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Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer (Review)

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[Intervention Review]

Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer

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ABSTRACT

Background

Postoperative air leak is a frequent complication after pulmonary resection for lung cancer. It may cause serious complications, such as empyema, or prolong the need for chest tube and hospitalization. Different types of surgical sealants have been developed to prevent or to reduce postoperative air leaks. A systematic review was therefore undertaken to evaluate the evidence on their effectiveness.

Objectives

To evaluate the effectiveness of surgical sealants in preventing or reducing postoperative air leaks after pulmonary resection for lung cancer.

Search methods

We searched the electronic databases MEDLINE (1966 to September 2008), EMBASE (1974 to September 2008), and the Cochrane Central Register of Controlled Trials (CENTRAL)(*The Cochrane Library*, Issue 3, 2008) and listed references. We hand searched conference proceedings to identify published and unpublished trials.

Selection criteria

We included randomized controlled clinical trials in which standard closure techniques plus a sealant were compared with the same intervention with no use of any sealant in patients undergoing elective pulmonary resection provided that a large proportion of the patients studied had undergone pulmonary resection for lung cancer.

Data collection and analysis

Four reviewers independently selected the trials to be included in the review, assessed methodological quality of each trial and extracted data using a standardized form. Because of several limitations, narrative synthesis was used at this stage.

Main results

Sixteen trials, with 1642 randomized patients in total were included. In thirteen trials there were differences between treatment and control patients in reducing postoperative air leaks. This reduction proved to be significant in six trials. Three trials showed a significant reduction in time to chest drain removal in the treatment group. In two trials, the percentage of patients with persistent air leak was significantly smaller in the treatment group. Finally, three trials including 352 patients showed a statistically significant reduction in length of hospital stay.

Authors' conclusions

Surgical sealants reduce postoperative air leaks and time to chest drain removal but this reduction is not always associated with a reduction in length of postoperative hospital stay. Therefore, systematic use of surgical sealants with the objective of reducing hospital stay cannot be recommended at the moment. More and larger randomized controlled clinical trials are needed.

PLAIN LANGUAGE SUMMARY

The use of sealants after lung cancer resection reduce postoperative air leaks and, in many cases, the length of hospitalization

Air leak (air coming out of the remaining lung tissue) after lung removal for lung cancer is a common postoperative complication that prolongs hospital stay. Surgical sealants (glue), synthetic or made from blood products, have been developed to prevent or to reduce the incidence of air leaks. They are applied during the operation over the lung surfaces that show air leaks. This review of randomized trials found that the use of surgical sealants seems to reduce postoperative air leaks and length of hospitalization. Nevertheless, more and larger randomized trials are needed to clearly determine the effects of surgical sealants, especially on length of hospitalization.

BACKGROUND

Worldwide, carcinoma of the lung is the main cause of cancer deaths. Over a million new cases are diagnosed annually (World Cancer Report 2003), about 80% of which are of non-small cell histological types (Rankin 1986; Travis 2004). About 20% of patients with lung cancer undergo surgical resection. Most of them are tumours of non-small cell type. One of the most common complications of lung resection is persistent air leak that happens in more than 5% of patients (Rice 1992). Persistent air leaks and inadequate control of postoperative pain are identified as the most common causes of delays in discharge from hospital after thoracic operations (Wright 1997). The air leak may come from the lung parenchyma as a result of surgical manoeuvres or mechanical stapling. In areas of emphysema, an air leak may appear at the site where the staple penetrates the lung tissue. These parenchymal air leaks are usually minor complications and resolve spontaneously within a few days. However, they may be responsible for long postoperative hospital stays and, occasionally, they may require reoperation (Duque 1997). The air leak may also come from a bronchial stump, either after segmentectomy, lobectomy, bilobectomy or pneumonectomy. Segmental or lobar fistulas usually resolve with prolonged chest tube drainage, although they may require reoperation. Bronchopleural fistula after pneumonectomy is a life-threatening complication associated with a high mortality rate, is commonly associated with post-pneumonectomy empyema and requires specific and immediate treatment (Duque 1997).

It is, therefore, important to prevent this complication, either to avoid a prolonged postoperative stay and to prevent infection of the pleural space caused by the opening of the bronchial stumps, which is commonly associated with spillage of purulent material into the contralateral lung and subsequent pneumonia, worsening this serious complication. A variety of surgical sealants have been used in thoracic surgery to prevent air leaks, to prevent and treat bronchopleural fistulas, to prevent oesophageal fistulas, or to control bleeding in cardiac and vascular surgery (Bayfield 1996; Kjaergard 1996; Macchiarini 1999; Radosevich 1997). However, the effectiveness of such sealants has not been fully established in patients with lung cancer undergoing pulmonary resection.

Description of the condition

Prevention of postoperative air leak after pulmonary resection for lung cancer by using surgical sealants is one of the key points of the postoperative outcome in thoracic surgery.

