisches Therapiekonzept zur Behandlung von TraumapatientInnen verfolgt. Hierbei wird das individuelle, tatsächlich vorliegende Gerinnungsprofil der PatientInnen anhand von VET dargestellt. Die nachfolgende zielgerichtete Therapie basiert hauptsächlich auf der Gabe von Gerinnungsfaktorkonzentraten wie Fibrinogen oder Prothrombinkomplexkonzentrat. Ein klarer Vorteil in Bezug auf das Überleben der PatientInnen konnte jedoch bis jetzt für keine der beiden Therapiestrategien nachgewiesen werden. Das Ziel dieses Reviewartikels ist es, die aktuell verfügbare Literatur für unterschiedliche diagnostische und therapeutische Vorgehen bei PatientInnen mit TIC zusammenzufassen.

**Introduction**

Uncontrolled bleeding remains a significant cause of early and preventable death following major trauma.<sup>1</sup> Recent data confirm that the majority of bleeding trauma patients die within the first 2 hours of hospital admission.<sup>2</sup> Trauma-induced coagulopathy (TIC), which is present in one-quarter to one-third of severely injured patients on emergency room admission, is associated with higher blood loss, higher transfusion rates, and a higher incidence of multiple organ failure in comparison to patients without TIC.<sup>3</sup> Moreover, trauma patients with established TIC have a nearly fourfold higher mortality rate than those with similar injury severity scores without TIC.<sup>4</sup>

To improve survival, early hemostatic intervention is of paramount importance. A recent study in trauma patients revealed that each 15-minute increase in time spent to achieve sufficient hemostasis was independently associated with higher incidences of 30-day mortality, acute renal injury, acute respiratory distress syndrome, multiple organ failure, and sepsis.<sup>5</sup> Thus, many trauma centers across the world have implemented massive transfusion protocols (MTPs). Following the activation of a MTP, red blood cells (RBCs), fresh frozen plasma (FFP), and platelet concentrates (PCs) are delivered from the blood bank in a fixed ratio, most commonly a 1:1:1 ratio.<sup>6</sup> However, the optimal ratio of these components is still a matter of debate.<sup>7</sup>

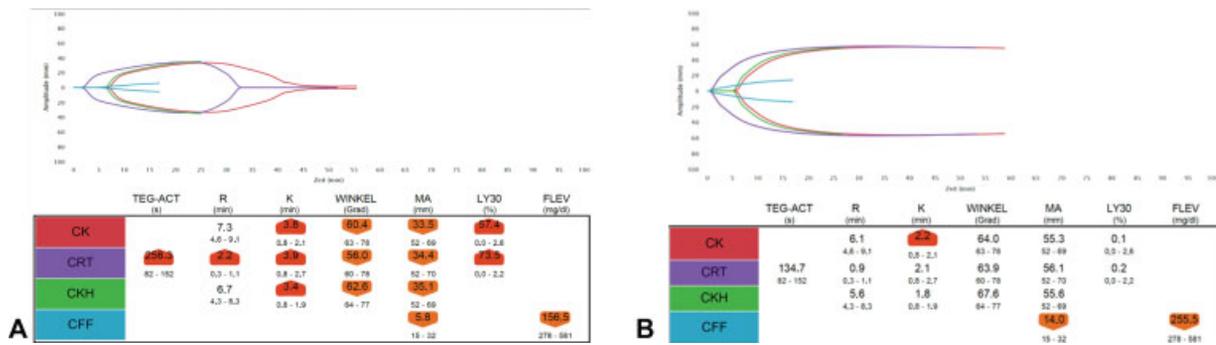
In contrast to this regimen, several European trauma centers have established a more individualized hemostatic approach to coagulopathic trauma patients.<sup>8,9</sup> Viscoelastic testing (VET)—using tests such as ClotPro (Enicor, Munich, Germany), rotational thromboelastometry (Tem Innovations, Munich, Germany), or thromboelastography (TEG; Haemo-

netics Corporation, Boston, Massachusetts, United States)—is used to evaluate the individual hemostatic competence of bleeding trauma patients.<sup>10</sup> Thereafter, adapted coagulation therapy—primarily based on purified coagulation factor concentrates (CFCs)—is administered according to the patient's individual need.<sup>11,12</sup> In this concise review, we discuss the pathophysiology of TIC and summarize the current evidence for different diagnostic and therapeutic strategies.

