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Summary  
Guidelines of official societies for diagnosis and therapy of intraoperatively occurring hypocoagulability rely mainly on data of patients receiving whole blood transfusions. They recommend—provided that laboratory evaluation shows deficiency (values >1.5 fold normal)—administration of fresh frozen plasma, cryoprecipitate and platelet concentrates (platelet count < 50 000 or < 100 000/µl). This article describes the pathogenesis of coagulopathy in the light of the special intraoperative setting, emphasizes recent changes of blood component preparation, transfusion triggers, effects of volume therapy and challenges standard laboratory assays as reliable guide for intraoperative hemostatic therapy. The role of thrombelastographic monitoring is discussed as well as an alternative strategy to compensate deficiencies by the use of coagulation factor concentrates instead of or in addition to transfusion of FFP, a new concept which is illustrated by the presentation of an actual case report.

Pathogenesis of perioperative coagulopathies  
Loss, consumption, dilution  
The majority of coagulation defects that present intraoperatively and acutely as the result of massive haemorrhage in patients without relevant primary disease are caused by loss, consumption and dilution, and come under the heading of dilution coagulopathies. In all these cases, the results of routine tests, prothrombin time (PT) and activated partial thromboplastin time (aPTT), are pathological at an early stage. With major blood loss, thrombelastography also shows a delay in the initiation of coagulation. The firmness of the clot is reduced as are the platelet count and the concentrations of antithrombin, procoagulant factors and fibrinogen, while the d-dimer concentration rises.

Although these laboratory tests are also indicative of disseminated intravascular coagulation (DIC), the genesis is different: consumption of all the plasma and cell components necessary for haemostasis is induced by endothelial lesions and the release and influx of coagulation activating substances, in contrast to the varying degree of phase-dependent systemic activation of coagulation and disseminated formation of microthrombi in the sense of classical DIC (80). By definition then, this is a consumption coagulopathy exacerbated by volume replacement, loss, and possibly acidosis and hypothermia (polytraumatised patient), but not classical DIC.

Critical platelet counts of less than 50 000/µl or 100 000/µl are not to be expected in patients without concomitant disease until more than 150% of the circulating volume has been lost (2, 3, 12, 67, 68). Concentrations of procoagulant clotting factors, considered to be sufficient at 20–30% or even less, depending on the factor (1, 61, 68), can also be maintained for a long time by mobilisation from the endothelial, perivascular and hepatic stores. Deficiencies are only to be expected after the loss of >200% of the blood volume (2, 3, 34, 68).

In contrast, coagulation factor I (fibrinogen) is used as a substrate in the coagulation process, during which it is converted to fibrin by the action of thrombin, and then cross-linked by FXIIIa to stabilise the initial clot. As an acute phase protein, the concentration of fibrinogen is increased by inflammation, neoplastic processes and many other conditions, as well as immediately after surgery. However, a recently published experimental animal study showed that fibrinogen synthesis can no longer compensate for the increased consumption with even moderate blood loss (35% of the blood volume) (54). This means that a fibrinogen deficiency will arise sooner or later, depending on the baseline concentration and the dynamics of the blood loss (34, 57–59, 72). A deficiency of this nature is aggravated by the necessary fluid replacement, which not only further reduces the concentration by dilution but, with the use of colloidal plasma expanders, also has a functional effect on fibrin polymerisation (15, 19, 39). Fibrinogen concentrations of 1–1.5 g/l are considered to be critical (2, 3, 5).
It must be remembered that measured serum concentrations do not necessarily correlate with the fibrin that can actually polymerise (20, 35, 58). Evidence that an acquired fibrinogen deficiency can be associated with an increased tendency to perioperative bleeding was first published in the early 1980s (11, 53) and confirmed by more recent studies (34, 62).

Under the conditions valid at the present time, with substantial blood loss (>50% of the blood volume) and initial low normal baseline concentrations, a fall in the fibrinogen concentration and reduction in clot firmness is to be reckoned with at an early stage (39).

Apart from patient-specific factors (initial conditions, blood volume), the rate and extent to which an intraoperative dilution coagulopathy develops depends considerably on the nature and duration of the surgical procedure, the cause of the bleeding and how well it can be controlled surgically (arterial as opposed to venous bleeding, oozing haemorrhage, the size of the wound, entry into spongy bone, greater need for volume replacement with longer operations).

Cardiac surgery (extracorporeal circulation, heparin/protamine management) and hepatic surgery (liver transplantation, rupture of the liver) present particularly complicated conditions, which will not be considered in more detail here.

