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Use of BioGlue in Aortic Surgery: Proper Application Techniques and Results in 92 Patients

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ABSTRACT

Background. Surgery for pathology of the proximal aorta requires aortic wall reconstruction, re-approximation of the graft to native vessels, and potentially root replacement and valve resuspension or replacement. The purpose of this study is to describe proper application techniques and the results obtained with the adjunctive use of BioGlue Surgical Adhesive in this challenging patient population.

Methods. Between August 1998 and June 2002, 92 consecutive patients underwent ascending/arch repairs, ascending/root repairs, Ross procedures, or ascending/arch repairs with a concomitant Ross procedure using BioGlue as an adjunct for anastomotic hemostasis.

Results. Twenty-six patients (28.3%) in this series required no postoperative blood products. The mortality rate for this single-surgeon series was 3.3%. No device-related complications were observed. The incidence rate for postoperative pseudoaneurysm formation was 3.3%.

Conclusions. This series demonstrates the safety and effectiveness of BioGlue as a hemostatic adjunct in proximal aortic surgery. Use of the product helped to facilitate a minimal reliance on blood products and a low mortality rate.

INTRODUCTION

Surgery of the proximal aorta and aortic valve is challenging and can be complicated by an inability to obtain immediate intraoperative anastomotic hemostasis. Surgical adhesives and sealants have been investigated for many years as both hemostatic adjuncts for sealing anastomotic repairs and as adhering and reinforcing agents for the fragile layers of the aorta in dissection cases. Early work with cyanoacrylate adhesives [Weissberg 1964a, 1964b; Goetz 1966] demonstrated that this product can be associated with necrosis of the arterial wall, and consequently this product has not been widely used in cardiothoracic surgery. More recent clinical series have demonstrated that use of gelatin-resorcinol-formalin (GRF) glues (Cardial; Technopole, Sainte-Etienne, France) is associated with a high redissection rate when this product is used to adhere the aortic layers in type A aortic dissection repair [Ennker 1994; Neiderhauser 1998; Fukanaga 1999; Bingley 2000; Kazui 2001; Yoshitatsu 2004]. The general consensus amongst these authors is that the formalin component of this adhesive is arteriotoxic. GRF has not been approved for use in the United States.

BioGlue Surgical Adhesive (CryoLife, Kennesaw, GA, USA) was introduced in the United States for acute type A dissection in 2000 and for large vessel anastomosis in 2002. BioGlue is a protein-based tissue adhesive composed of bovine serum albumin (45% solution) that is crosslinked with glutaraldehyde (10% solution) in a 4-to-1 volume ratio. BioGlue is provided in a dual-chambered cartridge that requires no special storage, mixing, or reconstitution. A tortuous double helix mixing tip properly mixes the product as it is being delivered to the patient. BioGlue sets up quickly, reaching approximately 80% of its bonding strength in 30 seconds and becoming fully polymerized in 2 minutes. The glutaraldehyde and protein molecules are carefully stoichiometrically balanced so that only the surface tissue proteins are crosslinked when the product is applied.

As with all medical devices, the improper use of BioGlue may be associated with negative outcomes, especially when it is applied in an excessive manner. Downing has reported what appears to be an increase in the incidence of pseudoaneurysm following type A dissection repair with BioGlue and he postulates that inappropriately gluing in lieu of suturing may contribute to this outcome [Downing 2003]. Kazui has pointed out that deleterious outcomes such as pseudoaneurysm formation may be a byproduct of technical flaws in the application of the glue [Kazui 2003]. Our intention with this paper is to provide a detailed outline of the proper application techniques for the product and to demonstrate successful outcomes when using these techniques in a series of complex operations.

MATERIALS AND METHODS

We performed a retrospective review of all patient charts to determine the effect of the application of BioGlue on perioperative outcome parameters and complications. Data collected included surgical pathology, procedure information, intraoperative information, and postoperative outcome. Data were collected for patients through hospital discharge,

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at subsequent follow-up visits, and at the time of follow-up imaging. The mean follow-up time for this patient cohort was 430 days (range, 0-2178 days). A total of 11 patients were not seen for follow-up, and 3 patients died prior to hospital discharge.

