Coagulation Factor Concentrates

11

Lars M. Asmis

11.1 Introduction

Perioperative management of coagulation involves the use of blood products. Patients have typically been transfused whole blood or derivatives of whole blood, including red blood cell (RBC) concentrates, platelet concentrates (PC), and plasma. Fractionated plasma products, in the form of single and combined coagulation factor concentrates, have been available for decades. Following isolated human coagulation factors, recombinant coagulation factors eventually became a part of standard medical practice. Both isolated and recombinant types of coagulation factor preparations can contain nonactivated or activated coagulation factors. A third group of drugs used to manage perioperative bleeding includes medications that alter either the activity (e.g., tranexamic acid) or the plasma levels (e.g., desmopressin) of coagulation-related proteins. The latter group of drugs will be discussed in Chap. 12.

The transfusion of any blood product requires a thorough risk–benefit evaluation (Dunbar et al. 2012; Hardy 2012; Berseus et al. 2013; Shaw et al. 2013). From the very beginnings of transfusion medicine, it has been known that the use of cell-containing transfusion products, such as RBC concentrates, is associated with potential side effects. Transfusion reactions, due to blood group incompatibility in RBC transfusion, are potentially lethal treatment complications. Due to the way they are produced, platelet concentrates may harbor a significant risk of sepsis. Storage at room temperature is conducive to bacterial growth in these products that may lead to patient harm (Stroncek and Rebulla 2007). Fresh frozen plasma (FFP) was originally considered a "cell-free" product. As a cell-free product containing physiological coagulation factors and inhibitors, it was assumed to be safe. It has

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since been shown that FFP may be contaminated with fragments of cellular origin, termed as microparticles, as well as soluble mediators including antibodies and interleukins (George et al. 1986; Theusinger et al. 2011). These contaminants can potentially lead to adverse effects. A rare but dangerous complication of FFP transfusion is transfusion-related acute lung injury (TRALI) that is associated with increased mortality (Inaba et al. 2010).

The ongoing quest for efficient and safe transfusion products has resulted in the development of isolated coagulation factor concentrates (i-CFC) and recombinant coagulation factor concentrates (r-CFC). This chapter focuses on isolated (single) and combined coagulation factor concentrates. Based on differences in regulation and approval procedures in various countries, there are relevant geographical differences in the availability and use of coagulation factor products. Indications for the various products vary significantly from country to country. Substitution of i-CFC in acquired coagulation factor deficiencies represents on-label use in some countries, while it is off label in others. This chapter discusses the most frequently used coagulation factor concentrates.

11.2 Coagulation Products

11.2.1 Fibrinogen Concentrate

11.2.1.1 Background

Fibrinogen was the first coagulation factor to be discovered. In an open wound, the white aggregates of fibrin strands can be seen with the naked eye. In the nineteenth century, Home coined the term "fibrin," and Virchow postulated that there was a precursor molecule, which he called "fibrinogen." In 1905, fibrinogen was already defined as a coagulation factor I (FI) in a review by Morawitz (1905). Hiippala and colleagues established fibrinogen's key role in perioperative hemostasis and demonstrated that it was the first coagulation factor to reach critical levels in massive bleeding (see "Indications", below) (Hiippala et al. 1995).

11.2.1.2 Description

Fibrinogen, synthesized in the liver, is an abundant plasma protein with concentrations typically ranging between 1.5–4.0 g/l and 6–13 μmol/l. Fibrinogen's molecular weight is approximately 340 kDa. It is a heterodimer with two sets of α, β, and γ chains. The six chains are N covalently linked in the central E domain. Two sets of α, β, and γ chains extend from the E domain to form 2 so-called D domains at their distal ends. Thrombin (FIIa) cleaves activation peptides from the central (E domain) end of the α and β chains, releasing two sets of fibrinopeptides, A and B, thereby exposing polymerization sites. After the release of these fibrinopeptides, the molecules are called fibrin or fibrin monomers. The fibrin monomers aggregate to form soluble fibrin strands that form by the interaction of the D and E domains of neighboring molecules. Initially, the interaction between fibrin monomers is reversible; the

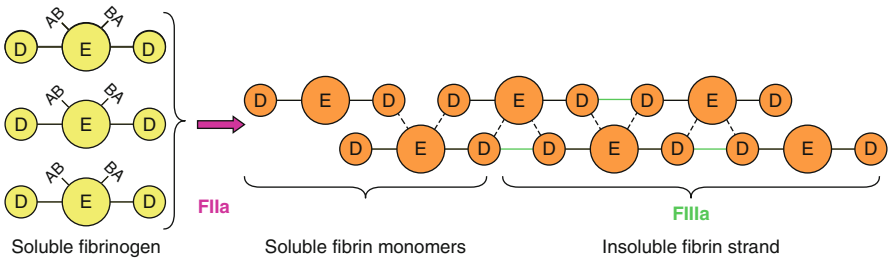

Fig. 11.1 Model of fibrinogen polymerization. Thrombin (*FIIa*)-induced cleavage of the fibrinopeptides A and B from soluble fibrinogen molecules leads to the generation of soluble fibrin monomers that reversibly aggregate into a soluble fibrin monomer gel. Activated factor XIII (*FXIIIa*) can irreversibly stabilize the monomers into an insoluble and stable fibrin strand through covalent cross-linking

resulting fibrin strand can potentially disintegrate again. Only once factor XIII (FXIII) has covalently cross-linked the individual fibrin monomers does the fibrin strand become irreversibly interconnected (Nieuwenhuizen 1995; de Maat and Verschuur 2005; Sorensen et al. 2011b; Levy et al. 2012) (see Fig. 11.1).

The three polypeptide chains (Aα, Bβ, and γ) are encoded by three distinct genes, all residing on chromosome 4. The three genes contain interleukin 6 (IL-6) response elements, which explains why fibrinogen is an acute phase reactant.

Fibrinogen is a glycoprotein that has a plasma half-life of approximately 100 h (Blomback et al. 1966). Liver disease and sepsis increase turnover. In liver cirrhosis, glycosylation may be altered, leading to acquired dysfibrinogenemia, characterized by circulating fibrinogen molecules with reduced biological activity. Degradation of soluble fibrinogen is mediated by "normal protein degradation, the coagulation process, and unknown pathways." Stabilized fibrin (and soluble fibrinogen) degradation occurs by plasmin-induced proteolysis (de Maat and Verschuur 2005).

Fibrinogen has at least four major biological functions: it is a substrate of coagulation; it is a cross-linker in platelet aggregation; it is a coagulation inhibitor as "antithrombin I"; and it is a substrate for interaction with other proteins (Weisel and Litvinov 2013). Most other coagulation factors are serine proteases capable of specifically recognizing target molecules and activating many of them. For example, one activated molecule of factor X (FXa) can activate more than 1,000 prothrombin molecules (FII), while one thrombin molecule can activate more than 1,000 molecules of fibrinogen. Enzymatically active coagulation factors can continue to interact with many other target molecules while fibrinogen, in its role as substrate, will be consumed. One activated molecule of fibrinogen will give rise to one molecule of fibrin in the resulting clot. Fibrinogen's second role is that of the cross-linker in platelet aggregation. Once platelets have been activated "outside in," an "inside-out" activation will occur that leads to an altered structure of the glycoprotein IIb/IIIa (GP IIb/IIIa) receptor on the platelet surface. This structural change permits the interaction of one fibrinogen molecule with several GP IIb/IIIa receptors on several

platelets, leading to the formation of platelet aggregates. The third role involves fibrinogen's ability to bind thrombin (Sorensen et al. 2011b). Finally, there is FXIII, which is reported to covalently link α2-plasmin inhibitor (α2-PI) on to fibrinogen (Richardson et al. 2013). This reaction is important for the stability of the resulting fibrin clot (see below).

