Chapter

The Role of Biosurgical Hemostatic Sealants in Cardiac Surgery

Michael S. Firstenberg, Jennifer M. Hanna and Stanislaw P. Stawicki

Abstract

The focus on superb quality and value of medical and surgical care has become a cornerstone of modern clinical practice. Within the realm of cardiothoracic surgery, quality is synonymous with technically excellent, safely conducted operative procedure followed by an uneventful patient recovery and follow-up. Critical to this process of clinical value creation is meticulous attention to all aspects of every step along the management continuum. From surgical quality improvement perspective, the reduction in blood loss and thus minimization of blood/blood product transfusions are of critical importance. This chapter focuses on the role of biosurgicals as useful adjuncts to achieving the ultimate goal of uneventful cardiac procedure and thus set the patient's clinical course for optimal postoperative recovery and long-term well-being.

Keywords: biosurgical, bleeding, hemostasis, cardiac surgery, transfusions, coagulopathy, surgery, complications, coagulation

1. Introduction

A major focus for healthcare providers involved in the management of the cardiothoracic surgical patient is not only addressing the primary surgical problem, but improving all aspects of the overall care of the patient and providing the best value of care. To ensure that value-based aspects of the overall care equation are met or exceeded, the management of expenses is inextricable in the context of optimizing patient outcomes. Specifically, the overall goals of reducing length of stay, eliminating infections, minimizing readmissions, and optimizing other clinical outcomes – especially reducing mortality and perioperative complications – are quickly becoming quality indicators that serve as evaluation standards for both surgeons and hospitals alike. While there is a trend towards minimizing incisions and the invasiveness of surgery with the goal of quickly returning patients back to normal daily activities, clearly there must be a balance of safely achieving the primary goals of surgery in providing a durable solution to a specific clinical problem. Within the ever more complex arena of surgical value-based healthcare, the optimization of the utilization of blood and blood products is becoming increasingly important in patients undergoing cardiothoracic surgery.

Overall, each year, surgical procedures in the United States are associated with the administration of 15 million units of packed red blood cells (PRBCs) [1]. Without a doubt, not only are the absolute number of PRBCs being transfused increasing, but once patients receive a transfusion, they are becoming more likely to receive multiple units of blood and blood products. The reasons for this are complex and often attributed to the complexity of the surgical procedures patients are undergoing. But there is also the reality that patients are more likely to be medicated with antiplatelet agents, anticoagulants, and have associated co-morbidities that increase their risk for bleeding and bleeding related complications [2]. In addition, a growing challenge is that there appears to be a decreasing pool of eligible donors of blood and blood products. It has been estimated that up to 40–60% of all patients who undergo open heart surgery will receive a blood transfusion during their index hospitalization, and cardiac surgery is responsible for the consumption of 10–15% of the total blood supply in the United States [3]. The significance of these numbers cannot be underappreciated, as there is a growing recognition that transfusions are associated with worse short and long-term patient outcomes. In addition, the use of blood and blood products after cardiac surgery has been associated with other adverse consequences beyond worse clinical outcomes, including increased length of stay, increase risk for early (<30 day) readmission, and increased overall costs of care. Furthermore, even for those patients who do not receive a transfusion, there are concerns that the development of a post-operative anemia – specifically a significant change in baseline hemoglobin from pre- to post-operative – has also been associated with worse outcomes and a prolongation of the recovery period [4].

