

Transfusion in trauma: why and how should we change our current practice?

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Purpose of review

Major trauma is often associated with hemorrhage and transfusion of blood and blood products, which are all associated with adverse clinical outcome. The aim of this review is to emphasize why bleeding and coagulation has to be monitored closely in trauma patients and to discuss the rationale behind modern and future transfusion strategies.

Recent findings

Hemorrhage is a major cause of early death after trauma. Apart from the initial injuries, hemorrhage is significantly promoted by coagulopathy. Early identification of the underlying cause of hemorrhage with coagulation tests (routine and bedside) in conjunction with blood gas analysis allow early goal-directed treatment of coagulation disorders and anemia, thereby stopping bleeding and reducing transfusion requirements. These treatment options have to be adapted to the civilian and noncivilian sector. Transfusion of blood and its components is critical in the management of trauma hemorrhage, but is *per se* associated with adverse outcome. Decisions must weigh the potential benefits and harms.

Summary

Future transfusion strategies are based on early and continuous assessment of the bleeding and coagulation status of trauma patients. This allows specific and goal-directed treatment, thereby optimizing the patient's coagulation status early, minimizing the patient's exposure to blood products, reducing costs and improving the patient's outcome.

Keywords

blood management, coagulation, hemorrhage, transfusion, trauma

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Introduction

Hemorrhage is known to be a major cause of early death after injury and has been shown to be responsible for 30–40% of trauma mortalities [1–3]. Furthermore, hemorrhage with consecutive multiple transfusions has been shown to significantly worsen clinical outcomes [4*,5].

Management priorities in trauma patients are to ensure adequate ventilation, oxygen delivery, hemorrhage control and to restore tissue perfusion to vital organs. Early and continuous reassessment of the bleeding and coagulation status of trauma patients allows specific goal-directed treatment, thereby optimizing the patient's coagulation status, minimizing exposure to blood products, reducing costs and improving the patient's outcome [6*,7].

Mechanism of hemorrhage in trauma patients

Hemorrhage reduces the preload that is required to ensure adequate cardiac output and peripheral oxygen delivery. Inadequate tissue perfusion, not always associ-

ated with overt hypotension, can trigger a neurohumoral cascade, leading to sequential organ failure. Mortality from established organ failure has not changed since it was first described almost 30 years ago [8]. Diagnosing and treating hemorrhage early remain imperative. The American College of Surgeons has developed the classification scheme stratifying blood loss from stage 1 (<15% of total circulating blood volume) to stage 4 (>40% of total circulating blood volume) [9]. Young people in good health may compensate well for large-volume blood loss, up to 50% of the total circulating blood volume. Then, they may develop sudden cardiovascular compromise when compensatory mechanisms fail. In contrast, elderly people may tolerate much smaller blood losses only.

Anatomical bleeding

Active hemorrhage as a result of major injuries is life-threatening and leads to hemorrhagic shock and exsanguination if not treated immediately. Bleeding may be stopped temporarily by external compression and tourniquets; however, surgical or interventional (e.g. arterial embolization) repair is required for final hemorrhage control.

Coagulopathic bleeding

An abnormal coagulation status is frequently present early after major trauma at admission to the emergency department (ED) and is associated with a five-fold increase in mortality [10,11^{••}–13^{••}]. Traditionally, acute traumatic coagulopathy has been thought to be due to consumption of coagulation factors, dilution from intravenous fluid therapy, hypothermia and metabolic acidosis. It has recently been shown, however, that none of these factors is initially responsible for the acute traumatic coagulopathy [12^{••},13^{••}]. These factors become significant only in the later phase of traumatic coagulopathy. Studies by Brohi *et al.* [11^{••}–14^{••}] have described an early and previously unknown acute traumatic coagulopathy before any of the above-mentioned traditional causes of traumatic coagulopathy were present. It has been shown that tissue injury and hypoperfusion followed by the activation of the anticoagulation thrombomodulin protein C pathway plays the central role in the pathogenesis of acute traumatic coagulopathy. As a result of overt activation of protein C, acute traumatic coagulopathy is characterized by coagulopathy in conjunction with hyperfibrinolysis (Fig. 1).

