Haemostatic resuscitation in trauma: the next generation

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Purpose of review
To discuss the recent developments in and evolvement of next generation haemostatic resuscitation in bleeding trauma.

Recent findings
Mortality from major trauma is a worldwide problem, and massive haemorrhage remains a major cause of potentially preventable deaths. Development of coagulopathy further increases trauma mortality emphasizing that coagulopathy is a key target in the phase of bleeding. The pathophysiology of coagulopathy in trauma reflects at least three distinct mechanisms that may be present isolated or coexist: acute traumatic coagulopathy, coagulopathy associated with the lethal triad, and consumptive coagulopathy. The concepts of 'damage control surgery' and 'damage control resuscitation' have been developed to ensure early control of bleeding and coagulopathy to improve outcome in bleeding trauma. Haemostatic resuscitation aims at controlling coagulopathy and consists of a ratio driven strategy aiming at 1 : 1 : 1, using tranexamic acid according to CRASH-2, and applying haemostatic monitoring enabling a switch to a goal-directed approach when bleeding slows. Haemostatic resuscitation is the mainstay of trauma resuscitation and is associated with improved survival.

Summary
The next generation of haemostatic resuscitation aims at applying a ratio 1 : 1 : 1 driven strategy while using antifibrinolytics, haemostatic monitoring and avoiding critical fibrinogen deficiency by substitution.

Keywords
haemostatic, next generation, resuscitation, trauma

INTRODUCTION

Mortality from major trauma continues to be a worldwide problem [1], and massive haemorrhage remains a major cause of potentially preventable deaths. Development of coagulopathy further increases mortality considerably, and coagulopathy is a key target in the phase of bleeding [2]. The concepts of 'damage control surgery' (DCS) and 'damage control resuscitation' (DCR) have been developed during the past 10 years to ensure early control of bleeding and coagulopathy in order to reduce morbidity and mortality in trauma haemorrhage [3,4]. Indication for DCR lies in the mechanism of injury and the degree of physiological derangement, and the main components are the following:

- Haemostatic resuscitation – early use of blood products to avoid further coagulopathy in respect to fluids and dilution.
- Permissive hypotensive resuscitation to decrease bleeding and support bleeding control.
- Regaining homeostasis and avoid further coagulopathy related to hypothermia, acidosis and electrolyte disturbances (hypocalcemia, hyperkaliemia).

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Curr Opin Crit Care 2016, 22:591–597
DOI:10.1097/MCC.0000000000000359

KEY POINTS

- Coagulopathy is a key target for diagnosis and aggressive treatment in the bleeding phase.
- Haemostatic resuscitation aims to control coagulopathy early and consistently in bleeding trauma patients.
- The next generation of haemostatic resuscitation applies a ratio 1 : 1 : 1 driven strategy while using antifibrinolytics, haemostatic monitoring for further goal-directed therapy, and avoids critical fibrinogen deficiency by substitution.

This review will discuss the recent developments possibly involving the next generation of haemostatic resuscitation.

COAGULOPATHY OF TRAUMA AND MASSIVE HAEMORRHAGE

The pathophysiology of coagulopathy in trauma can be stratified into three distinct types that often exist in varying degrees, as single entities in the less sick patient but coexist with the potential to amplify in the bleeding trauma patient: acute traumatic coagulopathy (ATC), coagulopathy associated with the lethal triad and consumptive coagulopathy.

