Next-Generation HydroGel Films as Tissue Sealants and Adhesion Barriers

Steven L. Bennett, Ph.D.,* David A. Melanson, B.S.,* David F. Torchiana, M.D.,† David M. Wiseman, Ph.D., and Amarpreet S. Sawhney, Ph.D.*

**Confluent Surgical, Inc., Waltham, Massachesetts †Harvard Medical School, Massachusetts General Hospital, Boston, Massachusetts*

ABSTRACT ***Background:*** **The development of conveniently sprayed, tissue-adherent, inert hydrogel films has made possible the creation of novel products that can serve a dual function, as a surgical sealant to achieve immediate hemostasis, and as a barrier to prevent adhesion formation over time.** ***Methods:*** **A sprayable, in situ formed absorbable hydrogel film was evaluated as a tissue sealant in a heparinized canine carotid artery graft model. PTFE grafts with leaking end-to-side anastomoses were treated with the synthetic sealant, and hemostasis was evaluated upon restoration of blood flow. Also, the hydrogel films were evaluated as an adhesion barrier in a rabbit pericardial abrasion model.** ***Results:*** **The sprayable, in situ forming hydrogel film was shown to immediately seal carotid-PTFE anastomoses in six of six applications. Hydrogel application in a rabbit pericardial abrasion model resulted in a statistically significant reduction in the number and tenacity of adhesions.** ***Conclusions:*** **This novel in situ formed sprayable hydrogel film has demonstrated a dual function as an effective tissue sealant and as an adhesion barrier in cardiovascular preclinical models. These next generation synthetic biomaterials are currently undergoing clinical investigations.** *(J Card Surg 2003;18:1-6)*

In some surgical situations wound closure by suturing or stapling is either ineffective or impractical. Surgical sealants can play an important role in preventing continued seepage of fluids in these situations and may provide a new means to surgical wound closure. For example, in cardiac and vascular surgery, particularly when employing vascular grafts and patches of a synthetic nature, bleeding from the sutured repair can continue due to the needle track of the suture being larger than the suture itself. Difficulty in controlling intraoperative bleeding can result in increased operating room time, the need for blood transfusion products, pulmonary hypertension, and increased mortality. An effective sealant designed to augment vascular closures could significantly reduce the time required to obtain hemostasis.

Repeat cardiac operations experience higher levels of morbidity and mortality than primary procedures. It is believed that postoperative pericardial and sternal adhesions contribute significantly to these increased risks.[1-3] The prevalence of these reoperations has also increased, constituting upward of 10% to 20% of the annual caseload for some centers.[4] Adhesions add to the overall operating time, morbidity and mortality of these reoperations, and may also compromise ventricular function, as substantiated in animal studies.[5,6]

Several blood-protein-based surgical sealants developed to date have demonstrated the ability to decrease the time to achieving hemostasis. However, the composition of these materials may not lend to their further use as postsurgical adhesion barriers. Thus, there remains a need for the development of a material that can serve the dual function of being an effective sealant for providing

Address for correspondence: Amar Sawhney, Ph.D., Confluent Surgical, Inc., 101 A First Ave, Waltham, MA 02451. Fax: (781) 693,2331; e-mail: asawhney@confluentsurgical.com
This work was funded by a research grant from Confluent Surgical, Inc.

acute hemostasis as well as serving as a barrier to adhesion formation during the critical postsurgical period.[7,8]

A novel synthetic material that has been specifically engineered to polymerize rapidly and safely in situ has been developed. This material, which starts as dual-component aqueous solutions, can be transformed into flexible, inert, tissue-adherent absorbable hydrogel films upon mixing. The resulting hydrogel serves to seal the underlying native and graft surfaces against leakage.

Further, the synthetic composition does not allow tissue in-growth, thus keeping tissue surfaces separate while healing. This separation, or mechanical barrier effect, then preserves the previously established surgical planes through the postoperative period. Over time the hydrogel liquefies to form water-soluble materials that are absorbed and readily cleared from the body. This dual-function material (sealants and adhesion barriers) is expected to be useful in numerous surgical areas where surgeons are concerned about attaining leak-proof wound closure and prevention or reduction of postsurgical adhesion formation.

MATERIALS AND METHODS

Sprayable hydrogel sealant and adhesion barrier

A new synthetic, self-curing hydrogel is under development as a sealant that can serve as an adjunct to the standard methods of sutured or stapled repair of vascular grafts, dura mater, and lung parenchyma. The surgical sealant (Confluent Surgical, Inc., Waltham, MA) consists of two aqueous solutions that when mixed together rapidly polymerize to form a biocompatible absorbable hydrogel suitable for sealing.

