Coagulopathy and Bleeding Management for Aortic Dissection Surgery

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Introduction

Patients who undergo surgical repair following aortic dissections have multiple hemostatic abnormalities due to numerous factors that contribute to coagulopathy and bleeding [1]. Anticoagulation and its reversal, exposure to extracorporeal circulation, tissue injury due to blood exposure in the false lumen, and further acquired defects [2] can all contribute to impaired hemostasis. Bleeding management in this patient population requires a multimodal approach [3, 4]. Developing specific bleeding management strategies and algorithms to guide transfusion decisions is an integral part of patient blood management which not only reduce allogeneic blood transfusions but optimize clinical care [5, 6]. Cardiac surgical patients undergoing aortic dissection repair are exposed to extensive surgery and often long cardiopulmonary bypass times, which place them at high risk for developing coagulopathy [7]. This chapter will review therapies focused on this patient population, including coagulation testing, blood product transfusion, and pharmacologic strategies to decrease bleeding.

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Coagulation Testing

In patients who are bleeding following aortic surgery, coagulation testing is important to help define contributing hemostatic defects. Although standard laboratory coagulation tests are typically available (i.e., prothrombin time, partial thromboplastin time, platelet counts, fibrinogen levels), these have limitations with regard to specificity and reporting time. As a result, viscoelastic testing with the use of thromboelastography (TEG) or thromboelastometry (ROTEM) is increasingly used in bleeding management as it examines multiple aspects of the hemostatic system. Since whole blood is used for these tests, their samples require reduced preparation compared to standard laboratory tests, and thus reduced time, before actionable information can be obtained.

In cardiac surgical patients, impaired platelet function, in addition to reduced numbers, is a significant cause of bleeding [8]. However, platelet specific function testing is not widely available despite the use of viscoelastic testing and other point-of-care (POC) analyzers such as VerifyNow® and PFA-100®. POC platelet tests have not been validated in acutely bleeding patients since thrombocytopenia and hematocrit significantly influences their reported values. Even with standard TEG and ROTEM, it is important to understand that results are also affected by platelet number, and not function, due to the activators within the test (e.g., kaolin, tissue factor). Until better platelet function testing for the post-CPB period is developed, platelet transfusions for assumed dysfunction will continue to be administered empirically or based on platelet numbers [9].

Despite the lack of studies supporting platelet function tests in the perioperative management of cardiac surgical patients, multiple studies have shown that using pre-determined algorithms can decrease bleeding and transfusion requirements after cardiac surgery. Transfusion algorithms based upon objective measurements decrease the empirical administration of hemostatic factors [10]. Furthermore, algorithms based upon POC viscoelastic testing have been shown to reduce bleeding, the need for allogeneic transfusions, returned to the operating room for bleeding, and overall cost of transfusional therapy in aortic dissection patients [11]. An example of a viscoelastic tracing is provided in Fig. 1.

While POC tests have gained widespread use, most institutions have internally developed their own algorithms using these devices. In many randomized studies, point-of-care testing and transfusion algorithms decrease transfusions and improve hemostasis [10, 12–15]. However, different POC platforms have been used in these studies, along with different transfusion triggers. This is why meta-analyses of viscoelastic POC devices tend to show minimal effects [16–18]. Therefore, it is not clear whether the actual testing devices or the algorithms, which guide transfusion and decrease empirical administration, have the largest impact on reducing blood product usage.

