Coagulopathy in trauma and massive perioperative bleeding

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A B S T R A C T

New concepts have been recently proposed specifically to understand coagulopathy related to major trauma, massive hemorrhage, and hemodilution. Although not yet fully understood, systemic generation of the anticoagulant activated protein C and uncontrolled systemic release of thrombin seem to be involved in early trauma coagulopathy. During late trauma coagulopathy and during massive perioperative bleeding, dilutional coagulopathy seems to be predominant. Although hemostatic defects are primarily attributed to low procoagulant activity, anticoagulant and antifibrinolytic factors are also decreased proportionally to the extent of hemodilution. Trauma-induced and dilutional coagulopathy, therefore, represent coagulation disorders with complex pathomechanisms requiring multimodal therapies. Massive transfusion protocols with fresh frozen plasma (FFP):red blood cells (RBC):platelets ratios close to 1:1:1 have been advocated in some studies, but their effectiveness and safety remain controversial. A better understanding of trauma-induced coagulopathy and dilutional coagulopathy, together with the increasing availability of viscoelastic coagulation monitors in the emergency and operating rooms have led to novel approaches to massive bleeding using coagulation factor concentrates. Given the paucity of clinical data on the efficacy, safety, and cost-effectiveness of coagulation factor concentrates, prospective clinical trials are required to comparatively evaluate coagulation factor concentrates and conventional hemostatic component therapies for trauma-induced and perioperative massive hemorrhage.

Introduction

Multiple vascular lesions result in major bleeding and coagulopathy with consecutive massive transfusion of allogeneic blood products in up to 3% of patients with massive trauma and in those undergoing major surgery.[1] The pathophysiology and severity of coagulopathy depend on whether massive bleeding occurs as a result of trauma or of major surgery.[2] Such differences can be attributed in part to the mechanism of vascular lesion, injured organ, extent of hemorrhage, type of resuscitative fluid, amount of released tissue factor, and prophylactic use of antifibrinolytic therapy.[1-5] In trauma patients, both the initial volume and hemostatic treatment and the monitoring of hemostasis by conventional coagulation testing are often delayed.[6] Therefore, trauma patients often present with hypovolemia, shock, and hypothermia. Coagulopathy is often related to early trauma-induced coagulopathy (ETIC), which has been recently described.[7-8] During the late phase of trauma-induced coagulopathy after volume resuscitation, dilution is a substantial contributor.[5] In contrast, most coagulopathic patients undergoing major elective and emergent surgery present with normovolemia due to timely volume resuscitation with colloids and crystalloids and allogeneic blood products, including erythrocyte concentrates, platelet concentrates, and fresh frozen plasma (FFP). Therefore, dilutional coagulopathy may be the main problem in the surgical patient with coagulopathic bleeding.[4] In addition, monitoring of hemostasis is planned in advance in elective cases, and therefore, adequate hemostatic treatment(s) can be implemented early.[9-11] Finally, unlike congenital bleeding disorders, which are mostly due to a single factor deficiency (*e.g.*, hemophilia, afibrinogenemia), coagulopathy encountered in trauma and major surgery is of a multi-factorial nature. All elements in coagulation, including procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic proteins exhibit various degrees of deficiency.[4,12]

The pathomechanisms of coagulopathy related to massive trauma and dilutional coagulopathy are not yet fully understood and still under debate. They are discussed in this review together with the clinical implications and the various therapeutic approaches.

Volume resuscitation in major bleeding and massive transfusion

In adult patients, blood loss of up to 15% of total blood volume (BV) has minimal physiological consequences. When the blood loss is increased to 15-30%, mild hypotension and tachycardia result. Blood loss of more than 30% is considered major and may result in a shock with a high risk of trauma-induced coagulopathy. First steps in the resuscitation of the hypovolemic patient include the infu-

sion of crystalloids and colloids to stabilize systemic circulation.[13] Despite some advantages in better sustaining intravascular volume and, therefore, normovolemia, colloids are claimed to interfere with hemostasis. Colloids, such as hydroxyethyl starch solutions, gelatins, and dextrans impair platelet function, inhibit fibrin polymerization, and may induce acquired von Willebrand syndrome.[14-16] They may also increase fibrinolytic tendency probably due to interaction with fibrin polymerization and α_2-antiplasmin-plasmin interactions.[15,17] However, hemostatic impairments due to colloids most likely depend on the amount and the physicochemical characteristics of the colloid solution, and their clinical significance remains controversial.

