Tissue Sealants in Cardiac Surgery

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Louis P. Perrault and Fatima Zohra Moukhariq

High Yield Facts

- Tissue sealants, adhesives, and hemostatic agents are second defense line against surgical bleeding.
- Topical hemostatic agents are divided into four classes: mechanical, flowable, fibrin, and active sealants.
- Mechanical hemostatic agents are physical barriers such as collagen, gelatins, and cellulose that are applied over the bleeding site.
- Flowable products are made of microfibrillar collagen and they are used to block blood flow at wound sites by turning fibrinogen into fibrin.
- Active products contain concentrated amounts of thrombin in order to cleave fibrinogen and form blood clots.
- Fibrin based sealants (e.g. Tisseel®) have great biocompatibility, biodegradability, elasticity, drug delivery, and low toxicity.
- Fibrin based sealants carry risk of viral transmission.
- Polyethylene glycol polymer products (e.g. Coseal®) are bioabsorbable and take 3 months to degrade.
- Polyethylene glycol polymer products swell up to 400% in the presence of moisture.
- Bovine serum albumin and glutaraldehyde (e.g. Bioglue®) products are affordable, easy to prepare, and have a 3-year shelf life at 25 °C.
- Albumin and glutaraldehyde products carry risk of toxicity due to glutaraldehyde degradation by-products and disease transmission due to the albumin coming from a bovine source.
- Thrombin gelatin matrix products (e.g. Floseal®) have the ability to conform to wound contours and to fill deep lesions.
- Thrombin gelatin matrix products carry the risk of disease transmission and swelling that might obstruct surrounding tissues.

Introduction

The use of anticoagulants and antiplatelet agents may increase the risk of anastomotic bleeding during cardiovascular surgery [1]. The perioperative and postoperative complications of such an event include blood loss, perianastomotic hemorrhage, pseudoaneurysm formation, the need for reoperation, and increased risk of acute graft thrombosis and failure [1]. Other consequences of bleeding are hemodynamic instability, impairment of visualization of the surgical field, prolonged clamping as well as procedure time [2]. The ramifications can be extreme such as increased mortality through the prevalence of the lethal triad known to be reached when acidosis, hypothermia, and coagulopathy occur simultaneously [2].

The first line of defense against bleeding during surgery involves the use of suture ligation, staples, cauterization, and the application of manual compression over the bleeding anastomotic edge with a gelatin sponge or other mechanical agents [1–3]. However, the manual pressure can result in tissue trauma, whereas sutures can cause further bleeding through the needle holes [2]. For this reason, there is a wide usage of tissue sealants, adhesives, and hemostatic agents as second defense line against surgical bleeding. The primary role of these tools is to complement sutures by allowing the

L. P. Perrault (✉)
Cardiac Surgery Department, Montreal Heart Institute, Montreal, QC, Canada

Department of Surgery and Pharmacology, Université de Montréal, Montreal, QC, Canada
e-mail: louis.perrault@icm-mhi.org

F. Z. Moukhariq
Department of Surgery and Pharmacology, Université de Montréal, Montreal, QC, Canada

Research Center, Montreal Heart Institute, Université de Montréal, Montreal, QC, Canada

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riddance of body fluid leakage through needle holes, and providing superior abilities to withstand a stronger pressure at the site of wound closure [4].

Surgeons use these different agents to ensure reconnection of tissues and restoration of their original functions [5]. These surgical products differ in chemical composition, physical properties, as well as in the mechanism used to achieve their results [6]. For example, the general mechanism of tissue sealants consists of allowing healing via the formation of stable, elastic, long lasting, and insoluble chemical bonds in presence of water molecules [6]. Easy and fast application, excellent cosmetic results, unneeded suture removal, diminished pain, and minimal tissue trauma are the major advantages of the use of these products [5]. Another upside is their potential use in patients prone to bleeding with coagulopathy [4], hemophilia, and during urgent interventions for which it is not possible to wait for effects of anticoagulants to wear off.

Definitions and Classification of Topical Hemostatic Agents, Tissue Sealants, and Adhesives

Hemostatic agents prevent bleeding, but they do so by stimulating the coagulation cascade and forming a blood clot over the wound site [7]. Topical hemostatic agents are divided into four classes: mechanical, flowable, fibrin, and active sealants [8] (Table 12.1). Mechanical hemostatic agents are physical barriers such as collagen, gelatins, and cellulose that are applied over the bleeding site [7]. This matrix provides a platform for platelet aggregation and stimulates the extrinsic coagulation cascade for blood clot formation [7]. Flowable products are made of microfibrillar collagen and they are used to block blood flow at wound sites by turning fibrinogen into fibrin [8]. Active products contain concentrated amounts of thrombin in order to cleave fibrinogen and form blood clots [8].