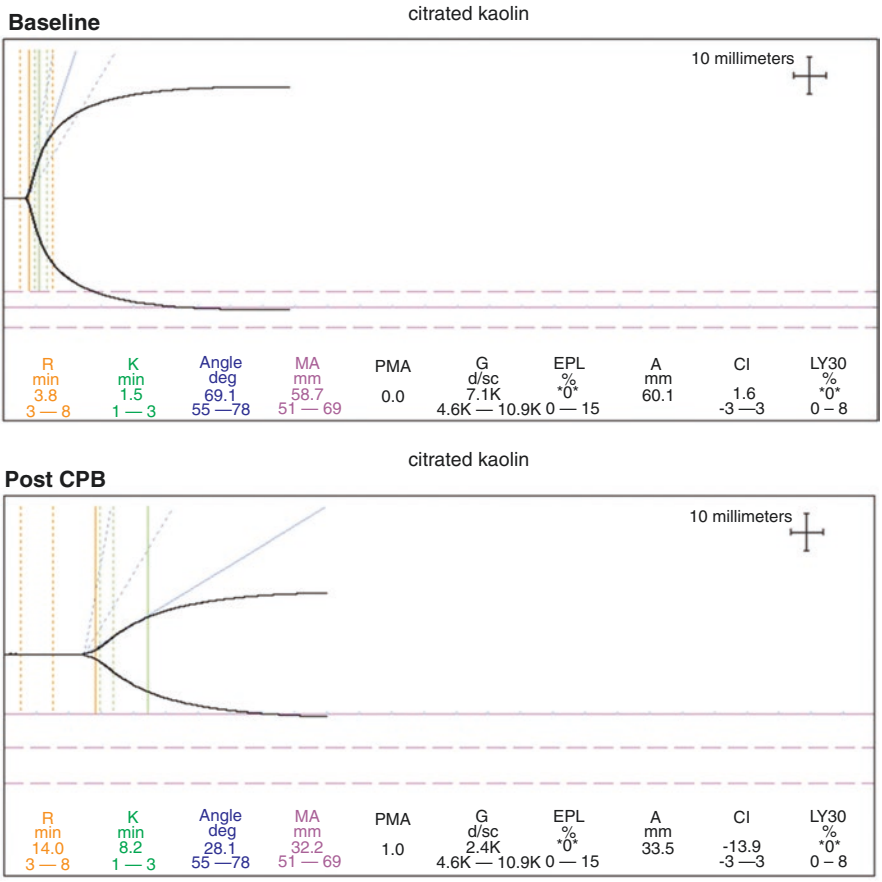

Fig. 1 Examples of normal and hypocoagulable viscoelastic tracings. These are 2 tracings from a TEG® 5000 machine (Haemonetics, Braintree, MA). Although this is a static image, it should be noted that the tracing develops over time and can be read in a dynamic fashion. The top tracing ("Baseline") depicts a normal coagulable state, while the bottom one ("Post CPB") shows hypocoagulability. Measured components are depicted in color with their solid lines depicting the final value and the dashed reference lines representing the normal range. The R time (orange) is measured in minutes and represents initial thrombin generation and fibrin formation. The K time (green) is the amount of time for the clot strength to reach 20 mm in amplitude and represents a measure of fibrin build-up. The angle (blue) is formed by a tangential line to the curve at the K time and provides information on the speed of fibrin cross-linking. MA (purple) is the maximum amplitude of the clot strength and reflects fibrin and platelet interactions. The black numbers are derived from the curve and calculated. A: clot amplitude at any given time along the curve. PMA: projected MA, with a value of '0.0' meaning the clot is likely to reach an MA in normal limits and a value of '1.0' indicating it is unlikely. G: shear elastic modulus strength of the clot which is derived from MA. CI: coagulation index, which is a TEG® value calculated from the measured values to provide a summary of coagulability; CI >3.0 is indicative of hypercoagulability and a CI< –3.0 indicative of hypocoagulability. Fibrinolysis is not depicted on these curves (tracings were each stopped after ~50 min) since the patient was already receiving antifibrinolytic therapy, which is typical in cardiac surgery. EPL: estimated percent lysis at 30 min after MA reached and is continually updated until LY30 point is reached. LY30: percent lysis at 30 min after MA reached

Transfusion Therapy and Transfusion Guidelines

Multiple studies continue to define the role of transfusional therapies in acute bleeding in cardiac surgery. Unfortunately, most of the studies to date have focused on red blood cell (RBC) transfusions and defining the ideal hemoglobin as a transfusion trigger. There is less objective data available that evaluates the role of hemostatic blood components, which include fresh frozen plasma (FFP), platelets, and cryoprecipitate. Despite few controlled trials, there are an increasing number of guidelines and practice documents for bleeding management in cardiac surgical patients [19, 20]. Although these guidelines are reported as generally applicable recommendations, there are also other important considerations regarding the use of specific blood products in cardiac surgical patients that need to be considered. The rationale for the transfusion of individual blood components will be addressed in the following sections.

Red Blood Cells

Although many studies have focused on a specific hemoglobin trigger in cardiac surgery, multiple factors should be assessed when deciding on RBC transfusions in aortic dissection surgery. With acute hemorrhage, the rate of bleeding, which can be quite high in these situations, much be taken into account [21]. Transfusion decisions when hemoglobin concentrations are approximately 7–10 g/dL should be based on any potential or continuing bleeding rate and magnitude, and the intravascular volume status [21].

In general, the number of patients being transfused RBCs during cardiac surgery has significantly decreased over the past decade [22]. In a large, multi-center, randomized study, the TRICS III trial demonstrated a 'restrictive' (Hgb <7.5 g/dL) transfusion trigger was non-inferior to a 'liberal' trigger (Hgb <9.5 g/dL in the ICU) with respect to important patient outcomes [23]. It should be noted, however, that few patients in transfusion trials are undergoing aortic surgery, which is often an emergency and may be complicated by other undiagnosed patient co-morbidities and underlying coagulopathies. Hemoglobin triggers for RBC transfusion are not to be taken as absolute indications, and patients undergoing aortic dissection repair should be transfused if signs of inadequate perfusion are present.

Fresh Frozen Plasma (FFP)

FFP is overused in most surgical patients, often because of empirical therapy or to treat abnormal prothrombin times (PT) and/or partial thromboplastin times (PTT). Although these standard coagulation tests are used clinically to evaluate bleeding, they do not reflect bleeding in surgical patients and can be abnormal in patients who are not bleeding. Despite the extensive use of FFP, there is no data supporting its efficacy outside of

trauma patients requiring massive transfusion [24]. Analyses of randomized controlled trials have been unable to demonstrate consistent evidence of benefit for plasma in most clinical scenarios [25]. The use of plasma to treat elevated international normalized ratios (INRs), especially when the INR is less than 1.7, is problematic since the INR of the FFP itself is about 1.5 [26]. Paradoxically, the overuse of FFP is therefore more likely to result in dilution and exacerbation of coagulopathy. The use of PCCs is now preferred over FFP for reversal of vitamin K antagonists [27].

This is not to say that FFP has no role in the treatment of aortic dissection patients. It has been well demonstrated that multiple plasma proteins, including coagulation factors and anticoagulation factors, significantly fall during aortic surgery with prolonged CPB [28]. FFP has a role in restoring these important proteins, although its use should be judicious. In situations of massive transfusion (see below), FFP is recommended as part of a balanced resuscitation. Although rare, catastrophic thrombosis following cardiac surgery can happen when only procoagulant therapies are administered following prolonged CPB [29]. More research is needed to determine the role of FFP in preventing this deadly event.

