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Experience with an Albumin-Glutaraldehyde Tissue Adhesive in Sealing Air Leaks after Bullectomy

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ABSTRACT

Background: The purpose of this study was to evaluate the effectiveness of an albumin-glutaraldehyde tissue adhesive (BioGlue surgical adhesive) in preventing air leaks after bullectomy.

Methods: Between January 1999 and June 2002, BioGlue was applied over the staple or suture lines of 21 consecutive patients who underwent resection of bullae for persistent or recurrent pneumothorax. An age- and sex-matched control group of 19 bullectomy patients from our center was used for comparison.

Results: Air leak duration was significantly reduced in the BioGlue group (mean, 0.42 days; range, 0-2 days), compared with the control group (mean, 3.68 days; range, 2-11 days; $P < .001$). Chest tube drainage time was reduced to a mean of 2.33 days (range, 2-4 days) in the BioGlue group, compared with a mean of 5.42 days (range, 3-12 days) in the control group ($P < .05$). Morbidity and hospital stay length were slightly lower in the BioGlue group. There was no mortality or BioGlue-related complication in this patient cohort.

Conclusions: The use of BioGlue as a surgical lung sealant significantly decreased the duration of postoperative air leaks and the time to chest tube removal. Use of BioGlue facilitates the postoperative course following bullectomy.

INTRODUCTION

Postoperative air leakage following pulmonary resection is a common complication. Prolonged air leaks are reported to occur in 15% of patients undergoing lung surgery, an incidence increasing to as high as 55% in patients with emphysematous lungs [Rice 1992, Loran 2002]. Although air leaks are an accepted morbidity following thoracic surgery, patients and surgeons are discouraged by the need for prolonged periods of chest tube drainage and extended hospital stays. In addition, the cost of the operation and the risk of further complications such as empyema, infection, and deep vein thrombosis are increased when postoperative air leakage occurs [Wong 1997].

Despite pertinent thoracic surgical techniques, technical advances in sutures and staplers, and the development of various sealant materials, the occurrence of postoperative air leaks has not been eliminated. In March 1999, an albumin-glutaraldehyde tissue adhesive, BioGlue surgical adhesive (CryoLife, Kennesaw, GA, USA), received CE mark approval for use in pulmonary surgery.

The purpose of this study was to evaluate the performance of this novel bioadhesive following its application over the suture and staple lines with demonstrated air leakage in patients who underwent bullectomy for recurrent or persistent spontaneous pneumothorax.

MATERIALS AND METHODS

Between January 1999 and June 2002, BioGlue was applied in 21 consecutive patients who underwent thoracotomy for resection of emphysematous bullae. The indication for surgery was persistent or recurrent spontaneous pneumothorax. Bullectomy was performed by the use of regular linear GIA (60 or 80 mm) or TA (60 or 90 mm) staplers (U.S. Surgical, Norwalk, CT, USA). We used neither a buttressing material nor the inverted walls of the incised bullae to reinforce staple lines. Small bullae were resected after the placement of a hemostat at the base of the bulla. The pulmonary parenchyma was then approximated with a continuous polypropylene suture. BioGlue was then applied over the staple and suture lines where an air leak was observed. A median of 5 mL of BioGlue was used per patient (range, 5-10 mL), depending on the size of the area that was leaking air. Air leakage was particularly apparent at fixation points that overlapped. Mechanical pleurodesis with gauze was performed in all patients.

The application of BioGlue was performed in close coordination with the anesthesiologist. We applied the tissue adhesive after achieving almost the maximum expansion of the lung at a pressure of 30 to 40 mm Hg and allowed no motion of the lung for at least 30 seconds after application. A smooth amber-colored film was seen on the glued area after the completion of BioGlue polymerization, which occurred within 30 to 120 seconds (Figure 1).

We compared this group of patients with a historical cohort of 19 patients who underwent bullectomy for the same pulmonary diseases but without the use of BioGlue. The control group was matched for age, sex, and primary-to-secondary spontaneous pneumothorax ratio.

