Efficiency of fleece-bound sealing (TachoSil®) of air leaks in lung surgery: a prospective randomised trial

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Abstract

Objective: Persistent air leakage following pulmonary resection is a major limiting factor for discharge from hospital. The aim of this study was to evaluate the sealing capacity of TachoSil® for the closure of alveolar air leaks following parenchymal resections and to determine its effect on time to chest drain removal and duration of hospitalisation. Methods: A total of 173 patients undergoing lobectomy or segmentectomy were enrolled in a single-centre, randomised study to compare the efficacy of TachoSil® with standard treatment. Alveolar air leaks were evaluated intraoperatively by submersion of the resection site in saline and were graded according to the Macchiarini scale as 0 (no bubbles), 1 (single bubbles), 2 (stream of bubbles), 3 (coalescent bubbles). Patients with grade 1 or 2 air leaks were randomised to TachoSil® or standard treatment. Grade 3 patients received standard treatment until the air leak was downgraded to grade 1 or 2 at which point they were randomised. Patients with grade 0 leakage were excluded. The primary efficacy endpoints of the study were postoperative quantification of air leakage on postoperative days 1 and 2. Other efficacy measurements included mean time to chest drain removal and mean time to hospital discharge.

Results: The mean intraoperative post-treatment air leakage was significantly lower in the TachoSil® group (153.32 ml/min, range: 10–450 ml/min) compared with the standard treatment group (251.04 ml/min, range: 15–970 ml/min; P = 0.009). The significant difference in air leakage volume observed intraoperatively post-treatment was maintained postoperatively. TachoSil® showed a trend towards reduced incidence of postoperative leakage when measured >48 h or >7 days after surgery (30.7% vs 38.96% and 24% vs 32.46%, respectively). The mean times to chest drain removal and to hospital discharge were significantly reduced following the use of TachoSil® (5.1 days vs 6.3 days, P = 0.022 and 6.2 days vs 7.7 days, P = 0.01, respectively). Conclusions: The use of TachoSil® following pulmonary resection resulted in a reduction in air leakage compared with standard techniques. This reduction in air leakage resulted in a significant reduction in both the time to chest drain removal and the period of hospitalisation.

Keywords: Air leakage; Lung tissue sealing; TachoSil®

1. Introduction

The incidence of intraoperative pulmonary air leakage during lung surgery is reported to be as high as 70% [1]. Persistent air leakage, lasting longer than 7 days, occurs in 15–25% of patients and is a major limiting factor for discharge from hospital due to the need for prolonged chest tube drainage [2].

Standard therapy for treating air leaks after lung resection involves surgical stapling or suturing techniques and electrocautery. Approaches to decrease the intensity and duration of air leaks include the use of a variety of sealants, such as fibrin glue [3–5], synthetic polyethylene glycol-based materials [1,6,7] and collagen patches coated with fibrinogen and thrombin [8]. A recent systematic review evaluating the effectiveness of sealants in preventing or reducing postoperative air leaks after pulmonary resection for lung cancer concluded that while surgical sealants seem to reduce postoperative air leaks, they had no effect on length of hospitalisation and that some may even increase the risk of infectious complications [2].

A recent study that investigated the efficacy and safety of a fixed combination of a collagen patch coated with human fibrinogen and thrombin (TachoComb®) over conventional treatment suggested that there was no additional value of added sealant if air tightness was achieved with standard techniques [8]. However, significant reductions in intraoperative air leakage, as well as in the intensity and duration of postoperative leakage, were demonstrated for a subgroup of patients with established air leakage at randomisation. The aim of this study was to compare the air sealing capacity

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References and suppliers omitted for brevity.
of TachoSil® (TS) with approved routine surgical procedures for the closure of alveolar air leaks following parenchymal resection in a large group of patients with proven intraoperative air leakage and to determine whether there was any effect on time to chest drain removal and duration of hospitalisation.

2. Materials and methods

2.1. Study design

This was a randomised, prospective, open-label, parallel group study carried out at a single centre. The study was conducted according to the ethical principles of the Declaration of Helsinki and in accordance with Good Clinical Practice. The trial population comprised patients undergoing lobectomy (n = 148) or segmentectomy (n = 25) (limited resection in case of reduced functional operability) for non-small cell lung cancer performed through anterolateral or posterolateral thoracotomy. Complete mediastinal lymph node dissection was performed in all patients. Clinical (preoperative) tumour stage was according to the International Union against Cancer (UICC) I and II. Neoadjuvant radio-chemotherapy was an exclusion criterion. Patients undergoing video-assisted thoracoscopic lobectomies as well as lobectomies for non-malignant reasons were excluded from the study. The schedule for inclusion was determined by the patient’s admission to hospital. Interlobar fissure was from the study. The baseline characteristics of the patients in the TS and ST groups were comparable (Table 1). The surgical variables were similar for the two treatment groups; no statistical significance occurred. The first intraoperative spirometric measurement was performed by the anaesthetist immediately after the submersion test and prior to treatment, the second intraoperative measurement followed treatment of air fistulae.