2. Background

As discussed above, blood transfusions are associated with a variety of potential adverse clinical complications [4]. Allergic reactions after transfusions are well known and might be associated with other significant immunologic responses such as post-operative fevers, which might prompt additional testing, blood draws, and potential interventions, the least of which is starting broad-spectrum antibiotics, that might precipitate other expensive, resources-intensive, and occasionally dangerous therapies [5]. Transfusion related lung injury (TRALI) can also be clinically challenging and can result in prolongation of the need for post-operative mechanical ventilation and the complications associated with being on the ventilator beyond brief periods of time. In addition, while infectious complications after transfusions are becoming less common with advanced blood banking techniques, they do nonetheless occur, and when they do occur, the implications can be significant with regards to worse outcomes, increased costs, and increased resource utilization. For example, despite advanced blood banking techniques and testing, Hepatitis B infections can still occur in 1 out of every 200,000 transfusions, while the Human Immunodeficiency Virus (HIV) is believed to be transmitted in about 1 out of 2 million transfusions. Some estimates suggest that as little as 1–2 units of PRBCs transfused after cardiac surgery can result in a twofold increase in overall post-operative mortality [6]. Furthermore, it has been reported that each unit of PRBCs given is associated with a 27% relative increase in the risk of developing a post-operative infection – most commonly, pneumonia [7]. At baseline, a major infection after cardiac surgery will develop in 1 out of 20 patients. However, for those receiving transfusions, this risk of infection increases to about 1 out of 8 [8].

Additionally, growing evidence suggests that bleeding and transfusions can result in a substantial increase in healthcare costs. As mentioned above, but more

specifically, significant bleeding has been correlated with an increase in surgical site infections, all types of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, ventilator associated pneumonias, central line associated bloodstream infections, and *Clostridium difficile* infections, all of which significantly increase the associated length of stay, need for post-discharge resources, and total health-care costs [9, 10]. These expenses and complications also need to be considered in the context of the risk of developing major morbidity and/or mortality from the consequences of acute on chronic organ-system dysfunction (or multi-organ failure) associated with any type of coagulopathy, especially when the bleeding results in hypotension and organ malperfusion syndromes. Even if not directly associated with an identifiable complication, bleeding and the need for transfusions is associated with increased costs associated with the patients remaining in the intensive care unit (ICU). Even though prolonged ICU stays are associated with increased complications and costs, the simple decision to keep a patient in an ICU after cardiac surgery when a bleeding event has occurred (independent of, but often associated with the need for blood or blood products) is also associated with a substantial increase in hospital costs, increased overall length of stay, less efficient bed utilization, and potentially lost opportunity costs. As such, factors and process interventions aimed at improving blood and blood product utilization are often a major focus of any ICU stay reduction initiatives or justification for developing a hospital-wide blood conservation program [11].

As discussed, transfusion rates associated with cardiac surgery have been directly linked to overall programmatic quality and costs. Therefore, an objective blood conservation program can substantially reduce the cost associated with blood and blood product utilization. These concepts are especially important with the trend towards fixed payment and bundled payment systems in which additional postoperative charges or complications (such as re-explorations or readmissions) may not be reimbursed, hence placing the hospital at substantial financial risk.

Other issues, such as the burden of retained blood in the chest, while difficult to quantify, can result in a variety of negative postoperative problems including:

a. the development of tamponade,

b. low cardiac output,

c. chronic pleural effusions,

d. extended or prolonged monitoring in the intensive care unit,

e. prolonged drainage or monitoring of chest tubes – which can result in increased post-operative pain and the need for narcotics,

f. potential delayed in post-operative extubation while monitoring bleeding which can result in a variety of issues and complications from prolonged mechanical ventilation,

g. mediastinitis,

h. acute pericarditis – with associated/confounding ECG changes and/or arrhythmias,

i. long-term development of constrictive pericarditis.

All of these can have substantial short and long-term adverse implications on the patient who is recovering from a major cardiac operation, the least of which are the increased risks of all types of infections, as well as other sequelae, such as a "trapped lung" from chronic pulmonary consolidation.