**Pathophysiology of Trauma-Induced Coagulopathy**

Historically, TIC was characterized as a net result of blood loss; dilution of the remaining coagulation factors due to volume replacement therapy; and impaired preconditions for sufficient hemostasis such as hypothermia, hypocalcemia, and shock-related acidosis.<sup>13</sup> Recent evidence provides a more detailed picture, characterizing TIC as a complex, multifaceted process. Data suggest that shock-related hypoperfusion due to massive blood loss causes extensive inflammation, activation of the neurohumoral system, and endothelial injury.<sup>14</sup> Damage of the inner layer of the endothelium, known as the glycocalyx, causes shedding of heparins and thrombomodulin that provoke endogenous anticoagulation.<sup>15</sup> Moreover, endothelial activation results in the substantial release of tissue plasminogen activator which can convert considerable amounts of plasminogen to plasmin, and thus create a profibrinolytic state.<sup>3</sup> The occurrence of hyperfibrinolysis has been shown to be a strong predictor of poor outcome following trauma.<sup>16,17</sup>

Additionally, platelet dysfunction has been described following major injuries. A recent study reported an inhibitory effect of plasma gathered from major trauma patients



**Fig. 1** An example of TEG traces observed before and after treatment of fulminant hyperfibrinolysis. (A) Typical pattern of hyperfibrinolysis with an early dissolution of the clot. (B) TEG tracing after administration of TXA and fibrinogen replacement. CFF, fibrin polymerization test; CK, kaolin activated test; CKH, kaolin activated test with heparinase; CRT, rapid TEG (extrinsically and intrinsically activated test); K-time, kinetic time; LY, % lysis at 30 minutes; R-time, reaction time; MA, maximum amplitude; TEG-ACT, thromboelastography-activated clotting time; TXA, tranexamic acid.

when mixed with platelets from healthy uninjured volunteers, suggesting that soluble plasma components are able to downregulate platelet function.<sup>18</sup> However, the exact mechanism of trauma-related platelet inhibition is still a matter of debate. Several mechanisms such as diminished platelet aggregation in response to agonists, defects in deposition to collagen, exhausted platelets due to stimulation, complement activation, or downregulated glycoprotein receptors have been discussed.<sup>19</sup> Importantly, trauma-induced platelet dysfunction occurs early after injury, is independent of platelet count, and is associated with poor outcome.<sup>20</sup>

### Diagnosis of Trauma-Induced Coagulopathy

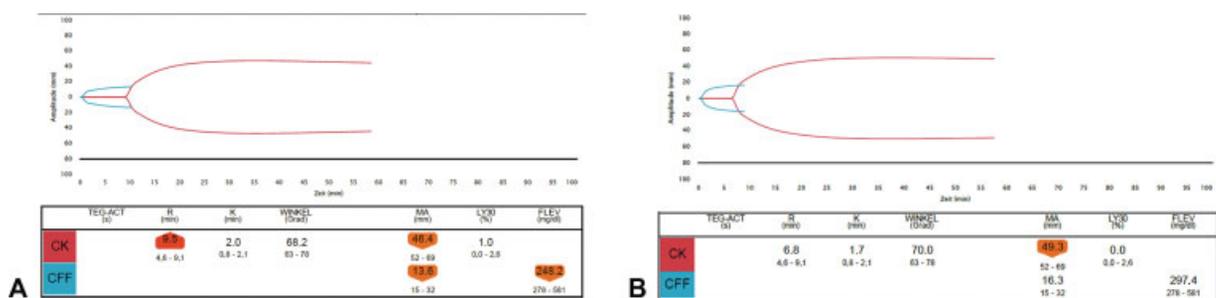
#### Standard Coagulation Tests

As described previously, rapid restoration of sufficient hemostasis is crucial in bleeding trauma patients. Thus, the presence of TIC must be diagnosed in a timely manner. Accordingly, current guidelines recommend early and repeated monitoring of hemostasis with standard coagulation tests and/or by means of VET.<sup>21</sup> However, standard coagulation tests such as prothrombin time, activated partial thromboplastin time, or international normalized ratio fail to adequately reflect the complex nature of TIC. These tests only provide an initial snapshot of the coagulation process and measurements stop at a time point when only 5 to 7% of the thrombin is generated.<sup>22</sup> Interestingly, despite this drawback being described more than a decade ago, many scientists and clinicians still

