Bruno Riou, M.D., Ph.D., Editor

Case Scenario: Management of Trauma-induced Coagulopathy in a Severe Blunt Trauma Patient

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COAGULOPATHY-RELATED diffuse bleeding, which is complex and difficult to manage, is observed in around 20–30% of all severe trauma patients.[1,2] Its management remains critical to patient survival; however, the optimal approach to treatment remains a matter of debate.[3] Early recognition and adequate aggressive management of this *Trauma-induced Coagulopathy* (TIC) has been shown to substantially reduce mortality and improve outcomes in severely injured bleeding patients.[3,4] To date, the use of fresh frozen plasma (FFP) is an integral part of massive transfusion protocols in most trauma centers and its early use has been advocated.[2–4] Moreover, the use of FFP is associated with well-established risks such as multiple organ failure or transfusion-related acute lung injury (TRALI), and there is insufficient evidence to guide the optimal use of this resource.[5–7] To overcome these weaknesses, several European authors advocate the use of fibrinogen concentrates and/or prothrombin complex concentrates (PCC),[4,8] with preliminary clinical studies suggesting an increased efficiency based on biological parameters and a reduction of mortality.[9,10] Hence, recent European guidelines recommend the use of fibrinogen concentrates and suggest increasing the fibrinogen target level to 1.5–2.0 g/l.[3]

The purpose of this case scenario is to identify key points essential for the treatment of TIC.

Case Report

A 26-yr-old man, without significant medical history and weighting around 100 kg, sustained a severe motorbike collision. He was initially admitted to a general hospital after being transported by a fire rescue team. On the first clinical examination, the patient was hemodynamically stable and alert. X-rays showed multiple fractures (open humerus and closed femur diaphysis, wrist). A whole-body computed tomography showed a traumatic rupture of the aortic arch, a bilateral pulmonary contusion with small hemothorax, a renal contusion, and multiple pelvic fractures (left acetabulum, and bilateral inferior and superior ramus of the pubic bone) without contrast extravasation. Progressively the patient became hemodynamically unstable, 3 units of packed erythrocytes were given together with 1 g of tranexamic acid (TXA, 10 mg/kg) and 1000 ml hydroxyethyl starch (Voluven®, Fresenius, Germany). Pelvic stabilization was done with a pelvic belt (SAM Pelvic Sling II, SAM Medical Products, Tualatin, OR). General anesthesia was induced after rapid sequence induction, with etomidate and succinylcholine, and mechanical ventilation was started. General anesthesia was maintained with an association of midazolam and sufentanyl. The patient was therefore sent to our trauma center. During helicopter transport, hemodynamic control had necessitated both fluid infusion (normal saline and Voluven® [1000 ml]) and continuous infusion of norepinephrine (1 mg/h). One gram of TXA was also injected during the transport.

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At admission, patient's hemodynamic status was as follows: systolic blood pressure, 110 mmHg; heart rate, 100 beats/min. Because of the absence of severe traumatic brain injury, norepinephrine was immediately decreased to 0.5 mg/h to reduce blood loss. The initial admission hemoglobin was 9.7 g/dl and the International Normalized Ratio determined by the Coaguchek® (Roche, Meylan, France) was 0.9. Despite the results of the Coagucheck®, rotational thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) showed a typical pattern of coagulopathy with decreased clot amplitude on EXTEM (fig. 1A) and FIBTEM (fig. 1B), suggesting, respectively, an increase in prothrombin time (PT) and a decrease in fibrinogen level. Twenty U/kg of PCCs (2000 U, Kanokad®, LFB Laboratoire, Courtaboeuf, France) and 45 mg/kg of fibrinogen (4.5 g, Clottafact®, LFB Laboratoire) were therefore administered to the patient and resulted to the correction of coagulation abnormalities on EXTEM (fig. 1C) and FIBTEM channels (fig. 1D).

Laboratory parameter analysis from blood sample drawn at admission subsequently confirmed the coagulopathy (fibrinogen, 1.1 g/l; PT, 18 s; platelets, 102,000/ml) which was associated with a moderate metabolic acidosis (lactate, 3.1 mM; base excess, −6.3). Interestingly, it should be observed that the results of blood sample analysis done at admission were available only after completion of the second ROTEM® analysis. As observed with the ROTEM® analysis, hemostasis parameters improved with the administration of factor concentrates (fibrinogen, 2.2 g/l; PT, 14.8 s).

The patient was taken to the operating room for plate fixation of left humerus and intramedullary femur nailing. Two orthopedic surgeons did the procedures simultaneously to reduce surgery time, as part of the damage control surgery principle. During orthopedic surgery, an additional 2 packed erythrocytes units were given together with 669 ml of blood saver restitution (Cell Saver 5, Haemonetics, Braintree, MA) and 1 g of TXA. Then, after a period of stabilization and rewarming in the postanesthesia care unit, the patient was sent to the cardiac surgery unit and a stent was inserted in the aortic arch (Medtronic Valiant, Santa Rosa, CA).