Table 12.1 Classification of FDA approved topical hemostatic agents[#a]

Mechanical	Flowable	Fibrin/Synthetic	Active
Gelatin sponge (may be used with thrombin) Porcine gelatin • **Gelfoam** (Pfizer Pharmacia) • **Surgifoam** (Ethicon J&J) • **Gelfoam plus** (Baxter Healthcare Corp.)	Gelatin	Fibrinogen + thrombin (human pooled plasma) • **Tisseel** (Baxter) (Human pooled plasma thrombin, human pooled fibrinogen, synthetic aprotinin) • **Evicel** (J&J) (Human pooled plasma thrombin, human pooled fibrinogen, human albumin)	Bovine thrombin • **Thrombin-JMI** (King)
Collagen Bovine • **Avitene sheets** (non-woven web) (Davol) • **Ultrafoam collagen sponge** (Davol)	Gelatin matrix + thrombin • **Surgiflo** (J&J) (Porcine gelatin) • **FloSeal** (Baxter) (Bovine gelatin and human pooled plasma thrombin)	Cyanoacrylate Butyl cyanoacrylate + MS (GEM Srl) • **Glubran 2** (GEM)	Human pooled plasma thrombin • **Evithrom** (Omrix Biopharmaceutical)
Cellulose • **Surgicel** (J&J) • **Surgicel Nu-Knit** (J&J)			Recombinant thrombin • **Recothrom** (ZymoGenetics)
Chitin and chitosan-based hemostatic agents • **Celox** (SAM Medical Products) • **HemCon** (HemCon Medical Technologies Inc.) • **QuickClot** (Z-Medical Corp.)			
Polysaccharide spheres • **Arista** (Medafor)			

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[a][2–11]

Table 12.2 Classification of FDA approved tissue sealants[a]

Fibrin products	Albumin and glutaraldehyde	Polyethylene Glycol (PEG) polymer	Cyanoacrylate
Fibrinogen + thrombin • **Tisseel** (Baxter) (Human pooled plasma thrombin, human pooled fibrinogen, synthetic aprotinin) • **Evicel** (J&J) (Human pooled plasma thrombin, human pooled fibrinogen, human albumin)	45% Bovine serum albumin + 10% glutaraldehyde • **Bioglue** (Cryolife)	Two PEG polymers • **Coseal** (Baxter)	n-Butyl cyanoacrylate + n-Octyl cyanoacrylate • **Omnex** (Ethicon)
		PEG + Trilysine amine • **Duraseal** (Covidien)	

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[a][2–10, 12]

Table 12.3 Classification of FDA approved tissue adhesives[a]

Fibrin products	Albumin and glutaraldehyde	Cyanoacrylate
Fibrinogen + thrombin • **Tisseel** (Baxter) (Human pooled plasma thrombin, human pooled fibrinogen, synthetic aprotinin) • **Evicel** (J&J) (Human pooled plasma thrombin, human pooled fibrinogen, human albumin)	45% Bovine serum albumin + 10% glutaraldehyde • **Bioglue** (Cryolife)	Butyl cyanoacrylate + MS (GEM Srl) • **Histoacryl** (B. Braun) • **Glubran 2** (GEM)

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[a][2–12]

Tissue sealants prevent leakage of fluids or blood from blood vessels and other structures without necessarily relying on the coagulation cascade [9]. In contrast, tissue adhesives, also known as glues, can attach blood vessels or two skin or muscle flaps together by creating bonds between tissues [9]. Sealants have four major types of products and some of them overlap with the three products found under the category of adhesives (Tables 12.2 and 12.3). The source of the different products in each category can be natural or biological, synthetic, and semi-synthetic [5]. The general qualifications sought in such useful tools in surgery is efficient adhesiveness, short compression time, immediacy of action, long shelf life, easy storage, nontoxicity, low cost, and short preparation time and application [2].

Clinical Use in Cardiovascular Surgery

Tissue sealants, adhesives, and hemostats are useful in cardiovascular surgery such as coronary artery bypass grafting, heart valve and aorta repair and replacement, heart transplant, aneurysm repair, and the placement of ventricular assist devices [6]. They are particularly used in procedures where there is a high risk of bleeding in surgeries such as aortic valve replacement, surgery for the ascending and descending aorta, patch plasty, carotid endarterectomy or in patients over 60 years old [2]. In the 2017 European guidelines for patient blood management for adult cardiac surgery, the routine use of topical sealants is not recommended [9]. For instance, the guidelines stipulate that they should not be considered in case of generalized bleeds but rather when the bleeds are localized and persistent [9].