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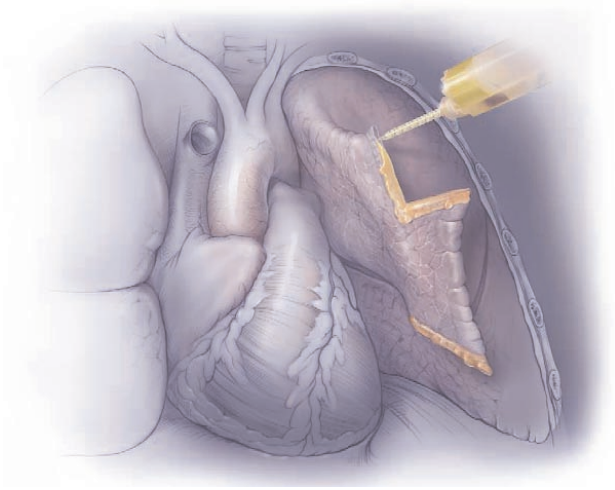

Figure 1. BioGlue was applied with the lung inflated to near maximum capacity. The lung was held motionless for 30 seconds after application.

Statistical Analysis

The two groups were compared with either the unpaired Student *t* test for continuous variables or with the chi-square test with the Yates correction for differences between categorical variables. A *P* value of <.05 was considered statistically significant.

Tissue Adhesive Description

BioGlue consists of purified bovine serum albumin and glutaraldehyde. These two components bind to each other and to cell surface proteins and the extracellular matrix. The reaction is spontaneous, is independent of the coagulation status of the patient, and results in a strong but flexible implant. The resorption process is similar to that of silk sutures and takes approximately 2 years. As the BioGlue is resorbed, it is replaced with normal fibroangioblastic granulation tissue. Both components of the adhesive are supplied in a prefilled cartridge stored at room temperature. These components are mixed within the double-helix syringe outlet of the delivery system and appear as a liquid at the end of the applicator tip (Figure 2).

RESULTS

The mean patient age of the BioGlue group was 51.8 years (range, 23-76 years) with a median age of 55 years. The female-male sex ratio was 5:21 (24% women). The primary-to-secondary spontaneous pneumothorax ratio was 7:21 (33.3% primary pneumothorax). The mean patient age in the control group was 59.2 years (range, 38-77 years) with a median age of 60 years. The female-male sex ratio was 4:19 (21% women). The primary-to-secondary spontaneous pneumothorax ratio was 6:19 (31.6% primary pneumothorax).

Two chest tubes (apical and basal) were inserted in all patients. The tubes were placed on suction (–10 cm water) postoperatively until the morning of the first postoperative day (POD), when they were placed to water seal. Chest tubes

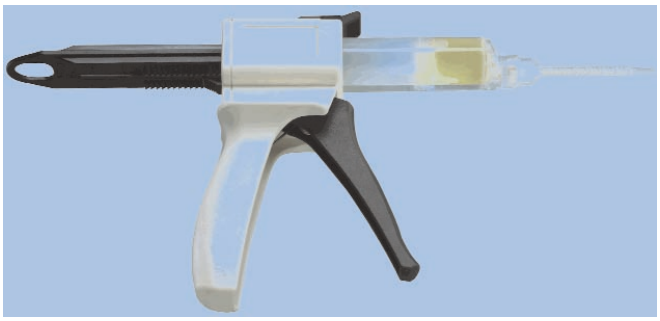

Figure 2. The BioGlue surgical adhesive delivery system is shown with the double-helix mixing tip attached.

were assessed daily by both the surgeon and the resident. The apical chest tube was removed on the first POD in patients without air leakage or when the air leak had stopped. The basal chest tube was removed when fluid drainage measured less than 250 mL in a 24-hour period.