Protein C is activated through a thrombin-dependent reaction, with thrombomodulin and the endothelial protein C receptor. Once protein C is being activated (aPC), it exerts its profound anticoagulant effects by irreversibly inactivating factors Va and VIIIa (coagulopathy). This reaction is augmented by the cofactor protein S, and serves to limit continued thrombin production. In addition to its direct inhibition of fibrin formation, aPC resolves already formed clots through its derepression of fibrinolysis. aPC directly inhibits plasminogen activator inhibitor 1 (PAI-1), which usually serves to limit tissue plasminogen activator (t-PA)

activity. Without the limitation of PAI-1, t-PA is free to enhance the conversion of plasminogen to plasmin and thereby enhance fibrinolysis (hyperfibrinolysis).

The activation of the thrombomodulin protein C pathway has clinical significance; high thrombomodulin and low protein C plasma levels were associated with increased mortality, blood transfusion requirements, acute renal injury and reduced ventilator-free days early after trauma [11^{••}–14^{••}].

Diagnosis and monitoring of bleeding

There are different methods available to assess and monitor bleeding, and these should all be used to offer the patient optimal treatment.

Assessment of hemorrhage and volume status

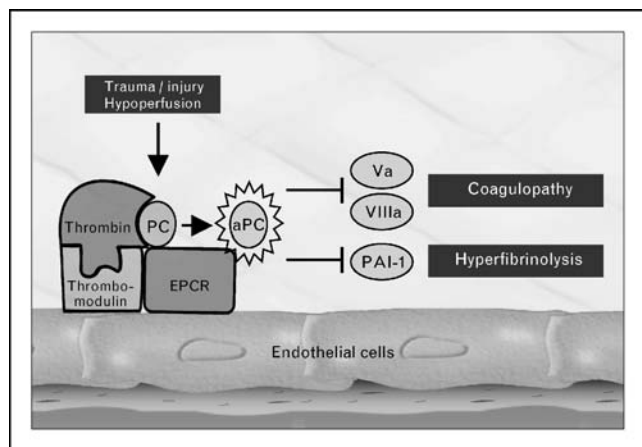
Blood pressure and heart rate are vital signs, which are nonspecific in the evaluation of hemorrhage. Mixed and central venous oxygen saturation are more sensitive and reliable measurements of acute volume loss [15,16[•],17]. The degree of metabolic acidosis, as measured by the base deficit from an arterial blood gas sample, is helpful to evaluate the degree of shock. Base deficit has been shown to correlate with transfusion requirements, ICU stay and ultimate outcome [18,19]. During initial resuscitation, base deficit typically correlates with serum lactate level. Interestingly, the ability to clear lactate to normal is one of the most important predictors of survival following hemorrhage and injury [20–22]. Serial blood gas determinations (arterial and venous) may be helpful in determining whether blood loss is continuing or not.

Assessment of coagulation

Most commonly, routine laboratory-based coagulation tests [e.g. prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT) and fibrinogen], platelet numbers and hemoglobin (Hb) concentration are being used to assess the patient's current coagulation status [23]; however, the value of these tests has been questioned in the acute bleeding situation because there are delays from blood sampling to obtaining results (45–60 min), coagulation tests are determined in plasma rather than whole blood, no information is available on platelet function and the assays are performed at a standard temperature of 37°C rather than the patient's temperature [24].

