Principles of perioperative coagulopathy

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Perioperative coagulopathy impacts on patient outcome by influencing final blood loss and transfusion requirements. The recognition of pre-existing disturbances and the basic understanding of the principles of and dynamic changes of haemostasis during surgery are pre-conditions for safe patient management. The newly developed cellular model of coagulation facilitates the understanding of coagulation, thereby underscoring the importance of the tissue factor-bearing cell and the activated platelet. Amount of blood loss as well as amount and type of fluids used are the main factors involved in the development of dilutional coagulopathy, which is the most frequently observed cause of coagulopathy in the otherwise healthy surgical patient. Recent data from studies using viscoelastic coagulation studies confirm the central role of fibrinogen in stable clot formation and provide essential knowledge about its changes during blood loss and fluid administration. Besides early decrease in clot firmness during mild-to-moderate dilution, profound dilution results in a critical decrease in thrombin generation as well as a reduction in numbers and function of platelets. Although our knowledge of perioperative coagulopathy has dramatically increased over the past few years, several questions such as critical thresholds for fibrinogen, platelets, impact of FXIII and TAFI remain unanswered and need to be investigated further.

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Since the late 1980s, there has been consistent growth in the evidence showing that allogeneic blood transfusions frequently needed in surgical patients are associated with considerable adverse effects. Besides the nowadays small risk of transmitting infectious diseases, transfusion-induced
immunomodulation and its consequences such as increased risk for infection, persistent microchimaerism and recurrence of cancer remain even today serious side effects, as well as transfusion-related circulatory overload (TACO) and lung injury (TRALI).1–4 Because the competence of the haemostatic system contributes substantially to final blood loss and transfusion requirements, knowledge of the underlying mechanisms of coagulopathy is an important factor for successfully employing concepts aimed at minimising patient exposure to allogeneic blood transfusion. Importantly, surgical patients are not only prone to develop coagulopathic bleeding, but they are also at risk for thrombosis, especially in the postoperative period.5 Defining risk profiles or discussing the need for postoperative thrombosis prophylaxis is, however, beyond the scope of this article.

Disruption of endothelium and exposure of tissue factor and collagen to the blood stream initiate a complex process starting with platelet adhesion and leading to the localised formation of a stable clot within a few minutes. Keeping in mind the complexity of the system and of control mechanisms, many anaesthetists view haemostasis as a highly sophisticated black box, impossible to understand. By discussing simplified models of haemostasis and the commonly observed pattern of changes, the present review intends to encourage anaesthetists to acquire a basic understanding of the dynamic changes of haemostasis as generally occurring during surgery.

Preoperative evaluation

Patients’ history and physical examination

Pre-existing bleeding disorders most frequently result from disturbed platelet function or von Willebrand disease Type I (vWD).6 These are overlooked if the results of platelet count and routine coagulation tests are used to assess haemostasis only. Many platelet disorders result from anti-platelet medication or co-existing diseases and are sufficiently characterised, while diagnostic assessment of hereditary platelet disorders can be difficult.7 Moreover, to confirm or exclude the various types of vWD, time-consuming specific laboratory tests may be needed and, thus, intra-operative diagnosis in the acutely bleeding patient is not feasible.8 Therefore, patients’ history (including the patients’ and the families’ bleeding history) and a careful preoperative physical examination are essential for timely detection of patients susceptible to pre-existing haemorrhagic disorders.9 However, mild coagulation factor deficiencies and platelet dysfunction can be aggravated by surgical trauma and fluid administration, thus, first manifesting themselves during surgery.