The two reactive solutions are sprayed onto tissue, rapidly cross-linking to form a conformal, flexible, poly(ethylene glycol) (PEG) based film that has excellent tissue adherence. The sealant contains a safe blue dye as a colorant that enables easy visualization of the sealant application. The system can be stored at room temperature, and the device takes only minutes to prepare.

The cross-linked hydrogel is more than 90% water at application and has built-in hydrolyzable linkages. These linkages allow the sealant to break down over approximately 4 weeks, leading to the liberation of water-soluble molecules that are rapidly cleared through the kidneys.[9] No toxic byproducts are created when this material absorbs. Due to its synthetic nature this material is a poor food source for bacteria.

This family of hydrogel materials has undergone extensive preclinical testing, and has been evaluated as a laparoscopically applied adhesion barrier during gynecological surgery in two clinical trials.[10,11] Unlike preformed hemostats or adhesion barriers, the unique liquid-to-solid transformation allows for simple application in challenging environments (laparoscopy, endoscopy), and to complex shapes such as vascular anastomoses and reproductive organs. The rapid polymerization of these materials even allows for application to beating hearts.

A rabbit model was used to evaluate the potential of these hydrogels in the reduction of epicardial adhesions. An acute preclinical study in the canine was performed to evaluate the sealing capability of these hydrogels in vascular reconstructions.

Rabbit pericardial adhesion prevention study

Twelve female New Zealand White Rabbits, 3–4 kg in body weight, were used for this model previously described by Wiseman et al.[12] The animals received humane care in accordance with the National Institutes of Health Animal Care and Use Guidelines.

The animals were sedated, placed in dorsal recumbency, intubated, and maintained under inhalation anesthesia. A median sternotomy was performed to expose the heart. The pericardial sac was opened and a standardized superficial abrasion was performed with dry gauze on the anterior (ventral) surface of the heart, creating a "central strip" (CS) of roughened tissue. The rabbits were randomized into a control group that received no further treatment and a treatment group that had the hydrogel applied over the abraded anterior epicardium, to a thickness of 1–2 mm (Fig. 1) Following in situ polymerization the film and the surrounding tissue were rinsed four times with 20 mL of buffered isotonic saline. Excess fluids were then suctioned and the pericardium was not closed. The sternum was closed with interrupted sutures and the fascia and skin were closed in layers. The rabbits were recovered and pain medication (butorphanol,

COLOUR FIG

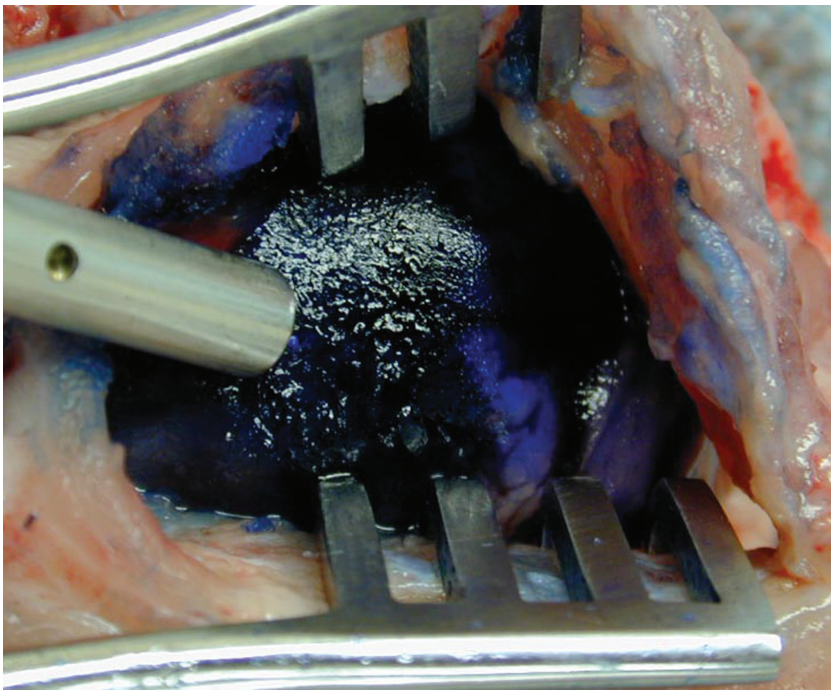

Figure 1. *Hydrogel application to the anterior surface of a beating rabbit heart following dry gauze abrasion. Dye added to sealant makes treated areas clearly visible.*