Between August 1998 and June 2002, 92 consecutive patients underwent ascending/arch repairs (n = 36), ascending/root repairs (n = 27), Ross procedures (n = 24), or ascending/arch repairs with a concomitant Ross procedure (n = 5) by a single surgeon at a single institution. The average patient age at the time of surgery was 58.3 years (range, 23-85 years) and men predominated in this series (64 patients, 69.6%). Preoperative New York Heart Association status for this cohort was I in 17 patients (18.5%), II in 35 patients (38.0%), III in 29 patients (31.5%), and IV in 11 patients (12.0%).

This series includes 65 elective cases (70.7%), 11 emergent cases (12.0%), and 16 urgent cases (17.4%). Eighteen of the 92 patients (19.6%) were undergoing revision surgery. Many patients presented with a comorbid condition, including coronary artery disease in 23 patients (25%), chronic obstructive pulmonary disease in 7 patients (7.6%), renal failure in 2 patients (2.2%), and cardiac tamponade in 1 patient (1.1%). Patient presentation was complicated by abnormal neurological status in 13 patients (14.1%), dependence on a ventilator in 5 patients (5.4%), hemodynamic instability in 5 patients (5.4%), ischemia in the extremities in 3 patients (3.3%), and preoperative coagulopathy in 2 patients (2.2%).

The primary condition requiring surgical intervention included ascending aortic aneurysms in 39 patients (42.4%), type A dissections in 22 patients (23.9%), 10 of which were acute in nature requiring either emergent or urgent care, aortic insufficiency in 10 patients (10.9%), and aortic stenosis in 17 patients (18.5%). A complete description of the operative pathology is provided in Table 1. Procedures performed for these patients, including Ross procedures, aortic root replacements, and aneurysm repairs, are detailed in Table 2. BioGlue was applied to seal the suture lines in anastomotic repairs and between the tissue layers in dissections. An average of 1.5 10-mL cartridges of BioGlue were used in each patient (range, 1-3 10-mL cartridges).

BioGlue Application Techniques in Cardiac Surgery

For anastomotic repair sites, we first carefully constructed the anastomosis using proper suturing techniques. Prior to applying BioGlue to intended anastomotic sites, all anastomoses were dried using sponges. Areas in which the application of BioGlue was to be avoided were covered with moist sterile gauze. The delivery device was primed immediately prior to application of the glue to the intended site. Once the delivery device had been properly primed, we immediately applied a thin, even layer of the glue to the anastomosis in a slow controlled manner making sure that a uniform layer no more than 2 mm in thickness was applied to the entire anastomosis 1 cm in either direction of the suture line. During application and for 2 minutes immediately following application, slight tension was applied to the conduit to assist in molding the conduit to its anatomic position once systemic flow was re-established. We always

Table 1. Surgical Pathology*

Pathologic Lesion	No. of Patients
Ascending aortic aneurysm	39 (with AI in 28 pts, CAD in 14 pts, arch aneurysm in 20 pts, AS in 7 pts, MR in 6 pts, annulo-aortic ectasia in 1 pt, bicuspid AV in 1 pt, coarctation of descending aorta in 1 pt, and coronary artery dissection in 1 pt)
Acute type A dissection	12 (with AI in 5 pts, arch tear in 2 pts, CAD in 1 pt, and arch aneurysm in 1 pt)
Chronic type A dissection	10 (with AI in 3 pts, multiple thoracic aneurysms in 5 pts, arch aneurysm in 5 pts, TAAA in 2 pts, and CAD in 1 pt)
Aortic insufficiency	10 (with ASD in 2 pts, MR in 2 pts, CAD in 1 pt, TI in 1 pt, and VSD in 1 pt)
Aortic stenosis	17 (with CAD in 6 pts, AI in 2 pts, MR in 2 pts, TI in 1 pt, descending aortic aneurysm in 1 pt, and iatrogenic proximal arch dissection in 1pt)
Severe ulcerative atherosclerotic lesion in ascending aorta	1
Large pseudoaneurysm in LVOT status post AVR	1
Annuloaortic ectasia with chest pain	1
Chronic hemolysis secondary to prosthetic AV and MV	1
Total	92