3. Blood conservation programs

A key component of reducing blood utilization is the development of a team-based approach to blood conservation [12]. Simple things such as reducing the number of blood draws, trying to convert patients to more elective procedures, and reducing the dilutional effects associated with administration of excessive intravenous fluid all can contribute significantly to reductions in surgical blood loss. In addition, the growing utilization of antiplatelet and anticoagulation agents (some of which are irreversible or require expensive antidote reversal agents) in patients undergoing cardiac surgery has created a unique set of challenges. Therefore, any and all opportunities to discontinue antiplatelet and/or anticoagulation medications (unless there are absolute or carefully considered relative contraindications) and allow for return of normal platelet and coagulation function prior to cardiac surgery have been shown to further reduce blood and blood product utilization after major surgical interventions [13]. Other patient factors may contribute to major bleeding complications. Among those factors are baseline low platelet counts, anemia, renal failure, liver disease, morbid obesity, routinely administrated prophylaxis for deep-vein thrombosis for hospitalized patients (especially if not discontinued in a timely manner), as well as the need for emergent procedures and catheterizations. The routine use of heparin-based medications in patients with acute coronary syndromes or critical coronary lesions has been associated with the consumption of key coagulation factors and linked to an increased risk of post-operative coagulopathies. All of these factors have been associated with increased blood utilization and transfusion rates. Without a doubt, there must be an emphasis on a team-based approach to blood conservation that must focus on a continuous modification and improvement in the associated patientcare processes and variables to every extent possible [13].

An extremely important point is the recognition that many patients are on some type of blood thinning agent. Not only is it imperative that the need, both in the short-term as well as the long-term, for such agents be objectively evaluated (especially since many patients have been on therapies for years for reasons they cannot even remember, for indications that might have only required a short course of therapy but there is a reluctance to discontinue, or for reasons for which there might be little evidence-based data to support long-term use), but it is just as important that all healthcare providers understand the implications of varying doses, bio-availabilities, mechanisms of action, and drug-drug interactions, as well as the potential impact of homeopathic medications or herbal supplements, availability and use of reversal agents, patient compliance. Additionally, it is important they understand the overall impact that either using these medications or potentially withholding them prior to surgery may have on surgical bleeding and transfusion rates.

There is also growing evidence that extensive testing of patients during their hospitalization may contribute to the development of an iatrogenic or hospital-acquired anemia and, hence, also lead to an increase in transfusion rates. In one study, for a routine hospital admission for cardiac surgery, it has been estimated that an average patient receives approximately 115 separate tests. This, in turn, translates into almost several hundred milliliters (or 1.5–2 units) of blood drawn for diagnostic purposes alone [14]! Minimizing or optimizing these labs may have

an inherent benefit in reducing the incidence of iatrogenic-induced anemia that subsequently results in transfusions. Furthermore, the development of reasonable transfusion triggers is also important and should be based upon physiologic criteria and subjected to continuous quality improvement initiatives that hold all members of the team accountable. Nevertheless, despite the growing evidence that demonstrates the potential benefits of a restrictive transfusion policy, it must be remembered – and potentially discussed daily in the context of individualized patient care – that some patients might benefit from a transfusion [1].

Probably the most important and obvious source of postoperative transfusions is the occurrence of surgical bleeding. Steps taken to reduce surgical bleeding are of critical importance, and while good surgical technique and avoidance of excessive tissue trauma is always important, it is not the sole explanation for why patients might bleed after surgery. As discussed previously, there are extensive reasons why patients, even with the most meticulous of surgical techniques, experience peri-operative bleeding events. Obviously, avoiding preoperative anticoagulants and antiplatelet agents is critical, but there are also a variety of intra-operative steps that can be taken to reduce the risks for peri-operative bleeding. Such steps include pre-bypass retrograde autologous blood priming, intra-operative banking of blood, and minimization of bypass times, just to name a few (of which a comprehensive discussion of each is beyond the scope of this chapter). In addition, there are a variety of biologically active agents that can augment the natural clotting process in patients undergoing cardiothoracic surgery [15, 16]. Understanding the biologic mechanisms of action, especially in the context of an inherent clotting defect(s) within a specific patient may be helpful when dealing with this challenging problem. A cornerstone to this concept is at least a basic understanding of the clotting cascade and the normal hemostatic process with regards to where certain agents act to interrupt the body's normal response to tissue injury and clotting (**Figure 1**).

