A prospective, randomized, controlled trial of the effectiveness of BioGlue in treating alveolar air leaks

Patrick Tansley, FRCS, Faisal Al-Mulhim, FRCS, Eric Lim, MRCS, George Ladas, FETCS, and Peter Goldstraw, FRCS

Objective: The use of tissue glues has been advocated to reduce post-thoracotomy alveolar air leaks, but outcomes have been inconclusive. The aim of this study was to determine the effectiveness of BioGlue (CryoLife Europa Ltd, Hampshire, United Kingdom) in eliminating post-thoracotomy alveolar air leaks.

Methods: A prospective, randomized, single-blind, controlled trial was conducted in which patients were stratified according to the severity of post-thoracotomy air leak that could not be controlled by conventional surgical techniques. They were allocated to a control arm (surgical treatment only) or an interventional arm (surgical treatment and BioGlue). Duration of air leak, intercostal drainage, and hospital stay comprised primary study end points.

Results: From December 2002 to January 2005, 52 patients were randomized, 29 (56%) of whom were men. The mean age was 59 ± 15 years, and other characteristics were comparable in both groups. Indications for surgery were malignancy in 46 patients (88%), carcinoid tumor in 2 patients (4%), and infective disease in 4 patients (8%). Patients in the BioGlue arm had shorter median duration of air leaks, 1 (0-2) versus 4 (2-6) days ($P < .001$); intercostal chest drainage, 4 (3-4) versus 5 (4-6) days ($P = .012$); and hospital stay, 6 (5-7) versus 7 (7-10) days ($P = .004$), compared with controls. No major complications were encountered using BioGlue.

Conclusions: This study demonstrates clear benefit from BioGlue in the treatment of alveolar air leaks through reduction of air leak duration, chest drainage time, and hospital stay. Systematic use of BioGlue may be warranted in adult thoracic surgical procedures (except pneumonectomy and decortication) when an air leak remains after all other steps to control it have failed.

From the Department of Thoracic Surgery, Royal Brompton Hospital, Sydney Street, London.

Presented at the fourth joint meeting of the European Society of Thoracic Surgeons/European Association for Cardiothoracic Surgeons, Barcelona, September 2005, for which Patrick Tansley won the Young Investigator's Award.

Received for publication Nov 3, 2005; accepted for publication Feb 24, 2006.

Address for reprints: Peter Goldstraw, FRCS, Department of Thoracic Surgery, Royal Brompton Hospital, Sydney Street, London, SW3 6NP, United Kingdom (E-mail: p.goldstraw@rbht.nhs.uk).

J Thorac Cardiovasc Surg 2006;132:105-12
0022-5223/\$32.00

Copyright © 2006 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2006.02.022

Prolonged alveolar air leak (AAL) after thoracotomy is generally defined as an air leak that lasts more than 7 days. AAL prevalence is greater than 15%, and it may result in serious complications including longer duration of intercostal drainage and increased immobility with associated risks of infection, empyema, and thromboemboli.¹⁻³ These complications may lead to greater postoperative pain and longer hospital stays with increased associated costs.⁴

Various attempts have been made to prevent or reduce the incidence of post-thoracotomy AAL including additional surgical techniques, postoperative water-seal drainage, and surgically applied sealants.⁵⁻¹²

Experimental use of fibrin glue initially showed promise in reducing AAL,¹³ but more recent clinical studies showed less benefit,^{14,15} and others were compromised by nonrandomized methodology or routine use of glue irrespective of the presence or degree of AAL,¹⁶⁻¹⁹ which may have diluted the effect of the sealant by populating both the control and intervention groups with patients destined to do well regardless of group assignment.

BioGlue (CryoLife Europa Ltd, Hampshire, United Kingdom) surgical adhesive is a topically applied mixture of bovine serum albumin and glutaraldehyde. In North

Abbreviations and Acronyms

AAL = alveolar air leak
 POD = postoperative day

America, it is approved for use as an adjunct to standard methods of hemostasis in open surgical repair of large vessels.^{20,21} It also has European approval for use in a wide range of soft tissue repairs.²²

The aim of this trial was to determine the effectiveness of BioGlue in eliminating post-thoracotomy AAL using clinically relevant outcome measures.

