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Coagulation management in multiple trauma: a systematic review

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Abstract *Purpose:* The management of trauma patients suffering from active bleeding has improved with a better understanding of trauma-induced coagulopathy. The aim of this manuscript is to give recommendations for coagulation management. *Methods:* A systematic literature search in the PubMed database was performed for articles published between January 2000 and August 2009. A total of 230 articles were included in the present systematic review. *Conclusions:* The “coagulopathy of trauma” is a discrete disease which has a decisive influence on survival. Diagnosis and therapy of deranged coagulation should start immediately after admission to the emergency department. A specific protocol for massive transfusion should be introduced and continued. Loss of body temperature should be prevented and treated. Acidaemia should be prevented and treated by appropriate shock therapy. If massive transfusion is performed using fresh frozen plasma (FFP), a ratio of FFP to pRBC (packed red

blood cells) of 1:2–1:1 should be achieved. Fibrinogen should be substituted at levels of <1.5 g/L. For patients suffering from active bleeding, permissive hypotension (i.e. mean arterial pressure ~65 mmHg) may be aimed for until surgical cessation of bleeding. This option is contraindicated in injuries of the central nervous system and in patients with coronary heart disease, or with known hypertension. Thrombelastography or -metry may be performed to guide coagulation diagnosis and substitution. Hypocalcaemia <0.9 mmol/L should be avoided and may be treated. For actively bleeding patients, pRBC may be given at haemoglobin <10 g/L (6.2 mmol/L) and haematocrit may be targeted at 30%.

Keywords Coagulopathy · Trauma · Bleeding · Massive transfusion · Thrombelastography · Emergency department

Introduction

Massive bleeding following traumatic injury remains the second most common cause of death in industrialised

countries. For trauma patients dying in hospital, uncontrollable haemorrhage is the most frequent preventable cause of death [1]. This review discusses the state-of-the-art of coagulation management in actively bleeding trauma patients.

Methods

A systematic search in PubMed was conducted in August 2009 on the topics of “trauma and coagulation” as well as “therapeutic options”. All publications beginning in the year 2000 were considered. The PubMed search headings and some statistical details of the cited publications can be found online in the “Electronic supplementary material”. The query was limited to clinical trials, meta-analyses, randomized controlled trials (RCTs) and reviews. The results were compared and duplicates were removed. The remaining articles were sorted according to their relevance. For clarification purposes or missing publications, the limitation “starting 2000 and human” was abandoned. As Germany is the only country where the use of blood products is regulated by a special transfusion law requiring the publication of cross-sectional guidelines, the German Medical Association’s 4th revised edition of the *Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives* [2] was an additional focus of the article. Because of their great significance, two papers published in 2010 were included: CRASH-2 [3] and the European trauma guidelines [4]. After considering the publications’ references, we selected a total of 230 articles that formed the basis of our review. On the basis of the 2001 classification published by the Oxford Centre of Evidence Based Medicine (CEBM, www.cebm.net), an evaluation of the level of evidence (LoE) of the cited articles was consensually made by the authors. Almost half of these articles were downgraded as they were contextually not totally accurate. To evaluate the LoE of our core findings, the CEBM classification system using grade A (LoE 1), B (LoE 2–3) or 0 (LoE 4–5) was chosen. These preliminary recommendations were discussed at several meetings of the writing team, revised and finally approved in recommendations.

Results and discussion

The term “multiple trauma” refers to heterogeneous injury patterns. For decades, perioperative coagulation therapy was performed according to “gut instinct” and “expert opinions”. A growing number of experimental and clinical studies have been published based on scientific data. Although the pathophysiological context of the particular therapies and deranged coagulation is coherent and consistent, RCTs are lacking for almost all recommendations. Like the *Cross-sectional Guidelines for Therapy with Blood Components and Plasma Derivatives*, our recommendations are mostly based on case observations and non-randomized trials. Hence, only a grade of recommendation (GoR) “0” can be given for many. Therefore and because of the cost of the particular

therapies, it must be emphasised that *the options listed are indicated only for patients with massive, life-threatening haemorrhage* [5].