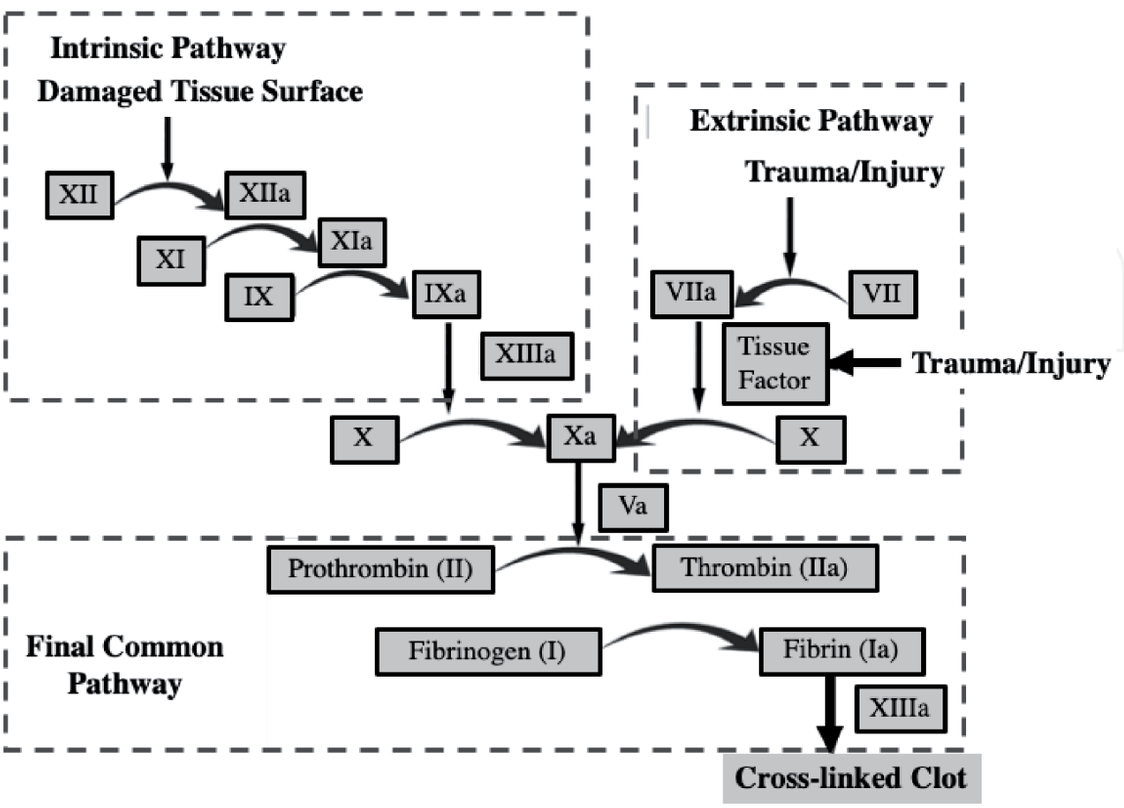

Figure 1.
Intrinsic, extrinsic and final common pathways of the clotting cascade.

Intraoperatively, hemostatic agents are typically supplied as pastes, gels, foams, powders, glues, sprays, and woven cloths or meshes [17].

