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A 2014 Update on Coagulation Management for Cardiopulmonary Bypass

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Abstract

Coagulopathy after cardiac surgery with cardiopulmonary bypass is a serious complication that may result in massive bleeding requiring transfusion of significant amounts of blood products, plasma, and platelets. In addition to increased patient morbidity and mortality it is associated with longer hospital stay and increased resource utilization. The current review discusses aspects in cardiopulmonary bypass–induced coagulopathy with emphasis on point-of-care testing and individualized "goal-directed" therapy in patients who develop excessive bleeding after cardiac surgery.

Keywords

cardiopulmonary bypass, coagulation, coagulopathy, antifibrinolytics, point-of-care monitoring

Introduction

Excessive bleeding due to coagulopathy is a serious complication of cardiac surgery with cardiopulmonary bypass (CPB). Despite significant advances in the field, 5% to 10% of the patients who have cardiac surgery suffer from massive blood loss (being defined as chest tube bleeding >2000 mL over the first postoperative 24 hours, or the need to transfuse 10 red blood cell [RBC] units or more over a 24-hour period)[1] and up to 5% of all cardiac surgery patients require reexploration to achieve hemostasis.[2-6] Therefore, timely control of coagulation is of prime importance in order to avoid excessive blood loss that will result in multiple red cell and coagulation product transfusions and surgical reexplorations. All of these have been associated with increased incidence of perioperative complications, including mortality as well as prolonged hospitalization and increased hospital resource utilization.[6-8] Nevertheless, despite the increased evidence regarding the various adverse effects of blood product transfusions,[9] the publication of transfusion guidelines,[10-12] and acceptance of lower transfusion triggers, allogeneic blood product usage remains as high as 50% in patients after cardiac surgery.[13]

This review will cover aspects in CPB-induced coagulopathy with regard to pathophysiology and identification of predictors for excessive bleeding after cardiac surgery. In addition, coagulation monitoring especially with point-of-care coagulation tests and transfusion algorithms are reviewed. An overview of the use of pharmacological agents, including factor concentrates and recombinant coagulation factors in the context of severe bleeding after cardiac surgery is provided.

Cardiopulmonary Bypass–Induced Coagulopathy: Interaction Between Coagulation, Fibrinolysis, and Inflammation

On initiation of cardiopulmonary bypass and exposure of the patient's blood to the bypass circuit, a complex interaction between the coagulation, fibrinolysis, and inflammatory systems begins.[14-16] This may result in coagulopathy and excessive bleeding, as well as systemic inflammatory response syndrome (SIRS)—like response due to activation of both cellular and humoral components of the inflammatory system.[14] The causes of CPB-induced coagulopathy are multifactorial and include increased fibrinolysis as well as a decrease in coagulation factors as a result of increased consumption or dilution by the CPB priming solution.[17-20] Other factors include platelet dysfunction in addition to a decrease in platelets numbers (30% to 50% decrease from baseline) due to hemodilution, sequestration, destruction, and consumption.[21-23] Moreover, the

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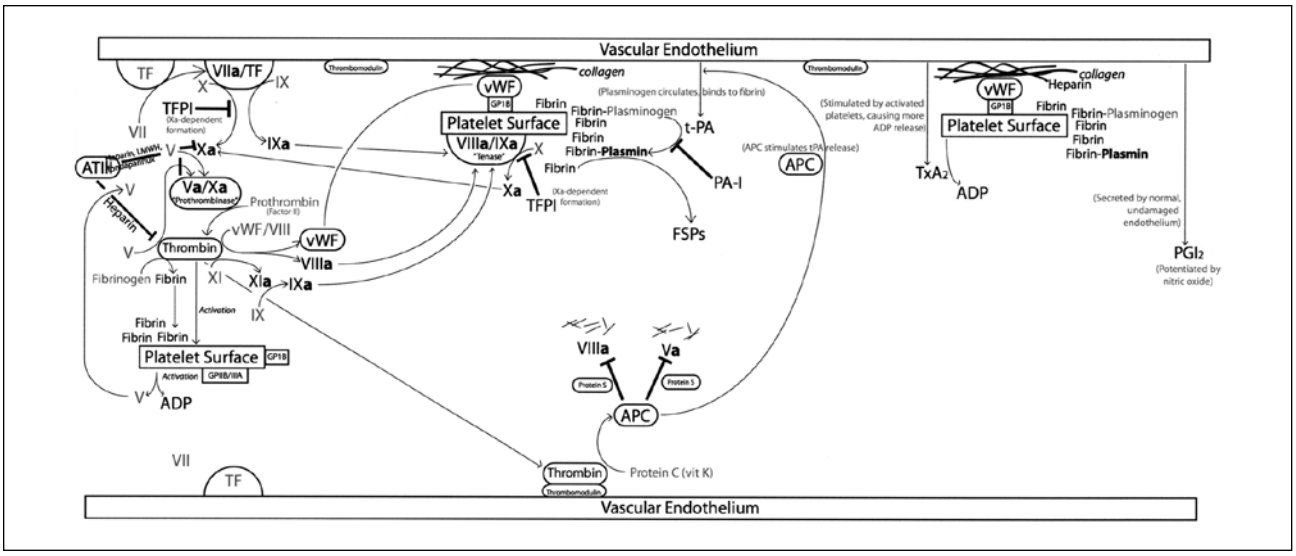