11.2.1.3 Indications

11.2.1.3.1 Acquired Fibrinogen Disorders

Hiippala's pioneering work identified the clinical relevance of fibrinogen in massively bleeding patients (Hiippala et al. 1995). He studied 60 massively bleeding patients and measured platelet counts and coagulation factor levels. Based on "critical levels," or thresholds, which he took from a prominent coagulation textbook of the time, he observed that the fibrinogen threshold of 1.0 g/l was reached at 142 % of blood loss. Other parameters he monitored only fell below their respective thresholds considerably later: platelet count at 230 %, FII at 201 %, FV at 229 %, and FVII at 236 %.

Others corroborated the finding that fibrinogen will be the first factor to reach critical levels in massive bleeding (Martini et al. 2005; Fenger-Eriksen et al. 2009c). Acquired hypofibrinogenemia is thus a frequently observed problem in massively bleeding patients. Suggested treatment thresholds lie ≥1.5 g/l (Fenger-Eriksen et al. 2009a). A less frequent problem is acquired dysfibrinogenemia. This may occur in end-stage liver cirrhosis as a consequence of an altered glycosylation of fibrinogen molecules that interferes with the plasma assembly of fibrin monomers. The laboratory hallmark of this disorder is longer thrombin time and a reduced ratio of functional to antigenic fibrinogen tests (<0.7).

11.2.1.3.2 Congenital Disorders of Fibrinogen

Congenital disorders of fibrinogen are registered indications for fibrinogen substitution in many countries. There are various such disorders, including afibrinogenemia (no measurable protein), hypofibrinogenemia (<1.5 g/l), and dysfibrinogenemia. Afibrinogenemia and dysfibrinogenemia are orphan diseases with frequencies of approximately 1:1,000,000 (Peyvandi et al. 2012a). Experienced physicians should manage prophylaxis and treatment of acute bleeding in these patients as these diseases can also manifest a thrombotic phenotype depending on the molecular pathophysiology. Suggested treatment thresholds lie in the area of 0.5–1.0 g/l (Bolton-Maggs et al. 2004; Acharya and Dimichele 2008).

11.2.1.4 Monitoring

Tests for fibrinogen were proposed in the middle of the last century: the Schulz method in 1955 and the Clauss method in 1957 (Schulz 1955; Clauss 1957; Nieuwenhuizen 1995; Lowe et al. 2004). Interestingly, Hartert had published his work on thromboelastography several years before that, in 1948, but functional fibrinogen tests for viscoelastic point-of-care (POC) devices (including functional "fibrinogen" tests on ROTEM, TEG, and related devices) were only standardized and validated much later (Hartert 1948).

The Schulz method is an antigenic test performed in citrate plasma: fibrinogen is heat denatured and the precipitable protein is measured in a graded tube. One of the pitfalls of this test is the presence of other precipitable proteins, not related to fibrinogen, which falsely increase outcomes. Turnaround time is approximately 60 min.

The Clauss method is a functional test of fibrinogen in which a coagulation time is measured in prediluted plasma, rendering fibrinogen the rate-limiting reagent. The addition of (bovine) thrombin is the start signal and formation of soluble fibrin is the stop signal. This coagulation time can be converted into a fibrinogen concentration. Strong inhibitors of thrombin (including direct anti-FIIa inhibitors), excessively high levels of fibrin degradation products (including D dimers), and other inhibitors may falsely lengthen the coagulation time resulting in falsely low fibrinogen results. Turnaround time is approximately 40 min.

Fibrinogen tests in viscoelastic POC devices represent functional tests. The addition of tissue factor induces whole blood to coagulate. Platelet function is inhibited by specific inhibitors. The maximum clot firmness, or maximum amplitude, is measured after a defined time. The results are not only dependent on the fibrinogen concentration, but may be influenced by hematocrit, FXIII, heparin, hydroxyl-ethyl starch, gelatin, and albumin (Solomon et al. 2011; Ogawa et al. 2012; Schlimp et al. 2013). None of these tests is standardized, and the international, gold standard test is currently debated.

11.2.1.5 Efficacy and Safety

To date, there is only limited evidence from three, small randomized controlled trials (RCTs) evaluating fibrinogen concentrate in acutely bleeding patients. A cystectomy trial ($n = 20$), a coronary artery bypass grafting (CABG) trial ($n = 20$), and an elective thoracic/thoracoabdominal aneurysm trial have been published. The cystectomy trial showed that fibrinogen concentrate increased maximum clot firmness and reduced postoperative transfusion in patients whose blood loss was substituted by hydroxyl-ethyl starch (Fenger-Eriksen et al. 2009b). In the CABG trial, patients were randomized to 2 g of fibrinogen concentrate preoperatively or placebo. This raised fibrinogen levels by 0.6 g/l. No adverse effects of fibrinogen substitution were observed (Karlsson et al. 2009). The largest trial, including 62 patients scheduled for elective thoracic/thoracoabdominal surgery, showed that thromboelastography-guided hemostatic therapy using fibrinogen concentrate was more effective than placebo to control bleeding. Fibrinogen substitution was also compared with cycles of FFP/platelets and found to be superior to one cycle and at least as effective as two cycles of the prespecified transfusion protocol. This trial's approximate target level of fibrinogen was 3.6 g/l (Rahe-Meyer et al. 2013a).

The RCT cited above are too small to draw any conclusions regarding safety. In the Rahe-Meyer RCT, one patient in the treatment group died after cardiorespiratory arrest, potentially of thromboembolic origin. In the placebo group, there were four deaths and two thromboembolic events. Based on the limited evidence, reviews describe fibrinogen concentrate as being safe (Fenger-Eriksen et al. 2009a; Levy et al. 2012; Warmuth et al. 2012).

The manufacturer of fibrinogen concentrate conducted a post-marketing program of pharmacovigilance between 1986 and 2008. More than one million grams of fibrinogen were administered, with 48 adverse events reported and 9 cases of arterial or venous thromboembolism. Of these nine patients, seven had congenital fibrinogen disorders and two had acquired fibrinogen disorders (Fenger-Eriksen et al. 2009a). The numbers cited suggest an estimated incidence of thromboembolic events of less than 1 per 10,000. Allergic reactions occurred at a frequency of less than 1 per 10,000. Underreporting of adverse events in the post-marketing phase is a well-known problem, so these numbers need to be interpreted with caution and corrected when data from large RCT become available.

11.2.1.6 Dosing

The following dosing regimen has been suggested in the context of classic coagulation testing: dose (g) = desired increase in g/l × plasma volume (plasma volume = 0.07 × (1-hematocrit) × body weight (kg)) (Acharya and Dimichele 2008). In the context of thromboelastographic/metric testing, 2 g of fibrinogen in a 70-kg patient generally increase the FIBTEM by 4 mm (Rahe-Meyer et al. 2009). The manufacturer of fibrinogen concentrate recommends 30–60 mg/kg or 2–4 g in a 70-kg patient (Fenger-Eriksen et al. 2009a). This dose will increase plasma fibrinogen by approximately 1 g/l (Solomon et al. 2010). Threshold and target values for fibrinogen have changed considerably in the recent years (see Sect. 11.3) (Sorensen et al. 2011b). In the recent Rahe-Meyer RCT, the target post-substitution fibrinogen level was 3.6 g/l or a maximum cloth firmness (MCF) of 22 mm in ROTEM in patients undergoing major aortic replacement surgery.

