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# Efficacy and safety of TachoSil® versus standard treatment of air leakage after pulmonary lobectomy☆,☆☆

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**Abstract**

**Objectives:** Alveolar air leakage remains a serious problem in lung surgery, being associated with increased postoperative morbidity, prolonged hospital stay and greater health-care costs. The aim of this study was to evaluate the sealing efficacy and safety of the surgical patch, TachoSil®, in lung surgery. **Methods:** Patients undergoing elective pulmonary lobectomy who had grade 1 or 2 air leakage (evaluated by the water submersion test) after primary stapling and limited suturing were randomised at 12 European centres to open-label treatment with TachoSil® or standard surgical treatment (resuturing, stapling or no further treatment at the surgeons' discretion). Randomisation was performed during surgery using a centralised interactive voice response system. Duration of postoperative air leakage (primary end point), reduction of intra-operative air leakage intensity (secondary end point) and adverse events (AEs), including postoperative complications, were assessed. **Results:** A total of 486 patients were screened and 299 received trial treatment (intent-to-treat (ITT) population: TachoSil®, $n = 148$; standard treatment, $n = 151$). TachoSil® resulted in a reduction in the duration of postoperative air leakage ($p = 0.030$). Patients in the TachoSil® group also experienced a greater reduction in intra-operative air leakage intensity ($p = 0.042$). Median time until chest drain removal was 4 days with TachoSil® and 5 days in the standard group ($p = 0.054$). There was no difference between groups in hospital length of stay. AEs were generally similar in both groups, including postoperative complications. **Conclusions:** TachoSil® was superior to standard surgical treatment in reducing both postoperative air leakage duration and intra-operative air leakage intensity in patients undergoing elective pulmonary lobectomy.


*Keywords:* Lobectomy (lung); Complications

## 1. Introduction

Alveolar air leakage remains a serious problem in lung surgery, being associated with increased postoperative complications, prolonged hospital stay and greater health-care costs [1—4]. Intra-operative air leakage during lung surgery has been reported to occur in 48—88% of patients [5—7], with persistent postoperative air leakage (>7 days) occurring in up to 25% of patients [8].

Surgical suturing and stapling are the standard methods for the prevention and treatment of air leakage, while various surgical sealants have been developed to help further prevent or reduce air leaks. These include liquid fibrin sealants [9,10], synthetic hydrogels [5,11] and collagen fleece-bound sealants, such as TachoSil® (Nycomed, Linz, Austria), a ready-to-use fixed combination of equine collagen patch coated with human fibrinogen and thrombin [6,7].

In a previous study in patients undergoing pulmonary lobectomy, TachoSil® reduced the percentage of patients

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with persistent air leakage 48 h after surgery compared with standard surgical treatment (39% vs 49%) [6]. However, less than half of the patients had air leakage following primary stapling, thereby reducing the power of the study. *Post hoc* analysis of the subgroup of patients with persistent air leakage (grade 1 or 2) suggested TachoSil® was more effective than standard treatment.

To further investigate these findings, this study was designed to prospectively assess the sealing efficacy and safety of TachoSil® compared with standard surgical treatment after pulmonary lobectomy in patients with grade 1 or 2 air leakage.

## 2. Patients and methods

### 2.1. Study design

This was a prospective, randomised, parallel-group trial conducted at 12 centres in Europe (Germany, $n = 3$; Italy, $n = 3$; Austria, Belgium, Denmark, Hungary, Sweden and Switzerland, $n = 1$). The trial was open label because the appearance of TachoSil® made it impossible to blind the two treatments during surgery. Relevant Ethics Committees approved the protocol and the trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice and any applicable local regulations. All patients provided written informed consent. The trial is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting of randomised controlled trials [12].

The trial population included patients aged $\geq$18 years with lung cancer scheduled for elective pulmonary lobectomy with planned antero- or postero-lateral incision and intrapulmonary lymphadenectomy. Patients were excluded if they had previous lung surgery (on the same side), chemotherapy or radiotherapy (within the previous 3 or 4 weeks, respectively), pre-existing advanced obstructive pulmonary disease (forced expiratory volume in 1 s (FEV1) $<$40%), a history of allergic reactions after application of human fibrinogen, human thrombin or collagen of any origin, previous exposure to TachoSil® or were undergoing emergency surgery. Patients with serious complications during surgery, including the need for adhesiolysis, pneumonectomy, wedge or sleeve resection or who were treated with any fibrin sealant, were also excluded.