Figure 1. Graphic presentation of intravascular clot formation.
Abbreviations: TF, tissue factor; TFPI, tissue factor pathway inhibitor; AT III, antithrombin III; ADP, adenosine diphosphate; vWF, von Willebrand factor; APC, activated protein C; FSP, fibrin split products; t-PA, tissue plasminogen activator; PA-I, plasminogen activator inhibitor; TXA_2, thromboxane A_2; PGI_2, prostaglandin I_2; GPIIb/IIIa, glycoprotein IIb/IIIa.

hypothermia that is frequently induced with CPB also contributes to decreased activity of platelets and coagulation factors.[1,2,24] Furthermore, this coagulopathy is also influenced by factors such as patients' comorbidities (eg, renal or hepatic failure) or the perioperative use of anticoagulants and/or platelet inhibitors. In addition, bleeding may be further exacerbated by the complexity of the surgery (coronary artery bypass surgery vs complex aortic surgery), the duration of cardiopulmonary bypass and in emergent procedures or redo operations.[25,26].

The coagulation cascade is classically divided into two pathways that converge into a common pathway during the activation of factor X to factor Xa. The intrinsic pathway is activated by contact with a foreign surface and the extrinsic pathway is activated by tissue factor. The ultimate goal of coagulation is the generation of fibrinogen, which binds activated platelets together via the glycoprotein IIb/IIIa receptor.[20,27] Unfortunately, while the "classic" pathways are useful for understanding the in vitro coagulation tests used by clinicians, they are grossly oversimplified. In reality, the coagulation cascade does not proceed down a series of steps, but rather is made up of an elaborate, interrelated series of reactions with positive and negative feedback systems in place, the so-called "cell-based coagulation model." Clinically, coagulation begins with tissue injury leading to the exposure of tissue factor (TF) to factor VII in the blood stream as well as to the exposure of extracellular matrix proteins to the platelet surface (Figure 1). TF activates factor VII and this complex leads to the formation of factors IXa and Xa, which have a key role in the formation of prothrombinase (Va/Xa) and tenase (VIIIa/IXa), respectively. Tenase accelerates the production of factor Xa, while prothrombinase produces thrombin, which leads to the separation of factor VIII from the von Willebrand factor (vWF), the conversion of fibrinogen to fibrin (and activation of factor V), as well as, platelet activation.[2,17] Thrombin formation ultimately leads to the activation of factor IX (a critical component of tenase), which shifts the coagulation process away from membrane bound TF and toward the phospholipid surface of platelets.

Activation of the coagulation system also triggers fibrinolysis. Fibrin generation triggers synthesis of endogenous fibrinolytic enzymes such as urokinase and tissue plasminogen activator (t-PA). In addition factor XIIa activates plasmin. This enzyme splits fibrin and fibrinogen into D-dimers that are small fragments with no coagulation activity.[24,28] An increasing body of literature reports that the level of fibrinogen (and other coagulation factors) is significantly reduced after CPB[27,29,30]and that low levels of fibrinogen are associated with increased bleeding after cardiac surgery.[31,32] Karkouti et al[33] have recently published a retrospective analysis of 4606 cardiac surgery patients reporting that a fibrinogen level less than 200 mg/dL after CPB was associated with increased risk for bleeding and RBC transfusion further emphasizing the important role of fibrinogen in maintaining hemostasis after cardiac surgery.

