

USE OF TISSUE SEALANTS IN CARDIAC SURGERY

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The field of cardiac surgery remains one characterized by a wonderful blend of challenging pathology, intricate physiology, and significant technical challenge. Present trends toward minimally invasive surgery and procedures on older patients with more advanced stages of illness are creating new challenges for the cardiac surgeon. The already established coagulopathic substrate caused by heparin anticoagulation with or without fibrinolysis from the cardiopulmonary bypass pump establishes an environment in which improvements in methods to achieve hemostasis are clearly beneficial. The evolving and rapidly developing field of hemostats and tissue sealants provides an extremely useful new technology that will be of great value. This chapter discusses the currently approved and available tissue sealants that are effective in cardiac surgery. Both on- and off-label indications, as well as newer uses of these agents, are described.

As the craft of surgery has evolved over many centuries, the use of suture to approximate tissue layers and to close bleeding blood vessels has become a widely established standard form of treatment. Sutures have been available for this purpose since the second century BC.¹ In contrast, however, the use of surgical glue is a recent phenomenon that has gained the attention of clinicians only in the latter portion of the twentieth century. One factor stimulating the development of new surgical techniques has been the explosive growth in the methods of treating coronary artery disease in the twentieth century. Dr. John Gibbons performed the first cardiac operation using cardiopulmonary bypass in 1954. By 1977, more than 300,000 coronary artery bypass graft (CABG) operations were being performed each year.

The prototype of modern surgical glue, fibrin sealant, was first available in Europe in 1972. Although widely used outside of the United States for 25 years, this agent did not initially receive approval from the United States Food and Drug Administration (FDA). The FDA was concerned about the risk of viral disease transmission with this two-component pooled-plasma tissue-adhesive product and thus withheld approval. More recently,

clinical trials demonstrating efficacy of these products have been subject to concerns over clinical relevance beyond statistical significance. However, as consensus is building over the value of these agents, the ability to obtain market approval appears to be increasing. The FDA approved fibrin sealant in May 1998, with indications including hemostasis in cardiac and splenic surgery, as well as colonic sealing. Since 1998, multiple new agents have received approval for use, and new generations of agents are undergoing laboratory evaluation as well as clinical testing. Thus, the field of tissue sealants is a new and growing field that should provide multiple valuable materials for use by the cardiac surgeon.

A simple analogy gives insight into the value of these new surgical sealants. To best facilitate the manipulation of surgical tissue, a skilled surgeon, much as an accomplished cabinetmaker, must have the appropriate tools. The master cabinetmaker has a wide variety of saws to choose from, as does a skilled surgeon in choosing the appropriate scalpel or scissors. Similarly, the cabinetmaker has different screws and nails with which to join materials, and the surgeon has a variety of different suture materials, which are best suited for particular situations requiring tissue apposition. The cabinetmaker also uses glue as an important element in the creation of fine furniture. Until recently, however, the surgeon has not had the ability to use surgical glues or sealants. Thus, these new agents are an extremely important and valuable new addition to the surgical armamentarium. These materials are particularly useful for the cardiac surgeon whose specialty requires the utmost precision and technical expertise. The cardiac surgeon, much as the master artisan of fine furniture, now has a useful new class of adhesives that can be extremely helpful in facilitating successful clinical outcomes.

It can be useful to consider additional elements of the artisan analogy. The skills of a fine cabinetmaker are acquired over a number of years in a process that may require mentoring by a capable, competent, and caring mentor. A similar training period has been the mainstay of clinical cardiac surgery. During this period of training, the

surgeon develops clinical skill in manipulating tissues as well as clinical judgment in the care of patients. The use of surgical adhesives, being a new technology, has not been an integral part of the educational process of young surgeons in training. Thus, their experience with these agents is relatively recent and underdeveloped. The new surgical hemostats and tissue adhesives are associated with a learning curve. Each agent requires its own appropriate indication, specific method of preparation, and application technique. Thus, it is important to get both cognitive and hands-on knowledge of the appropriate uses of these agents. Inappropriate use of these materials can limit their success and minimize their value to the surgeon.

In addition to the agents discussed in this chapter, new agents are presently under development and are being introduced rapidly into the marketplace. Each of these agents can be judged against the standard of an ideal tissue adhesive. The characteristics of an ideal tissue adhesive (Table 1-1) include efficacy, safety, usability, affordability, and approvability.² For these agents to be licensed by the FDA, they must be safe and effective. If an agent is considered safe, there must be no adverse effects in either the long- or short-term as a result of the agent or its metabolites. There must be no risk of infection, tissue injury or destruction, or carcinogenicity as a result of using the material. In terms of efficacy, the material should be capable of performing in an objectively measured and clinically appreciated manner. In other words, the agent must provide a statistically significant and, most importantly, clinically relevant benefit in patients. The issue of efficacy can be a particularly challenging one. Efficacy of these agents for each surgical specialty may be different, and even within a surgical specialty, efficacy varies from one specific application to another. For example, a cardiac surgeon who desires to seal a vascular anastomosis and to prevent bleeding needs an agent that can prevent needle-hole bleeding and that can seal weakened tissues. It may be desirable to have the agent exhibit these activities prior to removing vascular clamps and pressurizing an anastomosis. On the other hand, after the vascular clamps are removed and bleeding is evident at an anastomosis, it may be desirable to have an agent that can effectively stop active bleeding at a specific site. Thus, effi-

cacy, even in a limited application such as anastomotic hemostasis, may require different capabilities. A liquid agent can be very effective at providing hemostasis and sealing an anastomosis prior to active hemorrhage after the removal of vascular clamps. However, a more substantial material may be required to stop active bleeding, as a liquid agent could be easily washed away by the flow of blood. Thus, efficacy can be different depending upon the specific surgical application.