Red blood cell (RBC) concentrates are transfused to sustain hemoglobin levels (*i.e.*, oxygen carrying capacity). The European guideline currently suggests hemoglobin levels of 7-9 g/L in bleeding trauma patients.[18] The transfusion of ten or more RBC units (*i.e.*, replacement of one BV) within 24 h is generally considered as a massive transfusion in adults.[19] However, other arbitrary and individual definitions include six or more RBC units within 6-12 h and over 50 units of blood product used within 24 h including RBC, platelet concentrates, and FFP.[5,19] Experts generally suggest shorter time periods than 24 h in which the transfusion must be given.[19]

The effect of acute loss of RBC on coagulation, especially in the trauma patient, is unclear.[20] However, low hematocrit potentially impairs hemostasis. In the arterial circulation, platelets are preferentially distributed near the vessel wall (margination) due to the red cell mass.[21,22] The platelet count measured in a static blood sample, therefore, may not correctly reflect the *in vivo* platelet concentration next to the injured vessel wall, and this may explain the relatively low incidence of spontaneous bleeds until the platelet count falls to below 10,000/μL. RBC also facilitate platelet aggregation by releasing adenosine diphosphate (ADP) in shear flow.[23] In addition, *in vitro* experiments have shown that the RBC surface can activate factor IX and may work as a reactive surface for procoagulant reactions.[24] While these data support hemostatic roles of RBC,[22] mild hemodilution and anemia have been associated with improved hemostasis or hypercoagulability on thromboelastometry.[25-27] Thromboelastometric measurements are conducted under low shear rates, and high red cell mass can be *in the way* of spreading fibrin strands and their interaction with platelet glycoprotein (GP) IIb/IIIa receptors.[28] Therefore, clinical significance of improved thromboelastometric parameters in anemia remains unclear.

Coagulopathy in trauma

Trauma-induced coagulopathy can be divided into an early phase (acute traumatic coagulopathy [ATC] or ETIC) and a late phase. Despite increasing evidence of ETIC, there is a lack of clinically relevant definitions. Its pathomechanism is not fully understood, but it seems to involve the systemic generation of anticoagulant activated protein C.[7,8] The shedding of thrombomodulin from endothelia during hypoperfusion and shock has been presumed to be responsible.[8,29] Recently, we have suggested that the massive release of procoagulants, such as tissue factor (TF) in major trauma or anionic phospholipids in brain injury may lead to an excessive thrombin burst, which cannot be controlled at the injury site.[4] Under the normal physiological condition, accumulated platelets and clotting fibrin (formerly also known as antithrombin I[30]) during clot formation hamper the diffusion of IX and X activated by TF at injury site.[31] Therefore, prothrombinase activity that supports thrombin generation is localized within the forming clot. In case of excessive TF release, thrombin generation cannot be restricted to the injured vessel wall, and uncontrolled (non-hemostatic) thrombin circulates downstream to the injury site (Figure 1). Thrombomodulin-mediated activation of protein C leads to proteolytic degradation of activated factors V and VIII, thereby limiting thrombin generation away from the injury site. Systemic thrombin activity is also associated with binding to protease-activated receptors (PAR), and with consecutive release of tissue plasminogen activator (tPA). The latter can lead to the conversion of plasminogen to plasmin on fibrin, and fibrinolysis.[4] Recent studies using thromboelastometry showed that overt fibrinolysis could be found in up to 25% of trauma patients. The highest incidence is found in patients with the severest injuries (injury severity scores ≥25), and early hyperfibrinolysis has been associated with increased mortality.[32-34] It has been suggested that fibrinolysis is an integral part of ETIC[35] providing a rationale for early treatment with antifibrinolytics.[36,37]

After massive bleeding accompanied by aggressive volume resuscitation, trauma-induced coagulopathy during the late phase can be regarded as dilutional coagulopathy. In major trauma cases, hypothermia and acidosis (metabolic or respiratory) exacerbate coagulopathy.