*AI indicates aortic insufficiency; pts, patients; CAD, coronary artery disease; AS, aortic stenosis; MR, mitral regurgitation; AV, aortic valve; TAAA, thoracoabdominal aortic aneurysm; ASD, atrial septal defect; TI, tricuspid insufficiency; VSD, ventricular septal defect; LVOT, left ventricular outflow tract; AVR, aortic valve replacement; MV, mitral valve.

Table 2. Procedures Performed

Surgical Procedure	No. of Patients
Ascending aneurysm repair	7
Ascending aneurysm and hemi-arch repair	7
Ascending aneurysm and total arch repair	10
Aortic root replacement only	11
Aortic root replacement:	
with valvuloplasty (David Procedure) and ascending aneurysm repair	3
with valvuloplasty (David Procedure) and ascending and hemi-arch repair	3
with valvuloplasty (David Procedure)and ascending, and total arch repair	2
with ascending aneurysm repair	6
with ascending aneurysm and hemi-arch repair	11
with ascending aneurysm and total-arch repair	3
Ross procedure only	21
Ross procedure:	
with ascending repair	3
with ascending and hemi-arch repair	5
Total	92

allowed the glue to polymerize for a full 2 minutes before pressurizing the anastomosis.

BioGlue Application in Valve Conduit Replacement Procedures

After implantation of the valve conduit, retrograde cardioplegia was turned off and the anastomoses were dried. The left and right main coronary arteries were covered with moist surgical gauze prior to BioGlue application to ensure that no glue entered into the coronary arteries. During application and polymerization, the distal end of the valve conduit was held closed using forceps, and slight tension was applied to the valve conduit.

In all valve conduit cases, BioGlue was first applied to the proximal anastomosis. During application of BioGlue, care was taken to avoid passing the delivery tip over the open end of the conduit. This minimized any chance of glue entering the conduit. We also used care not to allow excessive glue to pool, especially posterior to the anastomosis, to prevent impairment of the left main coronary button implantation. Once the proximal anastomosis was finished, we completed the left coronary button, the distal anastomosis, and finally the right coronary button. When completing the final conduit to aortic anastomosis the left ventricular suction should be discontinued to eliminate the unlikely aspiration of glue into the lumen.

Additionally, we used BioGlue to ensure hemostasis when reattaching the coronary buttons. We used a small amount of BioGlue no more than 1 to 2 mm in thickness to seal the needle holes. In all cases, we took great care to avoid letting the glue pool on the left main coronary to ensure that the artery remained open and patent. A balloon catheter that is appropriately sized for the lumen of the vessel may be used to aid during drying and molding the suture line. This is especially helpful in these smaller arterial anastomoses.

BioGlue Application in Thoracic Aortic Procedures

It is worth repeating that care was taken around the aortic valve and coronary ostia when the application was done at the aortic root prior to completion of the distal anastomosis. This caution is to ensure that no glue leaked onto the valve leaflets or pooled around the ostia, which could impede flow in the coronaries. When addressing the distal anastomosis, a small amount of glue was applied directly to the suture line to seal the needle holes.

Specific Techniques for Acute Type A Dissection

The dissected layers of the aorta were initially cleared of blood and thrombus material and dried with surgical sponges. For the distal end of the dissection repair, a balloon catheter was inserted into the true lumen to create a "basin," limiting the distal application of BioGlue. In addition, the dissected layers of the aorta were closely approximated by inserting a dilator, sponge, or catheter into the true lumen to preserve the natural architecture of the vessel. BioGlue was then dispensed into the false lumen as far distally as the distal balloon catheter allowed, proceeding from distal to proximal with a spiraling-out motion for a smooth application. We completely filled the false lumen with an approximately 2-mm thick layer of BioGlue without any external clamping or other manipulation. We were always careful to avoid overfilling the false lumen and spilling BioGlue into the true lumen or onto surrounding tissue. The glued layers were then reinforced with felt strips as previously described by Frist and Miller [Frist 1986].

