BioGlue® in 2011: What Is Its Role in Cardiac Surgery?

Castigliano M. Bhamidipati, DO, MSc;* Joseph S. Coselli, MD;†‡ Scott A. LeMaire, MD†‡

*Department of Surgery, State University of New York Upstate Medical University, Syracuse, New York;†Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas; and the ‡Cardiovascular Surgery Service, The Texas Heart Institute at St. Luke’s Episcopal Hospital, Houston, Texas

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Abstract: BioGlue surgical adhesive was developed as an adjunct for achieving hemostasis during cardiovascular surgery, and it was approved for use in the United States by the Food and Drug Administration in 2001. When applied to cardiovascular tissues, the glutaraldehyde and bovine serum albumin that comprise BioGlue produce strong crosslinking that bonds tissues and seals defects. These features have made BioGlue particularly well suited for preventing bleeding from fragile cardiovascular anastomoses such as those inherent in the repair of acute aortic dissection. Over the 10-year period since its approval, several studies and clinical reports have illuminated the relative risks and benefits of using BioGlue during cardiovascular operations. Understanding these merits and limitations of BioGlue is essential to ensuring its safe and effective use. Keywords: BioGlue, review, surgery, surgical adhesives.

Hemostasis is a critical element of successful cardiac surgery because uncontrolled intraoperative and postoperative bleeding causes significant morbidity and mortality. Unfortunately, several factors interact to trigger bleeding in patients who undergo cardiac operations. For example, cardiac operations can be complicated by coagulopathy, which may arise from prolonged use of cardiopulmonary bypass, systemic hypothermia, the preoperative use of antiplatelet medications, and other factors. Additionally, some operations, such as those performed to repair aortic dissection, involve suturing tissues that are extremely fragile.

Several surgical adhesives have been developed to improve hemostasis by reinforcing suture lines and repairing fragile tissue (1). The major types of adhesives include aldehyde-based glues, fibrin sealants, collagen-based adhesives, polyethylene glycol polymers (hydrogels), and cyanoacrylates. A unique feature of the aldehyde-based glues is their excellent adhesive strength that results from creating strong protein crosslinking bonds. The first aldehyde-based glue to gain popularity in cardiac surgery was gelatin–resorcinol–formaldehyde–glutaraldehyde (GRFG) glue, also known as “French glue.” This adhesive comprises a formaldehyde/glutaraldehyde mixture and a solution of gelatin, resorcinol, and calcium chloride. Although GRFG has been widely used in Europe and Asia, it has not been approved for use by the Food and Drug Administration (FDA) in the United States, largely because of concerns about tissue toxicity related to the high concentration of formaldehyde used in GRFG (2).

The other commonly used aldehyde-base glue, BioGlue® (CryoLife Inc., Kennesaw, GA) surgical adhesive, is a two-component agent composed of 45% purified bovine serum albumin (BSA) and 10% glutaraldehyde. The two components are dispensed from a double-barrel syringe and mix within the delivery tip in a predefined ratio. The glutaraldehyde molecules covalently bond (crosslink) the BSA molecules to each other and, on application, to the tissue proteins at the repair site, creating a mechanical seal independent of the coagulation cascade. Because BioGlue does not contain formaldehyde, it is thought to have less tissue toxicity than GRFG glue. BioGlue was approved for use by the FDA in 2001 and has since been used in countries throughout the world. Over the 10-year period since its FDA approval, several animal studies and clinical reports have illuminated the relative benefits and risks of using BioGlue during cardiovascular operations. Understanding these merits and limitations of BioGlue is essential to ensuring its safe and effective use.
CHARACTERISTICS AND APPLICATION TECHNIQUE

Compared with other surgical adhesives and sealants, BioGlue demonstrates excellent tensile and shear strengths. These features have made BioGlue particularly well suited for preventing bleeding at fragile cardiovascular anastomoses. BioGlue also adheres to woven and knitted synthetic vascular grafts by creating mechanical interlocks within the interstices of the graft material. In addition, because BioGlue is stored and used at room temperature (it has a shelf life of 3 years at 25°C), and because it requires no preparation before use, this product offers the advantage of immediate availability.

