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Effectiveness of fibrin sealant after pulmonary resection: a propensity score matching analysis

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Abstract

Introduction: Alveolar air leak is a common and troublesome complication after pulmonary resection because it can lead to longer hospital stay and chest tube drainage time.

Aim: As fibrin sealants are useful in the management of alveolar air leaks, we evaluated their benefit in patients undergoing pulmonary resection.

Material and methods: This retrospective study included patients who underwent pulmonary resection in our hospital between 2016 and 2021. We grouped patients on the basis of whether fibrin sealant was used during surgery and compared outcomes between those with (fibrin sealant group) and without (control group) sealant use after propensity score matching (1 : 1).

Results: During the study period, 375 patients underwent pulmonary resection; of these, fibrin sealant was applied at the staple line in 107 patients (fibrin sealant group), whereas sealant was not used in 268 patients (control group). After propensity score matching (1 : 1), there were 95 patients in both groups. There were no differences between the two groups in duration of chest tube drainage (3 days vs. 3 days; $p = 0.753$) or length of hospital stay (5 days vs. 4 days; $p = 0.499$). However, the sealant group showed higher cost of hospitalization (USD 4,360 vs. 3,614; $p < 0.001$). Multivariate analysis for identifying risk factors of persistent air leak revealed that male sex and chronic obstructive pulmonary disease were associated.

Conclusions: Our results indicate that application of fibrin sealant was not effective in reducing length of hospital stay, duration of chest drains or air leakage.

Key words: alveolar air leak, pulmonary resection, chronic obstructive pulmonary disease, sealant.

Introduction

Alveolar air leak is one of the most common complications after pulmonary resection and accounts for approximately 20–30% of all postoperative morbidity [1–3]. It not only increases length of hospital stay but is also associated with pain, risk of postoperative empyema thoracis, and associated complications [4]. Standard protocols for intraoperatively controlling air leaks include meticulous dissection of the structures along the anatomical plane between the lobe and the segment, suture techniques, and stapling. Currently, many products such as fibrin glue and synthetic and polymeric sealant are available and have been reported to reduce parenchymal air leak after pulmonary resection [5, 6]. However, these sealants are expensive, especially in developing countries.

Aim

Therefore, this study analyzed whether fibrin sealant use can improve postoperative outcomes, including reducing length of hospital stay, after pulmonary resection.

Material and methods

This retrospective study was approved by a local ethical committee (242/64E) and included patients who underwent pulmonary resection in the cardiothoracic surgery unit between January 1, 2016, and July 30, 2021. During this period, 375 patients underwent elective pulmonary resection, and all data were extracted from institutional medical records. Patients requiring emergency surgery and those younger than 18 years old were excluded from this study. All eligible patients were categorized into one of two groups, viz., the fibrin sealant group ($n = 107$) or control group ($n = 268$).

Both intraoperative parameters and postoperative outcomes, including cost of hospital stay, were compared between the two groups. Demographic and surgical variables such as age, gender, smoking history, underlying disease, chronic obstructive pulmonary disease (COPD), approach type (open thoracotomy (OT) vs. video-assisted thoracic surgery (VATS)), operation types (wedge, segmentectomy, or lobectomy), laterality (right or left), and redo surgery,

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were evaluated. Primary outcomes were duration of chest tube, length of hospital stay, and cost of hospital stay.

Surgical protocol

All procedures were performed under general anesthesia by board-certified cardiovascular thoracic surgeons using the lung isolation technique. Sealant application and the use of either VATS or OT depended on surgeon preference.

A fibrin sealant called Tisseel (Baxter Healthcare, Immuno Co, Vienna, Austria), composed of human-derived fibrinogen and thrombin, was used throughout and was applied either on the raw surface of lung parenchyma or on the staple line at the resection site to prevent alveolar air leak. Patients in whom the fibrin sealant was used were included in the fibrin sealant group, whereas the others were included in the control group.