Description of the intervention

A variety of surgical sealants have been used in thoracic surgery to prevent air leaks, to prevent and treat bronchopleural fistulas, to prevent oesophageal fistulas, or to control bleeding in cardiac and vascular surgery (Bayfield 1996; Kjaergard 1996; Macchiarini 1999; Radosevich 1997).

How the intervention might work

Sealing air leak after a lung cancer resection by using surgical sealants should avoid a prolonged postoperative stay and prevent infection of the pleural space caused by the opening of the bronchial stumps, which is commonly associated with spillage of purulent material into the contralateral lung and subsequent pneumonia, worsening this serious complication.

Why it is important to do this review

The effectiveness of such sealants in patients with lung cancer undergoing pulmonary resection has not been fully established.

OBJECTIVES

To evaluate whether standard closure techniques plus a sealant are more effective than standard tissue closure techniques alone in patients undergoing elective pulmonary resection for lung cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled clinical trials in lung cancer patients.

Types of participants

Patients undergoing elective pulmonary resection mainly for lung cancer. We considered patients with pulmonary metastatic cancer, benign lung diseases and lung volume reduction surgery if they represented a small proportion in a lung cancer trial.

Types of interventions

Standard closure techniques, such as stapling or suturing, plus a sealant, compared to the same intervention with no use of sealant. We treated bronchial and parenchymal sutures separately.

Types of outcome measures

We considered the following outcomes:

Primary outcomes

Postoperative hospital stay.

Secondary outcomes

Postoperative morbidity and mortality, postoperative chest tube time

Search methods for identification of studies

We searched MEDLINE (through PubMed) from 1966 to September 2008, EMBASE (through OVID) from 1974 to September 2008, and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 3, 2008), and we also searched listed references and handsearched conference proceedings to identify published and unpublished trials. We adapted a search strategy for all databases (see Appendix 1).

The authors have participated in the main conferences since the last review of this topic and identified no further relevant studies on the topic (16th European Conference on General Thoracic Surgery, European Society of Thoracic Surgeons. Bolonia, Italy. 8-11 June 2008).

Data collection and analysis

Four independent reviewers evaluated the abstracts obtained from the electronic and manual searches. We obtained a hard copy of the identified studies to determine whether they met the inclusion criteria. Any disagreement was resolved by consensus. Bibliographic references were handled with the ProCite

software.We entered complete information related to methods, characteristics of participants, characteristics of the intervention, the different groups of comparison, as well as the results, follow-up time, and funding entity of every study in a spreadsheet specifically designed for this purpose.

We attempted only a narrative synthesis at this stage due to the heterogeneity of studies regarding type of intervention (type of sealant), outcome measures and analysis.

Assessment of risk of bias in included studies

In order to estimate the validity of the included studies, the risk of bias in the results of each eligible study was assessed according to the criteria mentioned in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Criteria for judging risk of bias were sequence generation (a description for allocating interventions to participants based on a random process), allocation sequence concealment (a description of any method to secure implementation of the random assignments to prevent that allocations could have been foreseen), blinding of participants, personnel and outcome assessors (a description of measures used to blind study participants and personnel for knowledge of which intervention a participant received), and incomplete outcome data (a description of the level of completeness of each outcome, including attrition and exclusions).

RESULTS

Description of studies

Our preliminary literature searches identified 34 potentially eligible studies (one unpublished) which investigated the role of surgical sealants for preventing air leaks after pulmonary resections in patients with lung cancer. We excluded non-randomized clinical trials and case-control studies.

We eventually included four new randomized controlled clinical trials in the update of this review (Anegg 2007; Droghetti 2008; Tansley 2006; Marta 2008). Twelve trials were included from the previous version of the review (Allen 2004; Belboul 2004; Fabian 2003; Fleisher 1990; Lang 2003; Macchiarini 1999; Mouritzen 1993; Porte 2001; Wain 2001; Wong 1997; Wurtz 1990; Wurtz 1992).

A total of 1870 patients were included in the sixteen trials. Of the 1870 patients, 218 were not eligible and 10 were pilot patients who were randomized but not included in the final statistical analysis. Overall, 1642 patients were randomized to receive either standard closure techniques or the same standard closure techniques plus a surgical sealant and were included in the final statistical analysis. The patients in all the studies were in their late fifties or early sixties and most of them were male.

Only five trials (Anegg 2007; Belboul 2004; Droghetti 2008; Lang 2003; Marta 2008) were conducted exclusively in patients with lung cancer. In the others trials the proportion of lung cancer patients was high: 20 out of 28 (71.4%) (Fleisher 1990); 36 out of 50 (72%) (Wurtz 1990); 40 out of 50 (80%) (Wurtz 1992); 97 out of 114 (85%) (Mouritzen 1993); 53 out of 66 (80.3%) (Wong 1997); 16 out of 24 (66.6%) (Macchiarini 1999); 108 out of 124 (87%) (Porte 2001); 77 out of 100 (77%) (Fabian 2003); and 48 out 52 (92%) (Tansley 2006). In Wain 2001, 156 out of 172 (90%) were patients with lung cancer or metastasis. In Allen 2004, these data were not available.