Following lobectomy, primary stapling and limited suturing were used as considered necessary by the surgeon. Air leakage was then assessed by a water submersion test under standard airway pressure of 20–25 cm $H_2O$, with the air leakage intensity graded by the Macchiarini scale as 0 (absent, no apparent leak), 1 (mild, countable bubbles), 2 (moderate, stream of bubbles) or 3 (severe, coalesced bubbles) [13]. Air leaks had to originate from the pulmonary parenchyma and not from the bronchi. In case of leakage from several sites, patients were graded, based on the most severe. Patients with grade 1 or 2 air leakage were randomised to treatment with TachoSil® or further standard surgical treatment. Patients with grade 3 air leakage underwent further stapling and/or limited suturing to achieve grade 1–2 before being randomised. Block randomisation stratified by the centre was performed during surgery using a centralised interactive voice response system (IVRS).

TachoSil® is a surgical patch (9.5 cm $\times$ 4.8 cm) consisting of a thin collagen carrier sponge with a dry coating of human fibrinogen and human thrombin. This product was pre-moistened in warm physiological saline immediately before application under aseptic conditions, with as many patches as needed being used. The TachoSil® patch was held against the lung tissue for 3–5 min. For patients randomised to standard treatment, resection sites were closed with resuturing, stapling or no treatment at the surgeon's discretion, based on usual practice.

After the first application of trial treatments, patients underwent another water submersion test. The trial treatment was repeated if air leakage control was considered insufficient. A third application was also permitted, after which rescue treatment was allowed. Rescue treatment resulted in the patient being considered a treatment failure and could include any surgical technique or sealant (fibrin or non-fibrin), except TachoSil® in patients randomised to standard surgical treatment.

Standard double drainage of the chest cavity was performed using two 24 Charrier drains (anterior–superior and posterior–inferior positions, the lower site for fluid collection) connected to a Sentinel Seal chest drainage unit (Sentinel Seal Dual Collection Chamber System, Tyco Healthcare, Gosport, UK). Continuous suction at 10–15 cm $H_2O$ was applied for $\geq$3 days. After 3 days, drainage could be maintained using water seal without suction. Air leakage was assessed at rest and under provocation by coughing at a continued suction of 10–15 cm $H_2O$. If no air bubbles appeared in the water reservoir, air leakage was considered absent.

Postoperative air leakage was assessed on the evening of the day of operation and subsequently twice daily (morning and evening) until chest drain removal.

### 2.2. Efficacy and safety end points

The primary efficacy end point was the duration of postoperative air leakage. The secondary efficacy end point was the reduction of intra-operative air leakage intensity after the first application of trial treatment. The percentages of patients air leak-free at the last intra-operative water submersion test and remaining air leak-free at discharge from the surgical ward were also assessed (*post hoc* analysis), as were time until removal of last chest drain and hospital length of stay. Adverse events (AEs; from screening to follow-up at 1 month after surgery) were reported, including the occurrence of predefined postoperative complications, incomplete lung inflation, pneumothorax and the need for additional procedures (chest drainage, re-operation, respiratory assistance and blood transfusion). Vital signs and clinical laboratory measurements were also reported.

### 2.3. Statistical analysis

The sample size was based on the results of a previous trial of similar design in which median duration of postoperative air leakage was 1 day in patients treated with TachoSil® and 2 days in patients receiving standard treatment [6]. A simulation was performed using a log-rank test to show

statistical significance at $\alpha$ = 5%, and resulted in an estimated sample size of 300 patients to provide a power of 94% to show a difference between treatments.