Activation of coagulation is also closely linked to inflammatory responses. Hemostatic initiation, contact activation, tissue factor expression, and other pathways amplify inflammatory responses to collectively produce

end-organ damage as part of host defense mechanisms.[14] Plasmin and kallikrein enhance the inflammatory response by activating components of the contact activation system as well as other inflammatory pathways.[34] Thrombin generation is highly regulated, so coagulation will be achieved at the site of injury without causing systemic thrombosis. In addition, thrombin can also activate inflammation directly via protease activated receptors (PARs) or indirectly via activation of protein C (APC).[34] Moreover, thrombin formation also activates the thrombomodulin–protein C complex on the surface of the vascular endothelium, resulting in a negative feedback on thrombin generation due to inhibition of factors V and VIII by APC, thus further exacerbating the anticoagulant effects of CPB.[35-37] Several of the key coagulation factors (such as factor Xa) and their products have pro-inflammatory effects. Finally, factor Xa interacts with receptors on mast cells to cause degranulation through a variety of different mechanisms, including receptor activation, activation of monocytes and macrophages and release of interleukin-1 and tumor necrosis factor.[18,34,36,38]

Taken together, the initiation of CPB triggers a complex interaction between coagulation, fibrinolysis and inflammation. These responses may result in excessive bleeding as well as end-organ injury due to activation of the inflammatory response and result in increased morbidity and mortality. Thus, early interventions to reduce bleeding and restore normal coagulation after cardiac surgery may decrease complications and improve patient outcome.

Coagulation Testing and the Use of Transfusion Algorithms

Several laboratory tests are available to assist the clinician in the management of a known or suspected coagulopathy. Understanding how these tests are conducted and interpreted allows developing algorithms to guide the clinician when to transfuse the patient and what products to use. Most studies demonstrate a reduction in transfusion needs when an algorithm is used.[39,40] In most algorithms a transfusion is indicated when bleeding is associated with a prothrombin time (PT)/activated partial thromboplastin time (aPTT) ≥1.5 times normal, a platelet count is less than 100 000/μL or the fibrinogen concentration is less than 150 mg/dL.[41,42] Measurement of D-dimers or fibrin split products is also available to determine whether overfibrinolysis is also present.[43]

The failure of preoperative prothrombin time and partial thromboplastin time to predict perioperative bleeding has been well described.[44-47] This, combined with the considerable time delay associated with traditional coagulation tests (which may take up to an hour[2]), has led to focus on the use of "point-of-care" (POC) tests that can be performed on-site with a mean turnaround time of 20 minutes in most cases.[48,49] At least 7 prospective randomized trials[39,50-55] and 1 large, retrospective analysis[56] have examined the use of POC-based transfusion algorithms in cardiac surgery patients, with all but one[54] demonstrating decreased transfusion requirements and/or fewer surgical reexplorations. In addition, a reduction in hospital costs[55-57] and a significant decrease in the off-label use of recombinant factor VIIa (rFVIIa) as a rescue therapy[55,57,58] has also been reported.

The use of thromboelastography (TEG) and rotational thromboelastometry (ROTEM) has been the focus of extensive research in the management of bleeding cardiac surgery patients.[2,43,58-61] These are useful guiding tools for the clinician and algorithms based on their use have been shown to decrease transfusion requirements; however, the use of these coagulation monitoring devices require quality control follow-up and trained technicians for their operation. In addition, these devices are still not available in every medical center. An excellent review about these devices and their use during cardiac surgery has been recently published by Görlinger et al.[2]

Platelet dysfunction is an important cause of perioperative bleeding after cardiac surgery and may be the result of preoperative use of antiplatelet agents such as clopidogrel or the more novel thienopyridines, prasugrel and ticagrelol.[62] In addition, CPB has been reported to downregulate glycoprotein (GP) Ib and GPIIb/IIIa receptors and inhibit platelet aggregation.[22,23,63,64] Furthermore, extracorporeal circulation has been also reported as associated with irreversible platelet damage, mainly because of mechanical trauma and platelet defragmentation.[18,22,23] Conventional laboratory tests for platelet number are of limited value as they only provide information about platelet number and they do not provide any information regarding platelet function. Therefore, monitoring of platelet function during and after cardiac surgery is crucial in the management of the bleeding patient. Several devices are available for POC testing of platelet function and most of them are based on evaluation of platelet aggregation in response to an agonist such as collagen, thrombin, adenosine diphosphate (ADP) or arachidonic acid.[43,65] It is important to mention, however, that most of these devices have been developed primarily to measure the response to antiplatelet medications and to identify individuals who are "poor responders" to these agents.[66] Nevertheless, at least 3 recent publications (2 retrospective analyses and 1 prospective investigation) have reported that abnormal platelet function measured by POC tests after CPB, predicts excessive bleeding and the need for increased transfusion postoperatively.[67-69] Thus, the integration of a POC platelet test in the evaluation of hemostasis in patients after cardiac surgery with CPB, may be beneficial in identification and early treatment of patient who are at high risk for excessive bleeding after CPB.