Acute coagulopathy of trauma

Bleeding in massively injured patients increases with additional coagulopathy [6]. Coagulopathy following trauma was assumed to be secondary, i.e. caused by loss/dilution and amplified by acidaemia/hypothermia (“lethal triad”, “bloody vicious circle”) [7]. Recent literature has proved the existence of a distinct, multifactorial, primary disorder, secondarily amplified by consumption, loss and dilution [8, 9]. Acute coagulopathy of trauma (ACoT) significantly impairs survival [10], correlates independently with an eightfold increase in mortality within 24 h [9] and a quadrupled total mortality [10]. Patients arriving at the emergency department (ED) coagulopathic stay longer in the intensive care unit (ICU) and hospital, have an increased risk for renal insufficiency and multiple organ failure, need longer ventilatory support and show a tendency towards increased lung injury [9, 11]. Tissue trauma causes hypoperfusion and hyperfibrinolysis [12]. The intensity of hyperfibrinolysis correlates with trauma severity [13]. Some 30% of the massively injured patients show ACoT upon arrival in the ED [8–10, 14]. The exact mechanism of ACoT is still unclear; Brohi [11] published a possible pathophysiological mechanism focusing on activation of the protein C pathway and hypoperfusion (Fig. 1). There is no intravascular thrombosis in the early phase of trauma; the definition of disseminated intravascular coagulation (DIC) does not apply in the case of ACoT [15]. Some authors do think ACoT and DIC are related and contradict Brohi’s explanations [16].

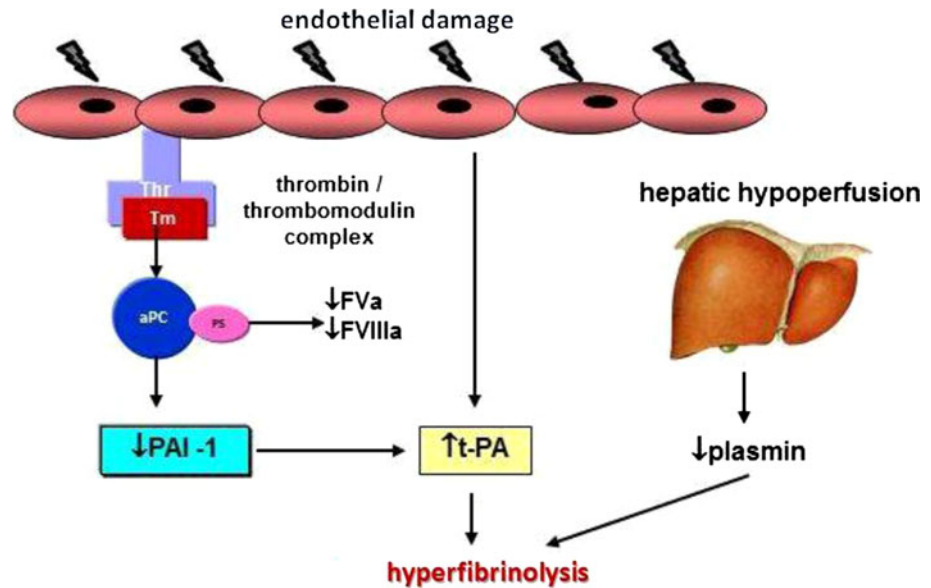
Recommendation The “coagulopathy of trauma” is a discrete disease which has decisive influence on survival. Diagnosis and therapy of deranged coagulation should start immediately in the ED (GoR A).

Diagnostics

ACoT presents clinically with non-surgical, diffuse bleeding from mucosal or damaged tissue, new bleeding from vesical/gastric tubes or from puncture sites. Coagulation screening tests such as prothrombin time (PT) or activated partial thromboplastin time (aPTT) are weak predictors of bleeding tendencies in the critically ill [17]. These tests measure only the first 20–60 s of clot formation; a process which is probably not complete for 15–30 min.

Routine laboratory tests cannot assess the effect of hypothermia, acidosis, hypocalcaemia or anaemia on haemostasis [18]. Abnormal coagulation tests are increasingly frequent with increasing injury severity [19].

Fig. 1 Hypoperfusion causes increased endothelial expression of thrombomodulin. The thrombin–thrombomodulin complex activates protein C, which (together with protein S) inhibits the accelerators FVa and FVIIIa. Additionally, larger quantities of aPC decrease plasminogen activator inhibitor, the most essential antagonist for tissue plasminogen activator. Together with decreased plasmin levels, hyperfibrinolysis is triggered (modified from [11]). *Thr* thrombin, *Tm* thrombomodulin, *aPC* activated protein C, *PS* protein S, *PAI-1* plasminogen activator inhibitor 1, *t-PA* tissue plasminogen activator



Trauma registers have demonstrated that an increased PT correlates with significantly higher mortality [10, 19]. PT/aPTT alone should not be used to guide haemostatic therapy, whereas serum lactate and base deficit are sensitive tests to monitor the extent of bleeding and shock [4].