Co-existing diseases susceptible for concomitant haemorrhagic disorders

Co-existing diseases such as severe infection/sepsis, hepatic or renal insufficiency, amyloidosis, thyroid dysfunction, connective tissue disease, immunologic, myeloproliferative and neoplastic diseases or cardiovascular diseases with turbulent circulation should alert the anaesthetist to the possible presence of disseminated intravascular coagulation (DIC), imbalances in fibrinolysis, thrombocytopenia/thrombocytopeny, coagulation factor deficiencies or acquired von Willebrand syndrome.10 Among these, diagnosis of acquired von Willebrand syndrome is challenging because it requires sophisticated laboratory tests in the presence of severe bleeding that persists until specific treatment is administered.11,12 Acquired von Willebrand syndrome is categorised as type 1 (qualitative lack of vWF) or more commonly as type 2 disorder, which refers to a reduction in the high-molecular-weight von Willebrand factor multimers (HMW:vWF) and a decrease in platelet-dependent functions. The underlying aetiologies include auto-antibodies to vWF, adsorption of vWF into tumour cells or activated platelets, increased proteolysis and mechanical destruction of HMW:vWF multimers under high shear stress.

Standard laboratory screening

Although routine coagulation tests for prothrombin time (PT) and activated partial thromboplastin time (aPTT) show poor correlation with bleeding risk, they are traditionally performed preoperatively.13,14 Routine coagulation tests show good reproducibility and are useful to guide therapy with
oral anticoagulants or unfractionated heparin. These tests were initially developed to detect and differentiate the deficiency of coagulation factors of the intrinsic or extrinsic pathway with high sensitivity. Importantly, they do not reflect anticoagulatory proteins, vWD (except types with decreased FVIII) or deficiency of FXIII. However, only a few patients will exhibit congenital coagulation factor deficiency. Haemophilia A, B and von vWD represent 95–97% of all congenital deficiencies of coagulation factors, while the remaining defects are very rare.15

Usually these patients have shown bleeding symptoms since early childhood, and diagnosis is established and treatment already predetermined by a haematologist. Of course, patients with end-stage liver disease or those receiving oral anticoagulants, unfractionated heparin or exhibiting vitamin K deficiency will present with pathological PT or aPTT values. Associated with severe bleeding, an acquired coagulation factor deficiency can result from antibodies directed against individual coagulation factors.16 Acquired coagulation factor deficiency should be suspected in patients with unexplained pathological results for PT or aPTT, history of previous exposure to fibrin glue or spontaneous soft-tissue or retroperitoneal haematoma. Diagnosis is confirmed by plasma change tests, low concentration of a single coagulation factor and detection of the specific inhibitor. Lastly, among the preoperatively assessed laboratory parameters, fibrinogen concentration is of interest because patients showing low initial fibrinogen concentrations are prone to develop fibrinogen deficiency already at much smaller blood loss volumes than are patients with initially high fibrinogen levels.17

Besides impairment of platelet function, thrombocytopenia may be present. In general, thrombocytopenia may result from decreased synthesis or increased consumption. However, thrombocytopenia is most frequently acquired and associated with immunological and infectious diseases, radiation, bone-marrow disease, uraemia, liver disease, medication, transfusion, vWD Type IIB or disseminated intravascular coagulation.10

Basic understanding of the clotting process

The basic pre-conditions for clot formation are physiological milieu, highly effective activators and accelerators, localising matrix, sufficient substrate and stabilising factors (Fig. 1). In addition, clot formation overshoot is prevented by several limiting control mechanisms and the activity of the counterbalancing fibrinolytic system.

The several steps of the complex coagulation cascade cited in every textbook describe the initiation of coagulation as it occurs in test tubes and are thus useful in explaining how coagulation tests work. By contrast, the newly developed cellular model of coagulation18 enables a better understanding of the clotting process as it occurs in vivo (Fig. 2).

Although closely linked, primary and secondary haemostases are separately discerned for didactic reasons.

Primary haemostasis

Simply stated, exposure of subendothelial collagen initiates platelet spreading, platelet adhesion and shape change, platelet granule secretion and initial platelet aggregation. These initial steps are facilitated by the bridging activity of vWF, the binding of fibrinogen to platelet glycoprotein receptors (GPIIb/IIIa) and the small amount of thrombin, which is built up during the initiation of coagulation.