After surgery, a small chest tube (24-French or 28-French) was inserted to drain air and fluid, and it was routinely connected to a thoracic suction device that was set to a pressure of -10 mm Hg. The intercostal chest drain was removed when there was no air leakage and drainage was < 300 ml of pleural fluid per day.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand (COA number: 242/64E), and individual consent for this retrospective analysis was waived.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as

Table I. Patients' demographic data between control group and fibrin sealant group before and after propensity score matching analysis

Data	Before match			After match		
	Control group (*n* = 268)	Fibrin sealant group (*n* = 107)	*P*-value	Control group (*n* = 95)	Fibrin sealant group (*n* = 95)	*P*-value
Age; median (P25–P75)	59 (41–68)	64 (54–71)	< 0.001*	64 (53–70)	63 (53–71)	0.395
Sex, *n* (%):			0.781			0.772
Male	137 (51.1)	53 (49.5)		46 (48.4)	48 (50.3)	
Female	131 (48.9)	54 (50.5)		49 (51.6)	47 (49.5)	
Smoking status, *n* (%):			0.068			0.540
Non-smoker	211 (78.7)	93 (86.9)		79 (83.2)	83 (87.4)	
Smoker	57 (21.3)	14 (13.1)		16 (16.8)	12 (12.6)	
Underlying disease, *n* (%):						
Dyslipidemia	52 (19.4)	31 (29.0)	0.044*	26 (27.4)	25 (26.3)	0.870
Diabetes	46 (17.1)	18 (16.8)	1.000	20 (21.1)	14 (14.7)	0.344
Hypertension	79 (29.5)	45 (42.1)	0.019*	43 (45.3)	37 (39)	0.378
Cardiovascular disease	14 (5.2)	7 (6.5)	0.623	11 (11.6)	5 (5.3)	0.190
COPD	13 (4.9)	8 (7.5)	0.326	9 (9.5)	7 (7.4)	0.601
Other disease	49 (18.3)	33 (30.8)	0.008	29 (30.5)	28 (29.5)	0.874
Operation type, *n* (%):			< 0.001*			0.586
Wedge	166 (61.9)	47 (43.9)		40 (42.1)	47 (49.5)	
Lobectomy	93 (34.7)	47 (43.9)		46 (48.4)	40 (42.1)	
Segmentectomy	9 (3.4)	13 (12.2)		9 (9.5)	8 (8.4)	
Laterality, *n* (%):			0.190			0.281
Left side	90 (33.6)	44 (41.1)		28 (29.5)	35 (36.8)	
Right side	178 (66.4)	63 (58.9)		67 (70.5)	60 (63.2)	
Malignancy, *n* (%)	58 (21.6)	24 (22.4)	0.890	22 (23.2)	20 (21.1)	0.727
Approach, *n* (%):			0.003*			0.434
Open	47 (17.5)	6 (5.6)		10 (10.5)	6 (6.3)	
VATS	221 (82.5)	101 (94.4)		85 (89.5)	89 (93.7)	

Table II. Peri- and post-operative outcomes compares between control group and fibrin sealant group before and after propensity score matching analysis

