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The Use of a Novel Tissue Sealant as a Hemostatic Adjunct in Cardiac Surgery

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ABSTRACT

Background: In spite of advances in the management of bleeding associated with cardiac surgery, hemorrhage remains a troublesome problem, particularly in complex cases and high risk patients. In minimally invasive cardiac surgery, limited exposure and tight quarters may make accurate suturing difficult, and increase the risk of surgical bleeding. A surgical sealant that effectively prevents suture line bleeding would be a valuable resource for cardiac surgeons and might help to facilitate minimal access cases.

Methods: We undertook acute canine studies with a new polyethylene glycol–based tissue sealant (FocalSeal™, Focal, Inc., Lexington, MA) to determine its effectiveness in controlling bleeding from graduated needle punctures sites in the arteries of heparinized animals. For chronic canine studies, the sealant was applied to the suture line of a left internal mammary artery (LIMA) to left anterior descending (LAD) anastomoses. The anastomoses were then evaluated for patency and tissue reaction after a three-month recovery period.

Results: The sealant prevented bleeding from arterial puncture wounds up to 2.5 mm in diameter. Three months following the application of sealant to coronary anastomoses, no adverse tissue reaction was found on histologic examination. All anastomoses treated with the sealant remained patent.

Conclusions: When applied as a hemostatic adjunct to sutures at a coronary anastomosis, the sealant appears to be an effective means of preventing bleeding without adverse tissue reaction or scarring.

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INTRODUCTION

Various concoctions have been in use throughout the history of surgery to close wounds, control bleeding, and prevent infection. The Egyptians used fresh meat as a hemostatic agent, as well as poultices of wax, grease, and barley [Sigerist 1951]. A formulation used by Native Americans, consisted of hot sand, eagle down, and the scrapings from the inside of animal hides [Stone 1932]. During the Hundred Year War, the famous battlefield surgeon, Amroise Paré used a mix of rose oil and turpentine when the traditional boiling oil was in short supply [Kocher 1997]. He found that the wounds healed better with this practice and that the patients course was remarkably improved.

A biological sealant was first described in cardiovascular operations by Spangler in 1976 [Spangler 1976]. Since then, surface application of collagen materials (e.g., Avitene™, C.R. Bard, Inc., Murray Hill, NJ; Surgicel™, Johnson & Johnson Medical, Inc., Arlington, TX; Gelfoam, Upjohn Company, Kalamazoo, Michigan), with and without thrombin impregnation and mechanical compression, has proven modestly effective in many instances [Rousou 1984]. More recently, biological adhesives consisting of fibrin-based sealants or cryoprecipitate have been shown to decrease bleeding complications [Basu 1995, Rousou 1989, Matthew 1990]. Fibrin sealant has evolved from homemade versions of biologic "glue" created at the operating table from a mixture of cryoprecipitate, thrombin, and calcium. It is now a commercial product, FDA approved in the United States, and marketed by several vendors [Spotnitz 1995, Kjaergard 1996, Rousou 1989]. Gelatin resorcinol glue ("the French glue") has been used for many years in Europe. Composed of gelatin, resorcinol, formaldehyde, and glutaraldhyde (GRFG), "the French glue" has been used primarily to reinforce the fragile tissues of acute aortic dissections. Clinically, fibrin-based sealants and GRFG glue have emerged as the most commonly used sealants [Bachet 1999].

A range of tissue reactivity has been reported for both biological and synthetic surgical sealants. Flimsy subperi-

Table 1. Ideal properties for a sealant applied to an anastomosis in cardiac surgery

Ideal Sealant Properties		Ideal Anastomosis
1. Effectively prevents bleeding 2. Stops established bleeding 3. Flexible	⇨	1. Fluid tight
4. Non-toxic to tissues 5. Non-scarring	⇨	2. Atraumatic, remains patent
6. Non-antigenic 7. Not blood-product based	⇨	3. Host compatable
8. Simple, rapid preparation 9. Easy to apply 10. Sets quickly, on cue	⇨	4. Efficient surgical procedure

cardial adhesions have been observed following the use of cryoprecipitate and fibrin sealant [Basu 1995]. The GRFG glue contains the toxic agents resorcinol and glutaraldehyde, which cause an inflammatory reaction and extensive, dense adhesions [Ennker 1994, Basu 1995, Walker 1997]. Dramatic tissue necrosis has been documented with the surgical application of cryanoacrylate [Herrmann 1966, Raekallio 1964, Woodward 1964]. In cardiac surgery, it remains a concern that these adhesives, or their healing response, could cause injury, particularly to delicate valve leaflets, coronary vessels, or graft conduits.