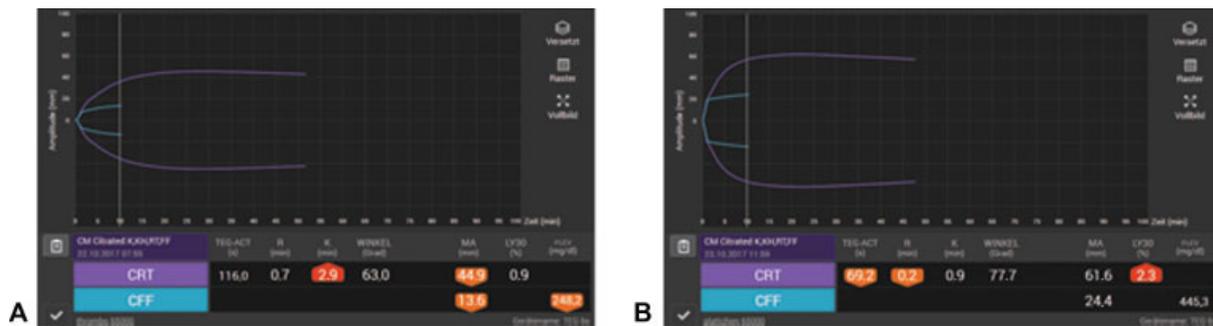
rely on standard coagulation tests for the definition of TIC and the management of patients.

#### Viscoelastic Testing

VET provides a more comprehensive depiction of the coagulation process from the initiation and speed of clot formation to clot firmness and a potential early breakdown of the clot.<sup>23</sup> In short, the principle of VET is based on the elastic properties of clotting whole blood.<sup>24</sup> As the blood clots, it increasingly opposes the movement of parts of the measuring device which latter is recorded and typically depicted as a curve. Therefore, in addition to measuring the onset of clot formation, VET can also characterize the further dynamics of clot formation as well as a possible breakdown of the clot. →Figs. 1–2 to 3 show typical TEG curves in bleeding trauma patients. Both low clot amplitude and premature breakdown of the clot have been recognized as predictors of poor outcome following trauma.<sup>16,25</sup> VET can be run as point-of-care-applicable measurements with test results being available much faster than standard coagulation tests.<sup>10</sup> In contrast to standard coagulation tests, due to the faster turnaround times, VET has the potential to individualize hemostatic therapy according to the patient's actual needs. A recent study in trauma patients revealed that goal-directed coagulation therapy guided by VET resulted in significantly lower mortality compared with administering treatment according to standard coagulation tests.<sup>26</sup>



**Fig. 2** Therapeutic effect of fibrinogen concentrate on clot firmness. (A) Low clot firmness in all tests. (B) TEG tracing after 4 g of fibrinogen concentrate. CFF, fibrin polymerization test; CK, kaolin activated test; K-time, kinetic time; LY, % lysis at 30 minutes; R-time, reaction time; MA, maximum amplitude; TEG-ACT, thromboelastography-activated clotting time.



**Fig. 3** Effect of platelet concentrate on clot amplitude. (A) Low clot amplitude in CK, CRT, and CFF. (B) Substantial improvement of clot firmness after 2 PCs and 2 g of fibrinogen concentrate. CFF, fibrin polymerization test; CRT, rapid TEG (extrinsically and intrinsically activated test); K-time, kinetic time; LY, % lysis at 30 minutes; R-time, reaction time; MA, maximum amplitude; TEG-ACT, thromboelastography-activated clotting time.

### Identification of Patients Prone for Massive Transfusion

Massive transfusion (MT) occurs in patients who suffer from uncontrolled blood loss and require high amounts of blood transfusion over a short period of time. Both the volume of blood loss and the time frame in which blood transfusion is needed are important factors in MT. However, no universally accepted definition of MT exists so far. The most frequent definitions of MT in adults include (1) transfusion of  $\geq 10$  RBCs within 24 hours, (2) transfusion of  $>4$  RBCs in 1 hour, and (3) replacement of  $>50\%$  of the patient's total blood volume by blood products within 3 hours.<sup>27</sup> To improve survival, rapid identification of patients at risk for MT is essential. Many scores for identification of these patients have been established so far, but overall positive predictive values are still poor.<sup>28</sup> Thus, it remains challenging to identify patients at risk for MT immediately on emergency room admission. A combination of the easily available parameters, hemoglobin and base deficit, has been shown to strongly correlate with hemostatic derangement on hospital admission.<sup>29</sup> Accordingly, current guidelines recommend using a combination of hemoglobin and serum lactate and/or base deficit together with clinical assessment and shock index to identify patients at risk for MT.<sup>21</sup>