Fibrin glue, a sealant that consists of a sealer solution (fibrinogen, factor XIII, fibronectin, aprotinin and plasminogen) and a thrombin solution (thrombin and calcium chloride) was used in six trials (Fabian 2003; Fleisher 1990; Mouritzen 1993; Wong 1997; Wurtz 1990; Wurtz 1992). A synthetic sealant consisting of polyethylenglycol, trimethylene carbonate and acrylate was used in two trials (Macchiarini 1999; Porte 2001). A water soluble polyethylene glycol-based gel photopolymerizable was used in one trial (Wain 2001). A polymeric biodegradable sealant (polyethylenglycol-based cross-linker, functionalized with succinate groups ([PEG-(SS)2]) with human serum albumin-USP) was used in two trials (Allen 2004; Tansley 2006). TachoComb, an absorbable patch consisting of an equine-collagen fleece coated with human fibrinogen and human thrombin, was used in one study (Lang 2003). TachoSil, a further development of the TachoComb that does not contain any other component than human fibrinogen and human thrombin, was used in three studies (Anegg 2007; Droghetti 2008; Marta 2008). Vivostat, an autologous fibrin sealant, was used in the remaining trial (Belboul 2004).

In six trials (Allen 2004; Anegg 2007; Marta 2008; Porte 2001; Tansley 2006; Wong 1997) patients were randomized after checking intraoperative air leaks. In the other ten trials the staple lines and cut surfaces of the lung parenchyma were routinely covered with the sealant regardless of the presence of air leaks. The sixteen trials differed in the way the sealant was applied: aerosolized spraying mechanism, double syringe (with or without photopolimerization by a xenon light) and direct application of an absorbable patch.

The presence of air leaks was evaluated (in some studies also scored according to Macchiarini's method) intraoperatively by immersing the lung tissue in saline serum and ventilating the lung. If there are leaks, air bubbles are seen coming out from the lung. Postoperatively, the air leaks are seen and measured, either in the underwater drainage chamber which is connected to one or two chest tubes (air bubbles are seen in the water seal and, in some studies scored according to Cerfolio`s classification of 1998), or using a digital mass airflow sensor device connected to the chest drain-suction unit.

Seven trials reported data on persistent air leak (Anegg 2007; Droghetti 2008; Fabian 2003; Fleisher 1990; Porte 2001; Tansley 2006; Wain 2001). Persistent air leak was defined in all of them as the presence of air leak on the seventh postoperative day or beyond. The other nine studies did not define persistent air leaks or did not study this issue specifically.

The characteristics of the 16 included studies are shown in Table 1.

Included studies

More information about included studies can be found in the Characteristics of included studies table.

Allen 2004. USA. Multicenter prospective randomized control study. Ninety-five patients requiring pulmonary resections other than pneumonectomy and decortication were assigned to the sealant group (standard surgical treatment plus polymeric biodegradable sealant) and fifty-three patients to the control group (standard procedures to control air leaks with no addition of sealant). Primary outcome was proportion of patients who remained air leak free following surgery. Secondary outcome was the proportion of intraoperative air leaks in each group that were sealed or reduced,

proportion of patients in each group that was free of air leaks immediately following surgery, duration of postoperative air leak, chest tube duration and length of hospitalization. Randomized patients included only those who had at least one significant air leak (≥ 2.0 mm in size) after pulmonary resection.

Belboul 2004. Sweden. Prospective blinded randomized study. Forty patients undergoing a standard pulmonary lobectomy were randomized; 20 patients were assigned to the autologous fibrin sealant group and 20 patients were assigned to the control group (standard lobectomy with no additional interventions). Outcomes were: rate of air leak on the day of the operation and daily thereafter until chest drains were removed, time to chest tube removal, 24-h and chest-tube drainage (bleeding/exudation) volume at removal of chest tube, duration of thoracic epidural analgesia treatment and length of postoperative hospital stay. All patients had lung tumours limited to one lobe.

Fabian 2003. USA. Prospective randomized blinded study. One hundred patients undergoing planned open anatomic resection or wedge resection were randomized intraoperatively. Fifty patients were assigned to the treatment group (patients treated with an application of fibrin glue at the end of the procedure) and 50 to the control group (received no additional treatments). Outcomes were incidence and duration of air leaks, prolonged alveolar air leaks, the volume of pleural drainage, the time to tube removal and the postoperative length of stay and any complications related to treatment.

Fleisher 1990. Canada. Randomized controlled clinical trial. Twenty-eight patients undergoing lobectomy. Fourteen were included in the fibrin group (after division of lung fissures with stapling devices, two millilitres of fibrin glue were applied to staple lines and any cut surfaces of the lung regardless of the presence or absence of air leaks), and 14 were controls (division of lung fissures with stapling devices, without additional fibrin glue). Outcomes were the duration of postoperative air leaks, chest tube drainage and postoperative hospitalization.