Recognizing the individual mechanisms of action, advantages, and limitations of each agent is important for their optimal and efficient use. Surveys of surgeons have shown that integration of biological agents to control hemostasis can result in a substantial reduction in postoperative bleeding [18]. However, similar surveys have also demonstrated that, often as a lack of understanding of how each agent works and where it interacts within the clotting cascade, the effectiveness of some agents is limited by inappropriate use – e.g., using the wrong agent to treat the problem. Many patients will require a combination of agents to effectively control problematic bleeding. In our opinion, the ideal agent should consistently achieve rapid hemostasis, provide the adhesive strength necessary to minimize being washed away, be sufficiently strong to withstand arterial pressures, and be readily available, cost-effective, easy to use, easy to store at room temperature and easy to prepare with minimal training and little opportunity for waste. The ideal agent should also be biologically tolerated with minimal, if any, risk for pathologic or immunologic short or long-term implications. And, of course, the risk of transmission of an infectious agent must be zero. The management of bleeding in the setting of a surgical procedure, as mentioned, is associated with significantly higher operative times, operative costs, rates of reoperation, increased infections, and an increase in peri-operative morbidity and mortality. The evidence is growing that suggests that biological agents may play a role in reducing all of the negative clinical outcome parameters while also substantially reducing the amount of time in the operating room managing bleeding by rapidly achieve adequate and stable hemostasis [19]. A key component of the use of these agents is the availability of accurate and timely, even point of care, laboratory studies to help target specific potential defects in the clotting cascade with appropriate blood products and medical therapies [20]. The role of thromboelastography, platelet function assays, activated clotting times, and standard coagulation tests (prothrombin times, bleeding times, etc.) cannot be over-emphasized, but a comprehensive review of these tools is outside the scope of this text. Likewise, medical therapies, such as desmopressin (DDAVP), anti-fibrinolytic agents, recombinant factors, and other agents that target specific deficiencies in the clotting cascade and hemostatic processes must be also considered.

4. Role of biosurgical agents

The use of biological agents during surgical procedures, and especially in high-risk operations like cardiac surgery, can result in a significant decrease in transfusion rates, hospital lengths of stay, and readmission rates. Aggressive and timely control of surgical bleeding can have a major and significant impact on the overall cost of care, particularly by reducing the risks for developing postoperative complications. We believe that a fundamental concept is that, independent of the clinical impact on the patients, the costs associated with the use of these biologic agents can clearly be offset by the expenses saved by avoiding the costs of bleeding and transfusions [21].

Understanding the coagulation cascade and the body's response to vessel and tissue injury is a cornerstone to using the right agent for the right clinical scenario. The pathway consists of the following steps:

1. Vessel injury,

2. Vasoconstriction,

3. Platelet plug formation,

4. Fibrin clot formation, and finally

5. Fibrinolysis

Each of these steps are extremely complex with regards to the cellular response, the role of cytokines, chemo-attractant compounds, and the overall biochemical response to tissue injury and subsequent healing. Nevertheless, each step is also a potential site for therapeutic intervention. While the clotting cascade, including the intrinsic, extrinsic, and common pathways, is extremely complex, a basic understanding of the principles is important for the effective management of postoperative bleeding. It is important to recognize that antiplatelet agents such as clopidogrel, ticagrelor, and aspirin will impact the clotting cascade at different points than anticoagulants such as heparin, Coumadin, and some of the newer generation anticoagulants (each of which also have different mechanisms, sites of action, and options for reversal). Understanding how all of these different drugs impact the hemostasis process cannot be overstated [22]. Furthermore, some drugs such as protamine sulfate are useful for the rapid reversal of heparin, but can induce a coagulopathy if not dosed properly. A significant problem in using biological agents is the lack of education, standardization, and the spectrum of options clinically available. Even simple drugs such as fibrin sprays may vary in how they are produced in the sense that human sources behave immunologically different than bovine- or porcine-based products. Furthermore, defining how effective these agents can be is extremely difficult as a function of the variability in how to qualify or quantify the amount of bleeding and the response to any therapy. Even a simple metric like transfusion rates or need for surgical re-exploration is extremely variable and subjective. The primary focus should be choosing the optimal biological agent for a given clinical situation and specific surgical site. One approach to better understanding how to manage surgical bleeding is to consider five different situations (as enumerated below) and recognizing that more than one situation can exist for a given clinical picture but that different therapeutic interventions might be best considered for a specific situation (**Figure 2**). These situations are:

1. Continuous oozing

2. Problematic bleeding

3. Difficult to access bleeding

4. Potential risk for re-bleeding

5. High-pressure vessel bleeding

Defining each category is also particularly important. Continuous oozing is defined as bleeding that will not stop with simple compression or packing and, in general, is annoying and time consuming. One commonly encountered example is suture line bleeding. Problematic bleeding reflects bleeding that is accessible and can be a source of problems in the perioperative period (such as requiring post-operative transfusions of blood and/or blood products), might be more than routinely encountered for a given procedure, tends to be resistant to conventional interventions, requires immediate attention, and most importantly, is disruptive to the normal progression of an operation. Problematic bleeding is often

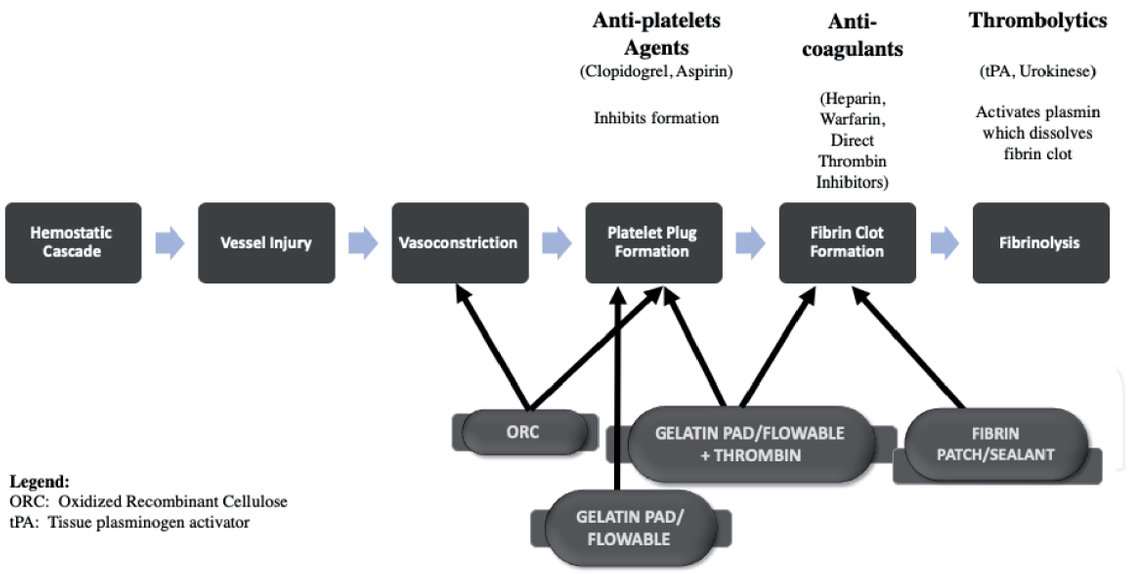

Figure 2.
Clotting pathway with different sites of action of commonly used anti-platelet and anti-coagulant medications with potential biosurgical opportunities for management of hemostasis (see text).

