Resuscitation and transfusion management in trauma patients: emerging concepts

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Purpose of review
Severe trauma is associated with hemorrhage, coagulopathy and transfusion of blood and blood products, all associated with considerable mortality and morbidity. The aim of this review is to focus on resuscitation, transfusion strategies and the management of bleeding in trauma as well as to emphasize on why coagulation has to be monitored closely and to discuss the rationale of modern and future transfusion strategies.

Recent findings
Coagulopathy and uncontrolled bleeding remain leading causes of death in trauma, lead to blood transfusions and increased mortality as it has been recently shown that blood transfusion per se results in an adverse outcome. In the last years, damage control resuscitation, a combination of permissive hypotension, hemostatic resuscitation and damage control surgery, has been introduced to treat severely traumatized patients in hemorrhagic shock. Goals of treatment in trauma patients remain avoiding metabolic acidosis, hypothermia, treating coagulopathy and stabilizing the patient as soon as possible. The place of colloids and crystalloids in trauma resuscitation as well as the role of massive transfusion protocols with a certain FFP : RBC ratio and even platelets have to be reevaluated.

Summary
Close monitoring of bleeding and coagulation in trauma patients allows goal-directed transfusions and thereby optimizes the patient’s coagulation, reduces the exposure to blood products, reduces costs and may improve clinical outcome.

Keywords
goal-directed transfusions, ROTEM, thrombelastometry, transfusion management, traumatic coagulopathy

INTRODUCTION
Although considerable progress has been made in the field of trauma resuscitation in the last few years, hemorrhage and coagulopathy remain one of the major causes of mortality in civilian trauma patients and combat casualties [1,2]. Some studies claim that up to 20% of deaths in trauma could be preventable as the majority is linked to uncontrolled bleeding [3–5]. One-third of patients arriving in the emergency rooms have already or will present coagulopathy further increasing the risk of uncontrolled bleeding [6–8]. Morbidity and mortality in trauma-induced coagulopathy is up to four times higher than in patients who do not present this state. It thus remains a crucial goal of resuscitation management to correct and prevent this type of coagulopathy by early aggressive treatment in order to increase the chances of survival [8,9,10*,11]. This review will focus and discuss the ways of resuscitation, volume management, transfusion management, the use of point-of-care devices and the actual views and understandings of coagulopathy in trauma, the concept of damage control as well as related costs.

COAGULOPATHY IN TRAUMA
Coagulopathy in trauma was classically described as being caused by hypothermia, metabolic acidosis,
The liberal use of colloids thus cannot be generally 
diluted from excessive intravenous fluid and the 
the consumption of coagulation factors [12]. This 
Coagulopathy occurring within the first half–
an-hour after trauma is not related to hemodilution 
but to hypoperfusion of tissues inducing an increase 
of tissue plasminogen activator (tPA) and thrombomodulin [11,23]. Thrombomodulin activates protein C which in combination with protein S inhibits factor Va and VIIIa on one side and leads to an 
inhibition of plasminogen activator inhibitor-1 (PAI-1) on the other side. The combination of high 
levels of tPA and low levels of PAI-1 leads to a hyper-
fibrinolytic state [6,11,23,24,25*]. Another theory postulates that acute traumatic coagulopathy is 
not induced by activation of tissue factor but is the 
result of the consumption of coagulation proteases 
and the development of a disseminated intravascular 
coagulation syndrome with a significant fibrinolytic 
and hyperfibrinolytic component [26**,27].
Up to 60% of the patients having major trauma 
will present acute traumatic coagulopathy regardless 
of the pathophysiology which is behind 
this phenomenon. Hyperfibrinolysis is of clinical 
importance as it results in increased transfusion 
requirements and increased mortality and morbidity [18**,28–30]. Furthermore, coagulopathy leads 
to massive transfusion which is commonly defined 
as an administration of greater than 10 units of RBCs 
within the first 24 h. Different scores for predicting 
massive transfusions are found in the literature; 
variables used include blood pressure, injury mechanism, age, injury severity score (ISS), temperature, laboratory values (pH, PT, and base excess), point-of-care devices (ROTEM, TEM, International GmbH, Munich, Germany), sex and focused assessment 
with sonography for trauma (FAST), but none of 
these scores is able to correctly classify every patient. 
Nevertheless, the continuing interest in their use 
suggests that an early identification of patients in need for massive transfusion might be useful either 
to start early treatment to prevent it or to be aware of the risk [31–33,34**,35–37].