Recommendation Diagnosis of ACoT by “classical” coagulation parameters like PT, aPTT or platelet count is insufficient. Yet, no better parameter is available (GoR 0).

Thrombelastography/-metry

Coagulation monitoring in massively injured patients by means of thrombelastography (TEG) or -metry (ROTEM) has been increasingly analysed. These devices not only measure the start of clot formation, but also its velocity, maximal amplitude and lysis. A number of TEG- or ROTEM-based algorithms have been published for this setting [20], enabling faster therapeutic decisions [8, 21].

TEG differentiated the mechanism related to clotting abnormalities in porcine models and may permit focused treatment of clotting alterations associated with hypothermia and haemorrhagic shock [22]. With a sensitivity and specificity between 74 and 100%, ROTEM rapidly detects systemic changes of in vivo coagulation, in particular trauma-induced hyperfibrinolysis [8, 13]. In 33 severely injured patients, ROTEM-based diagnosis of hyperfibrinolysis predicted outcome: fulminant (within 30 min), intermediate (30–60 min) or late hyperfibrinolysis resulted in 100, 91 or 73% mortality, respectively. Results suggested a disproportionally higher incidence of hyperfibrinolysis in injuries with increasing severity [23].

The implementation of TEG or ROTEM for trauma coagulation management is promising, particularly with

regard to hyperfibrinolysis [2], and suggested by the recently published European trauma guidelines [4]. Further prospective evaluation and an evidence-based determination of the parameters’ cut-off levels are required [5, 24].

Recommendation ROTEM/TEG may be performed to guide coagulation diagnosis and substitution (GoR 0).

“Damage control resuscitation”

“Damage control surgery” delays definitive anatomical therapy in favour of stabilising vital physiology. Damage control resuscitation (DCR) deals with trauma-induced coagulopathy [25]. This concept includes permissive hypotension, prevention of acidaemia, hypocalcaemia and hypothermia, as well as haemostatic resuscitation [4, 24].

Permissive hypotension

This approach consists of targeting a lower than normal blood pressure to support clot formation, and infusing fluids sparsely while maintaining sufficient perfusion. Clinical use of this concept is based on Bickell’s publication [26]: in 598 adult patients with penetrating torso injuries and a prehospital systolic blood pressure (SBP) of ≤ 90 mmHg, the delay of aggressive fluid resuscitation until surgical intervention improved outcome (shortcomings in study design, retrospective analysis, conduction and interpretation [27]). Data from the German Trauma Registry proved that increased prehospital fluids cause increased coagulopathies [9]. Prehospital intravenous fluid replacement therapy in serious trauma effected no advantage or disadvantage [28]. Titration of initial fluid

therapy to an SBP of 70 mmHg during active haemorrhage did not affect mortality [29]. A Cochrane review found no evidence from RCTs for or against early or larger volumes of intravenous fluid administration in uncontrolled haemorrhage [30].

Recommendation Despite a lack of evidence-based proof and based on pathophysiological considerations, for actively bleeding patients, permissive hypotension, i.e. mean arterial pressure (MAP) \sim 65 mmHg or SBP \sim 90 mmHg, may be targeted until surgical cessation of bleeding. This option is contraindicated in injuries of the central nervous system, coronary heart disease, or hypertension [4, 31] (GoR 0).

(Re)warming

Hypothermia \leq 34°C notably impairs platelet function and coagulation factor activity [18]. Initial fluid therapy should be carried out with warmed infusions [25, 32] and any volume therapy only via a warming device with a fluid temperature of 40–42°C [32]. Passive (insulating foil, blankets, removal of wet clothes) and active (fluid warmers, heated air, heat radiation) measures are needed. Room temperature should be raised in the ED as well as in the operating room, at best to a thermally neutral range (28–29°C) [4].

Desmopressin partially reverses hypothermia-induced impairment of primary haemostasis in vitro [33]. RCTs in trauma are lacking.

Recommendation Loss of body temperature should be prevented and treated by appropriate means to achieve and maintain normothermia [4] (GoR B).

