Volume and Blood Management

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Learning Objectives

- Volume therapy during the initial trauma resuscitation
- Transfusion and coagulation management including an example of a coagulation and transfusion algorithm
- Proper management of anticoagulated trauma patients
- Laboratory screening for oral anticoagulants in trauma patients
- Reversal and treatment of residual anticoagulant effects in case of an ongoing bleeding

7.1 Introduction

Traumatic injuries are one of the leading causes of death worldwide. Uncontrollable bleeding is thereby still the main preventable cause of death in severely injured patients [1]. A key element of *the European guideline on management of major bleeding and coagulopathy following trauma* is therefore to identify and stop the bleeding as fast as possible [2]. Beside surgical care for the cause of bleeding, trauma resuscitation also means detecting and treating systemic coagulation disorders quickly in order to stabilize the patient. Systemic coagulation disorders in the context of trauma are multifactorial in nature: Bleeding causes a loss of coagulation factors and requires fluid therapy to maintain circulation which leads to a further dilution of the remaining coagulation factors [3, 4]. Acidosis and hypothermia additionally impair the enzymatic activity of the coagulation factors, while protein C is simultaneously activated to prevent excessive, uncontrolled clot formation. Subsequently, the activated protein C forms a complex with protein S, which inactivates the coagulation factors Va and VIIIa by proteolysis with corresponding anticoagulatory effect. Inhibition of the "thrombin-activated fibrinolysis inhibitor" additionally leads to an increase in fibrinolysis. The pathological coagulation activation and, at the same time, excessive clot dissolution (hyperfibrinolysis) leads to further consumption and loss of coagulation factors. This process can quickly become aggravated and self-sustaining, causing so-called trauma-induced coagulopathy [3]. Trauma-induced coagulopathy is now established as an independent clinical pathology leading to an increased morbidity and mortality [5]. To tackle this issue, focused trauma management should already start in pre-hospital care, e.g., by administration of tranexamic acid [6]. Trauma patients are then admitted to a trauma center depending on their injury pattern. In the case of multiple injuries, primarily specialized

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trauma centers should be contacted to provide the best possible care. Parallel to surgical care, initial anesthesiologic care is also provided including stabilization of airway, ventilation, circulation, coagulation, and consciousness. Regarding transfusion and coagulation management a multimodal Patient Blood Management program should be an inherent part of modern, evidence-based trauma care [7, 8]. This chapter will focus on distinct Patient Blood Management strategies that may be implemented in the specific setting of trauma care.

7.2 Volume Therapy

Traumatic hemorrhage leads to a mismatch of oxygen supply and tissue demand due to reduced perfusion [9]. The impaired microcirculation is a main factor for secondary damage after a hemorrhagic shock. Volume therapy therefore aims to improve macro and especially microcirculation and thus organ perfusion [10]. In severely injured patients a venous access should be placed as soon as possible followed by a goal-directed volume resuscitation in order to keep the circulation at a low-stable level and thus without increasing the bleeding [2, 11]. The optimal fluid for volume therapy is still discussed. Colloid solutions were not able to show advantages over crystalloid solutions for volume resuscitation [12–14], but are afflicted with more side effects, especially hydroxyethyl starch [10, 15, 16]. Therefore, colloids are not recommended for volume therapy of trauma patients in first line [2]. In patients not responding to crystalloid solutions, a bolus of gelatin may however be considered as an alternative [2, 16, 17]. Albumin solutions should not be used, as they increased mortality in patients with concomitant traumatic brain injury [18]. Regarding hypertonic solutions, no empiric recommendations are made in guidelines [2]. Hypertonic crystalloids are proven to be safe but failed to show any improvement in survival or neurological outcome after traumatic brain injury. As they have no advantages over balanced crystalloid solutions, they should not be used in first line, but may be considered in special circumstances as an alternative (e.g., severe traumatic brain injury with increased intracranial pressure). Most common crystalloid solutions in clinical routine are balanced full electrolyte solutions (e.g., Ringer's acetate malate or Ringer's lactate) or physiological saline 0.9% solution. Normal saline is still the most commonly administered crystalloid, although its use has long been associated with hyperchloremia, metabolic acidosis, potassium increase, kidney damage up to dialysis, and increased mortality [19]. Based on physiological considerations and the results of initial reviews, a more favorable side effect profile was postulated for balanced electrolyte solutions. Recently, it was shown that balanced electrolyte solutions reduced the incidence of persistent renal dysfunction, new renal replacement therapy, and mortality compared to saline 0.9% [20, 21]. In conclusion, a restrictive, goal-directed volume resuscitation using balanced crystalloid solutions to maintain the circulation at a low-stable level is recommended [2].