No platelet administration or additional blood product was necessary during the first 24 h. Platelet count remained always up to 100,000/ml. Blood gas analysis which was

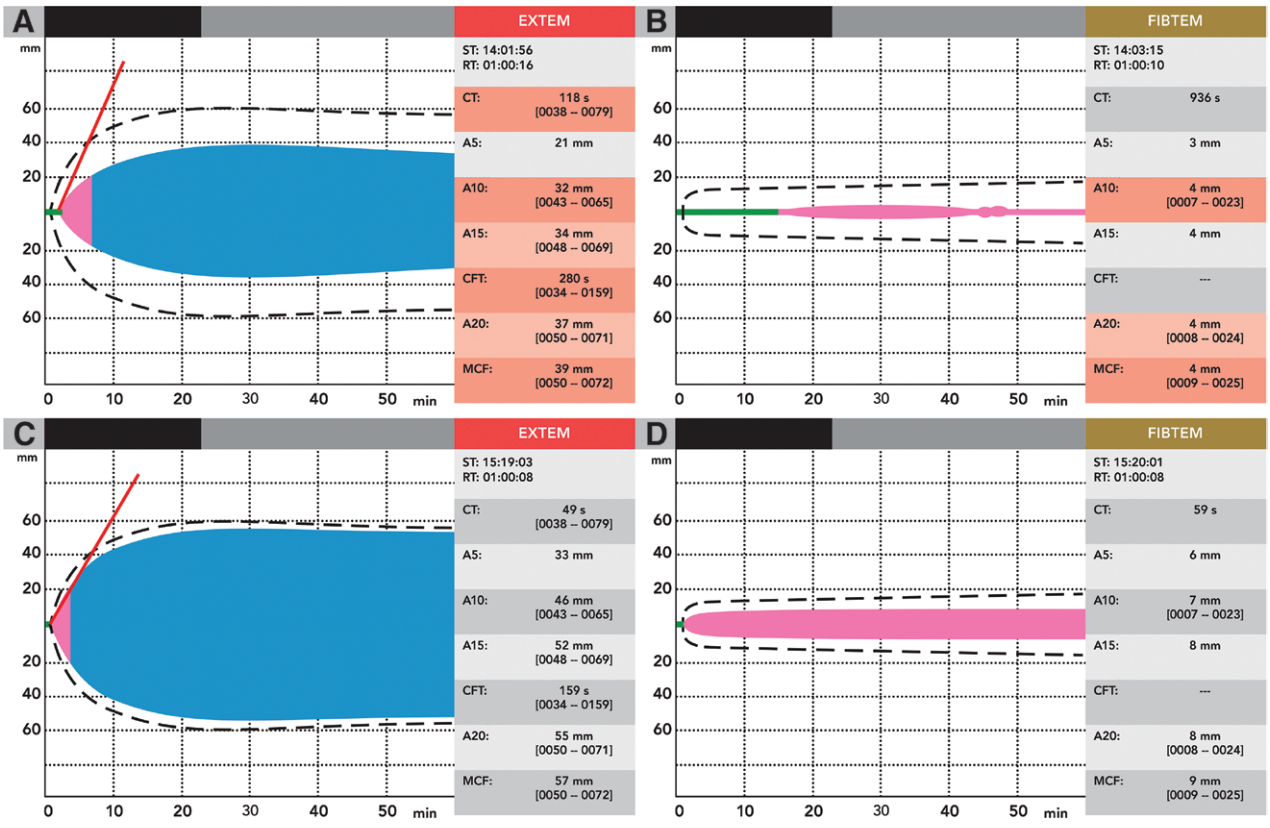

Fig. 1. Rotational thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) tracing of the patient described in the case section, depicting coagulopathy as attested by an increase in the clotting time (CT) as well as a decrease in the clot amplitude at 5 (A5), 10 (A10) and 15 min (A15), in the EXTEM (*A*) and FIBTEM (*B*) channels. Normal values are indicated in the brackets and *dashed lines* demonstrate the limits of a normal tracing. Coagulopathy was confirmed by standard laboratory values and was seen to be improved after the administration of fibrinogen and prothrombin complex concen Tem International GmbH, Munich, Germany) trates, both on ROTEM® (EXTEM, *C* and FIBTEM, *D*) and standard laboratory tests, as detailed in the case section. Clotting time (CT), clot formation time (CFT), A (clot amplitude) at 5 (A5), 10 (A10), 15 (A15), and 20 min (A20), maximum clot firmness (MCF). RT = running time; ST = standing time.

repeated by 2 h during the first 12 h showed that metabolic acidosis remained moderate (maximum lactate level, 5.0 mM and maximum base excess, −8.2).

Thromboembolism prophylaxis was started on day 2 with enoxaparin (40 mg/day). Extubation was done on day 5 and he was transferred to the ward the days after. No thromboembolic complication was observed during the course. The patient was finally discharged from the hospital to a rehabilitation care unit on postinjury day 28.

