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Air-leak management after upper lobectomy in patients with fused fissure and chronic obstructive pulmonary disease: a pilot trial comparing sealant and standard treatment☆

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Abstract

A pilot trial to compare the efficacy of two different procedures to prevent postoperative air-leak in chronic obstructive pulmonary disease (COPD) patients submitted to upper lobectomy for non-small cell lung cancer. Sixty patients with COPD and lung cancer at the upper pulmonary lobes eligible for lobectomy were enrolled and randomly assigned either to standard treatment (ST) with stapling device or to electrocautery dissection and application of a collagen patch coated with human fibrinogen and thrombin (TachoSil®) (experimental treatment [ET]) for the intra-operative completion of their fused fissures. Thirty patients were enrolled in each group during a three-year period. Preoperative characteristics were similar between the two groups. Statistically significant reduction of air-leak was registered in the ET group when overall incidence of postoperative air-leak (55% vs. 96%; $P=0.03$), postoperative air-leak (mean 1.63 ± 1.96 vs. 4.33 ± 4.12 days; $P=0.0018$), chest-drain (mean 3.53 ± 1.59 vs. 5.90 ± 3.72 days; $P=0.0021$) and hospital stay duration (mean 5.87 ± 1.07 vs. 7.50 ± 3.20 days; $P=0.01$) were considered. The use of TachoSil® to prevent postoperative air-leak after interlobar fissure completion in patients with COPD submitted to upper lobectomy seems to be safe and more effective than the ST based on stapling device application.

Keywords: Pulmonary lobectomy; Lung tissue sealing; COPD; Stapling devices

1. Introduction

Lung cancer remains an important cause of death among smokers, and this condition is often associated with chronic obstructive pulmonary disease (COPD). Surgical resection offers the best chance for curing lung cancer, and lobectomy is the most frequently performed operation.

Lobectomy is carried out by the division of the parenchyma through scission of the pulmonary fissures. Persistent postoperative parenchymal air leakage (PAL) is the most common complication after major pulmonary resection and it is reported with an incidence of 3–25%. This occurs more frequently when interlobar fissures are incomplete, lung resection is performed in patients with COPD and after upper lobe resection [1, 2].

We designed a prospective, randomized, pilot trial to compare the use of electrocautery and application of sealant with the use of surgical stapler to complete interlobar fissures and to control postoperative air leakage during upper pulmonary lobectomy in COPD patients with fused fissures.

2. Materials and methods

The study was performed at the Thoracic Surgery Unit of the University of Eastern Piedmont (Novara, Italy) during the period from 1 January 2006 to 31 December 2008. Patients affected by lung cancer and associated COPD scheduled for upper pulmonary lobectomy were eligible for inclusion in the study.

2.1. COPD preoperative evaluation

All enrolled patients had COPD ranging from grade 1 to 3 according to Global Initiative on Obstructive Lung Disease guidelines [3]. The COPD index was calculated according to Korst and associates to evaluate the severity and purity of obstructive airway disease; preoperative forced expiratory volume in the 1st second expressed as percentage of predictive in decimal form (FEV_1%) was added to the preoperative ratio of FEV_1 to FVC [4]. Patients with low COPD index are those with the most severe airway obstruction. Only patients with COPD index <1.5 were considered affected by COPD. All patients with COPD eligible for upper

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lung resection were informed of the purpose of the trial with particular focus on the risks and benefits of the procedures and everyone signed a consent form before entering the trial.

2.2. Surgery, sealing techniques and randomization

Upper lung lobectomies were carried out through a postero-lateral muscle sparing thoracotomy. Arterial and venous branches were dissected, ligated and sectioned, whereas lobar bronchus was sutured and sectioned by application of a stapler with 3.5 mm length stitches. Patients with dense pleural fusion at thoracotomy were excluded in order to avoid prolonged air-leaks from sites other than the fissure. At thoracotomy, interlobar fissures were defined according to Craig classification and only grade 3 and 4 patients (visceral cleft evident for part of the fissure and complete fusion of the lobes with no evident fissure line, respectively) were included in the study [5].

Sixty patients were randomized into two groups of 30. Randomization was performed intra-operatively after confirmation of a lung tumour involving only the upper lobe with fused fissures and requiring lobectomy for complete control of the disease. Closed envelopes containing notes reading either 'experimental treatment (ET)' for electrocautery and sealant or 'standard treatment (ST)' for conventional treatment with staplers were used. The two groups were matched for sex, age, risk factors, duration of surgery and severity of COPD (Table 1).