The desired properties of a suitable surgical sealant vary with the intended use. The major application of a sealant in cardiac surgery is as a hemostatic adjunct to sutures at the site of a vascular anastomosis. The properties of an ideal sealant for cardiac surgery and their usefulness in the creation and maintenance of an ideal anastomosis are listed in Table I (◎).

FocalSeal™, an absorable polyethylene glycol–based hydrogel, has many of these properties. It has been found to be effective in European clinical trials as a sealant to prevent airleak in pulmonary resections [Ranger 1997, Macchiarini 1999] and in neurosurgery to repair dura [Alleyne 1998]. Preliminary studies in a canine model [Tanaka 1999] have indicated potential for reinforcing anastomoses in the treatment of acute aortic dissection. We hypothesized that the gel would be potentially applicable as a hemostatic agent and set out to evaluate this question in both acute and chronic laboratory studies.

MATERIALS AND METHODS

Animals were cared for in conjunction with the NIH guidelines for the care of laboratory animals. The protocol was approved by the Massachusetts General Hospital Subcommittee on Research Animal Care. Adult dogs of either gender were anesthetized through a foreleg vein with thiopental sodium 25/mg/kg. The animals were endotracheally intubated and ventilated with room air enriched with oxygen. Isofluorane was titrated (1–2%) to maintain a plane of surgical anesthesia. The femoral vein was cannulated to deliver medications. The animal was given 3000 units of heparin intravenously. An additional 1000 units of heparin were given, as needed, to maintain an Activated Clotting Time greater than 160 seconds. Both carotid and femoral arteries were surgically exposed. A series of graded puncture wounds were made in the arteries, starting with a 30-gauge needle and working upwards in diameter. After ten minutes, the control puncture wounds were either sealed or sutured to prevent exsanguination.

Prior to application of the water-based sealant, the vessels were clamped and cleared of areolar adventitial tissue. After the vessel injury was created, a few drops of an eosin-based, photo-initiating primer solution was applied and distributed with a small brush (see Movie 1 ◎). The sealant compound was then dripped onto the primer. A brush was used to mix the sealant into the primer, followed by application of more sealant. The sealant was polymerized by a 40 second application of light (480–520 nm wavelength) from a xenon source. The vessel was then unclamped, and any bleeding was recorded.

In chronic studies, the animals were anesthetized in the same manner. A 7 Fr introducer was placed into the femoral artery for subsequent angiography and attached to a pressure transducer to monitor arterial pressure. The EKG was also monitored by skin leads. A left anterior thoracotomy incision was made in the fourth intercostal space. The internal mammary artery (IMA) was mobilized with electrocautery under direct vision. The animal was heparinized with 3000 units intravenously. Through heparin titration, the Activated Clotting Time (ACT) was prolonged for greater than 160 seconds. The LAD was encircled with Silastic tapes. Preconditioning was performed with two, three-minute LAD occlusions. A five-minute interval was allowed to pass between occlusion periods.

The LAD was then occluded and the IMA anastomosed to a 2.0–3.0-mm arteriotomy, using running 7-0 prolene sutures (average suturing time: 14.5 minutes, range: 5–20 minutes). A 50-mg Xylocaine bolus, and bretylium 125 mg was given prior to and immediately after the anastomosis. The LAD was unclamped gradually. This technique was used to prevent abrupt complete reperfusion, which tends to result in malignant ventricular ectopy. This could be intractable and fatal in some animals. Two different sealant formulations, FocalSeal-L sealant or FocalSeal-S was then applied to the area of the anastomosis as described above. FocalSeal-L is a long-term sealant designed to slowly resorb over the course of more than one year. FocalSeal-S is a faster degrading formulation that resorbs within 6 months.