11.2.1.7 Key Points and Prospects

Preliminary evidence from these three RCTs indicates that fibrinogen concentrates can play an important role in the management of perioperative bleeding. Further research is needed to confirm the treatment's efficacy and safety for this indication.

11.2.2 Factor XIII Concentrate

11.2.2.1 Background

Factor XIII (FXIII) was the last coagulation factor to be discovered. First indications of its existence date back to the 1920s. Fibrin clots that formed in the presence of calcium became insoluble in the presence of weak bases (Barkan 1923). A similar experiment was performed in 1944 with purified fibrinogen. The authors concluded that an additional "stabilizing factor" to calcium was necessary to explain their findings (Robbins 1944). Duckert first described human FXIII deficiency in 1960 (Duckert et al. 1960). The protein was attributed with its current name in 1963 by the International Committee on Blood Clotting Factors (Muszbek et al. 2011).

11.2.2.2 Description

FXIII is a transglutaminase, an enzyme that cross-links proteins. This clearly distinguishes it from the classic coagulation factors that are serine proteases – enzymes that cleave proteins. In plasma, FXIII bound to fibrinogen forms a tetramer with two catalytic A domains and two inhibitory B domains. Cellular FXIII, present in platelets, monocytes, and bone marrow-derived cells, has two catalytic A domains (Muszbek et al. 2011; Levy and Greenberg 2012).

The catalytic A domain is an 83 kDa protein that can be activated by proteolytic activation (by thrombin) or non-proteolytic activation (in the presence of high calcium concentrations).

The FXIIIA encoding genes reside on chromosome 6 (6p24-25). It is expressed in bone marrow-derived cells including megakaryocytes, macrophages/monocytes, and in hepatocytes. The B domain, which lacks enzymatic activity, is an 80 kDa protein. The FXIIIB gene is located on chromosome 1 (1q31-32.1) and is expressed primarily in hepatocytes (Hsieh and Nugent 2008).

In the context of the fibrin clot, FXIII has two functions with fibrin and fibrinogen as its main substrates. FXIII-mediated cross-linking of soluble fibrin monomers results in the generation of an insoluble or stabilized fibrin strand that is essential for in vivo hemostasis. Furthermore, FXIII mediates the cross-linking of fibrinolysis inhibitors to fibrinogen, e.g., the α2-plasmin inhibitor (α2-PI, also called α2-antiplasmin) (Mosesson et al. 2008; Fraser et al. 2011). Fibrinogen circulating in a context of sufficient FXIII will be rich in α2-PI cross-linked to it. This type of fibrinogen will eventually give rise to fibrin strands rich in α2-PI. The presence of the fibrinolysis inhibitor in the fibrin strands hypothetically assures an increased stability of the hemostatic plug. Fibrinogen with low α2-PI supposedly gives rise to fibrin strands that are more prone to plasmin's fibrinolytic activity and may thus be associated with an increased risk of bleeding.

11.2.2.3 Indications

11.2.2.3.1 Acquired FXIII Deficiency

Acquired FXIII deficiency has been described in a variety of clinical settings due to consumption of the coagulation factor and due to inhibition by acquired inhibitors (Levy and Greenberg 2012). Consumption of FXIII can occur in massive bleeding, but its incidence is not very well defined in the literature. A study in 1,004 adult patients in a university hospital setting showed a prevalence of 21 % of patients with values below the reference range. A 62 % incidence of acquired FXIII deficiency was found in a population of patients with acute leukemia. In view of this high frequency, some published algorithms for bleeding management incorporate FXIII. Conditions associated with large wound areas, such as chronic inflammatory bowel disease (IBD: ulcerative colitis and Crohn's disease), massive burns, extensive orthopedic surgery of the spine, etc., are known to be associated with low FXIII levels. However, whether low levels of FXIII are associated with a clinical bleeding diathesis in the context of IBD, for example, is contested (Van Bodegraven et al. 1995; Chamouard et al. 1998). Acquired deficiency due to autoantibody formation is an extremely rare event, with less than 100 reported cases to date (Boehlen et al. 2013).

11.2.2.3.2 Congenital FXIII Deficiency

The prevalence of congenital FXIII deficiency is estimated at 1 per million. Areas with high rates of consanguinity have higher incidences. Treatment of the rare patients who require FXIII substitution in this context should be carried out in specialized centers. Heterozygote carriers of FXIII deficiency, with FXIII levels below the reference range (in the range of 50 %), will generally not present with a bleeding tendency under normal circumstances. Under special conditions, including postpartum bleeding, major trauma, and severe perioperative bleeding, FXIII levels may fall to levels that are conducive to a clinically relevant coagulopathy (Hsieh and Nugent 2008) (and personal observation).

11.2.2.4 Monitoring

FXIII monitoring can be done using functional and antigenic tests. The usual test is clot solubility in monochloroacetic acid solution, but this functional test is neither standardized nor quantitative. Quantitative FXIII activity tests use activated FXIII to assay its transglutaminase activity. This can be done in two main ways: (1) measurement of ammonia released as an early byproduct of the transglutaminase reaction (ammonia release assays) and (2) measurement of amine substrates that are covalently linked to another substrate (amine-incorporation assays). More commercial kits use the first method than the second. As there are non-FXIII-dependent ammonia-releasing reactions that can account for up to 15 % of the measured activity, FXIII measurements <20 % should be interpreted with caution and confirmed in an experienced laboratory. It should be noted that high ammonia concentrations in severe hepatic dysfunction can interfere with ammonia release assays. Antigenic tests can be directed against subunit A, subunit B, or the combination of both (Hsieh and Nugent 2008; Karimi et al. 2009). In the context of perioperative FXIII monitoring, any automated, rapid, reproducible, and precise test is suitable. Knowing the lower detection limit and test range used in one's institution is important. Peyvandi's review shows that FXIII correlates badly with clinical bleeding (Peyvandi et al. 2012b).

Some literature suggests that, due to absent or inadequate testing strategies, acquired FXIII deficiency goes largely undetected (Lawrie et al. 2010). Classic global coagulation tests, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), are "blind" to FXIII (see Fig. 11.2). Specialized tests, such as thrombin time and fibrinogen according to Clauss, do not incorporate FXIII activity. The common stop signal for all the coagulation time-based tests is the appearance of soluble fibrin monomers in the test vial. Fibrin monomers can be detected optically or mechanically. Whatever the method, coagulation time measurements stop prior to the onset of FXIII's action.

11.2.2.5 Efficacy and Safety

Two RCTs evaluating human FXIII concentrate have been published to date. Rasche et al. compared FXIII substitution versus placebo in 60 patients with acute leukemia (Rasche et al. 1982). Although FXIII treatment resulted in increased FXIII levels,

