Is Acrylate Co-monomer (Glubran-2) Useful in the Prevention of Prolonged Air Leaks After Pulmonary Lobectomy?

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Abstract Many synthetic materials are being used in order to reduce the frequency of prolonged air leak (PAL) in thoracic surgical practice. This study presents our experience with the topical application of acrylate co-monomer (Glubran-2) as a synthetic tissue adhesive in an attempt to decrease troublesome postoperative air leaks in patients undergoing resection for non-small cell lung carcinoma. Of the 112 patients who had undergone resection for lung carcinoma, 69 patients having lobectomy or bilobectomy were included in this study. The application group (group A) consisted of 33 patients where a synthetic tissue adhesive (Glubran-2) was used and compared with the control group (group C, $n=36$) retrospectively. There was no difference between the groups regarding demographic details and operative variables. Both groups were compared in view to PAL, chest tube duration, in-hospital stay and hospital costs. There was no significant difference between group A ($n=11$, 33 %) and group C ($n=6$, 17 %) for the development of PAL ($P=0.11$). Hospital stay was 16.1 ± 6.7 days in group A and 15.3 ± 5.8 days in group C ($P=0.66$). The surgical cost was significantly higher in group A ($\text{€}806 \pm 127$) than the group C ($\text{€}624 \pm 94$) ($P<0.001$). There was no significant difference between the groups regarding overall hospital costs ($P=0.41$). In this study, the use of Glubran-2 following lung resection for non-small cell lung carcinoma did not

decrease the incidence of PAL. Neither did it have a favorable effect concerning in-hospital stay nor did it decrease overall hospital costs while increasing surgical costs as expected.

Keywords Lung cancer surgery · Surgery · Complications · Lobectomy · Pulmonary resection · Lung cancer

Introduction

Air leak is a frequent and bothersome complication in lung surgery. Although it can usually be treated with a tube thoracostomy, it creates problems for both the patient and the physician such as immobilization, increased postoperative pain, and prolonged inpatient stay. The condition known as prolonged air leak (PAL), which is seen in approximately 15 % of lung resection patients and continues for more than 7 days postoperatively, increases the inpatient duration by about 5–6 days [1, 2]. PAL may require additional procedures such as placement of a new thorax tube, chemical pleurodesis, or rethoracotomy [3, 4].

Several methods are used to repair the lung parenchyma. Those that have become standard such as using a stapler or sutures cause more trauma in the tissue. Tissue adhesives are seen as superior as they are more flexible and can better adapt to lung volume changes [5]. However, they need to be systemically nontoxic, bacteriostatic, and nonirritating to the tissues.

Glubran-2 (*N*-butyl-2-cyanoacrylate and methacryloxy sulfolane co-monomer) (GEM S.r.l Italy) is a new synthetic tissue adhesive and hemostatic agent in a ‘ready-to-use’ applicator that is applied topically and can be used both in laparoscopic and open surgeries. It has better properties than previously available cyanoacrylate adhesives regarding

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elasticity and polymerization temperature. On contact with live tissue in a moist environment, it polymerizes rapidly to create a thin but elastic film of high tensile resistance, which guarantees firm adherence of tissues. Polymerization occurs at a temperature of 45 °C so that there is no thermal damage to underlying tissues.

In this study, we have investigated whether the use of Glubran-2 as a tissue adhesive in lung surgery would lower hospital costs by controlling air leak retrospectively.

Materials and Methods

A total of 112 patients who had undergone lung resection for lung cancer between January 2006 and January 2007 were evaluated retrospectively. Of them, 43 patients with neo-adjuvant treatment, wedge resection or pneumonectomy were excluded. Remaining 69 cases that underwent lobectomy or bilobectomy were retrospectively analyzed in two groups as those who had been administered tissue adhesive or not. The application group (all patients signed informed consent before surgery) consisted of 33 patients who had been administered synthetic tissue adhesive (Glubran-2), while the control group consisted of 36 patients who had not been administered tissue adhesive. Complete mediastinal lymph node dissection was performed in all patients. There were no intraoperative mortalities. The lung parenchyma had been separated with a stapler or electrocautery in cases where an incomplete fissure was found and the stump was closed primarily. The tissue adhesive had been applied for approximately 3–5 min to the dissected parenchyma or stapler line and the bronchial stump. The lung undergoing the procedure was not ventilated for 5 min, and a parenchymal leak check was performed by administering saline solution into the thorax and reventilating the lung at 25 cm H₂O pressure. The leakage amount was minimized with additional surgical procedures (suturing, electrocautery application) in patients with significant air leak in both groups. The presence of air leaks could be best detected by measuring the volume of air loss on the circuit by an anesthetist, but instead of this technique we used naked-eye observation. The thorax was closed after the insertion of a double (anterior and posterior) drain that was connected to a continuous suction device with a pressure of –20 cm H₂O in the early postoperative period, and the presence or absence of air leak and the amount of fluid drained within the first 24 h were recorded. Later follow-up was daily. As a routine part of our clinical practice, postoperative air leak was observed twice daily during ward rounds by the surgical team and marked in a comprehensive follow-up chart. In order to detect presence of an air leak, patients were asked to breathe deeply and cough for at least three times and also pose a maneuver of Valsalva in each ward round visit. PAL was