Usability is also a critical element in allowing surgical sealants to be used in the operating room. To use these agents, the material frequently has to be reconstituted and prepared by the operating room staff. A complex and time-consuming reconstitution procedure for the tissue adhesive makes the agent harder to use and reduces surgeon and nurse enthusiasm for the material. An agent requiring a prolonged period of preparation also requires significant anticipation on behalf of the staff in order for it to be ready. This anticipation can result in a costly wasting of an agent if it is later determined that the agent is no longer required. Thus, the most useful agent is rapidly reconstitutable and does not require specialized storage facilities; instead, it can be kept on the operating room shelf. Also inherent in the concept of usability is the degree to which specialized applicators are available for delivering the tissue sealant to the appropriate surgical site. For example, a linear suture line may require a specific applicator capable of providing tissue sealant to a limited area with specific precise control of the flow of sealant. On the other hand, application to a large diffuse bleeding area may require a spray device capable of delivering efficiently and effectively the material over a broad surface. Additional examples include comparison of the applicators required for efficient use during a cardiac surgical operation requiring a median sternotomy versus a procedure performed through a smaller incision that may require a thoracoscope. The design and choice of specific applicators are critical elements in the successful use of tissue sealants.

Affordability is an important element because cost-effectiveness is under continuous review and health care dollars are limited and carefully monitored. The cost of an ideal tissue adhesive may be the most significant element in its success in the marketplace. The cost-effectiveness of surgical tissue sealants can be increased by achieving a reduction in operating room time, hospital length of stay, and outpatient recovery time. However, additional supporting data with respect to cost issues are still required as the present number of studies proving cost-effectiveness is extremely limited. Finally, approvability or the ability of the tissue adhesive to obtain licensure by the FDA, and hence market access, is an essential element. It took fibrin sealant 25 years to gain approval for use in the United States. It is hoped that newer agents entering the marketplace can be designed and tested so that the approval process is facilitated while maintaining excellent standards of safety and efficacy.

TABLE 1-1. Characteristics of an Ideal Tissue Adhesive

1. Safety	The product and its metabolites must produce no short- or long-term negative effects.
2. Efficacy	The agent must be proven scientifically and clinically effective.
3. Usability	The material must be easily reconstitutable in the operating room and applicable in an efficient manner.
4. Cost	The use of the adhesive should reduce the overall cost of the procedure.
5. Approvability	The licensure of the product should be obtainable within a reasonable period of time.

The following sections discuss the currently available tissue adhesives that may be useful for the cardiac surgeon in detail. These agents represent the first generation of materials of this type, but they are already proving very useful to the surgeon experienced in their capabilities. In addition to the obvious on-label clinical benefits of the agents, off-label additional advantages of these agents, including the ability to provide the capacity for drug delivery and tissue engineering, are illustrated.

Available Agents

Each of the available agents is reviewed below. All are FDA approved and discussed in the order of market approval since May 1998 (Table 1-2).

Fibrin Sealant

Fibrin sealant received approval by the FDA in May 1998. On-label indications include use as a hemostatic agent in cardiac surgical operations and in splenic trauma repair.³ It is also approved for sealing colonic anastomoses at the time of colostomy closure. The commercial form of fibrin sealant comes as a two-component liquid with hemostatic and adhesive properties. It consists of concentrated human thrombin and fibrinogen containing trace amounts of calcium and factor XIII. The materials are derived from pooled human plasma. The fibrinogen in the presence of thrombin is cleaved and cross-linked to produce the final form of the fibrin sealant. The mixture contains bovine aprotinin, which functions as a stabilizer of fibrin and retards fibrinolysis. Polymerization of the fibrin sealant from the liquid components to a gel form

takes approximately 15 s, and reaches its final stage within approximately 2 min. The strength of fibrin sealant is influenced by the concentration of fibrinogen, and the speed of the polymerization process is regulated by the concentration of thrombin. The FDA has approved distribution of fibrin sealant by two different companies, which both market the identical product (Tisseel VH, Baxter Healthcare, Glendale, California, and Hemaseel APR, Haemacure Corporation, Sarasota, Florida).

Because both the fibrinogen and thrombin components of fibrin sealant are derived from human plasma, there is a potential risk of viral or other blood-borne disease transmission. To minimize this risk, donors are screened to eliminate those at highest risk for blood-borne diseases, and the product undergoes heat pasteurization and ultrafiltration. These methods are designed to enhance viral inactivation. To date, there are no documented cases of hepatitis or human immunodeficiency virus transmission from this product in more than 5 million cases worldwide. Because the product contains bovine aprotinin used as an antifibrinolytic in order to modify the rate of fibrin sealant degradation, there is a small risk of allergic reaction. Reports of complications with fibrin sealant in its present commercial form are rare.

