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Preliminary results with the use of an albumin-glutaraldehyde tissue adhesive in lung surgery

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Summary

Background:

The purpose of this study was to test the performance of an albumin-glutaraldehyde tissue adhesive, BioGlue[®] Surgical Adhesive (BioGlue) in the sealing of air leaks from pulmonary parenchyma and bronchopleural fistulas.

Material/Methods:

Between March 2000 and November 2001 BioGlue was applied in 38 randomly selected patients, who underwent 39 operations. The mean age was 51.4 years (range 19 to 75 years). A median of 5 cc of BioGlue was used per patient (range 5 to 20 cc). The operations included 36 thoracotomies, 2 video-assisted thoracoscopies and one rigid bronchoscopy.

Results:

The duration of air leak ranged from 0 to 2 days with a median of 1 day. The duration of total (air and fluid) chest tube drainage ranged from 1 to 12 days with a median of 3 days. Complications were observed in 3 patients (8%) and included atelectasis in one and residual space in 2. Three patients died because of preexisting respiratory failure unrelated to BioGlue application. Hospitalization ranged from 4 to 16 days with a median of 6 days and was prolonged in some patients because of their primary disease (empyema, bronchopleural fistula, etc.).

Conclusions:

The use of BioGlue proved to be safe and effective in the sealing of lung lacerations and in preventing air leakage from suture or staple lines in emphysematous lungs. It was also successful in sealing bronchopleural fistulas when applied either intra-bronchially through the rigid bronchoscope or during thoracotomy.

key words:

pulmonary • air leak • tissue adhesive • thoracic

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BACKGROUND

Postoperative air leak following lung surgery is one of the most common problems encountered in thoracic surgery. Lacerations of the lung parenchyma can result from dissection, lung sutures or staples. In contrast to minor leaks that can be treated easily, prolonged air leaks contribute significantly to increased morbidity, length of hospitalization and costs associated with thoracic operations. Therefore, prevention or elimination of postoperative air leaks is an important goal in thoracic surgery. Despite technical advances in sutures and staplers, intra-operative lung tissue trauma cannot be eliminated. Prolonged air leaks are reported to occur in 15% of patients undergoing lung surgery [1]. As a result, various sealant materials have been developed in order to replace or support sutures and staplers. Such a material should be strongly adherent to the lung, flexible, compliant, nontoxic, nonirritating, and non-antigenic. Recently, an albumin-glutaraldehyde tissue adhesive called BioGlue® Surgical Adhesive ('BioGlue', CryoLife Inc., Kennesaw, Georgia, USA), has been approved for surgical use in Europe. We conducted a retrospective study to test the performance of this novel bio-adhesive following its application to a pulmonary surface that was leaking air or to bronchopleural fistulas (BPF).

MATERIAL AND METHODS

Between March 2000 and November 2001, BioGlue was applied in 38 randomly selected patients who underwent 39 surgical procedures. These included 36 thoracotomies, 2 video-assisted thoracic surgical procedures, and 1 rigid bronchoscopy. All patients gave preoperative consent to treatment with BioGlue if needed during the operation. The risks and benefits of using this tissue adhesive, including but not limited to the possibility of infection, early removal of chest tubes, etc., were explained to all but one patient in this study group. The one exception was a patient who had sustained an iatrogenic lung laceration during video-assisted thoracic surgery (VATS), thus requiring treatment with BioGlue.

This study group consisted of 29 men and 9 women who underwent 39 surgical procedures (one patient underwent bilateral thoracotomies for metastasectomy). The procedures included 36 thoracotomies, 2 VATS and 1 rigid bronchoscopy. The patients' mean age was 51.4 years (range 19 to 75 years), and the median was 57 years. A median of 5 cc BioGlue was used per patient (range 5 to 20 cc) depending on the area of air leakage. Patient data regarding indications for surgery and type of surgical procedure are shown in Table 1.

Tissue adhesive description

BioGlue consists of purified bovine serum albumin and glutaraldehyde. These two components bind to each other and to the cell surface proteins and extracellular matrix. The reaction is spontaneous, 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 two years.

As BioGlue is resorbed, it is replaced with normal fibroangioblastic granulation tissue. Both components of the adhesive are supplied in a prefilled cartridge. 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. Various applicator lengths make it possible to use BioGlue not only during open lung surgery, but also during video-assisted thoracic surgery and rigid bronchoscopy.