Effects of hypothermia and acidosis on coagulation

Hypothermia and acidosis, commonly observed during extended resuscitation in major trauma, can differently affect thrombin generation, fibrin synthesis/polymerization, and fibrinolysis. In a porcine model, hypothermia (32ºC) was demonstrated to slow down the process of thrombin generation. In case of acidosis (pH 7.1), thrombin generation was significantly impaired, resulting in a decreased hemostatic capacity.[38] In a similar model, it was shown that hypothermia decreased fibrin synthesis, while acidosis increased fibrin degradation.[39] In an *in vitro* study, the rate of fibrin polymerization was reduced synergistically by hypothermia (≤33ºC) and acidosis (pH ≤7.1).[40] The rate of fibrinolysis seemed to remain constant during hypothermia (32ºC), but acidosis increases fibrin degradation.[39] In summary, the correction of acidosis and hypothermia is essential for optimal activity of coagulation factors, clot formation, and clot stability.

Coagulopathy in perioperative massive bleeding

Effects of hemodilution on coagulation factors and blood components

Volume resuscitation and timely administration of allogeneic blood products are pivotal in the management of massive bleeding during elective surgery. While circulatory shock, acidosis, and hypothermia can be avoided in most cases, large amounts of crystalloids, colloids, or RBC can lead to dilutional coagulopathy with reduced

levels of most hemostatic elements.[12,41,42] Whereas the extent of dilution is proportional to the amount of infused volume based on *in vitro* experiments,[12,41,42] this is less clear for *in vivo* situations. For example, plasma FVIII and von Willebrand factor (vWF) can be acutely released from endothelial cells by stress hormones, including epinephrine and vasopressin, during the perioperative period.[43,44] Further, platelet count is often higher than predicted by the extent of dilution, presumably due to the release of sequestered platelets from the spleen, lung, and also from the bone marrow in premature forms.[45] Importantly, the critical level of a hemostatic element occurs at a different time point during hemodilution. The critical level of fibrinogen (1 g/L) is observed after a loss of about 150% of circulating BV, while critical concentrations of enzymatic coagulation factors and platelet count are reached after a loss of more than 200% of BV.[46]

Although hemostatic defects are primarily attributed to decreased procoagulant factors levels, anticoagulant and antifibrinolytic factor levels are also decreased proportionally to the extent of hemodilution. Dilutional coagulopathy, therefore, represents a coagulation disorder with a complex pathomechanism requiring specific therapy.[4]

Regulation of thrombin generation in dilutional coagulopathy

Thrombin generation is a critical process for achieving hemostasis after vascular injury. During the initiation and propagation of coagulation, local thrombin concentration rapidly increases from less than 1 nM to as high as 500 nM.[12] Despite a reduced prothrombin level due to hemodilution, *in vitro* models showed that the peak level of thrombin activity is less affected relative to the prothrombin level after hemodilution.[12,41] While the prothrombin level was decreased to 17% after *in vitro* hemodilution with saline, the peak thrombin level was reduced to 32% of baseline, and endogenous thrombin potentials was similar to baseline.[12] The discordance could be, at least partly, explained by reduced antithrombin (AT, formerly antithrombin III) due to hemodilution.[12] Decreased AT activity prolongs the half-lives of FXa and thrombin[47] and, thus, it potentially contributes to improved hemostasis during a "hypocoagulable" state after hemodilution.[12,48] Although thrombin is an essential enzyme for hemostasis and survival, uncontrolled thrombin activity can be harmful. Multiple mechanisms including fibrin(ogen),[30,31] AT bound to endothelial heparan sulfate,[49] and the thrombomodulin-protein C system are important in scavenging free proteases (*e.g.*, FXa, thrombin) in circulation, and in limiting excessive thrombin generation (Figure 1).[4] Systemic thrombin activity is associated with a release of tPA,[50] potentiating fibrinolytic (plasmin) activation. These responses during hemodilution are similar to ETIC, and are sometimes indistinguishable from disseminated intravascular coagulopathy (DIC), which can be observed during sepsis and other clinical states.[51] However, microvascular thrombosis has not been reported in dilutional coagulopathy or ETIC.