The chest was then closed. Air and fluid was aspirated with a 20Fr. catheter in the pleural space. A LIMA angiogram was performed. If the anastomosis could not be demonstrated to be patent, the animal was sacrificed (1 control animal). The femoral cut-down was then closed. All animals were allowed to recover from anesthesia. Post-

Table 2. Microscopic pathology of LIMA-to-LAD anastomosis sites, 3 months following application of FocalSeal™ sealant

	Patent Grafts (3 months)	Acute Inflammation (Scale 0–4)	Chronic Inflammation (Scale 0–4)	Fibrosis (Scale 0–4)	FBGC (Scale 0–4)	Foamy Histiocytes (Scale 0–4)
Control (n = 5)	2/5 (40%)	0.4	1.6	3.4	1.6	1.5
Focal Seal-S (n = 5)	5/5 (100%)	0	1.3	3.6	2.0	2.5
Focal Seal-L (n = 5)	5/5 (100%)	0.1	1.7	2.7	1.8	1.8

FBGC = foreign body giant cells.

operative pain was treated for four days with buprenorphine, 0.3 mg IM twice daily, and/or fentanyl, 5-mg patches. After several days of recovery in the animal facilities, the dogs were sent to a farm where they were boarded for three months.

At the time of completion of the study, the animals were anesthetized, as above. A repeat angiogram was performed. The chest was opened after euthanasia with pentobarbitol 100 mg/kg.

Gross appearance was recorded with a video camera and still photos. The area of the IMA to LAD anastomosis was fixed in formalin. The specimens were processed for routine hematoxylin and eosin and trichrome staining. Slides were reviewed by a cardiac pathologist (HTA) who was blinded to the experimental status of the animal. The degree of acute and chronic inflammation and the presence of fibrosis as well as the number of foamy histiocytes, or foreign body giant cells, were scored on a scale of 0 to 4+.

RESULTS

As applied in these studies, the FocalSeal sealants were clear, flexible and typically several millimeters thick. In the acute studies, the sealant provided hemostasis in carotid artery puncture sites up to 2.8 mm diameter at 190 mm Hg of pressure (see Movie 1 ◎). The control animals bled incessantly from all needle puncture injuries to the femoral artery and carotid artery larger than 23 gauge. A 1-cm incision in the carotid artery, closed with two sutures and no sealant, bled profusely upon brief release of the proximal clamp. Sealant, applied at the incision site, provided complete hemostasis after removal of all clamps (see Movie 2 ◎). Through heparin titration, the Activated Clotting Time (ACT) averaged 213 seconds throughout the surgery. The total clamp time for application of the sealant averaged 2 minutes. The application of the sealant in acute studies is demonstrated in Movie 1 (◎).

In chronic studies, there was no difference in the gross appearance between the control animals and those receiving sealant as an adjunct to a sutured LIMA-LAD anastomosis. No differences were measured in adhesion formation or wound healing. Table 2 (◎)shows the results of the microscopic pathology. Four of six control anastomoses are patent and ten of ten anastomoses, with sealant, were patent. The histology of the specimens is shown in Figure 1 (◎).

DISCUSSION

Excessive mediastinal bleeding is a significant complication of cardiac operations. Bleeding after cardiopulmonary bypass occurs in 3% to 14% of cases [Czer 1989]. It is associated with increased postoperative mortality and increased risk of cardiac failure, dyrrhythmias, and infections [Verska 1972, Michelson 1980]. When mediastinal re-exploration for hemostasis is indicated, the most frequent anatomic sources are the vascular anastomoses, branches of vein grafts, cannulation sites, and sternum [Czer 1989]. Postoperative bleeding may either be surgical (due to failure to adequately control focal bleeding sites) or diffuse (caused by coagulopathy). An effective and non-toxic surgical sealant could potentially assist in controlling either type of bleeding.

The sealant employed in this study is a macromer consisting of a water-soluble polyethylene glycol molecule, a biodegradable polylactic acid, trimethylene carbonate, and a polymerizable acrylic ester [Sawhney 1993]. An eosin-based primer penetrates the tissue, crosslinks with itself, and provides a mechanical interlink to the sealant compound [Sawhney 1993, Hubbell 1994, Pathak 1994]. The primer and sealant work in unison; the primer provides tissue penetration and tissue adherence and the sealant contributes desirable elastic properties. The primer also helps initiate the photo-polymerization of the sealant's acrylic ester group upon exposure to a blue-green xenon light source [Alleyene 1999].