Materials and Methods**BioGlue and Application**

BioGlue surgical adhesive is a topically applied mixture of bovine serum albumin and glutaraldehyde. It is supplied in a prefilled cartridge and stored below 25°C. The components of the product are mixed within a double-helix applicator attached to a syringe. Polymerization with tissues occurs immediately on application, and bonding strength is reached within 2 minutes. Evidence of incomplete resorption of BioGlue has been identified at 2 years.²³

Participants

This was a prospective, randomized, single-blind, controlled study with 3 participating consultant surgeons. Before the study was begun, approval was obtained from the Royal Brompton, Harefield, and National Heart Lung Institute Ethics Committee. Informed patient consent was obtained before each operation. The study was performed at the Royal Brompton Hospital during a 25-month period (December 2002 to January 2005). Inclusion criteria included adults aged more than 18 years undergoing any thoracic surgical procedure (including redo surgery) likely to result in AAL, with the exception of decortication for acute empyema because of the potential risk of BioGlue acting as a foreign body, which may increase risk of infection as shown after the use of other lung sealants.¹¹ Exclusion criteria included age less than 18 years, pregnancy/breastfeeding, previous ipsilateral treatment with BioGlue, no air leak at the end of the surgical procedure, and pneumonectomy surgery.

Randomization

Randomization was undertaken with sequential closed envelopes stratified by the severity of air leak in permuted blocks of 6. In each case, the operating surgeon decided on trial entry on the basis of any grade of air leak that could not be controlled by conventional surgical techniques comprising sutures and diathermy. Patients in whom AAL could be controlled in this way were not included.

Intervention

After completion of each surgical procedure, the thoracic cavity was filled with warm water (malignant cases) or saline (benign cases) to ensure that all dissected fissures, staples, suture lines, and pulmonary parenchymal surfaces were immersed. The lung was then mechanically ventilated to inflate any atelectatic zones. An

TABLE 1. Intraoperative air leak grading

Air leak grading	Intraoperative physiologic definition
0	No leak
1	Minor leak
2	Moderate leak not detected by anesthetist but easily visible to surgeon
3	Major leak detected by anesthetist through loss of ventilation volume

end-inspiratory airway pressure of 25 cm water (2.5 kPa) was applied to assess the degree of air leak, which was graded 0 to 3 using a simple, easily reproducible technique (Table 1).

Air leaks of grades 1 to 3 prompted a conventional surgical control attempt by sutures and diathermy as determined by the operating surgeon. If AAL persisted after all appropriate measures had been taken, grade-dependent, closed-envelope randomization was undertaken between the interventional arm (BioGlue) and non-interventional (surgical treatment only) control arm. Fluid was evacuated from the chest cavity. In the interventional arm, BioGlue was then applied to the deflated lung to avoid any potential disruption of its structural integrity during the bonding process as a result of air leak. The amount applied was kept to the minimum considered appropriate by the operating surgeon, but as many packs were used as required to ensure the lung was airtight. It was directly squirted on with the product applicator by the consultant or a senior trainee under direct consultant supervision. A 2-minute pause was then timed to allow the BioGlue to reach bonding strength before the lung was reinflated, and assessment for air leaks was repeated until lung integrity was ensured. No BioGlue was applied to bronchial stumps or sleeve anastomoses.

All patients had 1 or 2 drains, as clinically appropriate, placed to the apex (anteriorly and/or posteriorly, with basal holes cut in addition) before chest closure and were managed on an underwater-sealed basis. Fifty of the 52 randomized cases were cared for by 2 surgeons who managed patients according to an identical postoperative chest drain protocol, and 1 patient in each arm was managed by a surgeon who did not apply suction to the underwater seal. The chest drain protocol involved the intraoperative application of 5 kPa (51 cm water) negative pressure suction at the end of each case, continuing until any air leaks had stopped. It was then converted to an underwater seal only without suction for a period of 24 hours. If no further air leaks were present, drains were then removed.