The duration of postoperative air leakage and the length of hospital stay were compared between treatments using a log-rank test (stratified for centres) at a significance level of $\alpha$ = 5%. A life-table analysis was performed, with time of sealing attributed to a time interval (between assessments) since the actual time points were not known. An exploratory parametric survival analysis of the primary end point, which took account of the interval censoring, was done using an accelerated-failure-time model. In this analysis, the median time until air leakage cessation was estimated. For patients where the duration of postoperative air leakage could not be assessed because of missing assessments, duration was right censored at the time of the last available assessment. In patients needing rescue treatment, the duration was right censored at the maximum duration of postoperative air leakage among all patients. Three additional sensitivity analyses were performed, one in which patients in the standard group not receiving any additional treatment were excluded, a second in which censored values in the TachoSil® group were assigned the maximum duration of postoperative air leakage in the treatment group (worst-case scenario) and a third in which patients with Heimlich valves were considered treatment failures and assigned the maximum duration of postoperative air leakage across all patients.

For the duration of postoperative air leakage and time until chest drain removal, a log-rank test of equality over treatments was performed controlling for centre, and survival curves were estimated using the life-table method. To test the effect of treatment on total volume of drainage, an *F*-test, based on a two-way analysis of variance (ANOVA), was performed, controlling for centre. Reduction in intra-operative air leakage intensity was compared between treatments using a Wilcoxon test. Descriptive statistics were determined for other end points.

The analysis of duration of postoperative air leakage and reduction of intra-operative air leakage intensity was based on the intent-to-treat (ITT) population, which consisted of all patients, who were randomised and received treatment. Descriptive end points were analysed based on the safety population.

## 3. Results

### 3.1. Patients

A total of 486 patients were screened, and 299 received trial treatment (ITT population: TachoSil®, *n* = 148; standard treatment, *n* = 151). One patient who was randomised to standard treatment received TachoSil®; this patient was included in the TachoSil® group for safety analysis (safety population: TachoSil®, *n* = 149; standard treatment, *n* = 150).

Baseline characteristics and surgical variables were similar in the two groups (Table 1). Sixteen patients had grade 3 air leakage at the first submersion test, and underwent additional suturing/stapling. At randomisation, 148 patients (49.5%) had grade 1 air leakage and 150 (50.2%) had grade 2 (data missing for one patient).

### 3.2. Trial treatments

In the TachoSil® group, a single patch was used in 79 patients (53%), whereas 42 patients (28%), 24 (16%), three (2%) and one (1%) received 2, 3, 4 and 5 patches, respectively (mean patches per patient, 1.7 ± 0.9). Twenty patients had two treatment rounds, and six required a third application. Two patients in the TachoSil® group needed rescue treatment. In the standard treatment group, 42 patients (28%) had

Table 1
Baseline characteristics and surgical variables (ITT population).

| | TachoSil® (*n* = 148) | Standard treatment (*n* = 151) |
|---|---|---|
| Male/female (%) | 69/31 | 66/34 |
| Age (years) | 64 ± 10, 65 (33–83) | 64 ± 8.5, 65 (34–82) |
| Age >65 years (%) | 49 | 47 |
| Body mass index (kg/m$^2$) | 25.8 ± 4.5, 25.5 (15.2–38.6) | 26.1 ± 4.3, 25.5 (17.3–38.6) |
| Smokers (%) | 32 | 31 |
| Users of alcohol (%) | 30 | 27 |
| FEV1 (ml) | 2477 ± 706, 2380 (1050–5000) | 2495 ± 766, 2390 (103–7200) |
| TLC (ml) | 6169 ± 1334, 6120 (2300–9720) | 6138 ± 1294, 6150 (2520–9780) |
| RV (ml) | 2654 ± 989, 2540 (780–7830) | 2606 ± 854, 2470 (720–7150) |
| Antero- or postero- lateral thoracic incision (%) | 56/44 | 54/46 |
| Lymphadenectomy (%) | 97 | 93 |
| Type of resection (%)[a] | | |
| Right upper lobectomy | 37 | 33 |
| Right lower lobectomy | 14 | 15 |
| Left upper lobectomy | 22 | 26 |
| Left lower lobectomy | 18 | 15 |
| Middle-lobe lobectomy | 5 | 5 |
| Upper bi-lobectomy | 0 | 2 |
| Lower bi-lobectomy | 4 | 2 |
| Intensity or air leakage (%)[a] | | |
| Grade 1 | 51.4 | 47.7 |
| Grade 2 | 48.6 | 51.7 |

Data are mean ± standard deviation, median (range). FEV1: forced expiratory volume (1 s); TLC: total lung capacity; RV: residual volume
[a] Type of resection in two patients and intensity of air leakage in one patient unknown in the standard treatment group.