Discussion

Pathophysiology of TIC

Severe trauma with direct injury to major blood vessels and organs can induce hypovolemic shock and exsanguination if treatment is not provided immediately. The genesis of TIC is complex and multifactorial.[1,2,11] It involves initially an endogenous coagulopathy (*acute traumatic coagulopathy*) resulting from the combination of tissue trauma and systemic hypoperfusion, characterized by systemic anticoagulation and hyperfibrinolysis, putatively through endothelial activation of protein C.[12,13] Acidosis and hypothermia with dilution induced by fluid resuscitation contribute to a further impairment of coagulation that will exacerbate the acute traumatic coagulopathy, resulting in TIC (fig. 2).[2,11,14]

Early Diagnosis and Point-of-care Devices

One of the key challenges during the management of trauma remains the early recognition of TIC.[2] Urgent diagnostic and therapeutic decisions are often necessary to avoid multiorgan failure resulting from prolonged hemorrhagic shock.[3,4] In addition to the vital signs (arterial pressure and heart rate) and visual estimation of blood loss, these decisions often require serial measurements of blood coagulation parameters to react promptly to persistent or recurrent bleeding. Clinically, the treatment of coagulopathic bleeding is compromised by current coagulation monitoring test that can take from 45 to 60 min.[15] The entire blood volume of the bleeding patient may have been exchanged several times during this time interval, making the results of the laboratory test obsolete. Different point-of-care devices have been developed to rapidly determine PT (and/or International Normalized Ratio, Coaguchek®, INRatio® [Alere, San Diego, CA]),[12,15] or to describe viscoelastic continuous profiles of whole blood clot formation by utilizing the ROTEM® (Tem International GmbH) or the TEG® (Haemonetics Corp.; fig. 3).[16,17] Point-of-care PT can help in the triage process; however, the potential for false-negative results remains, as described in the case section.[12,15] ROTEM® and TEG® both utilize the principles of thrombelastography. The primary difference between instruments is that the TEG® operates by moving a cup filled with blood in a limited arc. This blood engages a pin/wire which transduces the increase in viscosity as clot formation occurs. The ROTEM®, on the contrary, has an immobile cup containing blood. Here, the pin/wire oscillates and captures the changing viscosity with clotting.[11] The computer-processed signal from either thrombelastography is presented as a tracing of clot formation (figs. 3 and 4). The two instruments can identify accurately coagulopathic patients early, often within 5 min.[12,17] Hence, in coagulopathic patients, ROTEM® analysis shows that 5 min after activating coagulation with tissue factor (EXTEM) or inhibiting platelets with cytochalasin D (FIBTEM), clot amplitude is decreased and coagulation time is increased (fig. 1) compared to a normal tracing (fig. 4). Good correlation has been shown between

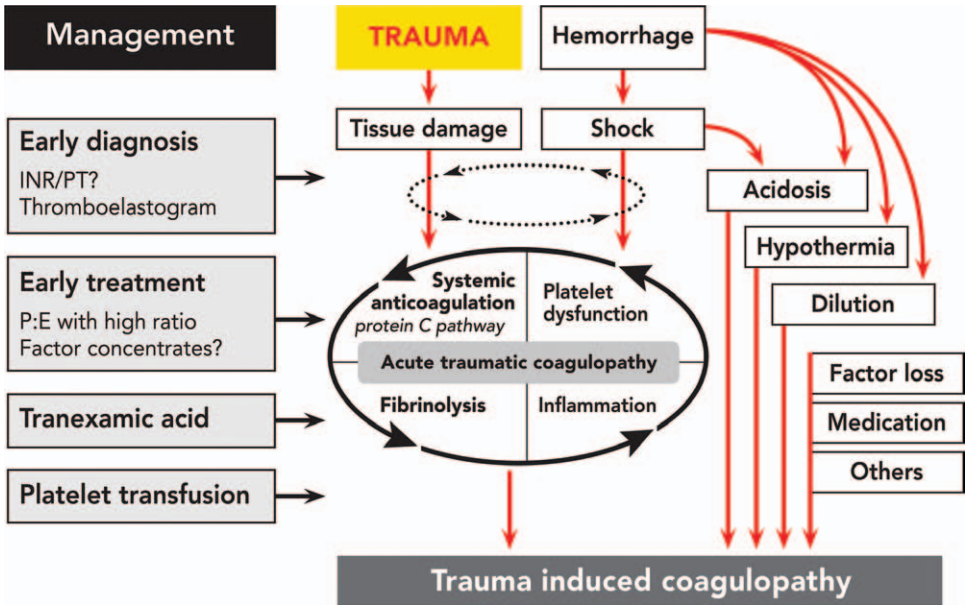

Fig. 2. Mechanisms of trauma-induced coagulopathy. INR = International Normalized Ratio; PT = prothrombin time.