Application of BioGlue during thoracotomy

Regular GIA 3.8 mm or TA 3.5 mm staplers (U.S. Surgical, Norwalk, Connecticut, USA) were used in patients who underwent thoracotomy with resection of emphysematous bullae or wedge resection of the lung. Endo-GIA 3.5 mm staplers (U.S. Surgical, Norwalk, Connecticut, USA) were used during video-assisted thoracic surgery. At the end of the procedures, the staple lines were covered with BioGlue. Patients who sustained deep lung lacerations following decortication for empyema were treated with manual suturing with running polypropylene sutures prior to the application of BioGlue. In contrast, patients who developed superficial lacerations during the lysis of adhesions or other procedures were treated with BioGlue application only. Furthermore, we used BioGlue to seal a small hole in the bronchus intermedius discovered during a redo-thoracotomy in a patient with BPF. During both thoracotomy and VATS, the application of BioGlue was performed in close coordination with the anesthesiologist. We applied the tissue adhesive after having achieved almost maximum expansion and allowed no motion of the lung for at least 30 seconds. A smooth brown film was seen on the glued area when the polymerization of BioGlue was complete (usually within 30 to 120 seconds). Proof of air seal was achieved with underwater pressure inflation of the lung at 35 mm Hg.

Application of BioGlue during VATS

By using long (27 cm) applicators via the thoracic ports, we succeeded in applying the tissue adhesive during VATS in 2 patients. The first patient underwent multiple thoracoscopic wedge resections for lung biopsies. All of his staple lines were reinforced with BioGlue. The second patient underwent thoracoscopic drainage of a post-traumatic hemothorax. During the procedure, he sustained an iatrogenic lung laceration that was 1 cm long and 0.5 cm deep. This laceration occurred while suction was being used during the lysis of adhesions. In both patients the air leak stopped immediately after the surgical procedure.

Application of BioGlue during rigid bronchoscopy

Using a rigid bronchoscope (Dumon II, Bryan Corporation, Woburn, MA, USA), we managed to apply the tissue adhesive via a long (27 cm) applicator to a 0.5 cm hole on the right main bronchial stump. This male patient presented to us with BPF following a right pneumonectomy for lung cancer that had been performed elsewhere one month earlier. This BPF had initially been

Table 1. Operative data for 38 patients who underwent air leak sealant application.

Indication for operation	Type of surgical procedure	No. of pts.
Biopsy of lung nodules or lesions	Thoracotomy/wedge resection	5
Biopsy of lung nodules or lesions	VATS/wedge resection	1
Empyema	Thoracotomy/decortication	6
Organized hemothorax	Thoracotomy/drainage/decortication	1
Organized hemothorax	VATS/drainage	1
BPF after bilobectomy	Thoracotomy/suture closure of BPF/pleural flap/thoracoplasty	1
BPF after pneumonectomy	Rigid bronchoscopy/BioGlue application	1
PTX/emphysematous bullae	Thoracotomy/bullae resection	19
Bronchogenic cyst	Thoracotomy/cyst resection	1
Hydatid cyst of the lung	Thoracotomy/wedge resection of cyst	1
Inflammatory lung tumor	Thoracotomy/lobectomy	1

Pts – patients; VATS – video-assisted thoracic surgery;

BPF – bronchopleural fistula; PTX – pneumothorax

Table 2. Range of postoperative air leak, chest tube drainage and hospitalization in relation to surgical indication in study patients.

Indication for surgery	No. of pts.	Air leak (days)	CT drainage (days)	HS (days)
Benign or malignant lung lesions	6	0–1	2–3	4–7
Empyema	6	0–2	4–8	7–14
Organized hemothorax	2	0 and 1	2 and 2	4 and 5
BPF	2	0 and 2	5 and 8	6 and 12
PTX/emphysematous bullae	19	0–2	1–3	4–7
Bronchogenic cyst	1	0	2	6
Hydatid cyst of the lung	1	0	12	15
Inflammatory lung tumor	1	1	8	16

Pts – patients; CT – chest tube; HS – hospital stay;

BPF – bronchopleural fistula; PTX – pneumothorax

treated with a chest tube thoracostomy and antibiotics for ten days. A 0.5 cm hole on the left edge of the bronchial stump was discovered during flexible bronchoscopy. The Dumon II rigid bronchoscope allows for the simultaneous use of different accessories and rigid 0° optics connected to an endoscopic camera. Through an adult tracheal tube (260 mm/12.2 mm) we directed the applicator tip just above the hole of the bronchial stump. Again, coordination with the anesthesiologist was critical to the success of the procedure. Under apnoeic conditions of about one minute to allow for complete polymerization, BioGlue sealed the hole in the bronchial stump. We did not accept oxygen saturation of less than 90% during the procedure. The air leak ceased immediately after the procedure, and the chest tube was removed 4 days later. The patient was discharged on the 6th postoperative day.