7.3 Transfusion Management

The body tolerates acute anemia by increasing cardiac output. Primarily the stroke volume of the heart is increased, secondarily its beat frequency. A critical hemoglobin value is reached when the oxygen supply (as the product of cardiac output and the oxygen content of the blood, of which the hemoglobin concentration is a relevant part) falls below the body's oxygen requirement. Below this, the body's oxygen debt reaches a critical level, which is always fatal if left untreated (at least in animal models) [22]. However, in individual cases, very low hemoglobin levels of up to 1.4 g/dL can be survived without erythrocyte transfusion if cardiac output is increased significantly, a relevant perfusion pressure is maintained and the body's oxygen requirement is reduced [23]. Only few prospective, randomized trials investigated the optimal hemoglobin levels as transfusion triggers in trauma patients. The largest studies have been conducted in patients in intensive care, cardiac surgery, and orthopedics. Mentioned studies aimed, but failed

to prove that a liberal transfusion strategy is superior to a restrictive strategy [24]. Different clinical outcomes were analyzed, including mortality and morbidity consisting of cardiogenic shock, acute renal and pulmonary failure, ability to walk (in orthopedics), rebleeding, and long-term survival. Even in high-risk populations, there was no evidence of improved outcome with liberal transfusion triggers [24]. Also in patients with craniocerebral trauma, a liberal transfusion regime was not associated with an improved neurological outcome [25]. Moreover, a restrictive transfusion strategy was associated with a lower risk of severe or life-threatening bleeding [26]. Based on this data, a transfusion trigger of 7 g/dL is recommended as "the new normal" in all critically ill patients, especially in trauma patients [27]. However, in patients with a concomitant acute coronary syndrome a transfusion trigger of 8 g/dL may be considered. Traumatic blood loss, especially in body cavities in thoracic and abdominal trauma, is often not contaminated and can therefore be re-transfused, especially after preparation in the cell saver. This procedure should be considered early on during trauma care, especially if an emergency insertion of thoracic drainage or an emergency laparotomy is performed.

7.4 Coagulation Management

Coagulation management in trauma patients can be done in two different approaches. It can be based on the transfusion of fresh frozen plasma, packed red blood cells, and platelet concentrates in a fixed ratio [28], or on a goal-directed substitution of coagulation factors [17, 29, 30]. The second approach requires repetitive point-of-care measurements prior and after a targeted factor substitution according to a predefined coagulation algorithm and has been shown to be superior [31–33].

When a trauma patient is admitted to the resuscitation area, coagulation management starts by taking patients medical history, if possible. Physicians should especially focus on preexistent coagulation disorders or anticoagulant medication. In addition to patient's history, blood samples are taken for point-of-care and laboratory measurements to assess blood coagulation at admission and to confirm an eventual, residual anticoagulant effect. Platelet function tests (e.g., Multiplate®, ROTEM platelet®, or TEG® platelet mapping) may be performed if platelet aggregation inhibition is suspected. These tests allow to detect platelet inhibitors and enable to counteract the inhibition of the cyclooxygenase pathway (e.g., acetylsalicylic acid) with desmopressin, or a targeted platelet transfusion depending on the present aggregation inhibitor [34].