BioGlue requires a bloodless field to adhere, so it is not useful for controlling active bleeding; therefore, BioGlue is generally applied to an anastomosis before perfusion is restored (i.e., during the clamp period). Before BioGlue is applied to the tissue, the applicator tip is carefully primed to evacuate air and to ensure the components are properly mixed. This adhesive has very low viscosity, making it difficult to control during application, particularly if it is rapidly released. Slowly releasing the glue during application tends to increase its initial viscosity and improves control. BioGlue is applied so that a thin (approximately 2-mm) layer covers tissue anastomoses. The adhesive begins to polymerize within 20–30 seconds and reaches maximum bonding strength in 2–3 minutes.

LABORATORY STUDIES

Several animal studies have examined the use of BioGlue in a myriad of cardiovascular operations. The principal outcome measures of these studies have been hemostasis, anastomotic patency, and local tissue reaction. Several investigators have explored the potential for using BioGlue to create coronary artery bypass (CAB) anastomoses. Gundry and colleagues (3) performed left internal thoracic artery (LITA) to left anterior descending (LAD) coronary artery anastomoses by using only BioGlue during cardiopulmonary bypass in three goats. Necropsy at 24 hours, 10 months, and 1 year revealed patent anastomoses, and histopathologic analysis showed minimal inflammatory reaction. Van Nooten and colleagues (4) performed LITA to LAD anastomoses by using only BioGlue during beating-heart operations in eight dogs. There were two early deaths, one resulting from anastomotic bleeding and one resulting from graft occlusion and myocardial infarction. The six surviving dogs underwent angiography 6 months after the operation; all anastomoses were patent, although distal coronary narrowing was noted in two dogs. Histopathologic examination performed at 6 weeks revealed an early inflammatory reaction inside and outside the arteries, and new endothelialization was noted in 80% of the cases. Histopathologic analysis performed at 3 months showed granulomatous infiltration. Ultrastructural examination revealed localized intimal degeneration. In a more recent study, Wippermann and colleagues (5) performed LITA to LAD anastomoses by using only BioGlue in beating-heart operations in four pigs. Three of the anastomoses remained patent at 3 months, and histopathologic examination revealed a severe inflammatory reaction with extensive fibroblastic proliferation; this tissue reaction was substantially worse than those observed in anastomoses created with GRFG or cyanoacrylate glues, raising concern about the use of BioGlue for coronary anastomoses. Similar concerns were raised by Schiller and colleagues (6,7), who evaluated small-vessel anastomoses by using a rabbit carotid artery anastomosis model. Histopathologic analysis performed 60 days after anastomoses were created by using BioGlue revealed marked inflammatory infiltration and calcification involving the arterial wall and the surrounding capsule.

Other investigators have focused on the use of BioGlue as an adjunct to secure hemostasis by reinforcing large vessel suture lines, which has relevance to a broad range of cardiac operations, including repair of proximal aortic aneurysms and dissections, aortic valve replacement, and cardiac transplantation. A study by Hewitt and colleagues (8) compared BioGlue with a topical absorbable hemostatic agent in descending thoracic aortic anastomoses in anticoagulated sheep; the results showed reduced blood loss in the BioGlue group. Histopathologic examination of tissue samples explanted 3 months after surgery showed a minimal inflammatory response. Fürst and Banerjee (9) found only low-to-medium-grade inflammation in rabbit aortas examined within the first week after BioGlue was applied. Rocker and colleagues (10) performed graft replacement of the abdominal aorta in five pigs, using only BioGlue to create the anastomoses between the aorta and graft. The pigs underwent conventional contrast aortography, computed tomographic angiography, and angioscopy before being euthanized between 1 week and 4 months after surgery; these studies confirmed patent anastomoses in all pigs. Aortic histopathologic analysis revealed only the expected granulomatous and fibrous tissue changes. Witter and colleagues (11) recently reported their findings of an extensive histopathologic analysis of aortas from six pigs with aortic dissection that was repaired by applying BioGlue inside the false lumen. Tissues examined 1 month after surgery exhibited increased levels of granulocytes and macrophages. After 12 months, the inflammatory changes had abated and early atherosclerotic lesions had developed; importantly, there was no evidence of tissue necrosis or persisting dissection.