Secondary haemostasis: thrombin and clot formation

During initiation of coagulation, the exposed tissue factor (TF) and circulating FVIIa form the TF/ FVIIa complex (Fig. 2). This complex results in the formation of coagulation factors FVa and FXa and leads to conversion of prothrombin to thrombin in small amounts. During amplification and propagation of coagulation, this initial thrombin activates adherent platelets, facilitating platelet granule release and binding of coagulation factors, fibrinogen and Ca++. In addition, initial thrombin enables formation of FVIIIa, promoting more FXa formation. In parallel, thrombin-induced FXa activates FIXa, which, in turn, increases FXa formation. Lastly, thrombin activates FVa and, in the presence of FXa and
Fig. 1. The thrombin “reactor”. Tissue factor-bearing cells expose tissue factor to the blood stream, resulting in complex formation with circulating VIIa. By activating factors X and V a small amount of thrombin is formed. This initial thrombin activates platelets and factors XI, IX, X and co-factors VIII and V resulting in a thrombin burst necessary for cleavage of fibrinogen. The formed fibrin monomers polymerize spontaneously and are finally cross-linked by means of XIIIa.
Ca^{2+} bound to the surface of activated platelets, large amounts of prothrombin are rapidly converted to thrombin (thrombin burst).\cite{18}

Most thrombin is formed during clot formation.\cite{19} Every activated platelet exposes several thousand glycoprotein receptors (GPIIb/IIIa) for effective binding of fibrinogen and thus primary platelet aggregation. Following sufficient thrombin generation, fibrinogen is cleaved and the resulting fibrin monomers spontaneously polymerise to form uncross-linked fibrin. In fibrinogen knockout mice, afibrinogenaemia results in formation of unstable platelet plugs that are dislocated by shear forces and, thus, are able to cause paradoxical arterial thrombosis.\cite{20} Frequently overlooked, the final stability of the formed platelet/fibrin clot determines effective cessation of bleeding. The main stabilising factors are the thrombin-induced factors FXIIIa and thrombin-activatable fibrinolysis inhibitor (TAFIa).\cite{21} FXIIIa stabilises the clot by catalysing fibrin cross-linking (cross-linked fibrin) and incorporating antifibrinolytic proteins into the clot. TAFIa decreases fibrinolysis by reducing fibrin's binding sites for plasminogen and tissue plasminogen activator (t-PA).

Control mechanisms for overt coagulation activation (Fig. 3)

Broadly speaking, initial thrombin formation is limited by tissue factor pathway inhibitor (TFPI) and antithrombin (AT), which neutralise TF/FVIIa complex, FXa and thrombin. Endogenous heparin sulphate or exogenous heparin serve as co-factors for AT by increasing the speed of reaction dramatically. Interestingly, thrombin is also bound to the formed fibrin; thus, excessive thrombin levels are limited by intact fibrin formation (antithrombin I).\cite{22}

Binding of thrombin to endothelial thrombomodulin (TM) decreases the various pro-coagulant effects of thrombin and activates circulating protein C to activated protein C (aPC). aPC and its co-factor free protein S (PS) slow thrombin formation by inactivating the thrombin-accelerating co-factors FVIIIa and FVa (Fig 3 VIIIi, Vi).

Fibrinolytic system

Activation of circulating plasminogen to plasmin by t-PA, urokinase (u-PA), FXIIa or kallikrein results in proteolytic lysis of cross-linked fibrin, formation of D-dimers and even defibrination in severe
cases of hyperfibrinolysis due to plasmin’s ability to also degrade fibrinogen. However, neutralising systems usually prevent the development of this severe hyperfibrinolysis. They consist of $\alpha$-anti-plasmin-mediated binding of free plasmin and plasmin activator inhibitor (PAI), which inactivates plasminogen activators and the activity of the mentioned clot stabilising factors FXIIIa and TAFIa.