ACUTE TRAUMATIC COAGULOPATHY – ENDOGENOUS ANTICOAGULATION AND BEYOND

ATC, also denoted as acute coagulopathy of trauma and shock (ACoTS), is observed in 25–35% of trauma patients at hospital arrival, associated with significant tissue injury, shock and increased mortality. ATC is a hypocoagulable condition evidenced by increased prothrombin time [5,6] and by prolonged clotting time as evaluated by viscoelastic haemostatic assays (VHA) [7–9]. An important cause of this coagulopathy is the endogenous anticoagulation that develops to balance the increasingly more procoagulant vasculature, represented by the systemically injured endothelium [10,11▪▪]. Three important causes contributing to endogenous anticoagulation are first, auto-heparinization; second, protein C activation and third, hyperfibrinolysis, and these are all related to and driven by the state of the endothelium. In auto-heparinization, the endothelial glycocalyx, consisting of a thick layer of proteoglycans and glycosaminoglycans, becomes shedded secondary to the endothelial damage, resulting in release of heparan sulphate and similar constituents with heparin-like activity to the circulating blood [10,12,13]. Brohi *et al.* [14] reported reduced levels of protein C, attributed to increased production of activated protein C, contributing to the hypocoagulablity observed. Increased fibrinolysis, the most potent endogenous anticoagulation, is observed in patients with extensive and widespread endothelial activation and damage secondary to trauma, leading to enhanced release of tissue-type plasminogen activator (tPA) from the Weibel-Palade bodies of the endothelial cells, inducing premature resolution of the formed clot [15]. Hyperfibrinolysis is an important cause of severe haemorrhage and occurs in severely injured patients correlating with poor outcome [15,16].

COAGULOPATHY IN THE LETHAL TRIAD

The lethal triad is frequently observed in patients with massive haemorrhage and encompasses acidosis, hypothermia and coagulopathy associated with high mortality [17,18]. Hypothermia-induced coagulopathy is attributed to platelet dysfunction, reduced coagulation factor activity and, in the most extreme, induction of fibrinolysis [19]. Acidosis is often induced by hypoperfusion and to some extent excess administration of ionic chloride, that is NaCl, during resuscitation. Acidosis impairs almost all essential parts of the haemostatic process resulting in, for example, a change in platelet structure and shape [19] and reduced activity of coagulation factor complexes on the cell surface, ultimately resulting in impaired thrombin generation [20]. Both hypothermia and acidosis impair fibrinogen availability as hypothermia inhibits fibrinogen synthesis and acidosis accelerates fibrinogen degradation, leading to hypofibrinogenemia [21]. Coagulopathy secondary to dilution of coagulation factors and platelets is also an important part of the lethal triad and dilutional coagulopathy is further aggravated when synthetic colloids are administered. Thus, hydroxyethyl starch (HES) causes an efflux of plasma proteins from the blood to the interstitial space, reduces the plasma concentration of coagulation factor VIII and von Willebrand factor, inhibits platelet function and interferes with the interaction between activated FXIII and fibrin polymers [22,23]. This may contribute to the increased bleeding and mortality of HES administration in bleeding trauma [24]. Lastly, administration of blood products also contributes significantly to coagulopathy in massive bleeding and the 'best' haemostatic capacity possible to accomplish with administration of balanced RBCs, plasma and platelets (1 : 1 : 1) results in a haematocrit around 30%, a coagulation factor concentration ~60% and a platelet count of 80×10^9/l, which is far below normal concentrations [25].

CONSUMPTIVE COAGULOPATHY

Tissue injury induces an immediate activation of the coagulation system through exposure of tissue factor and other tissue or intracellular components, which promotes excessive thrombin generation [26]. To protect the organism against intravascular thrombi by excess fibrin formation, the initial coagulation activation is followed by enhanced plasminogen activation and fibrinolytic activity, and to prevent rebleeding by fibrinolysis, the plasminogen activator inhibitor (PAI)-1 level increases progressively in the hours and days hereafter. Importantly, extensive tissue injury and accompanying shock induces widespread endothelial injury, resulting in a prothrombotic state of the microvasculature that further promotes coagulation factor and platelet consumption, ultimately leading to coagulopathy and further risk of haemorrhage. Occasionally, the normal anticoagulant and fibrinolytic control mechanisms fail to restrict the haemostatic activity to the area of tissue damage resulting in disseminated intravascular coagulation (DIC) [27]. Another important driver of consumptive coagulopathy is the accompanying inflammatory response, which by inducing tissue factor expression on various cells supports a viscous cycle of reciprocal activation of the coagulation system [28]. Importantly, a critical driver of consumptive coagulopathy is sympathoadrenal overactivation. This occurs in response to excessive tissue injury and shock/hypoxia, leading to release of catecholamines in concentrations that are directly toxic for the endothelium, ultimately resulting in further endothelial damage and downstream coagulopathy [29]. Also, catecholamines are potent activators of platelets and promote coagulation factor release and activation, as reported by Cannon a century ago [30].