Fibrin polymerization and fibrinolysis

The cleavage of fibrinogen bound to platelet GPIIb/IIIa receptors and subsequent polymerization of fibrin are achieved during amplified thrombin generation and thrombin-mediated activation of FXIII. It is not known what minimal levels of fibrinogen and FXIII should be kept to minimize bleeding. The international guidelines prior to 2009 recommended minimal fibrinogen levels between 0.8 and 1.0 g/L,[13,52] a level similar to the management of congenital

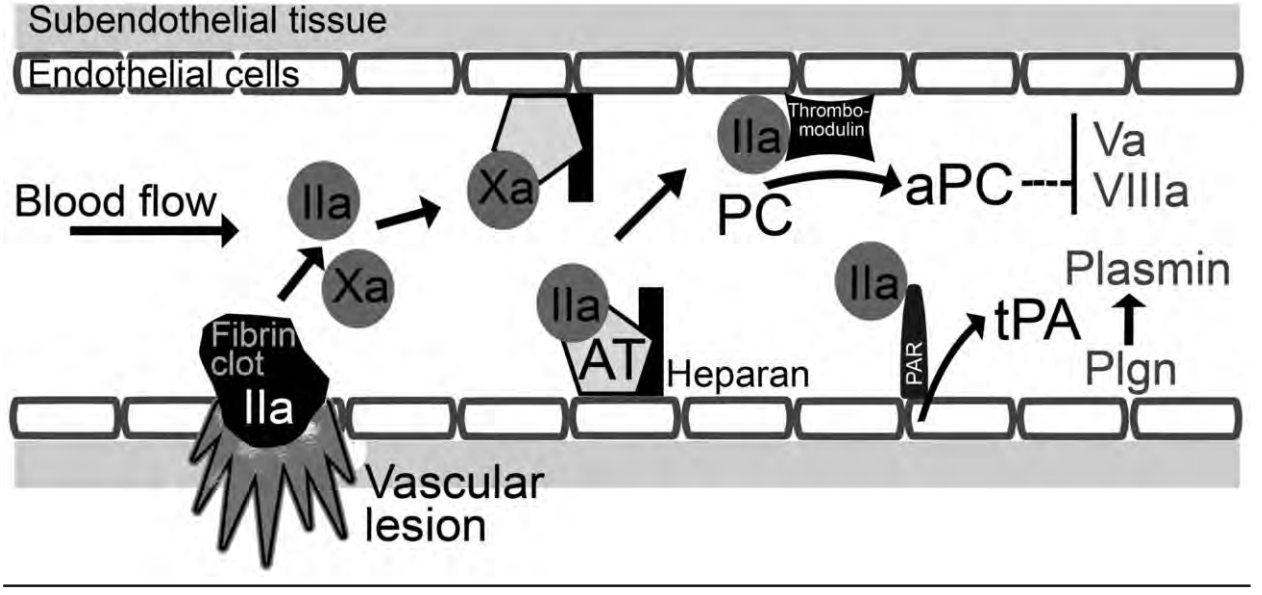

Figure 1. Control of local and free thrombin generation. Thrombin is an essential enzyme for hemostasis, but uncontrolled thrombin activity can be harmful. Under the normal physiological condition, accumulated platelets and clotting fibrin localize prothrombinase activity within the forming clot. Sub-threshold levels of FXa and thrombin (FIIa) circulating downstream from the injury site are rapidly neutralized by antithrombin (AT) bound to endothelial heparan sulfate. Thrombomodulin-mediated activation of protein C (APC) inhibits FVa and FVIIIa, thereby limiting thrombin generation. In trauma and massive hemorrhage, scavenging systems cannot locally control thrombin. Systemic thrombin activity is associated with a release of tissue plasminogen activator (tPA) leading to plasmin activation and fibrinolysis.

afibrinogenemia. However, the more recent European guideline recommends higher cut-offs (1.5-2.0 g/L) for perioperative coagulopathy.[18] This reflects recent clinical data supporting fibrinogen levels of 2-3 g/L during postpartum hemorrhage,[53] aortic replacement,[54] coronary bypass grafting surgery,[55] cystectomy,[56] and *in vitro* hemodilution.[41] For the minimal FXIII level, recent clinical data suggest levels of more than 50-60% to reduce bleeding tendency after major surgery, particularly in the presence of low fibrinogen levels (<1.5 g/L).[57,58]

Fibrinolytic activation is physiologically important in preventing excess fibrin formation that could completely occlude injured blood vessels. Endogenous antifibrinolytics including PAI-1, α_2-antiplasmin, and TAFIa are highly concentrated at the focal point of blood coagulation by activated platelets, FXIIIa, and thrombin.[59] Either reduced thrombin generation,[60] low α_2-antiplasmin,[61] or low TAFI level[62] might be associated with fibrin structure that is prone to fibrinolysis. During hemorrhage accompanied by hemodilution, tPA is released by thrombin, epinephrine, vasopressin, desmopressin, bradykinin, and other substances.[50] Endogenous antifibrinolytic proteins are progressively lowered, and their interactions are diminished.[63] Therefore, fibrin cross-linking is decreased, and the plasma half-life of plasmin becomes prolonged,[12,58] resulting in a pro-fibrinolytic state during hemodilution.