The types of bleedings for which the use of these products can be handy are raw surface bleeds, oozing venous-type bleeds, bone bleeding, and needle-hole bleeding [2]. Moreover, they can be convenient when there is a highly friable tissue since the strain imposed by sutures to close the wound would cause further damage to the surrounding tissues without sealing the opening. Surgeons usually base the choice of the agent used on their preference and their experience with the particular product rather than evidence-base practice [2]. To help manage bleeding in surgery, a reference chart of some possible scenarios and the appropriate choice of agent is suggested for surgeons (Fig. 12.1).

Barnard and Millner published a review on topical agents used in cardiac surgery focusing predominantly on randomized controlled trials (RCTs). Table 12.4 is a summary of key RTCs from this review [13].

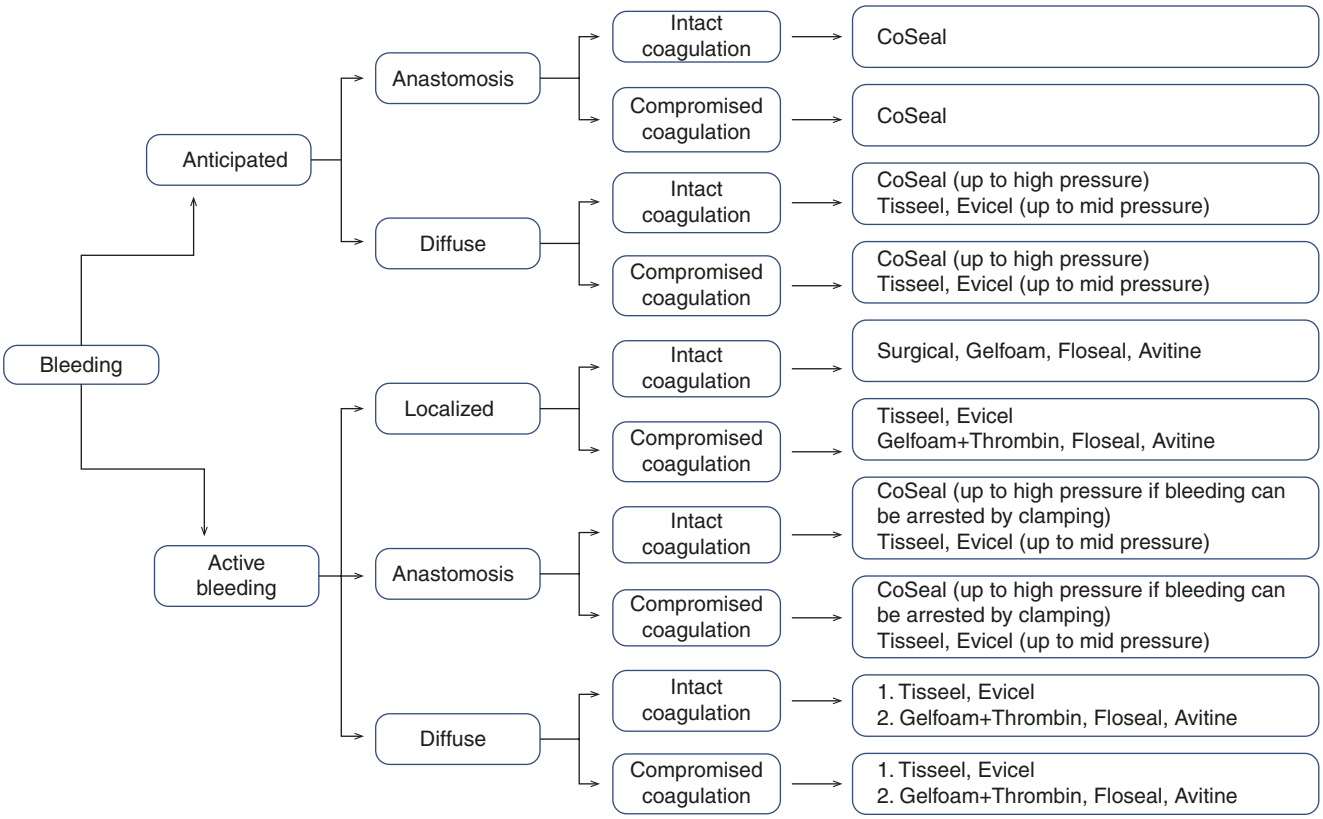

Fig. 12.1 Surgical scenarios in cardiovascular surgery [2]. (Adapted from Spotnitz, et al. [10])