Hyperfibrinolysis

Besides dilution coagulopathy, an imbalance between activated haemostasis and simultaneous fibrinolysis may be the cause of an unexpected increased tendency to bleed. If there is hyperfibrinolysis, which can be rapidly and conclusively identified by thromboelastography (49, 51, 75, 84), any clot that has formed breaks up again after a short time—large quantities of fibrinogen are thus used up ineffectively. Hyperfibrinolysis is associated with massive blood loss and it is necessary to administer antifibrinolytics and replace the consumed fibrinogen in order to stop the process. Most reports on hyperfibrinolysis come from trauma and liver transplantation surgery, obstetrics and gynaecology.

Pre-existing disorders of haemostasis

Coagulation defects existing prior to surgery may be the cause of an increased tendency to bleed at operation. From childhood, patients with severe inherited single factor deficiency (e.g. haemophilia A with FVIII deficiency, haemophilia B with FIX deficiency, afibrinogenaemia, severe forms of von Willebrand’s disease) usually show signs of bleeding in response to microtrauma (into mucosal membranes, soft tissues, and joints, or intracerebral bleeding). Patients are usually investigated haematologically at an early stage, so that appropriate replacement therapy can be predetermined and the perioperative management planned. However, mild and moderate factor deficiencies and disorders of primary haemostasis may first become apparent during a surgical procedure. These include hereditary coagulation defects, e.g. von Willebrand’s disease (incidence 1:100), moderate FXIII deficiency, or bleeding diathesis with vasculopathy (Ehlers-Danlos syndrome, Osler-Weber-Rendu syndrome). Hereditary FXI deficiency (haemophilia C) affects both men and women. It is associated with a very variable but also strong bleeding tendency.

Acquired disorders of haemostasis have to be considered; these include disorders of platelet function (treatment with platelet aggregation inhibitors, adverse effect of numerous medications, in hepatic, renal or bone marrow disease, and paraneoplastic conditions), immunological or mechanically-induced acquired von Willebrand’s syndrome (particularly in myeloproliferative disease, aortic stenosis, following valve replacement, etc.) or the occurrence of coagulation factor inhibitors (42). In general, a disorder of primary haemostasis has to be reckoned with more frequently than pre-existing coagulopathy. Disorders of primary haemostasis cannot be diagnosed by routine laboratory testing but severe forms should be detected by taking a routine standardised coagulation history (44).

A rare constellation to bear in mind is found in patients who have had heparin for a long time before a surgical procedure and may then present preoperatively with thrombocytopenia. Heparin-induced thrombocytopenia (HIT) has to be ruled out in these cases. These patients have a high risk of thrombosis and embolism, and require special management (27).

Problems of perioperative management of coagulation

Particular considerations

The intraoperative situation is characterised by the simultaneous effects and interactions of anaesthetics, endothelial injury, influx of procoagulant cell fragments and blood loss. These factors as well as the necessary volume replacement and transfusions directly affect the function of all organ systems. Losses of more than 30% of the blood volume require volume replacement (23). Through dilution, fluid replacement exacerbates the hypocoagulability, anaemia and thrombocytopenia developing due to loss and consumption; in turn, this further increases the blood loss and subsequent need for plasma expanders and transfusion. The dynamics of the situation depend on:

- type of surgical procedure,
- cause of bleeding,
- rate of blood loss,
- patient-specific factors.

These dynamics show great individual variation but, when there is substantial blood loss, rapid correction is required to prevent shock and organ failure.

While the indications for administering packed red blood cells can be established relatively quickly and confidently from rapidly-available haemoglobin measurements and/or the presence of physiological signs of anaemia requiring treatment (haemodynamic instability with normovolaemia, ECG changes, regional disturbances of myocardial wall movements), the indications for intraoperative haemostatic therapy are somewhat less clear.

Blood components instead of whole blood

Most publications on the genesis and treatment of perioperative coagulopathy come
from the time of whole blood transfusions and form the basis of recommendations for managing major blood loss (2, 5, 68). As it contains fibrinogen and coagulation factors (with the exception of unstable factors V, VIII, and VWF), whole blood ensures that blood loss is broadly compensated without the need for additional FFP to maintain adequate haemostasis. Plasma-free packed red blood cells (max. 20 ml plasma/unit) are not able to do this.

These facts explain why the development of thrombocytopenia was the primary cause of coagulation disorder in the time of whole blood transfusions (11, 12, 67), while today coagulopathy represents the main problem (29, 37, 74).

Additionally, in accordance with the recent guidelines, blood loss is now more often compensated by colloidal plasma expanders than was the case in the era of whole blood transfusions.

Transfusion triggers and dilution

Transfusion triggers based on the haemoglobin and haematocrit have since been set considerably lower (depending on comorbidity, Hb <7–9 mg/dl) than the state-of-the-art values valid ten years ago. At the same time, erythrocytes have both passive and active effects on haemostasis (29, 40, 83). Tolerance of lower haemoglobin levels means that more plasma expanders have to be given to prevent hypovolaemia and acidosis. These two conditions are associated with poor outcome and exacerbate existing or developing coagulopathy by adversely affecting thrombin generation.