Fibrin sealant components must be stored in a refrigerator at 2 to 6°C. The components are supplied as lyophilized powders, which must be reconstituted in a mixing and thawing process that includes saline containing calcium chloride and bovine aprotinin. The entire reconstitution process takes approximately 20 min and requires a special device supplied by the manufacturers to

TABLE 1-2. The Uses of Currently Approved Tissue Adhesives

<i>Brand Names</i>	<i>Components</i>	<i>FDA Approval</i>	<i>Indications</i>
Tisseel VH; Hemaseel APR	Fibrin sealant (pooled human plasma)	May 1998	Biologic hemostatic agent used in cardiopulmonary bypass procedures and splenic trauma, and for sealing of anastomoses in the closure of temporary colostomies.
Dermabond	2-Octyl-cyanoacrylate	August 1998	Device for topical closure of external lacerations and simple incisions.
FloSeal	Bovine collagen and bovine thrombin	December 1999	Device approved for surgical procedures (other than ophthalmic and urologic) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.
CoStasis	Bovine collagen and bovine thrombin + autologous human plasma	June 2000	Sprayable liquid hemostatic device for cardiovascular, general, hepatic, and orthopedic surgery.
FocalSeal-L	PEG polymer/hydrogel	May 2000	Light-activated synthetic device approved as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.
BioGlue	Bovine albumin cross-linked with glutaraldehyde	Human Device Exemption: December 1999; full approval: December 2001	Device approved as an adjunct to standard methods of achieving hemostasis in adult patients with open surgical repair of large vessels (such as aorta, femoral, and carotid arteries).
CoSeal	PEG polymer/hydrogel	December 2001	Totally synthetic device approved for use in sealing arterial and/or venous reconstruction.

facilitate the mixing and thawing process. The reconstituted components are mixed during the application and begin to set up within 15 s of application to the clinical site. The commercial manufacturer provides fibrinogen as a concentration of 75 to 115 mg/mL to enhance the strength of the product, and thrombin at a concentration of 500 IU/mL in order to facilitate the rate of reaction. The sealant is distributed in a 1 mL kit that contains 1 mL of fibrinogen and 1 mL of thrombin and costs \$75 to \$100 (US) per milliliter. The 1 mL kit produces 2 mL of the final fibrin sealant. Larger volume kits, specifically 2 mL and 5 mL, are available.

The advantages of the commercial product include high concentrations of fibrinogen and thrombin, which enhance the strength and rapidity of polymerization, thus increasing the usefulness of the agent in the operating room. Also, the addition of aprotinin as a stabilizer enhances the stability of the sealant, making it resistant to fibrinolysis. Because the components of the adhesive are virally inactivated, the risk of blood-borne disease transmission appears to be significantly reduced. This commercial form of fibrin sealant also avoids the use of topical bovine thrombin.

Additional methods of producing fibrin sealant were developed prior to the FDA's May 1998 approval of the commercial product. Specifically, surgeons used concentrated solutions of fibrinogen combined with topical bovine thrombin to produce fibrin sealant. Blood bank cryoprecipitate can be used as a source of concentrated fibrinogen, or a concentrated fibrinogen can be obtained from the patient's own blood or from outdated units of plasma devoid of unstable clotting factors.^{4,5} Methods of obtaining fibrinogen from the patient's own blood have the advantage of reducing the likelihood of blood-borne disease transmission. The use of outdated acutely frozen plasma avoids the waste of unstable clotting factors that are present in routine cryoprecipitate and is a valuable means of reversing coagulopathies in patients requiring the intravenous administration of clotting factors. The fibrinogen concentrations that can be obtained using cold or chemical precipitation techniques are less than those in the commercial product. Specifically, they vary between 15 and 35 mg/mL. Thus, this material may be weaker than that which is obtainable commercially. An additional limitation of the noncommercial form of fibrin sealant produced in the blood bank is that there is no stand-alone human thrombin product presently available in the United States. Thus, in order to produce fibrin sealant, it is necessary to combine concentrated human fibrinogen with the commercially available topical bovine thrombin. Reports of coagulopathy as a result of the use of topical bovine thrombin exist.^{6,7} This is believed to occur when the body produces an antibody response to impurities in the bovine thrombin which can cross-react with the body's own clotting factors producing a coagulopathic state.

There is literature supporting fibrin sealant use in a wide variety of on- and off-label applications. Reports exist using both the commercial and blood bank-derived products.^{8,9} In fact, the use of fibrin sealant in cardiac surgical procedures appears to account for the majority of fibrin sealant presently employed. This occurs predominantly in reoperation CABG procedures, valve replacements or repairs, complex congenital heart operations, and surgery on the aorta. It can be used to seal suture lines (Figures 1-1 and 1-2), vascular conduits, cannulation sites, vascular anastomoses, patches, dissections, catheterization sites, and diffusely bleeding surfaces. Particularly in reoperative cardiac surgery (Figures 1-3 and 1-4), fibrin sealant can be used to stop diffuse bleeding from the mediastinum secondary to scarring and adhesion. It may reduce the perioperative need for blood products.

There are two types of primary application devices for fibrin sealant available through the commercial manufacturers. One device is capable of providing for linear application of the sealant by using a dual syringe holder that allows for mixing of the components and delivery



FIGURE 1-1. Closure of the apex of the left ventricle at the site of an aneurysm repair.

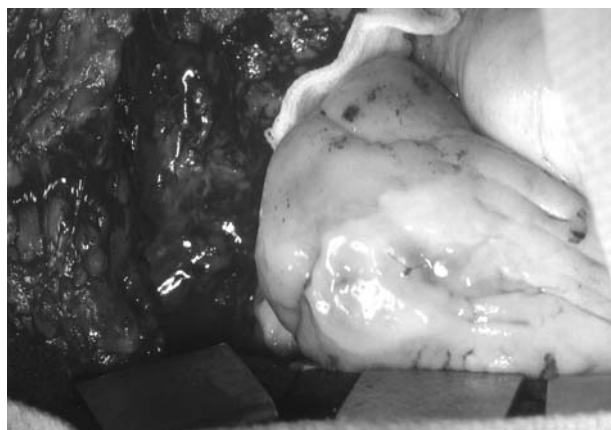


FIGURE 1-2. Fibrin sealant at the site of the left ventricle aneurysm repair after application by using a gas-driven spray applicator.