One of the most important point-of-care diagnostics are the viscoelastic coagulation tests such as rotational thromboelastometry (ROTEM®) [35]. Four channels investigate and determine coagulation disorders from different pathways: EXTEM (activated by tissue thromboplastin) reflects the extrinsic pathway of the coagulation system, INTEM (surface activation) reflects the extrinsic pathway of the coagulation system, FIBTEM (inhibition of platelets by cytochalasin D) determines functional fibrinogen levels, and APTEM (addition of aprotinin or tranexamic acid) inhibits an ongoing hyperfibrinolysis [35]. In summary, these four channels provide all information to detect low fibrinogen levels, trauma-induced hyperfibrinolysis, low platelet counts, and delayed clotting initiation within a few minutes. This allows a targeted substitution of fibrinogen, tranexamic acid, and other coagulation factors. A factor-based ROTEM® guided coagulation management reduced the exposure of trauma patients to allogeneic blood products and increased survival without in increasing risk for thromboembolic events [17, 30, 36, 37]. Apart from point-of-care testing, standard laboratory coagulation tests are also essential to obtain additional information of the coagulation system. Mandatory are the parameters platelet count, prothrombin time, diluted thrombin time, anti-Xa activity, factor V activity, factor XIII activity, and fibrinogen levels–if no viscoelastic test is available.

Blood coagulation needs an acceptable physiological basis in order to work properly. If this basis is deranged from the beginning on, further

hemostatic therapy will be less effective. Therefore, it is crucial that the following parameters should be controlled initially as follows: Normothermia (>35 degrees Celsius), normocalcemia (free Ca^{++} >1.15 mmol/L), normal acid-base status (pH >7.2), hematocrit 0.21–0.24 (or hemoglobin value 7.0–8.0 g/dL), and permissive hypotension until bleeding control (MAP 55–60 mmHg or 80–90 mmHg in case of a concomitant traumatic brain injury).

The fibrinolysis inhibitor tranexamic acid improves survival of bleeding trauma patients with or without concomitant brain injury [38, 39]. It is crucial to administer tranexamic acid as soon as possible—necessarily within 3 h of injury—to obtain mentioned survival benefit [40]. Therefore, tranexamic acid (Bolus of 15 mg/kg or 1 g i.v.) should already be administered empirically in the pre-hospital setting and the dose should be repeated at hospital admission [2, 6, 41]. Fibrinogen is the first coagulation factor dropping to a critical low level in case of a major bleeding. Therefore, fibrinogen concentrate (2–4 g i.v.) needs to be substituted if ROTEM® findings present a FIBTEM ≤7 mm. Factor XIII concentrate (15 U/kg i.v.) may be given empirically after 6 g of fibrinogen or at if the factor XIII activity in the laboratory results drops below 60%. Platelet concentrate transfusion (1 Unit) is indicated in case of confirmed thrombocytopenia (<50 G/l or <100 G/L in case of a traumatic brain injury) or an EXTEM/INTEM "maximum clot firmness" <40 mm. Platelet count should be reassessed before transfusion of each additional concentrate. Fresh frozen plasma (4 Units) should be administered if the factor V activity drops below 20%. Once fibrinogen, platelets, factor V and XIII are corrected and the prothrombin time is still prolonged (expressed as quick value <30%, INR >2.3 or extended EXTEM clotting time) 4-factor prothrombin complex concentrate (1000–2000 IE) is indicated and may be given as a slow continuous infusion. Protamine should be administered to antagonize residual heparin activity (dose 1:1). This is however uncommon in trauma patients primarily admitted by the emergency medical service. If bleeding still persists despite mentioned anesthesiologic and surgical care, a hematology expert should be consulted. Further therapy options such as administration of von Willebrand concentrates may be indicated only according to expert's advice (Fig. 7.1).