Interlobar fissure was then completed by two different procedures following randomization.

In the ET group, pulmonary lobes were separated by electrocoagulation and application of ligatures when visible vascular or bronchial branches were identified. After completion of the fissures, PAL was evaluated by submersion of the resection site under saline and gentle reventilation of the residual lobe with a peak pressure of about 25 cm H_2O.

Table 1
Demographic, clinical and functional data of the experimental and control group

Variables	ET group	ST group	*P*-value
Sex (male)	23/30	21/30	0.74
Age (years), mean±S.D.	68±15	66.5±13.5	0.68
Smoker	27/30	24/30	0.47
COPD parameters			
FVC%, mean±S.D.	96±17	94±14.5	0.62
FEV_1%, mean±S.D.	64±9	66±8.5	0.38
FEV_1/FVC, mean±S.D.	57±8	59±9	0.36
COPD index, mean±S.D.	1.22±0.23	1.24±0.21	0.76
RV%, mean±S.D.	118±24	116±26	0.75
TLC%, mean±S.D.	100±15	98±14	0.59
TLCO%, mean±S.D.	68±18	70±17	0.66
PaO_2-pre (mmHg), mean±S.D.	72±8	69±9	0.17
$PaCO_2$-pre (mmHg), mean±S.D.	37±4	38±5	0.39
Duration of surgery (min), mean±S.D.	135±48	129±39	0.59
Length of fissures (mm), mean±S.D.	119±57	126±49	0.61
Right upper lobectomy	26/30	25/30	0.86

ET, experimental treatment; ST, standard treatment; S.D., standard deviation; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; RV, residual volume; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide; PaO_2, arterial blood oxygen pressure; -pre, preoperative; $PaCO_2$, arterial blood carbon dioxide pressure.

Leakage was measured by the anaesthesiologist considering the tidal deficit of the ventilator and was expressed by ml/min. Leakage was then graded following the Macchiarini scale as 0 (no leakage), 1 (single bubbles), 2 (stream of bubbles), 3 (coalescent bubbles) [6]. Aerostatic procedure was the application of a sterile, ready to use, completely absorbable $9.5\times4.8\times0.5$ cm^2 collagen patch coated with human fibrinogen and thrombin (TachoSil®). The patch was submerged under saline and then applied to the moderately ventilated lung by pressing it to the air-leaking surface at least 1 cm beyond the margin of dissection. Mean Tachosil® patches used per patient was 3.2 (range 2.5–4).

In the ST group, pulmonary lobes were separated by routine procedure with use of commercially available STs. Then the lung was ventilated to a pressure of 25 cm H_2O after submersion in saline to register air leakage expressed by ml/min of tidal volume loss and according to Macchiarini scale.

2.3. Drainage management

All patients received two pleural drainage (28 F and 32 F) under water-seal. Chest tubes were then connected to 10 cm H_2O continuous suction during the first 12 postoperative hours and then they were left under water-seal during the remaining duration of the postoperative hospital stay. Persistence of air leakage was registered every 6 h postoperatively up to its spontaneous cessation. The first chest tube was removed 24 h after surgery and the second one when there was no more evidence of air leakage and drained fluid volume was <200 ml during the preceding 24 h.

2.4. Statistical analysis

All described statistical procedures were carried out with the StatSoft version 7 software package (StaSoft Inc, Tulsa, OK, US). *P*-value for efficacy and safety parameters were considered to be significant if <0.05. The experimental and control procedures were compared by the unpaired *t*-test or the Wilcoxon's two-sample test applied to discrete or continuous data, whereas dichotomous or categorical data were analysed by the χ^2-test or Fisher exact test when required.

3. Results

During the 36 months period, 60 patients (44 male, 73.4%) affected by grade 1–3 COPD by the GOLD scale and lung cancer localised at the upper pulmonary lobe, mean age 68.5 years (range 58–78 years), were included in the present study and randomly received approved routine stapler control or electrocautery dissection and sealing with TachoSil® of their fused fissure for aerostasis. Demographic, clinical and preoperative functional characteristics are summarised in Table 1. In particular, the two groups were absolutely similar when sex, age, smoke exposure, preoperative pulmonary function, length of fissures and duration of operation were compared; in particular there was no difference in operating time between the two procedures.