Postoperatively, air leakage volume (ml/min) was measured using a digital mass airflow sensor device (AIRFIX®) connected to the chest drain-suction unit. Details concerning this device, and the applicability of this technique as a standard quantification tool for air leakage are reported elsewhere [10]. Postoperative measurements of volume were made in the morning of postoperative days 1 and 2.

In patients with persistent air leakage (>7 days) regular measurements were performed every second day.

2.2. Measurement of air leakage volume

The first intraoperative spirometric measurement was performed by the anaesthetist immediately after the submersion test and prior to treatment, the second intraoperative measurement followed treatment of air fistulae.

Postoperatively, air leakage volume (ml/min) was measured using a digital mass airflow sensor device (AIRFIX®) connected to the chest drain-suction unit. Details concerning this device, and the applicability of this technique as a standard quantification tool for air leakage are reported elsewhere [10]. Postoperative measurements of volume were made in the morning of postoperative days 1 and 2. Other efficacy measurements included mean time to chest drain removal and mean time to hospital discharge.

2.3. Efficacy parameters

The primary efficacy endpoints of the study were postoperative quantification of air leakage on postoperative days 1 and 2. Other efficacy measurements included mean time to chest drain removal and mean time to hospital discharge.

2.4. Statistics

The statistical method used was the t-test for independent samples. A P value <0.05 was considered to be significant.

3. Results

A total of 173 patients were screened for inclusion in the study; 21 patients without intraoperative leakage (grade 0) were excluded. Initially, grade 3 leakage was detected in 43 patients, all of whom were to be downstaged to grade 1 or 2 following surgical fistula management. Prior to randomisation, grade 1 leakage was found in 29 and grade 2 leakage in 123 patients. A total of 152 patients with grade 1 or 2 leakage were randomised; 75 to the TS group and 77 to the ST group.

The baseline characteristics of the patients in the TS and ST groups were comparable (Table 1). The surgical variables were similar for the two treatment groups; no statistical
significance could be detected in regard to the baseline characteristics. The mean consumption of sutures in the ST group was 2.8 (range: 1—5).

3.1. Intraoperative air leakage: pre- and post-randomisation

The mean intraoperative air leakage volume prior to randomisation was 711.8 ml/min overall (median: 500 ml/min; range: 40—3600 ml/min). At randomisation, the degree of leakage in the two treatment groups was similar. In the TS group, 13 and 62 patients had grades 1 and 2 leakage, respectively. In the ST group there were 16 patients with grade 1 and 61 patients with grade 2 air leaks.

Post-treatment, air leakage was detected in all patients in both treatment groups. The mean intraoperative post-treatment air leakage was significantly lower in the TS group (153.32 ml/min, range: 10—450 ml/min) compared with the ST group (251.04 ml/min, range: 15—970 ml/min; \( P = 0.009 \)) (Fig. 1).

3.2. Postoperative leakage on days 1 and 2

The significant difference in air leakage volume observed intraoperatively post-treatment was maintained postoperatively. On postoperative day 1, the mean leakage was 43.6 ml/min for the TS group compared with 86.1 ml/min for the ST group (\( P = 0.004 \)). On postoperative day 2 the respective values were 20.1 ml/min compared with 42.46 ml/min (\( P = 0.023 \)) (Fig. 1).

On postoperative day 1 air leakage was detected in 47/75 patients (62.67%) in the TS group and in 53/77 patients (69.64%) in the ST group (\( P = 0.331 \)). On postoperative day 2 air leakage was detected in 22/75 (30.26%) and in 30/77 (38.96%) of patients in the TS and ST groups, respectively (\( P = 0.234 \)).

3.3. Duration of air leakage

Air leakage present after >48 h was detected in 23/75 (30.7%) and in 30/77 (38.96%) patients in the TS and ST groups, respectively (\( P = 0.234 \)). On day 3 the mean leakage in the TS group was 68.63 ml/min (range: 40—150 ml/min) compared with 87.46 ml/min (range: 30—240 ml/min) in the ST group.

Persistent air leakage (for >7 days) was detected in 18/75 (24%) and in 25/77 (32.46%) patients in the TS and ST groups, respectively (\( P = 0.282 \)). On day 8, the mean leakage in the 18 patients in the TS group was 44.65 ml/min (range: 25—80 ml/min) whereas it was 67.21 ml/min (range: 30—125 ml/min) in the ST group (Fig. 1).

3.4. Time to chest drain removal and hospital discharge

The mean time to chest drain removal was 5.1 days in the TS group compared with 6.3 days in the ST group (\( P = 0.022 \)). The mean time to hospital discharge was 6.2 in the TS group compared with 7.7 days in the ST group (\( P = 0.01 \)) (Fig. 3).