For the proximal end of the dissection repair, the dissected layers of the aorta were also closely approximated using a dilator, sponge, or catheter. If necessary, moist gauze pads were placed over the aortic valve leaflets, protecting them from inadvertent application of BioGlue. BioGlue was then dispensed to fill the false lumen. Felt strips were again sutured into place to reinforce the glued layers of the lumen. Graft material was then sutured directly onto the tissues adhered and reinforced with BioGlue at both the proximal and distal aspects of the dissection repair. We always allowed BioGlue to completely polymerize without any manipulations for a full 2 minutes prior to suturing through the adhered tissue layers.

Table 3. Perioperative Blood Products

Blood Product	Median	Number of Units Transfused	
		Minimum	Maximum
Packed red cells	2.0	0.0	13.0
Fresh frozen plasma	1.0	0.0	13.0
Platelets	0.6	0.0	5.0
Cryoprecipitate	0.2	0.0	3.0

RESULTS

The median operative time for patients in this cohort was 334 minutes with a range of 205 to 785 minutes. The median pump time was 211.5 minutes (range, 126-435 minutes). Hypothermic circulatory arrest with selective cerebral perfusion when necessary was employed in 40 patients, with a median time of 12 minutes (range, 5-53 minutes). Patients averaged 3.2 days in the intensive care unit (range, 4 hours-30 days) and a total of 7.7 days in the hospital (range, 3-85 days).

Blood Products

Use of BioGlue for immediate intraoperative sealing of anastomoses positively influenced the use of blood products in this series. Median estimated blood loss was 1031 mL, with a range of 370 mL to 5350 mL. Our use of blood products is detailed in Table 3. Interestingly, 26 patients in this series (28.3%) required no perioperative blood products.

Morbidity

Thirty-nine of the 92 patients (42.4%) experienced at least one postoperative complication. These included 8 patients (8.7%) with transient neurological deficit, 4 patients (4.3%) with cerebrovascular accident, 3 patients (3.3%) with postoperative pseudoaneurysm formation, 1 patient (1.1%) with a graft infection, 1 patient (1.1%) with emboli of the right eye, and 1 patient (1.1%) requiring postoperative bronchoscopy. A total of 2 patients (2.2%) were noted as having postoperative renal failure; however, both of these patients presented with

Table 4. Patients Experiencing Cerebrovascular Accident

Age	Sex	Diagnosis	Etiology	Outcome
65	Male	Acute type A dissection	Unknown	Discharged postoperative day 9
58	Male	Acute type A dissection	Malperfusion	Discharged postoperative day 8
46	Male	Acute type A dissection	Malperfusion	Died postoperative day 5
77	Female	Severe atherosclerosis	Severe ASHD	Died postoperative day 85

renal failure preoperatively. There were no new onsets of renal failure in this series. No patient experienced postoperative paraplegia or paraparesis, and no postoperative comorbid event was determined to be related to the use of the surgical adhesive. There were no redissections at the root in this patient cohort. Details for patients experiencing perioperative stroke and postoperative pseudoaneurysm formation are provided in Table 4 and in the text below, respectively.

Postoperative pseudoaneurysm formations occurred in 3 patients (3.3%) in this cohort. One small pseudoaneurysm occurred at the posterior aspect of the left ventricular outflow tract in a patient 16 months after a Ross procedure. At 21 months postoperatively, the pseudoaneurysm remained small and the patient continues to be clinically followed without the need for additional surgical intervention. A second pseudoaneurysm occurred at the proximal anastomosis in another patient whose status was 6 years postrepair of acute type A aortic dissection. Once diagnosed with the pseudoaneurysm, the patient was readmitted for an elective repair procedure. A third patient presented with hemoptysis and a pseudoaneurysm secondary to graft infection at both the proximal and distal ends of the anastomosis of an ascending aortic graft approximately 8 months after an acute type A dissection repair procedure. Surgical intervention using an aortic homograft to remove and replace the infected graft resolved the pseudoaneurysm and infection.