Reduction of acidaemia

A pH \leq 7.2 impairs coagulation [2, 18]. Because the main cause of acidosis is hypoperfusion, it will persist until restoration of sufficient tissue perfusion. The base excess (BE) affects coagulation [18], and is a prognostic factor for complications and death [4]. The critical range for BE begins between -6 and -10 mmol/L [34]. Massive transfusion of packed red blood cells (pRBC) further increases the acid load [35].

Buffering does not stop coagulopathy [36] and is recommended only in combination with administration of drugs affecting coagulation.

Recommendation Acidaemia should be prevented and treated by appropriate shock therapy (GoR B).

Correction of ionised calcium

A reduction in ionised calcium following transfusion is caused by the anticoagulant citrate and is particularly

marked when using fresh frozen plasma (FFP). The faster the transfusion is given, the faster the reduction occurs [2].

Recommendation Hypocalcaemia <0.9 mmol/L should be avoided and may be treated [2, 4, 18] (GoR 0).

Replacement therapy for coagulation

Packed red blood cells

A growing number of publications demonstrate the detrimental effects of RBC transfusion on patient survival [25]. However, the involvement of RBC in coagulation is proven [18, 37]. Restrictive transfusion triggers in coagulopathic patients may be detrimental [38], as affected haemostasis appears long before impaired oxygenation [37].

Recommendation Because of the beneficial effects of higher haematocrit (Hct) levels on primary haemostasis, for actively bleeding patients, RBC may be given at haemoglobin (Hb) <10 g/L (6.2 mmol/L) and haematocrit may be targeted at 30% [2, 4] (GoR 0).

Fresh frozen plasma

In a systematic review, Stanworth [39] found little evidence that FFP is an effective treatment for massive transfusions. Infusing only 10 mL/kg body weight (BW) caused a plasma dilution of 21% for almost 3 h. Sufficient increases in coagulation factors demanded 30 mL/kgBW or an average of 2.5 L of FFP [17].

Although transfusion of any blood product can cause transfusion-related acute lung injury (TRALI), it is most often induced by FFP [40]. An FFP/RBC ratio $>1:1.5$ caused an almost doubled risk of TRALI [41]. A significant association was found between transfusion of FFP and ventilator-associated pneumonia (VAP) with shock, VAP without shock, bloodstream infection with shock, and undifferentiated septic shock in surgical patients [42]. The relative risk (RR) for transfusion of FFP and all infections was 2.99. The magnitude of risk of infection associated with each unit of FFP was approximately 4%. In 14,070 trauma patients FFP transfusion was an independent predictor of ALI: RR after 1–5 FFP of 1.66 and with >5 FFP of 2.55 [43].

Recommendation In ongoing, severe bleeding, sole coagulation substitution by FFP may not be sufficient (GoR 0).

FFP/RBC ratio

Even if the use FFP increases the risks of pulmonary and bloodstream infections and prospective trials are missing, there is growing evidence that a high FFP/RBC ratio may

be beneficial for patients with life-threatening haemorrhage: Instituting a civilian massive transfusion protocol (FFP/pRBC/platelets 1:1:1) led to a drastic reduction in early coagulopathy, in mortality within 24 h, and mortality within 30 days for blunt trauma [44]. A 4-year retrospective study with 135 trauma patients reported that an FFP/pRBC ratio of 1:1 conferred a survival advantage in patients requiring massive transfusion [45]. Comparing an ED transfusion protocol (FFP/pRBC <1:2) with that of an ICU (FFP/pRBC 1:1) showed that coagulopathy present at hospital admission persisted at ICU admission, and severity of coagulopathy at ICU admission was associated with survival outcome [46]. A significantly reduced 30-day mortality for massively transfused patients with $\geq 2:3$ was noted [47]. Holcomb [48] examined records of 467 massively transfused civilian trauma patients: FFP/pRBC $\geq 1:2$ made for a better 30-day survival. The combination of high plasma and high platelet to RBC ratios was associated with increased 6-h, 24-h and 30-day survival, as well as increased ICU-, ventilator- and hospital-free days. A total of 133 patients with >10 pRBC within 6 h revealed: Median FFP/RBC in survivors was 1:2, in non-survivors 1:4. The highest survival rate was for a ratio between 1:2 and 1:3, whereas 1:1 led to increased mortality [49]. 713 patients had a survival benefit depending on an FFP/pRBC favouring $>1:1$. A ratio $>1:1$ caused more ventilator days and longer ICU stays [50]. A 24-h survival benefit accompanied by an increased risk of TRALI was found in 415 patients with FFP/pRBC $>1:1.5$ [41]. Scalea [51] prospectively noted no significant difference in outcome when comparing patients who had a 1:1 FFP/RBC ratio with those who did not receive any FFP. The authors concluded that with an overall mortality of 4% within 24 h (6% for the 81 patients with massive transfusion), their study examined different patients than most other publications. A linear survival benefit with increasing FFP/pRBC towards 1:3 (excluding severe head injuries) was published: FFP/pRBC was the second most important predictor of outcome after admission GCS [52]. Snyder et al. [53] retrospectively conducted an outcome study of 134 patients requiring ≥ 10 units (U) of pRBC/24 h. The authors noted a significantly reduced 24-h mortality of 40% at a ratio of FFP/pRBC $\geq 1:2$ (median 1:1.3) compared with 58% with $<1:2$ (median 1:3.7). This significance was no longer detectable if the exact time of transfusion was considered. The authors proposed a “survival bias”: the non-survivors did not die because they received less FFP, but rather received less because they died. Reviewing 66 randomised, massive transfusion trauma patients (≥ 10 U of pRBC/24 h) at 16 level-1 trauma centres higher 6-h FFP/pRBC and PLT/pRBC ratios lead to improved 6-h and in-hospital mortality [54].