Clinical studies

Several recent clinical studies support the proposed pathomechanism of dilutional coagulopathy. In cardiac and non-cardiac surgery involving mild to moderate hemodilution, thrombin generation after surgery seems to be preserved, whereas fibrin polymerization was more relevantly impaired.[56,64] In agreement, optimizing fibrin formation by supplementation with fibrinogen concentrate successfully improved postoperative hemostasis involving several studies in elective surgery.[10,54,56,65] Further, the prophylactic use of antifibrinolytics has been shown to reduce profibrinolytic tendency during non-cardiac and off-pump cardiac surgery with progressive hemodilution.[66,67] Experimental data suggest that antifibrinolytic activity can be maintained by supplementing FFP[12,63] or FXIII.[68] However, due to the lack of large, well-designed clinical trials, the pathomechanism of coagulopathy remains highly disputed, and there is a paucity of clinical evidence for any specific treatment of trauma-related coagulopathy.

Hemostasis monitoring

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) represent the most commonly used screening tests for coagulation abnormalities during major bleeding and massive transfusion. Hemostatic defects after massive transfusion based on the conventional laboratory data are often indistinguishable between trauma and major surgery. Using the cut-off values of INR and aPTT of more than 1.5 times normal has been suggested as an indicator of clinically relevant coagulopathy.[5,13,69] Recently, these cut-offs have been questioned, and PT cut-off values of more than 1.2 times normal have been proposed as an indicator of coagulopathy.[29] However, conventional PT and aPTT poorly correlate with clinical coagulopathy, and there is little evidence for their usefulness in the evaluation of bleeding.[5,18] There are several reasons for this: 1) Perioperative and trauma bleeding are typically associated with multiple coagulation defects resulting from hemodilution, consumptive loss, fibrinolysis, anticoagulant use, hypothermia, and other mechanical and metabolic derangements; 2) PT and aPTT do not provide any information on the *in vivo* interaction of platelets with coagulation factors; 3) PT and aPTT are hardly affected by AT or protein C derangements, but thrombin generation might be relevantly altered;[70] and 4) it is not possible to estimate the overall stability of a hemostatic thrombus using PT/aPTT because both tests are terminated at very low thrombin levels (~10 nM, less than 5% of peak thrombin generation)[71] and before fibrin is polymerized by factor XIIIa.

Besides the above-mentioned limitations, PT/aPTT testing is typically performed in the laboratory, and there is a substantial time delay.[6] In this regard, whole blood-based viscoelastic assays, such as thromboelastography (TEG™) or thromboelastometry (ROTEM™) might be advantageous because they can be performed as point-of-care tests. The main endpoint of ROTEM/TEG is the polymerization of fibrin in the presence of activated platelets. Therefore, these assays are particularly useful for the evaluation of hemodilution, fibrinogen deficiency, factor XIII deficiency, and fibrinolytic state (Figure 2).[27] In addition, the low shear rate (0.1/s) environment of TEG/ROTEM precludes the evaluation of von Willebrand factor and platelet adhesion. *In vitro* thromboelastometric findings, therefore, cannot be simply transferred to *in vivo* conditions. However, TEG/ROTEM-guided transfusion algorithms have been successfully implemented in the treatment of bleeding patients after major surgery and trauma.[9-11,27,54,72] Although in trauma patients, the clinical relevance of TEG/ROTEM has not yet been adequately tested, the goal-orientated coagulation therapy based on TEG/ROTEM seems to be advantageous compared with the fixed-ratio administration of blood products during damage control resuscitation.[27]

The calibrated automated measurement of thrombin generation is presently limited for research purposes, and its clinical utility in massive bleeding needs to be further evaluated. Similarly, the predictive value of novel point-of-care impedance platelet aggregometry during trauma and surgical bleeding requires additional evaluations.[44,73]