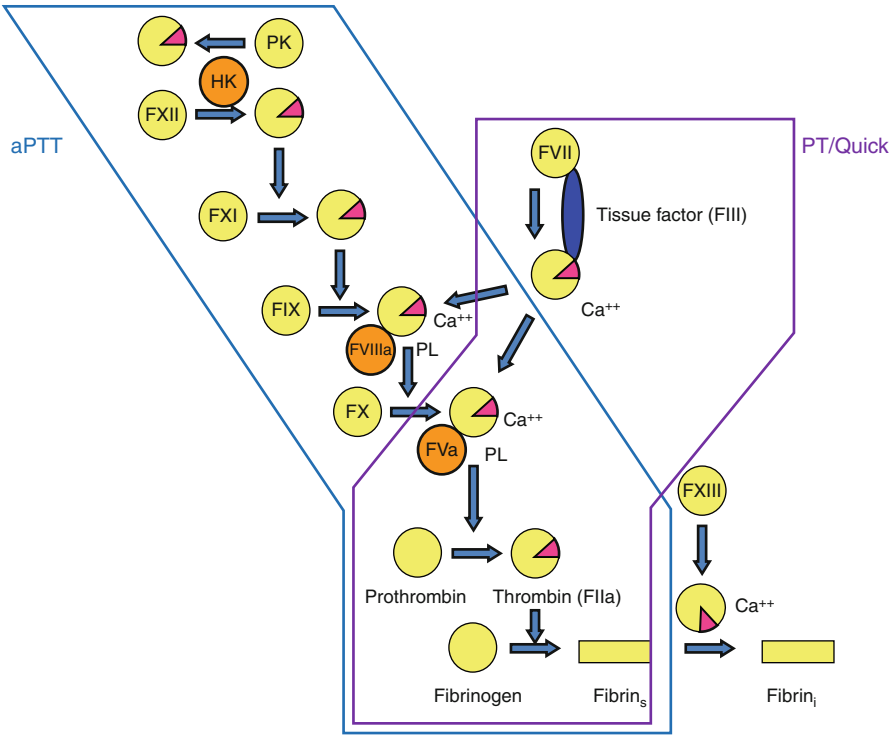

Fig. 11.2 The cascade model of coagulation and coagulation tests. Coagulation factors are depicted as circles. *Yellow circles* indicate enzymatically active coagulation factors (exception: fibrinogen, which is not enzymatically active, but a substrate). *Yellow circles* with a *pink insert* represent activated coagulation factors. *Orange circles* indicate cofactors. Tissue factor is depicted in *blue*, as it normally does not circulate in plasma. The factors involved in the activated partial thromboplastin time (*aPTT*) and prothrombin time according to Quick (*PT*) are circled by *light blue* and *purple polygons*, respectively. It is important that both FXIII and von Willebrand factor (not depicted) are not assayed in the so-called standard coagulation tests. Prothrombin complex concentrates contain FIX, FX, and FII and FVII to a variable degree. Substitution with PCC thus influences both PT and aPTT. Abbreviations: *Ca^{2+}* calcium, *$Fibrin_s$* soluble fibrin, *$Fibrin_i$* insoluble fibrin, *HK* high molecular weight kininogen, *PL* phospholipids, *PK* prekallikrein

there were no statistically significant differences in the number of bleeding complications or transfusions.

Korte et al. investigated maximal clot firmness using ROTEM measurement as the primary outcome in 22 cancer patients undergoing abdominal surgery. Patients were randomized to receive 30 IU/kg of human FXIII or placebo within the first 15 min of surgery. The trial was halted prematurely (prespecified primary outcome difference at interim analysis) because of an 8 % decrease in MCF in the treatment group compared with a 38 % decrease in the placebo group – a statistically significant difference (Korte et al. 2009).

11.2.2.6 Dosing

No prospectively evaluated treatment thresholds or target values have been established for the frequently acquired FXIII deficiencies.

In cases of congenital deficiency and in patients at a high risk of bleeding, 10 IU/kg of FXIII are given at 4–6 week intervals (Bolton-Maggs et al. 2004) for prophylaxis. This translates into 500–1,000 IU per application. In settings of acute bleeding, 10–20 IU/kg are recommended. This corresponds to single doses of 750–1,500 IU/kg for a patient of approximately 75 kg.

11.2.2.7 Key Points and Prospects

Similarly to fibrinogen, there are only preliminary data on the efficacy and safety of FXIII in the perioperative setting.

11.2.3 Von Willebrand Factor/Factor VIII Concentrates

11.2.3.1 Background

Von Willebrand factor (vWF) is named after the Finnish internist Erik A von Willebrand, who first described a family with the disease in 1926 (von Willebrand 1926; Federici et al. 2006). The family came from the Åland Islands in the Baltic Sea. In contrast to the hemophilias, both sexes were affected. The disease was characterized by a prolonged bleeding time, despite a normal platelet count, normal PT, (described by Quick in 1935), and normal-to-increased aPTT (described by Langdell in 1953). The disease's description was published under the designation "hereditary pseudohemophilia." In the 1950s, it became possible to measure FVIII and the first cases of "pseudohemophilia" were described in patients of both sexes who had reduced FVIII levels. In 1963, reduced platelet adhesiveness in affected patients became detectable (Salzman 1963). In 1971, using a specific antibody against FVIII, Zimmermann was able to show that there was another protein responsible for the phenotype (Zimmerman et al. 1971), initially called FVIII-related protein. In 1971, Howard and Firkin showed that an antituberculosis agent, ristocetin, could trigger platelet agglutination in normal subjects, but not in patients with von Willebrand's disease (Howard et al. 1973). Von Willebrand factor was finally isolated in 1972 (Bouma et al. 1972), and as there are several distinct underlying pathophysiological mechanisms, von Willebrand syndrome (vWS) is the recommended designation.

11.2.3.2 Description

VWF is a multimeric glycoprotein with monomers approximately 2,050 amino acids long. These monomers are assembled into dimers, which are subsequently polymerized into multimers of 2–20 units with a molecular weight of up to 20×10^6 D. VWF is encoded on the short arm of chromosome 12. It is primarily expressed and stored in endothelial cells (Weibel–Palade bodies) and megakaryocytes (α granules). Endothelial cells express DDAVP receptors that can induce vWF secretion. DDAVP stimulation can lead to three- to five-fold increase in plasma levels of vWF. Platelet activation and degranulation will also lead to a release of stored vWF (Laffan et al. 2004).

The vWF monomer has 4 N terminal D domains (D1, D2, D', D3), then 3 A domains (A1, A2, A3) followed by another D domain (D4), a B domain, and three terminal C domains (C1, C2, CK). VWF has three main functions, the first of which is binding and stabilizing FVIII. FVIII binds to the vWF N terminal D′-D3 domains. Its second function is interaction with platelets through glycoprotein GP Ibα expressed on the platelet surface. Platelet GP Ibα interacts with the vWF A1 domain. Third, vWF can bind to collagen in the subendothelium. Collagen-binding sites on vWF are in the A3 or A1 domains (Schneppenheim and Budde 2011). The vWF-cleaving protease, ADAMTS13, cleaves vWF in the A2 domain (Crawley et al. 2011).

VWF is a key molecule in hemostasis as it interacts with all three of its subsystems. It interacts with vascular wall collagen in cases of trauma or other causes of denudation of the vascular lining; it provides the landing strips for platelets by binding to their GP 1bα, thereby immobilizing them in the subendothelial matrix; and it stabilizes plasmatic FVIII. Similarly to fibrinogen, vWF plays a role in both primary and secondary hemostasis.

Endothelial cells release vWF as long chains of covalently linked dimers. These multimers are degraded by ADAMTS13 as they circulate. As the molecules decrease in size, they become less "sticky" (Schneppenheim and Budde 2011).