Recommendation If massive transfusion is performed using FFP, an FFP/RBC ratio of 1:2–1:1 should be targeted (GoR B).

Massive transfusion protocol

The term “massive transfusion” (MT) is mostly used for ≥ 10 U pRBC within 24 h [24], alternatively ≥ 10 U pRBC within 6 h [49]. The introduction of a massive transfusion protocol (MTP) with an FFP/pRBC of 1:1.5 resulted in a 74% reduction in the odds of mortality, and a higher 30-day survival, with a reduction in hospitalisation time and ventilator days. The authors concluded that an MTP delivered in an aggressive manner significantly reduces the risk of mortality as well as overall blood product consumption [55]. Using an MTP improved 24-h and 30-day survival and caused fewer deaths from coagulopathy [44].

Recommendation A specific protocol for massive transfusion should be introduced and continued (GoR B).

Platelets

In initial acute loss, the bone marrow and spleen increasingly release platelets (PLT). They decrease late in first-time bleeding. Following transfusion, the PLT disperse in the blood and spleen; the recovery rate in peripheral blood amounts to only 60–70%, or even less in conditions with increased PLT consumption [2].

A retrospective multi-centre study found an increased 30-day survival with PLT/pRBC $\geq 1:2$. PLT/RBC ratios and injury severity score were predictors of death at 6 h, 24 h and 30 days [48]. A multi-centre study of MT within 6 h found that PLT/pRBC $\geq 1:1$ produced significant improvements [54].

Recommendation For acute haemorrhage platelet transfusion is recommended in the case of transfusion-dependent bleeding if platelet counts are $<100,000 \mu\text{L}^{-1}$ [2, 4] (GoR 0).

Fibrinogen

Factor I (fibrinogen) is the substrate of plasmonic coagulation. It is essential for the formation of the fibrin net and, as a ligand for GPIIb-IIIa receptors on the platelet surface, for aggregation. Fibrinogen levels are the first procoagulatory factors to decline while other clotting factors and platelets critically drop in cases of much more extensive blood loss [2]. PT and aPTT demonstrate pathological values only in pronounced fibrinogen deficiency below 1 g/L [2]. The mean dose is around 3–5 g [2] or 50 mg/kgBW.

In vitro dilution by infusing crystalloids or colloids and particularly hydroxyethyl starch (HES) seems to impair the interaction of thrombin, factor XIII and fibrinogen [56]. Substituting fibrinogen (~ 3 g/70 kgBW) led to an improvement in ROTEM parameters [57]. Impaired clot formation during thrombocytopenia improved with administration of fibrinogen concentrate in a porcine model (reduced blood loss, prolonged survival) [58]. In patients

with combat-related trauma requiring massive transfusion, the transfusion of an increased fibrinogen to RBC ratio (>1 g/5 U pRBC) was independently associated with decreasing death from haemorrhage [59]. Substitution therapy with a fibrinogen concentrate generally improved global laboratory coagulation results and appeared to reduce blood loss. Requirements for RBC, FFP and platelet substitution also diminished during serious haemorrhage [60]. Purified, virally inactivated fibrinogen concentrate was effective in the management of 30 adult patients who received fibrinogen concentrate for acquired hypofibrinogenaemia (<1.5 g/L) and enabled rapid administration of a median fibrinogen dose of 4 g in an emergency setting [61]. The administration of fibrinogen concentrates in unresponsive, life-threatening haemorrhage with acquired hypofibrinogenaemia improved laboratory measures of coagulation and significantly improved 7-day survival. Observational data indicated a direct relationship between plasma fibrinogen levels and survival in acquired fibrinogen deficiency [62].

