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ORIGINAL ARTICLE

Adverse effects of fibrin sealants in thoracic surgery: the safety of a new fibrin sealant: multicentre, randomized, controlled, clinical trial†

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Abstract

OBJECTIVES: The safety of fibrin sealants (FS) has been questioned in the light of recent reports of adverse effects. We evaluated the safety of a new FS in a randomized controlled trial (RCT).

METHODS: Multicentre, open-label Phase II/III RCT to evaluate the safety of the new FS. The trial was approved by the Ethic Committee of each three participating Centre. FS includes two components (component 1: fibrinogen; component 2: thrombin), each of them subjected to two viral inactivation procedures. Out of 200 screened patients, 185 eligible patients (49 females, 136 males), aged between 18 and 75 years, undergoing major thoracic surgery were randomized to receive FS (#91 patients) as an adjuvant for air leak control or no treatment (#94 patients, control group). Safety variables were: percentage of subjects with adverse events associated with the therapy; formation of antibodies against bovine aprotinin; vital signs (blood pressure, body temperature, heart and respiratory rate); laboratory parameters.

RESULTS: Overall operative mortality was 3.2% (6/185), 1.1% in the FS group and 5.3% in the control group, respectively. Twenty patients (22%) had adverse events in the FS group and 22 (23.4%) in the control group. Atrial fibrillation (five patients in the FS group and four in the control group) and hyperpyrexia (five and seven patients, respectively, in the two groups) were the most common adverse events. No patient reported thromboembolic events (pulmonary embolism or deep vein thrombosis) during the in hospital stay or within 1 month from discharge. None of the adverse events was considered as treatment related. The formation of bovine aprotinin antibodies was reported in a total of 34 patients (37.4%) in the FS group and was not related to any adverse effect.

CONCLUSIONS: The present RCT did not show any increased risk of adverse events, and of surgical complications, related to the use of the new FS.

Keywords: Airway • Lung • Pleural Air leak/effusion • Glue • Tissue

INTRODUCTION

Alveolar air leaks (AAL) and broncho-pleural fistulas represent the most common complication after lung resection and significantly contribute to morbidity and mortality following thoracic surgery [1].

The persistence of air leakage (>5–7 days), occurs in up to 15% of the patients and it often requires additional treatments such as the repositioning of a pleural drainage catheter, the attempt to induce a chemical pleurodesis and in some cases a surgical revision [2]. Rapid and effective control of bleeding and aerostasis during thoracic surgery reduces blood loss and air leak and lead to a decrease in postoperative morbidity with a reduction in time to remove of drains and hospital stay. Various techniques, with different efficacy, have been used in order to minimize the occurrence of prolonged air leakage and to treat it during lung resection. The most common is the use of sealants, either sythethic or natural (albumin-glutaraldehyde, resorcinol–glutaraldehyde–formaldehyde, human fibrin etc) [3, 4]. Fibrin glue, a haemostatic or adhesive product made from human plasma and consisting of two components, fibrinogen and thrombin, is the most common sealant used in thoracic surgery [5]. The action of fibrin sealant (FS) simulates the last phase of the physiological coagulation process, the conversion of fibrinogen into fibrin which occurs after the cleavage of fibrinogen into fibrin monomers and fibrinopeptides. Thrombin acts as an enzyme and converts the fibrogen into fibrin between 10 and 60 s. The fibrin monomers aggregate together to form the coagulum: the thrombin-activated FXIII (FXIIIa) forms cross-links among different monomers acting as a stabilizer. In both

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processes, fibrin formation and coagulum stability, calcium ions play a major role acting as co-factors. The safety of FSs has been questioned in the light of recent reports of adverse effects, mainly thromboembolic events and fatal anaphylaxis and because of the lack of well designed randomized clinical trial (RCT) [6, 7].

In the present paper we evaluated the safety of a new FS, paying great attention to the number and percentage of patients that developed antibodies against bovine aprotinin, in a multi-centre, RCT.