In summary, given that trauma patients present with an inherent risk of coagulopathy concurrent with the rapidity of changes in the haemostatic system during massive bleeding, the importance of rapid diagnosis and therapy cannot be stressed enough [2,31,32].

MASSIVE HAEMORRHAGE AND HAEMOSTATIC RESUSCITATION

The prevailing transfusion paradigm advocating administration of RBC, plasma and platelets in successive steps directed by total blood loss [33–35] was challenged in 2005 by Johansson *et al.* [36] formulating an appeal for massive transfusion guidelines using RBC, plasma and platelets (PLT) in ratio 1 : 1 : 1 substituting the same balance as the patient bleeds.

Borgman *et al.* [37] were the first group in trauma to show an association between increasing plasma:RBC ratio during massive transfusion and dose-dependent mortality reduction (65 vs. 34 vs. 19%, $P < 0.001$) and this was confirmed in European trauma data by Maegele *et al.* [38] and subsequently by several groups [39–41].

Outside trauma, Johansson *et al.* [42], in massively bleeding patients, compared survival of patients undergoing surgery for a ruptured abdominal aortic aneurysm after implementing a transfusion strategy that included proactive administration of platelets together with plasma given in a 1 : 1 : 1 ratio with RBC. The authors found that patients treated under the new strategy had fewer postoperative transfusions and higher 30-day survival (66% vs. 44%, $P = 0.02$). Increased platelet count after massive bleeding was also found associated with survival with the highest survival at platelet count $>100 \times 10^9$/l, which also was confirmed in a another study of mixed patients with massive bleeding [43]. In postpartum haemorrhage too, a higher use of plasma reduced the risk of haemostatic interventions [44]. However, a challenge in these studies was the risk of survival bias emphasizing the need for prospective and randomized trials [45,46].

This was done by Holcomb *et al.* [47], first the prospective, observational, multicentre, major trauma transfusion (PROMMTT) study and subsequently the much warranted multicentre randomized clinical trial (RCT), the pragmatic randomized optimal platelet and plasma ratios (PROPPR) trial [48▪▪].

PROMMTT prospectively observed 905 trauma patients requiring at least three units of blood products in 24 h [47]. In a multivariable time-dependent Cox model, they found that a moderate and high early dose of plasma (plasma:RBC ratio 1–2 resp. ≥1) was independently associated with improved 6 h mortality with an adjusted hazard ratio of 0.42 resp. 0.23 ($P < 0.001$ for both), whereas only a high early dose of PLT (PLT:RBC ratio ≥1) was independently associated with an improved 6 h mortality with an adjusted hazard ratio of 0.37 ($P = 0.04$). Hence, Holcomb *et al.* confirmed that early and high dosing of plasma and PLT, equal to ratio 1 : 1 : 1, as compared to low ratios, affected early mortality, and that patients receiving low ratios are 3 to 4 times more likely to die. Hence, timing of plasma and PLT transfusions are important.