The sealant does not form covalent bonds with tissues [Oliva 1998]. The mechanism of hemostasis of the sealant is as a physical barrier [West 1996]. The function of the sealant as a hemostatic agent depends upon its ability to adhere to tissues, crosslink with itself, and form a bridge spanning gaps between tissues. Movie 3 (◎) demonstrates this principle in a dramatic fashion. An unsutured 5 mm punch hole in the canine carotid artery is rendered water tight with a bridge of translucent sealant. Pulsatile blood is seen beneath the translucent polymer. Unlike suture materials and gelatin resorcinol adhesives, the sealant does not bring tissues into approximation or bind tissues tightly together. Once polymerized, the tensile strength of the sealant is greater than fibrin, but less than GRFG [Oliva 1998].

Preclinical in vitro studies indicate that burst strength in 3-mm punch defects over 10 minutes is 12 times greater for FocalSeal-L (378 ± 98 mm Hg) than for fibrin glue (24 ± 17 mm Hg). In our study, the hydrogel forms a flexible, resilient seal, providing hemostasis while spanning puncture

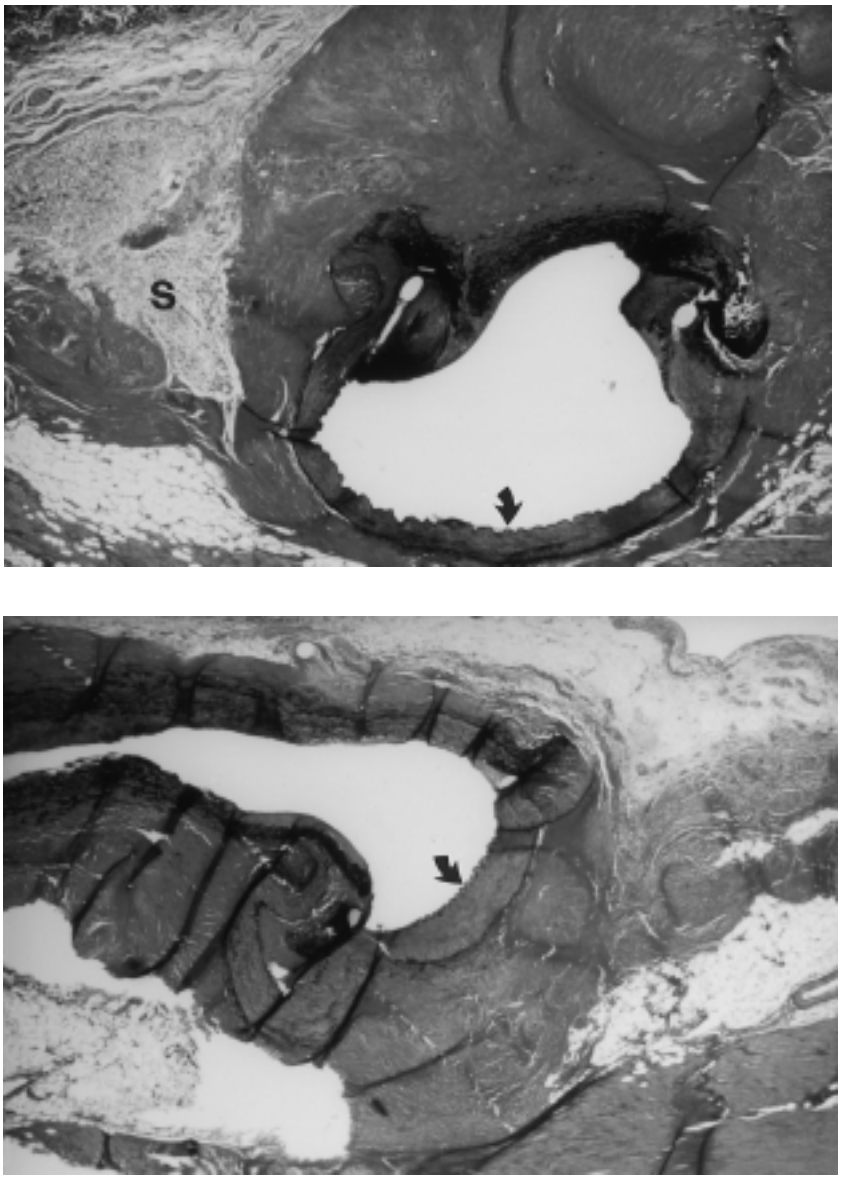

Figure 1. Microscopic pathology of LIMA-to-LAD anastomosis, three months following application of sealant. Low power photomicrograph of the anastomosis of the LAD (arrows) and the LIMA in an animal treated with sealant (A) and one without (B). Fibrosis is seen in both sections, with collagen staining red; the sealant-treated vessel shows a triangular area of collections of macrophages containing the sealant (S). (Verhoff's elastic stain; original magnification 25x).

holes up to 2.8 mm at systolic pressures of up to 190 mm Hg (see Movie 1 ◉). This supports the sealant's potential usefulness to prevent suture line bleeding caused by needle holes or other small gaps between tissues at an anastomosis site.

Synthetic adhesives do not promote the coagulation cascade in the same way that biological glues do [Guilmet 1977]. Therefore, most synthetic glues must be applied to an absolutely dry surface [Basu 1995]. In comparison, FocalSeal® adheres with high affinity to both moist and dry surfaces [Oliva 1998]. Because it forms a physical barrier and takes time to set, the sealant must be applied while the vessel is clamped or bleeding is controlled in some way, as the sealant does not retard active bleeding.

Unlike biological adhesives that require isolation and purification, such as fibrin-based glues, the sealant can be manufactured to a rigorous consistency. Also, because fibrin sealant and cryoprecipitate contains foreign proteins and are blood product based, they carry an inherent risk of immunological reaction with repeat exposure [Cmolic 1993]. Transfusion-acquired viral illnesses are also a danger, although this risk is very small [Radosevich 1997]. In comparison, the sealant under investigation is synthetic, and therefore, not likely to stimulate an antigenic host response or carry blood-born virus contamination.