With a falling haematocrit and constant intravascular volume, the relative increase of the plasma compartment alone leads to a reduction in the concentration of factors distributed in this compartment – particularly of fibrinogen, which reaches critical concentrations. In our own experience and using a mathematical model, the acceptance of lower transfusion triggers for the administration of packed red blood cells and the subsequent increased requirement for (usually colloidal) plasma expanders can unintentionally lead to the development of fibrinogen deficiency requiring treatment, at an earlier stage than described in studies from the 1980s and 1990s (72).

Percentage blood loss

Coagulation factor deficiencies (concentration <30%, fibrinogen <100 mg/dl) are usually not to be expected until there has been a loss of more than 100% of the circulating blood volume in the case of fibrinogen, or 200% for the other factors (2, 3, 34, 68).

The reference ranges for the concentrations of coagulation factors (70–140% on average) and fibrinogen (190–380 mg/dl) are very broad while, at the same time, the capacity for haemostasis varies greatly from person to person. This means that one patient with a low normal concentration of one or more clotting factors may show a normal coagulation status preoperatively and yet develop a clinically significant coagulopathy with even slight blood loss during the operation, while this may take much longer to develop in a patient with higher initial concentrations.

As a result, an estimation of required haemostatic therapy based on the percentage blood loss may sometimes be erroneous. In addition, it is difficult to quantify blood loss, which is usually underestimated (4, 33). Data from a computer simulation of a seriously injured patient, studying initial blood loss, dilution by fluid therapy and further blood loss depending on the blood pressure, clearly showed that immediate therapy is necessary to correct a coagulopathy by means of FFP (36).

Correction of haemostasis and outcome

It is often thought that haemostatic therapy is not worthwhile until bleeding is under surgical control. Vascular bleeding certainly has to be dealt with surgically or by radiological intervention, but a critically low capacity for haemostasis induces spontaneous haemorrhage and secondary damage. The more pronounced the decompensation of the haemostatic system, the harder it is to correct, so that conventional therapy is often unsuccessful. The many case reports on emergency off-label use of rFVIII make this eminently clear (47). Effective treatment is therefore crucial even with uncontrolled blood loss (3, 21, 36, 37).

Besides early specific haemostatic therapy, the effects of the fluid used for volume replacement have to be taken into consideration. Colloid plasma expanders affect the coagulation system far more than crystalloid solutions. The pharmacological properties of crystalloids mean that their intravascular retention time is considerably shorter. They cause oedema and have to be administered in large quantities in order to maintain a normovolaemic state (blood loss/volume administered for crystalloids 1:4, colloids 1:1). The exclusive use of crystalloids is therefore limited. Correction of acidosis and, as far as possible, hypothermia, combined with the maintenance of a high hematocrit, improves the haemostatic capacity (29, 40, 83).

Level I evidence-based studies to demonstrate a beneficial effect of early correction of coagulopathy under conditions of acute blood loss in humans are hardly possible for ethical reasons (control group) and because of the differences in individual therapy. Nor are studies of this nature to be expected in the future. Animal studies provide one alternative. It has been shown in dogs, for example, that too-late correction of haemostasis is associated with greater blood loss and ultimately higher transfusion requirements (48). Using a pig model with induced dilution coagulopathy and standardised injury to the liver, our study group reported that the administration of fibrinogen concentrate significantly reduces blood loss, in comparison with placebo. A follow-up study (identical model, fibrinogen versus placebo) showed that haemostatic therapy can significantly improve the survival rate (18).

Several clinical publications show that the presence of a haemostatic disorder alone and the resulting transfusion requirements in traumatised patients or those undergoing elective surgery is associated with a negative outcome (recurrent bleeding, necessity for revision, total blood loss, mortality) (9, 14, 24, 41, 45, 52, 55, 78). Figure 1 shows an example of the association be-
Perioperative diagnostic investigation of coagulation

Preoperative screening

Standard coagulation tests are part of the routine preoperative work up of a patient, even though their predictive value for increased intraoperative bleeding is low and patients with inherited single factor deficiencies are usually already known. A coagulation history taken prior to the operation is of greater use in detecting disorders of primary haemostasis, which are far more common (16, 44).

PT and aPTT measurements were introduced to monitor therapy with vitamin K antagonists (PT) and detect single factor deficiencies (aPTT). They have widely replaced the in vivo determination of bleeding time, but were not developed to predict an increased tendency to intraoperative bleeding (16, 43). Within Europe the activated clotting time (ACT) is used only to monitor heparin and protamine within the context of cardiac surgery.