Management of Bleeding and Transfusion Therapy After Cardiopulmonary Bypass

Excessive bleeding after cardiac surgery requires volume replacement as well as transfusion of red blood cells and coagulation factors to restore oxygen-carrying capacity and hemostasis and to avoid dilutional coagulopathy. Traditionally, coagulation therapy has been based on the administration of fresh frozen plasma (FFP), platelets, and cryoprecipitate. The routine use of FFP in cardiac surgery, however, has been questioned and has significantly decreased lately especially with the implementation of POC-based transfusion algorithms.[56,70] Prophylactic use of FFP has failed to correct coagulopathy and reduce bleeding after cardiac surgery and in critically ill patients.[26,71,72] Furthermore, very large FFP volumes (>15 mL/kg) are needed to restore effective hemostasis; however, the use of large volumes of FFP has been associated with transfusion-associated circulatory overload (TACO), which may not be tolerated in patients with limited cardiorespiratory reserve, transfusion-related acute lung injury (TRALI), infections, and sepsis.[73-76] In addition to conventional coagulation factors, massive bleeding may also require the use of factor concentrates (fibrinogen, prothrombin complex, factor XIII) as well as the off-label "rescue" use of rFVIIa to achieve hemostasis in refractory bleeding when hemostasis cannot be achieved using conventional therapy.[11,42,77-79]

It is important to remember that massive transfusion is frequently associated with hypothermia and acidosis, which can further exacerbate the coagulopathy, thus maintenance of normal body temperature and pH are crucial during any ongoing resuscitation effort.[2,80,81] In addition, allogeneic transfusions could result in complications such as TRALI that has been mainly reported after transfusion of FFP or platelets.[73-76] Thus the use of POC testing, transfusion algorithms and factor concentrates is advocated to tailor goal-directed therapy and reduce unnecessary transfusion of allogeneic blood components.[52,66]

Protamine

Protamine is routinely used to reverse the effects of unfractionated heparin after separation from CPB. It is not useful, however, in reversing the effects of low-molecular-weight heparin. It is a polypeptide that is isolated from salmon sperm containing 70% arginine residues and thus inactivates the acidic heparin, via a simple acid–base interaction.[82] Following the administration of protamine, there is a decrease in activated clotting time (ACT) and increase in the plasma concentrations of prothrombin, thrombin–antithrombin III complex as well as fibrin.[82] Protamine can cause a variety of adverse reactions, including acute pulmonary hypertension with associated right ventricular dysfunction, severe hypotension as well as anaphylaxis.[83-85] Patients with diabetes who are treated with NPH (neutral protamine Hagedorn) insulin are at increased risk for protamine-induced adverse events due to increased protamine sensitization.[82,86,87,82] Other risk factors for protamine-induced adverse reactions include fish allergy and history of non-protamine medication allergy,[88,89] men who have undergone vasectomies, because they may develop antibodies to sperm[90] and previous exposure to protamine during previous vascular or cardiac procedures.[91] Protamine can inhibit platelets and serine proteases, therefore excess administration of protamine should be avoided as it potentially may exacerbate coagulopathy.[92] Heparin rebound where heparin levels increase following the initial administration of protamine has been reported, and usually occurs several hours after the first dose of protamine. Small doses of 10 to 15 mg of protamine have been recommended to treat this phenomenon if associated with increased bleeding.[16,93]

Desmopressin

Desmopressin (DDAVP) is an analogue of arginine vasopressin and an agonist of the vasopressin V2 receptor. It stimulates the release of vWF and factor VIII from endothelial cells. The vWF stimulates platelets adherence by functioning as a protein bridge between the platelet glycoprotein Ib receptor and subendothelial vascular proteins. Desmopressin is used to treat type I von Willebrand disease and mild forms of hemophilia A.

An early study by Cattaneo et al[94] reported decreased bleeding after cardiac surgery with the use of this agent, however, subsequent studies have failed to produce a similar outcome. Furthermore, a review by Mannucci and Levi[95] reported a very marginal and clinically insignificant effect on blood loss with this agent. Thus, except in selected patient groups (uremic patients or patients with advanced liver dysfunction), there is little benefit in using desmopressin as a hemostatic agent in cardiac surgery patients.

Antifibrinolytic Agents

There are 3 antifibrinolytic agents that have been used in cardiac surgery patients: aprotinin and the synthetic lysine analogs epsilon aminocaproic acid (EACA) and tranexamic acid (TA). Multiple studies have shown reduction in bleeding and transfusion requirements with the use of antifibrinolytics in cardiac surgery patients, however, increasing concerns about safety, particularly with the use of aprotinin have been reported.[96-98] In this regard, the use of the lysine analogs seems to be associated with less adverse effects compared with aprotinin.