Postoperative air leaks were defined as the presence of a single bubble of air in the chest drains during the course of normal or forced expiration (coughing). Only senior trainees, with an agreed definition of postoperative air leak, performed daily objective assessments that were concurrently verified by independent senior nursing staff. Chest drains were removed when no further bubbles were identified during daily assessment. Persistent air leaks after 14 days of standard intercostal chest drainage were converted to Heimlich valve drainage. For statistical analysis in these cases, prolonged air leaks were considered present until removal of intercostal chest drains.

TABLE 2. Patient demographics

	Control arm (n = 27)	BioGlue arm (n = 25)	P value
Mean age (y), n (SD)	60 (15)	59 (16)	.670
Male sex, n (%)	15 (56)	14 (56)	1.000
Reoperation, n (%)	2 (7)	3 (12)	.662
Procedure, n (%)			
Lobectomy	12 (44)	9 (36)	
Lobectomy + lesser resection	3 (11)	3 (12)	.351
Segmentectomy	7 (26)	2 (8)	
Lingulectomy	1 (4)	1 (4)	
Metastasectomy	4 (15)	8 (32)	
Other	0	2 (8)	
Diagnosis, n (%)			
Malignancy (primary or secondary)	26 (96)	20 (80)	
Carcinoid	1 (4)	1 (4)	.140
Infection	0 (0)	4 (16)	
Severity of air leak, n (%)			
Mild	20 (74)	20 (80)	
Moderate	5 (18)	5 (20)	.640
Severe	2 (7)	0 (0)	

SD, Standard deviation.

Statistical Methods

The primary outcome measures were duration of air leak, intercostal drain time, and hospital stay. Any observed complications were also carefully noted. Patients were grouped according to treatment allocation and compared with *t* tests for normally distributed measures, Mann-Whitney tests for non-normally distributed measures, and Fisher exact test for proportions. In addition, a time-to-event Kaplan-Meier analysis was performed and compared using the Peto test.

Sample Size Calculation

On the basis of a retrospective review of data obtained in the thoracic surgical department at the Royal Brompton Hospital, 62% of patients were expected to have their chest drains removed on or before the third day. On this basis, our null hypothesis was that there would be no difference in the proportion of patients achieving chest drain removal at postoperative day (POD) 3. With 90% power and a significance level of 5% to detect a difference of 20%, it was calculated that 94 patients would be required to conduct the study. Allowing for 10% dropout, we planned to recruit 104 patients (52 in each arm) in total. An interim analysis was planned at halfway through the study after 52 patients had been recruited, and the trial would be stopped if conventional levels of statistical significance were achieved.

Results

Patients and Operations

During the 25-month recruitment period, 210 patients consented to be included in the study. Of these, 158 patients had no intraoperative air leak at the end of the procedure after

TABLE 3. Primary outcomes

	Control arm (n = 27)	BioGlue arm (n = 25)	P value*
Duration of air leak (d)	4 (2-6)	1 (0-2)	<.001
Duration of intercostal drainage (d)	5 (4-6)	4 (3-4)	.012
Duration of hospital stay (d)	7 (7-10)	6 (5-7)	.004

All numbers presented as median with interquartile range. **P* values obtained using Mann-Whitney test.

conventional surgical control measures, and no patient required pneumonectomy. Fifty-two patients fulfilled intraoperative criteria appropriate for randomization (25 in the BioGlue arm; 27 in the non-interventional arm). More than 1 pack of BioGlue was used in only 2 cases in the interventional arm. Forty-two patients had 2 drains placed, and 10 patients had 1 drain placed. Demographics of each group were well matched; the small discrepancy in the numbers of patients in each arm arose by chance because the trial was stopped midway through a randomization block for grade 3 air leaks (Table 2).

Primary Outcome Measures

At the interim analysis conducted halfway through the study, a shorter median duration of air leak ($P < .001$), intercostal chest drainage ($P = .012$), and hospital stay ($P = .004$) were identified in favor of the BioGlue arm (Table 3; Figures 1-3). In addition, 10 of 27 patients (37%) in the control group and 19 of 25 patients (76%) in the BioGlue arm had the chest drain removed on or before POD 3. The difference was 39% in favor of the BioGlue arm ($P = .004$). We decided to stop the trial early because of these results.