Timing

Most treatment regimens are based on the results of standard coagulation tests: prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration and platelet count (2, 5, 68). Theoretically, at least 25 minutes is needed for routine coagulation diagnostics but the logistics of large institutions mean that they often take an hour. A long wait is unacceptable when faced with acute dynamic blood loss (3, 37).

As a rule – and in contradiction of the guidelines – decisions about haemostasis have to be made clinically whenever point of care diagnostic methods are not used.

Limitations of the methods

PT and aPTT measurements have good reproducibility and are consistent, but vary considerably with the reagent used, and even with different batches of the same reagent (16). The introduction of the international normalised ratio (INR) compensates for this to only a limited extent. Both test procedures are based on very unphysiological processes, indirectly detecting the ex vivo formation of fibrin following artificial stimulation: citrated whole blood is centrifuged, the plasma recalcified and activated in a glass tube (with or without the addition of particles) with a reagent of varying sensitivity. Optical measurement (plasma opacification) detects the start of coagulation or fibrin formation indirectly. The rate of clot formation, its firmness and tendency to dissolution cannot be extrapolated from these test results.

The effects of platelet aggregation inhibitors, VWF, FXIII, and cell components on the in vivo coagulation processes have no influence on measurements using these methods. According to the latest haemostasis model, activated platelets play a decisive role in clotting in vivo, as amplification of coagulation takes place on their surfaces (61).

Patients with cirrhosis of the liver sometimes have normal thrombin generation, even though standard coagulation tests are pathological (81).

Finally, the aPTT may be prolonged to a variable degree without there being an increased risk of bleeding or even, in some circumstances, thrombosis. It may also be normal or abnormal in patients who have a high risk of bleeding (Tab. 1) (43).

Perioperative interpretation

When evaluating test results, it has to be remembered that the relation between measured...

\[\text{Transfusion requirements and mortality [41]}\]
Perioperative management of coagulation

clothing times and factor concentrations is not linear but exponential (Fig. 2). For this reason, pathological results are not necessarily associated with critical factor concentrations and there is still a broad physiological reserve (16). An analogy can be made to the maintenance of oxygen transport, which does not necessarily need a haemoglobin concentration within the normal range.

A PT result is thought to be critical when it is more than 1.5 times greater than the mean of the norm (2, 5). In vitro dilution of plasma with NaCl to a factor concentration of 30% gives results of this order of magnitude (68). In a study by Murray et al. (62) 17 out of 32 patients showed an increased tendency to intraoperative bleeding. This was associated with more highly abnormal PT and aPTT values than those found in the patients with no increased haemorrhagic tendency. Interestingly though, the coagulation factor concentrations (V, VIII, IX) measured at the same time were well above the 20–30% range that is considered critical. Fibrinogen concentrations were greatly reduced, however, and this is probably the reason for the increased bleeding tendency. Six of the eight patients with a PT of 16 s (>1.5 times normal) bled more heavily, while the other two did not. The authors concluded that the PT and aPTT are usually abnormal when blood loss is >50% of circulating volume (30 out of 32 patients) but that this is not always associated with an increased tendency to bleed.

A study by Ciavarella et al. (11) in patients receiving massive transfusions likewise showed that the variability of the PT and aPTT results is only partly induced by a fall in factor concentrations, and that low fibrinogen concentrations in particular increase the haemorrhagic tendency.

Burns et al. (6) showed that PT and aPTT results depend considerably on the test reagent used and whether just one coagulation factor is reduced or several at the same time. Paradoxically, the PT and aPTT are more abnormal when several factors are only moderately reduced (75%) than if just one factor is reduced to 50%.

Single factor deficiencies rarely arise in the perioperative situation, much more often all factors are reduced to a greater or lesser extent (14, 57, 62) and the fibrinogen deficiency that frequently occurs also influences the results of routine tests. In addition, determination of fibrinogen using the Clauss method may be confusing (false high values) as colloids and fibrin degradation products affect this optical method (35).

In summary, it can be said that the specific intraoperative conditions (dilution, fall in several coagulation factors, process dynamics), as well as the limitations of time and the methods used, explain why standard tests are of little preoperative or intraoperative predictive value for the risk of increased haemorrhage – even though they are useful in patients with a known history of bleeding diathesis. For the same reasons, these tests are not appropriate aids in decisions to start haemostatic therapy.

Perioperative management of coagulation

Diagnostic investigations

Diagnostic investigation prior to surgery starts with a standardised coagulation history. As a rule, results of classical laboratory testing are already available. If there is a positive history of clotting problems, any suspected disorder of haemostasis should be clarified – always including the standard tests and sometimes requiring tests only available in specialised laboratories (e. g. von Willebrand factor multimers, aggregometry). Besides these, the platelet function analyser (PFA-100) for near patient testing, can evaluate whether there really is any disorder of primary haemostasis, e.g. after taking acetylsalicylic acid (responder/non-responder), whether platelet function is adequate after stopping ASA (with normal bone marrow and normal thrombopoiesis a washout period of two days should be enough, although there are always inter-individual differences) or whether DDAVP is indicated (ASA, VWD). As the PFA-100 results depend on the haematocrit (>30%) and thrombocyte count (>100 000/µl), this method is worthwhile preoperatively – even if it has its limitations – but is of little value with substantial blood loss during an operation (30).