COLOUR FIG

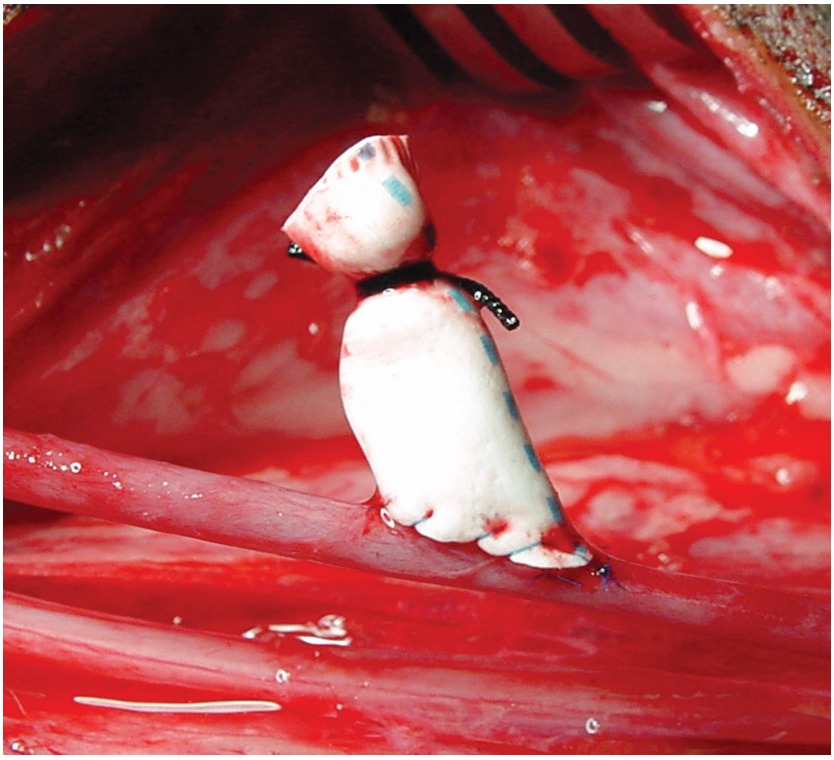

Figure 2. *Dead-end 4.0 mm PTFE graft end-to-side anastomosed to canine carotid artery. Needle hole leaks are plainly visible at the anastomosis site.*

0.1–0.2 mg/kg) was administered subcutaneously at 0, 6, and 12 hours after surgery.

The rabbits were sacrificed 14 days after surgery and a necropsy performed. A blinded observer scored the extent, tenacity, and density of adhesions to the heart in each animal.

Canine tissue sealant evaluation

An acute preclinical model was used to evaluate the capability of this hydrogel to perform as a tissue sealant.

Dead-end PTFE grafts (WL Gore, Flagstaff, AZ) were end-to-side anastomosed to carotid arteries in a heparinized canine model (Fig. 2). Anastomoses were sewn with 7-0 Prolene suture (Ethicon, Inc., Sommerville, NJ), with double the normal spacing between throws. Confirmation of anastomotic leaks was performed by briefly removing the vascular clamps prior to gel application. Graft sites were the treated with sealant, and after 30 seconds the clamps were removed (Fig. 3). The time to hemostasis was then measured.

RESULTS

Rabbit pericardial adhesion prevention study

Significantly more adhesions were noted along the CS in the control animals (89.0 $\pm$ 7.81% [mean $\pm$ SEM]) than in the hydrogel-treated animals (28.83 $\pm$ 7.19, $P = 0.0004$, Student *t*-test), a 68% reduction in adhesion content. These adhesions were most commonly seen at the cardiac apex. Control animals' adhesion tenacity was significantly greater than that in the hydrogel animals ($P = 0.0273$, X^2). A reduction in density of adhesions on the CS for hydrogel-treated animals was observed as well as improved epicardial visibility.

Canine tissue sealant evaluation

Prior to treatment, all anastomotic sites were found to be bleeding from the suture lines. Upon hydrogel sealant application, all six of the six anastomotic sites sealed immediately and no bleeding was evident upon clamp removal (mean BP = 100 mmHg). One site had gel bridged between the graft and gauze, and a small leak was created when the intervening gel was cut close to the graft. A second sealant application over the leak site resulted in immediate hemostasis. In all cases the hydrogel was found to adhere well to native tissue as well as to the PTFE graft. This hydrogel sealant set within 2 seconds without excess runoff from the application site. The blue color indicated the location and thickness of the sealant. The applicator delivered a fine spray of material and completely coated the anastomosis within 5 seconds.