Assessment of air leak

Two chest tubes (apical and basal) were inserted in all patients who underwent thoracotomy. These were placed for post-operative suction (10 cm of H₂O). The 2 patients who underwent video-assisted thoracic surgery had one chest tube placed for suction (10 cm of H₂O). The patient who underwent rigid bronchoscopy had a chest tube placed initially to a water seal that was draining air and pus. If a patient had no air leak immediately after the procedure or within the first hour after the procedure, that

patient was assigned to the 0 day air leak group. If a patient had air leak cessation during the first 24 hours, that patient was assigned to the 1 day air leak group. Patients with air leak cessation during the first 48 hours were assigned to the 2-day air leak group. Chest tubes were assessed daily by both the surgeon and the resident. The apical chest tube was removed on the 1st postoperative day in patients with 0 days air leak or when the air leak had ceased. The basal chest tube remained in place until fluid drainage was less than 200 cc per day, unless there was another clinical reason for chest tube use.

RESULTS

Postoperatively, the mean time to the last observable air leak was 0.6 days, and ranged from 0 to 2 days with a median of 1 day. Only 4 patients were assigned to the 2-day air leak group, while 20 were assigned to the 1-day air leak group. The air leak ceased immediately or within the first hour postoperatively in the remaining 19 patients.

With regard to the total drainage time (air and fluid), the mean time to the removal of the last chest tube was 3.4 days and ranged from 1 to 12 days. The median time was 3 days. In some patients we noticed an extended drainage time (without air leak), which was due to their underlying disease (empyema, BPF, etc.). Exclusive of the 2 patients who developed residual space, the prolonged

drainage could not be attributed to the use of BioGlue. The distribution of drainage time range and hospitalization in relation to surgical indications is given in Table 2.

Complications

Complications that could possibly be associated with the use of BioGlue were observed in 3 patients. All three of these patients underwent tissue adhesive application during thoracotomy. The complications included atelectasis in 1 patient and residual space in 2. If this study group were homogenous regarding the type of surgical procedure or the indications for surgery, we would be able to note a morbidity of 8%. With this cohort of patients, who underwent various surgical procedures, we studied only the effectiveness of BioGlue in regard to aerostasis. Interestingly, we did not observe any other complications.

The first patient underwent decortication for empyema. Extensive superficial lacerations that had been created during surgery were treated by applying BioGlue. On the 1st postoperative day she developed a persistent atelectasis of the right lower lobe and a low temperature that was treated with physical therapy and antibiotics. The air leak ceased on the 2nd postoperative day, and the fluid drainage on the 5th postoperative day. She was discharged on the 14th postoperative day. The atelectasis had resolved by her follow-up one month later.

The second patient underwent resection of large bullae and the staple lines were reinforced with BioGlue. Postoperatively, he developed a residual 'space' on the top of the right hemithorax. Air leak ceased on the 1st postoperative day. Chest tubes were removed on the 2nd and 3rd postoperative day. He was discharged on the 5th postoperative day. The space had resolved by the time of his follow-up evaluation 2 months later.

The third patient underwent a right lower lobectomy for a 2 cm by 3 cm parenchymal tumor. Air leak ceased on the 1st postoperative day. Chest tubes were removed on the 2nd and 8th postoperative day because of a residual space in the right hemithorax. This space was due to inadequate re-expansion of the right middle lobe. On the 9th postoperative day we noticed a yellowish fluid coming out of the last chest tube site and the patient underwent VATS, with the assumption of an early empyema. Fortunately, there was neither pus nor pseudomembranes inside the chest. Cultures were negative and the yellowish fluid drainage resolved two days later. It is worth mentioning that during the VATS procedure we noticed a widely spread film of BioGlue on the lower surface of the middle lobe that was possibly preventing its re-expansion. We had the anesthesiologist inflate both the upper and middle lobes with positive pressure. The middle lobe appeared to be somewhat 'trapped'. Nevertheless, the patient was discharged 7 days later without residual space.

In these three patients we had applied the maximum quantity of BioGlue (20 ml) because of significant air leak. In addition, it is possible that the bioadhesive had been applied without having the lung in almost maxi-

imum expansion. This represents our learning curve with this relatively new product.

With regard to the 3 patients who expired within 30 days postoperatively in the Intensive Care Unit, all of them were suffering from preexisting incapacitating respiratory failure. The first two patients underwent thoracotomy for persisting pneumothorax secondary to bullous emphysema. For these two patients, the air leak ceased immediately postoperatively and on the 1st postoperative day, respectively. The third patient underwent thoracotomy for lung biopsy. The air leak ceased immediately postoperatively, and the diagnosis was pulmonary fibrosis. None of these patients could be weaned off the ventilator despite the fact that they had no signs of inadequate lung re-expansion.