FIGURE 1-3. Spray application of fibrin sealant to stop capillary bleeding following reoperation CABG with mitral valve repair.



FIGURE 1-4. Operative field after completed spray application of fibrin sealant.

through a 19-gauge needle tip. This precise applicator tip is well suited for applying the sealant to localized suture lines but may clog if repeated applications are required. The manufacturers provide multiple tips to remedy this problem. The second major application method is a gas-driven spray application device. This device provides for the broad application of small aerosolized droplets of the adhesive components. Excellent mixing is produced over a wide surface area. This may result in a more efficient use of fibrin sealant and may reduce the volume of agent required for a specific application, resulting in improved cost-effectiveness. A variety of other catheter tips and handheld spray tips are also available for the discerning clinician.

There is a learning curve for the appropriate use of any of these new agents; it consists of hands-on use of the material and related device applicators. To most effectively apply fibrin sealant as a hemostat, the site of intended application must be as dry as possible. Because the agent is applied in a liquid form it is desirable to minimize active bleeding at the application site prior to appli-

cation of the sealant. Otherwise, during the period of polymerization, active bleeding washes away the liquid fibrin sealant before it can harden and produce hemostasis. One example of a method to reduce active bleeding to facilitate the application of fibrin sealant is the application of fibrin sealant to cardiovascular anastomoses prior to the release of cross-clamps. In this setting, the blood vessel is not pressurized and the fibrin sealant can be applied and polymerized prior to pressurization of the vessel and the development of active bleeding. If 2 to 3 min can be permitted for the formation of the fibrin sealant prior to release of vascular clamps, the fibrin sealant is very effective at reducing hemorrhage. Because fibrin sealant has polymerized in a relatively bloodless field in this setting, it is maximally effective at achieving hemostasis. Such an application of fibrin sealant, however, requires anticipation on the part of the surgeon. Specifically, the 20-min preparation time makes it necessary for the operating surgeon to request this material in advance of its use so that the circulating staff in the operating room can have it prepared before it is required. After reconstitution, fibrin sealant remains usable for approximately 4 h.

Although the application of fibrin sealant to a relatively bloodless field is desirable, this is not always practical. In such a case, the use of a carrier sponge of cellulose or collagen can be extremely helpful.⁹ The sponge can be soaked in fibrinogen and then activated with thrombin just prior to application. The sponge is then applied to the active bleeding site. Thus, the sponge serves as a method of carrying the fibrin sealant to the bleeding site and achieves hemostasis through the manual pressure of the surgeon's hand on the sponge against the bleeding site. If bleeding is controlled for the 2 to 3 min required for the polymerization of the fibrin sealant by using this technique, effective hemostasis will be achieved. Obviously, if bleeding continues, in spite of the pressure on the sponge, effective hemostasis will likely not be achieved after 2 to 3 min of pressure. This carrier sponge method of fibrin sealant delivery is the most effective means of using this agent to control active bleeding and can be a very valuable adjunct to cardiac surgical procedures. It must be remembered that the best treatment for an actively bleeding blood vessel is the placement of an appropriate suture by using excellent surgical technique. However, if the bleeding is not suturable, fibrin sealant may be an excellent adjunctive method for achieving hemostasis.

A particular note of caution should be provided to the cardiac surgeon using fibrin sealant or any other thrombin-containing tissue hemostat or sealant. The use of heparin during cardiopulmonary bypass and vascular surgical procedures to avoid thrombosis is a mainstay of modern surgery. The last step in the clotting cascade, where heparin has its effect, is at the level of thrombin. Thus, a competitive interaction of exogenous thrombin and heparin can occur that may result in a reversal of the heparin effect, causing thrombosis. This can be particularly

significant for a patient on cardiopulmonary bypass and could potentially result in thrombosis of the cardiopulmonary bypass pump. Patients in whom fibrin sealant is being used while on cardiopulmonary bypass should have the residual fibrin sealant components removed from the operative field by using the discard sucker. Do not use the pump sucker to clear these components; in fact, pump suckers should be removed from the operative field when fibrin sealant is being used. A second note of caution regards the thrombotic effect of thrombin in fibrin sealant on microvascular anastomoses. This was recently studied and it was suggested that thrombin concentrations ≤ 500 IU/mL as are currently available in the FDA-licensed product do not have significant deleterious effects on microvascular anastomoses.¹⁰ Thrombin concentrations of > 500 IU/mL may have a negative impact on these anastomoses.

Additional newer uses of fibrin sealant include its use in minimally invasive procedures, atrial and ventricular septal defect closure, free wall rupture, and adhesion prevention. Fibrin sealant has been used to assist with newly developed microvascular anastomoses that can be performed by using intraluminal stents, for bioengineering of vascular grafts, and for the slow-release distribution of medications and other therapeutic factors.¹¹

With respect to future capabilities, fibrin sealant is a versatile system capable of delivery of drugs and biologics.¹² Fibrin sealant can be used as a slow-release mechanism for a drug delivery of antibiotics, growth factors, and chemotherapeutic agents. Recent evidence suggests that fibrin sealant containing appropriate antibiotics may be effective at treating bacterial endocarditis and for sterilizing infected graft sites. A final note with respect to the capabilities of fibrin sealant beyond hemostasis and sealing of tissues includes its ability to provide lymphostasis. This is particularly remarkable in sites where extensive dissection is performed and seroma formation is likely. The literature also includes references to using fibrin sealant as a means of dealing with thoracic duct injuries occurring at the time of cardiac surgery in order to achieve lymphostasis.