### Treatment of Trauma-Induced Coagulopathy

#### Laying the Foundation: Damage-Control Resuscitation

The concept of damage-control resuscitation—primarily adopted in the military setting—has become the standard of care in most civilian trauma centers.<sup>30</sup> This treatment strategy for severely injured patients aims to prevent further coagulopathy and is primarily based on rapid control of blood loss, restricted crystalloid therapy in conjunction with permissive hypotension, and maintenance of normothermia. As such, it goes hand in hand with early, aggressive hemostatic therapy and can be thought of as the necessary foundation for any attempt to treat TIC.

Although different hemostatic reaction steps are highly temperature-dependent, low body temperature is a common finding on emergency room admission in severely injured patients. In a large cohort of patients, Wang et al demonstrated that hypothermia at admission was independently associated with increased odds of death.<sup>31</sup> Thus, all efforts

should be made to prevent further heat loss and to actively warm hypothermic patients who are admitted to the emergency room.<sup>21</sup> Immediately after initial assessment, patients should be covered with warming devices, in particular, during further diagnostic procedures, and only prewarmed fluids should be administered.

Acidosis has been shown to interfere with hemostasis and the presence of free ionized calcium is an indispensable prerequisite for the coagulation process.<sup>13,32</sup> Thus, current guidelines recommend the correction of pH in acidotic patients and calcium administration in hypocalcemic patients.<sup>21,33</sup> However, it is important to note that correction of pH alone only plays a minor role when compared with rapid treatment of the underlying mechanism of acidosis, which is commonly hemorrhagic shock.

#### Prevention of Clot Breakdown: Tranexamic Acid

In trauma patients, hyperfibrinolysis on hospital admission has proven to be a strong predictor of poor outcome.<sup>16,17</sup> **Fig. 1A** depicts the typical TEG pattern in a hyperfibrinolytic patient. As described previously, severely shocked patients are prone to activation of profibrinolytic pathways. It has been almost 10 years since a large, multicenter, randomized trial (CRASH-2 trial) has revealed a survival benefit in trauma patients associated with the use of tranexamic acid (TXA).<sup>34</sup> The results of this trial have been confirmed in several retrospective analyses from severely traumatized patients. Morrison et al reported a 6.5% reduction in mortality in severely injured military casualties treated with TXA compared with standard therapy.<sup>35</sup> Consequently, TXA application has become the standard of care for severely injured trauma patients around the world and is highly recommended by current guidelines.<sup>21,33</sup> **Fig. 1B** shows the improvement in TEG measurements after administration of TXA. The recommended initial dose for adult patients is 1 g over 10 minutes followed by another gram over the next 8 hours. Importantly, TXA should be given as early as possible, ideally in the prehospital phase, based on a clinical decision rather than on the basis of the findings of VET.<sup>21,36</sup>

#### Provision of Consumables: Fibrinogen

Fibrinogen is the first coagulation factor to reach critically low levels in hemorrhagic shock.<sup>37,38</sup> **Fig. 2A** shows the