In summary, thrombin is the key enzymatic motor of the clot formation process and fibrinogen is the major substrate during clotting, while platelets are the localising matrix, contribute to thrombin formation and are also a necessary substrate. To arrest bleeding the formation of a stable fibrin clot is the *sine qua non*. Even the highest and sustained thrombin burst is wasted if insufficient substrate is available, as demonstrated *in vitro* and *in vivo* during administration of rFVIIa.23,24

**Basic understanding of increased intra-operative bleeding**

Increased bleeding can be localised or systemic, and the main underlying problem can be surgical or related to impaired haemostasis. However, major surgical bleeding will quickly be accompanied by impaired haemostasis, as will moderate or occult continuous bleeding, albeit more slowly. During coagulopathic bleeding, the main underlying mechanism might be related to impairment of primary haemostasis, thrombin generation, deficiency/malfunction of substrates, decreased resistance to fibrinolysis or presence of hyperfibrinolysis. Furthermore, surgically induced endothelial lesions and influx of coagulation activating substances and microparticles activate coagulation and fibrinolysis, resulting in consumption of platelets and fibrinogen and increase of D-dimers. However, in the otherwise healthy surgical patient, activation of coagulation is mainly localised, which is in contrast to the clinical picture of disseminated intravasal coagulation (DIC). The coagulation system is closely linked to the inflammatory system. Therefore, patients presenting with infection, systemic inflammatory syndrome or severe sepsis show a completely different pathology, which is mentioned in a simplified manner here. In these patients, some of the haemostasis players are up-regulated while others are down-regulated.25 The resulting haemostatic competence changes dynamically with the stage of the underlying disease, varying from activated hypercoagulable states with diffuse microvascular thrombosis to consumptive hypocoagulability.

It is well known that patients on continuous anti-platelet medication show increased transfusion requirements and CPB-induced platelet dysfunction is a recognised factor that contributes to blood loss.
during and after cardiac surgery. However, the question as to whether relevant platelet dysfunction occurs during other types of surgery remains to be answered. The platelets' contribution to haemostatic competence, management of patients under anti-platelet therapy, as well as the special features of the coagulopathy of trauma are discussed as specific topics in this issue.

**Dilutional coagulopathy**

Dilutional coagulopathy mainly results from the synergistically and commonly combined effects of blood loss and fluid administration, leading to decreased quantity and quality of substrates, altered balance of activators and anticoagulants and probably reduced clot stability.

**Substrate deficiency**

Platelets and fibrinogen determine clot firmness, which is also influenced by FXIII. Clinical studies clearly showed that severe thrombocytopenia usually develops in the late course of blood loss (>150% of blood volume), that fibrinogen deficiency develops far before critical levels of other coagulation factors occur (>200% of blood volume) and that low fibrinogen concentrations and platelet counts are the most sensitive predictor of diffuse microvascular bleeding. The fact that fibrinogen is the first factor to reach critical levels is explained by the large amounts needed for clot formation (Table 1), the limited increase in fibrinogen synthesis and the simultaneously increased fibrinogen breakdown during blood loss. Hiippala and co-workers first described in 1995 that during blood loss, fibrinogen concentrations become critically low (<1 g l\(^{-1}\)) after a median blood loss of more than 100% of the calculated blood volume. However, all investigated patients showed high normal preoperative fibrinogen levels and several also exhibited supra-normal levels. By contrast, the study by McLoughlin investigating patients with borderline fibrinogen levels found critical fibrinogen concentrations already at a blood loss of about 50% of their blood volume. The assumption that initial fibrinogen concentration determines the percentage of lost blood volume at which a critically reduced concentration occurs was confirmed by a mathematical model that was also validated by patient data. Most textbooks and review articles cite a fibrinogen value below 1 g l\(^{-1}\) as critical with regard to increased bleeding. However, this figure refers to the findings of a small, old study in which all of four patients developed profuse microvascular bleeding and concomitantly showed fibrinogen values below 0.8 g l\(^{-1}\). Considering fibrinogen's significance for clot firmness, scepticism arises as to whether a threshold of fibrinogen concentration set at one-third of normal enables sufficient clot formation in surgical patients. Indeed, data from patients