Point-of-care coagulation monitoring devices assessing the viscoelastic properties of the developing clot in whole blood, for example thrombelastography (TEG) or rotation thrombelastometry (ROTEM), may overcome several limitations of routine coagulation tests [25,26]. In particular, these technologies allow the in-vivo assessment of coagulation system interactions with platelets

Figure 1 Pathogenesis of acute traumatic coagulopathy



aPC, activated protein C; EPCR, endothelial protein C receptor; PAI-1, plasminogen activator inhibitor 1; t-PA, tissue plasminogen activator.

and red blood cells (RBCs) and provide useful information on platelet function [27]. In addition, they may be performed at the bedside, allowing faster turnaround times. Furthermore, clot development can be visually displayed in real time, the assay is fibrinolysis sensitive and coagulation analysis can be done at the patient's temperature [28]. Nevertheless, results obtained from these in-vitro tests must be carefully interpreted in the clinical context.

Present and future transfusion practice in trauma patients

Different strategies can be used in trauma to control bleeding and to treat bleeding, including the use of blood products or specific coagulation factors. These aspects can have a significant impact on patient outcome.

Prevention of further bleeding

The initial phase after trauma – from injury to surgery/ intervention – has to be minimized and further bleeding should be prevented. Hill *et al.* [29] observed a significant decrease in mortality from shock by establishing a 60 min ED time limit for patients in hemorrhagic shock. Additionally, Hoyt *et al.* [30] showed that delayed transfer to theater is an avoidable cause of death, which can be minimized by reducing the time for diagnosis and resuscitation prior to surgery.

Without brain injury, a target systolic blood pressure of 80–100 mmHg should be maintained until the major bleeding is stopped [6[•]]. Aggressive fluid therapy to preserve tissue oxygenation and to restore the circulating blood volume leads to dilution of coagulation factors, hypothermia, increased hydrostatic pressure and further bleeding. The concept of low-volume fluid resuscitation, called 'permissive hypotension', prior to surgical source control maintains tissue perfusion at a lower level but sufficient for a short period of time without the adverse effects mentioned above [31]. The low-volume approach is not to be applied in traumatic brain and spinal injuries, as an adequate perfusion pressure is crucial to ensure tissue oxygenation of the injured central nervous system.

Transfusion of red blood cells

To transfuse RBCs, different triggers, Hb based versus physiological, have to be taken into consideration.

Hemoglobin-based transfusion triggers

According to current guidelines from the American Society of Anesthesiologists, RBC transfusion is recommended if the Hb concentration drops below 6–10 g/dl. Transfusions over 10 g/dl are rarely indicated and transfusions seem almost always to be indicated if Hb falls below 6 g/dl [32]. In Europe, a Hb target range of 7–9 g/dl is largely accepted in major trauma [6[•]].

Physiological transfusion triggers on the contrary are tachycardia, hypotension, oxygen extraction higher than 50%, mixed venous oxygen pressure of less than 32 mmHg, increase of lactate and ECG changes [6[•],33,34]. The depth of shock, hemodynamic response to resuscitation and the rate of actual blood loss in the acutely bleeding and hemodynamically unstable patient may also be integrated into the indication for RBC transfusion [35]; however, RBC transfusions should be used restrictively [36].

Alternatives to allogeneic red cell transfusion

In trauma, the only available alternative in clinical practice to allogeneic RBC transfusion is currently intraoperative blood cell salvage. It has been shown to be efficacious for reducing allogeneic blood transfusions [37]. The quality of salvaged blood seems to be better than stored packed RBCs, with less risk for the patient [37]; however, cell salvage is only applicable when the operative site is not contaminated.

Artificial oxygen carriers may represent a future alternative to RBC transfusions. There are two groups of artificial oxygen carrier currently under development: synthetically manufactured perfluorocarbons and Hb-based oxygen carriers [38]; however, none of these products has achieved market approval for Europe, USA or Canada so far.

Transfusion of fresh frozen plasma and platelets

Traditional indications for fresh frozen plasma (FFP) are massive bleeding due to multiple factor deficiencies, emergency reversal of vitamin K antagonists and treatment of thrombotic thrombocytopenic purpura (TTP) [32]; however, the clinical efficacy of FFP is largely unproven [6[•],39]. Large quantities of FFP (15 ml/kg body weight and more) are recommended to achieve an effect in massive bleeding [6[•],40,41]. Interestingly, there is only expert opinion but no evidence-based transfusion thresholds published for FFP administration [32,42]. There are significant adverse effects, however, associated with FFP transfusion-associated circulatory overload (TACO), allergic reactions, transfusion-related acute lung injury (TRALI), transmission of infectious pathogens [40,43,44^{••}] and a three-fold increase of nosocomial infections [45].