Lang 2003. Hungary. Multicenter randomized and prospective study. One hundred and eighty-nine patients undergoing standard lobectomy or bilobectomy for lung cancer were randomized. Ninety-six patients were assigned to the treatment group (standard surgical resection plus absorbable patch consisting of an equine-collagen fleece coated with human fibrinogen and human thrombin), and 93 to the control group (surgical standard procedures with no additional treatments). Primary outcome was incidence of air leakage 48 hours after lobectomy. Secondary outcomes were reduction of intraoperative air leakage intensity after the first test treatment, intensity and duration of postoperative air leakage up to postoperative day 9, postoperative mortality and morbidity.

Macchiarini 1999. France. Randomized controlled trial. Twenty-four patients requiring pulmonary resection other than pneumonectomy were randomized, 13 were assigned to the treatment group (a synthetic sealant that was applied to all identified surgical sites: staple lines, suture lines, areas of dissection or adhesiolysis) and 11 were controls (no addition of sealant after resection). Primary outcomes were persistence of air leaks during operation and duration of chest tube air leaks. Secondary outcomes were time from operation to chest tube removal and hospital discharge, hospitalization time and costs.

Mouritzen 1993. Denmark. Randomized controlled clinical trial. One hundred and fourteen patients undergoing pulmonary resections including pneumonectomy. Fifty-five were assigned to the sealant group (standard surgical treatment plus fibrin glue applied to bronchial stumps and lung surfaces) and 59 to the control group (standard surgical treatment with no additional fibrin glue). Primary outcomes were difference in air-tolerance-pressure before and after fibrin gluing, rate of patients with postoperative bronchopleural or pulmonary leakages and number of days with persistent air leakage. Secondary outcomes were length of stay in the intensive care unit, length of hospital stay, duration of intubation after surgery, number of days with chest tubes, rate of complications, daily amount of secretion from chest tubes, and general condition of the patient.

Porte 2001. France. Randomized controlled clinical trial. One hundred and twenty patients requiring pulmonary lobectomy or bilobectomy were randomized. Fifty-nine patients were assigned to the treatment group (a synthetic sealant was applied to all identified surgical sites leaking air or at risk of leaking air), and 61 patients were controls (after standard surgical treatment patients underwent no further procedures). Primary outcome was safety of surgical lung sealant by surveillance for unexpected adverse events during follow-up. Secondary outcomes were the percentage of alveolar air leaks effectively sealed at operation after sealant application, durability of alveolar air leaks sealing and potential effect of sealant on the in-hospital stay.

Wain 2001. USA. Randomized controlled clinical study. One hundred and seventy two patients undergoing lobectomy, wedge and segmental resections. One hundred and seventeen were assigned to the treatment group (standard surgical treatment plus a synthetic sealant was applied to all sites of surgical manipulation), and 55 patients were assigned to the control group (standard surgical treatment with no additional fibrin glue). Primary outcome was the percentage of patients free of air leakage throughout hospitalization. Secondary outcomes were control of air leaks intraoperatively, time to postoperative air leak cessation, time to chest tube removal, time to hospital discharge and safety outcomes.

Wong 1997. United Kingdom. Randomized controlled clinical trial. Sixty-six patients undergoing lobectomy segmentectomy or decortication were randomized. Thirty-three were assigned to the fibrin glue group (fibrin glue was applied to leaking areas), and 33 patients were assigned to the control group (standard surgical procedures to control air leaks were applied with no additional fibrin glue). Outcomes were days of postoperative air leaks, days of intercostal drainage, and length of in-hospital stay.

Wurtz 1990. France. A prospective randomized study. Fifty patients undergoing a pulmonary resection except pneumonectomy were randomized. Twenty five patients were treated with fibrin glue at the end of the procedure (intervention group) and 25 patients received no additional interventions (control group). Outcomes were quality of aerostasis, post-operative drainage, persistence of residual collection or faulty re-expansion after removal of drains, the need for repeated drainage and length of post-operative hospital stay.

Wurtz 1992. France. Prospective randomized study. Fifty patients undergoing a pulmonary resection except pneumonectomy were randomized, 25 patients (intervention group) were treated with

fibrin glue at the end of the procedure and 25 patients (control group) received no additional interventions. Outcomes were post-operative amount of drainage, persistence of residual collection or faulty re-expansion after removal of drains and length of post-operative hospital stay.

Marta 2008. Austria, Italy, Denmark, Germany, Hungary. Open, randomized, prospective, multicenter, parallel-group trial. Three hundred and one patients requiring pulmonary lobectomy were randomized. One hundred and forty-nine were assigned to the treatment group (standard surgical resection plus absorbable patch consisting of human fibrinogen and human thrombin), and 150 patients were assigned to the standard treatment group (surgical standard procedures with no additional treatments). Primary outcome was duration of postoperative air leak. Secondary outcomes were reduction of intraoperative air leakage intensity after treatment, number of days after removal of last chest tubes, adverse effects.