typical TEG pattern of a hypofibrinogenemic trauma patient. Hypofibrinogenemia in trauma is a result of multiple factors such as blood loss, fibrinogen consumption, impaired fibrinogen synthesis due to hypothermia, increased fibrinogen breakdown due to acidosis, dilution by fluids, and hyperfibrinolysis.<sup>39</sup> Low fibrinogen levels on hospital admission are strongly related to shock severity. When admitted to the emergency room, 81% of patients with a base excess less than  $-6$  mmol/L had fibrinogen levels less than 2 g/L, whereas 63% had a fibrinogen concentration less than 1.5 g/L.<sup>29</sup> Importantly, low fibrinogen levels at admission are an independent risk factor for mortality in trauma patients requiring MT.<sup>40,41</sup> Therefore, early replenishment of plasma fibrinogen levels in severe bleeding patients is recommended by current guidelines.<sup>21,33</sup> **Fig. 2B** depicts the influence of fibrinogen substitution on TEG measurements. The European guideline on management of major bleeding and coagulopathy following trauma sets a cutoff of  $<1.5$  g/L for fibrinogen substitution, whereas guidelines from the European Society of Anesthesiology on management of severe perioperative bleeding set this cutoff at 1.5 to 2 g/L. Depending on the severity of the underlying injury, 25 to 50 mg/kg of fibrinogen concentrate should be administered.<sup>33</sup> Particularly in the most severely injured patients, time to administration of fibrinogen concentrate might play a relevant role and preemptive administration has been associated with improved outcome.<sup>42</sup> A recent trial evaluating the effects of early use of fibrinogen concentrate in hemorrhagic shock could not confirm these results. It is however noteworthy that the “early” administration of fibrinogen concentrate was defined as within the first 6 hours after injury in the latter trial.<sup>43</sup>

### Alternative Provision of Consumables: Plasma Transfusion

Early transfusion of plasma in severely injured trauma patients has been associated with improved short-term survival.<sup>44</sup> In many trauma centers around the world, high-volume plasma transfusion—within the frame of a MTP—has been advocated to replace circulating volume and substitute depleted coagulation factors.<sup>6</sup> Typically, MTPs contain a fixed amount of RBCs, FFP, and PCs—predominantly in a 1:1:1 ratio.<sup>45</sup> Plasma contains all coagulation factors and inhibitors in a balanced manner. However, fibrinogen levels have been shown to be low in blood reconstituted by RBCs, FFP, and PCs.<sup>46</sup> In patients with critically low fibrinogen levels, a substantial increase in fibrinogen concentration—also when using a higher FFP:RBC ratio than 1:1—is almost impossible.<sup>47</sup> Chambers et al observed that the implementation of a MTP for trauma patients led to significantly higher plasma transfusion rates.<sup>38</sup> However, the higher amount of plasma transfused did not result in a faster normalization of fibrinogen levels. Moreover, despite following the MTP, patients did not maintain fibrinogen concentrations higher than 1.5 g/L. This is in line with an investigation by Rourke et al showing that severely bleeding trauma patients failed to maintain their fibrinogen level  $>1.5$  g/L when only plasma was transfused.<sup>48</sup> In this study, only patients who received cryoprecipitate as an additional source of fibrinogen showed fibrinogen levels higher than 1.5 g/L.

Another important shortcoming of plasma transfusion is the fact that FFP has to be thawed prior to use. Only high-volume trauma centers can afford to store prethawed universal donor AB plasma.<sup>49</sup> Thus, plasma transfusion is often associated with considerable time delays. Innerhofer et al compared a plasma-based transfusion protocol to hemostatic therapy with CFCs. The time to first hemostatic therapy was 10 minutes in the CFC group versus 50 minutes in the plasma group.<sup>12</sup> Furthermore, they were able to significantly reduce MT in the CFC group.

The use of plasma is not without several significant risks for patients: transfusion-associated circulatory overload, multiple organ failure, infections, transfusion-related acute lung injury, and acute respiratory distress syndrome have been described.<sup>50</sup> Of note, transfusion-associated adverse events are not scarce. Transfusion-associated circulatory overload has been described to occur in 6% of patients receiving allogeneic blood products and the risk of acute respiratory distress syndrome increases by 2.5% with every unit of plasma transfused.<sup>51</sup> Although current guidelines mention ratio-driven FFP:RBC transfusion as one of the two approaches for the initial management of bleeding trauma patients, they recommend a goal-directed management in the further course.<sup>21</sup> Furthermore, they specifically recommend against the use of FFP in patients without major bleeding and for the correction of low fibrinogen levels.