Study design

The study was performed in three Italian centres over a period of 15 months (September 2008 through December 2009): Careggi University Hospital, Florence; Azienda Ospedaliera S. Camillo Forlanini Hospital, Rome; Azienda Sanitaria Locale Pescara. This was a multi-centre, parallel group, randomized, controlled, open-label Phase II/III study (Registration Eudract code 2007-005583-27) to evaluate the efficacy and safety of a new FS, developed by Kedrion SpA (Castelvecchio Pascoli, Lucca, Italy; www.kedrion.com) as an adjuvant for air leak control in patients undergoing surgical lung resection (×Fig. 1). Inclusion and exclusion criteria are shown in Table 1. Consent was obtained before the operations from the subjects or their legal representatives who have read, understood and signed an informed writtten consent. Five thoracic surgeons were involved in the study. Procedures were performed with the same surgical techniques, including use of staplers (GIA DST, Covidien Norwalk, CT, USA) to create uncompleted fissure plans or to perform wedge resections. After lung resection procedures, areas of AAL were closed by conventional techniques. The lung was then ventilated to an airway pressure of 20 mmHg and AAL assessed using the Macchiarini scale [9]. Randomized patients included only those judged intraoperatively to have an AAL graded 1–3 [9]: patients were randomly assigned to a treatment with FS (FS group) or to no treatment (control group), by using sealed opaque envelopes marked with a patient identification code. The randomization was stratified for each centre on the basis of a 1:1 ratio between treatments. The assignment was made on the basis of a randomization list, previously prepared by the Study Statistician, for each centre involved in the clinical study and made accessible only to a person outside of the surgery team. In the control group, patients underwent no further procedures. For patients assigned to the treatment group, FS was applied to every identified surgical sites leaking air. After sealant application, the lung was ventilated again to an airway pressure of 20 mmHg and AAL reassessed.

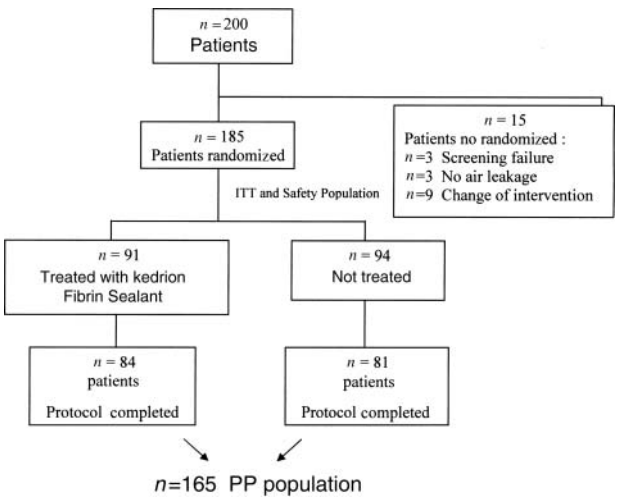

Figure 1: Study design, ITT, intention to treat population = patients randomized PP Population, patients who completed the study without any major protocol violations.

Table 1: Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 18 and 75 years	Thoracoscopy surgery
Primitive/secondary neoplastic pulmonary pathology or any parenchymal pathology to be treated with lung resection	Redo-ipsilateral thoracotomies
Patient candidates for anatomic/ atypical lung resection	Patients undergoing neo-adjuvant treatments
Open surgical access	Patients who underwent pneumonectomy
Life expectancy ≥6 months	Karnofsky performance status (KPS) ≤50
Informed consent form as approved by the EC	Immunodepression
	Laboratory values: Bilirubin >1.5 mg/dl; Alkaline phosphatase >120 IU/l; Creatininemy >1.5 mg/dl; WBC >10 000/mm^3;
	Known allergies
	Participation in another clinical study
	Missing written consent form

The first goal was to determine the efficacy of FS after its application to surface leaking air after lung resection. The primary efficacy endpoints were the duration of AAL and drainage from skin closure (in hours); the secondary efficacy endpoints were: (i) percentage of patients without AAL for the entire hospitalization time; (ii) percentage of patients without AAL at the end of the surgery and (iii) duration of postsurgery hospitalization. The efficacy was evaluated in a different paper not yet published. The second goal, which represents the aim of the present paper, was to assess, throughout the entire study, the safety of the FS by: (i) the percentage of subjects with adverse events associated with the therapy and (ii) the formation of antibodies against bovine aprotinin.

The design of this study is compliant with the 'Notes for Guidance on the Clinical Investigation of Plasma Derived Fibrin Sealant Products—CPMP/BPWG/1089/00' [8].

Ethics

The study protocol, protocol amendment, patient information sheet and informed consent document were submitted to the Independent Ethics Committee (IEC) of each participating centre prior to the start of any study-related procedure. The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on

Harmonisation (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Prior to study start, patients were given a full explanation of the aims of the study, the benefits, potential discomforts and risks of taking part in the study. They were also given a written explanation of the study in the study information sheet and informed consent was obtained.