Aprotinin. Aprotinin was the most extensively studied hemostatic agent in cardiac surgery patients. It is a polypeptide serine protease inhibitor, isolated from bovine lung, with a large molecular weight (6512 Da). Originally used for the treatment of pancreatitis,[99] aprotinin inhibits a wide range of enzymes, including plasmin, trypsin, chymotrypsin, kallikrein, thrombin, activated protein C, and factor IX. As such, aprotinin has complex interactions with both the coagulation and the inflammatory systems.

There are multiple studies that consistently demonstrated the efficacy of aprotinin in limiting the need for transfusions in cardiac surgery patients.[95] In a meta-analysis of 3212 patients, Levi et al[100] reported that treatment with aprotinin significantly decreased mortality (odds ratio 0.55; 95% confidence interval 0.34-0.90) after cardiac surgery when compared with placebo. Aprotinin was also associated with reduced need for transfusion (relative risk 0.61; 95% confidence interval 0.58-0.66) and was not associated with increased mortality, myocardial infarction, or renal failure.[101]

However, 2 large observational studies in coronary artery bypass graft patients reported a possible increase in the risk for postoperative complications and long-term mortality.[96,97] Shaw et al[98] reported similar findings in a single-center large retrospective analysis of 10 275 cardiac surgery patients, of which 1343 received aprotinin. Compared with patients who received lysine analogs or did not receive antifibrinolytic therapy at all, patients who received aprotinin had a higher mortality rate and higher increases in postoperative serum creatinine levels.[98] The Blood Conservation Using Antifibrinolytics: A Randomized Trial in Cardiac Surgery Population (BART) study[102] was a multicenter blinded prospective trial comparing aprotinin to either TXA or EACA. The investigators randomized 2331 high-risk cardiac surgical patients to receive aprotinin (n = 781), TXA (n = 770), or EACA (n = 780). The primary outcome was massive bleeding. Secondary outcomes included all-cause mortality at 30 days. Fewer patients in the aprotinin group had massive bleeding compared with the other 2 groups; however, this finding was not statistically significant. In contrast, there was a strong trend for increased mortality in the aprotinin group compared with the TXA or EACA groups (6.0% vs 3.9% vs 4.0%, respectively). Although it did not reach statistical significance, the study was terminated earlier than expected based on the mortality data.[102] Following these publications Bayer Pharmaceuticals (Berlin, Germany) removed aprotinin from the European and North American markets in November 2007.

As a recent development, the commercial use of aprotinin was reintroduced in Canada after the results of a Health Canada investigation (http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_124-en-g.php). The drug was approved for use in routine coronary revascularization surgery but not in complex, higher risk procedures. With respect to the BART study, the agency concluded that the study was underpowered to determine the risk of death among the three patient groups and that the increased mortality in the aprotinin group could have been from chance. Nevertheless, Karkouti et al[103] published a retrospective cohort of 15 356 patients of which 1017 received aprotinin. Using a propensity score method, the authors reported that aprotinin had a better risk–benefit profile than TXA in the higher risk patients, thus they concluded that the use of aprotinin in high-risk patients might be beneficial to reduce postoperative bleeding and other complications.[103]

Table 1. Dosing Recommendation for the Use of Antifibrinolytic Agents During Cardiac Surgery as Described in the "BART" Study.[102]

	Loading Dose (mg/kg)	Maintenance (mg/kg/h)	CPB Prime (mg/kg)
TXA	30	16	2
EACA	50	30	50

Abbreviations: BART, Blood Conservation Using Antifibrinolytics in a Randomized Trial; CPB, cardiopulmonary bypass; TXA, tranexamic acid (Cyklokapron); EACA, epsilon aminocaproic acid (Amicar).

Lysine Analogues. Epsilon aminocaproic acid and TXA are 2 synthetic agents that are thought to bind to the lysine-binding sites (which are the areas for fibrin binding) on plasminogen and hence competitively inhibit the conversion of plasminogen to plasmin, thus inhibiting fibrinolysis. At higher doses, TXA also inhibits clot-bound plasmin.[15,16] Multiple reports, including retrospective studies as well as prospective randomized trials and meta-analyses have consistently demonstrated that patients treated prophylactically with lysine analogues had less bleeding, decreased transfusion requirements and reduced need for reexplorations, compared with placebo.[104-107] As a result, the use of lysine analogues is recommended (as a level 1A recommendation) in cardiac surgery patients to reduce the risk of perioperative bleeding.[10,11] Dosing recommendation[102] for the use of antifibrinolytic agents during cardiac surgery is provided in Table 1.