11.2.3.3 Indications

11.2.3.3.1 Acquired Deficiency

Unlike other coagulopathies, such as fibrinogen or FXIII deficiencies, where acquired deficiencies are more frequent than inherited forms, acquired vWS is less frequent than its congenital variant. By 2000, fewer than 200 cases had been reported (Sucker et al. 2009). Based on those figures and the author's personal experience, underreporting is very likely. Acquired vWS has been described in association with underlying disorders including myeloproliferative disorders (where affected cells may bind and consume vWF), lymphoproliferative disorders (autoantibodies against vWF), other neoplasms, autoimmune disorders, cardiovascular disorders (vWF consumption due to aortic stenosis, i.e., Heyde syndrome), and drug effects (hydroxyl-ethyl starch is reported to reduce vWF antigen (vWF:AG), but interference with vWF function is also possible) (Mohri 2006; Federici et al. 2013). A high frequency of a new form of acquired vWS has been associated with patients using ventricular assist devices. The supposed mechanism is the mechanical destruction (versus the action of ADAMTS13) of the molecule (Dassanayaka et al. 2013). Interestingly, in the context of acute bleeding, consumption of vWF without any of the underlying disorders cited above is a rarely reported problem. This clearly distinguishes vWF from fibrinogen, which is the first molecule to reach critical levels in acute bleeding. This is possibly due to vWF's multiple production sites (megakaryocytes in bone marrow, endothelial cells) and storage pools (platelets, endothelial cells).

11.2.3.3.2 Congenital Deficiency

VWS is the most frequent congenital bleeding disorder, with a population frequency of approximately 1 % (Schneppenheim and Budde 2011). It can be categorized into three subtypes (Federici 2009a; Favaloro 2011):

- Partial quantitative deficiency or type I vWS
- Qualitative vWF deficiency or type II vWS (several type II forms are distinguished)
- Virtually complete quantitative deficiency or type III vWS

Regarding the perioperative assessment of bleeding risk and prophylactic measures, a distinction needs to be made between "real" vWS patients and those with low vWF levels related to other factors, including the association of low vWF with blood group O. However, in the context of acute bleeding, all these patients may potentially benefit from vWF substitution.

11.2.3.4 Monitoring

Perioperatively, vWF testing should be based on pretest probability. If a validated bleeding questionnaire is positive, then preoperative hemostasis testing is indicated (Tosetto et al. 2006). VWF:AG, vWF ristocetin cofactor (vWF:RCo), and their ratio are sufficient to detect most of the clinically relevant manifestations of vWS.

Historically, vWF:AG was the first to be measured. This can be done manually using ELISA technology, but also using modern tests. The discovery that ristocetin could agglutinate platelets was used to design the first functional vWF:RCo test. Large vWF molecules tend to have vWF:RCo to vWF:Ag ratios of close to 1. When vWF consumption increases, due to a stenotic heart valve, for example, there is an increased proportion of smaller, less "sticky" vWF molecules, and the vWF:RCo to vWF:Ag ratio will drop. Ratios of less than 0.70 are considered indicative of acquired vWS or forms of congenital type II vWS, characterized by qualitative vWF defects.

Exact subtyping of vWS can be done by specialized laboratories capable of measuring vWF collagen-binding capacity (vWF:CB), vWF FVIII-binding capacity (vWF:FVIII), and performing vWF multimer (vWF:MM) analysis (Laffan et al. 2004; Sucker et al. 2009).

11.2.3.5 Efficacy and Safety

In the perioperative setting, there are no RCT-based treatment algorithms available for either congenital or acquired vWF deficiencies. With regard to safety, it must be noted that vWF concentrates contain both vWF and FVIII. When substituting vWF, it must be remembered that over substitution of vWF may be associated with an increased risk of venous and arterial thromboembolism (VTE and ATE). Furthermore, in a vWF-deficient patient who is substituted using concentrates, the previously normal or even increased FVIII level (FVIII is an acute phase reactant) will be boosted by the concentrate. This may result in supranormal levels of FVIII, which are similarly associated with VTE and ATE (Federici 2009a, b). The relative content of vWF:RCo to FVIII varies depending on the product. For Haemate P®, the ratio is 2.5 to 1. The ratio is lower for other concentrates, with a minimum ratio of 1.1 to 1 (Federici 2005).

In the 1980s, cryoprecipitate and DDAVP were the only available treatment options for vWS patients. Cryoprecipitate is poorly standardized, and not all patients are responsive to DDAVP; thus, initial attempts were made toward

standardizing factor concentrates. The mid-1980s catastrophe of plasmatic products contaminated with hepatitis B, hepatitis C, and human immunodeficiency virus shocked both patients and treating physicians alike (Alter et al. 1972; Evatt et al. 1985; Kuo et al. 1989). The catastrophe led to the introduction of viral inactivation methods (Alter and Klein 2008), followed by donor screening in the 1990s (Vamvakas and Blajchman 2009). These steps dramatically reduced the risks associated with plasmatic products down to current levels of less than 2 cases per 100,000 (Legler et al. 2000).

11.2.3.6 Dosing

Treatment of vWS aims to correct the deficient adhesion of platelets to the subendothelium and to redress FVIII deficiency if necessary. Dosing recommendations are mostly based on similarities to congenital vWF deficiency contexts and some limited experience with acquired vWS (AvWS) (Federici 2005; Franchini 2008; Tiede et al. 2011). As a rule of thumb, substitution of 1 IU of vWF (RCo) per kg bodyweight will raise vWF activity by approximately 2 %. VWS acquired due to severe aortic stenosis (Heyde syndrome) or other valvular defects is probably one of the most frequent forms of AvWS. Either no substitution or a single preoperative dose of Haemate P® 500–1,000 IU IV can be considered (not evidence based, in line with (Mohri 2006; Federici et al. 2013) and personal experience). Once a defective heart valve has been replaced, vWF levels return to normal and within hours the bleeding diathesis will disappear. As in other indications, the severity of the AvWS, the clinical context (active bleeding or not, previous bleeding complications), and potential treatment complications, particularly thromboembolism, must be taken into consideration. Treatment thresholds and targets are discussed later in Sect. 11.3. There are differing vWF concentrates on the market. They can be categorized according to purification method, viral inactivation, vWF:RCO to vWF:AG ratio, vWF:RCO to FVIII ratio, and vWF MM content (Franchini 2008). The one for which most experience exists is Haemate P®. The pharmacokinetics of concentrates may also show interindividual variability (Kessler et al. 2011).

11.2.3.7 Key Points and Prospects

There is a lack of RCT data for vWF concentrates in the perioperative setting.

11.2.4 Prothrombin Complex Concentrates

11.2.4.1 Background

Prothrombin complex concentrates (PCC) were historically also referred to as PPSB. This latter abbreviation summarized the four coagulation factors: prothrombin (FII), proconvertin (FVII), Stuart–Prower factor (FX), and antihemophilic factor B (FIX). The first description of PCC dates back to more than 50 years ago when Didisheim described the preparation of this human plasma fraction and its potential application in humans (Didisheim et al. 1959). Surgenor described the original isolation procedure – barium sulfate elution – in 1959, and methodology improved over the

following years. In 1965, Tullis reported on the clinical use of prothrombin complexes in the New England Journal of Medicine (Tullis et al. 1965). First reports on the adverse thromboembolic effects of PCC led to the addition of heparin (Kasper 1975; Menache 1975). When cases of PCC-associated transmission of hepatitis B and further thromboembolism-associated deaths were described, an international task force was convened. This led to products being retracted from the market, stronger regulation regarding isolation procedures, product surveillance regarding the contamination by activated coagulation factors, the addition of inhibitors (antithrombin, protein C, and protein S) to the products, viral inactivation procedures, and a formal recommendation by the European Medicines Agency (EMEA) regarding minimal and desired potencies for the various factors (Hellstern 1999; Hellstern et al. 1999).