PROPPR is the largest multicentre prospective RCT in trauma resuscitation to date, comparing a plasma:PLT:RBC ratio of 1 : 1 : 1 and 1 : 1 : 2 in 680 severely injured haemorrhaging patients [48▪▪]. Transfusion services were standardized across the 12 US centres enabling the intervention to be initiated at 8 min after the blood bank call on activation of the massive transfusion protocol [49▪]. In

the 1 : 1 : 1 group more patients achieved haemostasis (86 vs. 78%, $P = 0.006$), fewer exsanguinated in the first 24 h (9 vs. 15%, $P = 0.03$), but mortality was not significantly affected at 24 h (13 vs. 17%, $P = 0.120$) or 30 days (22 vs. 26%, $P = 0.26$). Patients in the two groups received the same number of blood products during intervention and the same auxiliary fluid resuscitation, but achieved the desired difference in ratios signifying no presence of fluid dilution effects in the 1 : 1 : 2 group. Patients in the 1 : 1 : 2 group received more transfusions post intervention, and furthermore, cryoprecipitate was more frequently used (22 vs. 29%; $P = 0.01$) in the 1 : 1 : 2 in the first 24 h. This could be seen as a possible catch-up to the 1 : 1 : 1 strategy and increased use of cryoprecipitate has the potential to dilute the interventional effect accordingly [50▪]. Trauma interventions and timing were similar in the two groups not affected by or affecting the effect of the resuscitation [51▪], equally the incidence of complications [48▪▪]. So in essence, this high quality trial, even though some limitations of the PROPPR results exist, supports that a ratio driven strategy aiming at 1 : 1 : 1 should be considered as a pivotal part of HR in massively bleeding trauma. This approach is also recommended by several recent guidelines [National Institute for Health and Care Excellence (NICE), UK [52▪▪] on trauma, British Society of Haematology, UK [53] on major haemorrhage, and the Association of Anaesthetists of Great Britain and Ireland (AAGBI), UK [54] on blood transfusions among others].

HAEMOSTATIC RESUSCITATION – NEW DEVELOPMENTS

Tranexamic acid in haemostatic resuscitation

Antifibrinolytics such as tranexamic acid (TXA) have been evaluated in more than 250 RCTs encompassing more than 25 000 surgical patients providing evidence for worthwhile reduction in bleeding and exposure to RBC transfusion, without evidence of thrombo-embolic concerns [55,56▪,57]. In trauma, the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial, a multicentre RCT on the effect of TXA administration to trauma patients with suspected significant bleeding, reported of decreased mortality in patients randomized to TXA as compared to placebo [58]. The effect on mortality was even more pronounced if given early and furthermore in bleeding patients, but also present in nonbleeding patients by some beneficial, unexplained or unspecific effect unrelated to bleeding. These findings have been confirmed in further studies of military [59] and paediatric trauma [60], and when used in the prehospital setting [61▪]. TXA is now incorporated in many trauma transfusion guidelines as well as guided by VHA [2], according to the detected pathological hyperfibrinolytic response [16,62,63▪].

Fibrinogen concentrate and cryoprecipitate in haemostatic resuscitation

Fibrinogen is a key element in primary as well as secondary haemostasis [64]. Fibrinogen levels average 2–4 g/l in healthy individuals and have been shown to be affected by the mode of resuscitation [35,65] and the hyperfibrinolytic responses [16,62,63▪]. The 'critical level' at which fibrinogen deficiency causes a decrease in haemostatic competence is however debatable, but a level as high as 1.5–2 g/l is now being suggested as the target for substitution because decreased levels have been associated with worse outcomes in bleeding patients [52▪▪,66,67]. Fibrinogen can be substituted by fibrinogen concentrate or cryoprecipitate; however cryoprecipitate is more than fibrinogen substitution because most coagulation factors and vWF, vitronectin are present and it may not be comparable to fibrinogen concentrate primarily containing fibrinogen [68]. In regard to cryoprecipitate in trauma, the CRYOSTAT pilot trial showed that cryoprecipitate supplementation is feasible and that a definitive trial is warranted to see the effect on safety, transfusions, morbidity and mortality [50▪]. So far no prospective studies on the use of fibrinogen concentrate have been published in trauma, and the evidence for use in trauma is very limited [69]. However, there are several RCTs ongoing in trauma expected for publication soon (clinicaltrials.gov identifiers NCT02344069, NCT01475344, NCT02203968) and in the meanwhile efforts should be focused on monitoring and treating only coagulopathy related to critical fibrinogen deficiency.