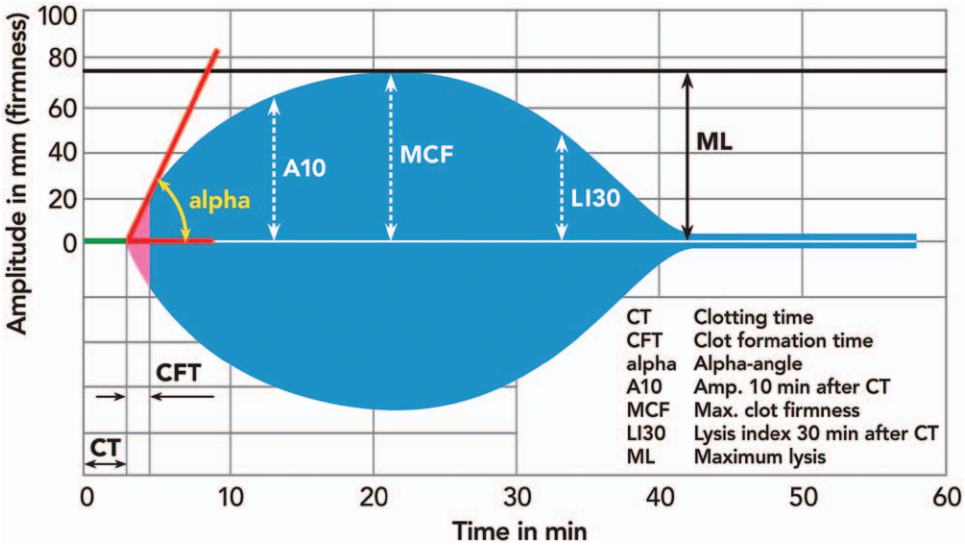

Fig. 3. Schema depicting the main parameters of the rotational thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) tracing, note the clot amplitude (A10 and MCF) and the CT.

standard coagulation parameters and ROTEM® or TEG® parameters; for example, between the clot amplitude at 15 min (EXTEM) and the PT or the fibrinogen level and the amplitude of the clot (FIBTEM) at 10 min.[16] ROTEM® and TEG® may also be effective in predicting the need for massive transfusion.[12,17]

In addition to global coagulation parameter monitoring, it is now also possible with the ROTEM® or the TEG® to specifically target coagulation defects that have been traditionally difficult to quantify at the bedside, including hyperfibrinolysis (fig. 5), or a fibrinogen deficit.[18,19] However, it should be mentioned that according to a recent report, the TEG® (using kaolin) was not able to distinguish coagulopathies caused by dilution from that caused by thrombocytopenia.[20]

What Are the Goals of TIC Management?

TIC is observed in up to 30% of severe trauma patients at admission in the trauma bay and increases mortality.[1,2] Early correction of TIC is, therefore, an important goal of the resuscitation process together with the correction of the other components of the lethal triad (*i.e.*, hypothermia and acidosis). Recent European guidelines emphasize the need for early diagnosis of TIC together with rapid correction through early replacement of FFP and platelets, with specific recommended targets for hemoglobin, platelets, PT, and fibrinogen (table 1).[3]

Transfusion-based Strategy: FFP and Platelet Concentrates

Platelet Transfusion. Regarding platelet transfusion, European guidelines recommend that platelets be administered to maintain a platelet count above 50×10^9/l and suggest maintaining a platelet count above 100×10^9/l in patients with multisystem trauma who are severely bleeding.[3] Recent studies have concluded that platelet transfusion decreases mortality during massive transfusion and that a high ratio of platelet to packed erythrocytes was correlated with improved survival.[21]

Table 1. Some of the European Guidelines for the Management of Coagulopathy[3]

Recommendation
R22: Monitoring and measures to support coagulation should be initiated as early as possible
R5: Patients presenting with hemorrhagic shock and an identified source of bleeding should undergo an immediate bleeding control procedure unless initial resuscitation measures are successful
R12: INR, aPTT, fibrinogen, and platelets should be employed to detect posttraumatic coagulopathy. INR and aPTT alone should not, but thrombelastometry may assist in characterizing the coagulopathy and in guiding hemostatic therapy
R11: Both serum lactate and base-deficit measurements should be employed to estimate and monitor the extent of bleeding and shock
R19: Crystalloids should be applied initially to treat the bleeding trauma patient. Hypertonic solutions may be considered during initial treatment. The addition of colloids may be considered within the prescribed limits for each solution in hemodynamically unstable patients
R20: Early application of measures to reduce heat loss and warm the hypothermic patient should be employed to achieve and maintain normothermia
R23: Ionized calcium levels should be monitored during massive transfusion. Calcium chloride should be administered during massive transfusion if ionized calcium levels are low or electrocardiographic changes suggest hypocalcemia

aPTT = activated partial prothrombin time; INR = International Normalized Ratio.

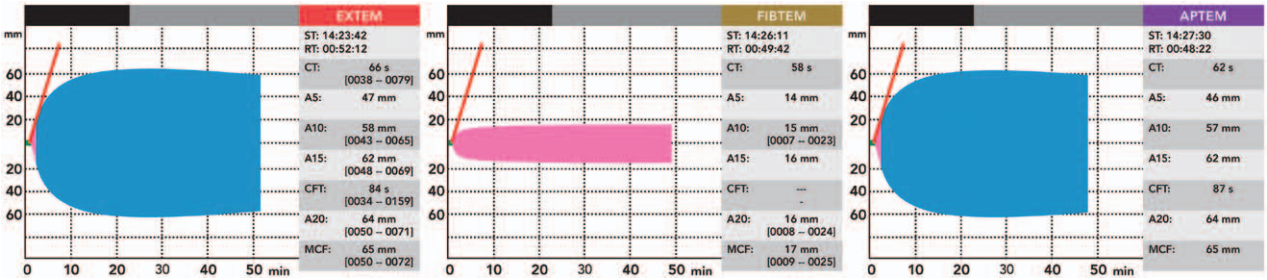

Fig. 4. Example of a patient admitted after a motor vehicle crash. On rotational thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) analysis, a normal pattern (clotting time [CT] and clot amplitude in the normal range) was observed after addition of tissue factor (EXTEM), cytochalasine D (FIBTEM), and aprotinin to the EXTEM (APTEM). Normal hemostasis was confirmed later by standard laboratory analysis (activated partial thrombin time, 28.8s; prothrombin time, 14.7s; International Normalized Ratio, 1.13; fibrinogen, 3.0 g/l). Clot formation time (CFT); A (clot amplitude) at 5 (A5), 10 (A10), 15 (A15), and 20 min (A20); maximum clot firmness (MCF).