7.5 Management of Anticoagulated Trauma Patients

The expanding use of oral anticoagulants is challenging trauma treatment nowadays. Physicians are increasingly encountering patients taking oral anticoagulants in a wide variety of situations. This underlines the growing importance of this topic. Substances used for oral anticoagulation are vitamin K antagonists (VKA) such as phenprocoumon or acenocoumarol and the newer direct oral anticoagulants (DOAC). Currently available DOAC include the thrombin (factor IIa) antagonist dabigatran, and the factor Xa antagonists rivaroxaban, apixaban, and edoxaban. Betrixaban is another factor Xa antagonist, but currently not available in Europe. Main indications are the therapy and secondary prophylaxis of venous thromboembolism, the prevention of stroke and systemic embolism in non-valvular atrial fibrillation, and thromboprophylaxis after hip and knee replacement. These pathologies predominantly affect older patients in whom comorbidities with an impact on oral anticoagulants excretion and bleeding risk occur more frequently [42].

7.5.1 Screening for Oral Anticoagulants

In an emergency setting—e.g., following trauma—it is important to identify patients taking oral anticoagulants fast and reliable in order to control bleeding. Unconscious patients are particularly challenging, since no medical history can be taken, and physicians must therefore recognize an oral anticoagulant effect by other means. Laboratory analyses are an important and unavoidable diagnostic tool for this purpose. They are not only able to detect an existing oral anticoagulant effect, but depending on the test,