Azadani and colleagues (12) recently compared the mechanical properties of BioGlue with those of several other commercially available surgical sealants; the authors
reported that BioGlue was by far the least compliant. Furthermore, BioGlue was much stiffer than human aortic tissue, polyester graft material, and glutaraldehyde-fixed porcine aorta. The authors concluded that the mechanical properties of BioGlue may restrict normal physiological vascular dilatation and create a compliance mismatch at anastomoses that could lead to pseudoaneurysms and other complications.

Having been impressed by BioGlue’s performance in our own early clinical experience with it, we conducted a series of studies in an effort to carefully delineate its potential limitations. In our first study, we sought to determine whether the adhesive would interfere with aortic growth, because we were intrigued by the possibility of using BioGlue during complex congenital cardiac operations (13). After creating aortic anastomoses in 10 4-week-old piglets, we randomly assigned half of the animals to receive BioGlue reinforcement circumferentially along the suture line. Seven weeks later, when compared with controls, the pigs that had received BioGlue exhibited impaired aortic growth, anastomotic stenosis, and histopathologic evidence of tissue injury and fibrosis. We concluded that BioGlue should not be used on cardiovascular anastomoses in pediatric patients.

In light of BioGlue’s poor viscosity, we then conducted an ex vivo study to determine whether the adhesive could leak through suture lines and needle holes when applied to an anastomosis (14). We applied BioGlue to anastomoses created in freshly harvested porcine aortas, gelatin-sealed polyester grafts, and expanded polytetrafluoroethylene grafts and found that BioGlue leaked through needle holes in 10% of the anastomoses. The leaks occurred in all conduit types but were most common in the porcine aortic anastomoses; leaks were identified in 22% of the aortic anastomoses. We concluded that the potential for intraluminal leakage and subsequent embolization should be considered when one evaluates the risks and benefits of using BioGlue.

Finally, given the well-recognized neurotoxicity of formaldehyde, we conducted a series of experiments in pigs to determine whether the glutaraldehyde component of BioGlue would cause injury to nerves and cardiac conduction tissue (15). We found that applying BioGlue to the phrenic nerve caused paralysis of the diaphragm; this did not occur in the control pigs, in which albumin was applied to the nerve. Histopathologic examination of the exposed nerve sections revealed signs of cellular toxicity in the BioGlue group. Similarly, BioGlue applied to the cavoatrial junction overlying the sinoatrial node resulted in epicardial and myocardial coagulation necrosis in all 12 pigs. The region of focal degeneration extended to the sinoatrial node in two of these animals, both of which developed persistent bradycardia immediately after the adhesive was applied. These findings corresponded to those reported in the study by Fürst and Banerjee (9), who found that polymerized BioGlue released cytotoxic levels of glutaraldehyde that were capable of causing severe tissue injury. In searching for a protective strategy, we found that applying a water-soluble gel to nerve and cardiac tissue before applying BioGlue effectively (but not entirely) prevented tissue injury, and we concluded that this technique could be used to protect vulnerable structures adjacent to areas where adhesive application is needed.

**CLINICAL APPLICATIONS**

BioGlue has been successfully used in many types of cardiac operations, including repair of proximal aortic dissections, aortic root and arch reconstructions, valve repair and replacement procedures, repair of ventricular rupture or injury, postinfarction ventricular septal defect repair, and left ventricular endoaneurysmorrhaphy (16–22). BioGlue has been especially helpful in patients with severely weakened tissue, such as patients with connective tissue disorders who are undergoing thoracic aortic operations. Passage and colleagues (21) reported their experience with using BioGlue in 115 patients who underwent a wide variety of cardiac procedures; the authors concluded that the adhesive and hemostatic properties of BioGlue increased the ease of operation. The results of a randomized clinical trial provided further support regarding the use of BioGlue to secure cardiovascular anastomoses in a broad range of cardiovascular operations (22). This study showed that primary intraoperative anastomotic hemostasis was achieved more frequently in the BioGlue group (61%) than in the standard repair control group (39%; $p = .014$). The use of BioGlue did not reduce the administration of blood products. Although there was no difference in the incidence of stroke or paraplegia between the groups, the BioGlue group had a lower incidence of overall neurological deficits than the control group. Other adverse events, including death, occurred with similar frequency in the two groups.