Plasma Transfusion. Recent military and civilian experiences indicate that for patients requiring massive transfusion, an initial plasma (P) to erythrocytes (E) unit ratio (P:E ratio) approaching 1:1 is independently associated with improved survival.[2–5,22] However, most of the data are derived from retrospective studies that have missing data and analytical biases, limiting the conclusions that can be drawn from these results.[6,23] The most important source of bias comes from the impact of survival because patients who survive are more likely to receive FFP than patients who die, creating an artifactual association of survival with higher P:E ratios.[6,23] A very recent work, however, suggests that the observed mortality benefit associated with high component transfusion ratios is unlikely owing to survivor bias and that early attainment of high transfusion ratios may significantly lower the risk of mortality in patients receiving massive transfusion.[22] These data support the importance of immediate recognition of patients with TIC, patients who can then benefit from an early and massive transfusion.

FFP administration exposes patients to side effects, including increased susceptibility to infection, transfusion-associated circulatory overload, transfusion-related immunomodulation, and TRALI.[5,6] In the United Kingdom, the *Serious Hazards of Transfusion* (SHOT) database documented 162 cases of TRALI over an 8-year study period including 36 deaths and 93 cases of major morbidity, and identified TRALI as the most prominent cause of transfusion-related morbidity and mortality.[24] FFP from female donors has been particularly implicated in the pathogenesis of TRALI, and antileukocyte antibodies are found in 15–17% of female donors and 25% of multiparous donors but are rare in male donors.[25] To reduce this risk, blood centers have adopted policies to produce plasma components primarily from male donors.[26] Increasing the aggressive use of emergency plasma replacement also leads to the transfusion of ABO nonidentical units. These adverse events can be observed in all patients receiving FFP, and not only in those receiving a massive transfusion.[27] In trauma patients specifically, a similar negative outcome was seen with exposure to ABO nonidentical plasma being associated with increasing complications including acute respiratory distress syndrome and sepsis.[28]

Acting quickly is critical because coagulopathy appears immediately after trauma at the site of the injury.[29] The efficacy of plasma transfusion plays out in the first few hours of resuscitation, and there is a temporal relationship between aggressive plasma transfusions and survival.[30] Reducing the delay to transfusion requires the implementation of massive transfusion protocols, which incorporate local agreements with blood banks and trauma packs. As FFP is not immediately available due to the thawing process, other solutions have to be considered.[31] Thawed AB group or low titer group A plasma, which can be stored for 5 days, and freeze-dried plasma allow immediate delivery of plasma in the first trauma pack, followed by immediate thawing of conventional FFP for the subsequent packs.[26,31] Some high-volume centers will maintain a thawed plasma bank, allowing immediate access to group-specific plasma.

With the emergence of new data supporting the use of high P:E:Platelet ratios, the content of these packs will also need to be reorganized in order to provide the best possible resuscitation to these critically injured patients within the golden hour. The goal of increasing the P:E:Platelet ratio is to use component therapy to administer products roughly equivalent to whole blood in order to rapidly reverse or avoid development of coagulopathy during the initial resuscitation of an exsanguinating patient. Implementation of massive transfusion protocols, rather than treatment based on the case-by-case discretion of each provider, leads to early delivery of blood products which may result in a more rapid control of coagulopathy. The use of a massive transfusion protocol had been linked to a decrease in blood product use and mortality with minimal wastage of blood products.[32]

As immediate delivery of blood products is challenging, another strategy based on immediately available factor concentrates has been suggested.

Concentrates-based Strategy: Fibrinogen and PCC

A more selective approach to the correction of TIC has been suggested by a few European teams, using specific