Twelve of the 92 patients (13.0%) in this series required re-exploration for postoperative bleeding. In each case, the additional operation was needed for surgical bleeding. No anastomotic site bleeding was noted in any of the 12 patients requiring reoperation. The use of BioGlue did not complicate these additional surgical procedures.

Mortality

Mortality for this patient series was 3/92 (3.3%). Actuarial patient survival was 96 ± 2% at both 1 and 5 years after surgery. No patient in this series died in the operating room. No patient death in this series was noted to be attributable to the use of the surgical adhesive.

One patient who died in this series was a 46-year-old man who presented emergently with an acute type A aortic dissection complicated by flaccid paraplegia and moderate aortic insufficiency with profound left ventricular ischemia. This patient underwent emergent resection of the ascending and proximal arch dissection with resuspension of the aortic valve and coronary artery bypass grafting. The pump time for this procedure was 248 minutes. The patient survived the operation and was transferred to the intensive care unit where his postoperative course was complicated by malperfusion from the dissection element, causing major neurologic deficit. The patient was maintained on the ventilator for approximately 4 days without any neurologic recovery. It was decided to discontinue life support on postoperative day 5.

The second patient mortality was a 77-year-old woman who presented with severe atherosclerotic disease of the ascending aorta, aortic arch, and descending aorta with mobile atherosclerotic plaque. Additionally, this patient had a large ulcerated plaque in the ascending aorta in the takeoff of the left main ostia. The patient underwent an aortic root replacement with a 22-mm aortic homograft and coronary artery bypass grafting ×3. Pump time for this procedure was 224 minutes and the patient remained intubated for 11 days and remained in the intensive care unit for 30 days. The patient had a complicated postoperative course that included a postoperative cerebrovascular accident consisting of multiple embolic lesions and multiorgan failure. She died on postoperative day 85 as a result of multisystem organ failure.

The third patient mortality was an 81-year-old woman who presented emergently with an acute type A aortic dissection with aortic insufficiency, decreased neurologic status, and weakness in the bilateral lower extremities. The patient underwent resection of the ascending aortic dissection and proximal arch with resuspension of the aortic valve. Pump time for this patient was 136 minutes. The patient's postoperative course was complicated by the presence of blood in both the left and the right pleural cavities approximately 3 hours postoperatively, resulting in surgical exploration for mediastinal hemorrhage. There was no leakage of blood from the anastomotic sites, but there were several areas within the mediastinum that required cauterization. The patient recovered and was discharged to a rehabilitation center in an extended care facility. Approximately 2 months postoperatively, the patient experienced progressive illness, lightheadedness, weakness, and early mental status changes requiring intubation. The patient was found to have an acute urinary tract infection with significant bacterial load, contributing to her mental status. She was treated with antibiotics and seemed to be recovering. Approximately 2 hours before scheduled extubation, the patient was observed with bright red blood coming from her endotracheal tube. The patient's status deteriorated quickly into a bradycardiac rhythm with the resulting loss of pulses. Resuscitation measures were attempted to no avail. A request for autopsy was not granted.

DISCUSSION

In the United States and much of Europe, BioGlue is rapidly becoming the standard of care in the treatment of acute

thoracic aortic dissection. Bavaria and colleagues [Bavaria 2002] have published their technique on the inclusion of BioGlue in an integrated approach to the treatment of type A dissection. The adjunctive use of BioGlue contributed to an excellent early mortality rate of 9.8% in this series of 163 consecutive patients. Westaby and colleagues [Westaby 2002] reported on their technique for type A dissection that incorporates the use of BioGlue and note an early mortality rate of 5.3% in 95 patients. They did note the occurrence of some late pseudoaneurysm in referred patients treated with GRF glue at other centers but they note that this complication is not reported with BioGlue.