DISCUSSION

The liquid-to-solid transformation of these materials allows for simple application to complex shapes in open or minimally invasive surgery. Due to the low solids content, the PEG molecular structure and low concentration of acidic byproducts, these materials are extremely inert and well tolerated in the body. This feature makes them well suited to act as space fillers, keeping tissues separated while the inflammatory process subsides. The synthetic origin eliminates the risk of viral transmission, and reduces the risk of infection potentiation. Finally, the complete breakdown of the cross-linked network takes place over several weeks, causing the hydrogel to slowly liquefy. The liberated PEG molecules are then absorbed and quickly cleared from the body.

The tissue adherence of the hydrogel film is central to its ability to act as a sealant. When sprayed onto tissue or graft, the liquid hydrogel precursors diffuse into the surface irregularities, where they solidify and interlock with the tissue/graft surface to form an intimate hydrogel—tissue interface. The adherence, coupled with flexibility, also makes these materials capable of sealing lung dissection defects, commonly encountered in cardiac reoperations. (Fig. 4)

Many blood-protein-based surgical sealants function as hemostats, at least in part, due to their thrombogenic nature. These synthetic hydrogels are nonthrombogenic, and function as mechanical barriers by plugging suture holes and graft porosities. In this way they provide mechanical hemostasis until blood clots under the gel. The nonthrombogenic nature of these materials may provide an additional level of safety in the rare case where the sealant gets inside the vessel lumen.

CONCLUSIONS

Based on these preclinical results, it appears that these novel synthetic hydrogel films can

COLOUR FIG

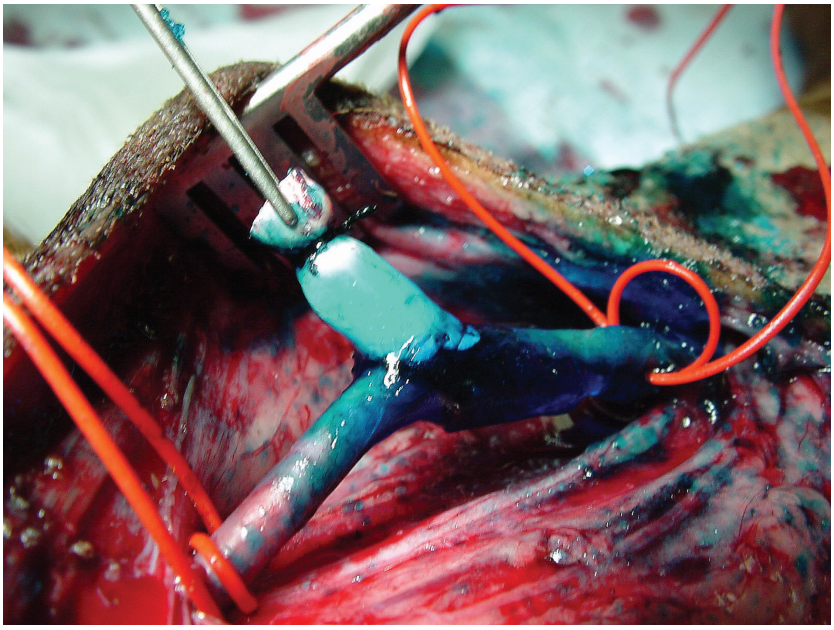

Figure 3. *Following sealant application at the anastomosis, vascular ties were removed from canine carotid artery, demonstrating complete hemostasis. Mean blood pressure = 100 mmHg.*