Fibrin sealant

The FS produced by Kedrion is obtained from human plasma, and consists of two components (fibrinogen and thrombin). Component 1 (powder and solvent for reconstitution—1 ml reconstituted) contains coagulable plasma proteins 42–78 mg (of which 45–50 mg of human fibrinogen), Factor XIII ≥6 U, plasminogen ≤0.2 U and bovine aprotinin 0.74–1.1 PEU. Component 2 (powder and solvent for reconstitution—1 ml reconstituted) contains ∼2 mg of human proteins, of which thrombin (Factor IIa of coagulation) 1000–1562 IU, and calcium chloride 0.275 mM. Both sealant components are subjected to viral inactivation procedures: treatment with a solvent–detergent mixture (SD), and heating of the lyophilized product for 30 min at a temperature of 100°C (fibrinogen) or nanofiltering by filters with a porosity of 35 and 20 nm in a layout sequence in order to guarantee the removal of very small sized viruses (such as Parvovirus B19) and of the agent responsible for transmissible spongiform encephalopathy (thrombin).

The SD viral inactivation method consists of treatment with an organic solvent mixture (tri-*n*-butyl phosphate) and a vegetable detergent (Tween 80). The SD method applied to the preparations of the coagulation factor under study has proved to be effective in the inactivation of both the human immunodeficiency virus type 1 (HIV-1) and the model viruses (pseudorabies virus, PRV–model for herpes virus; bovine viral diarrhoea–model for HCV). All viruses of major pathogen relevance in terms of transfusion (e.g. HIV, HBV, HCV) are lipid enveloped.

The dose of FS used in this RCT ranged by 5–20 ml and was based on the clinical requirements (such as the type of surgery, the size of the area and the number of applications). Packs of 5 and 10 ml were used in the study. FS was applied drop by drop or with a spray device avoid using pressure >20–25 psi (pound-force per square inch) at a distance of 10–15 cm from the surface of the lung. The nebulizer system was the preferred and most used application system (78/91, 85%).

Materials and Methods

From September 2008 to December 2009, a total of 200 patients were enrolled after screening (Florence $n = 85$; Rome $n = 89$; Pescara $n = 26$). Fifteen of these patients were not randomized: three for screening failure, three for the absence of air leakage and nine for intraoperative change of surgical procedure. Therefore, during the 15-month period, a total of 185 patients were randomized, 91 assigned to the FS group and 94 to the control group (Table 2), and evaluated in the present study (Fig. 1). The calculation of sample size was in accordance with the hypothesis that the treatment with the investigational medicinal product (IMP) resulted in a 20% reduction in the average drainage duration, equal to 1.2 days with a standard deviation of 2.5 days, with a type I error at 5% for a two tail hypothesis test, using the Mann–Whitney *U*-test and a power of 80%.

Table 2: Demographics

	Treatment with IMP, $n = 91$	No treatment, $n = 94$	Total, $n = 185$
Sex (%)			
Female	22 (24.18)	27 (28.72)	49 (26.49)
Male	69 (75.82)	67 (71.28)	136 (73.51)
Age (years)			
Mean (SD)	66.8 (9.04)	65.8 (10.8)	66.3 (9.97)
Median	68.5	68.5	68.5
Range	21.4–79.4	23.1–79.7	21.4–79.7
n	91	94	185
Weight (kg)			
Mean (SD)	75.2 (12.0)	75.2 (12.3)	75.2 (12.2)
Median	75.0	74.0	74.0
Range	50.0–110.0	46.0–108.0	46.0–110.0
n	87	92	179
Height (cm)			
Mean (SD)	167.9 (8.42)	168.3 (8.77)	168.1 (8.58)
Median	170.0	168.0	169.0
Range	147.0–189.0	150.0–188.0	147.0–189.0
n	87	92	179
BMI (kg/m^2)			
Mean (SD)	26.7 (3.73)	26.6 (4.12)	26.6 (3.93)
Median	26.3	26.4	26.3
Range	16.9–37.7	19.1–38.1	16.9–38.1
n	87	92	179
Co-morbidities (%)			
Emphysema	10 (10.99)	7 (7.45)	17 (9.19)
TBC	0 (0)	2 (2.13)	2 (1.09)
Diabetes	10 (10.99)	12 (12.77)	22 (11.9)
Surgical procedures (%)			
Lobectomy	66 (72.53)	73 (77.66)	139 (75.14)
Atypical resections	20 (21.98)	15 (15.96)	35 (18.92)
Segmentectomy	5 (5.49)	6 (6.38)	11 (5.95)