Intraoperative air leaks were observed in all patients and were independent of the treatment group. All air leaks were from parenchymal perforations that were less than 2 mm in size. After the application of BioGlue, we did not check for further intraoperative air leakage; however, all patients (both groups) were evaluated in the recovery room for air leakage. We observed that all patients in the control group had an air leak in the recovery room (100%), in contrast to only 8 of the 21 patients treated with BioGlue (38%). Using the chi-square test with the Yates correction, we found this difference to be statistically significant ($\chi^2 = 14.71$; $P < .001$). Nevertheless, air leaks progressively resolved in these patients over time, suggesting that these early air leaks most likely represented the expulsion of air trapped during the surgical procedure.

On POD 1, air leakage had ceased in 20 of the 21 patients (95%) in the treatment group, in contrast to only 1 of the

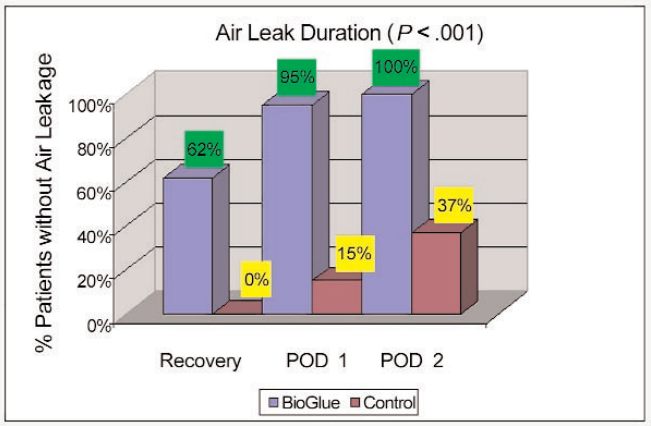

Figure 3. Percentages of patients without air leakage in the recovery room on the first postoperative day (POD 1) and on POD 2 in the treatment (BioGlue) group after sealant application (n = 21) and in the control group (n = 19).

19 patients (5%) in the control group. With the chi-square test with the Yates correction, we found this difference to be statistically significant (χ^2 = 18.87; P < .001). No patient in the treatment group had air leakage on POD 2, in contrast to 7 patients (37%) of the control group. Again, using the chi-square test with the Yates correction, we found this difference to be statistically significant (χ^2 = 16.05; P < .001). These differences in the percentages of patients free from air leaks in the two groups are shown in Figure 3.

In the BioGlue group, the mean time to the last observable air leak was 0.42 days (range, 0-2 days) with a median of 0 days. In the control group, the mean time to the last observable air leak was 3.68 days (range, 1-11 days) with a median of 3 days. The distribution of air leak duration in the control group was 1 day for 1 patient, 2 days for 6 patients, 3 days for 7 patients, and 4 days for 2 patients. For the remaining 3 patients, the air leak persisted for 8 days in one, 9 days in another, and 11 days in the third patient. Using the Student t test, we found the mean air leak duration to be significantly shorter in the group with the application of BioGlue than in the control group (t = 4.574; P < .001).

Chest Tube Drainage Time

With regard to the intercostal drainage time, the mean time to the removal of the last chest tube in the BioGlue group was 2.33 days (range, 2-4 days) with a median of 2 days. In the control group, the duration of chest tubes in the patients ranged from 3 to 12 days with a mean of 5.4 days and a median of 5 days. Using the Student t test, we again found a statistically significant decrease in mean intercostal drainage time for BioGlue-treated patients compared with the mean intercostal drainage time for the control group (t = 2.274; P < .05).

A graphic representation of the comparison of air leak and chest tube drainage times in days is shown in Figure 4.

Complications

In the BioGlue group, we did not notice any complications that could possibly be associated with the use of the tissue adhesive. We did not observe any immune responses in any patient. Postoperatively, one patient who was treated with BioGlue developed atrial fibrillation, and another developed respiratory failure, accounting for a morbidity rate of 9.5%. Both patients were treated successfully, and no mortalities occurred in the BioGlue group.

In the control group, 3 patients developed prolonged air leaks, 1 patient developed respiratory failure, and 1 patient developed pneumonia. This last patient died of sepsis in the intensive care unit, accounting for a mortality rate of 5.2%. The remaining patients were treated successfully in the ward. The morbidity rate was 26.3%. Using the chi-square test with the Yates correction, we noted no significant differences between the two groups in complication rates (χ^2 = 0.95; P > .05).