Observed Complications

A total of 24 complications occurred in 17 patients. Five patients (2 in the BioGlue arm and 3 in the control arm) had prolonged AAL resulting in delayed removal of the intercostal chest drains. The drain was converted to a Heimlich system on POD 9 (outside the usual protocol on POD 14) in 1 patient (BioGlue arm) to allow safe transfer to a computed tomography scanner before eventual removal on POD 29; the AAL in the other patient in the BioGlue arm settled on POD 12, after which the drain was removed on POD 13. The drains were removed on POD 12 ± 5 (mean $\pm$ standard deviation) in 3 patients in the control arm despite the continued presence of air leaks, which were not considered to be of clinical importance. No patients required subsequent reinsertion of drains.

Two patients in the control arm required reintubation for respiratory failure and readmission to the intensive care unit; 1 patient recovered and was discharged on POD 9, and 1 patient had multiorgan failure and died on POD 16.

Figure 1. Percentage probability of air leak after surgery. Intraoperative randomization at time point zero. Subsequent assessment in the recovery room shown adjacent to time point zero. Number of patients at risk at any time are shown above the x-axis.

Other more minor complications resulting in delayed discharge included diarrhea in 3 patients (1 in the BioGlue arm; 2 in the control arm); nonsignificant arrhythmias in 2 patients (control arm); bowel complications requiring conservative management in 2 patients (control arm); difficult analgesic management in 2 patients (control arm); clinically unimportant pneumothoraces after the initial intercostal chest drain removal in 2 patients (1 apical and 1 basal; both in the BioGlue arm) requiring conservative management only; pneumothorax requiring further intercostal drain insertion in 1 patient (BioGlue arm); prolonged fluid drainage for no obvious reason in 1 patient (control arm), which delayed intercostal drain removal by 3 days; and prolonged fluid drainage in 2 patients (BioGlue arm), one for no identifiable reason but it required 4 extra days of chest drainage, and one noninfected chylous leak caused by a thoracic duct injury that required closure at redo-thoracotomy, resulting in delayed intercostal drain removal by 6 extra days.

Discussion

Biologic glues are not an alternative to meticulous surgery. However, there has been much recent investigation into their value as adjunctive therapy for patients with difficult air leaks at surgery that do not respond to conventional surgical techniques. Unfortunately, some studies using a variety of glues have lacked rigorous scientific method and have enrolled heterogeneous groups of patients, thus producing results and conclusions from which little can be drawn.

At the time this study was designed, the 4 prospective, randomized, controlled trials that compared standard closure techniques plus sealant with standard closure techniques alone in elective lung resection (mainly for lung cancer) published conflicting results regarding treatment effectiveness for postoperative AAL.²⁴ Two of the trials using fibrin glue showed no statistical differences between treatment and controls when comparing reduction of duration of AAL, intercostal drainage, and length of hospitalization.^{14,15} However, the other 2 trials, 1 of which used fibrin glue and 1 of which used a novel synthetic hydrogel sealant (FocalSeal, Focal Inc, Lexington, Mass), showed a significant reduction in postoperative AAL in the treatment groups but no differences in hospital stay, intercostal chest drainage, or other complications.^{25,26} Despite the conclusion that surgical sealants may offer some benefit in reducing postoperative AAL, the non-uniformity of evidence meant that their systematic clinical use could not be advocated and that further randomized, controlled trials were recommended.²⁴

A more recent review examined 8 similar trials.²⁷ Of the 12 trials thus examined in total, 9 showed a statistically significant difference between treatment and control groups in reducing postoperative AAL.^{17,25,26,28-33} However, in only 1 trial each did this lead to a significant reduction in duration of intercostal chest drainage¹⁷ or hospital stay.²⁸ The authors concluded that although surgical sealants seemed to reduce the duration of postoperative AAL, duration of intercostal chest drainage and hospitalization was

Figure 2. Percentage probability of continued requirement for intercostal chest drainage after surgery. Recovery room assessment at time point zero. Number of patients at risk at any time are shown above the x-axis.

largely unaffected. As a result of these inconclusive results from heterogeneous trials using a variety of sealants, it was again concluded that their systematic use could not be recommended and that further randomized control trials are needed.²⁷