CONCEPT OF DAMAGE CONTROL

New studies on the pathophysiology of acute coagulopathy in trauma and data published by the U.S. army lead to a shift in the treatment of trauma patients using multiple approaches to control tissue hypoperfusion, acidosis, trauma coagulopathy and hypothermia [38].

The first goal in this concept which aims at controlling hemorrhage is to stop the bleeding 
which mainly requires a surgical intervention. The second step of this concept is stopping
hypoperfusion, correcting acidosis, reversing hypothermia and getting coagulation under control. As severely injured trauma patients do not tolerate prolonged operative procedures, effective hemorrhage control is accomplished with the concept of damage control surgery by applying temporary, yet life-saving surgical procedures immediately after injury, with delayed definitive corrective surgery at a later date after the patient has been stabilized in the ICU.

So far, there is no evidence to support neither reversal of acidosis with bicarbonate nor repletion of calcium and magnesium, which could be desirable. Administration of fix packages of red blood cells, fresh frozen plasma and platelets has been discussed in the past years both in the civilian and military sector for patients suffering severe injury and needing massive transfusions. As this topic is discussed controversially, it will be mentioned under the section ‘resuscitation concepts, volume and transfusion management’ in this review.

At the present time, prospective trials supporting damage control resuscitation in case of major bleeding trauma are missing even if these concepts are widely accepted in practice and are mentioned in guidelines [39,40].

LABORATORY RESULTS AND POINT-OF-CARE DEVICES

Diagnosis of coagulopathy in trauma remains a problem. Laboratory tests differ from one laboratory to another and not all tests are available 24 h a day in every hospital. Activated partial thromboplastin time and partial thromboplastin time are mainly used. However, the problem is that there is a lack of consensus on the definition of traumatic coagulopathy and on the cut-off values that should be used [10*,41*,42]. Another problem is that these laboratory tests are performed in plasma only, not revealing the entire reality of coagulation in whole blood in vivo, although some studies claim that activated partial thromboplastin time and partial thromboplastin time are independent predictors for mortality in trauma patients [7,43,44]. Furthermore, the time these results take to be available is usually in the range of 45–75 min which is far too long in a bleeding patient. In addition and importantly, acute hyperfibrinolysis cannot be detected [18**].

In the last few years, rotation thrombelastometry (ROTEM), a viscoelastic test in whole blood, is increasingly used in trauma in both the civilian and combat setting, progressively replacing thromboelastography (TEG, Hemoscope Corporat, Niles, IL, USA) [45*,46*]. ROTEM provides within 5–10 min information on the initiation of coagulation, clot strength as well as coagulation factors, fibrinogen, platelets and hyperfibrinolysis as part of acute traumatic coagulopathy [18**,47,48]. A recent study using ROTEM was even able to provide guiding information whether massive transfusion would be needed in patients or not [33]. Also mortality after trauma is independently associated with low clot strength values determined by ROTEM [49*].

As it is possible to distinguish different hemostatic disorders following trauma, viscoelastic tests, particularly ROTEM, provide a means of individualizing coagulation management for patients and guiding transfusion resuscitation. However, in order to achieve this in a standardized way, algorithms are needed (detailed information is provided in the next section) [11,50,51].

RESUSCITATION CONCEPTS, VOLUME AND TRANSFUSION MANAGEMENT AND ALGORITHMS

One major progress in trauma resuscitation was the introduction of permissive hypotension which limits fluid therapy, either by delaying the time of administration or minimizing the volume given [38]. The goal of this approach is to reduce fluid administration and thus to reduce dilutional coagulopathy as well as hypothermia induced by cold solutions by accepting a low systolic blood pressure until the bleeding source is surgically under control [52].

Data on permissive hypotension are unfortunately sparse and controversial. One older randomized controlled trial from 1994 reported a reduction of around 10% in mortality in patients with penetrating trauma who had a permissive hypotension until surgery [53]. Other studies were not able to reproduce these results and a systematic review in the Cochrane Database from 2003 could not confirm benefit or harm form permissive hypotension [54].

In the last year, three interesting studies on that subject were published, two in animals and one in humans. One study in rats showed that hypotension with a mean arterial pressure of 50–60 mmHg in uncontrolled hemorrhagic shock had the most benefit on survival provided that the hypotensive period was of less than 90 min [55*]. In contrast, a pig model with blast injuries showed poorer outcome with permissive hypotension compared to normotensive resuscitation [56].