Hospital Stay

Because of the earlier removal of chest tubes and the reduced morbidity, we observed a trend toward a reduced length of hospital stay in the BioGlue group. Hospitalization times for the BioGlue-treated patients ranged from 4 to 7 days with a mean of 5.1 days, compared with a hospitalization time ranging from 7 to 27 days with a mean of 9.52 days for the patients in the control group. Using the Student t test, we did not find a statistically significant difference in mean hospitalization times between the two groups (t = 0.0007; P > .05).

Follow-up

All patients underwent clinical examination and chest radiography at 1 and 6 months postoperatively. Follow-up data are available for 20 of the 21 BioGlue patients (95%),

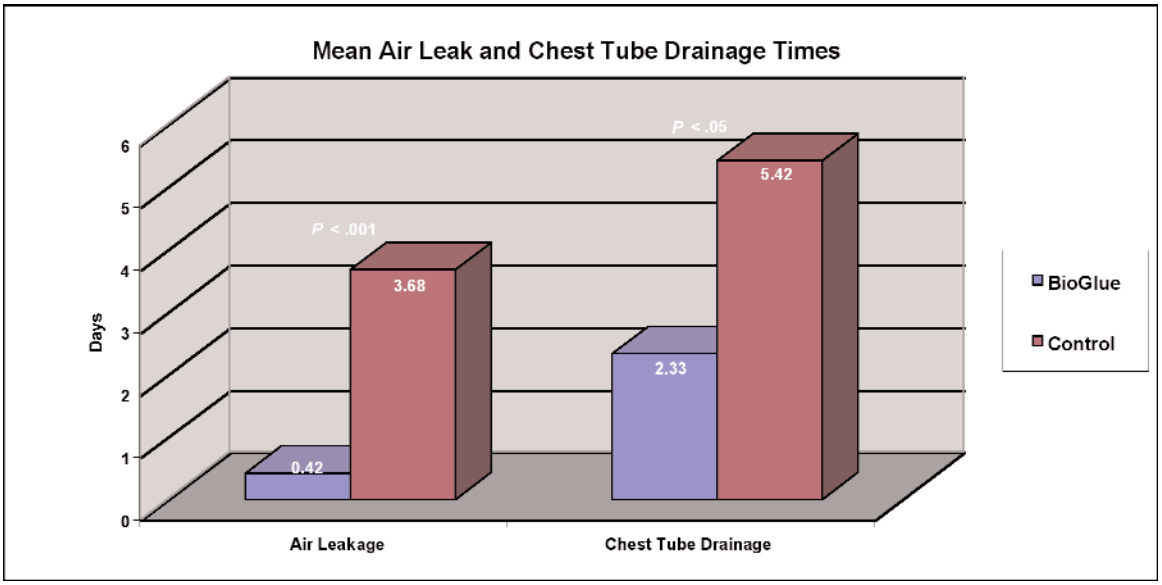

Figure 4. Duration of air leakage and chest tube drainage in days in the treatment (BioGlue) group after sealant application (n = 21) and in the control group (n = 19).

and follow-up times ranged from 1 to 23 months (mean, 12 months). Patients were also contacted by telephone for subjective evaluations. Based on our subjective and objective evaluations, we are not aware of any further sequelae in this patient cohort.

DISCUSSION

Persistent air leakage after general thoracic surgery is the most common postoperative complication that prolongs hospitalization, particularly in patients with emphysematous lungs. Malnutrition, hyperglycemia, immunosuppression, and a low forced expiratory volume in 1 second are known factors contributing to the persistence of air leaks. Longer periods of intercostal drainage result in patient immobility, distress, and an increased risk of complications and hospital costs [Cooper 1994, Wong 1997, Loran 2002].