The safety of the IMP was evaluated throughout the entire study on the percentage of subjects with adverse events associated with the therapy and the formation of antibodies against bovine aprotinin. An adverse event was any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An adverse event could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medical (investigational) product. A serious adverse event/reaction was any adverse event or adverse reaction that, regardless of the dose: (i) resulted in death; (ii) was life threatening; (iii) required in-patient hospitalization or prolongation of existing hospitalization; (iv) resulted in persistent or significant disability or incapacity; (v) caused a congenital anomaly or birth defect. A non-serious adverse event/reaction was an adverse event/reaction that did not meet the above criteria. The principal investigator (A.G.) assessed the association between the adverse event and the on-going treatment in accordance with the following WHO definitions: certain, probable, possible, unlikely, unclassified. The term 'unlikely' has been substituted by the term 'not related' when the event was

experienced by a patient in the control group. The investigator also had to evaluate the clinical significance of all abnormal laboratory values based on standard laboratory reference values. Any clinically significant abnormality had to be fully investigated. The term 'clinically significant' referred to any abnormal value that, according to the investigator, represented an important clinical problem that required the intervention of a physician or that otherwise could fall within the definition of a 'serious' adverse event. Adverse events categorized as 'serious' have been reported to the regulatory authorities (Ethic Committee) immediately, whereas minor adverse events are merely documented in the annual summary sent to the regulatory authority. The number and percentage of patients that developed antibodies against bovine aprotinin were presented only for the group of patients treated with the IMP. Vital signs and laboratory parameters were listed for each patient. All subjects had blood drawn for laboratory exams at the preoperative screening and at the follow-up clinic visit 30–40 days after surgery. At the preoperative screening, serum exams, including anti-HAV, HBs-Ag, anti-HVC, anti-HIV-1 and -2 antibodies, were also performed. In compliance with the Note for Guidance on the Clinical Investigation of Plasma Derived Fibrin Sealant Products—CPMP/BPWG/1089/00 [8], a serum sample was drawn from every patient enrolled in the study, before starting the treatment. Such sample was stored at a temperature below −70°C and used for possible future viral exams.

Statistics

Statistical analysis was performed using SAS® Software version 9.2. *P*-values < 0.05 were considered significant. Statistical methods were planned in the protocol and were then agreed and approved in the statistical analysis plan. The safety variables were analysed in the safety population (all randomized patients). Summary statistics (mean, standard deviation, median, minimum, maximum) were provided for continuous variables, and the number and percentage of patients in each category were provided for categorical data. The comparison between groups was performed by means of the Mann–Whitney *U*-test for continuous variables and by means of Chi-square test or Fisher's exact test for discrete variables.

The results of adverse events were analysed in a descriptive manner, reporting the type and absolute and relative frequency of all adverse events, IMP-related adverse events, IMP-non related adverse events, adverse events with not classified relation and serious adverse events.

RESULTS

Demographics are shown in Table 2. Usual smokers were 40 (44.0%) in the treated group and 37 (39.4%) in the control group; occasional smokers were 5 (5.5%) in the treated group and 8 (8.5%) in the control group. Pulmonary functions tests are shown in Table 3. Adverse events are shown in Table 4.

Overall operative mortality (serious adverse events with fatal outcome) was 3.2% (6/185), 1.1% (1/91) in the FS group and 5.3% (5/94) in the control group, respectively. (Chi-square: 2.62; *P* = 0.6). Adverse events with serious non-fatal and serious fatal (operative mortality) events are shown in Tables 4–6. All adverse events were considered as unlikely or not related to treatment.

Table 3: Preoperative pulmonary function tests and vital signs

	Treatment with IMP, *n* = 91	No treatment, *n* = 94
FEV1% predicted (*n*, %)		
>65%	78 (85.71)	85 (90.43)
≤65%	13 (14.29)	9 (9.57)
Heart rate (b.p.m.), supine		
Mean (SD)	74.8 (8.05)	73.5 (7.80)
Range	54–90	57–92
Respiratory rate (breaths/min), supine		
Mean (SD)	13.4 (1.94)	13.4 (1.42)
Range	10.0–24.0	11.0–20.0
Body temperature (°C)		
Mean (SD)	36.3 (0.30)	36.3 (0.24)
Range	35.8–37.6	35.8–36.8