Viscoelastic haemostatic assays in haemostatic resuscitation

VHA such as thrombelastography (TEG) and thromboelastometry (ROTEM) have shown to reduce bleeding, transfusions, and possibly mortality in different surgical populations [70–72]. In trauma care, VHA allows for rapid and timely identification of coagulopathy and individualized, goal-directed transfusion therapy [2,72]. Gonzalez *et al.* [73▪] recently investigated 111 severely injured bleeders and the effect of goal-directed resuscitation using the TEG as compared to conventional coagulation testing (CCT). Mortality improved (19.6% in TEG group vs. 36.4% in the CCT group; $P = 0.049$), and the transfusion of plasma and PLT diminished in the

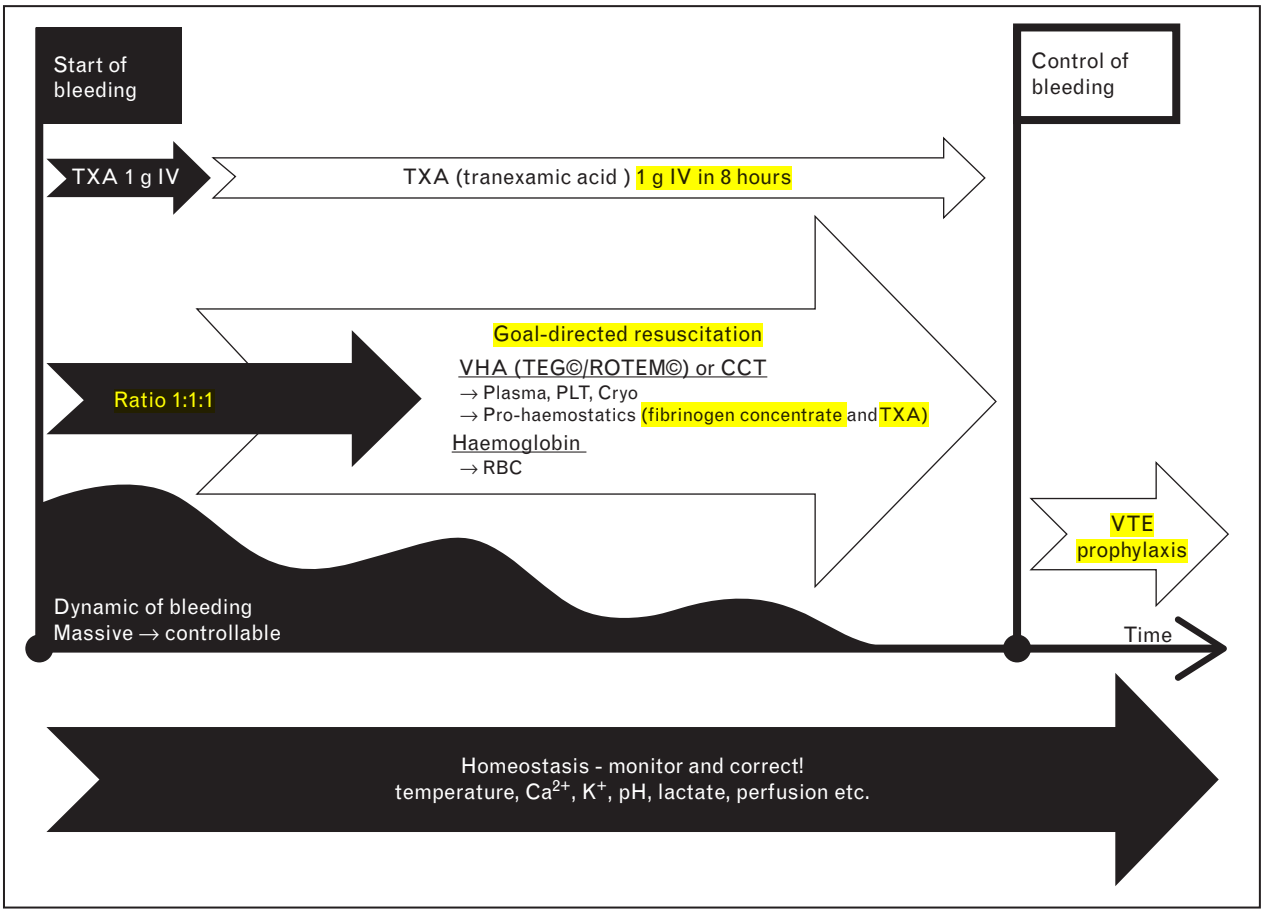

FIGURE 1. Haemostatic resuscitation in trauma – the next generation. The figure shows the phases from start of bleeding to control of bleeding (haemostasis). We initiate ratio 1 : 1 : 1 driven transfusion therapy of red blood cells, plasma and platelets during the initial phase of massive bleeding. VHA such as TEG/ROTEM is performed on arrival, allowing for an early shift towards VHA-guided therapy subsequently. VHA is repeated during resuscitation. If VHA is not available then conventional coagulation test may be used. Simultaneously, tranexamic acid is administered according to the CRASH-2 trial (Clinical randomization of an antifibrinolytic in significant haemorrhage), and efforts are made to ensure homeostasis and correct augmenting factors of coagulopathy and shock. When bleeding is controlled all transfusions stop, and there is a shift towards VTE profylaxis while homeostasis is still ensured. Ca^{2+}, ionic calcium; CCT, conventional coagulation test; Cryo, cryoprecipitate; K+, ionic potassium; PLT, platelets; RBC, red blood cells; ROTEM, thromboelastometry; TEG, thrombelastograph; TXA, tranexamic acid; VHA, viscoelastic haemostatic assay; VTE, venous thromboembolism.