<table>
<thead>
<tr>
<th>Coagulation factor</th>
<th>Plasma concentration (mg/L)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>48–123</td>
<td>48–123</td>
</tr>
<tr>
<td>VII</td>
<td>0.5</td>
<td>3–4</td>
</tr>
<tr>
<td>IX</td>
<td>4</td>
<td>18–30</td>
</tr>
<tr>
<td>X</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>V</td>
<td>4–14</td>
<td>4–36</td>
</tr>
<tr>
<td>VIII</td>
<td>0.15</td>
<td>8–12</td>
</tr>
<tr>
<td>XI</td>
<td>2–7</td>
<td>60–80</td>
</tr>
<tr>
<td>XII</td>
<td>15–47</td>
<td>40–50</td>
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<tr>
<td>vWF</td>
<td>5–10</td>
<td>6–12</td>
</tr>
<tr>
<td>XIII</td>
<td>2</td>
<td>192</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2000–4000</td>
<td>72</td>
</tr>
<tr>
<td>AT</td>
<td>0.15–0.39</td>
<td>70</td>
</tr>
<tr>
<td>PC</td>
<td>2–6</td>
<td>6–8</td>
</tr>
<tr>
<td>PS</td>
<td>20–25</td>
<td>24–58</td>
</tr>
<tr>
<td>TFPI</td>
<td>0.06–0.180</td>
<td>1.5</td>
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</tbody>
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undergoing neurosurgery, cardiac surgery or exhibiting peripartal bleeding clearly show increased blood loss when fibrinogen concentration drops below 2 g l\(^{-1}\).\(^{35–38}\) Interestingly, this was the same threshold found to be associated with significant increase in clot firmness \textit{in vitro}.\(^{39}\) Fibrinogen measurements are poorly standardised, especially at the very low and the very high levels, and are influenced by the presence of colloids and fibrin-degradation products and do not necessarily correlate with fibrin polymerisation.\(^{40–42}\) Therefore, the establishment of a critical functional threshold for fibrinogen/fibrin polymerisation might be more useful. Our own clinical experience shows that diffuse microvascular bleeding appears when fibrin polymerisation (measured by the viscoelastic ROTEM technique) drops below a MCF of 7 mm in a FibTEM test, a value that usually corresponds to a fibrinogen concentration of 1.5 g l\(^{-1}\).\(^{42,43}\) This clinical experience has been recently confirmed by results of a study conducted in women developing postpartum haemorrhage.\(^{44}\) It should be noted that fibrinogen concentrations are increased in elderly patients and those with inflammation, malignant disease and in various other conditions. In these patients, huge blood loss can be tolerated until fibrinogen becomes critically low.

As with fibrinogen, the critical threshold for platelet numbers in surgical patients are currently not known and refer mainly to consensus statements or expert opinions.\(^{32}\) A recent experimental study showed that high-dose fibrinogen compensated for reduced clot firmness during thrombocytopenia and also slowed blood loss resulting from inflicted liver injury.\(^{45}\) Furthermore, data from Lang and co-workers indicate that fibrinogen increases clot strength independently of platelet count.\(^{46}\) Therefore, the actual relationship between the two substrates might be more important than the concentration of fibrinogen or platelet counts alone and the functionality of platelets seems to be more relevant than numbers of platelets. As FXIII is also involved in clot firmness, variability of clot firmness further increases, which might explain the difficulties in establishing clear thresholds for single components such as fibrinogen or FXIII in surgical patients. Interestingly, Gerlach found the highest incidence of re-bleeding and need for revisions in neurosurgical patients when all three determinates of clot firmness, that is, fibrinogen, FXIII and platelets, were decreased, although the decrease was moderate for each of these factors.\(^{35}\)