Droghetti 2008. Italy. Randomized, prospective, controlled parallel-group trial. Forty patients were randomized. Twenty patients were assigned to the treatment group (electrocautery surgical dissection of interlobar fissures plus a collagen patch with human fibrinogen and human thrombin) and 20 were assigned to the standard treatment group (routine surgical procedure with staplers with no additional treatments). Primary outcomes were the percentage of demonstrated intraoperative alveolar air leak effectively sealed after application of the sealant and to compare the proportion of patients in the sealant and control groups who were free of air leaks throughout hospitalization. Secondary outcomes were postoperative air leaks, the moment of chest tube removal, length of hospitalization, costs of the procedure and hospitalization, safety of the sealant treatment by surveillance of the incidence and severity of complications.

Anegg 2007. Austria. Randomized, prospective, open-label, parallel group study carried out at a single center. One hundred and fifty-two patients were randomized. Seventy-seven were assigned to the treatment group (parenchymal suturing, stapling or electrocautery plus a collagen patch with human fibrinogen and human thrombin), and 75 were assigned to standard treatment group (standard surgical procedure with parenchymal suturing, staplers, and electrocautery with no additional treatments). Primary outcome was quantitative measure of postoperative air leaks at days one and two. Secondary outcomes were mean time to chest drain removal, mean time to hospital discharge.

Tansley 2006. United Kingdom. Prospective, randomized, single-blind, controlled study. Fifty-two patients were randomized. Twenty-five were assigned to the treatment arm (parenchymal suturing or stapling plus a mixture of bovine serum albumin and glutaraldehyde), and 27 were assigned to the non-interventional arm (standard surgical procedure with no additional treatments). Primary outcomes were duration of air leak, duration of intercostal drainage, and duration of hospital stay. Secondary outcomes were postoperative complications other than air leaks.

Excluded studies

Eighteen studies were excluded (see Characteristics of excluded studies table). The reasons for exclusion were comparative but non-randomized studies and randomized controlled trials in animals.

Risk of bias in included studies

Twelve trials (Anegg 2007; Belboul 2004; Marta 2008; Droghetti 2008; Fabian 2003; Macchiarini 1999; Mouritzen 1993; Tansley 2006; Wain 2001; Wurtz 1990; Wurtz 1992; Wong 1997) had an adequate type of randomization (sequence generation), three trials (Allen 2004; Lang 2003; Porte 2001) had an unclear type of randomization and one trial (Fleisher 1990) had no data about type of randomization. Regarding the risk of bias related to an adequate or inadequate allocation sequence concealment, nine trials (Anegg 2007; Belboul 2004; Droghetti 2008; Fabian 2003; Macchiarini 1999; Mouritzen 1993; Tansley 2006; Wain 2001; Wong 1997) presented a proper allocation concealment, whereas the allocation concealment was unclear in six trials (Allen 2004; Lang 2003; Marta 2008; Porte 2001; Wurtz 1990; Wurtz 1992) and was not adequate in one trial (Fleisher 1990).

In two studies (Allen 2004; Tansley 2006) air leaks were assessed by qualified hospital staff, including investigators. Blinding of outcome assessment was not specified in the other fourteen studies. One study (Droghetti 2008) clearly specified that it was a pilot study and no attempts were made to calculate a sample size to provide statistical power sufficient for confident evaluation of the results.

There were no withdrawals in six trials (Belboul 2004; Droghetti 2008; Fleisher 1990; Marta 2008; Wong 1997; Wurtz 1990). Withdrawal in the remaining ten trials was clearly specified.

In all trials but two (Anegg 2007; Marta 2008) the period of patient recruitment and whether patients were consecutive or not were clearly described.

Follow-up was limited to the postoperative period in ten trials (Allen 2004; Belboul 2004; Fleisher 1990; Lang 2003; Marta 2008; Mouritzen 1993; Tansley 2006; Wong 1997; Wurtz 1990; Wurtz 1992). In five studies (Anegg 2007; Droghetti 2008; Macchiarini 1999; Porte 2001; Wain 2001) the follow-up was extended beyond the perioperative period (6 to 18 months). Patients discharged with valves were followed up until chest tube removal in two trials (Fabian 2003; Tansley 2006).

Effects of interventions

The outcomes measured in the different trials differed slightly, but most of the authors emphasized the duration of postoperative air leaks, day of chest tube removal and length of postoperative stay.

Primary outcomes

1. Length of hospital stay. In three trials (Allen 2004; Anegg 2007; Tansley 2006) the length of hospital stay was significantly reduced in the treatment group: treated patients were discharged on the sixth postoperative day and patients in the control group patients on the seventh in both the Allen's and Tansley's trials; and at 6.2 days (treatment group) and 7.7 days (control group) postoperatively in Anegg 2007. In two studies these data were not available (Lang 2003; Marta 2008). The other eleven studies did not find statistically significant difference.