The third study, a randomized control trial in humans, in which 271 patients were recruited, where a mean arterial pressure of 50 versus 65 mmHg during initial surgery was compared showed already in the preliminary data with
90 patients that the group with the lower mean arterial pressure received less blood products, smaller volumes of intraoperative fluids, was less likely to develop postoperative coagulopathy and had a significantly lower all cause early mortality rate [57]. However, in the group with higher mean arterial pressure, the mean arterial pressure was higher than defined in the protocol and ISS was higher and blunt trauma more frequent compared to the low mean arterial pressure group. The final results once all patients are recruited will be available soon and may give future useful information.

Volume management with the longstanding crystalloids versus colloids debate is also being discussed controversially. Two large systematic reviews of 65 randomized controlled trials and with 90 trials of colloids compared to crystalloids in patients requiring volume replacement published in 2011 in the Cochrane Library by Perel and in 2012 by Benn showed that there is actually no evidence that resuscitation with colloids reduces the risk of death compared to resuscitation with crystalloids [58,59]. The first randomized, double-blind, controlled trial (called FIRST trial) recently published comparing saline with HES 130/0.4 in trauma resuscitation showed that lactate was lower in the HES group at day 1. Renal injury was only present in the saline group. Maximum sequential organ failure was lower in the HES group, but the HES group required significantly more blood and blood products. Outcomes were similar in terms of renal function and organ recovery, with no differences in mortality [60]. The liberal use of colloids thus cannot be generally advocated in trauma, except in situations in which the administration of crystalloids has proven ineffective; a negative effect on blood coagulation has to be expected.

Reduction of intracranial brain pressure, by improving cardiovascular output, cerebral oxygenation and reducing cerebral edema by administering small volumes of hypertonic saline in traumatic brain injury is reported [61]. There are no trials providing compelling evidence to support the use of hypertonic saline, neither for traumatic brain injury nor for hemorrhagic shock. The study by Bulger et al. [62] published in 2011 showed no significant difference in mortality at 28 days, but this study was terminated early because of concerns of a potential increase in mortality observed with a subgroup of patients receiving hypertonic saline but no blood transfusions within the first day.

As the use of blood products in trauma resuscitation often cannot be avoided, there were discussions coming up in the last few years on the optimal ratio of fresh frozen plasma and red blood cells to be delivered tending to a 1 : 1 ratio to control coagulopathy [38].

The problem is that a high percentage of data are from the military setting, in which the type of trauma is not comparable to the civilian sector and where the availability of bedside monitoring and factor concentrates is scarce. Results to be found in the literature confer: some report a reduction of up to 50% in patients receiving high ratios of FFR : RBC; some that FFP is beneficial in massive transfusions; others that FFP is of little benefit and leads to higher complications especially ARDS and multiorgan failure; and that coagulation is still not better or that there was no improvement in survival [63–76]; in addition, these retrospective studies on FFP : RBC ratio have to be interpreted with caution. The main criticism does not so much relate to the fact that cause and effect are difficult to establish with retrospective data, but rather to the danger of a so-called ‘survivor bias’. This means that those patients who survived longer were more likely to receive FFPs in contrast to patients who died early after admission. A recent work by Ho and colleagues addressed this problem. Searching the MEDLINE database (from 1966 to 2011), they identified a total 26 studies from 2007 to 2011 comparing high and low FFP : RBC ratios for bleeding trauma patients. Fifteen of these 26 studies were classified as survivor bias-unlikely. Importantly, 10 of these 15 studies showed an association between higher FFP : RBC ratio and improved survival, whereas five did not [77]. Therefore, the argument of a potential survivor bias is not valid to reject all observational studies. Only well designed, randomized controlled trials can give a conclusive answer to this question. To date, there is one multicenter, prospective, randomized trial on the way, the PROPPR (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) trial (http://ct.gov/show/NCT01545232?term=PROPR&rank=1).

There is overwhelming evidence that blood and its products like FFP and platelets are associated with mortality, morbidity, increased length of stay, multiorgan failure, infections, transfusion overload, sepsis and TRALI [78]. Thus, the balance between risk and benefit of blood and its products has to be weighted carefully. Increased use of platelets and red blood cells was also discussed in addition with fibrinogen, showing no strong evidence for better outcome [76,79,80]. One major problem of all
those retrospective observational trials is that not all patients surviving have the same type of injuries [70,81].