\section*{Activator deficiency}

The observations that pro-coagulant coagulation factors are commonly critically reduced in the late stages of blood loss only\(^{28,30,42,43}\) might be explained by the facts that they are needed at low concentrations (\textit{Table 1}), are decreased through blood loss and dilution but, as enzymes, are not consumed by the reaction they promote. In addition, the only coagulation factor needed at a relatively high concentration is prothrombin and its concentration shows a linear relationship to thrombin generation.\(^{47}\) Prothrombin is usually present at relatively high plasma levels and also shows a relatively long-lasting half-life (\textit{Table 1}). By contrast, small concentrations of other coagulation factors are needed for sufficient thrombin generation.\(^{48}\) FVIII deficiency rarely occurs because of endothelial release and the acute phase response, and FV is stored in platelet granules in a quantity of up to 20% of plasma concentrations. Interestingly, the decrease in concentrations of coagulation factors is not uniform during surgery. In patients undergoing cardiac surgery, Davidson observed that factors FII and FX decreased significantly more than did factors FV and FVII, while FVIII did not change at all.\(^{49}\) In that study, a more than 50% reduction in thrombin generation (endogenous thrombin potential; ETP) was associated with increased bleeding and was mainly governed by FII and FX levels, a finding also observed in patients undergoing various types of surgery.\(^{50}\) Importantly, thrombin generation not only depends on sufficient pro-coagulant factors and co-factors, but also on the activity of the counterbalancing factors.\(^{51}\) As these factors also decrease during blood loss and fluid administration, thrombin generation may remain sufficient, as shown in surgical patients by Horne and co-workers, although concentrations of pro-coagulants were reduced to some extent.\(^{52}\) The even mild decrease in several coagulation factors is sensitively detected by standard coagulation tests that soon show pathological values, especially when more than one single factor is decreased\(^{53}\); but these tests do not reflect the activity of anticoagulatory proteins and thus the system’s balance.
Impaired clot stability, hyperfibrinolysis

Although patients with congenital FXIII deficiency usually show spontaneous bleeding at levels below 4%, increased postoperative or unexpected intra-operative bleeding has been observed in surgical patients already at levels below 60%. In vitro data show that with FXIII concentrations below 60%, clot firmness decreases and profoundly at concentrations below 30%. Unfortunately, at this time, the dynamics of TAFI in surgical patients and its impact on bleeding tendency are largely unknown and the results of clinical studies need to be awaited.

Hyperfibrinolysis occurs rarely in surgical patients except in those on cardiopulmonary bypass and during liver transplantation. Furthermore, hyperfibrinolysis may be present in obstetrics, severely traumatised patients and patients undergoing urological procedures. The degree and speed of clot dissolution can vary, and slight or late lysis can resolve spontaneously or proceed to hyperfibrinolysis with complete clot dissolution within a few minutes. As a consequence severe bleeding arises, which, if not treated with anti-fibrinolytics, readily culminates in a profound deficiency of all players in the coagulation system. Interestingly, Tanaka found in vitro that, during induced hyperfibrinolysis, the addition of rFVIIa increased lysis of the clot in the absence of anti-fibrinolytics.

The need for monitoring

The amount of blood loss at which the above-mentioned specific deficiencies need to be watched out for varies considerably in the individual patient; it strongly depends on the patient’s blood volume and initial haemostatic competence, which is highly variable. Furthermore, surgical factors (cardiopulmonary bypass, vascular surgery, large tissue trauma, bleeding from spongiosal bone surfaces and obstetric bleeding), the type and amount of fluid used and alterations in the physiological milieu influence speed of development and type of mainly underlying deficiencies. Notably, deficiency of substrate, impairment of thrombin generation or increased fibrinolysis can occur independently or consecutively. Thus, a monitoring that ideally displays the actual balance of all haemostasis players and one that quickly allows differential diagnosis of main deficiencies is undoubtedly helpful for safe patient management.

Specific effects of intravenous fluids

During considerable blood loss, on the one hand, the disadvantages that fluids have on haemostasis are far outweighed by their beneficial effect on the circulatory system. On the other hand, patients showing minor blood loss but receiving inappropriately large amounts of fluids may suffer iatrogenic coagulopathy. Besides, the more pronounced volume-expansion colloids exert specific effects on the activity of vWF and the clot formation process. Experimental data also show that effects seen after 0.9% NaCl solution differ from that following Ringer’s lactated solution.