Hemostatic interventions for coagulopathy

Massive transfusion protocols

FFP appears to be the ideal hemostatic mean, since it contains all components, including procoagulant, anticoagulant, and antifibrinolytic factors, albumin, and immunoglobulins.[74] Several retrospective analyses demonstrated the potential benefit of massive transfusion protocols using the empirical transfusion FFP:RBC ratio of 1:1 in military and civilian trauma patients.[1,75] The survival rate was significantly worse with the low FFP:RBC ratio (*i.e.*, <1:2) relative to the high ratio (>1:1). However, there are significant confounders in these studies particularly related to the survivor bias and the speed of blood loss.[76] The efficacy of FFP might be significantly less than described.[76] Although FFP may increase procoagulant, anticoagulant, and antifibrinolytic proteins when used in adequate

amounts,[12,77,78] clotting factor activities in FFP are only about 80% with large variations.[74] While FFP transfusion sustained levels of soluble clotting factors in an *in vitro* study,[12] *in vivo* studies using an FFP:RBC:platelet ratio of 1:1:1 found a reduction of hemostatic elements to about 60%.[79] Beside its questionable therapeutic effectiveness,[65] there are safety concerns about the routine use of FFP.[80,81] FFP and RBC contain large amounts of citrate, used as an anticoagulant, potentially leading to deleterious hypocalcemia. However, the negative effect of citrate has never been proven and remains in debate. Further, there are the risks of viral transmission and transfusion-related acute lung injury (TRALI) with FFP. These risks could be markedly minimized using novel virus inactivation/filtering technologies and an altered donor selection (*e.g.*, male-donor only police, exclusion of women that were pregnant). Finally, FFP should not be considered as a fluid replacement therapy.[18] However, FFP in massive trauma might be an exception due to acute hypovolemia.[1,75,82] The use of fixed-ratio hemostatic transfusion protocols is not advocated in bleeding patients undergoing elective surgical procedures.[83]

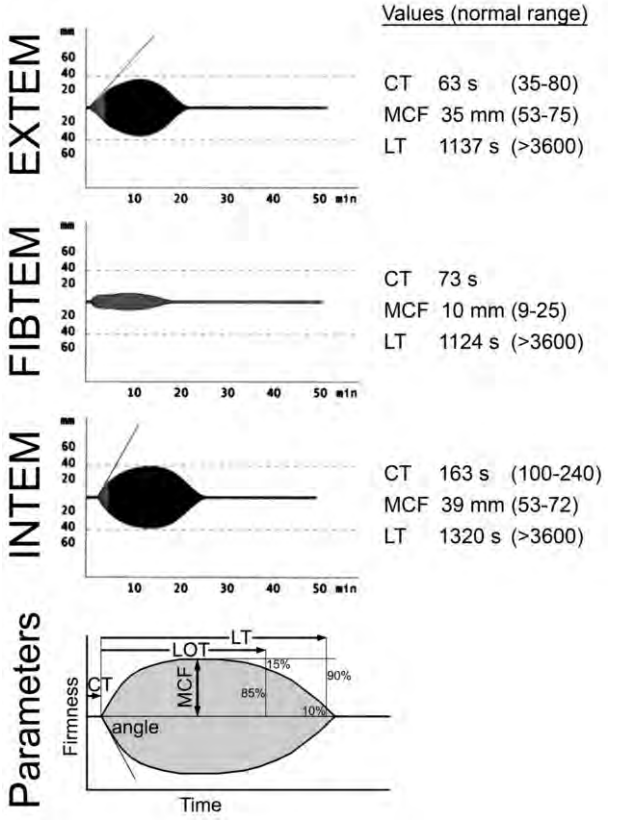

Figure 2. Thromboelastometry after massive hemorrhage during elective surgery. Thromboelastometric traces in massive hemodilution due to incidental surgical lesion of the vena cava inferior during ventral spine surgery with a consecutive blood loss of about 4-5 L. The patient was resuscitated with crystalloids (5000 mL), colloids (1500 mL), 7 units of RBC concentrates (2000 mL), 5 units of FFP (1250 mL), and 4 g of fibrinogen concentrate. At the end of surgery, the surgical field looked dry. Blood loss from the surgical drain increased after 1 h in the intensive care unit. Based on thromboelastometric traces, the patient was treated with 1 g of tranexamic acid and 2 g of fibrinogen concentrate. The rest of clinical course was unremarkable. Abbreviations: CT=coagulation time; MCF=maximal clot firmness; LT=lysis time; LOT=lysis onset time