Secondary outcomes

1. Morbidity.
   - Empyema: In four trials some patients developed empyema. (Macchiarini 1999; Porte 2001; Wain 2001; Wong 1997). In

one of them (Wong 1997), 3% of patients in the control group developed empyema and 0% in the treatment group. In the other three trials only patients in the treatment group developed empyema. The percentage of empyema was 3.8%, 6.78% and 3% in Macchiarini 1999, Porte 2001 and Wain 2001respectively. These differences were not statistically significant. Mean air leaks duration: Six trials found statistically significant differences between treatment patients and control (Droghetti 2008; Fabian 2003; Marta 2008; Porte 2001; Tansley 2006; Wain 2001 ;).

2. Mortality. No mortality related to the use of sealants was described.
3. Chest tube removal. Three trials found statistically significant differences between treatment patients and controls (Anegg 2007; Fabian 2003; Tansley 2006). The mean duration to chest tube removal in days in the treatment group and in the control group was 3.5 and 5, respectively, in the Fabian's trial; 4 and 5, respectively, in the Tansley's trial, and 5.1 and 6.3, respectively in the Anneg's trial. In four trials these data were not available (Lang 2003; Porte 2001; Wurtz 1990; Wurtz 1992). The other nine studies did not find any statistically significant differences.
4. Mean duration of air leaks. Mean duration of air leaks in hours in Porte's trial was 33.7 in the treatment group and 63.22 in the control group and 30.9 and 52.3 respectively in Wain's trial. Mean duration of postoperative air leaks in days was 1.1 in the treatment group and 3.1 in the control group in the Fabian's trial; 1 and 4 respectively in the Tansley's trial; and 1.7 and 3.7 respectively in the Droghetti's trial. In the Marta's trial, following surgery, treatment patients had a lower incidence of alveolar air leaks at all cut-off time points. Six trials did not find any statistically significant differences between treatment patients and control (Allen 2004; Fleisher 1990; Lang 2003; Macchiarini 1999; Mouritzen 1993; Wong 1997). In four trials these data were not available (Anegg 2007; Belboul 2004; Wurtz 1990; Wurtz 1992).
5. Persistent air leaks. Only in seven trials were these data available. The difference between treatment patients and control group was clearly reported as statistically significant in two of them (Anegg 2007; Fabian 2003). In the Fabian's trial, the percentages of patients with persistent air leaks were 2% in the treatment group and 16% in the control group. In the Anegg's trial, the percentages were 24% and 32.46% respectively. One study (Tansley 2006) found a difference in the percentage of patients with persistent air leaks but the authors did not report if the differences were significant: 2 (8%) patients in the treatment arm and 3 (11%) patients in the control arm had persistent air leak.
6. Postoperative air leaks. In twelve trials (Allen 2004; Belboul 2004; Droghetti 2008; Fabian 2003; Lang 2003; Macchiarini 1999; Marta 2008; Mouritzen 1993; Porte 2001; Tansley 2006; Wain 2001; Wurtz 1992) a significantly higher percentage of treated patients than control patients reduced or remained free of air leaks during hospitalization, leading to a shorter median duration of air leaks and/or intercostal chest drain.
   - Wurtz: 58% of postoperative air leaks in treated patients vs. 72% in controls.
   - Mouritzen: 39% of postoperative air leaks in treated patients vs. 66% in controls.
   - Macchiarini: 77% of patients remaining free from air leaks in the treated group vs. 9% in the control group.
   - Porte: Mean percentage of patients free of air leaks at day 4 was 87% in the treatment group vs. 58.5% in the control group.
   - Wain: 39% of treated patients remained free of air leaks during hospitalization vs. 11% in the control group.
   - Fabian: Overall incidence of air leaks in the treatment group 34% vs. 68% in the control group.
   - Lang: Air leak intensity was reduced in 74% in the treatment group vs. 51% in the control group.
   - Allen: The sealant group had significantly fewer patients with postoperative air leaks: 65% compared with the control group: 86%
   - Belboul: Significantly fewer patients had air leak at any time in the treatment group:40% vs. 80%
   - Tansley: Patients in the sealant arm had significantly shorter median duration of air leaks and intercostal chest drain ($P < 0.001$ and $P = 0.012$ respectively)
   - Marta: Significantly fewer patients had lower incidence of alveolar air leaks at all time points in the treatment group leading to a statistically significant reduction in post-operative air leakage duration compared to standard surgical treatment ($P = 0.030$).
   - Droghetti: statistically significant reduction of the overall incidence of air leakages were found in the sealant group: 50% vs. 95%.