In a bleeding patient, platelets should be kept at more than $50 \times 10^3 / \mu\text{l}$ and more than $100 \times 10^3 / \mu\text{l}$ in patients with traumatic brain injury (TBI) [6[•],7]. The adverse effects of platelets are similar to those for FFP, except there is a much higher risk of bacterial contamination [46]. Therefore, the indication to transfuse platelets is to be restrictive. As for FFP, there are only expert opinions available about when to transfuse platelets; no studies on an evidence-based level have been published so far.

Replacement of specific coagulation factors

Several coagulation factors are available and can be substituted selectively; in this section, a brief overview of those most commonly used is given.

Fibrinogen

Fibrinogen is the substrate for forming a clot. Several in-vitro and animal studies [47^{••},48,49] have shown that fibrinogen substitution is essential to reverse dilutional coagulopathy. Furthermore, several human studies (civilian and noncivilian) confirmed these data, showing that early and aggressive replacement of fibrinogen in patients with severe hemorrhage and dilutional coagulopathy improves clot strength significantly and may lead to better survival [50,51^{••}–53^{••}].

Factor XIII

Factor XIII is the key coagulation factor to stabilize the clot. Schroeder *et al.* [54] and Nielsen *et al.* [55,56] have proven a relation between decreased factor XIII activity and reduced clot firmness (maximal amplitude/maximum clot firmness, MA/MCF) by computerized TEG. Trauma and major hemorrhage is known to be a cause of acquired factor XIII deficiency [57]. It seems reasonable to substitute factor XIII early, thereby improving clot firmness, reducing bleeding and minimizing the use of blood products [58–60].

Prothrombin complex concentrates

Prothrombin complex concentrates (PCCs) provide a source of the four vitamin K-dependent coagulation factors, and, consequently, PCCs are recommended in both Europe and the United States for emergent reversal of oral anticoagulants [61–65]. Furthermore, Bruce and Nokes [66[•]] recently demonstrated that the use of PCCs in trauma patients leads to a considerable reduction in the use of blood products (FFP, RBCs and cryoprecipitate) and that survival improved and bleeding stopped earlier. Therefore, PCCs might have a place in control of trauma-related bleeding, although this indication is currently off label.

Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa) leads to a ‘thrombin burst’, thereby transforming fibrinogen into fibrin. Before treating patients with rFVIIa, patients should fulfill certain criteria, for example thrombocytopenia and hypofibrinogenemia must be corrected [67–69]. One study [70] on trauma has shown a reduction in RBC transfusions in rFVIIa-treated patients; however, rFVIIa is not an alternative to surgical bleeding control, and its use in trauma is still an off-label indication. Risks and benefits have to be carefully evaluated before usage and economic aspects taken into consideration [71].

Pharmacologic agents

Two groups of drugs are frequently used to control bleeding, antifibrinolytics and protamine sulfate. Antifibrinolytics such as aminocaproic acid (ϵ -aminocaproic acid) and tranexamic acid are used to inhibit overt fibrinolysis, which act by blocking the lysine-binding site on plasmin [6[•]]. Protamine sulfate reverses the anticoagulant effects of heparin by binding to it. It is a highly cationic peptide. It binds to heparin to form a stable ion pair, which does not have anticoagulant activity. The half-life of protamine is shorter than the half-life of heparin, which could lead to recurrent anticoagulation and bleeding after apparently successful reversal of heparin. On the contrary, the heparin–protamine complex may also be partially metabolized or may be attacked by fibrinolysin, thus freeing heparin. Protamine administered alone has a weak anticoagulant effect.