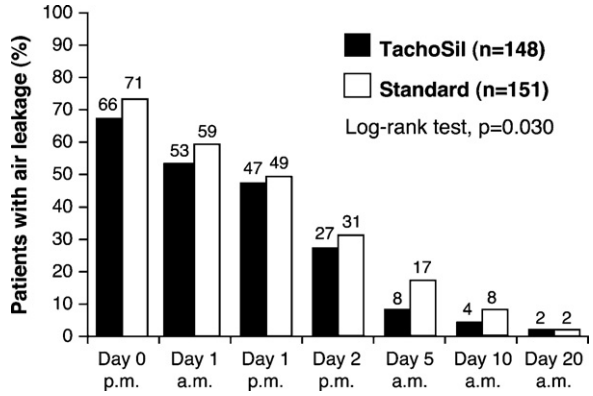


Fig. 1. Percentage of patients without air leakage at selected time points (evening of day 0 to day 20) after surgery (ITT population).

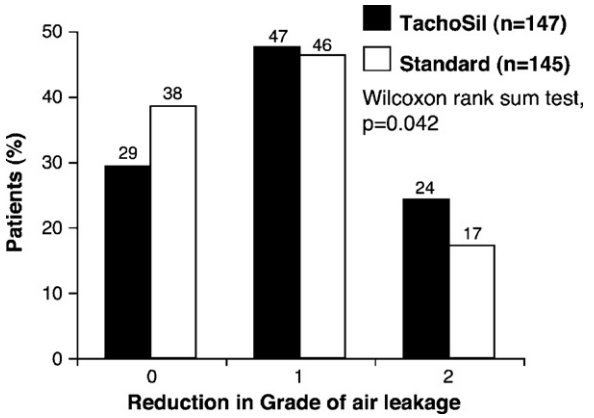


Fig. 2. Reduction of intra-operative air leakage intensity (ITT population).

no additional standard treatment after randomisation, 79 patients (53%) were sutured (single, $n = 14$; continuous, $n = 65$), 23 (15%) were stapled and four (3%) received other standard treatment. Three patients had a second round of further standard treatment. No patients in the standard treatment group needed rescue treatment.

### 3.3. Duration of postoperative air leakage

Patients with postoperative air leakage at selected time points are shown in Fig. 1. The percentage of patients without air leakage was higher in the TachoSil® group at all time points up until day 17, at which point air leakage occurred in only three patients in each treatment group. The more efficacious air sealing by TachoSil® was confirmed by a log-rank test showing a significant between-group difference in the duration of postoperative air leakage ($p = 0.030$).

An exploratory parametric analysis, based on an accelerated-failure-time model, resulted in an overall estimated mean effect difference between the treatments of 1.36 units on the timescale (95% CI: 0.89, 2.10; $p = 0.153$). Although non-significant, this corresponded to an estimated 36% increase in the duration of postoperative air leakage in the standard treatment group compared with TachoSil®. The estimated median time until cessation of air leakage was 14.5 h with TachoSil® and 19.5 h with standard treatment.

In a *post hoc* analysis, 68% of patients in the TachoSil® group and 42% of patients in the standard treatment group were air leak-free at the last intra-operative water submersion test (OR 5.27 (95% CI: 1.26–21.96); $p = 0.022$). The proportions of these patients remaining air leak-free at discharge from the surgical ward were 30% and 19% for TachoSil® and standard treatment, respectively (OR 4.93 (95% CI: 1.33–18.31); $p = 0.017$).

Duration of postoperative air leakage remained significantly shorter in the TachoSil® group ($p = 0.014$) after exclusion of standard group patients, who did not receive any additional treatment ($n = 42$), and also when patients, who received Heimlich valves (TachoSil®, $n = 3$; standard treatment, $n = 6$), were assigned the longest recorded postoperative duration of air leakage (20 days) ($p = 0.032$). When censored patients in the TachoSil® group ($n = 4$) were assigned the longest postoperative air leakage duration, the difference between groups just failed to reach statistical significance ($p = 0.051$).

### 3.4. Reduction of intra-operative air leakage intensity

Patients in the TachoSil® group experienced a greater reduction in intra-operative air leakage intensity compared with patients receiving standard treatment ($p = 0.042$) with 71% of TachoSil® patients achieving a reduction of 1–2 grade units compared with 62% in the standard treatment group (Fig. 2).