It has been observed that the sealant swells over a period 24 hours after being polymerized due to water absorp-

tion. Depending on the mechanical effect this has, a sealed vessel might either be stretched opened by this process or compressed. In vitro studies have indicated that this swelling does not result in vessel compression. Our chronic canine study of the sealant circumferentially applied to a LIMA-to-LAD anastomosis indicated 100% angiographic patency after a 3-month period. We have initiated studies to further evaluate the effects of the hydrogel swelling on blood vessel diameter in vivo.

After approximately 10 days following application, cryoprecipitate is still present in tissues (resorption time: 4 weeks), and fibrin sealant is almost completely reabsorbed [Basu 1995]. The resorption rate of GRFG may be as long as 6 months [Basu 1995].

The half-life of the hydrogel matrix can be altered by adjusting the sealant formulation. It is possible to adjust the formulation and the hydrolysis rate for the application at hand. Our current study investigated two formulations of the sealant, designated FocalSeal®-S and FocalSeal®-L, that hydrolyze within six months and over more than one year, respectively. In a prior study, the hydrogel was reformulated to act as an adhesion barrier, followed by resorption over a five-day period [Sawhney 1994, West 1996]. Further potential uses for this polymer include specific formulations that may prevent the adhesions between cardiac, pericardium, sternum, and other mediastinal tissues reducing the technical difficulty of cardiac re-operations.

The use of polymers and hydrogels as a controlled repository of medications or agents has been explored by others [Sawhney 1992, Chowdhury 1996, McNeill 1996]. Another potential future use of the sealant is to release substances to act locally at blood vessels or anastomosis. For example, potential options include substances that could inhibit thrombin or platelet deposition, prevent adhesions, stimulate local vasodilation, or release vascular growth factors or antibiotics into particular anatomical locations.

In conclusion, we found that a synthetic, absorbable polyethylene glycol–based hydrogel proved to be an effective hemostatic adjunct to sutures at vascular anastomotic sites without evidence of early or late tissue toxicity. Regardless of the other potential applications for this interesting new sealant, it appears very promising as a mechanical barrier to bleeding and hopefully will become available for clinical use in the near future.

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Disclosure

David Torchiana, MD, is a scientific advisor for the Genzyme Corporation.

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