Cyanoacrylate

2-Octyl-cyanoacrylate (Dermabond, Ethicon Inc., Somerville, NJ) was approved in 1998 as a new mechanism of closing skin incisions. Approved for topical skin application only and not indicated for internal use, this agent can be used for the closure of skin wounds that are not under extreme tension. It is the only commercially available tissue adhesive approved by the FDA for skin closure. The agent is helpful in closing traumatic skin lacerations, as well as for closure of skin incisions at the time of elective surgical procedures.^{13–15} The skin edges are held in apposition while the cyanoacrylate is applied in layers along the entire length of the wound for a width of approximately 1 to 2 cm. The manufacturer recom-

mends repeated applications, separated by 30 s each, for a total of three layers of the material. The tissue adhesive works by polymerizing as it comes in contact with hydroxyl ions. A spontaneous release of heat occurs as the 2-octyl-cyanoacrylate forms, causing a sensation of warmth in the patient. The cyanoacrylate itself is extremely strong with internal bonding strength that exceeds the strength of the skin itself. The agent remains adherent to the skin for approximately 7 to 10 days during the period of wound healing, and is then spontaneously shed from the wound as the superficial layers of skin exfoliate. Thus, the adhesive is removed as the superficial layers of the skin are sloughed. The recommendation against using this material in high tension areas is not because of weakness in the adhesive itself, but rather because of the weakness of the superficial layers of the skin to which the adhesive bonds. Consequently, it is not recommended for use across joint surfaces or other extremely high-tension areas. The cyanoacrylate can be removed if necessary by application of petroleum-based products, which reduces the adherence strength of the agent and results in its easier removal.

Cyanoacrylate is marketed by the manufacturer in crushable 0.5 mL ampules (Figure 1-5) that cost approximately \$25 (US). Depending on the length of the incision, it may take multiple ampules to cover a wound sufficiently. The ampules can be stored at room temperature. Application of the material to the skin surface is facilitated by the single-dose delivery system, which, after crushing, allows the liquid cyanoacrylate to be effectively delivered to the skin surface.

Because of its high strength characteristics, easy storage, and inexpensive costs, the internal use of cyanoacrylate is extremely desirable. However, cyanoacrylate is presently approved for external use only. Significant carcinogenicity in animals and humans treated internally with cyanoacrylates has been reported.¹⁶ Until a safer form of this agent is developed, its use in internal settings is not recommended.



FIGURE 1-5. Ampule applicator of cyanoacrylate used for delivery of tissue adhesive.

With respect to the specific use of this agent, as with any wound closure technique, meticulous technique and thorough cleansing of the wound prior to closure is important. Accurate approximation of the skin edges by using forceps or fingers with eversion of the skin edges is recommended. For the ideal cosmetic result, a subcutaneous layer of sutures should be placed prior to closing the skin with cyanoacrylate. This minimizes contraction of the subcutaneous tissues that may cause wound dimpling and accentuate the negative appearance of a scar.

This agent can be an effective adjunct to routine methods of skin closure. For example, after closure of saphenous vein harvest-site incisions by using subcutaneous and subcuticular sutures, cyanoacrylate can be an adjunctive technique for sealing the skin. It functions as an effective barrier against the leakage of serous or lymphatic drainage from the leg wound sites and may reduce the risk of infection associated with these weeping incisions. Particularly in obese patients who require extensive dissection to harvest saphenous veins, this adjunctive technique may be effective in reducing wound drainage and potentially eliminating saphenous vein harvest-site infections.

With respect to new developments in the future of cyanoacrylate tissue adhesives, it is possible that less carcinogenic forms of this agent with minimal inflammatory responses in tissues can be developed. Efforts to develop cyanoacrylates with enhanced biodegradability may result in materials that can be characterized by great strength and can be used internally with a satisfactory safety profile.

Collagens and Thrombins

Active bleeding can be controlled effectively by using bovine thrombin and collagen because it is delivered as a gel rather than a liquid.^{17,18} This product (FloSeal, Fusion Medical Technologies, Mountain View, California) is approved by the FDA as a hemostatic device that is effective at controlling bleeding during a wide variety of surgical procedures, including cardiac and vascular surgery.^{17,18} The thicker consistency of this material, which simulates toothpaste (Figure 1-6), enhances its ability to remain at a site of active bleeding without being washed away. The manufacturer recommends the use of manual pressure for a period of 2 to 3 min following application of the agent in order to achieve hemostasis. A moist sponge will not stick to the device as the material sticks only to objects covered with blood. Thus, this agent maximizes effectiveness by remaining at the active bleeding site, allowing manual pressure application, and combining the commercial product's bovine collagen and thrombin with the patient's own blood fibrinogen to form a gel patch that can swell by as much as 20%. Repetitive applications of the bovine collagen and thrombin gel, if bleeding persists, are possible and are highly effective at controlling active bleeding. The swelling of the agent itself adds to the tamponade effect of the materials, but at present it is not



FIGURE 1-6. Application of bovine collagen and thrombin to site of bleeding at aortic suture line.

recommended for use in urologic or ophthalmologic procedures. This device costs approximately \$140 (US) for a 5 mL kit that can be stored at room temperature. To prepare for application of the gel, bovine collagen and thrombin are mixed in a process that requires less than 5 min of preparation time in the operating room suite. With widespread approval for a variety of hemostatic indications, the agent is widely used in cardiac, vascular, spinal, and head and neck surgery to achieve rapid hemostasis at a site of active bleeding.