The dynamics of overt intraoperative coagulopathies depend on the surgical procedure and variable individual factors. While the initial and subsequent blood loss as well as hypothermia and acidosis exacerbate the situation during the care of a polytraumatised patient, disorders of haemostasis develop much more slowly during major elective surgery. If there is acute loss through damage to major vessels, the blood loss and transfusion requirements are greatly increased. As mentioned previously, orientation using standard tests and PFA-100 is very limited. Anaesthetists, who are usually the people faced with the management of these patients, therefore need a coagulation test that is as close as possible to the in vivo situation and which identifies a critical haemostatic capacity as quickly and distinctly as possible, to allow prompt and effective targeted treatment.

Since 1998, our department has used a point of care method which meets all

![Fig. 2](image-url)
these requirements: thromboelastometry (ROTEM®, Pentapharm GmbH, Munich). It is based on the classical thromboelastography (TEG) method developed by Hartert (31).

Measurements made in whole blood present the dynamics and quality of the entire coagulation process graphically and numerically (49, 51). Evaluation for rough guidance is available within a few minutes of activated test procedures, e.g. differentiation of factor deficiencies, the presence of inhibitors or hyperfibrinolysis, fibrinogen and/or platelet deficiencies (26, 39, 58–60, 63, 65, 69, 75). Severe platelet function disorders (Glanzmann’s disease, abiciximab) can also be recognised with TEG. Furthermore, patients with hypercoagulability states can be identified; these patients require no treatment despite substantial blood loss and/or are postoperatively at high risk of thrombosis and have to be managed accordingly (28, 56, 66). Parameter variation is below or within the range of that of standard tests, particularly for clot firmness and the α angle, with coefficients of variation of 1–5%, and for clotting time (CT) and clot formation time (CFT), with 3–12% (46).

Most studies on perioperative monitoring with TEG have been conducted in cardiac or liver surgery where substantial blood loss and marked disorders of haemostasis are particularly common. Amongst other things, this method (7, 9, 60, 64, 70, 71, 79, 82):
- makes it possible to use blood components sparingly, in a targeted manner,
- differentiates between bleeding due to coagulation problems and secondary haemorrhage requiring surgical revision,
- makes heparin and protamine management much easier.

Of course, thromboelastography also has its limitations. The ex vivo method requires that blood comes into contact with foreign surfaces, which induces clotting. Shear forces due to flow are absent, so that disorders of primary platelet adhesion and aggregation under flow conditions are not detected (VWF, ADP blockers, ASA). ROTEM is also abnormal if there is von Willebrand’s disease with reduced FVIII concentration (type 2N, “Normandy”). Patients on treatment with coumarin derivatives show CT prolongation (outside the normal range) in the extrinsic activated test, increasing with the INR, as an expression of the reduced concentration of vitamin K-dependent clotting factors. Clot firmness and fibrin components of the clot are normal or elevated, as coumarins do not directly affect either fibrin polymerisation or the interaction with platelets.

Therapeutic options

Guidelines recommend the administration of FFP to treat coagulopathy (2, 5, 33), even though there is some doubt as to its effectiveness. The results of a recently published analysis are very disappointing: of 57 very heterogeneous studies (including plasma exchange for non-surgical indications) that investigated the benefit of FFP therapy, only six studies (five of them not in the surgical field) demonstrated a possible positive effect of FFP administration (76). Factor concentrates are the established treatment for inherited factor deficiency (e.g. haemophilia, FXIII deficiency, afibrinogenemia/dysfibrinogenemia) and to counteract vitamin K antagonists. In clinical practice, however, they are rarely used as alternatives or in addition to FFP in the treatment of perioperative coagulopathy (3).

Factor concentrates provide effective correction of critical levels of clotting factors within a short time and without volume overload, whereas FFP is either too late, because of the time required between ordering and thawing the product, or not sufficient to improve the situation if the dosage guidelines of 10–15 ml/kg body weight are followed (10, 32). Administration of FFP, consisting mainly of 5% albumin and water, only leads to a negligible increase in the individual coagulation factors because of the simultaneous plasma expansion and its low physiological concentrations of coagulation factors and inhibitors. A study conducted on patients in intensive care with abnormal standard tests, corrected preoperatively with FFP, found no coagulation factor deficiencies requiring treatment in the majority of the patients, despite the abnormal results. However, true deficiencies were only corrected by administering FFP at a dose of 30 ml/kg body weight, while the usual dose did not achieve any increase in concentrations (10).