Cryoprecipitate

Cryoprecipitate is obtained from thawing FFP. The proteins that precipitate in a small volume include fibrinogen, factors VIII, XIII, and von Willebrand factor. Prior to administration, individual units of cryoprecipitate from multiple donors are pooled in the blood bank and administered usually as 5–10 units. Although initially developed for treating hemophilia due to its high factor VIII levels, the primary use of cryoprecipitate currently is to replete fibrinogen levels when specific fibrinogen concentrates are not available, or for acquired Factor XIII deficiency [30].

In Europe and other countries, cryoprecipitate is not available, and specific purified fibrinogen concentrates are used to treat bleeding. In the current era, the target hemostatic level of fibrinogen is 150–200 mg/dL (1.5–2.0 g/L), but the normal fibrinogen levels in plasma range from approximately 200–400 mg/dL and higher. Fibrinogen is critical to clot strength, and fibrinogen repletion for aortic surgery has been extensively studied and will be discussed later in factor concentrates. The levels of fibrinogen less than 100 mg/dL (1 g/L) can a prolong the clot-based coagulation tests PTT and PTT, and FFP administration is unlikely to correct. Cryoprecipitate or other methods of fibrinogen repletion should be considered in patients following aortic surgery as part of a multimodal protocol to manage bleeding [31].

Platelets

One of the major causes of bleeding in aortic surgery is both platelet dysfunction due to activation and extracorporeal circulation, as well as thrombocytopenia due to dilution and consumption. As previously stated, monitoring platelet function in

acutely bleeding patients is problematic. As a result, platelets are administered based on a platelet count, as well as empirically administered when patients are bleeding. Most platelets transfused are obtained from single donors by apheresis or, alternatively, pooled multi-donor concentrates.

Following cardiac surgery, including aortic surgery, most transfusion algorithms suggest a threshold for platelet administration to be less than 100,000/μL, which is similar to neurosurgical procedures. As a reminder, normal platelet counts are 150,000–400,000 platelets/μL. Although viscoelastic testing is thought to assess platelet function, this is highly dependent on what activators are used, as well as fibrinogen levels.

Massive Transfusion

In aortic surgical patients, extensive bleeding may occur that requires large volume transfusions. This is often referred to as 'massive transfusion,' which is defined as the acute replacement of more than one blood volume or more than 10 units of PRBC within several hours [32, 33]. Treatment of the coagulopathy should include volume replacement, normothermia, resolution of acid-base abnormalities, and blood component therapy.

Most aortic surgical centers who routinely perform these procedures have protocols and facilities that are capable of providing allogeneic blood products as well as factor concentrates in a timely manner. However, in patients who have major bleeding, using fixed ratios of 1:1:1 for RBCs, plasma, and platelets, is standard management and part of damage control resuscitation [34]. Additionally, because of fibrinolysis, an antifibrinolytic should be considered in the bleeding cardiac surgical patient. Further management strategies include targeting fibrinogen levels in the form of cryoprecipitate or fibrinogen concentrates [34]. However, point-of-care monitoring and other goal-directed therapy can follow with fibrinogen levels and facilitate additional potential therapeutic approaches. The role of off-label use of factor concentrates to manage bleeding that cannot be controlled by conventional measures is still evolving (see below).

Adverse Effects of Transfusions

Allogeneic blood product transfusions are extensively used in aortic surgical patients, of which potential acute adverse effects include hypersensitivity reactions, sepsis, acute respiratory failure defined as transfusion-related acute lung injury (TRALI), and even volume overload describe is transfusion associated circulatory overload (TACO) [35–37]. In general, the higher the quantity of blood products transfused, the greater probability of developing acute respiratory distress syndrome (ARDS) [38].

Pharmacologic Therapies

Multiple systemic and topical pro-hemostatic agents are used during cardiac surgery. One of the unique aspects in this patient population is the ability to preemptively treat patients for potential bleeding problems, specifically with antifibrinolytic agents. The multiple agents used will be reviewed in this section.

Antifibrinolytic Agents

One of the mainstay therapies for both preventing and treating hemorrhage in patients following aortic surgery is the use of antifibrinolytic agents. There are multiple causes and initiation of fibrinolysis, both due to cardiopulmonary bypass as well as the activation that occurs following aortic dissection [39–43]. Efficacy in decreasing bleeding and transfusion is well established, as noted by the guidelines published by the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists [44].

The current antifibrinolytic agents used are the lysine analogues: epsilon aminocaproic acid (EACA) and tranexamic acid (TXA). Both occupy the lysine binding site of plasminogen, preventing it from interacting with fibrin [45]. An extensive database supports the efficacy of antifibrinolytic agents in cardiac surgery to decrease bleeding and transfusion [46]. Although TXA is the primary agent used worldwide, it does come with potential for causing seizures, which is likely a dose-dependent effect [47]. Large scale clinical trials in CABG patients have suggested that cumulative doses above 50 mg/kg should be avoided [48]. Given that the risk of seizures may be increased when circulatory arrest is used, many clinicians often use EACA in this setting despite its potential to have an increased risk of renal failure and fewer studies in cardiac surgical patients [49, 50].

Protamine

One of the benefits of heparin anticoagulation is that it is acutely reversible with protamine, a highly basic peptide isolated from salmon sperm that binds heparin by forming a simple acid-base interaction [51]. Protamine rapidly reverses heparin to allow clot formation. Protamine can cause adverse reactions, including anaphylaxis, acute pulmonary vasoconstriction, and right ventricular failure, and hypotension [51]. Different reactions to protamine have been reported ranging from minimal cardiovascular effects to life-threatening cardiovascular collapse. Risk factors for protamine reactions have been reported to be allergies to NPH insulin and men who have had vasectomies, while aspirin administration may be protective [52].