### 3.5. Chest drain removal and hospital length of stay

The median number of days until removal of the (last) chest drain was 4 days (range 1–25) in the TachoSil® group and 5 days (range 1–21) in the standard treatment group ($p = 0.054$). There was no significant difference between TachoSil® and standard treatment in least squares mean (±SE) total volume of chest tube drainage ($1723 \pm 89.2$ vs $1624 \pm 89.64$ ml; $p = 0.39$) or median (range) hospital length of stay (8 (1–36) vs 9 (4–28) days; $p = 0.35$).

### 3.6. Postoperative complications and additional procedures

Postoperative complications and additional procedures reported as AEs are summarised in Table 2. A total of 39

Table 2
Postoperative complications and additional procedures (safety population).

| | TachoSil® ($n = 149$) | Standard treatment ($n = 150$) |
|---|---|---|
| Postoperative complications (%), total: | 26 | 33 |
| Pneumonia | 6.0 | 6.0 |
| Pulmonary embolism | 0 | 0.7 |
| Atelactasis | 6.0 | 7.3 |
| Surgical wound infection | 0.7 | 0.7 |
| Cardiac arrhythmia | 6.7 | 8.0 |
| Progression of soft tissue emphysema | 0.7 | 1.3 |
| Bleeding | 1.3 | 2.7 |
| Other | 13 | 16 |
| Additional procedures (%), total: | 11 | 11 |
| Additional chest drainage | 4.7 | 4.0 |
| Blood transfusion | 4.7 | 6.0 |
| Re-operation | 4.0 | 3.3 |
| Respiratory assistance | 2.7 | 2.0 |

Table 3
Occurrence of incomplete inflation of the lung and pneumothorax (safety population).

| | Incomplete inflation of lung % (events/patients assessed) | | Pneumothorax % (events/patients assessed) | |
|---|---|---|---|---|
| | TachoSil® | Standard | TachoSil® | Standard |
| Day 1 | 28.7% (33/115) | 21.1% (24/114) | 38.1% (43/113) | 31.8% (35/110) |
| At drain removal | 22.0% (27/123) | 20.9% (27/129) | 29.5% (36/122) | 33.3% (42/126) |
| After drain removal | 20.7% (29/140) | 19.3% (27/140) | 29.4% (40/136) | 34.3% (47/137) |
| Discharge | 20.5% (23/112) | 19.6% (22/112) | 24.8% (27/109) | 27.7% (31/112) |
| Follow-up (1 month) | 10.3% (8/78) | 7.5% (6/80) | 11.8% (9/76) | 10.3% (8/78) |

Chest X-ray was not mandatory on day 1 or follow-up.

patients (26%) in the TachoSil® group and 50 patients (33%) in the standard treatment group had postoperative complications, with the most common being cardiac arrhythmia, atelectasis and pneumonia. Additional procedures were required in 11% of patients in both groups. The percentages of patients with incomplete lung inflation and pneumothorax were similar in the two treatment groups during the entire postoperative course (Table 3).

### 3.7. Adverse events

In total, 270 AEs were reported, 137 in the TachoSil® group ($n = 66$, 44%) and 133 in the standard treatment group ($n = 66$, 44%). The most frequently reported were pneumonia, atelectasis, atrial fibrillation, constipation, bronchopleural fistula, flatulence, pyrexia, pneumothorax, pleural effusion and anaemia, all of which are well-known complications of the surgical procedure or underlying cancer. With the exception of atrial fibrillation (TachoSil®, $n = 11$; standard treatment, $n = 5$), AEs were reported with similar frequency in both groups. Four deaths occurred, three in the TachoSil® group (candida sepsis plus atelectasis, cerebrovascular accident and pneumonia aspiration plus bronchial fistula) and one in the standard treatment group (bronchopleural fistula). Deaths occurred from 4 to 64 days after surgery and all were considered to be related to the underlying disease or complications of surgery. There were no significant differences between groups with regard to vital signs or clinical laboratory measurements.