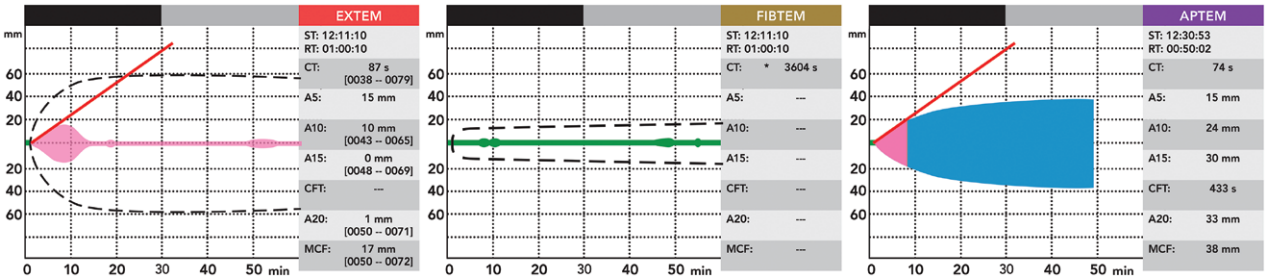

Fig. 5. Patient admitted after a motor vehicle crash and cardiac arrest (different from the one described in the case section). Rotational thromboelastometry (ROTEM®, Tem International GmbH, Munich, Germany) analysis (EXTEM) showed a typical pattern of hyperfibrinolysis with an important reduction in clot amplitude and an immediate breakdown of the clot. After addition of aprotinin (antifibrinolytic agent, APTEM), the clot improved and became stable. In parallel, the FIBTEM was completely flat indicating a severe fibrinogen deficiency. Coagulopathy was confirmed by standard biology (activated partial thrombin time, 122 s; prothrombin time, 24 s; International Normalized Ratio, 2.1; fibrinogen, 1.1 g/l). Normal values are indicated in brackets and *dashed lines* demonstrate the limits of a normal tracing. Clotting time (CT); clot formation time (CFT), A (clot amplitude) at 5 (A5), 10 (A10), 15 (A15), and 20 min (A20); maximum clot firmness (MCF).

coagulation factor concentrates according to deficiencies identified by ROTEM®.[2,4,9] Indeed, fibrinogen concentrates and PCC are already licensed in several European countries for the treatment of congenital and acquired deficiencies and have previously been given with success to trauma patients,[8,10,33,34] and in other settings.[35]

Fibrinogen Concentrate. Fibrinogen is a key protein for hemostasis and clot formation.[36] During trauma, fibrinogen metabolism is altered by hemorrhage and acidosis (accelerating fibrinogen breakdown), hypothermia (inhibiting fibrinogen synthesis), and hydroxyethyl starch infusion (abnormalities of fibrinogen polymerization).[11,35] Fibrinogen is, therefore, one of the first blood components to decrease to suboptimal levels early during the course of trauma coagulopathy.[29,37] Thus, fibrinogen supplementation is recommended in patients with massive bleeding to maintain plasma fibrinogen levels above 1.5–2.0 g/l.[3] Fibrinogen may be administered as a part of a massive transfusion protocol (*e.g.*, systematic administration of 3 g (or 50 mg/kg) after each 6 erythrocytes units), based on standard laboratory results or guided by thromboelastometry/graphy as a part of early goal-directed coagulation management.[2,4,10] Fibrinogen contributes to hemorrhage control by increasing clot firmness.[14]

PCC. The use of PCC has been studied recently for use in trauma resuscitation.[4,8,22,38] PCC is a concentrated formulation of vitamin K-dependent clotting factors (II, IX, and X), designed to treat hemophilia B and widely used to reverse the effect of vitamin K antagonists.[39] In the United States, these are referred as three-factor PCCs (*e.g.*, Profilnine® SD, BD Pharma, Columbia, SC; Bebulin® VH, Baxter Healthcare Corporation, Westlake Village, CA), whereas in Europe, four-factor PCCs, with additional factor VII (Kanokad®, LFB Laboratoire; Octaplex®, Octapharma, Boulogne, France; Beriplex® P/N, CSL Behring, Paris, France), are available. Experimental and clinical data suggest that PCCs may be effective in reversing TIC; however, high level of evidence is still lacking and thus, it is not possible to support their routine use in clinical practice.[3,8,40] However, it should also be mentioned that all of the published data showing a benefit with the use of PCCs in trauma hemorrhage has been done with four-factor PCCs. Use of factor concentrates in the setting of trauma hemorrhage is attractive because they are immediately available, eliminating the time delay associated with cross-matching, thawing, and transfusion of FFP. They may also be beneficial by reducing transfused volumes and reducing the potential harmful risks associated with allogeneic blood transfusions.[10] Moreover, the PCC manufacturing process includes at least one step of viral reduction or elimination, which minimizes the risk of transmitting infectious agents. Pharmacovigilance data from the World Federation of Hemophilia‖ have demonstrated that no cases of proven infection transmission have been reported with PCC use.[41] According to an *in vitro* model, PCC has an important effect on thrombin generation but acts only modestly on clot firmness.[14] Use of PCC has been described in association with fibrinogen concentrates with the administration of both products guided by the ROTEM® as part of an early goal-directed coagulation management protocol (fig. 1).[4,9,10] With this goal-directed strategy, Schochl *et al.*[9] have demonstrated the possibility of treating TIC without FFP with favorable outcomes. In a second retrospective study, they have suggested that ROTEM®-guided hemostatic therapy may reduce the exposure of trauma patients to allogeneic blood products, a laudable goal.[10] These data are very promising and support further randomized trials which are necessary for incorporating the use of PCC into routine practice. PCC carries its own risks. Thromboembolic complications are the major risk of PCC therapy.[41] The thromboembolic risk also depends on the composition of the PCC and, in particular, the balance between activators and inhibitors, the absence of activated factors, and the presence of heparin or antithrombin, protein C, and protein S.[39,42] Significant improvements in PCC preparations have been made in the last 20 years. Measures have been taken against the thrombogenic potential of these drugs. Therefore, the composition

‖ Available at: www.wfh.org. Accessed January 22, 2013.

of PCCs should meet the precise criteria recommended by the European Medical Agency# such as the presence of antithrombin in addition to heparin, no overloading with factor II and factor X, and low factor VII and factor IX potencies.[43] An increase in the risk of thromboembolism and disseminated intravascular coagulation has been recently suggested in an experimental model of hemorrhagic shock when high doses (50 U/kg) of PCC were used.[42] The imbalance between pro- and anticoagulant factors may be responsible for these effects that were not observed when standard doses of 35 U/kg were used. Furthermore, the long-term safety of PCC has never been assessed.