Protamine administration for heparin reversal after cardiac surgery is often highly empirical administering large doses of protamine for persistent bleeding when bleeding is related to multiple other factors. What should be remembered is that protamine itself can inhibit platelet aggregation and prolong the ACT. Multiple studies report that excess protamine beyond what is needed for actual reversal decreases clot strength. Clinicians' routine administration of additional protamine to treat a prolonged activated clotting time may actually further increase clotting time and contribute to excess bleeding [53]. Therefore, approaches to avoid excess protamine using heparin protamine titrations or fixed protamine doses based on time and duration of cardiopulmonary bypass are important as part of a multimodal strategy [54].

Desmopressin

Desmopressin (also called DDAVP) is an analog of vasopressin that releases large von Willebrand factor multimers from their storage site in endothelial cells [55–58]. Rapid administration can cause hypotension, and as a result, it should be given slowly using doses of 0.3 mcg/kg to avoid vasodilation [59, 60]. despite its extensive use in cardiac surgical patients, 18 trials of desmopressin in 1295 patients undergoing cardiac surgery only demonstrated small reductions on blood loss with ~115 mL median volume reduction), and little data supporting any efficacy [60, 61]. The best use for DDAVP in cardiac surgery may be in patients with impaired renal function.

Fibrinogen Concentrate

Fibrinogen is a critical coagulation factor that has been extensively studied in aortic surgical patients for repletion using fibrinogen concentrates. Fibrinogen levels also have been reported to be predictors of perioperative bleeding [62, 63]. As previously discussed, both cryoprecipitate and purified fibrinogen concentrates are the two major methods of repeating fibrinogen levels. However, fibrinogen concentrate has been the focus of most trials to date.

In one of the first prospective, randomized, and blinded studies of patients undergoing elective aortic replacement surgery, 61 patients were randomized to receive either fibrinogen concentrate or placebo [64]. Fibrinogen levels were determined using viscoelastic monitoring with FIBTEM testing following separation from cardiopulmonary bypass and protamine reversal. Fibrinogen concentrate administration reduced transfusions compared to placebo (2 units versus 13 units), and transfusion avoidance occurred in 13 of 29 patients receiving fibrinogen concentrates compared to none of the placebo-treated patients. Of note, the FIBTEM test is a point of care viscoelastic testing method that removes the platelet contribution

for clot formation by inhibiting platelet activation to evaluate fibrinogen levels or abnormalities in clot formation, and generally correlates with laboratory-based fibrinogen assays (Clauss assays).

Other retrospective studies and prospective studies have reported fibrinogen concentrate administration and aortic surgery reduces bleeding and the need for transfusions both intraoperatively and postoperatively [65–69]. In another study of patients undergoing elective aortic valve and ascending aorta replacement, fibrinogen concentrate reduced 24-h postoperative bleeding and blood product administration [66]. Bleeding and transfusion were also reduced in a similar retrospective evaluation of fibrinogen repletion using purified concentrates and guided by of-care fibrinogen measurements using FIBTEM for post-bypass bleeding following thoracoabdominal aortic aneurysm repair [67]. The need for subsequent blood product transfusion was reduced in these patients, as was 24-h chest tube drainage volume.

Because of the success of reducing both bleeding and allogeneic blood transfusion using fibrinogen concentrates, the concept was expanded to a worldwide multicenter randomized clinical trial that evaluated 519 patients from 34 different medical centers to fibrinogen replacement using a five-minute bleeding mass to determine whether patients would be treated. A total of 152 patients met inclusion criteria for fibrinogen repletion with similar median and interquartile ranges of pretreatment 5 min bleeding masses of 107 (76–138) grams in the fibrinogen group compared to placebo with 91 (71–112) grams. In the fibrinogen concentrate and placebo groups, respectively ($P = 0.13$). Of note is that patients who received fibrinogen concentrates received more allogeneic blood products in the first 24 h postoperatively: 5.0 units (2.0–11.0), when compared with placebo, 3.0 (0.0–7.0). Most of the prior studies that showed marked efficacy of fibrinogen concentrates reducing bleeding were from a single European center with a large active aortic surgical program. In the large multicenter study, low bleeding rates and normal fibrinogen levels, along with the inability to follow a complex transfusion algorithm, likely influenced the results. The overall message for the clinician is that preemptively raising fibrinogen levels alone without treating the underlying coagulopathy is not likely beneficial and levels should be targeted as discussed above.

Recombinant Factor VIIa (rFVIIa)

Recombinant activated factor VII (rFVIIa) is approved in most countries for the treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets. However, clinicians have used it off label for intractable bleeding, including in cardiac surgical patients.

In one of the first prospective trials, Gill et al. enrolled patients following cardiac surgery who were bleeding more than 200 mL/h and had not been otherwise treated [70]. In this phase II, dose-escalation study, 35 patients were randomized to receive

rFVIIa at doses of 40 mcg/kg rFVIIa, 69 patients received 80 mcg/kg rFVIIa, and 68 patients received placebo. Although the primary endpoint was serious adverse events, secondary end points included rates of re-exploration, additional transfusions, and amount of blood loss. There were no statistically significant differences in adverse events among the groups however, significantly fewer patients treated with rFVIIa group underwent re-exploration for bleeding (P = 0.03) or required allogeneic transfusions (P = 0.01) [70].