11.2.4.2 Description

PCC are subdivided into two major categories based on their composition: three-factor concentrates (containing FII, FIX, and FX – some contain traces of FVII) and four-factor concentrates (containing all four factors, FII, FVII, FIX, and FX). PCC were originally intended for the treatment of hemophilia B or hereditary deficiency of FIX. In view of this, PCC were "labeled" according to their FIX content. Most current PCC contain 500 or 600 IU of FIX per vial and thus have this figure in their brand name. Procedures aimed at increasing product safety are frequently carried out (and an appropriate suffix added to the product name), such as nanofiltration (N or NF or F), pasteurization (P), solvent detergent treatment (SD or D), and vapor and/or heat (VH or T). It is important to know that PCC from different producers differ significantly in their relative and absolute content of the various coagulation factors (Samama 2008; Sorensen et al. 2011a). Based on the variable yield achieved during production, different lots from the same producer also vary in composition, which is the reason why their factor content is generally indicated as a range and not a single figure.

A further categorization of PCC is possible based on whether or not activated coagulation factors are included in the formulation. Current PCC, registered for most of the indications noted below, are nonactivated PCC. Activated PCC (aPCC) represent a formulation that was designed and intended for use with hemophilia patients who had acquired antibodies directed against the coagulation factor that they had a deficiency for – so-called inhibitor patients. Factor eight inhibitor bypassing agent (FEIBA) is the only registered plasma-based aPCC. It contains FII, FIX, and FX, primarily but not solely in their nonactivated forms, and FVII largely in its activated form (FVIIa) (Cromwell and Aledort 2012).

11.2.4.3 Indications

11.2.4.3.1 Acquired Disorders

Most coagulation factors are synthesized in the liver, including FII, FVII, FIX, and FX. After synthesis in the hepatocyte, they are modified prior to secretion into the blood stream. One of the modification steps is mediated by γ carboxylase, the vitamin K-dependent enzyme that is the site of action of vitamin K antagonists.

Acquired deficiencies of FII, FVII, FIX, and FX can occur for several reasons, including (1) coagulation inhibition due to vitamin K antagonists (VKA), (2) coagulation factor consumption in the context of coagulopathy or uncontrolled bleeding, (3) inhibition of coagulation by direct anticoagulants, and (4) other rare causes.

The most frequent cause of an acquired prothrombin complex deficiency is the use of VKA. Approximately 1 % of the population is estimated to be anticoagulated at any given time. In randomized trials for atrial fibrillation, the bleeding risk of patients treated by VKA ranged from 1.3 to 4.2 % per year (Wiedermann and Stockner 2008).

Coagulation factor consumption in uncontrolled bleeding will lead to a critical prothrombin complex factor deficiency after loss of approximately 200–240 % of the calculated blood volume (Hiippala et al. 1995). Coagulation factor consumption can also occur in the absence of active blood loss, e.g., in disseminated intravascular coagulopathy.

While the reversal of VKA effects on coagulation is a well-established indication for PCC, the data on PCC use to reverse the effects of novel oral anticoagulants (NOAC), including direct FIIa inhibitors (dabigatran) and direct FXa inhibitors (including apixaban, edoxaban, rivaroxaban, and others), is only now emerging (Eerenberg et al. 2011). The FEIBA aPCC has recently been included in European guidelines for the treatment of NOAC-related bleeding (Kozek-Langenecker et al. 2013). However, to date, no RCTs have been published on PCC or aPCC use in actively bleeding patients (Siegal and Cuker 2013).

Rare causes of acquired deficiencies involving one or more factors of the prothrombin complex include severe nutritional vitamin K deficiency, an acquired inhibitor (antibody) directed against FIX in hemophilia B patients, a propeptide mutation of the FIX gene leading to pseudohemophilia B in patients treated with VKA (Ulrich et al. 2008), absorption of FX to amyloid protein in systemic AL amyloidosis, and inhibitors directed against thrombin (FIIa) in patients with the same disease (Thompson et al. 2010).

11.2.4.3.2 Congenital Disorders

The deficiency of FIX, or hemophilia B, as one of the "more" frequent congenital bleeding disorders has a frequency of 1:60,000. Since the licensing of FIX concentrates, these products have largely replaced PCC as first-line treatment of hemophilia B. In principal, however, they remain a treatment option for hemophilia B replacement therapy. In several countries, individual concentrates for "rare" coagulation disorders (less frequent than hemophilia A or B) including severe FVII deficiency (frequency $1{:}0.3–0.5 \times 10^6$), FX deficiency (frequency 1×10^6), and FII deficiency (frequency $1{:}2 \times 10^6$) are not readily available or do not exist. For these conditions, three- and four-factor PCC remain relevant treatment options for managing bleeding (Bolton-Maggs et al. 2004).

The FEIBA aPCC is indicated in hemophilia patients, particularly those who have developed inhibitors (Aledort 2008).

11.2.4.4 Monitoring

Factors II, VII, and X are key factors in determining PT; thus PT will detect deficiencies of these factors and is suitable for PCC monitoring (see Fig. 11.3). The activity and antigen levels of these three factors can also be used for this purpose. Characteristics including plasma half-lives are given in Table 11.1. FIX is a vitamin K-dependent (VKD) factor, as are the three mentioned above. However, it is not a key determinant of PT. For FIX, aPTT and FIX determinations are the sensitive tests necessary to monitor substitution.

Point-of-care (POC) technologies including rotational thromboelastometry (ROTEM) and thromboelastography (TEG), as well as other systems, can assay

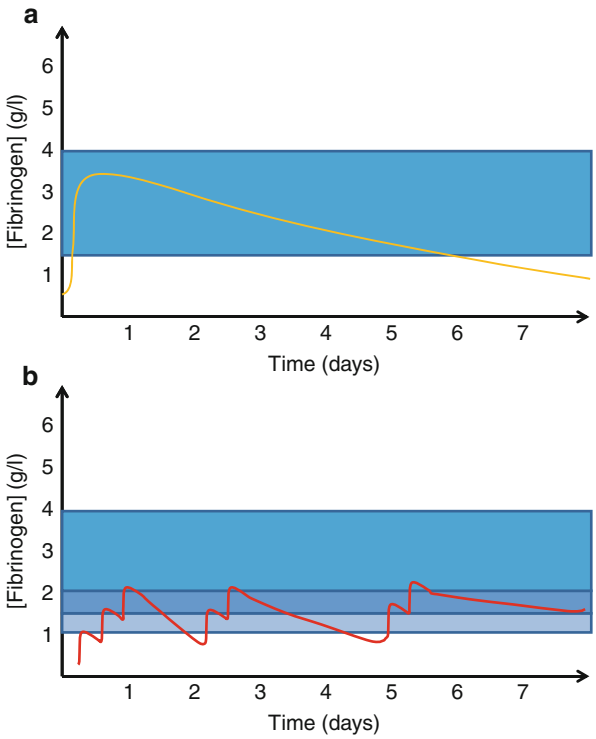

Fig. 11.3 The threshold and target question. (**a**) Depicts the time course of plasma fibrinogen concentration in a fictive patient, e.g., with hereditary afibrinogenemia (*yellow curve*). After (one big) substitution, the concentration increases into the normal range (depicted by *dark blue* area) and drops off with a half-life of approximately 72–100 h over the following days. (**b**) Illustrates the time course of a fictive perioperatively bleeding patient (*red curve*). The transfusion threshold in this example is set at 1.0 g/l (*lower border of dark blue box*) and the transfusion target at 2.0 g/l (*upper limit of light blue box*). Initially multiple (small) substitutions are needed to reach the transfusion target value. After two more instances of substitution, the fibrinogen levels stabilize as the fictive patient ceases to bleed. Note that in the acutely bleeding patient, the observed half-life of fibrinogen is initially much shorter than 72 h and only later approaches the value described under physiological conditions