TEG group in the early phase of resuscitation, but RBC transfusion remained unaffected. However, an important limitation to this study is the mode of volume resuscitation which was predominantly done with use of fluids (41 at 2 h, 81 at 6 h, 141 at 24 h), and the plasma:RBC ratio and PLT:RBC ratio were very low (<0.5 resp. <0.1) in the initial phase. This has the potential to cause further dilution and coagulopathy, which did not improve in either arms of the RCT during the interventions. Furthermore, other important limitations of this study are the large VHA intervention effect causing a surprisingly large difference in mortality in a relatively small study. Other noteworthy limitations include timing, standardization of and number of VHA/CCT-analyses, time to available blood products, nonstandardized use of TXA in the study, and possible baseline differences between the groups like higher ISS, more severe TBI, lower sBP, prebaseline treatments. Further RCT on VHA versus CCT is ongoing and warranted in trauma with a standard of care using a ratio 1 : 1 : 1 driven strategy (Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (iTACTIC); ClinicalTrials.gov Identifier: NCT02593877), but meanwhile, VHA should be considered for rapid and timely monitoring and treatment of coagulopathy as part of a resuscitation concept in trauma [2,72,74].

In summary, haemostatic resuscitation aims at controlling coagulopathy in bleeding trauma

patients and consists of a ratio driven strategy aiming at 1 : 1 : 1, using TXA according to CRASH-2, and applying haemostatic monitoring so that when bleeding slows it allows us to shift towards a goal-directed approach using further blood products, TXA dosing and fibrinogen substitution and more (Fig. 1).

CONCLUSION

Haemostatic resuscitation is the mainstay of trauma resuscitation and is associated with improved survival. The next generation of haemostatic resuscitation aims at applying a ratio 1 : 1 : 1 driven strategy while using antifibrinolytics, haemostatic monitoring in order to shift towards goal-directed therapy when bleeding slows, and to avoid critical fibrinogen deficiency by substitution.

Acknowledgements

None.

Financial support and sponsorship

P.I.J. has received unrestricted research grants from Haemonetics Corp., TEM International, Octapharma and CSL Behring.

Conflicts of interest

There are no conflicts of interest.

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