A more extensive safety study of 4468 subjects that included 4119 patients and 349 healthy volunteers reported a higher rate of arterial thromboembolic events among those subjects who received rFVIIa compared to placebo (5.5% vs. 3.2%) [71]. Interestingly, venous thromboembolic events were similar (5.3% vs. 5.7%). It should be noted that major bleeding in cardiac surgical patients increases the risk of serious adverse events, including operative mortality, as does increased transfusion of blood products [72]. Therefore, when evaluating 'rescue therapies' such as rFVIIa, these risks must be weighed against potential complications of the therapy. In patients major aortic surgery with refractory bleeding, rFVIIa as salvage therapy has been reported and recommended [73].

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) are purified, freeze-dried coagulation factors derived from pools of plasma that include factors II, VII, IX, and X in concentrations that depend on the manufacturer [74]. In the United States, both three factor and four factor PCCs are available. The three factor PCCs were originally for hemophilia therapy and included factor IX products that include Profilnine SD [Grifols, Barcelona, Spain], Bebulin VH [Baxter], and Factor Eight Inhibitory Bypassing Activity(FEIBA) VH [Baxter] [75]. Bebulin and Profilnine contain low levels of factor VII, while FEIBA contains the activated form of VII (VIIa). Four-Factor PCCs are approved for warfarin and other vitamin K antagonist reversal. Three-factor PCCs are often administered for bleeding rather than vitamin K antagonist reversal and used for off-label indications, including bleeding in surgical patients. Kcentra (CSL Behring) is the only four component PCC available in the United States but is called Beriplex P/N in other countries. Other four component PCCs available in most countries and include Octaplex (Octapharma, Vienna, Austria) [75–79]. While PCCs have been around for decades, modern agents differ in that most also include low levels of anticoagulants including Protein C and Protein S, as well as antithrombin.

In Europe, viscoelastic monitoring is used extensively for goal-directed bleeding management, and algorithms for bleeding in cardiac surgical patients routinely include the use of four component PCCs, although the body of evidence for this is currently small. Retrospective evaluation of a large database reported that initial treatment using POC testing with PCCs, decreased bleeding as well as thrombotic complications [80]. There was also a reduced need for allogeneic transfusion with FFP, but platelet transfusions were increased [80].

Much like rVIIa, PCCs have also been reported as rescue therapy for life-threatening bleeding refractory to conventional treatment. One report of 25 patients who received FEIBA as rescue therapy included aortic root replacement and heart transplants. Following a mean FEIBA doses of 2154 units, FFP and platelet transfusions decreased without need for re-exploration [81]. One Canadian multicenter phase II study is underway, the Factor Replacement in Surgery Trial (NCT04114643), to better evaluate the role of factor concentrates versus FFP in cardiac surgical bleeding.

Topical Hemostatic Agents

In aortic surgical patients, hemostatic agents are often applied as adjunctive measures to promote hemostasis. Multiple agents have been reported in cardiac surgical patients, and commonly encountered ones are summarized in Table 1. They are typically applied directly to the site of oozing within the surgical field. In patients with active bleeding, the application of such agents can be challenging, which may limit their efficacy. Although much of the data evaluating these agents is from retrospective analyses, there are some randomized clinical trials that have been previously reviewed [82]. Topical agents can be broadly classified into those that provide a mechanical barrier, those that contain an active hemostatic agent, or those that combine both of these elements.

Table 1 Topical hemostatic agents commonly used in aortic surgery

Class of agent	Brand name (manufacturer)	Major component
Mechanical agents	Avitene (Bard Davol Inc, Warwick, RI)	Bovine collagen
	Gelfoam (Baxter, Deerfield, IL)	Porcine gelatin
	Surgicel (Ethicon/J&J, New Brunswick, NJ)	Cellulose
Non-active sealants	Bioglue (Cryolife, Kennesaw, GA)	Bovine albumin + glutaraldehyde
	Coseal (Baxter, Deerfield, IL)	Polyethylene glycol
Active agents	Thrombin JMI (Pzifer, New York, NY)	Bovine thrombin
	Evithrom (Ethicon/J&J, New Brunswick, NJ)	Pooled human thrombin
	Recothrom (Baxter, Deerfield, IL)	Recombinant human thrombin
Combination agents	Floseal (Baxter, Deerfield, IL)	Human thrombin + bovine gelatin
	Surgiflo (Ethicon/J&J, New Brunswick, NJ)	Human thrombin + porcine gelatin
	Evicel (Ethicon/J&J, New Brunswick, NJ)	Human thrombin + human fibrinogen
	Tisseal (Baxter, Deerfield, IL)	Human thrombin + human fibrinogen

Mechanical hemostatic agents are used to provide a barrier at the site of bleeding to allow for potential hemostatic activation and provide a scaffold for the accumulation of critical hemostatic factors. Because they rely on the patient's coagulation system, they should be left in place until clot forms. The most widely used agent of this type is simply bone wax, whose application is almost ubiquitous with sternal closure. Other agents are mainly derived from porcine gelatin or bovine collagen, which in its anhydrous form, can bind bleeding surfaces. Collagen sponges are similar to microfibrillar collagen but obtained from bovine tendon or skin.

Synthetic sealants are also applied to reduce bleeding in a mechanical fashion. A synthetic polyethylene glycol has been extensively used in Bentall thoracic aortic surgery [83]. For major aortic and other cardiac surgical patients, Coselli et al. examined the use a "bioglue" that contains bovine albumin with glutaraldehyde and reported improved hemostasis at anastomotic sites [84]. Despite the potential efficacy, glutaraldehyde may have the potential for tissue injury compared to other potential topical hemostatic products [85].