The results of indirect fibrinogen assays (derived fibrinogen and Clauss' method) should be interpreted cautiously when colloids are used [63].

Recommendation In cases of acute bleeding or relevant disposition to bleeding, one should aim for a level >1.5 g/L and determine fibrinogen concentrations with the method according to Clauss (≥ 2 g/L if colloids were infused) [2, 4] (GoR B).

Prothrombin complex concentrates

Factors II, VII, IX and X of the prothrombin complex as well as the proteins C, S and Z are standardised with respect to their content in factor IX [2]. Adverse reactions such as thromboembolic episodes, DIC and/or hyperfibrinolysis are extremely unlikely, even when larger doses are administered [2]. No general antithrombin substitution is required [2].

The main reasons for administering prothrombin complex concentrates (PCCs) are to help ensure viral safety during use of plasma products and to minimise the risk of TRALI. In coagulopathy, the prothrombin complex deficiency may be pronounced to such a degree that (in addition to FFP infusion) substitution with PCC is required [2]. Substitution of fibrinogen and PCC after a standardized liver cut in a porcine dilution model using 6% HES 130/0.4 caused significant reduced blood loss and survival of all pigs whereas 80% of controls died [64]. PCC shortened the time to haemostasis after either bone or spleen trauma in animals and reduced the volume of blood lost. Subsequent to bone injury, PCC versus 40 mL/kg FFP also accelerated haemostasis and diminished blood loss; substitution with PCC effectively normalized coagulation and significantly improved haemostasis and blood loss [65].

Recommendation In acquired deficiencies, the application of PCC (initially 1,200–2,400 IU or 20–25 IU/kgBW) may help to stop the bleeding (GoR 0).

Antifibrinolytics

Hyperfibrinolysis in trauma appears to be more frequent than previously assumed [66] and its intensity correlates with injury severity [13]. It is most common in patients with chest, blunt abdominal, pelvic, or head trauma. Damage to inhibitory mechanisms or an excessive release of plasmin shift the coagulation system towards increased fibrinolysis with massive bleeding. Antifibrinolytic treatment of ACoT is logically based on the mechanism proposed by Brohi [11]. ROTEM provided rapid and accurate detection of hyperfibrinolysis in severely injured trauma patients [4, 13, 23]. The administration of fibrinogen is only indicated following interruption of the coagulation disorder by antifibrinolytics [2]. A 2004 Cochrane review found insufficient evidence from RCTs of antifibrinolytics in trauma to either support or refute a clinically important treatment effect [67]. In the double-blind, randomised, multi-centre and multinational CRASH-2 trial [3] 10,060 adult trauma patients with or at risk of severe haemorrhage received 1 g of tranexamic acid (TxA) in 10 min plus 1 g over 8 h, and 10,067 matched patients received 0.9% saline. TxA significantly reduced all-cause mortality and mortality due to bleeding. Vascular occlusive events did not differ significantly.

Recommendation TxA (1–2 g or 1 g in 10 min plus 1 g over 8 h) should be considered for use in bleeding trauma patients (GoR B).

Desmopressin

Desmopressin (DDAVP) enhances platelet adhesion to the vessel wall and increases factor VIII (FVIII) and von Willebrand factor (VWF) plasma concentrations [68]. The clinical indications for DDAVP have rapidly expanded beyond haemophilia and von Willebrand disease (thrombocytopenia, uraemia, hepatic cirrhosis, antiplatelet drugs) [69]. The maximal effect occurs after 90 min [68]. Repetitive doses may release tissue plasminogen activator (tPA) and thus may cause hyperfibrinolysis. Some authors recommend that repeated administrations should be accompanied by TxA [68]. Trials with DDAVP in cardiac surgery reported a non-significantly elevated incidence of myocardial infarct in the DDAVP-treated group [68]. Desmopressin partially reverses hypothermia-induced impairment of primary haemostasis in vitro [33]. A Cochrane review [70] found no convincing evidence that DDAVP minimises perioperative RBC transfusion in patients who do not have congenital bleeding disorders. Zotz [71] reviewed the same data for patients with blood

loss >1 L or a history of aspirin use. This therapeutic use of DDAVP caused a significant reduction in blood loss and transfused RBC. There are no RCTs for trauma patients.