Peri- and post-operative outcome	Before match			After match		
	Control group (*n* = 268)	Fibrin sealant group (*n* = 107)	*P*-value	Control group (*n* = 95)	Fibrin sealant group (*n* = 95)	*P*-value
Perioperative complication, *n* (%):			0.006*			0.364
No	268 (100)	103 (96.3)		95 (100)	93 (98)	
Arrythmia	0 (0)	2 (1.9)		0 (0)	1 (1)	
Others	0 (0)	2 (1.9)		0 (0)	1 (1)	
Operative time, median (P25–P75)	70 (45–140)	90 (60–150)	0.071	90 (60–150)	90 (50–150)	0.637
Estimated blood loss, median (P25–P75)	20 (10–90)	30 (10–100)	0.115	20 (10–100)	30 (10–100)	0.797
Blood transfusion, *n* (no%)	260 (97)	102 (95.3)	0.532	90 (94.7)	91 (95.8)	1.000
Postoperative ventilator needed, *n* (yes%)	3 (1.1)	5 (4.7)	0.045*	2 (2.1)	4 (4.2)	0.682
Immediate extubation, *n* (yes%)	257 (95.9)	101 (94.4)	0.584	90 (94.7)	91 (95.6)	1.000
Post-operative condition, *n* (yes%):						
Persistent air leak	44 (16.4)	25 (23.4)	0.140	18 (18.9)	23 (24.2)	0.481
Re-intubation	0 (0)	1 (1)	0.285	0 (0)	0 (0)	
Pneumonia	2 (0.8)	2 (1.9)	0.322	1 (1)	1 (1)	1.000
Re-operation	2 (0.8)	4 (3.7)	0.058	0 (0)	4 (4.2)	0.121
Hoarseness	0 (0)	2 (1.9)	0.081	0 (0)	2 (2.1)	0.497
Other	13 (4.9)	14 (13.2)	0.008*	5 (5.3)	12 (12.8)	0.125
Duration of chest tube, median (P25–P75)	4 (3–8)	3 (2–5)	0.068	3 (2–4)	3 (2–5)	0.753
Hospital stay, median (P25–P75)	4 (3–6)	3 (1–4)	0.463	5 (3–7)	4 (3–7)	0.499
Mortality rate, *n* (yes%)	1 (0.4)	1 (0.9)	0.322	1 (1)	1 (1)	1.000
Cost (US dollars), median (P25–P75)	3010 (2203–3925)	4391 (3445–5635)	< 0.001*	4360 (2693–4248)	3614 (2952–5451)	< 0.001*

median and interquartile range (Q1–Q3). Propensity score matching (1 : 1) was performed to minimize selection bias in both groups, and the variables included for propensity score matching were age, gender, diagnosis laterality, and operation type. Standardized mean difference between the groups was determined for all covariates.

The χ^2 test was used to compare categorical variables and differences between the two groups for dichotomous data. Skewed data were analyzed using the Mann-Whitney *U* test. Multivariable regression analysis was performed to assess the association between the two groups and primary outcomes. A *p*-value of < 0.05 was considered statistically significant. All statistical analyses were performed using STATA v. 16.0 software (StataCorp, College Stata, TX, USA).

Results

Records showed that 375 patients underwent pulmonary resection between 2016 and 2021; of these, sealant was used in 107 patients (fibrin sealant group), whereas it was not used in the remaining 268 patients (control group). Before propensity matching, patients in the fibrin sealant group were older (64 vs. 59 years, $p < 0.001$) and underwent lobectomy (43.9% vs. 34.7%; $p < 0.001$), segmentectomy (12.2% vs. 3.4%; $p < 0.001$), and VATS (94.4% vs. 82.5%; $p = 0.003$). There were no differences in sex, smoking status, laterality, or diagnosis (Table I).

After surgery, duration of chest tube (3 vs. 4 days, $p = 0.068$) and hospital stay (3 vs. 4 days; $p = 0.463$) were shorter in the sealant group; however, the differences were not statistically significant. There was no difference in operative time, blood transfusion requirement, blood loss, or postoperative complications. Cost of hospitalization was significantly higher in the fibrin sealant group than in the control group (USD 3,010 vs. 4,391; $p < 0.001$). Peri- and post-operative outcomes compared between the control group and fibrin sealant group before and after propensity score matching analysis are shown in Table II.

After propensity score matching (Table II), length of hospital stay was shorter in the fibrin sealant group than in the control group; however, the difference was not statistically

Table III. Multivariate linear regression analysis for factors associated with persistent air leak