encountered in "raw surfaces" or when dealing with very friable, inflamed, or highly vascularized tissues. Difficult to access bleeding can occur in irregular spaces that might be hard to get to technically or may be difficult to visualize. Examples of this include underneath or behind critical structure that might be difficult (or unsafe) or mobilize or explore – such as behind an aortic anastomosis. This situation is further characterized by the concern that accessing the space or getting to the source of bleeding may result in further harm, bleeding, or tissue damage. The potential for re-operative bleeding is real and presents a difficult challenge, such as after a vessel or structure is re-pressurized, expanded, or stretched with appropriate use in the post-operative period. The best approach here should always be proactive with regards to prevention, including meticulous surgical technique and avoidance of tissue or suture line areas of tension. When bleeding does occur, the decision to re-operate should be made quickly and appropriately to define and address the problem. It is well-established that even a medical coagulopathy can improve with a simple evacuation of a hematoma, even if a definitive surgical source (e.g., something that needs to be technically repaired) is not encountered. Surgeons must remember that re-operative interventions may themselves lead to further postoperative bleeding that may require additional clinical escalation, such as through the technical disruption of an otherwise stable suture line while searching for a potential source of bleeding or the accidental injury to a key structure in the course of re-entry into a body cavity [23]. Finally, high pressure bleeding is potentially deadly in that it might be arterial pressure and difficult to control if not immediately stopped. Even venous bleeding from large vessels or structures such as the right or left atrium can be immediately catastrophic if not addressed in a timely manner which is why protocols, guidelines, and systems must be in place for bedside exploration when a return to the operating room cannot happen either safely or quickly enough.

5. Specific agents

Once the type of bleeding is identified and consideration is given for additional technical interventions (e.g., more suturing or revision of surgical sites) or medical

therapies (e.g., reversal of heparin with protamine), an effective next step is to identify an ideal biosurgical agent. Surgeons must have access to a full spectrum of agents and be able to choose the best option for the best scenario. It is not uncommon that more than one agent is necessary for a given problem.

One commonly used type of biological agent is oxidized recombinant cellulose (ORC) [22]. These types of agents have a low pH which is helpful in that they not only induce vasoconstriction, but they can also potentially be bactericidal. They are often stable at room temperature and packaged in a manner that facilitates ease of use. They have the tendency to be reabsorbed over 1–2 weeks, which reduces the risk for serving as a nidus for infection or worrisome host reaction such as excessive scarring or adhesions formation. In brief, the primary mechanism is that ORC provides a stable matrix for platelet aggregation and adhesion. These agents are available in a variety of different consistencies, sizes, shapes, and strengths that can be selected based on the clinical circumstance.

Biological gels have similar mechanisms of action in that they provide a matrix for platelet aggregation and adhesion [24]. These can be used along suture lines, boney defects, and on raw tissue surfaces. Typically, these agents are mixed with saline or thrombin to generate a paste that can be used in difficult to access areas. As discussed above, when deciding on an agent, it is important to understand that some of these agents are recombinant and hence immunologically inert. However, some are human, bovine, or porcine based and therefore have the potential short and long-term inflammatory immunological host responses. Allergic reactions from re-exposures with animal-derived products have been described and can be problematic, especially in a patient recovering from complex cardiac surgery.

Another category of biosurgical agents are the fibrin sealants. This class of biosurgical agents provides all the necessary components to generate a clot [25]. Therefore, they can be used in patients who have defects in their clotting mechanisms for a variety of reasons. These agents can also be effective in patients that have been exposed to anticoagulant medications that inherently inhibit fibrin clot formation such as warfarin, heparin, and direct thrombin inhibitors. As such, by their mechanism of action, they are less effective in patients that have defects in platelet function from agents such as platelet inhibitors and aspirin. These agents are typically in the form of a topical spray that can be prepared in a short period of time and are easy to use [26].

Finally, there are a variety of non-biologic agents such as glues and adhesives that can be helpful in managing the full spectrum of bleeding and bleeding-related problems. Such agents, by definition, are not biologic (meaning they are not direct replacements or supplements to existing clotting factors – like thrombin, fibrin, and specific clotting factors, recombinant, animal-based, or human derived), and, hence, the mechanisms of action are based on their "glue-like" properties. They can induce a variety of foreign body reactions and, as they solidify, can be difficult to work with [27, 28].