Table 12.4 Summary of randomized controlled trials of hemostatic agents in cardiovascular surgery[a]

Agent	Control	Number	Outcome
Colgel	Surgicel	71[b]	Chest tube drainage in first 24 h was Colgel 373 ± 143 mL vs Surgicel 571 ± 144 mL ($p = 0.01$) and in the first 3 h it was 132 ± 41 vs 228 ± 57 mL, respectively ($p < 0.001$)
CoStasis[c]	Collagen sponges	72[b]	Bleeding controlled within 10 min with CoStasis 28/37 vs control 17/37; $p = 0.02$
Cyanoacrylate Sealant[c]	Oxidized cellulose	151[d]	Hemostasis mean time 119.3 vs 403.8 s ($p < 0.001$) and immediate hemostasis in 54.5% vs 10% in Cyanoacrylate Sealant and control, respectively
Tisseel[c]	Avitene/Surgicel	164[b]	92.6% bleeding control with Tisseel vs 12.4% with control agents at 5 min ($p < 0.001$)
Beriplast[c]	Surgery alone	52[e]	Fewer transfusions of FFP in the BP group compared with controls ($p \leq 0.05$). BP group shorter time to achieve hemostasis ($p \leq 0.05$), less bleeding intraoperatively ($p \leq 0.01$)
CoSeal[c]	Gelfoam thrombin	54[f]	Immediate hemostasis in CoSeal 48 of 59 vs control 10 of 27 ($p = 0.002$)
BioGlue[c]	Surgery alone	151[g]	BioGlue bleeding (18.8% of anastomoses) vs control (42.9% of anastomoses; $p < 0.001$)
FloSeal[c]	Gelfoam thrombin	93[b]	FloSeal stopped bleeding in 94% of the patients (first bleeding site only) within 10 min compared with 60% in the control group ($p = 0.001$)
rThrombin[c]	bThrombin	164[d]	Hemostasis at 10 min 94% bThrombin, 91% rThrombin; p = NS

BP Beriplast fibrin sealant, *bThrombin* bovine plasma-derived thrombin, *FFP* fresh frozen plasma, *NS* not statistically significant, *rThrombin* recombinant thrombin

[a][13]

[b]Cardiovascular procedures including re-do cardiac operations and ascending aortic aneurysm repair

[c]Studies sponsored by industry

[d]Peripheral vascular and arteriovenous procedures

[e]Procedures for congenital heart disease

[f]Implantation of Dacron grafts (DuPont, Wilmington, DE) for the repair of nonruptured aneurysms

[g]Cardiac and vascular repair procedures

Fibrin Sealants

Fibrin sealants are hemostats, adhesives, as well as sealants [9, 14]. They come from a biological source and are made of two basic components that are naturally occurring in humans and animals: fibrinogen and thrombin [4]. Both blood components are kept apart in one syringe with two barrels, which allow both components to interact solely at the moment of application. The action mechanism relies on the fact that the last step of the coagulation cascade is mimicked. Stable blood clots occur when thrombin cleaves fibrinogen into fibrin upon their contact with each other, which helps in wound healing and closure [3]. Within days or weeks, fibrinolysis dissolves the blood clots and no tissue inflammation is triggered since the sealant is entirely absorbed by macrophages and fibroblasts [1, 15].

Fibrin sealants lower risks of hemorrhage in patients who are undergoing a second cardiac intervention [6]. In ventricular assist devices surgery, the unavailability of presealed Dacron grafts results in the use of fibrin adhesive to seal prosthetic grafts [6]. During valve replacement, fibrin sealants containing antibiotics can be applied to the prosthesis as prophylaxis or treatment against bacterial endocarditis [6]. Promotion of blood clots formation via fibrin sealant is useful in off pump coronary artery bypass and minimally invasive direct coronary bypass since hemostasis can hardly be achieved through a small opening [6].

Advantages

Fibrin based sealants are the agents mostly used in cardiovascular surgery and across almost all types of surgeries. They have great biocompatibility, biodegradability, elasticity, drug delivery, and low toxicity [6]. These hemostatic agents can be applied to patients with coagulopathy or under the effects of anticoagulants since they already have all the required components to form blood clots independently from components generated by the patient's coagulation cascade [4].