Table 4: Adverse events

	Treatment with IMP, *n* = 91	No treatment, *n* = 94
Number of adverse events	23	38
Patients numbers with adverse events	20 (21.98%)	22 (23.40%)
Number of adverse events related to IMP	0	0
Patients numbers with adverse events related to IMP	0 (0.00%)	0 (0.00%)
Number of adverse events not related to IMP	23	38
Patients number with adverse events not related to IMP	20 (21.98%)	22 (23.40%)
Number of serious adverse events	8	21
Number of patients with serious adverse event	7 (7.69%)	10 (10.64%)

Table 5: Serious (non-fatal) adverse events

Treated group	Control group
One ischaemic stroke	One pleural infection and chronic respiratory failure and acute renal failure
One haemothorax	
One right massive haemothorax	One intestinal obstruction and unstable angina and wound dehiscence
One broncho-pleural fistula	
One hyperpyrexia and pleural infection	One atrial fibrillation, empyema, wound dehiscence and increased blood cells count
One broncho-pleural fistula	One infection, wound dehiscence and hyperpyrexia
	One ischaemic stroke and acute renal failure and pancreatitis

Table 6: Serious fatal adverse events (operative mortality)

Treated group	Control group
1 early respiratory failure	1 ARDS 1 haemothorax 3 myocardial infarctions

Although the number of adverse events was higher in the control group than in the treated group (23 vs. 38 events, Chi-square: 4.80; $P = 0.3$), the rate of patients with adverse events was similar in the two groups (20 patients in the FS group vs. 22 patients in the control group equals to 21.98 vs. 23.49% (Chi-square: 0.053; $P = 0.9$). Serious adverse events were reported in 7 patients (7.69%) of the FS group and in 10 (10.64%) of the control group (Chi-square: 0.48; $P = 0.9$) (Table 4).

Atrial fibrillation was the most frequently reported adverse event, and was reported in five patients (5.5% of safety population) in the treated group and in four (4.3%) in the control group. Pleural empyema was reported in one patient (1.1%) in the treated group compared with four cases (4.2%) in the control group (Chi-square: 1.75 $P = 0.7$). Other adverse events reported in more than one patient in either group were: cardiac arrest (two patients in the control group), renal failure acute (two patients in the control group), haemothorax (two patients in the treated group and one in the control group), broncho-pleural fistula (two patients in the treated group), hyperpyrexia (five patients in the treated group and seven in the control group) and wound dehiscence (three patients in the control group). None of the other adverse events was reported in more than one patient in either group.

No patient reported thromboembolic events (pulmonary embolism or deep vein thrombosis) during the in hospital stay or within 1 month from discharge.

The following clinically significant abnormalities of laboratory parameters (haematology and blood chemistry) were reported as adverse events: (i) leucocytosis was reported in two patients in the treated group and in 1 2 in the control group; (ii) increase of transaminase levels was reported in two patients in the control group; (iii) prolongation of activated partial thromboplastin time was reported in one patient in the control group; (d) increase of blood amylases was reported in one patient in the treated group; (e) The formation of bovine aprotinin antibodies was reported in a total of 34 patients (37.4%) in the treated group.

As regards efficacy, FS group showed a statistically significant reduction in postoperative AAL (9.52 vs. 35.8 h; $P < 0.005$) and in the percentage of patients with AAL at wound closure (81.11 vs. 100%; $P < 0.001$) but no significant difference was observed in time to chest drain removal.