6. Potential complications and concerns

An additional benefit of biological agents is that they, by definition and design, are much more biologically compatible than other potential "foreign" compounds. While, as discussed above, there are concerns of immune-mediated reactions from either a primary and repeat exposure to animal-based agents (in particular, bovine), such reactions are relatively uncommon – and have been predominately experiences in children who, as a function of their congenital heart disease, often require multiple complex surgical procedures [29, 30]. Interestingly, while there are

concerns about potential immunologic reactions, there is some evidence to suggests that, even in the setting of such a reaction, that the biologic hemostatic activity of thrombin-based medications is not always impaired [31]. Such immunological reactions, and potential cross-reactivities, have also been attributed to some of the other complications associated with other agents that impact the clotting cascade. The most commonly associated medication in this category is Aprotinin – a serine protease inhibitor that is an anti-fibrinolytic, and a platelet membrane stabilizer – that has since been withdrawn from commercial use in the context of concerning immune-mediated increased rate of peri-operative morbidity and mortality [32].

Of greater concern of some of the "glue-based" therapies is the development of localized cytotoxic complications. Despite routine use in complex cardiovascular procedures – such as aortic dissections – there are concerns about BioGlue's© (CryoLife Inc. Kennesaw, GA USA), a bovine serum albumin-glutaraldehyde adhesive impact on tissue healing [33]. The association with the late development of anastomotic complications, pseudoaneurysms, vascular strictures, coronary occlusions, and even embolic complications is well-described [34–36]. It is because of these concerns that some advocate that albumin-glutaraldehyde sealants should not be used in "growing tissues" and cautiously in children [37]. Nevertheless, despite extensive experiences and concerns regarding some of the long-term complications associated with these types of agents, they still remain a valuable tool in dealing with very difficult and surgical bleeding, especially in the setting of acute aortic syndromes and complex aortic surgery [38]. Some authors argue that the complications associated with BioGlue reflect more the nature of the surgery, the inherent pathology, and – potentially – some aspect of the surgical techniques used to manage catastrophic bleeding in the setting of extremely friable and disrupted tissues (as if often encountered with aortic dissections) [39, 40].

It cannot be emphasized enough that, as with all therapies in medicine and surgery, that use must be put into the context of balancing risks and benefits. Clearly, bleeding, bleeding related complications, and the transfusion of blood and blood-products introduce substantial short and long-term risks. Biologic agents to help attenuate such bleeding (and, hence bleeding related complications) can be very effective, especially in very complex and difficult surgical situations. Biosurgical agents can be life-saving in the setting of difficult to control surgical bleeding, acquired coagulopathic states, and other challenging technical scenarios. However, such agents are not without their own costs and potential risks. With large number of clinically available agents, it is imperative that clinicians be very much aware of the costs, mechanisms of active, and potential complications – as with any drug – of each. Most importantly, wide-spread use of such agents should not be a substitute for good surgical techniques.

7. Conclusions

Overall, reducing the need for transfusions while reducing the incidence of bleeding and bleeding associated complications is critical for optimizing patient outcomes and reducing the expenses associated with cardiovascular surgery. A multidisciplinary approach is critical in the development of an optimal blood conservation program. Recognizing preoperative patient comorbidities that might impact bleeding and might be modifiable is an important first step. Effectively managing the growing number of medications which patients are exposed to that impact the clotting cascade, and serve as either antiplatelets or anticoagulants is also critical in reducing postoperative bleeding. Avoiding or withholding these medications as long as possible prior to surgery is clearly beneficial, as long as no contraindications

t exist. Unfortunately, patients still require aggressive control of sources of bleeding in the operating room, and managing these can be difficult even in the setting of optimal surgical techniques. Often a variety of biological agents are necessary to help encourage surgical hemostasis [26]. There is growing evidence that the use of these agents can reduce both the risk of bleeding and bleeding-related complications, ultimately leading to improved clinical outcomes [41]. Ongoing educational initiatives and experiences play a key role in a multi-disciplinary approach to the difficult problem of peri-operative bleeding and blood product utilization.

Conflict of interest

Dr. Hanna has no financial conflicts of interest to disclose.
Dr. Stawicki has no financial conflicts of interest to disclose.

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