Until now, BioGlue has only been subjected to retrospective, nonrandomized, uncontrolled studies on heterogeneous groups of patients to examine its effectiveness in reducing AAL.³⁴⁻³⁶ Therefore, its use remains largely determined by individual surgeon preference. The aim of this study was to examine the management of AAL, of all degrees of severity, using BioGlue in a prospective, randomized, controlled manner, in a clinically relevant scenario in which an air leak persists after all conventional techniques have been exhausted. Inclusion criteria were deliberately broad in an attempt to reflect the practice of a typical thoracic surgical unit so results would be clinically relevant and widely applicable. Almost all patients underwent resection of pulmonary tissue to some degree (Table 2). The intraoperative air leak grading system was simple, pragmatic, and easily reproducible. It worked well and allowed easy inter-surgeon communication. A carefully stratified randomization process ensured that patients were well matched for the initial severity of air leak. It was not possible to measure the volume of glue applied to each leak, given the design of the applicator devices, and the urgent priority required for accurate surgical placement of glue, given the rapidity of bonding after application. However, the volume applied was kept to the minimum considered appropriate by each operating surgeon to ensure the lung was airtight. In only 2 cases

with multiple air leaks was more than 1 pack used, but again the minimum possible was applied to each individual leak. Although this area may constitute a limitation of the trial, variation was minimized as much as possible within practical limitations.

The number of drains inserted was dictated by the clinical need as assessed by the operating consultant surgeon. We did not believe it was ethical to impose any other regimen. Although we recognize this is a potential limitation of the trial, we do not believe it affected the results, because air leak presence was defined as a single bubble of air that should be identifiable irrespective of the number of drains placed. In addition, the shorter duration of air leak in the treatment arm is statistically independent of any difference in chest drain management.

In total, 50 of the 52 randomized cases were cared for by 2 surgeons who managed patients according to an identical postoperative chest drain protocol, and 1 patient in each arm was managed by a surgeon who did not apply suction to the underwater seal. The chest drain protocol involved the intraoperative application of 5 kPa (51 cm water) negative pressure suction at the end of each case, continuing until any air leaks had stopped. It was then converted to an underwater seal only, without suction, for a period of 24 hours. If no further air leaks were present, the drains were then removed. In this context we do not believe that there was any significant difference in postoperative chest drain management that would impair the results of the study. Moreover, "time to resolution of air leak," which was statistically

Figure 3. Percentage probability of in-hospital stay after surgery. Recovery room assessment at time point zero. Number of patients at risk at any time are shown above the x-axis.

significant, is independent of any differences in chest drain management.

The results clearly demonstrated advantage in the intraoperative use of BioGlue in reducing AAL, duration of intercostal chest drainage, and in-hospital stay after thoracotomy. All of these primary outcome measures demonstrated statistical significance consistently in favor of BioGlue. Figure 1 demonstrates that the beneficial effects of BioGlue occurred from the time of intraoperative administration because there was a greater incidence of patients leaving the operating room, compared with controls, without an air leak. In addition, air leaks then settled much more quickly in the BioGlue arm in comparison with the slower, steadier pace seen in controls. The translated clinical benefits were a shorter duration of intercostal chest drain requirement and hospital stay by 1 day each. In contrast, it can also be clearly seen in Figure 1 that almost all patients not receiving BioGlue had an air leak on leaving the operating room, and in 68% it was still present on POD 2. Although these results are not characteristic of our unit's practice, they may reflect the fact that for the purposes of the study, a single air bubble was considered to represent an "air leak." In regard to the relevant complications, 2 of the 3 pneumothoraces noted in the BioGlue arm after chest drain removal were small, clinically unimportant, and did not require treatment. A third required further drainage with successful outcome. We are unable to determine conclusively whether they occurred purely by chance. Certainly there was no statistically significant difference (Fisher exact test, $P = .10$); however, the number of complications are small, and we would regard

our observation of 3 recurrent pneumothoraces with appropriate caution. Possible bias toward earlier removal of drains in the treated group was minimized, because decisions were still governed on the basis of air leak, which was quicker to resolve in the BioGlue arm.