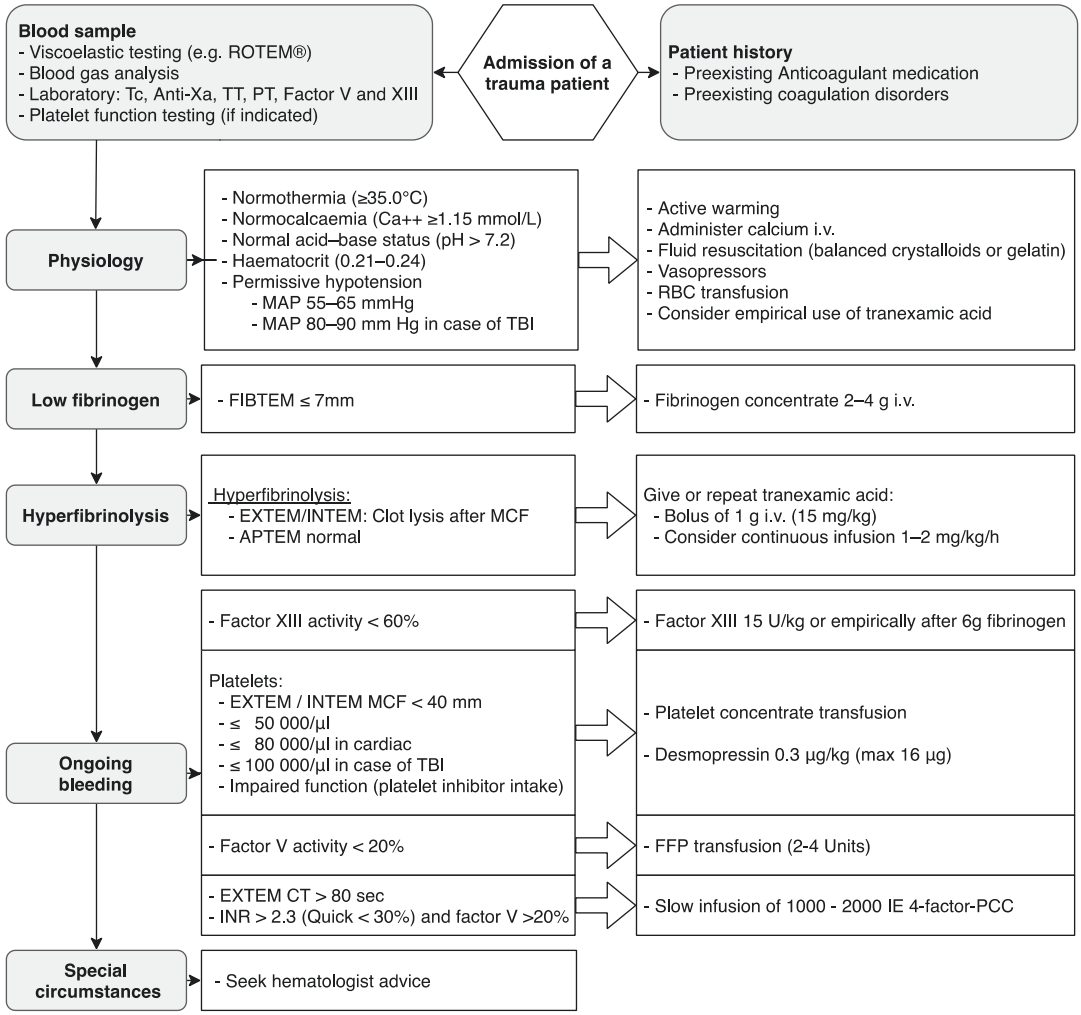

Fig. 7.1 Graphic illustration of the coagulation and transfusion algorithm of the Institute of Anesthesiology at the University Hospital Zurich

also able to quantify the underlying plasma level. In laboratory analyses, a distinction is made between so-called standard coagulation tests (prothrombin time expressed as a quick or INR value, activated partial prothrombin time, and thrombin time) and special measuring methods such as liquid chromatography with mass spectrometry or measurement of the anti-factor Xa activity (anti-Xa). The latter is currently recommended for quantifying the DOAC activity. While standard coagulation tests are available around the clock in every hospital, this is not the case for special measurement procedures such as anti-Xa measurement, especially in smaller hospitals [43]. Not all oral anticoagulants can be measured and quantified by the same test: VKA affect primarily PT/Quick test and INR, which serve for their monitoring and have no effect on thrombin time and fibrinogen. Dabigatran significantly prolongs thrombin time and fibrinogen may be underestimated in the presence of a high dabigatran plasma level. Factor Xa antagonists (rivaroxaban, apixaban, edoxaban) are the only class of oral anticoagulants with an impact on anti-Xa activity assays and have no effect on thrombin time or fibrinogen (Table 7.1).

Table 7.1 Overview of the impact of different OAC on coagulation assays

	PT/INR	Thrombin time	Anti-Xa assay
VKA	+++	–	–
Dabigatran	–/+	+++	–
Factor Xa antagonists	–/+	–	+++

7.5.2 Reversal and Treatment of Oral Anticoagulants

In case of an ongoing major bleeding of anticoagulated patients the effect of the respective anticoagulant should be reversed as follows [2].

7.5.2.1 Reversal of Vitamin K-Dependent Oral Anticoagulants

Patient's response to VKA is highly variable due to the interaction with the vitamin K cycle and hence interference with synthesis of vitamin K-dependent coagulation factors. Assessing the anticoagulant effect in a bleeding trauma patient with the international normalized ratio (INR) is essential because complications are closely related to the intensity of anticoagulation. After INR monitoring, emergency reversal of the anticoagulant effect of VKA should be done by the early use of both intravenous prothrombin complex concentrate (25–50 U/kg) and phytomenadione (5 mg) [2]. 4-factor prothrombin complex concentrate was proven to be more effective than fresh frozen plasma for VKA reversal without increasing complications and mortality. The risk of thromboembolic events is even lower if patients are treated with prothrombin complex concentrate compared to fresh frozen plasma [44].

7.5.2.2 Reversal of Factor Xa Inhibitors

In case of major bleeding, plasma levels of oral anti-Xa agents such as rivaroxaban, apixaban, or edoxaban should be measured and quantified with recommended anti-Xa assays before reversal. In case of a life-threatening bleeding residual anti-Xa effect should be reversed with intravenous tranexamic acid 15 mg/kg (or 1 g) and prothrombin complex concentrate (25–50 U/kg), or a specific antidote if available [2]. Andexanet alfa is such a specific antidote for rivaroxaban and apixaban. It binds the agents and hinders them to block coagulation factor Xa. As a result, the anticoagulant induced bleeding can be reduced [45]. Andexanet alfa is approved by the FDA in the United States and by the EMA in Europe for the treatment of uncontrollable bleeding while on rivaroxaban or apixaban, but so far it is still not commonly available. Additionally, intravenous desmopressin (0.3mcg/kg) may be considered as recently was shown that anti-Xa agents also impair platelet function [46]. So far it is still not fully understood how anti-Xa agents impact platelet function. Not recommended for reversal of factor Xa inhibitors are vitamin K, protamine, or fresh frozen plasma as they are not effective for reversal.