accepted as an air leak continuing after the postoperative seventh day. The total chest tube duration was determined as the last postoperative day when the tubes placed during surgery were removed. The first tube was removed when no pneumothorax was observed in the chest X-ray and air leak had stopped, while the second tube was removed if there was 100 ml or less fluid drainage within 24 h. The groups were classified according to age, sex, smoking history, PAL, inpatient duration, and operative and hospital cost. The surgical cost in the study group was found by adding Glubran-2 to the total cost. We took the expenses after the patient was transferred or admitted to the thoracic surgery department into account and did not include admission and diagnostic test expenses from other departments. All price data included VAT (value-added tax) at a rate of 8 %.

Statistical analyses were performed once the data were entered into the computer environment. Descriptive data were defined by frequency tables and the continuous variables by mean and standard deviation measures. The Pearson chi-square test, Fisher's exact test, and the Mann–Whitney U test were used to analyze the data. A *P* value of <0.05 was accepted as significant and absolute *P* values were calculated after analyses.

Results

The mean age in the tissue adhesive group was 59.8±9.6 (38–78). The respective value for the control group was 61.3±8.0 (48–77), and there was no statistically significant difference between the two groups (*P*=0.66). The sex distribution was 7.2 % (5) female and 92.8 % (64) male, and there was no significant difference between the two groups (*P*=0.36).

PAL was found in 11 (33 %) patients in the application group and 6 (17 %) patients in the control group for a total of 17 (25 %) patients. There was no significant difference between the two groups regarding PAL (*P*=0.11) (Fig. 1).

Fig. 1 Air leak level between the groups

Smoking history revealed a mean value of 42.7 ± 33.9 pack-year in the cases with PAL and 33.0 ± 25.5 pack-year in those without, and the difference was not statistically significant ($P=0.17$). Table 1 shows the relation between demographic features and PAL.

When we analyzed the groups according to whether the fissure was complete or incomplete, an incomplete fissure was present in 28 (84 %) cases in the application group and 26 (72 %) cases in the control group, and there was no significant difference between the two groups regarding PAL ($P=0.20$). A stapler had been used in 23 (69 %) cases in the application group and 25 (69 %) cases in the control group. PAL had developed in 16 of the 48 patients where a stapler had been used and in only 1 of the 21 cases where it had not with the difference being statistically significant ($P=0.01$).

The distribution of the patients who developed expansion problems revealed 3 (9 %) cases in the application group and 6 (17 %) cases in the control group, but the difference was not statistically significant ($P=0.35$).

Analysis of chest tube duration revealed mean values of 8.2 ± 5.8 days in the application group and 7.9 ± 3.9 days in the control group with no significant difference between the groups ($P=0.64$). Looking at the 24-hour drainage amounts, this value was 398.5 ± 217.4 ml for the application group and 409.7 ± 162.5 ml for the control group. This difference was not statistically significant ($P=0.45$).

Analysis of inpatient durations revealed longer durations in those with PAL (19.3 ± 7.3 days) compared to those without (14.5 ± 5.4 days), and the difference was statistically significant ($P=0.008$). The inpatient duration was 16.1 ± 6.7 days in the application group and 15.3 ± 5.8 days in the control group. There was no significant difference between the groups ($P=0.66$) (Table 2).

Cost analysis revealed a surgical cost of $\text{€}806 \pm 127$ in the application group and $\text{€}624 \pm 94$ in the control group, and the difference was statistically significant ($P<0.001$) (the cost of Glubran-2 was $\text{€}144$). There was no significant difference between the values for total hospital cost (Table 2).