Recently, a concern regarding an association between postoperative seizures and the use of TXA has been raised. One institution reported an increased incidence of postoperative seizures in cardiac surgery patients who were treated with TXA[108]; however, all the patients received high dose of TXA intraoperatively (61-259 mg/kg), their mean age was 70 years, and 21 of 24 had open-chamber procedures; thus additional factors may have contributed to the development of seizures. Additional reports have observed similar findings.[109] In addition, a recent study by Lecker et al[110] has revealed that TXA, in clinical relevant doses, inhibited the

Table 2. Comparison Between FFP, Cryoprecipitate, and Fibrinogen Concentrate.

	FFP	Cryoprecipitate	Fibrinogen Concentrate
Fibrinogen content per vial/unit, g	0.5	0.3	0.9-1.3
Volume per vial/unit, mL/unit	250	20	50
Fibrinogen concentration, g/L	2	8-16	20
Pretransfusion processing	Thawing Blood-type compatibility	Thawing Blood-type compatibility	Mixing in diluent No need for blood typing
Storage	Frozen	Frozen	Room temperature
Shelf life, months	12	12	30
Pathogen inactivation	Testing for pathogens	Testing for pathogens	Heat treated for viral inactivation
Risk for TRALI	Considerable	Lower than FFP	Minimal (does not contain immunoglobulins)
Other coagulation factors	All other coagulation factors	vWF XIII and VIII	Factor XIII

Abbreviations: FFP, fresh frozen plasma; vWF, von Willebrand factor; TRALI, transfusion-related acute lung injury.

neurotransmitter glycine and also caused disruption of the blood–brain barrier, allowing accumulation of TXA in the brain. These findings could explain the mechanisms involved in TXA-induced seizures.

Fibrinogen

Fibrinogen in addition to factor XIII and platelets are the major determinants of clot firmness. Plasma fibrinogen concentrations decrease significantly during and after CPB.[24] In addition, low levels of preoperative and post-CPB fibrinogen correlate with higher risk of bleeding.[31,111] Fibrinogen is only present in the intravascular space and has no extravascular reserves, and therefore it is the first clotting factor to drop below critical levels in case of severe bleeding.[30,112] Normal plasma fibrinogen concentration is 200 to 400 mg/dL and most transfusion algorithms recommend therapy when fibrinogen levels drop to less than 150 mg/dL.[10] Karkouti et al[33] have recently published a single-center retrospective analysis of 4606 patients who underwent cardiac surgery with CPB. The authors found a significant association between postoperative fibrinogen levels less than 200 mg/dL and the need for large volume (>5 units) RBC transfusion.[33] The authors indicated that based on their results a consideration for a higher transfusion trigger for fibrinogen should be considered. Fibrinogen can be effectively restored by administration of cryoprecipitate, or with fibrinogen concentrates. Administration of fibrinogen concentrate was reported as effective in decreasing bleeding after cardiac and aortic surgery.[55,113,114] The required dose of fibrinogen can be calculated based on the FIBTEM test of the ROTEM.[56,70,115] Several studies have reported that using fibrinogen concentrates as first-line therapy for bleeding guided by thromboelastometry, resulted in a reduction in allogeneic blood transfusion, as well as, a decrease in the transfusion requirement of other products and a reduction in thromboembolic complications.[55,56,116]

Fibrinogen concentration in the fibrinogen concentrate is well standardized, with a concentration of 0.9 to 1.3 g/vial (a final concentration of 20 g/L). In contrast, fibrinogen concentration in cryoprecipitate is significantly lower with a wide range of 8 to 16 g/L (average concentration of 10 g/L). Fibrinogen is also present in FFP but in much lower concentrations (Table 2). When bleeding is associated with low plasma levels of fibrinogen the use of a fibrinogen concentrate would require a significantly lower infusion volume, therefore avoiding dilution of the patients' RBCs and platelets and reducing the risk for TRALI and TACO.[2] Therefore, fibrinogen concentrate is as effective as cryoprecipitate and a much better source of fibrinogen than FFP.

Taken together, it seems that replacement of fibrinogen as first-line therapy in the setup of cardiac or complex aortic surgery is a promising approach in reducing bleeding and transfusion requirements. Further prospective studies are, however, needed to determine the efficacy of fibrinogen concentrates. A phase III prospective randomized multicenter study of fibrinogen concentrate therapy versus placebo in high-risk patients undergoing cardiac surgery is currently underway (Randomized Evaluation of Fibrinogen Versus Placebo in Complex Cardiovascular Surgery, NCT01475669) with an expected enrollment completion in the first half of 2014. This study should determine the efficacy and safety of fibrinogen concentrate as first-line therapy for bleeding after cardiac surgery in high-risk patients.