These clinical studies confirm the data from Hedin and Hahn. They showed that administering autologous FFP to volunteers (without blood loss or need for volume replacement) at a dose of 10 ml/kg body weight (mean dose: 1000 ml) increased the fibrinogen concentration by only 6% and the antithrombin by only 3% (32). With a clinically significant deficiency (CF <20–30%, fibrinogen <100 mg/dl) an increase of this order of magnitude is certainly not adequate.

This means that FFP can only effectively prevent coagulopathy if it is given prophylactically but such administration of blood products is considered problematic (74). In contradiction of this, all the guidelines agree that FFP should not be used for volume replacement (2, 5) but given only with evidence of true deficiency. It should be remembered that most cases of transfusion-related acute lung injury (TRALI) are caused by administering FFP. Even though it is one of the major factors in transfusion-related morbidity and mortality, the incidence of TRALI is underestimated. Apart from TRALI, which has an immunological basis, FFP always causes cardiopulmonary volume loading which may be particularly relevant clinically if there is restricted cardiac contractility, existing pulmonary disease or permeability disorders (13, 22, 77). Of course, FFP can theoretically also transmit transfusion-related infections, even if modern test methods and virus-inactivating processes have now made FFP extremely safe. For this reason and those given above, the unnecessary use of FFP should be avoided at all costs.

Thromboelastography and treatment

Despite the many promising publications on intraoperative monitoring using thromboelastography, this method for near patient testing is not universally known or available. Often only the standard coagulation tests and full blood count are available to guide treatment. Similarly, the incidence and sig-
nificance of fibrinogen deficiency are usually underestimated, even though there have been reports on this since the 1980s, confirmed by more recent studies. Current volume replacement regimens and the restrictive use of packed red cells even promote the development of fibrinogen deficiency. As fibrinogen must be present in a concentration 1000 times greater than the majority of procoagulant factors to provide adequate haemostasis, FFP is even less appropriate for correcting fibrinogen deficiency than for increasing the concentrations of the other factors.

In Anglo-American countries, cryoprecipitate and not fibrinogen concentrate is the treatment of choice for fibrinogen deficiency (2, 5); production of fibrinogen concentrate is more expensive and time consuming. Blood banks produce cryoprecipitate from FFP (after thawing at 4°C, re-centrifugation isolates the cryoglobulin fraction: fibrinogen, fibronectin, FVIII, VWF, and FXIII). Quality criterion: 75% of the packs produced (20–40 ml) must contain at least 140 mg fibrinogen and 70 IU/ml FVIII (5). Administration of 2 ml/kg body weight should raise the fibrinogen concentration by 100 mg/dl (3).

Our own work and that of others shows that, as the first coagulation factor to reach critical levels with blood loss, fibrinogen considerably affects clot firmness and hence further haemorrhage. The fibrin component of the clot is reduced during dilution (loss, volume replacement) by decreased concentration and disturbed polymerization. Optimisation of the fibrinogen concentration may counteract this (11, 17, 19–21, 34, 39, 53, 57, 59, 62). In diluted blood, neither in vitro replacement of FVIII and platelets nor rFVIIa had the same effect as fibrinogen replacement (17, 73). It is therefore obvious that:
- functioning of this clotting factor can be monitored most accurately by thromboelastography (especially if there is a low baseline concentration and requirement for colloids),
- fibrinogen concentrate should be given if values fall below the critical threshold.

While congenital fibrinogen deficiency (afibrinogenaemia, dysfibrinogenaemia) is treated by fibrinogen concentrate, sometimes given at weekly intervals, perioperative fibrinogen deficiency is usually treated with FFP. Fibrinogen concentrate is used only rarely or late, especially when conventional strategies have failed.

**The Innsbruck concept**

Standard tests carried out perioperatively do not permit the interindividual and situation-related differences or intraindividual variations in a patient’s haemostatic capacity to be assessed. Besides the previously-mentioned preoperative coagulation history and possible PFA-100 measurements and/or aggregometry, intraoperative monitoring by thromboelastometry is of prime importance. Besides this, standard coagulation tests, full blood count and individual factors are determined as appropriate in each case. With any operation where the blood loss is expected to be more than 50% of the blood volume, we carry out an initial ROTEM® test after induction of anaesthesia, to establish the individual’s haemostatic capacity. Further measurements are made during the operation if there is an increased bleeding tendency, a loss of >50% of the blood volume or an increased requirement for colloidal plasma expanders, and to monitor therapy after substitutes have been

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**Fig. 3** Case report
a) MRI; b) CT 3D-reconstruction; c) operation site after removal of wedge vertebra
As a rule, an increased tendency to bleed (seen as bleeding from wound margins, absence of clot formation in the area of the wound, diffuse haemorrhage without underlying surgical cause) can be attributed to a disorder of fibrinogen polymerisation (FIBTEM MCF < 7 mm). In accordance with our concept, this is counteracted by fibrinogen replacement and the therapeutic success monitored.