Table 1 Relation between demographic findings and prolonged air leak

		Prolonged air leak	<i>P</i>
Groups	Application	33.3 % (11/33)	0.109
	Control	16.7 % (6/36)	
Age	<60 years	20.5 % (8/39)	0.365
	≥60 years	30.0 % (9/30)	
Sex	Male	26.6 % (17/64)	0.323
	Female	0.0 % (0/5)	
Smoker	Yes	27.3 % (15/55)	0.491
	No	14.3 % (2/14)	

Table 2 Comparison of inpatient duration and cost relationship between groups

	Application group	Control group	<i>P</i>
Inpatient duration (days)	16.1 ± 6.7	15.3 ± 5.8	0.66
Operation cost (€)	806 ± 127	624 ± 94	<0.001
Hospital cost (€)	2974 ± 1162	2973 ± 756	0.414

Discussion

Different types of synthetic tissue sealants have been used to reduce air leak. PAL is a frequent complication after pulmonary resection for lung cancer. It may cause serious complications, such as empyema, and prolong the need for chest tube or inpatient stay. Synthetic tissue adhesives are deemed to be safe for patients but may lead to adverse conditions by causing some changes in the immune response. Porte et al. [6] have reported the development of infection in the pleural cavity requiring chest tube insertion in 4 of the 59 patients where they used Advaseal (Ethicon, Somerville, NJ). However, Allen et al. [7] have not come across any empyema cases among 148 patients in a multicenter study. They believe that the reason is the complete absorption of the adhesive they used [PGE-(SS)2] within 30 days. Empyema developed for a patient of the study.

Another product used to prevent alveolar leaks, *TachoComb* (collagen-coated human fibrinogen/thrombin), has been found to decrease air leak following lobectomy by Lang et al. [8]. Similarly Belboul et al. [9] used Vivostat (autologous fibrin sealant) and reported the decrease in both air leak and fluid drainage. We did not detect any decrease in air leak or fluid drainage amount.

The Heimlich valve was used in one patient in our study. McKenna et al. [10] reported a 96 % success rate regarding postoperative air leak and a decrease in hospital stay with this system. They used postoperatively in 25 patients who had undergone lung volume reduction surgery. Similarly Ponn et al. [11] reported a success rate of 98 % in 45 patients who had undergone lung resection. However, this system has risks such as obstruction by fibrin debris and ascending infection due to the open drainage system. Lodi and Stefani [12] have applied the portable chest tube they developed to 18 patients and reported that it enabled both air and fluid drainages, but the frequent application of pressure to the bag by the patient was required as the output valve did not allow the rapid exit of air. Rieger et al. [13] reported finding a solution to these problems by using a new portable chest tube system (Express Mini 500; Atrium Medical Corp).

PAL is one of the most important factors in a prolonged hospital stay [14]. Although surgical sealants reduce postoperative air leaks and time to chest drain removal, this reduction is not always associated with a reduction in length

of postoperative hospital stay [15]. Some authors have reported no statistically significant difference between the control and treatment groups regarding this variable [5, 6], while others found shorter durations when an adhesive was used [7]. We did not find a significant difference between the two groups in our study ($P=0.66$). Although good results have been demonstrated by biological agents such as *TachoComb* and *Vivostat*, these results cannot be and should not be compared to Acrylate co-monomer (Glubran-2) as it is a purely chemical synthetic tissue spray.

We also did not find a difference regarding total hospital cost, similar to Gündoğdu et al. [16]. Anegg et al. [17] have reported decreased chest tube duration and inpatient duration with TachoSil (fleece-bound sealing) and a resultant marked decrease in cost. Although there are no comments on surgical cost in other articles, we found a statistically significant increase in surgical cost in the application group in our study ($P<0.001$).

Albeit statistical power of the study is moderate (0.40), according to our knowledge, there is no any similar more effective studies in the literature. We think that this study is unique and original with this moderate power on this researched area. For higher power significance, a large number of subjects should be enrolled to further studies.

We concluded that the use of Glubran-2 as a tissue adhesive following lung resection did not decrease the incidence of PAL in this study. Neither did it have a favorable effect concerning in-hospital stay nor did it decrease overall hospital costs while increasing surgical costs as expected. However, we feel that further prospective studies with a larger number of patients may be required for better evaluation of its favorable outcomes such as very low incidence of immune response-related adverse effects associated with this tissue sealant. For assessment of benefit of Glubran-2, this agent would be tested in some cases of decortications with or without lung resection where air leak is significant.

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