COLOUR FIG

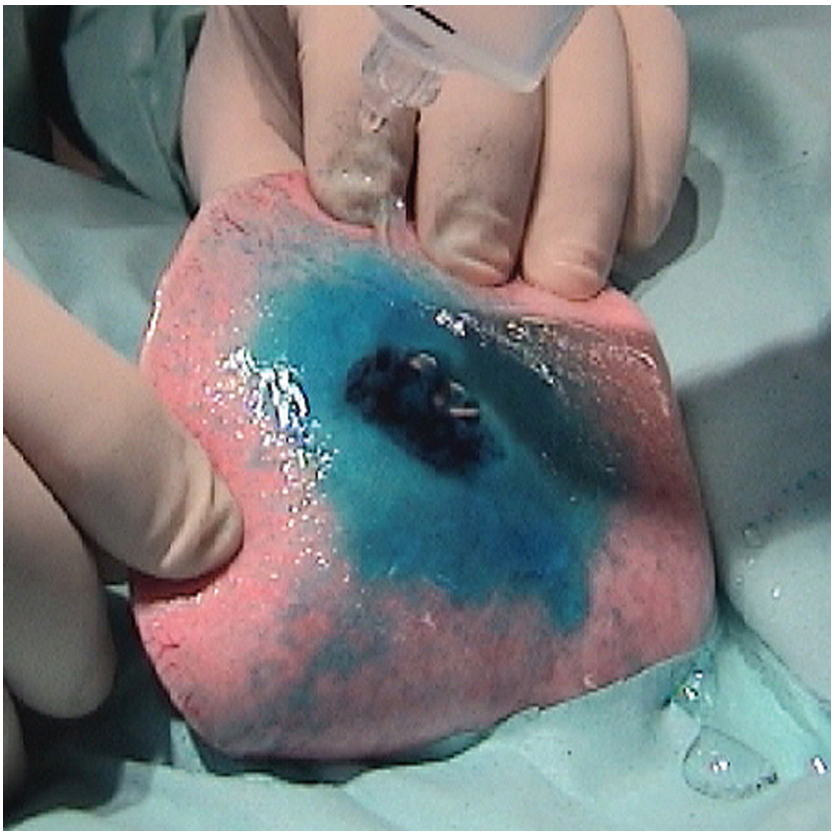

Figure 4. *Pressure-testing sealant application over canine lung coin defect. Pressure = 40 cm, H_2O.*

serve to reduce pericardial adhesions and also serve as highly effective tissue sealants. Clinical investigation of these materials is now being undertaken in the United States and Europe in several surgical settings.

REFERENCES

1. Schaff HV, Orszulak TA: The morbidity and mortality of reoperation for coronary artery disease and analysis of late results with use of actuarial estimate of event-free interval. J Thorac Cardiovasc Surg 1983;85:508.
2. Foster ED, Fisher LD, Kaiser GC: Comparison of operative mortality and morbidity for initial repeat coronary artery bypass grafting. The coronary artery surgery study (CASS). Ann Thorac Surg 1984;38:563.
3. Lytle BW, Loop FD, Cosgrove DM: Fifteen hundred coronary reoperations. Results and determinants of early and later survival. J Thorac Cardiovasc Surg 1987;93:847.
4. Nkere UU, Whawell SA, Sarraf CE, et al: Pericardial trauma and adhesions in relation to reoperative cardiac surgery. Thorac Cardiovasc Surgeon 1995;43:338.
5. Shapira N, Gordon C, Lemale GM: Occlusion of aortocoronary vein grafts in association with bovine pericardium. Am J Cardiovasc Pathol 1989;3:87.
6. Bailey LL, Ze-jian L, Schulz E et al: A cause of right ventricular dysfunction after cardiac operations. J Thorac Cardiovasc Surg 1984;87:539.
7. Okuyama N, Wang CY, Rose EA et al: Reduction of retrosternal and pericardial adhesions with rapidly resorbable polymer films. Ann Thorac Surg 1999;68:913.
8. Seeger JM, Kaelin LD, Staples EM et al: Prevention of postoperative pericardial adhesions using tissue-protective solutions. J Surg Res 1997;68:63.
9. Yamaoka T, Tabata Y, Ikada Y: Distribution and tissue uptake of poly (ethylene glycol) with different molecular weights after intravenous administration to mice. J Pharm Sci 1993;83:601-606.
10. Mettler L, Audebert A, Lehmann-Willenbrock E, et al: A prospective clinical trial of SprayGel™ as a barrier to adhesion formation: Interim analysis. Proceedings of the 10th Congress of the European Society for Gynaecological Endoscopy, Lisbon, Portugal. November 21-24 (2001):223-228.
11. Johns A, Ferland R, Dunn R. Initial feasibility study of a sprayable hydrogel adhesion barrier system in patients undergoing laparoscopic ovarian surgery. Presented at the 8th World Congress on Endometriosis, San Diego, CA. February 24-27:2002.
12. Wiseman DM, Kamp L, Linsky CB et al: Fibrinolytic drugs prevent pericardial adhesions in the rabbit. J Surg Res 1992;53:362-368.