Prolonged daily fluid outputs occurred in 3 patients (2 in the BioGlue arm; 1 in the control arm), all of whom underwent resection for malignancy. This did not affect statistical analysis for duration of air leaks measured independently, and despite the required extra duration of chest drainage in the patients in the BioGlue arm, time to overall removal of chest drains was still statistically significantly shorter in the BioGlue arm.

Small sample size, calculated for the original study to include 104 patients, may be a limitation of the trial. However, the trial was stopped at its halfway point, on the basis of interim analysis of results, because the predefined end points had been reached. Although the numbers may seem small, appropriate considerations were taken into account for power and sample size calculation.

The greater effect size identified in comparison with previous trials prompts the question of whether it relates to the product itself or alternatively to the exclusion of patients without air leaks at the end of the operation. This remains a difficult question to answer. Certainly the methodology of this trial sought to assess the product's effectiveness only in patients who had an air leak that was not controllable by conventional measures. This differed from some other trials in which lung sealants were applied irrespective of the presence of air leak, an action that may have diluted the effect

of the sealants examined by populating both the control and intervention groups with patients destined to do well regardless of group assignment.^{17,19} The fact that our trial differed in this regard may well have influenced the outcome and is the key to differentiating this trial from others. However, the product itself may also have conferred benefits not present in other sealants. The contribution of each component is difficult to quantify, but the outcome is likely to relate to an element of both factors. Because the product was evaluated in small groups in this trial, but in a methodologically appropriate manner, interpretation of the encouraging results in comparison with other trials should be left to the reader, but further large-scale studies are encouraged to extend and confirm the data.

Some generic concerns remain regarding tissue glues, including the potential risk of bloodborne disease transmission. Although we are not aware of any specific incidences with BioGlue, its bovine product formulation must be considered. In this respect, efficacious autologous fibrin preparations might confer advantage. Other concerns include foreign body implantation, exacerbated by slow resorption, that may predispose to empyema formation.^{11,23,37} Before the start of this study, 1 patient treated with BioGlue at thoracotomy presented with an empyema 6 weeks postoperatively. We cannot be certain whether this complication was a direct result of using BioGlue, although the possibility exists. Additional issues include the potential spilling of glue on large airway stumps preventing efficient stump burial and predisposing to bronchopleural fistula formation, potential toxicity, embolic phenomena, and inflammation.³⁸⁻⁴⁰

Historically, there has been considerable difficulty in establishing a clear message on the effectiveness of surgical sealants in preventing air leaks.^{24,27} Indeed, the comments in the first Cochrane review²⁴ on the need for further randomized, controlled trials initially prompted us to contribute to the evidence base. For a sealant to be shown to be effective, its application should lead to a reduction in the incidence and duration of air leak, as demonstrated in this trial. This prospective, randomized study is the first in which the sealant (BioGlue) succeeds in the reduction of air leak and demonstrates a reduction in drainage time with subsequent reduced hospital stay. The study suggests that the systematic use of BioGlue in the treatment of AAL after thoracotomy may be warranted in adult thoracic surgical procedures, with the exception of pneumonectomy and decortication, when an air leak remains after all other steps to control it have failed. In this context, our study makes a positive contribution to the information available to surgeons.