3.1. Postoperative complications (Table 2)

Postoperative complications by groups are listed in Table 2. The occurrence of overall complication was lower in the ET group without a significant difference when compared to the ST group; in particular no complications related to the use of TachoSil® or staplers were recorded.

3.2. Intra-operative, postoperative air leakage, chest drain and hospital stay duration (Table 3)

The quantification and incidence of intra-operative and incidence of postoperative air leakage such as the duration of air leakage (Fig. 1) in the ET group were recorded to be significantly lower when compared with that occurring in the ST group (Table 3).

We have not scored and recorded the daily air leakage amount because we think that there is no real utility in quantifying the air loss considering that the tube management is not dependent from the daily leakage quantity but it depends uniquely from the moment of the complete stop of leaking.

Persistent air leakage, defined as a chest-drain air leakage maintaining >7 days after operation was recorded in 1 out of 30 patients of the ET group and in 8 out of 30 patients in the ST group ($P=0.029$). In particular, persistent air leakage in the only one patient of the ET group spontaneously stopped on day 9, whereas among the eight patients of the ST group persistent air leakage stopped after a mean of 11.5 days (range 9–14).

Table 2
Postoperative complication between the two patients groups

Complications	ET group	ST group	P-value
Stapler of TachoSil use related	0	0	NS
Postoperative deaths	0	0	NS
Major complications	0	0	NS
Fever >38 °C	6	5	NS
Minor pulmonary embolism	0	1	NS
Minor bleeding	1	2	NS
Lobar atelectasis	2	3	NS
Pneumonia	1	1	NS
Atrial fibrillation	3	4	NS

ET, experimental treatment; ST, standard treatment; NS, not significant.

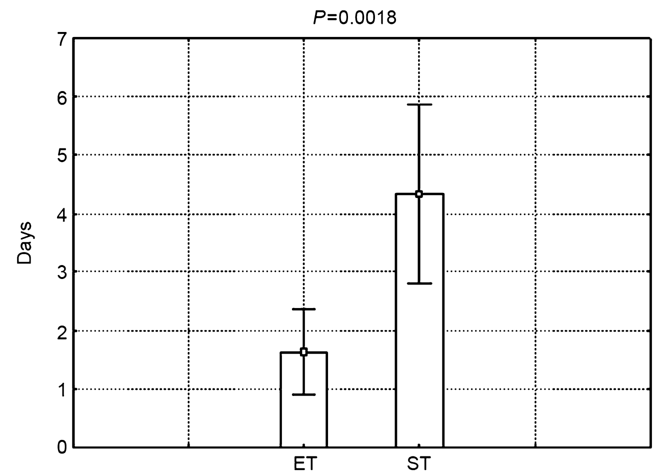

Fig. 1. Mean values and 95% confidence interval (CI) of days with air leakage. ET, experimental treatment; ST, standard treatment.

Chest-drain and hospital stay duration in the ET group were significantly lower when compared with the ST one (Table 3) (Fig. 2). Chest X-ray was routinely carried out on day 1 after surgery and after the second chest-drain removal the day before discharge. Chest X-ray findings were satisfactory in each case and no patients needed reconnection to suction for any reason (extensive subcutaneous emphysema or major pneumothorax). At discharge six patients of the ST and seven of the ET group had apical residual space of mild entity at their chest X-ray. All patients were discharged to their home and no one required subsequent access for early postoperative complication.

3.3. Short-term postoperative follow-up

Mean postoperative observation period was 23 months (range 6–41) and each patient received clinical and radiological evaluation every 3 months: during this period no

Table 3
Intra-operative, postoperative air leakage, chest-drain and hospital stay duration data

	ET group	ST group	P-value
Intra-operative leakage after sealing or stapling			
Rate	70%	90%	0.11
Mean±S.D. (ml/min)	182±162	293±209	0.026
Macchiarini scale			
0	9	3	
1	12	11	
2	9	16	
3	0	0	
Immediate after surgery air leakage rate	70%	90%	
PO day 1 air leakage rate	63%	90%	0.032
PO day 3 air leakage rate	20%	50%	0.03
Air leakage duration			
mean±S.D. (days)	1.63±1.96	4.33±4.12	0.001
Chest-drain duration			
mean±S.D. (days)	3.53±1.59	5.9±3.72	0.002
PO hospital stay			
mean±S.D. (days)	5.87±1.07	7.5±3.2	0.01

ET, experimental treatment; ST, standard treatment; S.D., standard deviation; PO, postoperative.