To be most effective, FFP must be readily transfused in large amounts at an early stage of trauma.[75] The high-dose FFP:RBC:platelet regimen may challenge the logistics and resources of blood banks. For example, one "unit" of platelets usually means five donor units. The use of pre-thawed FFP can reduce waiting times for transfusion and potential wastage, because they can be kept at 1-6°C for 5 days without significant losses of labile FV after initial thawing.[84]

In general, platelet transfusion is considered when platelet count falls to below $50\times10^3/\mu L$.[13] However, the threshold for platelet transfusion, especially in case of dilutional coagulopathy, remains unclear because anemia affects the margination of platelets under flow conditions,[21] and stress responses induce the release of sequestered platelets.[45] When drug-induced platelet dysfunction is identified or strongly suggested, transfusion of platelet concentrates is advised even at normal platelet count.[3] However, platelet transfusions can be associated with serious adverse events, such as bacterial or viral transmission, TRALI, stroke, and even death.[3 85]

In summary, although commonly used at trauma centers mainly in the United States (US), the effectiveness and safety of massive transfusion protocols with a fixed FFP:RBC:platelet ratio remain unproven and should be clearly restricted to the most severely injured patients with injuries that cannot be surgically controlled within a reasonable time.

Coagulation factor concentrates

The new concepts of pathomechanisms in trauma-induced and dilutional coagulopathy together with the increasing availability of viscoelastic coagulation monitors in emergency and operating rooms have led to novel approaches to massive bleeding. First-line hemostatic interventions have been managed with coagulation factor concentrates (Table 1) under the guidance of ROTEM/TEG.[9,10,54,56,72,86]

Table 1. Available products for serine proteases, antithrombin, and fibrinogen.

	Available concentrate(s)
Fibrinogen	pd-fibrinogen, cryoprecipitate
Prothrombin	PCC, FEIBA
Factor V	none
Factor VII	pd-FVII, r-FVIIa, PCC*, FEIBA
Factor VIII	pd-FVIII, r-FVIII
Factor IX	pd-FIX, r-FIX, FEIBA
FX	pd-FX, PCC, FEIBA
Factor XI	pd-FXI
Factor XIII	pd-FXIII, r-FXIII, cryoprecipitate
vWF	pd-vWF, cryoprecipitate, pd-FVIII/vWF
Protein C	pd-protein C, PCC*
Protein S	PCC*
Antithrombin	pd-AT, r-AT

Abbreviations: pd=plasma-derived; r=recombinant; PCC=prothrombin complex concentrate (*PCC products contain varying levels of FVII and of protein C and S); FEIBA=FVIII inhibitor bypassing activity; AT=antithrombin; vWF=von Willebrand factor

According to the recent European guideline, fibrinogen levels of 1.5 to 2 g/L should be aimed in the bleeding patient.[18] In the central European countries, specific plasma-derived fibrinogen factor concentrates are widely used to increase plasma fibrinogen levels. In the US and United Kingdom, cryoprecipitate is an alternative for the replacement of plasma fibrinogen, whereas FFP transfusion is not efficacious in raising plasma fibrinogen levels unless used in large amounts (about 30 mL/kg).[77] A high ratio of fibrinogen to transfused RBC units has been associated with reduced mortality in combat trauma patients.[87] High plasma fibrinogen levels (>3 g/L) may even compensate for low platelet count.[41] Increasing clinical data support the use of fibrinogen concentrate to reduce blood loss and transfusion of RBC and platelets after major surgery without increasing thrombotic complications. However, despite these encouraging findings, the evidence for the efficacy of fibrinogen is still limited in the bleeding patient.[88,89] To recommend fibrinogen supplementation definitively in the massively bleeding patient, the large prospective studies are needed.

The lower FXIII levels have been associated with increased perioperative blood loss, and the supplementation of FXIII has been shown to decrease blood loss in a small study with patients undergoing major cancer surgery.[57,58,68] Some institutional guidelines, therefore, have adapted a protocol to supplement FXIII when plasma levels fall to 60%. However, the evidence for such recommendations is scarce, and a large prospective study is required to define the role of FXIII supplementation in trauma and massive bleeding.