References

- Rice T, Kirby T. Prolonged air leak. *Chest Surg Clin N Am*. 1992;2:803-11.
- Stolz AJ, Schutzner J, Lischke R, Simonek J, Pafko P. Predictors of prolonged air leak following pulmonary lobectomy. *Eur J Cardiothorac Surg*. 2005;27:334-6.
- Adebonojo SA. How prolonged is "prolonged air leak"? *Ann Thorac Surg*. 1995;59:549-50.
- Varela G, Jimenez MF, Novoa N, Aranda JL. Estimating hospital costs attributable to prolonged air leak in pulmonary lobectomy. *Eur J Cardiothorac Surg*. 2005;27:329-33.
- Okur E, Kir A, Halezeroglu S, Alpaly AL, Atasalihi A. Pleural tenting following upper lobectomies or bilobectomies of the lung to prevent residual air space and prolonged air leak. *Eur J Cardiothorac Surg*. 2001;20:1012-5.
- Vaughn CC, Wolner E, Dahan M, Grunenwald D, Vaughn CC III, Klepetko W, et al. Prevention of air leaks after pulmonary wedge resection. *Ann Thorac Surg*. 1997;63:864-6.
- Venuta F, Rendina EA, De Giacomo T, Flaishman I, Guarino E, Ciccone AM, et al. Technique to reduce air leaks after pulmonary lobectomy. *Eur J Cardiothorac Surg*. 1998;13:361-4.
- Suter M, Bettschart V, Vandoni RE, Cuttat JF. Thoracoscopic pleurodesis for prolonged (or intractable) air leak after lung resection. *Eur J Cardiothorac Surg*. 1997;12:160-1.
- Samuels LE, Shaw PM, Blaum LC. Percutaneous technique for management of persistent airspace with prolonged air leak using fibrin glue. *Chest*. 1996;109:1653-5.
- Cerfolio RJ, Bass C, Katholi CR. Prospective randomized trial compares suction versus water seal for air leaks. *Ann Thorac Surg*. 2001;71:1613-7.
- Porte HL, Jany T, Akkad R, Conti M, Gillet PA, Guidat A, et al. Randomized controlled trial of a synthetic sealant for preventing alveolar air leaks after lobectomy. *Ann Thorac Surg*. 2001;71:1618-22.
- Wain JC, Kaiser LR, Johnstone DW, Yang SC, Wright CD, Friedberg JS, et al. Trial of a novel synthetic sealant in preventing air leaks after lung resection. *Ann Thorac Surg*. 2001;71:1623-8.
- McCarthy PM, Trastek VF, Bell DG, Buttermann GR, Piehler JM, Payne WS, et al. The effectiveness of fibrin glue sealant for reducing experimental pulmonary air leak. *Ann Thorac Surg*. 1988;45:203-5.
- Wong K, Goldstraw P. Effect of fibrin glue in the reduction of postthoracotomy alveolar air leak. *Ann Thorac Surg*. 1997;64:979-81.
- Fleisher AG, Evans KG, Nelems B, Finley RJ. Effect of routine fibrin glue use on the duration of air leaks after lobectomy. *Ann Thorac Surg*. 1990;49:133-4.
- Kjaergard HK, Weis-Fogh US, Sorensen H, Thiis J, Rygg I. Autologous fibrin glue-preparation and clinical use in thoracic surgery. *Eur J Cardiothorac Surg*. 1992;6:52-4.
- Fabian T, Federico JA, Ponn RB. Fibrin glue in pulmonary resection: a prospective, randomized, blinded study. *Ann Thorac Surg*. 2003;75:1587-92.
- Thistlethwaite PA, Luketich JD, Ferson PF, Keenan RJ, Jamieson SW. Ablation of persistent air leaks after thoracic procedures with fibrin sealant. *Ann Thorac Surg*. 1999;67:575-7.
- Gagarine A, Urschel JD, Miller JD, Bennett WF, Young JE. Effect of fibrin glue on air leak and length of hospital stay after pulmonary lobectomy. *J Cardiovasc Surg (Torino)*. 2003;44:771-3.
- Raanani E, Latter DA, Errett LE, Bonneau DB, Leclerc Y, Salasidis GC. Use of "BioGlue" in aortic surgical repair. *Ann Thorac Surg*. 2001;72:638-40.
- US Food and Drug Administration—New Device Approvals (CryoLife BioGlue Surgical Adhesive). Accessed on January 14, 2006 at <http://www.fda.gov/cdrh/mda/docs/P010003.pdf>
- History of BioGlue. Accessed on January 14, 2006 at http://www.cryolife.com/products/biogluen_historynew.htm
- Williams CP, Tran JLV, DeSouza M, Schuster K, Lenz S, Marra S, et al. Histopathology of tissue remodelling of thoracic aorta repaired with an adhesive protein hydrogel: a prospective study. Presented at Experimental Biology, San Diego, Calif, April 2003.
- Rami R, Mateu M. Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer. *Cochrane Database Syst Rev*. 2001;(4):CD003051.
- Mouritzen C, Dromer M, Keinecke HO. The effect of fibrin glueing to seal bronchial and alveolar leakages after pulmonary resections and decortications. *Eur J Cardiothorac Surg*. 1993;7:75-80.