Specific goal-directed transfusion, transfusion algorithms

Algorithms show decision-making treatment processes and problem-solving strategies by giving clearly defined and formalized guidelines. With the help of clinical algorithms, highly complex processes such as the management of bleeding can be translated into a clearly structured, logical pathway [72[•]]. Specific goal-directed transfusion can be achieved by using such algorithms, leading to a reduction in blood component used and to a possible better outcome by stopping bleeding in trauma early.

At our institution, we recently implemented a transfusion algorithm for massively bleeding patients (Fig. 2). This algorithm incorporates information obtained from the patient’s history, clinical presentation and routine coagulation laboratory and bedside viscoelastic coagulation tests. Interestingly, our experience implementing and adhering to a transfusion algorithm is in accordance with previous studies [27,72[•],73] showing significant reduction in the number of transfusions administered and decrease of blood loss and costs. For example, in the first 6 months after implementation of the algorithm, the use of FFP dropped by approximately 50% and RBCs as well as platelet administration decreased by approximately 20% each. Despite a moderate increase in costs for point-of-care coagulation monitoring and more frequent administration of specific coagulation factor concentrates (fibrinogen, factor XIII, PCC and rFVIIa), we had significant cost savings in these first 6 months after implementing our algorithm.

Adverse effects of transfusion

The administration of blood products is associated with several adverse effects [74], including viral or bacterial transmission [75]. This is perceived to be under control in developed countries [76]; however, there are other issues.

Figure 2 Transfusion algorithm

TRANSFUSION ALGORITHM		TRANSFUSION ALGORITHM	
CONDITION / COAGULATION VALUES	ACTION TO BE TAKEN	CONDITION / COAGULATION VALUES	ACTION TO BE TAKEN
BASELINE		BLOOD LOSS ≥ 60 % OF EBV (ESTIMATED BLOOD VOLUME) AND DIFFUSE MICROVASCULAR BLEEDING	
Patient's history, Routine Coags, ROTEM <ul style="list-style-type: none"> Acquired coagulation disorders (e.g. medication, HIT II) Hereditary coagulation disorders Routine lab. coags: Hb, Hct, PT/INR, aPTT, TT, Fibrinogen, Platelets EX-, IN-, FIB-, APTEM 	Volume replacement <ul style="list-style-type: none"> Cristalloids and colloids 	ROTEM EX-, IN-, FIB-, APTEM; HEPTEM in cardiac and vascular surgery	<ul style="list-style-type: none"> FXIII (Fibrogammin®) 15 IU/kg BW IV, if FIBTEM MCF remains ≤ 7 mm, give Fibrinogen and inform Backup
BLOOD LOSS ≥ 50 % OF EBV (ESTIMATED BLOOD VOLUME) AND DIFFUSE MICROVASCULAR BLEEDING	Correct and treat (aim): <ul style="list-style-type: none"> Hypothermia (T ≥ 35°C) Hypocalcaemia Acidosis Anemia (Hct ≥ 21 %) Hypertension (MAP 55 - 65 mmHg) (except TBI, MAP 80 - 90 mmHg) Volume replacement: <ul style="list-style-type: none"> Cristalloids and colloids 	<ul style="list-style-type: none"> EX-, INTEM MCF < 40 mm Platelets ≤ 50 000/μl (≤ 100 000/μl cardiac surgery and TBI) 	Volume replacement: <ul style="list-style-type: none"> Cristalloids and colloids
<ul style="list-style-type: none"> FIBTEM MCF ≤ 7 mm 	Fibrinogen 2 - 6 g IV, after a total of 6 g Fibrinogen - FXIII (Fibrogammin®)	Ongoing haemorrhage <ul style="list-style-type: none"> ROTEM EX-, IN-, FIB-, APTEM Coags including FXIII 	Keep FXIII ≥ 60%: FXIII ≤ 40 %, then <ul style="list-style-type: none"> Fibrogammin® 20 IU/kg BW IV FXIII ≤ 50 %, then <ul style="list-style-type: none"> Fibrogammin® 15 IU/kg BW IV
<ul style="list-style-type: none"> INTEM CT and CFT prolonged, HEPTEM normal and / or ACT prolonged, Heparinase-ACT normal 	Protamine sulfate	BLOOD LOSS ≥ 200 % OF EBV (ESTIMATED BLOOD VOLUME) AND DIFFUSE MICROVASCULAR BLEEDING	Platelet concentrate
<ul style="list-style-type: none"> EX-, INTEM decline of MCF after maximum plus APTEM normal (Hyperfibrinolysis) 	Tranexamic acid (Cyklokapron®) <ul style="list-style-type: none"> Bolus: 15 mg/kg BW IV Followed by 1 - 2 mg/kg/h 	EXTEM CT, CFT and MCF abnormal	Fresh frozen plasma <ul style="list-style-type: none"> 15 ml/kg body weight (i.e., 2 - 4 bags)
		ONGOING MASSIVE HAEMORRHAGE AND DIFFUSE MICROVASCULAR BLEEDING	Factors II, VII, IX, X- concentrate (Beriplex®P/N 500) <ul style="list-style-type: none"> 500 - 2000 IU IV depending on BW, INR
		<ul style="list-style-type: none"> No acidosis, no hypothermia, no hypocalcaemia, no DIC Fibrinogen substituted, Hct ≥ 21% Platelets ≥ 50 000/μl (≥100 000/μl cardiac surgery and TBI) 	Recombinant factor VIIa (NovoSeven®) <ul style="list-style-type: none"> Initial dose: 90 μg/kg BW IV Repeat if necessary after 2-4 hours at 45 μg/kg BW IV