At this time, the most effective strategy for the management of TIC remains unclear.[4] It is compulsory that the relative contributions of coagulation factor replacement and early diagnosis of factor deficiency are prospectively assessed.

Use of TXA

Hyperfibrinolysis is frequent in severe trauma and is related to the extent of injury and severity of shock.[44] In response to a trauma, a physiologic fibrinolysis is observed, which may become pathological in some cases (hyperfibrinolysis, fig. 5). Antifibrinolytic therapy, using agents such as TXA, is presumably effective in preserving a weak fibrin clot that is otherwise susceptible to plasmin. However, beyond clot lysis, inhibition of plasmin may be beneficial because plasmin may also play a role in coagulation through the transformation of prothrombin to thrombin, activation of fibrinogenolysis, and the cleavage of receptors on platelets.[45] In addition, proinflammatory effects have also been reported with plasmin activation, which therefore is susceptible to multiple organ failure or infection.[45]

Tranexamic acid is a synthetic antifibrinolytic derivative of the aminoacid lysine that inhibits fibrinolysis by blocking the lysine-binding sites on plasminogen. It reduces blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery and has been used for more than 25 years for reducing blood loss in elective surgery.[46,47] In trauma, the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 trial has recently demonstrated that if given early (<3 h), TXA reduces mortality in trauma patients.[48,49] Many of the included patients were not severely injured or bleeding, making the interpretation of the study findings difficult to put into context. However, with randomization of more than 20,000 patients in 40 countries, this double blind, placebo-controlled trial established TXA as an effective treatment for traumatic hemorrhage. It should be observed that the reduction of mortality related to bleeding was less than 1% (4.9 *vs.* 5.7%), and there were no statistically significant differences in transfusion volumes between groups, suggesting beneficial effects of plasmin inhibition other than on fibrinolysis, as suggested earlier.[49] In a recent study, Morrisson *et al.* described the use of TXA in a population of wounded soldiers in Afghanistan. Although the study was retrospective, the authors found in patients receiving at least one unit of erythrocytes an independent association of TXA with survival on multivariate analysis.[50] Moreover, the benefit was more prominent in patients requiring massive transfusion. In addition to the findings of these studies, TXA is inexpensive and in these trials demonstrated a neutral thromboembolic complication rate. Thus, the risk/benefit ratio is in favor of TXA, when given during the first 3 h after a trauma, ideally during the prehospital phase.

Recombinant Factor VIIa

Recombinant factor VIIa (rFVIIa), a potent procoagulant agent approved for controlling or preventing bleeding in hemophilia patients with inhibitors, has been widely used, off-label, for trauma patients.[51] However, its efficacy with respect to mortality outcomes has never been proven.[52] It is also highly expensive and may expose treated patients to an increased risk for thromboembolism.[53] A Cochrane review conducted by Stanworth *et al.*[54] who evaluated 13 trials demonstrated that the administration of rFVIIa was shown to reduce blood product administration (relative risk: 0.85) with an elevation of the thromboembolic risk (relative risk: 1.25). Therefore, rFVIIa should be considered relatively late in the management of refractory life-threatening hemorrhage, primarily in blunt trauma, when all conventional measures to control bleeding have failed (including embolization and surgery) and is not a substitute for the aggressive best-practices use of blood components.[3]

Damage Control Concept and Others Goals

The first goal of this concept is to stop bleeding by the way of surgical intervention or angioembolization. As severe trauma patients do not tolerate prolonged operative procedures, effective hemorrhage control is accomplished with the concept of damage control surgery (abbreviated initial surgery) by applying temporary, yet life-saving surgical procedures immediately after injury. Definitive planned surgery is performed after the patient has been stabilized in the intensive care unit.[4]

The second step is reversing hypoperfusion to reduce further cellular and organ injury. Permissive hypotension was suggested to limit fluid infusion and then to reduce dilutional coagulopathy and hypothermia as well as all the events linked to aggressive resuscitation with saline-based regimens including abdominal compartiment syndrome, acute respiratory distress syndrome, multiple organ failure, and mortality. However, if the extend and duration of hypotension and perfusion that can be tolerated remain unclear, a target systolic arterial pressure of 90 mmHg is usually recommended, in the absence of severe brain injury, until bleeding is controlled.[3]

The third goal is to correct the factors, which impair the TIC, including hypothermia, acidosis, hypocalcemia,

#Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003518.pdf. Accessed January 22, 2013.

consumption, and the dilution of clotting factors after administration of crystalloids and colloids.[11,44] Effective interventions for these conditions may improve trauma outcomes. Maintaining a normal body temperature is a first-line, effective strategy to improve hemostasis during massive transfusion. Erythrocytes play an important role in coagulation and a hematocrit higher than 30% may be required to sustain hemostasis. Hydroxyethyl starch solutions induce dilutional coagulopathy caused by acquired fibrinogen deficiency.[35] The clinical significance of this side effect remains unclear, but should be considered even when hydroxyethyl starch is used within their prescribed limits, especially in hemodynamically unstable patients.[3] Alternatively, plasma represents a volume expander with high oncotic pressures, proteins, and coagulation factors.