This concept of initial fibrinogen replacement is based on our own studies and publications by other authors (11, 17–21, 34, 53, 57, 62). If there is an increased bleeding tendency and the ROTEM result is normal, a disorder of primary haemostasis has to be ruled out. Rapid verification of the suspected diagnosis (e.g. von Willebrand’s disease) is usually not possible with routine methods.

If fibrinogen polymerisation remains inadequate despite replacement and adequate concentrations, FXIII deficit has to be considered. Clinical studies have shown that FXIII concentrations of around 60% are required to prevent intra- and postoperative bleeding (8, 24, 85).

Platelet transfusions are required if the clot firmness (maximum clot firmness, MCF, normal range 52–78 mm) is below a critical level despite sufficient fibrinogen and FXIII concentrations. Definition of critical values has to take the bleeding- and surgery-related dynamics into consideration. If further blood loss and volume replacement are to be expected, the critical levels should be set somewhat higher (MCF > 40 mm) than in the postoperative period. With an MCF of 35 mm, the bleeding tendency observed clinically is greatly increased.

With pronounced blood loss (>200% of blood volume), deficiencies of procoagulants also arise, which can be seen in the ROTEM tests as a prolonged CT. We treat these with prothrombin complex (factors II,
VII, IX and X). If the ROTEM CT remains prolonged even with this treatment, it must be assumed that there is a deficiency of FVIII, FV and FXI-XIII, which can be corrected by the administration of FFP or FXIII concentrate. While minimum concentrations of co-factor V are enough, FVIII is rarely reduced to a critical level, FXI deficiency can induce very variable but also severe haemorrhage, and FXII deficiency does not increase the bleeding tendency (1, 25, 68). The situation is different for FXIII deficiency, which is associated with greater bleeding. FXIII deficiency can be confirmed by laboratory tests, which are available in our department at any time. In addition, a functional FXIII deficiency can be detected by ROTEM measurements with or without the addition of FXIII, even though it still cannot be quantified.

With close monitoring of any secondary bleeding (checking drains, haemoglobin levels, haemodynamics), lower thromboelastography values can certainly be tolerated postoperatively (e.g. MCF <40 mm) than is the case with progressive blood loss at operation. As is well known, surgical procedures activate coagulation and inflammatory reactions, so besides secondary bleeding there is also the postoperative risk of thrombosis and embolism. Our patients are therefore monitored with ROTEM in the immediate postoperative period. Patients who show no signs of bleeding and/or disorders of haemostasis are given routine thrombosis prophylaxis after 6 hours.

**Case report**

As the result of a congenital malformation of the lumbar spine, a five-year-old boy suddenly developed rapidly-progressive kyphosis and scoliosis (Fig. 3a, b). Because of the threat of secondary damage, a complete excision of the wedge vertebra and dorsal stabilisation was indicated. From the outset, the surgical technique (opening epidural veins, bleeding from spongy bone, removal of the wedge vertebra in layers to protect nerve roots, additional dorsal stabilisation) meant that it would be a long operation associated with substantial blood loss.

Figure 4 shows the clinically relevant intraoperative ROTEM results. The intrinsic activated test (INTEM) and information on the fibrin components of the clot (FIBTEM) are shown each time to give a better overview of events. For the sake of completeness, Figure 4i also shows the extrinsic measurements (EXTEM), which changed in the same direction as the INTEM measurements. Figure 3c shows the operation site after removal of the wedge vertebra.

Nothing abnormal was detected in the coagulation history, preoperative findings, and the initial ROTEM measurements after the induction of anaesthesia (Fig. 4a). The boy (weight 22 kg, height 115 cm), had an estimated circulating blood volume of 1400 ml. After three hours, blood loss was 400 ml (30%). He was kept in balance with 600 ml Ringer lactate and 150 ml gelatin solution. The ROTEM results (Fig. 4b) already showed a reduction of more than 15% in the overall MCF (normal range: 50–72 mm) and a borderline value for the fibrin components of the clot (FIBTEM MCF, normal range: 9–25 mm). As the main blood loss was still to come, fibrinogen replacement was started.

Borderline fibrinogen polymerisation and greatly reduced MCF were again seen one hour later, with a blood loss of 1200 ml (80%) after the transfusion of 200 ml cell saver concentrate and two units of packed red cells (Fig. 4c). Fibrinogen was again given and 300 ml platelet concentrate (15 ml/kg body weight, equivalent to 15–20 × 10^9 platelets) were required. Transfusion of red blood cells via cell saver concentrate continued uninterrupted. There was no evidence of factor deficiencies in this ROTEM measurement (INTEM CT, normal range: <240 s) even though standard tests were highly abnormal at this point (PT 44%, aPTT 57 s), as was the fibrinogen concentration at 85 mg/dl.