Disadvantages

Fibrin based hemostatic agents deal with a broad range of bleeding circumstances [3], but they still carry their share of disadvantages. For instance, it is important to screen the source of thrombin and fibrinogen as there is a chance of disease transmission [1]. Virus-inactivated fibrin sealants were developed to avoid such eventualities, but they have poor bonding strength and a complex preparation procedure [5]. Acute thrombus formation leading to acute thrombosis at the operative site and distal embolization are also risks associated with the use of fibrin sealants [1]. The adhesiveness and mechanical strength of this type of sealants is greatly reduced when applied on wet surfaces [5]. For this reason, fibrin sealants should be applied with a carrier sponge or adjunct to sutures and staples [5].

Polyethylene Glycol Polymers

Polyethylene glycol polymers (PEG) are synthetic products that act as both sealants and hemostatic agents [15]. The two approved, marketed, and widely used products are Coseal® and Duraseal® [14]. Coseal® is mainly used for vascular surgery but can also be used to treat air leaks in thoracic surgery [14]. Coseal® comes with a common housing unit for two syringes, and a syringe clip that allows pushing out the content of both syringes simultaneously in the tip. This product is made of two PEG polymers, hydrogen chloride and sodium phosphate—sodium carbonate solutions [14] which form hydrogels that cross-link at the application site to promote tissue adhesion [8, 16]. Usually, PEG products require visible light to crosslink and increase intervention time significantly [15] but Coseal® overcomes this limitation on top of being a sealant stronger than fibrin based sealants [15].

Advantages

PEG products are bioabsorbable and take 3 months to degrade [5]. A study was conducted on aortic surgery patients to demonstrate the efficacy of Coseal® [7]. It was observed that Coseal® patients required significantly less red blood cells and fresh frozen plasma transfusions than the control group [7]. Moreover, Coseal® patients had lower postoperative chest drain volumes than the control group [7].

Disadvantages

Unfortunately, PEG products also have their share of disadvantages. The main concern with this category of products is the swelling of up to 400% with Coseal® in the presence of moisture [14, 17]. Surgeons using this product should consider the maximum swelling that might occur and be cautious about the possible damage to the surrounding anastomotic structures [17].

Albumin and Glutaraldehyde

Albumin and glutaraldehyde products are usually made of bovine serum albumin (BSA) , a glutaraldehyde activator, and formaldehyde [15]. Bioglue® by Cryolife is the only brand with FDA approval since it does not contain formaldehyde

[10]. Bioglue® is made of 45% purified BSA and 10% glutaraldehyde [18]. In surgery, bovine serum albumin-glutaraldehyde (BSAG) plays the role of a sealant as well as an adhesive [19]. The mechanism of action does not rely on the patient's coagulation cascade. Instead, BSAG polymerizes via crosslinking reaction between the aldehyde group in the glutaraldehyde and the lysine amine group supplied by BSA as well as by extracellular matrices or by cell surface proteins [19]. This product starts polymerizing after 30 s from its application and achieves high strength adhesiveness within 2 min [18, 19]. Unlike surgical sealants, BSAG requires priming before being applied via a dispenser gun or syringe [14]. The active components BSA and glutaraldehyde are kept apart in a dual chamber syringe system and mix at the correct ratio at the tip of the applicator [14, 16].

Albumin and glutaraldehyde products are useful in cardiovascular surgery. These products are employed in procedures such as aortic valve replacement, coronary artery bypass, and aneurysm repair of the abdominal aorta [15]. They are used particularly as sealants in large blood vessels anastomoses or as adhesives to reattach the intimal and adventitial layers in the repair of aortic dissection, aortic root, and arch reconstruction [9, 18].

Advantages

BSAG products are affordable, easy to prepare, and have a 3-year shelf life at 25 °C [14]. It has been reported in studies that this sealant lowers risks of reoperation and bleeding complications [19]. Moreover, it decreases blood utilization and has a long half-life of approximately 30 days [15, 19]. Conversely, many studies investigating safety concerns with this product were performed to look into organ embolization, tissue necrosis, pseudoaneurysm formation, nerve damage, tissue conduction trouble, and limitation of aortic growth [7–19]. Until now, studies have not found substantial evidence that BSAG causes pseudoaneurysm [19]. The study by Weiner et al. reports higher percentage of pseudoaneurysm in the non-glue group than the BSAG glued group [19].

Disadvantages

There is a risk of toxicity due to glutaraldehyde degradation by-products and disease transmission due to the albumin coming from a bovine source [14]. Like any glue, BSAG hardens, causing vessel stiffness, and decreases vessels elasticity and compliance [19]. Bioglue® was designed with less flaws than the common BSAG products such as not being cytotoxic, having the same stiffness as a healthy aorta and the ability to be applied in dry or wet environment [7].