As mentioned earlier, the major risk factor associated with products containing bovine thrombin is related to antibody formation.^{6,7} Impurities in bovine thrombin can potentially stimulate an immune response in human beings, resulting in the formation of antibodies that may cross-react with the body's own clotting factors. This antibody formation may cause inactivation of necessary human clotting proteins, causing a coagulopathy in the patient. Previous exposure may increase the likelihood of antibody responses and may lead to adverse outcomes.⁷ Efforts have and are being made by the manufacturers of bovine thrombin to enhance the purification of this material in order to reduce the risk of antibody formation. Coagulopathy, which is reported rarely with the use of bovine thrombin, appears to occur when the patient develops antibodies against bovine thrombin and factor V, which may cross-react with human clotting factors. Surgeons should consider this potential complication when using this agent, particularly in a reexposure setting. The gelatin matrix is biodegraded at the site of application over a period of approximately 6 to 8 weeks.

The unique value of this agent is its ability to be particularly effective at the site of active bleeding. Designed as a thicker material capable of being combined with pressure and with inherent swelling capacity, this agent is highly effective for active bleeding. However, as a sealant for use prior to the development of active bleeding, this agent is ineffective. The material requires the interaction with blood containing fibrinogen in order to provide

hemostatic effectiveness; thus it should be used in settings where active bleeding is occurring and not used as a sealant prior to the development of bleeding. It would not be effective at sealing a vascular anastomosis that was not pressurized and still under the application of vascular clamps. In this setting, without blood, the agent would not be activated. However, after removal of the vascular clamps, with the development of active bleeding from the anastomosis, this agent would be indicated and is useful. The manufacturer recommends a period of 2 min of pressure to maximize the hemostatic effect.

Thrombin, Collagen, and Plasma

This system consists of topical bovine thrombin and collagen, which can be combined with plasma obtained from the patient to form a hemostatic agent. The patient's own blood is fractionated into plasma and red cells by using a small tabletop centrifuge. The plasma can then be combined with topical bovine thrombin and collagen to form a fibrin sealant plus collagen (CoStasis, Cohesion Technologies, Palo Alto, California). The patient's own plasma is employed in this system and is combined with thrombin and collagen to produce a form of fibrin sealant based on the patient's own plasma fibrinogen enhanced with collagen. This material is prepared in the operating room at the time of the surgical procedure and was approved by the FDA in June 2000 as a device to stop active bleeding at the time of general, hepatic, and cardiovascular surgical operations.^{19,20} A small tabletop centrifuge permits the patient's plasma to be separated from red cells. This plasma fraction is obtained in a syringe as a source of the patient's own fibrinogen and platelets. It can be prepared in advance of the patient's surgery, saving valuable operating room time. A second prefilled syringe containing thrombin and collagen is then used in the operating room at the time of surgical need. A dual syringe applicator is used for mixing of the thrombin and collagen component with the fibrinogen component. The system produces a sprayable collagen-based material to enhance delivery options. The resultant fibrin mixed with collagen is an effective hemostatic agent, which is biodegraded in the body in a period of 8 weeks. The concentration of fibrinogen in this material does not equal that of commercial fibrin sealant, but the effectiveness of this resultant fibrin is augmented by its combination with collagen. A variety of kit sizes are available for this product, and prefilled collagen and thrombin syringes can be kept in a refrigerator for periods of up to 24 months. Because this product contains topical bovine thrombin, the caution suggested in earlier sections of this chapter with respect to the development of coagulopathy applies to this agent as well.

Platelet Gels

The perfusionist familiar with rapid transfusion, hemofiltration, or other blood cell saving devices is capable

of preparing platelet gels at the time of cardiac surgical operations.^{21,22} The disposables required are frequently provided by the manufacturers of cell washing equipment or cardiopulmonary bypass circuits (Sorin, Haemonetics, Medtronic, Cobe). A platelet gel consisting of fibrinogen, platelets, and white cells can be prepared from the patient's own blood by using technology (Harvest Technologies Corporation, Plymouth, Massachusetts) to maximize the yields of platelets. This gel may enhance bone and tissue healing. When the concentrated platelets, white cells, and fibrinogen-rich plasma are mixed with commercially available bovine thrombin, a platelet gel clot is formed. The fibrin that is formed is enhanced by platelets and white cells. It has been suggested that the additional growth factors and other substances in this environment may contribute to improved wound healing and reparative processes. Although not as highly concentrated as commercial fibrin sealant, it has been suggested that platelet gels may be more cost-effective. No randomized controlled study presently exists to support this contention. This product is not approved by the FDA for use in cardiac surgery.

Polyethylene Glycol Polymers

Polyethylene glycol (PEG) polymers represent a new hydrogel family of tissue adhesives that are capable of bonding effectively to human tissues. The first such agent approved in the United States by the FDA is a PEG polymer capable of achieving pneumatosis at the time of lung resection. This agent (FocalSeal-L, Focal Incorporated, Lexington, Massachusetts) was approved in May 2000 for closure of fissural pleural air leak incurred in elective pulmonary resection. This PEG polymer is a light-activated synthetic device that is capable of reducing air leaks following pulmonary operations. This strong adhesive is commercially distributed by the manufacturer in the form of a two-component material. Tissues are first treated with a primer which prepares the tissue for the application of the PEG polymer. The application process consists of the initial brush application of the primer to the surface of the lung. This is followed by the application of the PEG polymer to the lung parenchyma. The PEG polymer is carefully worked into the lung tissues by using a second brush applicator separate from that used to apply the primer. After application of the PEG polymer, a light source (470 to 520 nm), consisting of a resterilizable wand connected to a light source box, is used to activate the PEG polymer and to form the final tissue adhesive. The entire process takes approximately 10 to 15 min and does require careful technique.