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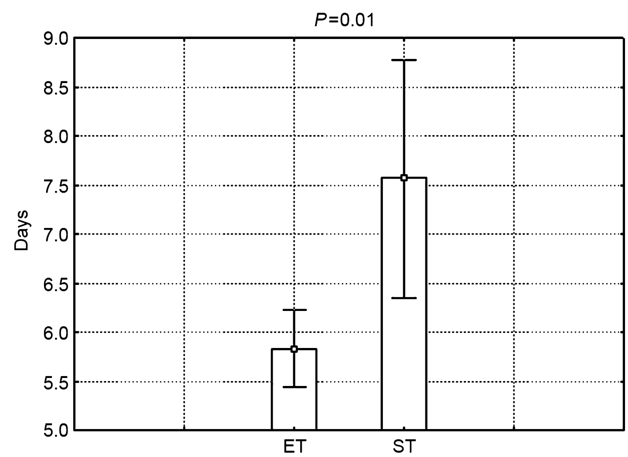

Fig. 2. Mean values and 95% confidence interval (CI) of hospital stay length. ET, experimental treatment; ST, standard treatment.

episodes of empyema, great pleural effusion or major pneumothorax were referred or identified. Those patients discharged to home with a radiological residual apical space demonstrated the complete reexpansion of the residual right lobes after a mean period of 4.5 months (range 3–6).

4. Discussion

Presently, lung neoplasms remain the leading cause of death world-wide for tumours. The most frequently carried out pulmonary resection for non-small cell lung cancer is pulmonary lobectomy.

Because of similar risk factors (in particular cigarette smoking), lung cancer is often associated with COPD. During the last years some authors demonstrated that patients with mild to severe COPD could have a better late preservation of pulmonary function after lobectomy than healthy patients [4, 7]. These results confirmed similar previous evidences based on daily practise and encouraged surgeons to operate on patients affected by both lung cancer and COPD with mild or severe deficit of the pulmonary function.

Pulmonary lobectomy frequently requires divisions across lung parenchyma because of partially to completely fused fissures and, therefore, inherently create a potential source of PAL.

Elderly, concomitant COPD, fused fissures and upper lung lobectomy have been demonstrated to be significantly associated with persistent postoperative PAL [1, 2].

PAL is reported to be the most common complication after lung resection [8]; the PAL results in a prolonged chest-drain duration which increases patient's risk of pleural infection, pulmonary embolism, respiratory distress and associated thoracic pain.

PAL and associated co-morbidities prolong the postoperative hospital stay which negatively affect procedure-related costs.

The routine use of surgical staplers, even buttressed by synthetic or organic strips, does not result in an adequate air sealing in most patients undergoing pulmonary lobectomy [2].

Many procedures to prevent postoperative PAL such as the use of fibrin glue, synthetic sealants, biodegradable sealants, reinforcement of pulmonary suture with Teflon or bovine pericardium or autologous blood patch have been described [9–13].

Recently the use of a fleece-bound sealing (TachoSil®) to reduce the postoperative occurrence and duration of PAL in pulmonary resected patients has been reported [14, 15].

None of these studies focused on a high risk population of patients (perhaps because it is not easy to enrol a high number of patients with such characteristics). Each type of resection (upper and lower lobectomies or segmentectomies) such as patients with COPD or with normal preoperative pulmonary function tests were considered together and the only data which occur systematically in these series is the intra-operative detection of air leakage from parenchymal laceration. It is well known that PAL after lower lobe resection, such as after segmentectomy or in patients with good preoperative pulmonary function test, frequently stops spontaneously without any significant impact on postoperative chest-drain and hospital stay duration and associated co-morbidities.

To our knowledge, the present study is the only one in the English literature which focuses on the prevention of postoperative PAL by the use of a sealant in upper lobectomies with fused fissures in patients with concomitant COPD (previously defined as potential risk factors of PAL).

Numbers are limited by the nature of the study which was aimed to enrol only patients with many presumable risk factors. This is only a pilot study and we have not previously calculated the sample size to obtain a statistical power for confident evaluation of our results.

The results of our study demonstrate that the application of TachoSil® after blunt and electocautery dissection of fused fissures, while performing upper lobectomy in COPD patients, significantly reduce the postoperative occurrence and duration of PAL when compared with the standard procedure of parenchymal stapling. This reflects in a shorter duration of chest-drain tubes with reduced incidence of postoperative co-morbidities and hospital stay duration.

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