In addition to the positive results obtained in type A dissection, BioGlue has also been demonstrated to be safe and effective for sealing large-vessel anastomosis. Coselli, Bavaria, Fehrenbacher, and colleagues [Coselli 2003] reported on a rigorous prospective randomized controlled study that examined the ability of BioGlue to seal anastomotic repairs when compared to standard surgical closure. BioGlue-treated anastomoses were shown to be statistically more likely to be immediately hemostatic when compared to the control anastomoses ($P < .001$). Adverse event profiles were equivalent in the 2 groups, with the exception of neurological defects, which were threefold less in the BioGlue group ($P = .009$). This study was pivotal in obtaining the current regulatory approval and labeling for this product in the United States. Passage and colleagues [Passage 2002] reported on a series of 115 consecutive patients that included aortic root replacements, aortic aneurysm repair, valve procedures, and ventricular repair procedures. In their series, 44% of patients required no perioperative blood products and they concluded that BioGlue was helpful in facilitating the operations. The utility of the product in large-vessel anastomosis has been underscored by the report by Goldstein and Beauford [Goldstein 2003] on left ventricular assist devices that suggest that surgeons ensure that BioGlue is available to seal both the inflow and outflow cuffs on these devices.

Although the safety and effectiveness of BioGlue for intracardiac repair has not been demonstrated, cardiac surgeons are beginning to realize the usefulness of the product for these applications. Case studies [Mejia 2003; Masroor 2004] have been published that demonstrate the clinical utility of the product in addressing challenging pathology such as atrioventricular disruption and type I myocardial rupture. In addition, Fink and colleagues [Fink 2004] have published a report of a small series of 5 patients where BioGlue was used as an adjunct in repairs of complex intracardiac structural defects, including posterior mitral annular groove defects and an aortic annular defect. They note a complete and durable repair at 6 to 29 months follow-up with no signs of late complications or glue embolization.

In our series, complete sealing of anastomoses and obliterating the false lumen with BioGlue contributed to a low overall mortality rate (3.3%) at 5-year follow-up in a complex cohort of patients and allowed us to minimize our reliance on blood products. Nearly 30% of our patients required absolutely no perioperative blood products, despite the high incidence of revision cases, multiple procedures, and comorbidities. Only 2 patients (2.2%) were reoperated on for pseudoaneurysm formation and one of the 2 had an infected graft.

A recent bench study [LeMaire 2004] has postulated that BioGlue may leak through the needle holes created by anastomotic repair and thus cause the patient to be at risk for embolus. We did not note any BioGlue embolic events in this series. We discontinue the left ventricular suction when it potentially may cause a negative intraluminal pressure prior to any glue application. Our cerebrovascular accident rate of 4.3% is in line with other recent aortic surgery reports [Ueda 2003; Islamoglu 2004; Strauch 2004] (range, 6.7%-14%) that did not include the use of BioGlue. Our transient neurological defect rate of 8.7% compares very favorably to that of Fleck and colleagues [Fleck 2003] who reported a transient neurological defect rate of 18% in a similar series of patients treated without BioGlue. Additionally, Coselli and colleagues [Coselli 2003], in their prospective randomized series comparing BioGlue patients to non-BioGlue patients, actually noted a statistically significant reduction in neurologic complications when BioGlue was used. This paper hypothesized that the reduction might be related to the surgeon's ability to maintain higher perioperative blood pressures when the anastomoses are mechanically sealed.

Our study has certain limitations that are inherent to this type of surgical research. Primarily, the study is retrospective in nature and does not include a concurrent control group. Also, despite our best efforts, we were unable to obtain postoperative follow-up on 14 patients. We do believe that our follow-up rate of 85% is excellent for this type of study.

In conclusion, our experience has demonstrated that careful and proper application of BioGlue can be associated with excellent early-term results in surgery of the aortic valve and proximal aorta. Our low mortality rate combined with the reduction in the reliance upon allogeneic blood products supports the suggested patient benefits that occur with the use of this adhesive as an adjunct to a good suturing technique. Further follow-up will be required to support our early hypothesis that proper application of BioGlue will allow for avoidance of mid and late term complications such as pseudoaneurysm and redissection.

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