Follow-up

The treated patients underwent clinical examination and chest X-ray at 1 and 6 months postoperatively. Follow-up data are available for the 35 survivors, ranging from 1 to 18 months (average 9.5 months). The patients were contacted by telephone for subjective evaluations. We are not aware of any further sequelae. Three additional patients succumbed to their co-existing cancer after 6, 8 and 11 months, during the follow-up period, without reporting any complications related to their surgery.

DISCUSSION

Persistent air leak after lung surgery remains a universal daily problem for thoracic surgeons, particularly in patients with emphysematous lungs [2]. Replacement or support of sutures and staplers with surgical tissue adhesives has been investigated for many years. The reasons for this interest are obvious: earlier removal of chest tubes, reduced postoperative pain, earlier recovery, shorter hospitalization, and lower costs.

The use of surgical bioadhesives for the repair of thoracic aortic dissection has been widely reported in the European literature. Gelatin-resorcinol-formaldehyde glue has been reported to significantly reduce both the incidence of re-operation and false lumen formation [3]. In addition to application in aortic surgery, the aforementioned glue has been reported to seal air leaks during thoracoscopic procedures [4]. However, the major disadvantage of this glue is the histotoxicity of the formaldehyde component. The use of other tissue adhesives without formaldehyde has also come to be accepted not only in Europe, but also in the United States. However, fibrin glue has a relatively low adhesive strength and cyanoacrylate glue has poor biocompatibility.

BioGlue, which consists of two components, a 10% glutaraldehyde solution and a 45% bovine serum albumin solution, is a relatively new item in the arsenal of surgical bio-adhesives, which does not possess the potential toxicity of formaldehyde [5].

Although our study group of 38 patients was not homogenous regarding the indications for surgery and surgical

approaches, we were able to demonstrate that BioGlue is successful and effective in the sealing of air leaks from the pulmonary parenchyma and from BPF. Our preliminary results, as shown in Table 2, provide evidence that this tissue adhesive is effective in the various surgical scenarios represented in this cohort. BioGlue completely sealed air leaks by the 1st postoperative day in 19 patients with bullous emphysema who underwent bullae resection for persistent pneumothorax. In the literature, air leaks after such lung volume reduction procedures are reported to occur in as many as 50% of patients [6].

Herget et al. reported that BioGlue is effective in the sealing of bronchial anastomosis and lung parenchyma defects in sheep [7]. Histopathology after 4 weeks detected few remnants of the tissue adhesive surrounded by fibrous scar in bronchial anastomoses and parenchymal repairs. Healing was not considerably complicated by foreign body reaction or tissue granulation. In our series, after an average of 9.5 months of follow-up, we did not encounter complications related to BioGlue toxicity in the human lung, nor did we see any recurrence of air leak or other complications related to the application of BioGlue. We did observe morbidity that could possibly be attributed to BioGlue application, and we have described these events in detail here. Although we have no histology specimens of lung tissue following BioGlue application, we had two opportunities to look at the polymerized BioGlue postoperatively. The first was by using VATS in the patient who had undergone thoracotomy 9 days earlier. The second was during repeat rigid bronchoscopy 30 days after intra-bronchial BioGlue application to seal a BPF. In both cases we observed a dark brown film covering either the lung parenchyma or the bronchial stump, without any signs of inflammation or granulation tissue formation.

It should be mentioned that we applied BioGlue in 6 patients who underwent decortication for empyema. We attempted to cover extensive lacerations of the lung parenchyma that had been caused by dissection and lysis of adhesions. The air leak ceased either immediately after the procedure or by the 2nd postoperative day in all six of these patients. Moreover, we had no complications related to a foreign body reaction or any recurrence of empyema. In contrast, in a study from France, Porte et al. reported an increased risk of empyema when using a photo-polymerized surgical lung sealant

(Advaseal, Ethicon, Inc., Somerville, New Jersey, USA), for reducing air leak after lobectomy [8].

CONCLUSIONS

BioGlue was demonstrated to be safe and effective in the sealing of air leakage from pulmonary parenchyma and bronchopleural fistulas. Its major advantages include ease of application, diversity of surgical use, secure tissue approximation, non-toxicity, and safety. Among the most important factors conditioning the success of the procedure are coordination with the anesthesiologist in order to achieve an almost maximum expansion of the lung at the time of applying BioGlue, and the application of reasonable amounts of the bioadhesive.

Although the study results are introductory, they are encouraging with regard to the effectiveness and safety of this surgical bioadhesive in lung surgery.

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