### Hitting the Accelerator: Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) contain either three (factor II, IX, and X) or four (additionally, factor VII) of the vitamin K-dependent coagulation factors and strongly augment thrombin generation.<sup>47</sup> Cardenas et al showed a correlation between the measurement of impaired thrombin generation and higher transfusion requirements as well as higher mortality.<sup>52</sup> Thus, PCC is increasingly used in an attempt to correct TIC. However, even without administration of PCC, trauma patients may exhibit excessive thrombin generation that primarily results from tissue damage and the consecutive release of procoagulants.<sup>53</sup> Thus, the extent of thrombin generation varies interindividually depending on the type and site of injury. Elevated thrombin generation has been shown to be an independent predictor of venous thromboembolic events in trauma patients.<sup>54</sup> Urgent reversal of vitamin K antagonists in bleeding patients is a clear and labeled indication for the use of PCC, which appears to have a favorable safety profile with regard to thromboembolic events in this context.<sup>55,56</sup> However, reliable data on the safety profile of PCC used in bleeding trauma patients without intake of vitamin K antagonists are scarce and several preclinical studies suggest a possibly increased risk of thromboembolic events due to an imbalance of pro- and anticoagulant proteins.<sup>57</sup> A recently published meta-analysis found a range of 0 to 41% for the rate of thromboembolic events after administration of PCC in bleeding patients with no prior intake of anticoagulants.<sup>58</sup> Importantly, the 15 included studies carried a relevant risk of bias with limited quality of the published data.

In most published studies outside the context of vitamin K antagonist reversal, PCC was used in conjunction with either FFP or fibrinogen concentrate. Zeeshan et al reported that the use of four-factor PCC as an adjunct to FFP was associated with improved survival and reduction in transfusion requirements compared with FFP alone in severely injured patients.<sup>59</sup> Interestingly, they observed no difference in the rates of thromboembolic events between the two groups. This latter finding is of particular interest because a recent study revealed that early PCC treatment in trauma patients resulted in a sustained increase of endogenous thrombin potential over a period of 4 days compared with patients who were treated with fibrinogen concentrate only.<sup>60</sup> Using it in a goal-directed fashion, PCC is usually administered at a later stage when—despite administration of fibrinogen as the first-line treatment—VET shows persistent signs of prolonged coagulation initiation.<sup>12</sup> Schöchl et al found a significant reduction of allogeneic blood transfusion in trauma patients treated with a combination of fibrinogen concentrate and PCC compared with a matched cohort of patients treated with FFP.<sup>61</sup> According to current guidelines, PCC administration in trauma patients who are not on vitamin K antagonists is recommended when VET shows signs of prolonged coagulation initiation despite the presence of normal fibrinogen levels.<sup>21</sup> However, since clotting times in VET are not sensitive to reduced levels of anticoagulant proteins (e.g., antithrombin), their use as a surrogate parameter for the administration of PCC still remains a matter of debate.<sup>57</sup>

### Stabilizing the Clot: Factor XIII

The main role of factor XIII is cross-linking fibrin to stabilize clot firmness and prevent fibrinolysis.<sup>62</sup> Severe hemorrhage in trauma patients seems to result in relevant reductions of FXIII concentration. Theusinger et al reported that in severely injured trauma patients, FXIII levels decreased by almost 20% from the time of injury to hospital admission.<sup>63</sup> Reduced factor XIII levels have been associated with increased intra- and postoperative bleeding.<sup>64,65</sup> However, specific trials investigating the possible association of factor XIII levels and bleeding in trauma patients are missing. If a CFC-based approach for the treatment of trauma patients is used, it needs to be remembered that little factor XIII is delivered. Therefore, current guidelines suggest the monitoring of factor XIII in bleeding trauma patients and administration of factor XIII concentrate if levels fall <30%.<sup>21,33</sup>

### Adding Cells: Platelet Transfusion

As described previously, platelet dysfunction—irrespective of long-term medication—is a common finding in severely injured patients. Thus, some authors suggest early PC transfusion in trauma patients to overcome trauma-induced platelet dysfunction.<sup>66,67</sup> However, the value of pre-emptive PC transfusion to overcome platelet dysfunction remains controversial.<sup>68</sup> Henriksen et al investigated the effect of early platelet transfusion in severely injured patients. Both platelet count and function decreased from emergency room admission to intensive care unit admission. Interestingly, reductions in platelet