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This transfusion algorithm has been created and implemented by the Institute of Anesthesiology, University Hospital in Zurich, Zurich, Switzerland, for specific goal-directed transfusion of blood products and coagulation factor concentrates. aPTT, activated partial thromboplastin time; EBV, estimated blood volume; ROTEM, rotation thrombelastometry; TBI, traumatic brain injury.

RBC transfusion has been found to be a highly significant and independent factor for an increased mortality and morbidity in a variety of surgical situations [77]. Nosocomial infections are several-fold more frequent in transfused than in nontransfused patients [45,78,79]. Another risk reflects the TRALI [80,81] occurring during or within 6 h of transfusion [82••]. The risk for TRALI is estimated to be one in 1000 to one in 4000 units transfused with a significant mortality [82••]. Furthermore, immune suppression or modulation potentially associated with multiple organ failure (MOF) and an increased cancer recurrence is another adverse effect of allogeneic blood transfusions [83–85], particularly with long storage times [86••].

Differences between civilian and noncivilian sectors

In recent publications by the US military, the use of fresh whole blood has been described for soldiers with life-

threatening injuries. Spinella and coworkers [87,88] found that survival improved 48 h and 30 days after whole blood transfusion compared with massive transfusion of stored red cells. The risk of transmission of infectious agents and other microorganisms remains higher for fresh whole blood than blood component therapy. In the civilian sector, such protocols thus are not applicable.

Trauma exsanguination protocols such as that described by Cotton *et al.* [89•] try to create whole blood conditions by transfusing fixed amounts of RBCs, FFP and platelets; however, this does not seem to be an adequate strategy in civilian trauma management, in which the goal must be specific management and replacement of blood components and factors according to online bedside coagulation monitoring, which may not be feasible in a military environment.

Conclusion

Although a lot of progress has been made in the field of trauma patients, treatment of massive bleeding still remains an interdisciplinary challenge for surgeons and anesthesiologists. Modern and future transfusion strategies are based on online bedside coagulation monitoring with specific goal-directed administration of antifibrinolytics, coagulation factors, RBCs, FFP and platelets to optimize coagulation early. This improves the patient's outcome, minimizes the patient's exposure to blood products and reduces costs.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 325).

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