Recombinant Coagulation Factors

These agents are becoming more available for the management of severe bleeding in cardiac surgery patients. The development of these products has been accelerated by the

risks associated with plasma-derived clotting factors (viral contamination, TRALI, TACO, etc).[117] Currently, these products are mainly indicated in the treatment of hemophilia patients with antibodies to factor VIII.[117]

Factor XIII

Factor XIII is an important final step in clot formation, cross-linking the fibrin monomers into fibrin polymers, thus stabilizing the initial clot. Factor XIII levels decrease significantly in patients during and after CPB.[112,118,119] and preliminary trials have demonstrated that the use of factor XIII at the end of CPB has resulted in decreased bleeding and transfusion requirements.[118,120] However, a recent multicenter, prospective, placebo-controlled trial of 409 moderate-risk cardiac surgery patients compared 2 groups of patients that were treated with recombinant factor XIII (17.5 vs 35 IU/kg) to a placebo group. The authors did not report any difference in transfusion avoidance, transfusion requirements or the need for reoperation among the various groups.[121]

Recombinant Factor VIIa

Recombinant factor VIIa (NovoSeven, Novo Nordisk, Bagsvared, Denmark) is mostly indicated to treat bleeding patients who suffer from hemophilia A and have antibodies against factor VIII. In the context of cardiac surgery rFVIIa is mainly used in an off-label fashion as rescue therapy in patients who have massive bleeding due to refractory coagulopathy.[122]

The recommended dose of rFVIIa in hemophilia patients is 90 to 100 μg/kg. In cardiac surgery patients, the optimal dose is yet to be determined. There are numerous reports, including several prospective, placebo-controlled trials, showing that the use of rFVIIa (either prophylactically or as rescue therapy) resulted in decreased bleeding, reduced transfusion requirements and fewer reexplorations compared with placebo.[77,78,123-125]

The major risk with the use of rFVIIa is thromboembolic complications. Levi et al[126] have published an analysis of 35 prospective randomized placebo-controlled trials using rFVIIa in an off-label fashion for treatment of refractory bleeding. The overall risk of thromboembolic adverse events was reported to be 11.1%; however, only arterial thrombotic events were significantly higher in the rFVIIa group compared with placebo (5.5% vs 3.2%; $P = .003$) particularly in older patients (>75 years of age). In a recent prospective randomized placebo-controlled trial by Gill et al,[77] the use of rFVIIa in post–cardiac surgery patients in the intensive care unit resulted in reduced bleeding, decreased need for transfusion of RBCs and coagulation products and less reoperations for bleeding control. The study was, however, terminated earlier than expected since a higher rate of severe adverse events (including stroke) was reported in the rFVIIa group, although these findings did not reach statistical significance.

It has been suggested that concomitant administration of fibrinogen increased the efficacy of rFVIIa in cardiac surgery patients and improved clot firmness.[127] Therefore, it is important to maintain normal fibrinogen plasma concentrations (≥200 mg/dL) to achieve optimal hemostatic effects when rFVIIa is administered.

In summary, rFVIIa is a potent hemostatic agent and as reported, its use is associated with increased risk of thrombotic/thromboembolic adverse events. Therefore, its use should be reserved to situations in which the benefit clearly outweighs potential risks, especially as rescue therapy for massive ongoing bleeding due to refractory coagulopathy.

Reversal of Vitamin K Antagonists–Induced Coagulopathy

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) are concentrates of the vitamin K–dependent coagulation factors (II, VII, IX, and X) that were historically used for replacement of factor IX in patients with hemophilia B.[128] They contain various concentrations of factor VII (3-factor PCCs do not contain activated factor VII whereas 4-factor PCCs also include small amounts of activated factor VII).[79] In addition, newer preparations also contain the anticoagulants antithrombin III, protein S, protein C, and small amounts of heparin to decrease the risk for excessive thrombosis[79] (Table 3). The dosing of these agents is typically based on the concentration of factor IX and the concentration ratio between factor XI and factor II is different between the various preparations.

Outside the United States, the 2 main agents in use are Beriplex P/N (CSL Behring, Marburg, Germany) and Octaplex (Octapharma, Vienna, Austria). These agents are used mainly for emergent warfarin reversal or as a substitute to the use of FFP. The PCCs that are available in the United States include two 3-factor agents: Profilnine (Grifols Biologicals, Inc, Los Angeles, CA) and Bebulin (Baxter, Westlake Village, CA). Recently, a 4-factor preparation Kcentra (CSL Behring, Marburg, Germany) was approved by the Food and Drug Administration and Octaplex (Octapharma, Vienna, Austria) is expected to be approved in the near future.[79] Another type of PCC is the factor VIII bypassing agent FEIBA (Baxter, Westlake Village, CA), which contains prothrombin, factor IX, factor X, and a small dose of factor VIIa (in addition to trace amounts of thrombin, factor IXa, and factor Xa). This factor is primarily indicated in hemophilia patients that have factor VIII–inhibiting antibodies; however, it has also been used for warfarin reversal.[129,130] PCCs and FEIBA are