This reduction in postoperative air leaks did not translate into any significant differences in the duration of hospital stay except in three trials. In Allen's trial, mean hospital stay was 6 days in the treatment group and 7 days in the control group; in Anegg's trial, 6.2 and 7.7 days respectively; and in Tansley's trial, 6 and 7 days respectively. Nor was there any difference in postoperative chest tube time except in three trials. In Fabian's trial, mean postoperative chest tube time was 3.5 days in the treatment group and 5 days in the control group; in Anegg's trial, 5.1 and 6.3 days respectively; and in Tansley's trial, 4 and 5 days, respectively. At the interim analysis of one trial (Tansley 2006), the difference in favour of the sealant arm in terms of shorter median duration of air leaks, intercostal chest drain and hospital stay, lead to stopping the trial earlier than planned.

DISCUSSION

Postoperative air leaks originating at the bronchial stumps or parenchymal surfaces after pneumonectomy or lesser pulmonary resections for lung cancer are a cause of prolonged hospital stay and may be the origin of empyema and other serious, life-threatening complications, especially when they occur after pneumonectomy. After pulmonary resection more than 70% of patients have intraoperative air leaks. Persistent air leaks (more than 7 days) occur in 15% to 25% of patients. Prolonged air leak is often the only morbidity associated with lung resection and the

only reason for prolonged length of hospital stay. Clinical trials specifically designed to study the effectiveness of surgical sealants to prevent postoperative air leaks in lung cancer patient are scarce. Only five of them (Anegg 2007; Belboul 2004; Droghetti 2008; Lang 2003; Marta 2008) were conducted exclusively in patients with lung cancer. In the other trials the proportion of lung cancer patients included in each trial was high.

A variety of sealants, synthetic (Eng 1989; Nomori 1999; Nomori 2000; Otani 1999; Sabanathan 1993), composed of pooled plasma (Grunenwald 1989) or single-donor plasma products (Matar 1990; Matthew 1990), or composed of fibrin plus synthetic products (Miyamoto 2003; Passage 2005; Potaris 2003) has been used with an apparent beneficial effect, although not in clinical trial settings. The therapeutic use of fibrin sealant is not limited to thoracic surgery; most surgical specialities have used it in one way or another, both in open surgery and in endoscopic procedures (Dunn 1999). In thoracic surgery, in addition to its intraoperative use to prevent or to reduce postoperative air leaks, sealants have also been used to treat postoperative bronchopleural fistulas (Hollaus 1998). Fibrin glue has been used alone or combined with polyglycolide non-woven felt to reinforce the target area (Mizuno 1995).

Fibrin glue has been the adhesive material most widely used in thoracic surgery during last 10 years. The interest in this product decreased since the randomized trials conducted by Fleisher and Wong demonstrated that there was no difference between the treatment and control groups in the number of postoperative air leaks, duration of chest drain and in hospitalization due to insufficient fibrin glue adhesion.

In Porte' s trial, Advaseal, a synthetic lung sealant, reduced perioperative and postoperative alveolar air leaks in patients who had moderate or severe air leaks after all conventional measures to reduce air leaks had been used. In this trial, the mean duration of hospital stay was not different in the control and treatment groups, mainly because of the higher percentage of empyema in the treated group. Empyema could be produced because this sealant did not maintain its adhesive properties over time and acted as a foreign body in the pleural space. Porte only used synthetic sealant in patients with major perioperative air leaks.

On Wain's trial, the benefit of sealant application was seen in both the high- and low-risk air leak subgroups of patients, implying that selection of patients for sealant application based on the risk for air leak alone may not be justified. Lang demonstrated that there is no evidence that a prophylactic use of an additional sealant after having achieved air tightness with standard surgery is of any value since the incidence of secondary air leaks, at least in a standard population undergoing lobectomy, is low.

Allen's trial is the only study with a shorter hospitalization for patients who had sealant applied, BioGlue, compared with controls. Nevertheless there is not any difference in chest tube duration. This could be due to several reasons: First, patients with air leaks may be kept in the hospital for observation one more day after the chest tube is removed, whereas if the chest tube is kept in just for high volume drainage, patients may be sent home immediately after removal of the chest tube. Second, more Heimlich valves were used in sealant patients (10%) than controls (2%). And third, the measurement may not be sensitive enough because the authors measured chest tube duration by days and not by hours.

In Fabian's trial fibrin glue was applied using a device that provides a fine aerosolized mist spray under pressure. This method allows precise coverage of large surfaces using small amounts of glue components. Reduced incidence of air leaks and persistent air leaks as well as earlier time to drain removal in treated patients, in contrast to other studies, may be related to the amount of product applied and to the method of application (pressurized mist system is superior to the two-syringe technique).

Since the last version of this review, four trials have been included (Anegg 2007; Droghetti 2008; Marta 2008; Tansley 2006). Three of them used TachoSil (Anegg 2007; Droghetti 2008; Marta 2008) and one of them used BioGlue (Tansley 2006). These recent trials do not support the increased risk of infectious complications in the treated group reported in previous studies. In fact there were no postoperative infectious complications associated to the application of the sealant.