Cyanoacrylates

Cyanoacrylates are synthetic adhesives and sealants that are commonly used to hold two skin edges together [14]. Some cyanoacrylate products might have hemostatic properties such as Histoacryl®, a tissue adhesive making small wounds closure possible. It was introduced in the late 1960s and along with the latest product, Glubran 2®, has been reported in more than 1000 clinical publications worldwide. Generally, cyanoacrylates are made of liquid monomers, which polymerize under 30 s in an exothermic reaction [15]. When applied, cyanoacrylates are exposed to anionic substances such as water or blood [5–15], resulting in a strong flexible bond made of long chains of polymers that holds the wound edges together [5].

Advantages

The upside of cyanoacrylates use is that they are waterproof, effective as fluid barrier, have excellent esthetic results, and they do not require wound dressing [4, 15]. Their greatest advantage is that they are bacteriostatic [16]. In addition, cyanoacrylates do not depend on the patient's coagulation state and can be used in case of coagulopathy [16]. Cyanoacrylates are usually less expensive than fibrin sealants and with the advancement in science, new formulas with less toxicity are emerging [16].

Disadvantages

Even though cyanoacrylates are the strongest adhesives and they create bonds that can last for few years, they are extremely cytotoxic [5, 20]. OMNEX® is an FDA authorized brand in cardiovascular surgery since the others are extremely cytotoxic for noncutaneous surfaces [5–21]. Unauthorized products can result in an acute and chronic inflammatory response [5–21]. Moreover, the human body is incapable of breaking these products down, resulting in the accumulation of their carcinogenous by-products in the tissue, cyanoacetate and formaldehyde [5, 15]. Another limitation is the restriction of the usual dynamic tissue movement since the instant solidification upon water exposure of this adhesive causes the formation of a rigid plastic-like seal that cannot accommodate the natural vascular motion [20].

Thrombin Gelatin Matrix

Thrombin gelatin matrix is a topical hemostatic agent that combines mechanical material (gelatin matrix) with an active component (thrombin) [5, 7]. Products in this group are classified according to the source of gelatin. For instance, Surgiflo®

gelatin comes from a porcine source and may or may not contain thrombin, whereas Floseal® is composed of bovine gelatin and human thrombin [9, 14]. The mechanism of action consists of the gelatin acting as mechanical barrier to obstruct the bleeding site and helps in promoting platelets aggregation [12]. Meanwhile, thrombin converts fibrin into fibrinogen [12]. The product must be applied to a wet field as it facilitates the conversion of fibrin and in turn the blood clot formation [8]. Both gelatin and thrombin come into two separate syringes and require mixing before application [14]. Once the paste is applied, a moist saline sponge should be used to apply a gentle pressure for 2 min to aid hemostasis [14].

Advantages

The upside of thrombin gelatin matrix products use is their ability to conform to wound contours and to fill deep lesions [12]. They also cause rapid hemostasis and have precise application [12]. Comparative studies have been performed to observe the effectiveness of Surgiflo® vs Floseal®. Floseal® demonstrated better results, faster hemostasis, reduction in complication and transfusions compared to Surgiflo® when used intraoperatively [12].

Disadvantages

The main concerns with this product are disease transmission and swelling that might obstruct surrounding tissues [14]. To avoid swelling, surgeons should remove excess product [14].

Cost Analysis at the Montreal Heart Institute

The total cost per year of hemostatic and biological products purchased at the Montreal Heart Institute is shown in Fig. 12.2. Over the last 10 years, the total cost of hemostatic and biological products quadrupled reaching $ 848,331. On the other hand, the total money spent on blood products in 2017 was $ 3,064,611 (Table 12.5). Also shown is the use of blood products that has decreased since 2013 (Fig. 12.3) and the use of hemostatic and biological products that has remained somehow more constant (Fig. 12.4). In addition, a cost analysis of re-exploration for bleeding after cardiac surgery demonstrated that the resource utilization costs were substantially higher in patients requiring re-exploration for bleeding and that included prolonged stays in the intensive care unit and blood transfusions [2].