The primer and polymer require storage at -20° and 4° C, respectively. Application of the PEG polymer costs approximately \$55 (US) per milliliter. The light source and wand needed for this system must be purchased separately.

The adhesive itself is very strong and has excellent adherence characteristics on the surface of the lung parenchyma.²³ In the multicenter trial used to obtain approval for this agent in patients undergoing lung resection, the polymer-treated patients were three times less likely to develop postoperative air leaks than were those patients who were treated with standard therapy alone.²⁴ This material remains present for as long as 6 months after application because it is biodegraded slowly. Approximately 36% is thought to remain at 6 months. Because this agent is relatively new, no long-term safety data are available. Physicians who are using this agent are encouraged to continue to exercise vigilance with respect to infection rates and potential long-term effects. The use of this agent in cardiac surgical applications has not been thoroughly explored or approved.

A second PEG polymer device (CoSeal, Cohesion Technologies, Palo Alto, California) was approved by the FDA in December 2001. This agent consists of two distinct PEG polymers that are combined to form a hydrogel sealant. This material is approved for use in sealing arterial and/or venous anastomoses during vascular reconstruction procedures. The synthetic device does not require light activation but cross-links to itself and to the underlying tissues on application. The agent is applied as a sprayable liquid through a dual syringe delivery system, and polymerizes within seconds of application. The agent is fully matured within approximately 60 s.

This PEG polymer is available in 2 and 4 mL single-patient use kits. The material is stored refrigerated at 2° to 8°C, and can be prepared within minutes in the operating room by using the delivery system kit, which is supplied with the product. Preparation involves mixing the two PEG polymers (which are supplied as a powder) with a liquid buffer solution, using a transferring syringe. The two then-ready PEG polymers are combined in the handheld device for application to the tissues. The material is resorbed within weeks of application.

Albumin Glutaraldehyde

Albumin cross-linked with glutaraldehyde received approval as a sealing agent in vascular operations on large vessels in December 2001. Prior to FDA approval, it had been used under a human device exemption for the treatment of patients with aortic dissection. The products consist of bovine albumin, which is cross-linked by glutaraldehyde to form a strong adhesive bond. The manufacturer supplies the material (BioGlue, CryoLife, Inc., Kennesaw, Georgia) as a gun (Figure 1-7) containing both albumin and glutaraldehyde, which are effectively mixed at the time of application. The adhesive solidifies within a period of 20 to 30 s. Maximum strength is achieved within a period of 2 to 3 min. In its initial use as a method of enhancing the strength of the aorta at the time of aortic dissection, albumin cross-linked with glutaraldehyde was extremely effective at sealing vascular



FIGURE 1-7. Applicator gun used to apply albumin cross-linked with glutaraldehyde to vascular tissues.

anastomoses and achieving hemostasis.^{25,26} The agent was carefully applied between the dissected layers of the aorta in order to reapproximate the intima and adventitia. In the process of aortic dissection, the media is destroyed and the thin adventitia and intima layers become very fragile and difficult to suture. The treatment of type A aortic dissection requires replacement of the ascending aorta with a tube graft in order to avoid hemorrhage, cardiac tamponade, and death. The ability to suture the tube graft to dissected aortic tissue can be significantly improved by the use of albumin cross-linked with glutaraldehyde. In addition to using the adhesive to help obliterate the false lumen space between the adventitia and intima, the glue can be used to seal the anastomoses themselves. Not only does the material result in a strengthening of the friable layers of the aorta, but it also can be used to prevent leakage of blood from the anastomotic suture line. Thus, this material is capable of strengthening the fragile aortic tissues and of sealing the anastomosis. Initial studies of perioperative morbidity and mortality suggested significant benefit from the use of albumin cross-linked with glutaraldehyde.

This material comes in kits containing albumin and glutaraldehyde. The cost of the kit is approximately \$450 (US). The material is stored at room temperature. Preparation requires assembly of the applicator gun, which can be completed in a period of several minutes by the scrub nurse in the operating room.

Cautions with respect to this agent include concerns over the long-term effects of this material on aortic tissues and the healing of vascular anastomoses. The literature cites some difficulties with an earlier glutaraldehyde, resorcinol, and formaldehyde (GRF) adhesive otherwise known as “French glue.” It has been suggested that this agent could be associated with long-term complications, including tissue degradation, which may lead to recurrent aortic root dissection, aortic insufficiency, and false aneurysm formation.²⁷ Long-term studies with respect to this newer form of albumin and glutaraldehyde, which

does not use formaldehyde in this setting, are pending, but concerns about similar problems exist.²⁸ For the present, caution needs to be used to avoid overdose of glutaraldehyde, which can result in tissue necrosis. The effects of glutaraldehyde could potentially reduce healing at the site of a vascular anastomosis. Thus, this agent should be used sparingly and with care. It is best to use an extremely thin layer and to guard against the application or dislodgement of the adhesive into a critical area such as a nerve or the ostium of a coronary artery. Potentially fatal myocardial infarction or later stenosis of the coronary artery due to inadvertent placement of this agent should be avoided. In addition, the use of this material in a circumferential fashion has effects similar to a running suture on vascular anastomoses that may be subject to later growth. Thus, the use of albumin cross-linked with glutaraldehyde in a pediatric population may result in a lack of growth of the anastomosis. Just as interrupted or absorbable sutures are more appropriate in the pediatric population in order to allow for later tissue growth, avoidance of the circumferential application of albumin cross-linked with glutaraldehyde can also help to facilitate later vascular anastomotic growth and enlargement.