Table 11.1 Factors relevant for coagulation

Name	Abbreviation	Function	MW (kDa)	µg/ml	µmol/l	IU/ml	t1/2 (h)
Fibrinogen	FI	Substrate of coagulation: forms fibrin	340	3,000	8.8235	n.a.	72–100
Prothrombin	FII	Serine protease (VKD): multiple targets	72	100	1.3889	0.60–1.40	60
Labile factor	FV	Cofactor to FX	330	10	0.0303	0.60–1.40	15
Stable factor	FVII	Serine protease (VKD): activates FX (and FIX)	50	0.5	0.0100	0.60–1.40	5
Antihemophilic factor	FVIII	Cofactor to FIX	185	0.1	0.0005	0.50–2.00	12
Christmas factor	FIX	Serine protease (VKD): activates FX	56	5	0.0893	0.60–1.40	18
Stuart–Prower factor	FX	Serine protease (VKD): activates FII	56	10	0.1786	0.60–1.40	30
Plasma thromboplastin antecedent	FXI	Serine protease: activates FIX	160	5	0.0313	0.60–1.40	45
Hageman factor	FXII	Serine protease: activates FXI	80	30	0.3750	0.60–1.40	
Fibrin-stabilizing factor	FXIII	Cross links soluble fibrin monomers ($fibrin_s$) to insoluble fibrin strand ($fibrin_i$)	320	60	0.1875	0.50–1.50	216
von Willebrand factor	vWF	Mediates platelet adhesion to collagen, stabilizes and transports FVIII	225xn	10	n.a.	0.50–2.00	10
Tissue factor	FIII	Main initiator of coagulation in vivo: cofactor to FVII/FVIIa	45	n.a.	n.a.	n.a.	n.a.

Coagulation factors I–XIII and von Willebrand factor are listed together with their abbreviation, function, molecular weight (MW), mean concentration in µg/ml and in µmol/l, reference range in IU/ml, and plasma half-life (under physiological conditions). Plasma half-life may be considerably shorter in the presence of bleeding. Tissue factor, the main initiator of coagulation in vivo, is principally a membrane-bound protein expressed on subendothelial cells. Under pathophysiological conditions it may (1) circulate bound to microparticles or monocytes, (2) circulate in truncated form as a free protein, or (3) be ectopically expressed on endothelial and other cells. Vitamin K-dependent (VKD)

FII-, FVII-, FIX-, and FX-dependent pathways. Tests targeting the "extrinsic" system (using tissue factor as the starting reagent) are available for thromboelastometric/graphic test systems. PCC influence the clotting times of such tests, including EXTEM and RapidTEG. However, as anticoagulated patients may present normal

clotting or R times in these whole blood tests, sensitivity is an issue. POC testing systems have the advantage of shorter turnaround times than routine coagulation tests. However, the fact that they generally use whole blood can have a negative impact on their sensitivity toward VKA, other anticoagulants, and possibly PCC.

11.2.4.5 Efficacy and Safety

Only a few RCTs have been published regarding the use of PCC in different settings. A French study with 59 patients evaluated two dosing regimens for urgent VKA reversal (Kerebel et al. 2013). An interesting study monitoring coagulopathic cardiac surgery patients showed reduced allogenic blood transfusion in 100 patients randomized to POC-based monitoring or standard care. The predefined treatment algorithm included PCC (Weber et al. 2012). Most of the data stems from cohort studies (Makris et al. 1997; Lubetsky et al. 2004; Riess et al. 2007; Pabinger et al. 2008).

PCC trials in an anticoagulant reversal setting have reported rates of thromboembolism, possibly related to PCC, in the percent range: approximately 1 % for VTE and up to 3 % for ATE (Majeed et al. 2012). A meta-analysis of 27 trials by Dentali reported a mean thromboembolism rate for PCC (three- and four-factor PCC combined) of 1.4 % (95 % CI 0.8–2.1 %) (Dentali et al. 2011). Sorensen reported thromboembolism in 1.5 % of PCC study patients (Leissinger et al. 2008; Sorensen et al. 2011a). The review also discusses the pathophysiology potentially related to the accumulation of coagulation factors with long half-lives, FII in particular. However, these thromboembolic complications may also be related to the underlying causes that mandate anticoagulation in the first place (Sorensen et al. 2011a). Nevertheless, thromboembolism in these settings appears to be more frequent than is observed in settings of fibrinogen or FXIII substitution.

11.2.4.6 Dosing

Clinical trials have not been able to resolve questions about the optimal dose of PCC. Doses reported in the studies cited above range from 7 to more than 80 IU/kg bodyweight. As RCT data is lacking, guidelines and other official dosing information are helpful (Makris et al. 1997; Mannucci and Douketis 2006; Weber et al. 2013). Algorithms dependent on the international normalized ratio (INR) exist. In perioperative bleeding, 20–30 IU/kg bodyweight has been suggested by a group of Austrian experts (OEGARI). The numerous confounding factors include differing target values for the INR; the fact that dosing algorithms are often based on pharmacological models which may or may not be applicable to a given patient; the question of whether the product is applied to an actively bleeding or non-bleeding patient; and the clinical context in which PCC are prescribed. Whenever possible, dosing should be standardized within institutions or clinics and should follow an evidence-based algorithm appropriate to the patient's clinical context (van Aart et al. 2006).

Factors reported to be associated with adverse outcome include repeated dosing (with potential accumulation of coagulation factors with a long half-lives, such as FII), coadministration with other coagulation products, and nonobservance of recommended infusion speeds (Pabinger et al. 2010).

11.2.4.7 Key Points and Prospects

There remains a paucity of RCT evidence on PCC. The evidence available points to a potential safety issue regarding thromboembolic events in the range of 1–3 %.

11.2.5 Recombinant Activated Factor VII

11.2.5.1 Background

Recombinant human activated factor seven (rFVIIa) was developed more than 20 years ago for hemophilia patients suffering from inhibitor formation. Antibodies directed against FVIII, or inhibitors, may complicate the treatment of hemophilia patients who are treated by FVIII products. The inhibitors may then neutralize the patient's own and the exogenous FVIII, leading to severe bleeding complications. Bypassing agents that circumvent the FIX/FVIII complex can stop bleeding in these patients. Pure plasma-derived FVIIa showed clinical efficacy in proof-of-principle experiments. Subsequently, recombinant FVIIa was developed and tested in clinical trials (Hedner 2007, 2012).

Distinguishing the clinical setting in which patients are treated with FVIIa appears relevant. On-label indications include only hypocoagulable patients. In off-label indications patients may be normo- or even hypercoagulable.

11.2.5.2 Description

FVIIa circulates in plasma and comprises approximately 1 % of the circulating plasma FVII pool. The precursor single-chain FVII molecule is synthesized in the liver and is one of the vitamin K-dependent coagulation factors. FVII is a 50 kD protein that has the shortest plasma half-life among coagulation proteins (see Table 11.1). The activation of FVII to two-chain FVIIa involves cleavage at a single peptide bond. This activation can be mediated by FXa, FVIIa itself, and other coagulation factors. By binding to surface-bound tissue factor, the enzymatic activity of FVIIa is dramatically increased. The cell surface-bound complex of calcium/tissue factor/FVIIa is capable of activating FX and FIX (Hedner and Brun 2007; Vadivel and Bajaj 2012).

Two mechanisms of action have been postulated for rFVIIa. The first is the tissue factor-mediated process described above on the surface of cells expressing tissue factor. The second is tissue factor independent and believed to occur by direct binding of FVIIa to the surface of activated platelets (Hoffman 2003; Logan and Goodnough 2010).