Much of the initial interest in using BioGlue focused on repairs of acute aortic dissection, operations made notorious by the bleeding problems associated with constructing anastomoses involving the extremely fragile torn aortic wall. In these cases, BioGlue is used to obliterate the false lumen and reinforce the fragile suture lines (Figure 1) (1). One of the earliest reports came from Kucükakasu and colleagues (23), who used BioGlue to successfully reinforce suture lines after repairing an iatrogenic proximal aortic dissection. Since then, several other groups have reported success with using BioGlue during operations for aortic dissection (16,21,24–28). These groups include Raanani and colleagues (24), who reported that BioGlue facilitated aortic valve repair in patients with acute dissection. In a retrospective study, Chao and Torchiana (28) compared patients who underwent acute proximal aortic dissection
repair with BioGlue (n = 13) vs. without BioGlue (n = 12) and found that BioGlue use was associated with significant reductions in total postoperative blood loss, packed red blood cell transfusion, and hospital length of stay.

There are many techniques for using BioGlue to reapproximate the dissecting membrane to the outer aortic wall. We have found it useful to tack the dissecting membrane to the outer wall with a few interrupted 6-0 sutures to keep the walls aligned during glue application (1). We then insert a Foley catheter with a 30-mL balloon into the true lumen and carefully inflate the balloon within the proximal descending thoracic aorta immediately distal to the left subclavian artery; this serves to prevent the glue from running down the false lumen into the descending thoracic and abdominal aorta. Avoiding the distal runoff of BioGlue also keeps the adhesive in the arch, thus optimizing bonding and preventing distal embolization through the false lumen. The false lumen of the aortic arch is then filled with a thin layer of BioGlue. The layers of the aorta do not need to be pressed together; in fact, the objective is to maintain an even coating of adhesive between the tissue layers as the glue bonds to the aorta and polymerizes. Once the dissected layers of the aortic wall have been bonded, the distal anastomosis between the vascular graft and the aortic arch is performed. After completing the anastomosis, we apply a thin layer of BioGlue to the outer surface of the distal suture line before restoring arch perfusion and proceeding with the proximal aspect of the repair. If needed, we then use similar techniques to apply BioGlue during repair of the aortic root. After the aortic valve is addressed (generally by resuspending the commissures), fresh and clotted blood is removed from the true lumen, 6-0 sutures are used to align the dissected layers, and a thin coating of BioGlue is applied within the false lumen. After the adhesive has set, the proximal anastomosis is performed and a thin layer of BioGlue is applied to the completed anastomosis before the aorta is unclamped.

AVOIDING PITFALLS

Although using BioGlue may provide benefits, this adhesive also has several limitations and poses risks that
warrant careful consideration. Several technical steps and precautions can be taken to maximize efficacy and minimize complications associated with using BioGlue. First, because blood interferes with tissue bonding, all clotted and fresh blood needs to be removed from the area before application. For example, during proximal aortic dissection repair, it is sometimes necessary to stop antegrade or retrograde cerebral perfusion briefly before BioGlue is applied to ensure a dry field. Similarly, although BioGlue is an excellent adjunct for creating a secure anastomosis, it is not helpful for controlling active bleeding once flow has been restored. In patients with active bleeding, additional sutures are first used to achieve hemostasis; after the bleeding has been controlled, BioGlue can be applied to strengthen the repair.