New Anticoagulant Agents

A new challenge for clinicians comes from the management of trauma patients taking the new anticoagulant agents that specifically target either factor Xa (rivaroxaban, apixaban) or thrombin (dabigatran).[55,56] Their use is recommended for thromboprophylaxis after elective surgery, such as hip replacement, as well as for the treatment of pulmonary embolism and for the prevention of stroke and systemic embolism in atrial fibrillation.[57] The first difficulty with their use comes from the absence of an accurate method to quantify the anticoagulation level. Although routine monitoring is not required, in certain clinical scenarios such as trauma, bleeding, or overdose, precisely knowing the anticoagulation level may be important.

The conventional laboratory tests are useful as a qualitative tool to determine normal from abnormal coagulation or to simply detect the presence of the drug. Increases in activated partial thromboplastin time and/or the thrombin clotting time suggest the presence of dabigatran, whereas a normal thrombin clotting time effectively rules out the presence of dabigatran. Direct antifactor Xa causes a prolongation of PTs in a concentration-dependent fashion, but PTs cannot be used to evaluate the pharmacodynamic effect. More recently, an antifactor Xa assay that uses rivaroxaban-containing plasma calibrators has been developed and may provide an optimal method for determining plasma rivaroxaban concentrations, although this method is not widely available.[55]

The lack of an available solution to effectively reverse the effects of these new anticoagulant agents is of great concern to trauma and emergency physicians. Currently, the only reversal option is emergency dialysis for dabigatran. However, performing a rapid dialysis in severely injured and bleeding patients remains, even in the most experienced trauma centers, a huge challenge. In this case, it is considered that 2 h of dialysis will remove approximately 62% of circulating dabigatran.[58]

Patients treated with rivaroxaban, apixaban, or dabigatran sustaining a severe trauma should receive the usual bleeding resuscitation, including erythrocytes. FFP is also likely useful to replace the loss of coagulation factors but, according to a recent review,[59] is probably inefficient for reversing the new anticoagulant agents. The use of coagulation factors has been suggested including nonactivated PCC, activated PCC (factor eight inhibitor bypass activity), and rFVIIa. rFVIIa induced a decrease in the bleeding time in rats taking dabigatran or rivaroxaban, but it does not reverse the effect of the drug. Nonactivated PCCs have been shown to normalize the PTs in human volunteers who received rivaroxaban, but did not normalize the activated partial thromboplastin time or thrombin time in subjects who received dabigatran. In humans, a recent *ex vivo* study suggests that rFVIIa, factor eight inhibitor bypass activity ,and PCC appear to be able to reverse the anticoagulant activity of rivaroxaban and dabigatran.[60] However, there is no study evaluating the effect of these coagulation factors in the bleeding patient. Whether the use of PCCs will be effective in stopping critical bleeding in this situation remains to be demonstrated with high-level studies.

Knowledge Gap and Future Perspectives

This case report not only illustrates the rapidity by which coagulopathy develops in a patient with severe trauma, but also emphasizes the new modalities of diagnosis and treatment of TIC.

Recent years have seen the development of new techniques for the rapid evaluation of hemostasis which allows not only the early diagnosis of TIC but also the determination of which specific component is involved in the coagulopathic process. Of particular interest is the fibrinogen deficit which can be diagnosed with the ROTEM® or the TEG®. However, it remains to be clearly demonstrated that the use of this point-of-care device will improve outcomes or result in a reduction of blood products consumption.

At the therapeutic level, we will have to definitively demonstrate with high-quality studies that using a high P:E:Platelet ratio is associated with an improvement in outcome without any increase in adverse events such as TRALI or infection. In North America, a multicenter randomized trial of two blood product ratios (P:E:Platelet: 1:1:1 *vs.* 1:2:1) called the Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial has been initiated and is currently in the process of enrolling patients. In order to avoid potential adverse events linked to these blood products, but also because the availability of blood product is becoming difficult, European authors have suggested using specific coagulation factors. These coagulation factors (fibrinogen, prothrombin complex, and rFVIIa) are immediately available with a very short preparation time. Administration of these factors may decrease the specific adverse effects linked to the use of blood products. However, although experimental evidence and small clinical studies are available with encouraging results, high-quality clinical studies are still required. Because of a theoretical risk of thromboembolic complication when coagulation factors are used, special attention will be required in these studies.

In conclusion, future research efforts will have to focus on the accuracy of early diagnosis of coagulopathy together with the use of both factor concentrates and/or high P:E:Platelet ratios.

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