function—measured by whole blood aggregometry—were most pronounced after transfusion of PC.<sup>69</sup> Additionally, reduced platelet aggregability has been shown when reconstituting blood in MTP-typical ratios of RBCs, FFP, and PCs.<sup>70</sup> A meta-analysis investigating the effect of higher PC:RBC ratio transfusion in trauma could not show any survival benefit.<sup>71</sup> Current guidelines suggest the monitoring of platelet function by point-of-care-applicable methods in addition to standard coagulation tests and VET if platelet dysfunction is suspected.<sup>21</sup> However, particularly in bleeding patients, point-of-care-available monitoring of platelet function carries several drawbacks, e.g., the unreliability of results in thrombocytopenic patients. According to current guidelines, platelet transfusion in bleeding patients is recommended when platelet count drops to <50,000/ $\mu\text{L}$ .<sup>21,33</sup> If blood loss continues despite adequate therapy or in patients with traumatic brain injury, a higher cutoff for transfusion (100,000/ $\mu\text{L}$ ) is advised. **–Fig. 3(A, B)** shows TEG measurements in a thrombocytopenic bleeding trauma patient before and after the transfusion of PCs, together with administration of fibrinogen.

## Thromboprophylaxis after Trauma-Induced Coagulopathy

TIC and its treatment lead to a pronounced prothrombotic state in patients who survive the initial hit of hemorrhage. In trauma patients who survive more than 3 days, pulmonary embolism is the third leading cause of mortality.<sup>72</sup> Therefore, the earliest possible initiation of thromboprophylaxis is of paramount importance in trauma patients. Pharmacologic thromboprophylaxis possibly augments a pre-existing bleeding risk, whereas mechanical methods can be used in the majority of patients. With regard to pharmacologic thromboprophylaxis, low-molecular-weight heparin has been shown to carry several benefits in comparison to unfractionated heparin.<sup>73</sup> Current guidelines recommend the use of intermittent pneumatic compression in immobile trauma patients while at risk for bleeding.<sup>21</sup> Once bleeding has been controlled, mechanical means should be combined with pharmacologic thromboprophylaxis within 24 hours. Particularly in patients with traumatic brain injury, the timing of initiation of pharmacological thromboprophylaxis represents a clinical challenge. A recent interdisciplinary consensus statement from Austria recommends initiating pharmacological thromboprophylaxis with low-molecular-weight heparin 24 hours after injury in patients with radiologically and clinically stable traumatic brain injury.<sup>74</sup>

## Conclusions

TIC does not represent a universal phenotype. In contrast, many aspects play relevant roles in this complex hemostatic disorder. Therefore, from a pathophysiological point of view, individualized and goal-directed coagulation management holds many advantages over a purely ratio-driven hemostatic therapy. **–Table 1** summarizes advantages and disadvantages of both treatment strategies. However, large-scale studies to prove a clinical benefit of one concept over the

**Table 1** Summary of the advantages and disadvantages of FFP- and CFC-based hemostatic treatment regimens

FFP	CFC
<p>Advantages</p> <ul style="list-style-type: none"> <li>• Delivery of all coagulation factors and inhibitors</li> <li>• Potential glycocalyx protection</li> <li>• Volume replacement</li> </ul> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>• Low concentration of fibrinogen</li> <li>• Higher risk of infection</li> <li>• Higher risk of ARDS</li> <li>• Risk of immunosuppression</li> <li>• Risk of TACO</li> <li>• Risk of TRALI</li> <li>• Need for cross-matching</li> <li>• Need for thawing prior to transfusion</li> </ul>	<p>Advantages</p> <ul style="list-style-type: none"> <li>• Well-defined concentration of the coagulation factors</li> <li>• Faster availability</li> <li>• Potentially better safety profile</li> </ul> <p>Disadvantages</p> <ul style="list-style-type: none"> <li>• Risk of thromboembolic complications</li> <li>• Higher expenses</li> <li>• Unavailability in some parts of the world</li> <li>• Off-label use in some parts of the world</li> </ul>

Abbreviations: ARDS, acute respiratory distress syndrome; CFC, coagulation factor concentrate; FFP, fresh frozen plasma; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury.

other are still missing. Following the rules of damage-control resuscitation and early administration of TXA are basic requirements of treating TIC that apply to all bleeding trauma patients. Fibrinogen is the first coagulation factor which reaches critically low levels in trauma patients and should be replaced early. If FFP is used for the initial management of trauma patients, high-volume transfusion is necessary. The role of PCC in bleeding trauma patients outside vitamin K reversal is still a matter of debate. Substitution of factor XIII might play a role, especially when a coagulation-factor-based treatment approach is followed. The exact role of PC transfusion still remains unclear. Due to the high risk of thromboembolic events, mechanical and pharmacologic means of thromboprophylaxis should be applied as early as possible in trauma patients.

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