26. Macchiarini P, Wain J, Almy S, Darteville P. Experimental and clinical evaluation of a new synthetic, absorbable sealant to reduce air leaks in thoracic operations. *J Thorac Cardiovasc Surg.* 1999;117:751-8.
27. Serra-Mitjans M, Belda-Sanchis J, Rami-Porta R. Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer. *Cochrane Database Syst Rev.* 2005;(3):CD003051.
28. Allen MS, Wood DE, Hawkinson RW, Harpole DH, McKenna RJ, Walsh GL, et al. Prospective randomized study evaluating a biodegradable polymeric sealant for sealing intraoperative air leaks that occur during pulmonary resection. *Ann Thorac Surg.* 2004;77:1792-801.
29. Belboul A, Dernevik L, Aljassim O, Skrbic B, Radberg G, Roberts D. The effect of autologous fibrin sealant (Vivostat) on morbidity after pulmonary lobectomy: a prospective randomized, blinded study. *Eur J Cardiothorac Surg.* 2004;26:1187-91.
30. Lang G, Csekeo A, Stamatis G, Lampl L, Hagman L, Marta GM, et al. Efficacy and safety of topical application of human fibrinogen/thrombin-coated collagen patch (TachoComb) for treatment of air leakage after standard lobectomy. *Eur J Cardiothorac Surg.* 2004;25:160-6.
31. Porte HL, Jany T, Akkad R, Conti M, Gillet PA, Guidat A, et al. Randomized controlled trial of a synthetic sealant for preventing alveolar air leaks after lobectomy. *Ann Thorac Surg.* 2001;71:1618-22.
32. Wain JC, Kaiser LR, Johnstone DW, Yang SC, Wright CD, Freidberg JS, et al. Trial of a novel synthetic sealant in preventing air leaks after lung resection. *Ann Thorac Surg.* 2001;71:1623-9.
33. Wurtz A, Gambiez L, Chambon JP, Saudemont A. Evaluation de l'efficacite d'une colle de fibrine en chirurgie d'exerese pulmonaire partielle. Resultats d'un nouvel essai controle chez 50 malades. *Lyon Chirurgie.* 1992;88:368-71.
34. Potaris K, Mihos P, Gakidis I. Experience with an albumin-glutaraldehyde tissue adhesive in sealing air leaks after bullectomy. *Heart Surg Forum.* 2003;6:429-33.
35. Passage J, Tam R, Windsor M, O'Brien M. BioGlue: a review of the use of this new surgical adhesive in thoracic surgery. *ANZ J Surg.* 2005;75:315-8.
36. Potaris K, Mihos P, Gakidis I. Preliminary results with the use of an albumin-glutaraldehyde tissue adhesive in lung surgery. *Med Sci Monit.* 2003;9:179-183.
37. Hewitt CW, Marra SW, Kann BR, Tran HS, Puc MM, Chrzanowski FA, et al. BioGlue Surgical adhesive for thoracic aortic repair during coagulopathy: efficacy and histopathology. *Ann Thorac Surg.* 2001;71:1609-12.
38. Furst W, Banerjee A. Release of glutaraldehyde from an albumin-glutaraldehyde tissue adhesive causes significant in vitro and in vivo toxicity. *Ann Thorac Surg.* 2005;79:1522-9.
39. LeMaire SA, Carter SA, Won T, Wang X, Conklin LD, Coselli JS. The threat of adhesive embolisation: BioGlue leaks through needle holes in aortic tissue and prosthetic grafts. *Ann Thorac Surg.* 2005;80:106-11.
40. Erasmi AW, Sievers HH, Wohlschlager C. Inflammatory response after BioGlue application. *Ann Thorac Surg.* 2002;73:1025.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Elsevier Inc.
Subscription Customer Service
6277 Sea Harbor Dr
Orlando, FL 32887

OR FAX TO:

407-363-9661

OR E-mail:

elspcs@elsevier.com

OR PHONE:

800-654-2452

Outside the U.S., call

407-345-4000