At about four o’clock, after six hours of surgery, the blood loss reached 2800 ml (200%) due to haemorrhage from epidural veins and spongy bone that was difficult to bring under control. ROTEM (Fig. 4d) found that the CT was still in the normal range, the MCF remained stable, but the fibrinogen was again borderline so that a further 1 g fibrinogen was administered. Monitoring (Fig. 4e) showed improvement of the clot firmness with clotting time still being normal, despite progressive losses (3600 ml, 260%) due to the surgery and brief haemorrhage from a lumbar artery.

In total, 4 g fibrinogen, 3 units of packed red blood cells, 700 cell saver concentrate, and 300 ml platelet concentrate had now been administered, along with 2000 ml crystalloids and 1500 ml gelatin solution. Blood gas analysis always showed a good acid-base balance. Hypothermia did not occur at any time during the operation.

The first abnormal CT measurement (Fig. 4d) arose with a blood loss of 300%. A reduced MCF and marked disruption of fibrin polymerisation (FIBTEM <2 mm) were again recorded. The routine parameters tested at the same time gave the following results: PT 36%, aPTT 123 s, fibrinogen 104 mg/dl, platelets 81 G/l and concentrations of 25–30% for most of the coagulation factors (FXIII 24%) with adequate VWF concentration (antigen and ristocetin).
Without knowing these results, which only became available much later, 30 IU/kg body weight prothrombin complex concentrate and an additional 1 g fibrinogen were given together with a further infusion of 300 ml platelet concentrate. ROTEM with the addition of FXIII also confirmed the suspicion of a FXIII deficiency (FIBTEM without and with FXIII; figures 4f, 4g). Fibrin polymerisation was corrected by the administration of 25 IU/kg body weight FXIII, and the MCF was adequate (Fig. 4h).

As the CT remained at the upper limit (suspicions of FXI deficiency) there was an indication to give 2 FFP (20 ml/kg body weight). The following check showed a very slight improvement in the ROTEM results after the FFP (Fig. 4i).

The balance after ten hours of anaesthesia: blood loss 5200 ml (360%), 5000 ml Ringer lactate, 2500 ml gelatin solution, 3 units of allogenically packed red blood cells, 952 ml autologous cell saver concentrate (equivalent to 5 units PRBC), 5 g fibrinogen, 600 ml platelet concentrate, 600 IU prothrombin complex, 500 IU FXIII, and 2 FFP.

The child was extubated without problem three hours after the operation, showed no signs of volume overload in the chest X-ray, no secondary bleeding, and required no further transfusion or factor concentrate throughout his entire inpatient stay. Immediate postoperative results of laboratory testing were normal, with the exception of a slightly prolonged aPTT, probably because of low FXII levels (PT 76%, aPTT 51 s, fibrinogen 237 mg/dl, haemoglobin 8.0 mg/dl, platelets 130 G/l). ROTEM was normal and could also exclude residual heparination (following the transfusion of almost 1000 ml cell saver concentrate) as the cause of the prolonged aPTT. Without the close ROTEM monitoring and continuous maintenance of adequate fibrin polymerisation, it would almost certainly have been impossible to maintain the haemostatic capacity successfully, during an almost four-fold blood exchange, with only 2 FFP and 600 ml platelet concentrate. On a purely mathematical basis, an additional 15 FFP would have been required instead of the 5 g fibrinogen concentrate.

Conclusions

Analysis of the literature shows that compensation of perioperative blood loss with plasma expanders and restrictive transfusion of plasma-free packed red blood cells favours the development of a coagulopathy (especially fibrinogen deficiency). Standard tests do not seem to be suitable for identifying clinically relevant intraoperative coagulation factor deficiencies promptly and confidently. Thromboelastography offers a point of care method that, making allowance for its limitations, provides a rapid and differentiated diagnosis of the deficiencies and disorders responsible for the coagulopathy. Since only fibrinogen deficiency comes into question intraoperatively, at least in the first instance, administration of fibrinogen concentrate often suffices. This strategy is used instead of a shotgun approach for all factors with FFP – which is anyway usually ineffective in the recommended dosage. Platelet transfusions, other coagulation factors and/or FFP are needed only with significant blood loss, especially if there is deficiency of FV and FXI. If allogenic blood products have not been given prophylactically, the administration of single factor concentrates seems to be superior to FFP in correcting deficiencies quickly and effectively, without adverse cardiopulmonary effects. Further studies are being planned to demonstrate conclusively the superiority of single factor concentrates.

References


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