DISCUSSION

Sealants have a widespread use in thoracic surgery even if there is a lack of robust scientific evidence for their efficacy [2] and, on the other hand, there is a lot of concern for conflicting results regarding safety [3]. Furthermore some sealants, Pleuraseal (synthetic) and Quixil (derived from human plasma) have recently undergone spontaneous recall which have rised questions regarding the safety. [10] (http://www.agenziafarmaco.gov.it/sites/default/files/nota_informativa_importante_su_quixil.pdf and http://www.covidien.com/recall/pages.aspx). Conventional FSs utilize components prepared from pooled human plasma (fibrinogen, thrombin) and, sometimes, animal-derived components (e.g. bovine aprotinin or thrombin). These carry a potential risk of transmitting human- or animal-borne infectious materials (e.g. viruses such as hepatitis B and C, human T-cell leukaemia, HIV-1 or prions responsible for diseases such as Creutzfeldt–Jakob disease (CJD) or bovine spongiform encephalopathy. There are additional concerns of antigenic reactions to foreign proteins and of thrombotic effects from high concentrations of added thrombin. An autologous FS free from added thrombin is available (such as Vivostat) and provides a definite means of preventing these potential adverse effects: anyway it needs time and personnel to be prepared, it is not ready to use, and it is' rather expensive [11]. The question of adverse effects of FSs in thoracic surgery has been recently rised in the light of papers addressing the issue of thromboembolism and anaphylaxis. To enhance safety, the product Tisseel/Tissucol VH (Baxter., USA), the most common FS used worldwide with two decades of experience, has been recently updated in the new generation Tisseel VH/SD, which has a double viral inactivation step to provide an increase margin of safety (http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con033569.pdf). In FSs an anti-fibrinolytic agent, natural (bovine aprotinin) or synthetic (tranexamic acid, -aminocaproic acid, gabexate mesilate and nafamostat mesilate) is added to act as a stabilizing agent. The most common anti-fibrinolytic agents are Tranexamic and aprotinin. Most studies have found fatal anaphylaxis [12] to be related to antifibrynolitic agents. Recent studies indicate tranexamic acid may be responsible for various adverse reactions when used in neurological applications, included chest wall resection with vertebral involvement [13]. Most of the formulations employed, including FS or Tisseel, contain aprotinin [14, 15] which has an immunogenic potency, with an elevated risk of hypersensitivity reactions at re-exposure to aprotinin if a significant level of aprotinin-specific immunoglobulin E or G antibodies are detected. Nevertheless the reported clinically relevant cases are very few or anedoctical compared with the large number of patients treated [16].

Up to now in patients with evidence of aprotinin antibodies, which have been found in 37.4% of cases included in the treated group of the present trial, in line with data from the literature, great care is suggested before reusing [15, 17]. Even if no evidence of allergic reaction has been found in the present RCT, in agreement with FDA and Baxter, we recommend FS not to be used more frequently than every 12 months in the same patient (http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con033569.pdf).

The present RCT paid great attention to the issue of safety with 1 month postoperative blood sample to evaluate laboratory data and clinical evaluation. The number of adverse events showed a trend for a less incidence in the FS group (23 vs. 38 equal to 25.27 vs. 40.42%) even if no statistically significant difference was found. The number of patients with adverse events was very close in both groups (Tables 4–6) (23.4 vs. 21.98%). At the clinical review none of the reported adverse events was considered as being treatment-related. Serious adverse events were reported in seven patients (7.69%)

in the treated group and in 10 (10.64%) in the control group. Adverse events with fatal outcome (operative mortality) occurred mostly in the control group than in the treated group (1 vs. 5 equal to 1.1 vs. 5.3%) without any statistically significant difference. Pleural empyema was reported in one patient (1.1%) in the treated group compared with four cases (4.2%) in the control group, but the difference showed no statistically significant difference. An higher incidence of pleural empyema in the control group is an interesting issue which can be related to the longer duration of air leak in this group. The alleged risk of pleural empyema due to the sealant inefficacy to maintain its adhesive properties over time which act as a foreign body in the pleural space has not been found in the present RCT [2, 18]. There is no clear explanation of such differences in the number of adverse effect or operative mortality. This study was designed to assess the safety of FS, and such hypothesis was fully verified in the light of the comparable characteristics of our groups. The issue of protective effect of FS can only be related to the shorter time of air leak in the treated group but needs further investigations. Fatal adverse events and other serious adverse events generally consisted of complications due to the surgical procedure or to the underlying respiratory disease. No patient showed thromboembolic events in both groups, but the number of patients is too small for a definitive asssessment of such complication, which has been mainly related to the high flow pressurized delivery system of the glue or to thombogenic effect of thrombin [5]. When applying FS or any similar product using a spray device, according to previous studies the pressure should be within the pressure range should never be >20–25 psi. Furthermore it should be avoid spraying closer than 10–15 cm from the surface of the tissue (http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm212129.htm). All these rules were carefully followed in the present RCT.

Laboratory parameters did not show any significant difference except for the percentage of bovine aprotinin antibodies, which is in line with data from the literature [9]. The question of the high percentage of patients becoming positive to bovine antibodies, even if is not related to any adverse effect, is not yet clarified and needs further evaluation. Waiting for such data we and others recommend of avoiding any re-exposure to products.

The number of patients with adverse effects and the operative mortality were higher in the control group, with no statistically significant difference. An hypothesis of a protective effect of FS, probably related to the efficacy in reducing the duration of air leak, needs further and larger evaluation.

In conclusion the present RCT showed the safety of the new FS with the absence of any increased risk of serious and non-serious adverse events, and of surgical complications, related to its use in thoracic surgery even if for finding differences in rare adverse effects more data will be needed in future trials.

Conflict of interest: none declared.

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