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Towards early individual goal directed coagulation management in trauma patients

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Major trauma is associated with significant blood loss due to trauma-related severity of injuries and trauma-related coagulopathy. Acute coagulopathy in trauma patients is frequent and has been associated with worse clinical outcome. In this issue of the Journal, Fries and Martini review the mechanisms of trauma-related coagulopathy and the central role of fibrinogen in the treatment of this entity. This is a very timely issue since the understanding of the coagulopathy of trauma and shock has indeed increased tremendously in the recent years. In addition, fibrinogen is increasingly viewed as the coagulation factor that in most massive bleeding cases is becoming critically low first.
Acute traumatic coagulopathy has traditionally been explained by the paradigm of an acquired disorder in the coagulation system through loss or impaired function of coagulation proteases and platelets. However, severe trauma leads to massive haemorrhage with activation and subsequent exhaustion of the coagulation system. Dilution from fluid resuscitation results in an additional relative deficiency of coagulation factors and platelets. Finally, physical factors such as acidaemia and hypothermia further compromise coagulation proteases and platelet function, worsening the evolving coagulopathy.

Recent studies have shown that nearly 25% of trauma patients present with a clinically significant and outcome relevant coagulopathy upon arrival in the emergency department \(^4\). Interestingly, this early coagulopathy occurred prior to any significant consumption or fluid administration and in absence of a relevant acidaemia or hypothermia. Therefore, it has been postulated that the early coagulopathy after trauma be physiologically and mechanistically distinct from the above-mentioned coagulopathy. This acute coagulopathy of trauma, also called endogenous acute coagulopathy (EAC) \(^5\) or acute coagulopathy of trauma and shock (ACoTS) \(^6\) is driven by the combinations of tissue trauma and shock with systemic hypoperfusion. Thereby, the anticoagulant thrombomodulin protein C pathway is overtly getting activated, resulting in reduced pro-coagulatory potential and increased fibrinolytic activity \(^7\)\(^-\)\(^8\). Once protein C is being activated through a thrombin-thrombomodulin dependent reaction, activated protein C (aPC) exerts its profound anticoagulant effects by irreversibly inactivating factors Va and VIIIa. In addition to its direct inhibition of fibrin formation, aPC resolves already formed clots through its derepression of fibrinolysis by direct inhibition of plasminogen activator inhibitor \(^1\)\(^9\)\(^-\)\(^10\).

After major trauma, surgeons and anaesthesiologists thus are facing a dual problem: There is the physical damage including vascular injury with “surgical” haemorrhage and frequently there is a component of coagulopathy with “coagulopathic” bleeding (and any combination thereof). The first type of blood loss requires surgical source control, the second treatment with pro-coagulatory substances such as labile / allogeneic blood products, coagulation factor concentrate and potentially anti-fibrinolytics. In this situation the physician is facing multiple problems at the same time: First, how can he or she analyze the situation within minutes and find out whether coagulopathy is present and what the main causes are. Second, what
products should be used for treatment, given the hazards, risks, unknowns and costs of allogeneic blood products, factor concentrates and anti-fibrinolytics.

A first option to boost blood coagulation following major trauma is to administer “massive transfusion packages” with a fixed, and these days, high fresh frozen plasma (FFP) to red blood cell (RBC) ratio, some even including platelets. The apparent success of such algorithms in improving survival of US Army combat victims has been described several times. However, there are also studies, in which no benefit of a high FFP:RBC on survival was found, and there is an important study showing that the introduction of “massive transfusion packages” resulted in a significant reduction of mortality without a change of the 24h FFP:RBC ratio. Interestingly, in this study FFP (169 min vs. 254 min) and platelets (241 min vs. 418 min) were administered much earlier following the introduction of “massive transfusion packages.” There are several important aspects to consider when interpreting results of studies showing a benefit of a high FFP:RBC ratio in traumatized patients: data are retrospective and primarily refer to young, previously healthy male patients with penetrating injuries. In addition, the FFP:RBC ratio usually is calculated for the first 24h of treatment. Therefore, there may be a significant selection bias in that clinicians allocated most resources including FFP to those patients most likely to survive. There may also be a survivor bias in that those with the worst injury and bleeding died too early to receive a high number of FFP. In addition, FFP transfusion is associated with adverse effects such as increased incidence of nosocomial infections, multiple organ failure, lung injury and potentially mortality. Therefore, although the use of FFP is suggested in massive bleeding, neither the recently published AABB guidelines nor the updated European guideline on the management of bleeding following major trauma recommends for transfusion of plasma at a FFP:RBC ratio of 1:3 or more.

A second option to early and individually optimize blood coagulation following major trauma is to assess each trauma patient’s blood coagulation on admission in the emergency room and throughout the surgery with point of care viscoelastic coagulation monitoring (be it thrombelastography, TEG®, Haemonetics Corp., formerly Haemoscope or rotational thrombelastometry, ROTEM®, tem International GmbH, formerly Pentapharm). These bed-side devices allow analysing the entire blood coagulation within 10-15 min including the detection of (hyper)fibrinolysis. With this information, coagulation can be readily and individually optimized, for
example with anti-fibrinolytics and blood coagulation factor concentrates and later, if necessary with labile blood products. With such an algorithm the use of RBC, FFP and platelets can be significantly reduced and survival of trauma patients significantly improved. The observed mortality in the study by Schoechl et al. was 24.4% which was significantly lower than the expected mortality based on the trauma injury severity score (TRISS) of 33.7%.

Fibrinogen may indeed be the key element of blood coagulation and the one element that is getting critically low first. In addition, fibrin polymerization is compromised by artificial colloids which are frequently used in the initial resuscitation of trauma victims. Interestingly, this form of blood coagulation compromise can be reversed by the administration of fibrinogen. Therefore, aiming at functional fibrinogen levels as assessed by thrombelastometry, appears reasonable and is also proposed by the updated European guideline on the management of bleeding following major trauma. If such thrombelastometric monitoring is not available, serum fibrinogen levels of 1.5 – 2.0 g/L should be aimed at. However, clinicians should be aware, that in presence of artificial colloids such as hydroxyethyl starch, gelatin or dextran, the most often used fibrinogen measurement method, the Clauss methods significantly overestimates fibrinogen concentration.

An additional benefit of bed-side coagulation monitoring like thrombelastometry is speed. If the coagulation status is being analyzed by point of care on arrival in the emergency department, the main coagulation problem is known within 15 min. The trauma patient can then immediately and specifically be treated according to an institutional transfusion algorithm with for example anti-fibrinolytics and coagulation factor concentrates. Importantly, guidelines aiming at individually optimizing the patient's coagulation status also avoid excessive pro-coagulatory potential with associated thrombotic complications. The time advantage of bed-side coagulation monitoring compares very favourable even with the improved times of FFP administration (169 min) described in the study by Riskin et al. following the introduction of a "massive transfusion package."

The review by Fries and Martini explaining the mechanisms of coagulopathy of trauma and shock and the central role therein of fibrinogen thus is an important contribution towards a better understanding of this complex situation and a better treatment of trauma victims. Their recommendation to view fibrinogen as a central
element of blood coagulation is in phase the updated European guideline on the management of bleeding following major trauma \(^1\). The first goal is that all hospitals treating trauma patients have an institutional algorithm how to proceed with a heavily bleeding major trauma patient. The ultimate goal is to find algorithms allowing early individual goal directed coagulation management in trauma patients. To introduce such concepts into general medicine, they need to be rigorously tested in large prospective randomized trials.

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