Research on animals has shown great benefits from the intraoperative use of fibrin sealants and other biologically absorbable glues in terms of postoperative air leak prevention. Fibrin glue has been demonstrated to reduce postoperative air leakage in both experimental and clinical studies. However, Wong and Goldstraw reported that the use of fibrin sealants does not add to the benefit of conventional techniques in reducing moderate-to-severe air leakage after thoracic operations. They also noted that other clinical studies were not randomized and involved heterogeneous groups of patients. In addition, they raised concerns regarding blood-borne infection (prepared from pooled human plasma) and costs associated with fibrin sealants [Wong 1997].

Our study, although retrospective, compared 21 BioGlue patients with a historical control of 19 patients matched for age, sex, underlying lung disease, and type of surgical procedure to avoid selection bias and heterogenicity. In addition, all patients in both groups had a similar degree of air leakage (parenchymal perforations of less than 2 mm) coming from tiny pulmonary parenchymal holes along the staple or suture line.

The use of surgical bioadhesives for the repair of thoracic aortic dissection has been widely reported in the European literature. Gelatin-resorcinol-formaldehyde (GRF) glue has been reported to significantly reduce both the incidence of reoperation and false lumen formation [Hewitt 2001]. In addition to its application in aortic surgery, GRF glue has been reported to seal air leaks during thoracoscopic procedures [Nomori 1999]. However, the major disadvantage of GRF glue is the histotoxicity of the formaldehyde component.

BioGlue consists of two components, a 10% glutaraldehyde solution and a 45% bovine serum albumin solution, and is a relatively new entry into the arsenal of surgical bioadhesives that do not possess the potential toxicity of formaldehyde. Herget et al reported that BioGlue is effective in the sealing of bronchial anastomoses and lung parenchymal defects in sheep and that healing is not significantly complicated by any foreign-body reaction or tissue granulation associated with BioGlue [Herget 2001].

Porte et al reported an increased risk of empyema in the use of a photopolymerized surgical lung sealant (AdvaSeal; Ethicon, Somerville, NJ, USA, and marketed as FocalSeal in the United States) for reducing air leakage after lobectomy [Porte 2001]. We have not encountered any complications related to BioGlue toxicity in the human lung, nor have we seen any allergic reactions in our use of the product. In contrast, there was no postoperative mortality in our series, and morbidity was less in the BioGlue group than in the control group, although the difference did not reach statistical significance. In the control group, the most common complication was persistent air leakage that resulted in a prolonged hospital stay. Two of the 3 patients who developed prolonged air leakage had emphysematous lungs. Furthermore, after an average of 12 months of follow-up, we have not seen any recurrence of air leakage or other complications related to the application of BioGlue.

In a multicenter trial, a group of 172 patients undergoing thoracotomy was intraoperatively randomized to receive the only sealant currently approved by the Food and Drug Administration (FocalSeal; Genzyme Biosurgery, Cambridge, MA, USA) or to have standard lung closure [Wain 2001]. Application of the sealant resulted in the control of air leaks in 92% of the treated patients. Postoperatively, 39% of the treated patients remained free of air leaks, compared with 11% of the control group patients. Moreover, in the treatment group, trends were observed toward earlier chest tube removal and earlier discharge. No significant differences were observed between the two groups with regard to postoperative morbidity and mortality [Wain 2001].

In our series, 62% of the BioGlue patients were free of air leaks in the recovery room, compared with 0% in the control group. Moreover, 95% of the BioGlue patients were free of air leaks on POD 1, and 100% were free of air leakage on POD 2. In contrast, only 15% and 37% of the patients in the control group were free of air leaks on POD 1 and POD 2, respectively. In addition, patients in the BioGlue group had a statistically significant decrease in chest tube drainage time as well as a trend for reduced length of hospital stay.

In conclusion, BioGlue is demonstrated to be safe and effective in the sealing of air leaks from suture or staple lines in patients undergoing bullectomy. Its major advantages include ease of application, diversity of surgical use, secure tissue approximation, nontoxicity, and safety. Coordination with the anesthesiologist to achieve an almost maximum expansion of the lung at the time of BioGlue application and the controlled application of a thin layer of the bioadhesive are of utmost importance for the success of the procedure.

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