Prothrombin complex concentrates (PCC) are approved for acute reversal of vitamin K antagonists in most European countries. PCC might be beneficial in the bleeding patient by way of increasing thrombin generation. However, there is a paucity of data on the use of PCC for coagulopathy due to hemodilution or trauma. In two different porcine models, PCC (30-35 U/kg) improved PT and bleeding tendency.[90,91] In several small retrospective studies, PCC was shown to restore vitamin K dependent factor levels and to be hemostatic in post-cardiac surgical and critically ill patients with coagulopathy refractory to platelets, FFP, and cryoprecipitate.[92,93] A routine use of PCC in bleeding surgical and trauma patients is not recommended because of potential prothrombotic risks, especially in the presence of AT deficiency due to hemodilution.[48]

Recombinant activated factor VII (rFVIIa) is used as an emergent medication in case of persistent severe bleeding after conventional hemostatic means have been exhausted. Two prospective randomized trials in trauma patients with massive transfusion (>8 units of RBCs) were not able to show the efficacy of rFVIIa in reducing transfusion requirements.[94] In contrast to hemophilic doses (90-300 μg/kg), the dose of rFVIIa should be reduced when low anticoagulant levels (*e.g.*, AT deficiency) after hemodilution are suspected. During obstetric hemorrhage, positive effects of rFVIIa have been recently reported without relevant numbers of thromboembolic complications.[95] However, a recent meta-analysis reported a relevant increase in arterial thromboembolic events with high doses of rFVIIa on an off-label basis.[96] Further, rFVIIa may only be efficacious when fibrinogen levels are supplemented first[97]

In summary, restoring coagulation factor levels, especially fibrinogen, with factor concentrates seems to be advantageous for rapid hemostatic interventions during major surgery or trauma. Given the paucity of data on the indications and safety of coagulation factor concentrates, larger randomized clinical trials are warranted.

Antifibrinolytics and other supportive drug therapy

Fibrinolysis is not uncommon during severe trauma[8,32,33] and hemodilution (Figure 2),[12] but is seldom tested. Lysine analogues, ε-aminocaproic acid and tranexamic acid, are the currently available antifibrinolytics. It is unknown if antifibrinolytic therapy could actually lower the requirement for fibrin(ogen), but antifibrinolytics presumably protect weak fibrin clot from plasmin-mediated breakdown. The overall reductions in blood loss and the need for allogeneic RBC transfusion by lysine analogues have been reported in cardiac, orthopedic, and hepatic surgery.[66] The prospective randomized CRASH II trial, including more than 20,000 trauma patients demonstrated lower all-cause mortality and death due to bleeding in patients treated with tranexamic acid (1 g loading followed by 1 g over 8 hours) compared with the placebo.[37] The beneficial effect of tranexamic acid was most pronounced with early therapy (≤1 h from injury).[36] The administration of tranexamic acid, therefore, is recommended in most trauma patients.

DDAVP (1-desamino-8-D-arginine vasopressin), an analogue of the endogenous vasopressin, has been shown to antagonize platelet dysfunction induced by GPIIa/IIIa inhibitors and aspirin *in vitro*.[98] Although the blood sparing effects of DDAVP have been suggested in major surgery, the meta-analyses failed to show marked benefits in perioperative hemostasis.[99,100] Clinical hemostatic efficacy of DDAVP is potentially limited by tachyphylaxis due to high levels of endogenous stress hormones and concomitant release of tPA.

Conclusion

Coagulopathy due to major trauma and massive bleeding during major surgery induces complex coagulation disturbances involving procoagulant factors, as well as anticoagulant and fibrinolytic factors. A better understanding of the time course of pathophysiological changes is necessary to attain an optimal balance between hemostatic and anticoagulant therapies. The clinical effectiveness and safety of aggressive transfusion of FFP and platelets *versus* purified factor concentrates for a rapid restoration of hemostasis is currently debated. It is desirable to use point-of-care testing to individualize the dose and timing of such interventions and to reduce potential complications from over-dosage. Future clinical trials for different factor concentrates are required to determine their indications and dosage in patients suffering from hemorrhage in trauma and major surgery.

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