According to the guidelines of the American Society of Anesthesiologists, red blood cell transfusion is recommended if the hemoglobin concentration drops below 6–10 g/dl. Transfusions over 10 g/dl are rarely indicated and transfusions seem almost always to be indicated if hemoglobin falls below 6 g/dl [82]. In Europe, a hemoglobin target of 7–9 g/dl is largely accepted in major trauma [39,83]. Physiological transfusion triggers on the contrary are tachycardia, hypotension, oxygen extraction higher than 50%, mixed venous oxygen partial pressure of less than 32 mmHg (4.3 kPa), increase of lactate and ECG changes [11,84,85]. The grade of shock, hemodynamic response to resuscitation and the rate of actual blood loss in the bleeding and hemodynamically unstable patient have also to be integrated into the indication for red blood cells transfusion; however, blood transfusions should be used restrictively and the risk versus the benefit has to be evaluated carefully [86].

In Europe and partially in other countries, several coagulation factor concentrates are available and can be substituted selectively. Fibrinogen is an essential substrate for clot formation. Several in-vitro and animal studies [87,88] have shown that fibrinogen substitution is capable of reversing 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 leads to better survival [19,89,90]. As hyperfibrinolysis might be a major problem in trauma, the use of tranexamic acid is essential [18**]. The CRASH-2 trial with over 20 000 patients included examined the effect of tranexamic acid versus placebo on mortality and transfusion requirement in adults with traumatic injury and hemorrhagic shock. All-cause mortality was reduced following tranexamic acid administration as was mortality from bleeding [91]. The maximal beneficial effects of tranexamic acid were achieved when tranexamic acid was administered within the first 3 h after trauma [92**]. Very recent studies confirm the fact that tranexamic acid is a useful tool in bleeding trauma patients [93**,94**].

Factor XIII is the key coagulation factor to stabilize the clot and additionally seems to have a certain influence on hyperfibrinolysis [95*,96]. Trauma and major hemorrhage are known to be a cause of acquired factor XIII deficiency [97]. It seems reasonable to substitute factor XIII early, thereby improving clot firmness, reducing bleeding and minimizing the use of blood products [98]. The effect of factor XIII on coagulation has been shown in a trial by spiking blood with factor XIII. This trial also showed that low concentrations of fibrinogen can be compensated by higher concentrations of factor XIII [47,96].

Prothrombin complex concentrates (PCCs) provide a source of vitamin K-dependent coagulation factors. Depending on different production techniques, there exist both three-factor (USA) and four-factor (Europe) PCCs that are recommended for emergent reversal of oral anticoagulants [99*,100,101**]. Furthermore, studies 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 and one should be aware of a possible thrombotic risk [102–110,111**].

Recombinant activated factor VII (rFVIIa) transforms fibrinogen to fibrin by inducing a thrombin burst. Risks and benefits of a treatment with rFVIIa have to be carefully evaluated and economic aspects taken into consideration, as the consensus view remains that there is no strong evidence to support rFVIIa use in the standard treatment for traumatic bleeding [112].

**COSTS**

As bleeding management is a highly complex process, algorithms are needed to get a standardized, logical and clearly structured pathway to treat this complex pathology [11,113]. Goal-directed transfusion algorithms have the potential of reducing blood components and leading to a favorable outcome by controlling the nonsurgical bleeding in trauma. At our institution, we recently implemented the second version of the transfusion algorithm for massively bleeding patients (Fig. 1). This algorithm incorporates information obtained from the patient’s history, clinical presentation, coagulation laboratory tests and bedside viscoelastic coagulation tests. Despite an increase in costs for point-of-care coagulation monitoring and more frequent administration of specific coagulation factor concentrates, algorithms may be cost saving and the future in treating traumatic bleeding. Interestingly, similar algorithms have shown to result in a lower than expected mortality and a shorter length of hospital stay in severely injured patients [30,51].
## Diagnostic Intervention

### Preoperative history

1. Coagulation-effecting drugs
   - Antiplatelet drugs
   - Heparin
   - Oral anticoagulation
2. Coagulation status?
3. HIT II?