Factor	Univariable			Multivariable		
	Coefficient	95% CI	*P*-value	Coefficient	95% CI	*P*-value
Group:						
Fibrin sealant vs non-fibrin sealant	0.242	(–1.42)–1.91	0.774			
Age	0.048	(–0.01)–0.10	0.071			
Sex:						
Male	3.115	1.51–4.72	< 0.001*	1.979	0.43-3.53	0.013*
Smoking status:						
Non-smoker	0.996	(–1.35)–3.34	0.403			
Underlying disease:						
Dyslipidemia	1.842	(–0.02)–3.70	0.052			
Diabetes	1.653	(–0.50)–3.81	0.132			
Hypertension	0.714	(–0.97)–2.40	0.404			
Cardiovascular disease	2.458	(–0.52)–5.43	0.105			
COPD	5.67	2.78–8.55	< 0.001*	4.176	1.38–6.97	0.004*
Operation type:						
Wedge	1.000	References				
Lobectomy	0.735	(–1.01)–2.48	0.407			
Segmentectomy	–0.761	(–1.01)–2.48	0.622			
Laterality:						
Left side vs. Right side	–0.036	(–1.80)–1.73	0.968			
Malignancy	–0.775	(–2.78)–1.23	0.446			
Approach:						
Open vs. VATS	4.642	1.72–7.56	0.002*	4.794	2.09–7.50	0.001*

significant (4 vs. 5 days; $p = 0.499$). Further, there were no differences in duration of chest drain or postoperative outcomes, including persistent air leak (PAL), pneumonia, or re-operation. However, hospitalization costs in the fibrin sealant group were significantly higher (USD 4,360 vs. 3,614; $p < 0.001$)

Multivariate linear regression analysis (Table III) showed that male sex (95% CI: 1.979 (0.43–3.53); $p = 0.013$), history of COPD (95% CI: 4.176 (1.38–6.97); $p = 0.004$), and open approach (95% CI: 4.794 (2.09–7.50); $p < 0.001$) were associated with PAL.

Discussion

Prolonged air leak (PAL), defined as air leak for > 5 days, is one of the most common complications encountered after pulmonary resection and is a major cause of longer hospital stay compared with other postoperative complications such as pneumonia, atrial fibrillation, or desaturation [7]. The reported incidence of intraoperative air leaks after pulmonary resection ranges between 48% and 70% [8]. Brunelli *et al.* reported that 15.6% of patients who underwent pulmonary resection had PAL that lasted > 7 days [9]. Although improvements in surgical techniques, such as avoiding dissection at fissure (fissure last technique), using a surgical stapler for parenchyma division, or buttressing the staple line using biological or synthetic materials, have helped in reducing PAL [10], several factors, including incomplete fissure, presence of emphysematous lung, and pleural adhesions, continue to cause PAL [5, 6, 8].

In 2022, Shintani *et al.* analyzed data from the national clinical database in Japan ($N = 30,967$) and concluded that male, older age, body mass index, and smoking are risk factors for PAL [11]. Pischik *et al.* analyzed data from 319 patients who underwent pulmonary resection in their institution, and they identified male gender, smoking history, chronic obstruction lung disease, and preoperative hypoproteinemia as the main risk factors for PAL; however, they found no differences between open or thoracoscopic approaches [12]. However, in our results, we observed that the open approach was associated with PAL. We believe that the reason why our data identifies the open approach as a risk factor is because the surgery is procedurally more difficult compared to the VATS approach.

The use of new products such as sealants, as adjuvant therapy, can help reduce alveolar leakage [6, 13–17]. Further, although most studies have demonstrated the safety of sealant use in surgical patients, a meta-analysis by McGuire and Yee used data from 2,357 patients to evaluate sealant use in pulmonary resection, and they reported that use of a polymeric sealant can significantly reduce postoperative alveolar air leak and length of hospital stay by 1 day [18].

In contrast, a randomized controlled trial by Wong *et al*., which compared fibrin glue and a control group, found no difference in duration of air leak and chest tube, or hospital stay [6]. Similarly, we also found no differences in duration of chest tube or hospital stay between the fibrin sealant and control groups.

Conclusions

We report that fibrin use does not reduce length of hospital stay, duration of chest tube, or air leakage.

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Disclosure

The authors report no conflict of interest.