11.2.5.3 Indications

On-label indications include hemophilia A or B with inhibitors, congenital FVII deficiency, and acquired hemophilia. The treatment of these rare disorders goes beyond the scope of this chapter and will not be discussed in detail. Off-label indications for which clinical trial evidence exists, include body trauma, brain trauma, cardiovascular surgery, intracerebral hemorrhage, upper GI bleeding in the context of cirrhosis, liver transplantation, and hematopoietic stem cell transplantation (Logan and Goodnough 2010).

11.2.5.4 Monitoring

Monitoring of FVIIa treatment requires specialized coagulation tests. Classic coagulation tests including prothrombin time, activated partial thromboplastin time, and FVIII or FIX activity are unsuitable for this purpose. Some specialized tests, including thrombin generation tests, thromboelastography/rotational thromboelastometry, and aPTT waveform analysis, have been used (Hoffman and Dargaud 2012).

11.2.5.5 Efficacy and Safety

In the trauma setting two main studies have been published. The multicenter blunt trauma study ($n = 70$) showed a significant decrease of red blood cell transfusion and a reduced frequency of acute respiratory distress syndrome. Mortality did not differ between FVIIa and placebo in either study (Beste et al. 2012).

In the cardiovascular surgery context, two RCTs could show a significant decrease in RBC transfusion (Diprose et al. 2005; Gill et al. 2009).

In coagulopathic patients with liver disease, most RCTs showed negative results; only one study could show a reduction in RBC transfusion requirements (Bosch et al. 2004; Lodge et al. 2005; Planinsic et al. 2005; Pugliese et al. 2007; Bosch et al. 2008).

Thromboembolic complication rates of up to 11 % have been reported in the off-label setting of normo- and hypercoagulable patients (Levi et al. 2010).

11.2.5.6 Dosing

Off-label use of FVIIa requires an individualized risk–benefit assessment, with a particular focus on thromboembolic complications.

Reported dosing schemes in the on-label context range from 15 to 30 μg/kg every 4–6 h to 90 μg/kg every 2 h IV. In the off-label context, doses ranging 5–200 μg/kg were studied (Warren et al. 2007; Logan and Goodnough 2010). In cases where an off-label use appears unavoidable, it is the author's opinion that the lowest possible dose should be used (van de Garde et al. 2006; Narayan et al. 2008).

11.2.5.7 Key Points and Prospects

For on-label indications the evidence suggests efficacy and safety.

For off-label indications, few RCTs have been able to show clinical benefit. Safety is a relevant issue with thromboembolic events up to 11 %.

11.3 The Threshold and Target Question

One of the big unanswered questions in perioperative coagulation management is that of the treatment threshold. Which level is appropriate for a given parameter? For example, at which fibrinogen concentration is it indicated to substitute the patient? Some recent transfusion guidelines either do not define a threshold at all or give a wide range of thresholds (Dzik et al. 2011; Sniecinski et al. 2012).

One widely held misconception is that a test's reference range holds the answer to the threshold question. This is false: a reference range is defined in a population of healthy individuals. Ideally, the number of individuals tested is large (>20) and

the population covers both sexes and all relevant age groups. The reference range reflects the distribution of normal values for a given parameter and typically includes the central 95 or 99 % of individuals. There is no evidence to suggest that values below the lower limit of this range are associated with bleeding or that they might represent a useful threshold for transfusion in the perioperative setting.

If the reference range is not the appropriate tool to define the parameter's threshold, another procedure must be agreed upon. To address this issue, there is a need for large RCTs that show reduced mortality in transfused or substituted patients and that define thresholds. Currently, such studies are not available. In their absence, threshold levels are best defined locally. What are the important factors to consider when defining a threshold?

The threshold question is test dependent on at least three levels. Classic coagulation tests measure coagulation factor antigen or activity levels. Antigen assessments are defined by weight per volume, while activity assays test a biological function in relation to the amount of coagulation factor contained in 1 ml of plasma. It is unclear which value is the more reliable for use in a transfusion algorithm. Moreover, for a given test type, e.g., functional fibrinogen, test results can vary depending on which test kit is used. Furthermore, fibrinogen measured using the same test can vary between individual laboratory platforms.

The clinical context is another relevant factor to be considered when setting a coagulation factor threshold; threshold levels for different indications may vary. For hereditary disorders, such as afibrinogenemia or FXIII deficiency, guidelines and experts propose 0.5 g/l and 5–10 % as levels generally sufficient for hemostasis (Ciavarella et al. 1987; Anwar et al. 2002; Mannucci 2010). Recent data show that these numbers are not appropriate in states of acquired deficiency. Instead, in the setting of hypofibrinogenemia induced by acute bleeding, fibrinogen levels from 0.8 to 2.0 g/l have been proposed (Spahn et al. 2007; Rossaint et al. 2010).

Another relevant clinical factor is the hemostatic state. An actively bleeding patient with acquired fibrinogen deficiency below a given cutoff may require treatment. In the absence of bleeding, the treatment is likely to be different. Transfusion thresholds for bleeding (therapeutic intention) and non-bleeding patient populations (prophylactic intention) need to be established. If the volume of blood loss is used as the transfusion trigger, then target concentrations should be defined. In fact, Rahe-Meyer et al. published a randomized trial in major aortic surgery where the threshold for fibrinogen transfusion was defined by the volume of blood loss; the target concentration was defined for a FIBTEM MCF of 22 mm, corresponding approximately to a fibrinogen level (Clauss) of 3.6 g/l (Rahe-Meyer et al. 2013b).

The timing of testing is another complicating factor. Classic coagulation tests are performed in citrate plasma. The centrifugation of whole blood and the production of cell-free citrate plasma necessitate time. Between drawing the blood, centrifugation, and producing the test result, a turnaround time of 30–40 min is common. However, within this time span, an acutely bleeding patient's coagulation status can change dramatically, undergoing multiple transfusions and substitutions. To minimize turnaround time in acutely bleeding patients, whole blood tests have been designed utilizing POC testing devices. Fibrinogen tests exist for such POC test

devices (FIBTEM for ROTEM and functional fibrinogen for TEG). These fibrinogen tests are performed on whole blood and measure other aspects of fibrinogen than the classic coagulation tests. Because of their design as whole blood tests, POC-based tests have a higher degree of outcome variability (Okuda et al. 2003; Theusinger et al. 2010).

Large outcome-based studies are necessary to properly answer the transfusion threshold question. These studies are scarce or nonexistent for isolated coagulation factor products. In the absence of appropriate evidence, institutions should standardize their approach and define test procedures in order to optimize treatment efficacy and patient safety. Locally defined thresholds should be reevaluated regularly and changed in response to new evidence.

11.4 Conclusions and Prospects

Isolated coagulation factor concentrates including fibrinogen, FXIII, vWF, and PCC represent some of the therapeutic options for patient management in perioperative settings. Evidence based on RCT is only beginning to emerge. Safety signals include thromboembolic rates in the range of 1–3 % for PCC. These risks appear to be less important for other isolated coagulation factor concentrates. Besides safety, healthcare cost needs to be integrated into the final risk–benefit evaluation of the use of coagulation products. RCTs designed for perioperative settings and investigating predefined treatment algorithms will help define the evidence-based strategies of the future.

Key Points

With current knowledge and in the absence of RCT-based strategies, an individualized risk–benefit evaluation should be performed for every patient prior to the use of isolated coagulation factor concentrates.

Transfusion thresholds and targets depend on the clinical context (congenital versus acquired hemostatic disorders, active bleeding versus no bleeding).

Transfusion thresholds and targets need to be validated locally.

Transfusion thresholds and targets need to be established in an evidence-based context.

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