### ROTEM after anesthesia induction
- Transplant surgery
- Cardiac and vascular surgery
- Difficult cancer surgery
- Liver insufficiency
- Intra-abdominal sepsis
- Trauma room entry

### Blood loss >50% with diffuse bleeding

#### ROTEM analysis
- EXTEM, INTEM, FIBTEM, APTEM
- HEPTEM in heart and vascular surgery

#### Target values
- Hypothermia (temperature >35°C)
- Hypocalcemia (Ca >1.15 mmol/l)
- Acidosis
- Anemia (haematocrit >0.21)
- Hypertension (MAP 55–60 mmHg)

#### Crystalloid and/or colloid volume substitution

### FIBTEM <7 mm
- Fibrinogen 2–4 g i.v. (maximal 3x2g), after a total of 6 g give FXIII

### INTEM (CT and CFT prolonged)
- Protamine sulphate 1 : 1 to heparin

### HEPTEM normal, and/or ACT pathological or heparinase ACT normal
- Tranexamic acid
  - 15 mg/kg bodyweight as bolus i.v.
  - 1–2 mg/kg/h during surgery i.v. as perfusion

#### Crystalloid and colloid volume substitution

### EXTEM/INTEM
- Decrease of MCF after maximum was reached
- APTEM: normal
  - Hyperfibrinolysis

#### Ongoing diffuse bleeding

### EXTEM/INTEM MCF <40 mm
- Fibrinogen up to 6 g, followed by factor XIII 15 U/kg bodyweight

#### Crystalloid and colloid volume substitution

#### Platelet concentrates
- Target area of factor XIII: > 60%
- Target area of factor V: > 20% (in particular in liver insufficiency or intra-abdominal sepsis 2–4 U FFP)

### Ongoing diffuse bleeding

#### Quick’s value < 30% and Factor V > 20%
- 4 factor prothrombin complex concentrate 1000–2000 IU
  - Factor II, VII, IX and X
  - Depending on the patients’ bodyweight

#### In case of massive transfusion
- Target haematocrit >0.21–0.24

#### If massive diffuse bleeding continues and

#### Treated acidosis
#### Treated hypothermia
#### Excluding hypocalcemia
#### Hematocrit > 0.21–0.24

#### Excluding DIC
- Fibrinogen was substituted
- Platelets <50 000/μl (<100 000/μl in cardiac surgery or in patients suffering from traumatic brain injury)

#### Recombinant factor VIIa
- 60 μg/kg body weight i.v.
- A second dose of 60 μg/kg bodyweight i.v. can be given again after 2–4 h, if bleeding is not completely stopped

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**FIGURE 1.** Second version of the transfusion algorithm of the University Hospital of Zürich – copyright 2012, Switzerland.
CONCLUSION
Tissue hypoperfusion and ischemia seem to be the major causes of coagulopathy of trauma characterized by hypocoagulopathy and hyperfibrinolysis. Close monitoring of bleeding and coagulation allows individualized and goal-directed treatment algorithms to optimize patients’ coagulation and to reduce the need and exposure to blood products resulting in improved clinical outcome.

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Conflicts of interest
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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 (pp. 726–727).


This review collated and summarized all the systematic review evidence relating to the diagnosis and management of trauma-related coagulopathy and transfusion, thereby covering the widest possible body of literature. There is need for randomized controlled trials to answer these questions. The approach described in this report provides a framework for incorporating new evidence.


A retrospective review of data over a 5-year period was performed to determine the associations between variables considered to contribute to mortality for adult major trauma patients receiving blood transfusions as part of their initial resuscitation. There were 772 patients included in this study. Acute traumatic coagulopathy, independent of injury severity, transfusion practice or other physiological markers for hemorrhage, was associated with early death in major trauma patients requiring a blood transfusion. Early recognition and management of coagulopathy, independent of massive transfusion guidelines, may improve outcome from trauma resuscitation.


26. This study showed that early induced trauma coagulopathy following injury is associated with decreased factor activities without significant differences in thrombin and fibrinogen generation, suggesting that despite these perturbations in the coagulation cascade, patients displayed a balanced hemostatic response to injury. The lower factor activities are likely secondary to increased hemodilution and coagulation factor depletion. J Trauma 2011; 70:1401–1407.


29. This study shows as previous did already that the maximum clot firmness after 10 min of ROTEM provides an early sensitive and specific assessment of coagulopathy after military trauma and may be of utility in guiding bespoke resuscitation.


33. This study summarizes the opinion of international experts on coagulation in trauma and its treatment in different countries.