References

1. Bronstein ME, Koo DC, Weigel TL. Management of air leaks post-surgical lung resection. Ann Transl Med 2019; 7: 361.
2. Cerfolio RJ. Recent advances in the treatment of air leaks. Curr Opin Pulm Med 2005; 11: 319-323.
3. Chee CB, Abisheganaden J, Yeo JK, Lee P, Huan PY, Poh SC, Wang YT. Persistent air-leak in spontaneous pneumothorax: clinical course and outcome. Respir Med 1998; 92: 757-761.
4. Brunelli A, Xiume F, Al Refai M, Salati M, Marasco R, Sabbatini A. Air leaks after lobectomy increase the risk of empyema but not of cardiopulmonary complications: a case-matched analysis. Chest 2006; 130: 1150-1156.
5. Tan C, Utley M, Paschalides C, Pilling J, Robb JD, Harrison-Phipps KM, Lang-Lazdunski L, Treasure T. A prospective randomized controlled study to assess the effectiveness of CoSeal(R) to seal air leaks in lung surgery. Eur J Cardiothorac Surg 2011; 40: 304-308.
6. Wong K, Goldstraw P. Effect of fibrin glue in the reduction of postthoracotomy alveolar air leak. Ann Thorac Surg 1997; 64: 979-981.
7. Irshad K, Feldman LS, Chu VF, Dorval JF, Baslaim G, Morin JE. Causes of increased length of hospitalization on a general thoracic surgery service: a prospective observational study. Can J Surg 2002; 45: 264-268.
8. Wain JC, Kaiser LR, Johnstone DW, Yang SC, Wright CD, Friedberg JS, Feins RH, Heitmiller RF, Mathisen DJ, Selwyn MR. Trial of a novel synthetic sealant in preventing air leaks after lung resection. Ann Thorac Surg 2001; 71: 1623-1628.
9. Brunelli A, Monteverde M, Borri A, Salati M, Marasco RD, Fianchini A. Predictors of prolonged air leak after pulmonary lobectomy. Ann Thorac Surg 2004; 77: 1205-1210.
10. Venuta F, Rendina EA, De Giacomo T, Flaishman I, Guarino E, Ciccone AM, Ricci C. Technique to reduce air leaks after pulmonary lobectomy. Eur J Cardiothorac Surg 1998; 13: 361-364.
11. Shintani Y, Yamamoto H, Sato Y, Shimizu K, Endo S, Okada M, Suzuki K, Fukuchi E, Miyata H, Chida M. A risk model for prolonged air leak after lobectomy using the National Clinical Database in Japan. Surg Today 2022; 52: 69-74.
12. Pischik VG, Maslak OS, Obornev AD, Zinchenko EI, Kovalenko AI. Risk factors and outcomes of prolonged air leak after pulmonary resections. Indian J Thorac Cardiovasc Surg 2019; 35: 564-568.
13. Tansley P, Al-Mulhim F, Lim E, Ladas G, Goldstraw P. A prospective, randomized, controlled trial of the effectiveness of BioGlue in treating alveolar air leaks. J Thorac Cardiovasc Surg 2006; 132: 105-112.
14. D'Andrilli A, Andreetti C, Ibrahim M, Ciccone AM, Venuta F, Mansmann U, Rendina EA. A prospective randomized study to assess the efficacy of a surgical sealant to treat air leaks in lung surgery. Eur J Cardiothorac Surg 2009; 35: 817-820.
15. Petter-Puchner AH, Simunek M, Redl H, Puchner KU, Van Griensven M. A comparison of a cyanoacrylate [corrected] glue (Glubran) vs. fibrin sealant (Tisseel) in experimental models of partial pulmonary resection and lung incision [corrected] in rabbits. J Invest Surg 2010; 23: 40-47.
16. Lequaglie C, Giudice G, Marasco R, Morte AD, Gallo M. Use of a sealant to prevent prolonged air leaks after lung resection: a prospective randomized study. J Cardiothorac Surg 2012; 7: 106.
17. Kilic B, Ersen E, Demirkaya A, Kara HV, Alizade N, Iscan M, Kaynak K, Turna A. A prospective randomized trial comparing homologous and autologous fibrin sealants for the control of alveolar air leak. J Thorac Dis 2017; 9: 2915-2922.
18. McGuire AL, Yee J. Clinical outcomes of polymeric sealant use in pulmonary resection: a systematic review and meta-analysis of randomized controlled trials. J Thorac Dis 2018; 10 (Suppl 32): S3728-S3739.