## 4. Discussion

Postoperative alveolar air leakage is a frequent complication of pulmonary surgery and a major cause of morbidity and prolonged hospital stay [1–4]. Standard procedures to prevent or reduce air leakage after lung resection include suturing, stapling and electrocautery. Other methods that have been proposed to reduce the occurrence of postoperative air leaks include staple-line buttressing or pleural tenting [14,15], postoperative water seal drainage [16] and the use of intra-operative autologous 'blood patches' [17]. Several surgical sealants have also been developed, including liquid fibrin glues [9,10], synthetic hydrogels [5,11,18], a glutaraldehyde–bovine albumin-based bioadhesive [19], and a collagen fleece-bound sealant (TachoSil®) [6,7].

The efficacy of surgical sealants in reducing the incidence and duration of postoperative air leaks has been previously investigated. A systematic review found that 8 of 12 randomised controlled trials reported a statistically significant difference between sealing treatment and control in reducing postoperative air leakage after pulmonary resection [8]. However, in only one trial was the use of a sealant associated with a significant reduction in duration of chest drainage [9] or hospital stay [18], and the authors concluded routine use of surgical sealants could not be recommended. Similarly, a more recent review reported a significant decrease in the duration of air leakage after sealant use in 6 of 11 randomised controlled trials [20]. Studies without a between-group difference tended to be earlier trials of liquid fibrin sealants, with small numbers of patients randomised, irrespective of whether intra-operative air leakage was present. Recent studies of more rigorous design that enrolled only patients with intra-operative air leakage have generally shown significantly reduced duration of postoperative air leakage with sealant use [7,10,11,19]. In a more recent study, the use of TachoSil® was shown to significantly reduce intra-operative air leakage, postoperative air leakage volume on days 1 and 2, time to chest drain removal and duration of hospital stay compared with standard surgical treatment [7].

In a previous trial of design similar to the present study, treatment with TachoSil® compared with standard surgical treatment did not reach statistical significance for the primary end point of incidence of air leakage 48 h after lobectomy. However, more than half (52%) of the patients had no intra-operative air leakage following primary stapling [6]. A *post hoc* analysis of the subgroup of patients with grade 1–2 air leakage showed that TachoSil® reduced postoperative air leakage compared with standard treatment (mean duration of $1.9 \pm 1.4$ vs $2.7 \pm 2.2$ days; $p = 0.015$).

In the current trial, patients were randomised during surgery, after standard surgical measures to address leakage had been applied. Patients with adequate air leakage control after primary stapling and limited suturing were thus excluded, reflecting the use of TachoSil® in clinical practice. TachoSil® was associated with a decrease in the intensity of intra-operative air leakage ($p = 0.042$), reflecting its immediate sealing properties. However, of more clinical relevance, treatment with TachoSil® was associated with a reduction in the duration of postoperative air leakage compared with standard surgical treatment ($p = 0.030$). The treatment difference was immediate and was maintained throughout the postoperative course, with a higher treatment effect (horizontal difference between the curves of Fig. 1) of TachoSil® in patients with prolonged air leakage. The 5-h reduction in estimated median time until cessation of air leakage with TachoSil® compared with standard surgical

treatment (14.5 vs 19.5 h) is a clinically relevant finding that suggests potentially quicker postoperative recovery. This was reflected in the difference between TachoSil® and the standard treatment in time to chest drain removal (median 4 vs 5 days), although this did not reach statistical significance ($p = 0.054$). No difference was observed between groups in the hospital length of stay; however, the study was not powered to detect such a difference. Because the TachoSil® patch has a high degree of physiological extensibility and pliability [21], it may be particularly useful in lung surgery, where surgical handling, including the application of tissue sealants, is complicated by respiratory movements.

The trial outcome with regard to the primary end point was not changed either by excluding the 42 patients in the standard treatment group not requiring additional treatment or by assigning the longest recorded duration of air leakage to the nine patients, who received Heimlich valves. Assigning the longest recorded duration of air leakage to the four patients in the TachoSil® group with unknown duration of air leakage also showed near significance ($p = 0.051$), despite this conservative approach lowering the overall difference between treatments.