Table 12.5 Total cost of blood products in 2017 at the Montreal Heart Institute

Blood products	Number of units	Cost per unit ($)	Annual cost ($)
Globular sediment PRC	3307	355	1,175,109
Cryoprecipitate	1324	157	208,371
Platelets (pooled and apheresis)	994	637	632,711
Frozen plasma	708	163	115,114
Apheresis platelet pack	33	435	14,362
Stable product transfused			761,865
Loss of labile products			157,079
Total			3,064,611

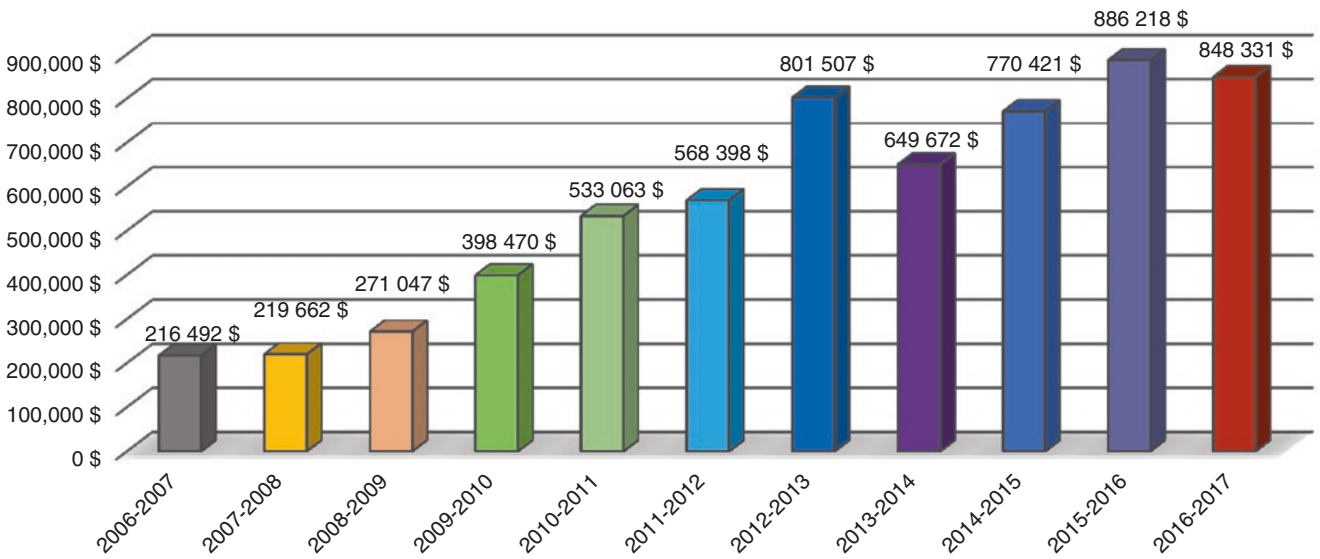

Fig. 12.2 Total cost per year of hemostatic and biological products purchased at the Montreal Heart Institute. (Adapted from Spotnitz, et al. [10])