Recommendation In diffusely bleeding patients with suspected thrombocytopenia, intravenous DDAVP administration at a dose of 0.3 mg/kg diluted in 50 mL saline, infused over 30 min, may be considered (GoR 0).

Factor XIII

Activated factor XIII (FXIII) is a transglutaminase which cross-links fibrin covalently in the presence of calcium ions. A firm three-dimensional fibrin net is formed resulting in definite haemostasis. FXIII is not determined by the screening tests PT and aPTT [2].

Acquired FXIII deficiency may be caused by increased turnover (e.g. following intravascular clotting, increased blood loss, hyperfibrinolysis) or by increased consumption (e.g. in major surgery) [2]. Perioperatively this may lead to massive bleeding [72]. For intracranial and cardiac surgery, the association of decreased perioperative FXIII with an increased risk of postoperative haematoma/bleeding was proven. Examination of the occurrence of unexplained intraoperative bleeding in elective surgery revealed that fibrinogen and FXIII were more rapidly consumed in bleeders. ROTEM showed a significant reduction in clot firmness. FXIII substitution (30 U/kg) in surgical cancer patients at high risk for intraoperative bleeding led to significantly reduced loss of clot firmness and a trend towards reduced blood loss [72]. RCTs in the trauma setting are lacking.

Recommendation In case a prompt determination of FXIII is not possible, the risk of persistent bleeding should be weighed against that of blind administration of FXIII, particularly in acute severe haemorrhage. In cases of bleeding, at least 15–20 U/kgBW may be substituted until haemostasis is achieved [2] (GoR 0).

Recombinant activated factor VII

Supraphysiological doses of recombinant activated factor VII (rFVIIa) cause a maximum number of tissue factor molecules to form complexes and activate the clotting system limited to the site of injury. A pathway for the initiation of coagulation is formed that is independent of sufficient activation of FIX, FVIII or tissue factor [73]. Because of the lower affinity of FVIIa to activated platelets, a supraphysiological dose is necessary to achieve haemostasis. FVIIa has almost no affinity at all to inactive platelets [2, 74].

Off-label use of rFVIIa has been published in numerous case reports, cohorts and some RCTs. Thromboembolic events have occurred in the arterial and venous vascular system, in particular in patients receiving rFVIIa off-label [2]. Early use of rFVIIa (within 2.5 h of trauma) was associated with decreased 24-h and 30-day mortality in severely injured combat casualties requiring massive

transfusion [75]. In the only positive class-1 study, Boffard [76] tested rFVIIa as an adjunctive therapy for bleeding control in severely injured trauma patients with 400 µg/kgBW. This resulted in a significant reduction in RBC transfusion and the need for massive transfusion in severe blunt trauma. A trend was seen for penetrating trauma, mortality and critical complications; no increased adverse events were observed. When patients who required admission to the ICU were analysed ($n = 110$, 50% received rFVIIa), total mean charges and costs were significantly lower in the group that received rFVIIa [77]. Hospital length of stay (LOS), days of mechanical ventilation and plasma utilization were lower in the rFVIIa group. However, the authors administered relatively small doses of rFVIIa (mean 41.9 ± 35.5 µg/kg, median 25.1 µg/kg). For off-label use, rFVIIa's effectiveness remains uncertain—either prophylactic or therapeutically [78]. In 22 RCTs with 3,184 patients (the only trauma patients were those of Boffard [76]), those receiving rFVIIa were less likely to need additional blood transfusions. Reduction in mortality was more likely if rFVIIa was given therapeutically. The incidence of arterial thromboemboly was higher in patients receiving rFVIIa. Nineteen RCTs focused on trauma: based on Boffard's publication [76] the authors gave a “level 1” recommendation for the use of rFVIIa in blunt trauma, and a “level 2” for halting trauma-associated haemorrhage when other therapies have failed with 400 µg/kg (a lower dosage may be as efficacious) [79]. A review of prospective, controlled trials that involved the therapeutic use of rFVIIa in the ED found no significant difference in mortality between rFVIIa and placebo [80]. A large multinational phase III trial of rFVIIa in trauma patients was recently terminated due to futility, because the planned reduction in mortality could not be achieved [24].