Colloids

A huge number of investigations have clearly demonstrated that colloids impair clot formation to a larger extent than do crystalloids. In summary, the most pronounced effects are shown with dextrans (which are not further discussed here), followed by differently prepared hydroxyethyl starch solutions (HESs), gelatines and albumin. Regarding the various HES preparations, increased molecular weight (MW) and degree of substitution are thought to correlate with increased side effects on haemostasis including expression of platelet glycoprotein receptors and coating of platelets. However, other studies show that increasing MW mainly influences intravascular half-life, while no differences were found for clot formation, PT, aPTT or vWF. The induction of a von Willebrand-like syndrome has been observed in patients receiving HES solutions, and a significant decrease in von Willebrand Ristocetin activity (localised at the high molecular part of the vWF, permits platelet adhesion to the endothelium and between each other) was also observed following infusion of gelatine. However, it can be assumed that, in most surgical patients, these effects are minor when using the rapidly degradable new HES solution at recommended doses. By contrast, in patients showing borderline vWF...
activity or repeatedly receiving highly substituted high-molecular-weight HES over several days, severe bleeding can be provoked. Although gelatin, HES130/0.4 and HES 200/0.5 showed no influence on endogenous release of molecular markers of fibrinolysis in vivo, a decreased resistance of clots to fibrinolysis has been observed with colloids in vitro. This might refer to colloid-associated interference with FXIII or to the fact that weaker clots dissolve faster.

**Crystalloids**

Some data indicate slight hypercoagulability during moderate dilution using 0.9% NaCl as compared with colloid solution, and imbalances in AT levels were assumed to explain these findings. However, these hypotheses could not be confirmed in orthopaedic patients. More clinically relevant, the administration of large amounts of 0.9% NaCl may result in the development of dilutional acidosis and diminished thrombin formation. Until now, only experimental data show decreased thrombin generation, impairment of clot formation and blood loss to be greater following 0.9% NaCl than Ringer’s lactated solution. In vitro data also show that hypertonic solutions significantly affect platelet aggregation and coagulation while in pigs, clot formation was better maintained with a single dose of hypertonic saline–HES solution as compared with gelatine or isotonic HES solution administered at commonly used amounts.

**Laboratory findings during dilutional coagulopathy**

Irrespective of the type of fluid used, standard coagulation tests have been shown to become pathological soon, and with colloids, this effect is more pronounced. Mild dilution mainly results in reduction of clot firmness, being significantly larger with colloids as with crystalloids, and delayed initiation of coagulation occurs only with profound dilution (>50%). A disturbance in fibrinogen/fibrin polymerisation as the possible underlying mechanism for decreased clot firmness was firstly suspected by results of a study conducted in orthopaedic patients and later confirmed by further clinical data. After 30–40% dilution, these studies showed a decrease in fibrinogen concentration, colloid-induced decreased clot firmness but sufficient platelet numbers and sustained thrombin formation. Furthermore, both studies show improved clot firmness with in vivo and ex vivo fibrinogen supplementation but no effect of platelets or FXIII when added ex vivo. However, the study of Mittermayr showed that the correlation between fibrinogen concentration and measured polymerisation disappeared, and improvement of polymerisation was less in patients receiving HES than in those receiving gelatine, a finding also made in previous in vitro studies. These data suggest that besides provoking acquired fibrinogen deficiency, HES solutions interfere with fibrinogen/fibrin polymerisation by a yet unknown mechanism.

In summary, administration of intravenous fluids diminishes the concentration of activators/anticoagulants and the substrate fibrinogen by expanding plasma volume. More specifically, artificial colloids further impair the process of fibrinogen/fibrin polymerisation. Mild-to-moderate dilution mainly affects clot strength while thrombin generation is maintained until profound dilution.

**Alterations in the physiological milieu**

Besides optimal pH value and body temperature, adequate quantities of ionised calcium and even red cells are necessary pre-conditions for optimal coagulation and clot formation. Hypothermia and acidosis are usually prevented during elective surgery by appropriate fluid management and use of pre-warmed fluids and warming systems. Nevertheless, intra-operatively decreased calcium may also result from citrate overload associated with blood transfusion or be a consequence of colloid administration. In addition, the justified restrictive use of red cell transfusion and compensation of blood loss through volume administration promotes the decrease of concentrations of coagulation factors and fibrinogen by the consequently increased plasma volume. Furthermore, the attenuation of the direct and indirect influence of red cells on haemostasis needs to be accepted. These facts might explain why the development of coagulopathy and the need for treatment can occur much earlier nowadays.
than described in older studies that used whole blood (containing stable coagulation factors) and higher transfusion triggers.