3.5. Safety

No adverse effects were observed intra- or postoperatively regarding the application of Tachosil™ and there was no increased infection rate in these patients. The rate of complications was similar for the two groups. In the TS group,

Table 1

<table>
<thead>
<tr>
<th></th>
<th>TS group (n = 75)</th>
<th>ST group (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (range)</td>
<td>58.5 (35—75)</td>
<td>56.9 (29—74)</td>
</tr>
<tr>
<td>Gender, male:female</td>
<td>54 (72%):21 (28%)</td>
<td>57 (74%):20 (26%)</td>
</tr>
<tr>
<td>Resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>65 (86%)</td>
<td>68 (88%)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>10 (14%)</td>
<td>9 (12%)</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>48 (64%)</td>
<td>44 (57%)</td>
</tr>
<tr>
<td>II</td>
<td>20 (27%)</td>
<td>28 (36%)</td>
</tr>
<tr>
<td>Ill</td>
<td>7 (9%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Leaks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>13 (17%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>62 (83%)</td>
<td>61 (79%)</td>
</tr>
</tbody>
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Fig. 1. Intraoperative and postoperative air leakage volume on days 1 and 2.

Fig. 2. Percentage of patients with air leakage >48 h and persistent air leakage >7 days.
In this study, consistent with the high incidence of intraoperative air leakage, we demonstrated significant reductions in air leakage volume on postoperative days 1 and 2 using TachoSil®. This represented reductions approaching 50%. Furthermore, the use of TachoSil® showed a trend towards a reduction in the proportion of patients with leakage after >48 h or >7 days as well as a reduction in the mean leakage volumes at these times. The mean duration of air leakage is also influenced to a great extent by an underlying pulmonary disease (mostly by chronic obstructive pulmonary disease and emphysema), by concomitant cardiovascular disease, by the type of suction device used and by the algorithm for appropriate drain management [2].

Importantly, the benefits of TachoSil® translated to significant reductions in time to chest drain removal and time to hospital discharge. According to the postoperative documentation in both groups, no significant difference in complication rate was detected. However, the fact that the patients in the Tachosil® group could have their chest tubes removed and thereby enabling them to be discharged from hospital more than 1 day earlier accounts for a significant reduction in pain and is more convenient for the patient. Regarding the portion of patients with persistent air leaks, use of Tachosil® accomplished a statistical trend in reduction of leakage and frequency (Fig. 2). However, only a minor portion of patients is affected by this complication and the vast majority still benefit from the effects of Tachosil® as described above. Given the beneficial effects of Tachosil® on reducing air leakage volume and the frequency of postoperative leakage this reduced period of hospitalisation is perhaps not surprising, since patients need to remain under clinical observation during the time of chest drainage. To our knowledge, this is the only randomised trial of sealants to demonstrate benefits in both time to drain removal and hospital discharge. The previous trial by Lang et al. [8] did not include these clinically relevant endpoints. In one randomised trial which compared a fibrin glue and thrombin solution with standard treatment, time to drain removal was reduced from 5 to 3.5 days [3], with no impact on time to hospital discharge. In another trial of a polymeric biodegradable sealant with human serum albumin, length of stay was reduced by 1 day compared with standard treatment [13].

TachoSil®, a fixed combination of a collagen patch coated with human fibrinogen and thrombin, was developed to achieve both haemostatic and tissue sealant effects, and was originally used for haemostasis in liver surgery, particularly in case of parenchymal bleeding not amenable to the usual surgical procedures [14]. It has also found application for the sealing of lymphatic fistulas during lymphadenectomy [15] as well as in kidney resection surgery [16]. Its high degree of elasticity when moistened makes it particularly suitable for sealing pulmonary parenchymatous tissue [17]. The safety of TachoSil® has been established in both lung and liver resection surgery [8,14].

The method used to determine air volume in this study has advantages over the semi-quantitative methods routinely used that are based on the relative intensity of air bubbles appearing in the water reservoir of the drainage system. The AIRFIX® system provides simple and reliable digital bedside quantification of air leaks while remaining compatible with standard thoracic drainage systems. Its application in the diagnosis and management of postoperative air leaks was recently reported [10].

In conclusion, the results of this study demonstrate that the use of TachoSil® following pulmonary resection resulted in a reduction in air leakage compared with standard procedures.
techniques. This reduction in air leakage volume resulted in a significant shortening of drainage period and time to discharge. Advantages of reducing the time to drainage tube removal may include more rapid mobilisation as well as a reduction in the pain associated with thoracic drainage [18]. Although this relatively small-scale study did not include a formal cost-saving analysis or show any significant differences in postoperative complications the reduction in time to chest drain removal and period of hospitalisation would have obvious cost saving benefits. However, further studies in larger patient populations are still necessary to investigate these issues.

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References