The effect of rFVIIa depends on several concomitant factors whose maintenance is paramount: fibrinogen ≥ 1 g dL⁻¹, haemoglobin ≥ 7 g/dL, platelets $\geq 50,000$ µL⁻¹ (better $\geq 100,000$), Ca²⁺ ≥ 0.9 mmol/L, temperature $\geq 34^\circ\text{C}$, pH ≥ 7.2 , and the exclusion of hyperfibrinolysis or heparin [2, 74, 81]. A common “standard dose” for off-label use is 90 µg/kgBW [73, 82]. However, the required dose is still under debate [81]. A repetitive dose may be needed within 30 min–2 h, although repeat dosing is more likely to indicate futility than to be effective [82].

The review by Mannucci [83] summarises: “This agent is not a panacea, but it has efficacy in patients with trauma and excessive bleeding that is resistant to other treatments.” Administration only if other (conventional) therapeutic options have not been effective is also proposed in current reviews [79, 82, 84]. Since 2009, NovoNordisk no longer recommends the off-label use of rFVIIa due to a doubling in the risk of (arterial) thrombosis between 1/10 and 1/100 (see German prescription recommendations dated May 2009, and NovoNordisk's statement: “Safety and effectiveness has not been established in these settings and the use is not approved by FDA”).

Table 1 Summary of therapeutic options in massive haemorrhage

1. Stabilisation of concomitant factors (prophylaxis and therapy)	Core temperature $\geq 34^{\circ}\text{C}$ pH ≥ 7.2 Ionised $\text{Ca}^{2+} \geq 0.9$ mmol/L	GoR B GoR B GoR 0
2. Substitution of oxygen carriers	pRBC (functionally, Hb 6[–8] g/dL; but haemostatically in massive bleeding, Hct $\geq 30\%$ or Hb ~ 10 g/dL [6.2 mmol/L])	GoR 0
3. Inhibition of possible (hyper-)fibrinolysis (always before fibrinogen!)	Tranexamic acid initial 1 g in 10 min + 1 g over 8 h or 2(–4) g (15–30 mg/kgBW)	GoR B
4. Substitution of coagulation factors (for ongoing, severe bleeding)	FFP ≥ 20 (rather 30) mL/kgBW And fibrinogen (2–)4(–6) g (aiming at ≥ 150 mg/dL [≥ 1.5 g/L]) And PCC initially 1,200–2,400 U (20–25 U/kgBW) If necessary 1–2 \times FXIII 1,250 U (15–20 U/kgBW)	GoR 0 GoR B GoR 0 GoR 0
<u>And</u> (suspecting thrombocytopeny) enhanced platelet adhesion + endothelial release of vWF and FVIII	DDAVP = desmopressin 0.3 $\mu\text{g/kgBW}$ in 30 min	GoR 0
5. Substitution of platelets for primary haemostasis	Platelets 2–3 U (for bleeding requiring transfusion aiming at 100,000/ μL)	GoR 0
6. If necessary thrombin burst	On a case-by-case basis, if other therapeutic options fail, and after consideration and correction of concomitant factors; rFVIIa initially 90 $\mu\text{g/kgBW}$	GoR B
For ongoing, severe bleeding	No antithrombin	GoR B

Recommendation For patients with traumatic haemorrhage rFVIIa may be used on a case-by-case basis, if other therapeutic options failed, and after consideration and correction of concomitant factors, especially in blunt trauma [4] (GoR B).

A summary of the above-mentioned therapeutic options in trauma-induced haemorrhage is presented in Table 1.

Antithrombin

Antithrombin (AT) deficiency in ACoT is not isolated as all pro- and anticoagulants undergo consumption [4]. The administration of AT in ongoing massive haemorrhage will increase bleeding and is not recommended [4]. In critically ill patients, AT increased the risk of bleeding events and failed to reduce overall mortality [85].

Recommendation Actively bleeding patients should not be treated with AT [4] (GoR B).

Conclusion

Recent scientific work enables a new view of the old problem of ACoT: traumatic coagulopathy is a distinct disease with hyperfibrinolysis as a (possible) key element. For life-threatening haemorrhage, sole application of FFP may not be sufficient. Early, aggressive, anticipatory and empirical (or better ROTEM-/TEG-guided) therapy with pRBC, FFP and purified factor concentrates together with consideration and correction of concomitant factors (temperature, pH, ionised calcium) will help rescue more of our patients.

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