Personal Experience

This section reviews the best uses of surgical tissue hemostats and sealants in cardiac surgery with respect to the author's personal experience. An attempt is made to differentiate between the agents to suggest the clinical situation in which each is best deployed. In the current cost-cutting environment, many operating rooms attempt to choose between the available agents, as opposed to stocking all of the materials, in order to save shelf space and to reduce expenses. In the author's experience, multiple agents are required for the effective care of cardiac surgical patients. Limiting the armamentarium to one or two agents may not allow for effective patient care. Multiple agents with different capabilities, just as multiple types of sutures, may be required for the best management of the patient.

Fibrin sealant is best used as a hemostatic sealant that is applied prior to significant active bleeding. Thus, it can be effectively used to control slow capillary bleeding from pericardial and epicardial adhesions at the time of reoperative cardiac surgery. This is particularly true when the agent is sprayed onto the operative field, allowing for a thoroughly mixed and thin layer of the hemostatic agent to be applied to the appropriate surfaces. Similarly, the agent can be applied to vascular anastomoses prior to removal of vascular clamps or prior to removal of the aortic cross-clamp. This allows the adhesive to polymerize and reach maximum strength prior to resumption of full intra-arterial pressure. If fibrin sealant is required at an active bleeding site, it is best to deliver it with a carrier sponge of cellulose or collagen. The carrier sponge allows the liquid fibrin sealant to be delivered to the active bleed-

ing site without washing away and also allows pressure to be applied to facilitate hemostasis.

The use of plasma and collagen with bovine thrombin or platelet gels with bovine thrombin is similar to that of fibrin sealant. These agents each have their own specific advantages and disadvantages with respect to strength, cost, and additional levels of effectiveness. These agents, however, remain members of the fibrin sealant family because they depend on the interaction of fibrinogen and thrombin to form fibrin as a means of achieving hemostasis and sealing. At present each requires the use of bovine thrombin.

Cyanoacrylate is an extremely strong tissue adhesive that can be used to close the skin. Its strength is limited only by the strength of the superficial layers of epithelium as the glue strength exceeds that of the superficial layers of the dermis. This extremely strong and relatively inexpensive material is not approved for internal use because of the risks of carcinogenicity. In the hands of the cardiovascular surgeon, this agent may be valuable for use as an adjunctive means of sealing the skin after routine suture closure of the skin has been achieved. In this setting, the adhesive can be used to prevent the leakage of serous lymphatic fluids from a wound. This use may be able to reduce incidence of wound infection and prolonged hospitalization that is sometimes associated with wound drainage at the site of a saphenous vein harvest.

Bovine collagen and thrombin gel matrix is a potent hemostatic agent for the treatment of active bleeding. Because it is applied as a toothpaste-like material rather than a liquid, it is not easily washed away from the site of active bleeding. In addition, direct pressure with a moist sponge can be applied to the gel without the danger of the gel sticking to the sponge. Rather, the gel will only stick to the bleeding site and not to the moist sponge. Thus, there are two advantages to this agent at the site of active bleeding. It is less likely to be washed away and it can be easily combined with manual pressure. In addition, the material can be reapplied repeatedly if necessary in order to completely achieve hemostasis. This agent obviously would not be effective at sealing anastomosis prior to active bleeding. It would not be indicated in this setting as it requires combination with fibrinogen found in blood for effectiveness.

PEG polymers can be used effectively to seal lung air leaks. There are situations in cardiac surgery, particularly in reoperative procedures, where air leaks in the surface of the lung develop. Elimination of these air leaks may be important to minimize the risk of wound infection and later complications. In this setting, the cardiac surgeon could employ these PEG polymers to control pulmonary parenchymal air leaks. The process of applying these agents is somewhat time-consuming at present. The new PEG polymer system recently approved for vascular anastomoses has not yet been used clinically in sufficient

numbers of the author's patients to allow the author to provide additional comments.

Albumin cross-linked with glutaraldehyde is an extremely powerful and strong tissue adhesive. It is capable of strengthening tissues as well as achieving strong tissue opposition. In addition, it can seal anastomoses. Although extremely strong, this agent needs to be used sparingly in order to avoid potentially toxic effects of glutaraldehyde on human tissue. In addition, its use at vascular anastomoses should be carefully considered because glutaraldehyde may reduce healing by retarding bridging of endothelial cells at the anastomotic site. The agent should be used carefully in anastomoses subject to further growth as circumferential application may, like running suture, restrict anastomotic growth and enlargement.

Future

The agents reviewed in this chapter represent the initial phases of development of new hemostatic tissue sealants and adhesives. Clinical trials and development work continue with a variety of agents. These materials, as well as those currently on the market, are valuable new additions to the surgical armamentarium.

A variety of additional off-label capabilities may be combined with those currently described, including drug delivery and tissue engineering. Cardiac surgeons have traditionally been on the forefront of new technology and development. At best, these new materials will be employed successfully by cardiac surgeons. Further new uses and capabilities may be developed. As with all new interventions, careful clinical observation and follow-up will be required to determine the best, safest, and most cost-effective uses of these modalities.

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