7.5.2.3 Reversal of Direct Thrombin Inhibitors

In case of major bleeding, dabigatran plasma levels should be measured by using diluted thrombin time (or thrombin time if not available) before reversal. The dabigatran effect should then be reversed in first line with its specific antidote idarucizumab (intravenous bolus of 5 g) [2, 47]. Additionally, intravenous tranexamic acid 15 mg/kg (or 1 g) may be administered. Dabigatran is known to impair platelet function to a much greater extent than anti-Xa agents. Therefore, intravenous desmopressin (0.3 mcg/kg) is considered at an early stage and platelet count should be maintained over 80.000/mcL in case of an ongoing major bleeding [2]. Not recommended for reversal of dabigatran are prothrombin complex concentrate, fresh frozen plasma, vitamin K, and protamine as they are not effective for reversal. Noteworthy, prothrombin complex concentrates immediately and completely reverses the effect of factor Xa inhibitors but has no influence on the anticoagulant action of dabigatran and should therefore not be used for reversal of direct thrombin inhibitors.

7.5.2.4 Reversal of Platelet Inhibitors

So far, no specific antidote is available to reverse the effect of platelet inhibitors. As a first step intravenous desmopressin (0.3 mcg/kg) should be administered in patients treated with platelet-inhibiting drugs. If bleeding persists, platelet concentrate transfusion may be considered in case of a platelet count of <50 G/L or <100 G/L in patients with a concomitant traumatic brain injury. Platelet count should be reassessed before transfusion of each additional concentrate. An in vitro study demonstrated that clopidogrel had no effect and prasugrel only a mild effect on transfused donor platelet function, whereas ticagrelor completely abolished platelet donor activation. Depending on the present platelet inhibitor, transfusion of a platelet concentrate may have limited effect on hemostasis. There is also no evidence that platelet concentrate transfusion only due to a documented platelet dysfunction improves outcomes in patients undergoing emergent neurosurgery.

7.6 Conclusion

Traumatic bleeding is still the main preventable cause of death in severely injured patients. Trauma resuscitation aims to detect and treat systemic coagulation disorders as early as possible in order to counteract coagulopathy and stabilize the patient. The initial trauma treatment comprises a restrictive, goal-directed volume resuscitation using crystalloid solutions and vasopressors on demand to maintain the circulation at a low-stable level. A goal-directed factor-based coagulation management was shown to improve outcomes and lower mortality following major trauma and is therefore recommended in first line. This approach requires a predefined coagulation algorithm including repetitive point-of-care measurements as well as a restrictive transfusion management. The increasing use of oral anticoagulants is challenging trauma treatment. Residual effects of anticoagulants should be assessed and quantified quickly with suitable laboratory tests and reversed in case of an ongoing major bleeding.

Take Home Messages

- Trauma-induced coagulopathy is an independent clinical pathology leading to an increased morbidity and mortality.
- Coagulation management should already start during the pre-hospital care, e.g., by administration of tranexamic acid.
- A restrictive, goal-directed volume resuscitation using balanced crystalloid solutions to maintain the circulation at a low-stable level is recommended.
- A goal-directed substitution of coagulation factors together with a restrictive transfusion strategy is associated with improved outcomes in trauma patients.
- The expanding use of oral anticoagulants is challenging trauma treatment nowadays. Laboratory screening for anticoagulants is therefore essential at admission.
- In case of an ongoing major bleeding in anticoagulated patients the residual anticoagulant effect should be reversed.

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