The compound for most active topical agents is thrombin, used either as a single therapy or combined by the surgeon with a mechanical agent (e.g., a gelatin sponge). The concept of topical thrombin is to locally activate the clotting cascade. Early topical thrombin preparations were bovine derived. Unfortunately, the xenogenic source induced antibody formation against human thrombin and factor V, causing potential hypersensitivity reactions as well as complex coagulopathic bleeding states. As a result, bovine thrombin is seldom used in the current era. The development of both purified and recombinant human thrombin has reduced these adverse reactions.

Therapeutic agents that combine both mechanical properties and have an active hemostatic agent fall into two categories: gelatin plus thrombin (often termed 'flowable' agents), and fibrin sealants. The gelatin used for flowable agents is either porcine or bovine derived and then combined with human thrombin. The product must be reconstituted when ready to use and is typically delivered via a specialized applicator. Fibrin sealants contain two critical hemostatic factors, thrombin, and fibrinogen. They can be administered as either a patch or in liquid form to provide local hemostasis, but require a relatively dry field to be effective. For these different agents, different sources of hemostatic factors are used in individual preparations and include human, bovine collagen and thrombin, and equine collagen. Fibrin sealants can also be mixtures of human fibrinogen, thrombin, and an antifibrinolytic agent to prevent clot lysis, traditionally aprotinin [86].

Summary

Coagulopathy and bleeding management requires a multimodal approach that includes fibrinogen repletion, providing appropriate procoagulants, and antifibrinolytic agents. When patients bleed, surgical sources of bleeding should also be considered, especially in an ICU setting. In addition to allogeneic blood

transfusions, factor concentrates are increasingly management strategies to consider in treatment algorithms. With major hemorrhage, specific protocols for massive transfusion should be considered. Bleeding management algorithms in cardiac surgical patients are increasingly used that include this multimodal therapy along with as well as goal-directed management with point-of-care viscoelastic testing.

References

1. Despotis GJ, Avidan MS, Hogue CW Jr. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. Ann Thorac Surg. 2001;72(5):S1821–31.
2. Levy JH, Tanaka KA, Steiner ME. Evaluation and management of bleeding during cardiac surgery. Curr Hematol Rep. 2005;4(5):368–72.
3. Levy JH, Despotis GJ. Transfusion and hemostasis in cardiac surgery. Transfusion. 2008;48(1 Suppl):1S.
4. Levy JH. Pharmacologic methods to reduce perioperative bleeding. Transfusion. 2008;48(1 Suppl):31S–8S.
5. Goodnough LT, Levy JH, Murphy MF. Concepts of blood transfusion in adults. Lancet. 2013;381(9880):1845–54.
6. Steiner ME, Despotis GJ. Transfusion algorithms and how they apply to blood conservation: the high-risk cardiac surgical patient. Hematol Oncol Clin North Am. 2007;21(1):177–84.
7. Levy JH, Dutton RP, Hemphill JC 3rd, Shander A, Cooper D, Paidas MJ, et al. Multidisciplinary approach to the challenge of hemostasis. Anesth Analg. 2010;110(2):354–64.
8. Ortmann E, Klein AA, Sharples LD, Walsh R, Jenkins DP, Luddington RJ, et al. Point-of-care assessment of hypothermia and protamine-induced platelet dysfunction with multiple electrode aggregometry (Multiplate(R)) in patients undergoing cardiopulmonary bypass. Anesth Analg. 2013;116(3):533–40.
9. Despotis GJ, Skubas NJ, Goodnough LT. Optimal management of bleeding and transfusion in patients undergoing cardiac surgery. Semin Thorac Cardiovasc Surg. 1999;11(2):84–104.
10. Avidan MS, Alcock EL, Da Fonseca J, Ponte J, Desai JB, Despotis GJ, et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. Br J Anaesth. 2004;92(2):178–86.
11. Hanke AA, Herold U, Dirkmann D, Tsagakis K, Jakob H, Gorlinger K. Thromboelastometry based early goal-directed coagulation management reduces blood transfusion requirements, adverse events, and costs in acute type A aortic dissection: a pilot study. Transfus Med Hemother. 2012;39(2):121–8.
12. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, et al. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. Anesthesiology. 2001;94(5):773–81; Discussion 5A–6A.
13. Despotis GJ, Grishaber JE, Goodnough LT. The effect of an intraoperative treatment algorithm on physicians' transfusion practice in cardiac surgery. Transfusion. 1994;34(4):290–6.
14. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. Anesth Analg. 1999;88(2):312–9.
15. Karkouti K, Callum J, Wijeysundera DN, Rao V, Crowther M, Grocott HP, et al. Point-of-care hemostatic testing in cardiac surgery: a stepped-wedge clustered randomized controlled trial. Circulation. 2016;134(16):1152–62.
16. Lodewyks C, Heinrichs J, Grocott HP, Karkouti K, Romund G, Arora RC, et al. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: a systematic review and meta-analysis. Can J Anaesth. 2018;65(12):1333–47.

17. Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. Br J Anaesth. 2017;118(6):823–33.
18. Deppe AC, Weber C, Zimmermann J, Kuhn EW, Slottosch I, Liakopoulos OJ, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: a meta-analysis of 8332 patients. J Surg Res. 2016;203(2):424–33.
19. Goodnough LT, Despotis GJ, Hogue CW Jr, Ferguson TB Jr. On the need for improved transfusion indicators in cardiac surgery. Ann Thorac Surg. 1995;60(2):473–80.
20. Karkouti K, Cohen MM, McCluskey SA, Sher GD. A multivariable model for predicting the need for blood transfusion in patients undergoing first-time elective coronary bypass graft surgery. Transfusion. 2001;41(10):1193–203.
21. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006;105:198–208.
22. D'Agostino RS, Jacobs JP, Badhwar V, Fernandez FG, Paone G, Wormuth DW, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2019 update on outcomes and quality. Ann Thorac Surg. 2019;107(1):24–32.
23. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377(22):2133–44.
24. Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma. 2007;62(1):112–9.
25. Muller MC, Straat M, Meijers JC, Klinkspoor JH, de Jonge E, Arbous MS, et al. Fresh frozen plasma transfusion fails to influence the hemostatic balance in critically ill patients with a coagulopathy. J Thromb Haemost. 2015;13(6):989–97.
26. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test results. Am J Clin Pathol. 2006;126(1):133–9.
27. Witt DM, Nieuwlaat R, Clark NP, Ansell J, Holbrook A, Skov J, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257–91.
28. Okita Y, Takamoto S, Ando M, Morota T, Yamaki F, Matsukawa R, et al. Coagulation and fibrinolysis system in aortic surgery under deep hypothermic circulatory arrest with aprotinin: the importance of adequate heparinization. Circulation. 1997;96(9 Suppl):II-376–81.
29. Williams B, Wehman B, Mazzeffi MA, Odonkor P, Harris RL, Kon Z, et al. Acute intracardiac thrombosis and pulmonary thromboembolism after cardiopulmonary bypass: a systematic review of reported cases. Anesth Analg. 2018;126(2):425–34.
30. Leslie SD, Toy PT. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. Am J Clin Pathol. 1991;96(6):770–3.
31. Nascimento B, Goodnough LT, Levy JH. Cryoprecipitate therapy. Br J Anaesth. 2014;113(6):922–34.
32. Hardy JF, de Moerloose P, Samama CM. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. Can J Anaesth. 2006;53(6 Suppl): S40–58.
33. Karkouti K, O'Farrell R, Yau TM, Beattie WS. Prediction of massive blood transfusion in cardiac surgery. Can J Anaesth. 2006;53(8):781–94.
34. Cap AP, Pidcoke HF, Spinella P, Strandenes G, Borgman MA, Schreiber M, et al. Damage control resuscitation. Mil Med. 2018;183(suppl_2):36–43.
35. Sheppard CA, Logdberg LE, Zimring JC, Hillyer CD. Transfusion-related Acute Lung Injury. Hematol Oncol Clin North Am. 2007;21(1):163–76.
36. Spiess BD. Risks of transfusion: outcome focus. Transfusion. 2004;44(12 Suppl):4S–14S.
37. Despotis GJ, Zhang L, Lublin DM. Transfusion risks and transfusion-related pro-inflammatory responses. Hematol Oncol Clin North Am. 2007;21(1):147–61.
38. Alam A, Huang M, Yi QL, Lin Y, Hannach B. Perioperative transfusion-related acute lung injury: the Canadian Blood Services experience. Transfus Apher Sci. 2014;50(3):392–8.

39. Levy JH, Tanaka KA. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg. 2003;75(2):S715–20.
40. Paparella D, Brister SJ, Buchanan MR. Coagulation disorders of cardiopulmonary bypass: a review. Intensive Care Med. 2004;30(10):1873–81.
41. Eaton MP. Antifibrinolytic therapy in surgery for congenital heart disease. Anesth Analg. 2008;106(4):1087–100.
42. Munoz JJ, Birkmeyer NJ, Birkmeyer JD, O'Connor GT, Dacey LJ. Is epsilon-aminocaproic acid as effective as aprotinin in reducing bleeding with cardiac surgery?: a meta-analysis. Circulation. 1999;99(1):81–9.
43. Sedrakyan A, Treasure T, Elefteriades JA. Effect of aprotinin on clinical outcomes in coronary artery bypass graft surgery: a systematic review and meta-analysis of randomized clinical trials. J Thorac Cardiovasc Surg. 2004;128(3):442–8.
44. Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. Ann Thorac Surg. 2007;83(5 Suppl):S27–86.
45. Levy JH. Pharmacologic preservation of the hemostatic system during cardiac surgery. Ann Thorac Surg. 2001;72(5):S1814–20.
46. Koster A, Faraoni D, Levy JH. Antifibrinolytic therapy for cardiac surgery: an update. Anesthesiology. 2015;123(1):214–21.
47. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg. 2009;110(2):350–3.
48. Myles PS, Smith JA, Forbes A, Silbert B, Jayarajah M, Painter T, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med. 2017;376(2):136–48.
49. Makhija N, Sarupria A, Kumar Choudhary S, Das S, Lakshmy R, Kiran U. Comparison of epsilon aminocaproic acid and tranexamic Acid in thoracic aortic surgery: clinical efficacy and safety. J Cardiothorac Vasc Anesth. 2013;27(6):1201–7.
50. Martin K, Wiesner G, Breuer T, Lange R, Tassani P. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. Anesth Analg. 2008;107(6):1783–90.
51. Levy JH, Adkinson NF. Anaphylaxis during cardiac surgery: implications for clinicans. Anesth Analg. 106(2):392–403.
52. Kimmel SE, Sekeres M, Berlin JA, Ellison N. Mortality and adverse events after protamine administration in patients undergoing cardiopulmonary bypass. Anesth Analg. 2002;94(6):1402–8, table of contents.
53. Mochizuki T, Olson PJ, Szlam F, Ramsay JG, Levy JH. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. Anesth Analg. 1998;87(4):781–5.
54. Sniecinski RM, Levy JH. Bleeding and management of coagulopathy. J Thorac Cardiovasc Surg. 2011;142(662-7):662–7.
55. Mannucci PM, Levi M. Prevention and treatment of major blood loss. N Engl J Med. 2007;356(22):2301–11.
56. Mannucci PM. Treatment of von Willebrand's disease. N Engl J Med. 2004;351(7):683–94.
57. Mannucci PM. Hemostatic drugs. N Engl J Med. 1998;339(4):245–53.
58. Mannucci PM. Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. Blood. 1997;90(7):2515–21.
59. Frankville DD, Harper GB, Lake CL, Johns RA. Hemodynamic consequences of desmopressin administration after cardiopulmonary bypass. Anesthesiology. 1991;74(6):988–96.
60. Rocha E, Llorens R, Paramo JA, Arcas R, Cuesta B, Trenor AM. Does desmopressin acetate reduce blood loss after surgery in patients on cardiopulmonary bypass? Circulation. 1988;77(6):1319–23.
61. de Prost D, Barbier-Boehm G, Hazebroucq J, Ibrahim H, Bielsky MC, Hvass U, et al. Desmopressin has no beneficial effect on excessive postoperative bleeding or blood prod-