41. This review looked at 35 randomized clinical trials and there has been little improvement in outcomes over the last few decades. No clear correlation has been demonstrated between transfusion requirements and mortality. The global trauma community should consider a coordinated and strategic approach to conduct well designed studies with pragmatic endpoints.


46. This is a very important study showing that mononuclear with kaolin (TEG) was unable to distinguish coagulopathies caused by dilution from that of thrombocytopenia. Algorithms based on the use of kaolin may lead to unnecessary transfusion with platelets, whereas the application of TEM-reactants (ROTEM) may result in goal-directed fibrinogen substitution.


48. This study provides additional evidence showing that ROTEM assays are useful in trauma patients. Treatment concepts should focus on maintaining fibrin polymerization and treating hyperfibrinolysis.


Resuscitation and transfusion management Theusinger et al.


This study shows that a target resuscitation pressure of 50–60 mmHg is the ideal blood pressure for uncontrolled hemorrhagic shock. Ninety minutes of permissive hypotension is safe in rats, with a 120 min of hypotensive resuscitation can cause severe organ damage and should be avoided.


This study shows that hypotensive resuscitation is a safe strategy for use in the trauma population and results in a significant reduction in blood product transfusions and overall IV fluid administration. Specifically, resuscitating patients with the intent of maintaining a target minimum MAP of 50 mmHg, rather than 65 mmHg, significantly decreases postoperative coagulopathy and lowers the risk of early postoperative death and coagulopathy. These preliminary results provide convincing evidence that support the continued investigation and use of hypotensive resuscitation in the trauma setting.


This study shows that in penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline. No firm conclusions could be drawn for blunt trauma.


This observational studies on transfusion in trauma comparing high versus low plasma:erythrocyte ratio were prone to survivor bias because plasma transfusion typically started later than erythroctyes. When early deaths were excluded, however, a bias against higher ratio can be created. Survivor bias could be reduced by performing before-and-after studies or treating the plasma:erythrocyte ratio as a time-dependent covariate. Without randomized controlled trials controlling for survivor bias, the current available evidence supporting higher plasma:erythrocyte resuscitation is inconclusive.


Improved survival was observed in patients receiving a higher plasma ratio over the first 24 h. However, temporal analysis of mortality using shorter time periods revealed those who achieve early high ratio are in less shock and less likely to die early from uncontrolled hemorrhage compared with those who never achieve a high ratio. Thus, the proposed survival advantage of a high ratio may be because of selection of those not likely to die in the first place, that is, patients die with a low ratio not because of a low ratio of.

This was the first randomized controlled study to evaluate the effect of tranexamic acid in traumatic brain injury patients and it found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, this analysis suggests that tranexamic acid administration might improve outcome in traumatic brain injury patients and provides grounds for evaluating this hypothesis in future research.


This study on hyperfibrinolysis showed that in thromboelastometric assays using whole blood, only tranexamic acid, factor XIII, and PCC significantly inhibited r-tPA-evoked hyperfibrinolysis, whereas rFVIIa had no effect. The effects of exogenous factor XIII were dependent on the presence of functional platelets.


This study showed that patients with a higher initial INR are less likely to achieve adequate INR reversal after receiving three-factor PCC and may require higher doses than were used in this study.


In severely hypothermic pigs, the application of PCC corrected trauma-induced coagulopathy and reduced blood loss. Thus, the infusion of PCC might be a reasonable approach to reduce the need for blood cell transfusion in trauma. Furthermore, the impact and safety of PCC application can be monitored through thrombin generation and thromboelastometry under hypothermia.


PCCs are used mainly for emergency reversal of vitamin K antagonist therapy, The aims of the present review are to examine thrombotic complications reported with PCCs and to compare the safety of PCCs with human fresh frozen plasma. The risk of thrombotic complications may be increased by underlying disease, high or frequent PCC dosing and poorly balanced PCC constituents. The causes of PCC thrombogenicity remain uncertain, but accumulating evidence indicates the importance of factor II (prothrombin). With the inclusion of coagulation inhibitors and other manufacturing improvements, today’s PCCs may be considered safer than earlier products. PCCs may be considered preferable to fresh frozen plasma for emergency anticoagulant reversal, and this is reflected in the latest British and American guidelines. Care should be taken to avoid excessive substitution with prothrombin, however, and accurate monitoring of patients’ coagulation status may allow thrombotic risk to be reduced. The risk of a thrombotic complication because of treatment with PCCs should be weighed against the need for rapid and effective correction of coagulopathy.