The study was conducted at 12 centres across eight countries, hence, findings are indicative of a general standard in lung surgery. A centre effect on duration of postoperative air leakage appeared from the statistical analysis. Differences in the type of resection (upper, middle or lower pulmonary lobe) or treatment variables (number of TachoSil® patches, use of stapler and type of sutures) did not account for this centre effect. The actual cause remains unclear. However, differences in postoperative patient care and chest drain management as well as minor differences in surgical techniques, including TachoSil® application and extent of additional treatment, may have contributed. Moreover, the pre-planned analysis of the primary end point still showed the significant superiority of TachoSil®, demonstrating the relevance of the results in general surgical practice.

One potential weakness of the current trial was its open-label design. However, the use of a centralised randomisation procedure performed intra-operatively minimised the inherent risk of selection bias, as shown by the similar baseline characteristics and surgical variables in the two groups.

Another possible limitation was the use of suction for 3 days, after which drainage could be maintained by water seal. Studies have suggested that placing chest tubes on water seal may resolve air leaks more rapidly than suction, although this is still debated [22,23]. However, suction was chosen to avoid a situation in which inadequate coughing resulted in air remaining in the chest without a frank air leak being present. In addition, the study design was based on standard practice in most European thoracic surgical centres. Importantly, chest tube management was identical for both treatment groups. Thus, the difference between groups appears valid.

TachoSil® was well tolerated with AEs generally similar in the two treatment groups. Atrial fibrillation was seen at a higher frequency in the TachoSil® group, but is common after lung surgery and all cases were considered related to the underlying disease or complications of surgery. The occurrence in this study is consistent with previous reports and the slightly higher incidence in the TachoSil® group appears to be coincidental.

Prolonged postoperative air leakage is generally considered the most important cause of postoperative pulmonary morbidity, prolonged length of hospital stay and increased hospital costs [2], and the use of TachoSil® for the closure of air leakage following lung lobectomy has indeed been shown to be cost-effective primarily due to shortened hospital stay [4]. Since superior air-sealing efficacy could be demonstrated in the present study in patients with relatively good pulmonary function, TachoSil® may be expected to be even more beneficial in the high-risk patient with poor quality of lung parenchyma and the patient needing more advanced surgery [24,25].

In summary, the findings of this trial suggest that TachoSil® is an effective and safe treatment for the reduction of postoperative alveolar air leakage in patients following elective pulmonary lobectomy. These findings support previous trials that have showed reduced incidence or duration of postoperative air leaks with sealing agents in patients with intra-operative air leakage, and provide further evidence that their use may be beneficial after lung surgery.

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Editorial comment

# Use of sealants in pulmonary surgery: evidence-based or industry-driven approach?

*Keywords:* Air leak; Sealants; Clinical trials

## 1. Current practice

In a power-vote survey undertaken in a recent joint European symposium [1], 240 thoracic surgeons were asked to anonymously respond to several multiple-choice questions aimed at establishing the current standards of practice on the use of sealants in our speciality.

Only 8% of surgeons declared to use sealants routinely in their practice, whereas 54% use them only when indicated. Seventeen percent of respondents felt that the use of sealants is mainly limited by their cost and 34% were uncertain as to their possible clinical usefulness.

## 2. What we already know: evidence from the literature

Including the trial published in this issue [2], there have been five randomised trials testing the efficacy of collagen fleece-bound sealants in pulmonary resection [3].

In general, they showed an intra-operative and post-operative reduction in intensity and incidence of air leak. The efficacy on duration of chest tubes and hospital stay was, however, inconsistent. Only two studies found sealants to impact on postoperative hospital stay. Furthermore, cost analysis has been inconclusive or non-existent in these trials. Statistics applied have been often inappropriate for the design of the study and the nature of data, and sample size analysis unreported.

Evidence-based literature does not support the routine use of these sealants in pulmonary surgery [3].

## 3. What we would need to know

We need to refine the methods to design and conduct clinical trials on sealants in pulmonary surgery:

- Air leak does not occur in all patients with the same risk. Multifactorial weighed risk scores have been proposed with the aim to provide a standardised and reproducible instrument for patients' selection in efficacy trials [4]. This would allow to get the most meaningful information and minimise the expense and risk of such trials in those patients unlikely to derive benefit.
- The intra-operative grading of air leak appears rather subjective and its association with postoperative air leak unproven. A more objective and reproducible method to quantify intra-operative air leak would be desirable (i.e., actual flow leak measured through the ventilator).