The mechanisms of hypothermia, acidosis and hypocalcaemia on haemostasis were recently described in detail in an excellent review and will only be summarised here. Basically, hypothermia decreases fibrinogen synthesis, the activity of the various proteases and also the functionality of platelets at temperatures <35 °C. By contrast, deep hypothermia can be accompanied by accelerated microthrombosis caused by increased GPIIb/IIa activation.

Since the pH optimum for thrombin generation is in the alkali range, a reduction in pH towards 7.1 nearly halves thrombin generation and even diminishes the efficacy of rFVIIa by TF-dependent and -independent formation of FXa. Besides reduced thrombin generation, an experimental model found fibrinogen concentration and platelet numbers at pH 7.1 to be reduced by about 30% and 50%, respectively; speed and quality of clot formation were consequently decreased. Interestingly, despite persisting acidosis, spontaneous recovery of thrombin formation was observed in that study after infusing animals with Ringer’s lactated solution, while no effects on thrombin generation occurred after pH correction to 7.4 using sodium bicarbonate. In addition, correction of acidosis did not influence low platelet numbers or low fibrinogen concentrations, suggesting increased consumption of fibrinogen and platelets triggered by acidosis.

Positively charged Ca ions play a pivotal role during coagulation, and these were formerly known as the coagulation factor FIV. Ca ions facilitate the assembly of coagulation factors on the platelet surface, increase the resistance of the formed fibrin, influence its polymerisation and are needed for normal platelet function.

In brief, perioperative coagulopathy can result from pre-existing deficiencies/malfunction of coagulation factors and platelets (hereditary, iatrogenic and acquired), which should be diagnosed preoperatively to plan appropriate management. Nevertheless, the most frequently occurring problem in patients undergoing extensive or long-lasting surgery is the development of dilutional coagulopathy. Dilutional coagulopathy results from blood loss, consumption and dilution of fibrinogen, coagulation factors and platelets and is aggravated by hyperfibrinolysis, hypothermia, acidosis and hypocalcaemia, which, however, are rare during elective surgery. The impact of dilutional coagulopathy varies with the amount of blood loss and amount and type of fluid used. Studies using viscoelastic methods clearly show that clot firmness diminishes first, mainly caused by decreased fibrinogen concentrations and disturbance of polymerisation. Development of critical thrombocytopenia and deficiency of thrombin formation usually occur only in the late stages of blood loss with profound dilution. This general pattern is modified by factors unique to the patient and specific surgical conditions. Importantly, coagulopathy increases blood loss, transfusion requirements and the need for surgical re-exploration, factors that are associated with increased costs, morbidity and mortality. A basic understanding of haemostasis and adequate monitoring are pre-conditions for limiting blood loss, and also for avoiding unnecessary transfusion or hypercoagulability, which puts patients at risk for thrombosis.

**Practice points**

1. Basic understanding of haemostasis facilitates timely recognition of deficiencies that need to be corrected to avoid increased blood loss.
2. Because marked inter-patient differences exist, patients should be monitored and treated accordingly.
3. The balance between activators and natural anticoagulants dictates thrombin formation, which is the key motor of coagulation. Deficiency of thrombin formation usually occurs only in the late stages of blood loss, but can be accelerated in an unphysiological milieu.
4. Clot formation is a pre-condition for arresting bleeding, and all the thrombin formed is wasted if sufficient substrates, fibrinogen and platelets are not available.
5. Besides clot formation, clot stability is important and is governed by factors FXIII, TAFI and the activity of the fibrinolytic system. Importantly, these are not reflected by PT or aPTT results.
Research agenda

Clinical research is warranted to the following:
1. Identify clear thresholds for critical fibrinogen concentration and polymerisation as well as for platelet numbers.
2. Investigate changes of platelet function generally occurring during surgery.
3. Evaluate dynamics of FXIII concentrations and TAFIa formation in surgical patients and their association with blood loss.

Conflict of interest

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In the past 5 years and related to the topic addressed in this article, Joachim Kienast has received educational grants or honoraria for consulting or lecturing, costs incurring for travel and hotel accommodations from the following company: CSL Behring GmbH (Marburg, Germany).

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