Several clinical reports support the findings of laboratory studies demonstrating BioGlue’s potential for local tissue toxicity. Adding to the concerns about toxicity to nerves and cardiac conduction tissue, several reports suggest that BioGlue may occasionally cause severe injury to aortic tissue and cause dissection or pseudoaneurysm formation (29–31). Reports after reoperations have described necrotic, fibrosed, and excessively thinned aortic tissue found at the site of adhesive application. As mentioned, because circumferential application of BioGlue has been associated with the development of vascular strictures and impaired aortic growth in juvenile pigs, this adhesive is not recommended for use during cardiovascular reconstructions in pediatric patients (13). Furthermore, BioGlue does not appear to be well suited for small-vessel anastomoses such as those involving coronary arteries. Khan and colleagues (32) reported a case of stenoses that developed at distal CAB anastomoses after BioGlue was used. The authors found marked fibrosis involving the LITA and vein graft conduits, which they attributed to a severe tissue reaction to the glue.

In addition to injuring adjacent tissues, spillage of BioGlue can lead to complications by creating masses, producing reactive fluid collections, and compressing adjacent structures (33–38). Economopoulos and colleagues (33) reported the case of a patient who developed superior vena caval compression as a result of a collection of BioGlue 8 months after the adhesive was used to control bleeding from the dome of the left atrium during a triple valve operation. Podila, Szafranek, and colleagues (34,35) removed BioGlue fragments and a surrounding large, chronic, thick-walled retrosternal fluid collection that developed after CAB; similar cases have been reported from other centers (36,38).

Another pitfall to consider is BioGlue embolization. Adhesive embolization can cause catastrophic complications and, as articulated by Carrell and colleagues (39), may occur by three mechanisms: 1) inadvertent direct spillage into the true lumen; 2) escape through dissection entry sites into the true lumen; and 3) leakage through anastomotic needle holes. The first two mechanisms can result from technical error; thus, careful attention and proper training of the surgical team will minimize this risk. It should be noted, however, that glue can leak through suture-line needle holes even when properly applied in accordance with the manufacturer’s instructions (14). It is likely that this complication is greatly underreported, because adhesive embolization is rarely suspected as a cause when ischemic complications arise and postmortem microscopy examinations are not routinely performed in patients who die from complications of cardiac operations (40). There have been several reports of BioGlue embolization causing major complications, including myocardial infarction, limb ischemia, and pulmonary embolism (41–44). Similarly, BioGlue can leak through proximal aortic suture lines, become deposited on prosthetic valve leaflets, and cause valve malfunction (45–47).

BioGlue’s potential for causing tissue injury, mass effect, and embolic complications mandates careful attention to preventative strategies. Great care is needed to avoid unintended spillage of BioGlue onto adjacent structures or into a cardiac chamber or vascular lumen. Any spilled adhesive should be rapidly evacuated with the wall suction (never with the cell saver or cardiotomy suctions). To protect surrounding tissues from contact with the adhesive, gauze sponges dampened with saline or water-soluble gel can be used to shield these tissues from unintentional adhesive runoff during glue application. Additionally, a moist sponge can be placed in the true lumen to cover the origins of the brachiocephalic arteries and prevent any adhesive that spills over the edge of the dissecting membrane from running into these vessels. Similarly, a moist sponge can be used to protect the aortic valve leaflets and the coronary ostia when BioGlue is being used to reconstruct a dissected aortic root. The left main coronary artery can also be protected by the gentle insertion of a red-rubber catheter to occlude the ostium. Finally, to reduce the chance of glue leaking into the lumen, it is important to temporarily stop the left ventricular sump suction while applying BioGlue to the ascending aorta or aortic root.

**SUMMARY**

Several of BioGlue’s characteristics—including its rapid availability, fast polymerization, and excellent bonding strength—make it well suited for preventing bleeding from fragile cardiovascular anastomoses. However, given the well-documented risks involved in using BioGlue during cardiac operations, we do not recommend using it routinely. During certain complex operations—especially in cases of acute aortic dissection—the benefits of using
this agent may truly outweigh the potential risks. Thus, the risk–benefit ratio for using BioGlue should be carefully considered on an individual basis. BioGlue should be used only when necessary to secure hemostasis and reinforce weak tissues in a patient- and risk-specific fashion. When the use of this adhesive is warranted by the clinical setting, several technical practices can be adopted to make it as safe as possible.

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REFERENCES


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