uct requirements associated with cardiopulmonary bypass. Thromb Haemost. 1992;68(2): 106–10.
62. Nielsen VG, Levy JH. Fibrinogen and bleeding: old molecule—new ideas. Anesth Analg. 2007;105(4):902–3.
63. Levy JH. Massive transfusion coagulopathy. Semin Hematol. 2006;43(1 Suppl 1):S59–63.
64. Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled Trial. Anesthesiology. 2013;118(1):40–50.
65. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Flinck A, Skrtic S, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost. 2009;102(1):137–44.
66. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, et al. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth. 2009;102(6):785–92.
67. Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, et al. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg. 2009;138(3):694–702.
68. Solomon C, Pichlmaier U, Schoechl H, Hagl C, Raymondos K, Scheinichen D, et al. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth. 2010;104(5):555–62.
69. Solomon C, Schochl H, Hanke A, Calatzis A, Hagl C, Tanaka K, et al. Haemostatic therapy in coronary artery bypass graft patients with decreased platelet function: comparison of fibrinogen concentrate with allogeneic blood products. Scand J Clin Lab Invest. 2012;72(2):121–8.
70. Gill R, Herbertson M, Vuylsteke A, Olsen PS, von Heymann C, Mythen M, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation. 2009;120(1):21–7.
71. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med. 2010;363(19):1791–800.
72. Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G, Surgical and Clinical Outcome Research (SCORE) Group. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. Ann Thorac Surg. 2013;96(2):478–85.
73. Pagano D, Milojevic M, Meesters MI, Benedetto U, Bolliger D, von Heymann C, et al. 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. Eur J Cardiothorac Surg. 2018;53(1):79–111.
74. Levy JH, Douketis J, Steiner T, Goldstein JN, Milling TJ. Prothrombin complex concentrates for perioperative vitamin K antagonist and non-vitamin K anticoagulant reversal. Anesthesiology. 2018;129(6):1171–84.
75. Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. Anesthesiology. 2008;109(5):918–26.
76. Brown KS, Zahir H, Grosso MA, Lanz HJ, Mercuri MF, Levy JH. Nonvitamin K antagonist oral anticoagulant activity: challenges in measurement and reversal. Crit Care. 2016;20(1):273.
77. Ghadimi K, Levy JH, Welsby IJ. Prothrombin complex concentrates for bleeding in the perioperative setting. Anesth Analg. 2016;122(5):1287–300.
78. Bershad EM, Suarez JI. Prothrombin complex concentrates for oral anticoagulant therapy-related intracranial hemorrhage: a review of the literature. Neurocrit Care. 2010;12(3):403–13.
79. Levy JH, Douketis J, Weitz JI. Reversal agents for non-vitamin K antagonist oral anticoagulants. Nat Rev Cardiol. 2018;15(5):273–81.
80. Gorlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology. 2011;115(6):1179–91.

81. Song HK, Tibayan FA, Kahl EA, Sera VA, Slater MS, Deloughery TG, et al. Safety and efficacy of prothrombin complex concentrates for the treatment of coagulopathy after cardiac surgery. J Thorac Cardiovasc Surg. 2014;147(3):1036–40.
82. Bracey A, Shander A, Aronson S, Boucher BA, Calcaterra D, Chu MWA, et al. The use of topical hemostatic agents in cardiothoracic surgery. Ann Thorac Surg. 2017;104(1):353–60.
83. Natour E, Suedkamp M, Dapunt OE. Assessment of the effect on blood loss and transfusion requirements when adding a polyethylene glycol sealant to the anastomotic closure of aortic procedures: a case-control analysis of 102 patients undergoing Bentall procedures. J Cardiothorac Surg. 2012;7:105.
84. Coselli JS, Bavaria JE, Fehrenbacher J, Stowe CL, Macheers SK, Gundry SR. Prospective randomized study of a protein-based tissue adhesive used as a hemostatic and structural adjunct in cardiac and vascular anastomotic repair procedures. J Am Coll Surg. 2003;197(2):243–52; Discussion 52–3.
85. Furst W, Banerjee A. Release of glutaraldehyde from an albumin-glutaraldehyde tissue adhesive causes significant in vitro and in vivo toxicity. Ann Thorac Surg. 2005;79(5):1522–8. Discussion 9
86. Schenk WG 3rd, Burks SG, Gagne PJ, Kagan SA, Lawson JH, Spotnitz WD. Fibrin sealant improves hemostasis in peripheral vascular surgery: a randomized prospective trial. Ann Surg. 2003;237(6):871–6. Discussion 6