Table 3. Comparison of the Characteristics of the Most Common PCCs That Are Available in Europe or North America.[a]

Product Name	Factor II	Factor VII	Factor IX	Factor X	Protein C/S	Other additives
Kcentra/Beriplex	111%	57%	100%	150%	Yes	Heparin, AT
Octaplex	98%	66%	100%	96%	Yes	Heparin
Bebulin	120%	13%	100%	139%	NR	Heparin
Profilnine	148%	11%	100%	64%	NR	None

Abbreviations: PCC, prothrombin complex concentrate; AT, antithrombin; NR, not reported by the manufacturer.
[a]There may be additional preparations available in different countries. The activity (in %) for each factor is relative to factor IX activity. See text for details regarding the different manufacturers.

considered as a fractionated component of blood, and thus can be accepted by Jehovah's Witness patients along with rFVIIa and other recombinant proteins.[131]

When compared with FFP, PCCs have a significant smaller infusion volume, thus reducing the risk for circulatory volume overload, especially in older patients. In addition, there is no need for cross matching or other blood bank–related processing. Furthermore, recently published data clearly demonstrate the rapid normalization of vitamin K–dependent factors within 30 minutes using PCC, while it takes a minimum of 3 hours for plasma transfusion (and vitamin K) to bring procoagulant levels to ≥50%.[132]

Several studies that compared the use of PCC with FFP in the context of excessive bleeding after cardiac surgery, reported that PCCs were superior to FFP in correcting the international normalized ratio and the need for RBC transfusion was significantly reduced.[133,134]

In contrast to off-label use of rFVII, the use of PCCs is probably not associated with an increased risk of thrombosis or thromboembolic events. A low risk of thromboembolic events (1:31 000) was described in the pharmacovigilance study of Beriplex[135]; Nevertheless, more safety data are needed especially in the context of severe perioperative bleeding. It is important to mention that it is highly recommended to avoid redosing of these agents in case the patient continues to bleed.[136-138]

The Impact of Point-of-Care Tests and Transfusion Algorithms on Outcome After Cardiovascular Surgery

As already mentioned above, most studies demonstrated reduced bleeding and transfusion requirements when POC tests and transfusion algorithms are used during or after cardiac surgery. In a meta-analysis of 16 trials that included 8507 cardiac surgery patients, Görlinger et al[26] reported a reduction in bleeding and allogeneic blood transfusion when POC tests were used compared to routine laboratory clotting tests and clinician discretion. Others have also reported reduction in surgical reexplorations,[52,139] decrease in the off-label use of rFVIIa for refractory coagulopathy and ongoing bleeding,[139,140] and a significant reduction in hospital costs.[55-57] Furthermore, several groups have recently demonstrated improvement of patient outcomes[55-57] when POC tests were used and fibrinogen concentrates and 4-factor PCC administered as first-line therapy. Of special interest is the study by Weber et al,[55] who reported a single-center randomized trial involving 100 patients undergoing complex cardiovascular procedures. The authors have reported a significant difference in allogeneic blood transfusion in the POC tests group compared with the routine tests group (3 vs 5 units, respectively; $P < .001$). In addition, an interim analysis demonstrated that secondary outcome parameters, composite adverse events rate (acute renal failure, sepsis, thrombotic complications, and allergic reactions), costs, and 6-month mortality were lower in the POC group. Although the study was not designed to detect differences in mortality between the two patient groups, the reported difference in 6-months survival between the groups has led to the early termination of the study with enrollment of only 100 patients (while the initial goal was to include 200 patients in the study). It is important to note that the 6-month mortality rate in the conventional group was 20%. This is a high mortality rate even after complex cardiovascular surgeries, which does not represent the general cardiac surgery patient population. Larger multicenter studies are needed to establish whether the results reported by Weber et al[55] can be reproduced.

Conclusion

Excessive bleeding due to CPB-induced coagulopathy is complex and multifactorial and could result in higher complications rate, as well as, increased mortality. In addition, the higher morbidity and mortality lead to longer intensive care unit and hospital stays, which lead to increased resource utilization and health costs. Although a growing body of data suggest that individualized goal-directed hemostatic approach that is based on POC-guided algorithms and the use of fibrinogen and PCC, as first-line therapy, has been associated with decreased allogeneic blood transfusion requirements, reduced incidence of thromboembolic adverse events, lower hospital costs, and

improved patient outcomes additional work is needed toward identifying specific and effective therapies that will reduce bleeding and transfusion in high-risk cardiac surgery patients and improve patient outcome.

Declaration of Conflicting Interests

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