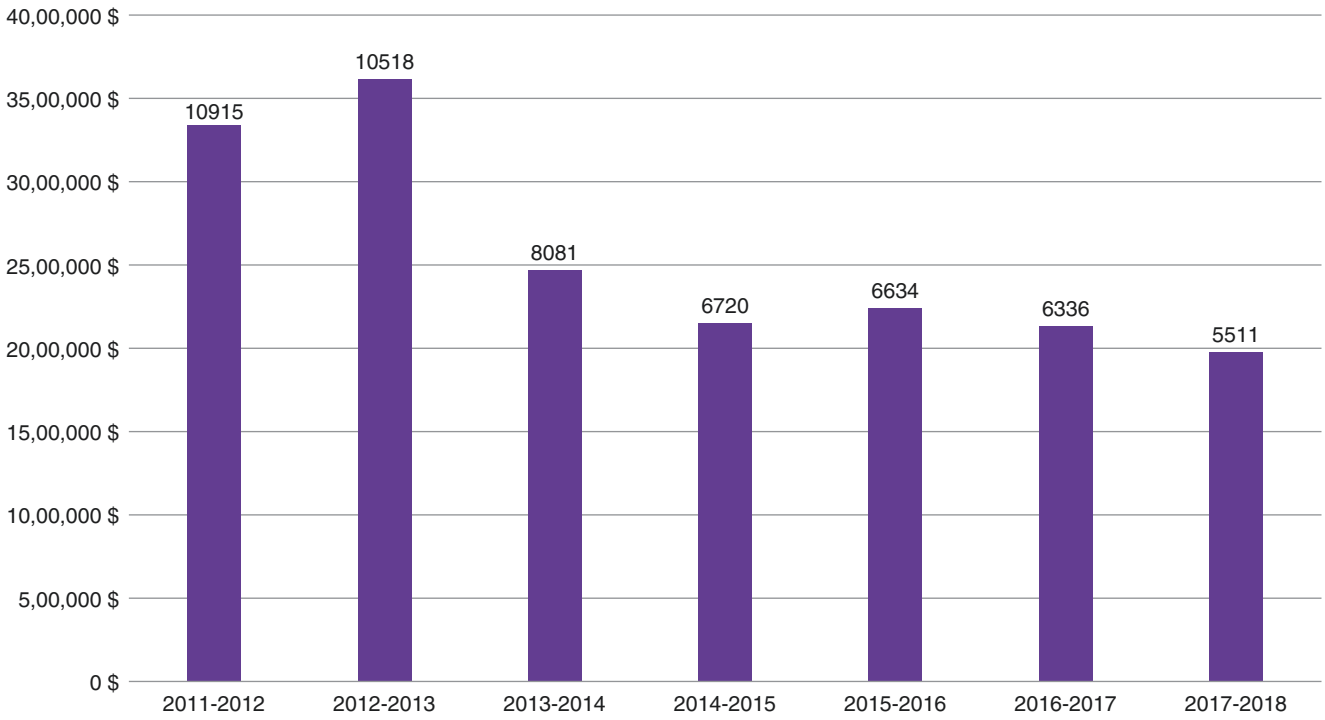

Fig. 12.3 Expenses and units: use of blood products, 2011–2018 at the Montreal Heart Institute. (Adapted from Spotnitz, et al. [10])

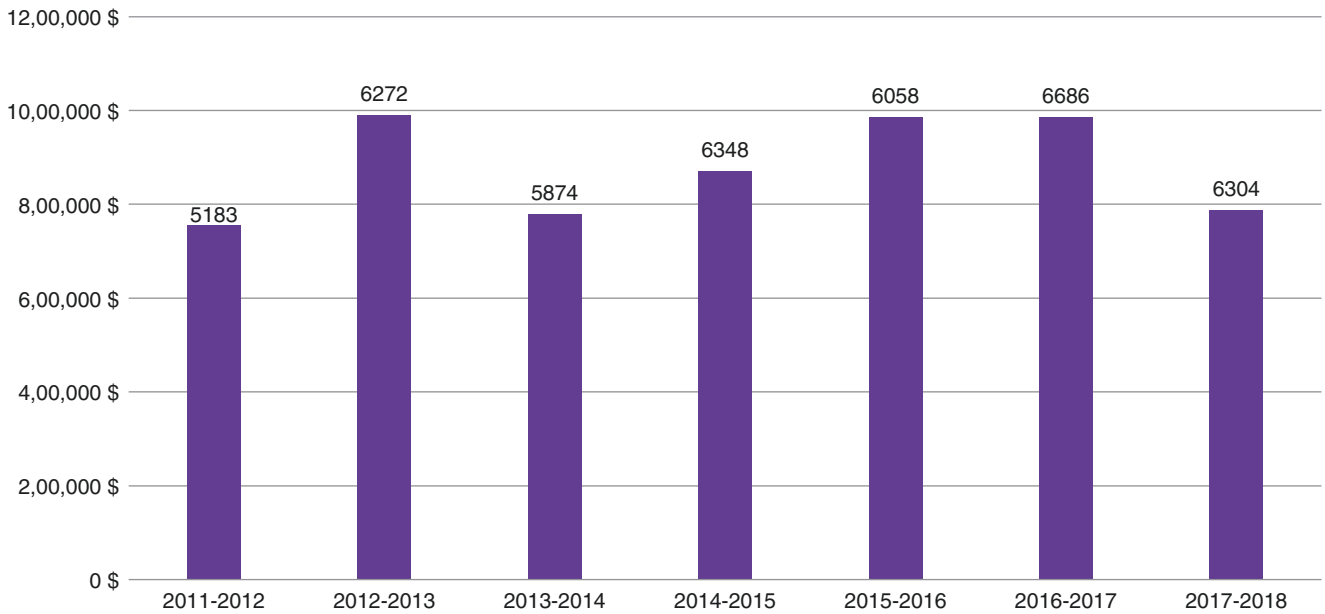

Fig. 12.4 Expenses and units: use of haemostatic and biological products, 2011–2018 at the Montreal Heart Institute. (Adapted from Spotnitz, et al. [10])

Conclusion

Topical hemostatic agents, tissues sealants, and adhesives are used in cardiovascular surgery as a second line of defense against bleeding. Several brands with different composition and properties are at the surgeons' disposal. It is important for surgeons to be aware of these products advantages, disadvantages and application methods to avoid future complications. Even though these products are effective in reducing costs and bleeding complications, no product on the market is currently completely devoid of disadvantages and limitations [22].

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