Three recent trials (Anegg 2007; Droghetti 2008; Tansley 2006) have found differences in duration of hospitalization. Two of these trials found statistically significant differences in mean hospitalization length in favour of the treatment arm. The difference in mean hospitalization days did not achieve statistical significance in Droghetti's trial (Droghetti 2008); however, it was shorter in the treatment group than in the control group (11.0 days versus 14.3 days). These recent data support the results of the only previous randomized trial (Allen 2004), in which the duration of hospitalization was significantly shorter in the treatment group. Nevertheless, eleven trials did not find statistically significant differences in hospitalization length.

The fact that different sealants have been used and different outcomes have been evaluated makes any in-depth analysis of the data difficult.

Summary of main results

In summary, in twelve trials (Allen 2004; Belboul 2004; Droghetti 2008; Fabian 2003; Lang 2003; Macchiarini 1999; Marta 2008; Mouritzen 1993; Porte 2001; Tansley 2006; Wain 2001; Wurtz 1992) there was a statistically significant difference in the reduction of air leaks in the treated subjects compared with controls. However, this benefit only had an effect on significant reduction of the length of hospital stay in three of them (Allen 2004; Anegg 2007; Tansley 2006).

Overall completeness and applicability of evidence

The relatively low number of patients in each trial and the various surgical sealants used mean that this evidence should be applied with caution.

Quality of the evidence

Sixteen trials, with 1642 randomized patients in total were analysed. The risk of bias was assessed for each study. The allocation sequence was adequately generated in 12 trials. Allocation was adequately concealed only in 5 trials and was unclear in 10. The knowledge of the allocated interventions was adequately prevented during the study in 2 trials and it was unclear in 11 trials. Incomplete outcome data were adequately addressed in all trials.

AUTHORS' CONCLUSIONS

Implications for practice

Surgical sealants have some beneficial effect in reducing postoperative air leaks, but systematic use of surgical sealants in clinical practice cannot be recommended at the moment.

Implications for research

Since the last revision, most new trials have a small number of patients that prevent solidly based conclusions. More and larger randomized controlled clinical trials with homogeneous criteria on type of sealant, method of sealant delivery, and patient selection are needed in order to produce reliable evidence on the usefulness of sealants.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allen 2004

Methods	Multicenter prospective randomized control study
Participants	One hundred and sixty-one patients requiring pulmonary resections other than pneumonectomy and decortication. There were 13 patients who did not complete the trial after randomization, 8 patients in the sealant group and 5 patients in the control group. Ninety-five patients were assigned to the sealant group and fifty-three patients to the control group
Interventions	A) Intervention group: standard surgical treatment plus polymeric biodegradable sealant. B) Control group: Standard procedures to control air leaks with no addition of sealant
Outcomes	Primary: proportion of patients who remained air leak free following surgery. Secondary: proportion of intraoperative air leaks in each group that were sealed or reduced, proportion of patients in each group that was free of air leaks immediately following surgery, duration of postoperative air leak, chest tube duration and length of hospitalization
Notes	Randomized patients only included those that had at least one significant air leak (≥ 2.0 mm in size) after pulmonary resection

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Insufficient information about this domain
Allocation concealment?	Unclear risk	Insufficient information to permit judgement
Blinding? All outcomes	High risk	Quote: "Postoperative air leaks were assessed by qualified hospital staff, including investigators..."
Incomplete outcome data addressed? All outcomes	Low risk	Quote: "patients were followed up at 1 month and questioned about complications since discharge from the hospital". Patients in the two groups who did not complete the trial after randomization are well described. The primary reason patients randomized but excluded of the trial are well described.

Anegg 2007

Methods	Randomized, prospective, open-label, parallel group study carried out at a single center
Participants	One hundred and fifty-two patients were randomized. Seventy-seven were assigned to the treatment group. Seventy-five were assigned to standard treatment group
Interventions	Inteventions A) Intervention group: parenchymal suturing, stapling or electrocautery plus a collagen patch with human fibrinogen and human thrombin. B) Control group: standard surgical procedure with parenchymal suturing, staplers, and electrocautery with no additional treatments
Outcomes	Primary: Quantitative measure of postoperative air leaks at days one and two. Secondary: Mean time to chest drain removal, mean time to hospital discharge
Notes	All the randomized patients had a non-small cell lung cancer. One hundred and forty-eight patients undergoing lobectomy; twenty five undergoing a segmentectomy

Anegg 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Randomisation, on the basis of the use of close envelopes containing notes reading either 'A' for Tachosil® or 'B' for conventional treatment, was performed intraoperatively...".
Allocation concealment?	Low risk	Quote: "Randomisation, on the basis of the use of close envelopes..."
Blinding? All outcomes	High risk	Postoperative air leakage volume measurements were made by the investigators.
Incomplete outcome data addressed? All outcomes	Low risk	Early and late outcomes were controlled in all patients.

Belboul 2004

Methods	A prospective blinded randomized study
Participants	Forty patients undergoing a pulmonary lobectomy. Twenty patients were randomized to the autologous fibrin sealant. Twenty patients were assigned to the control group
Interventions	A) Intervention group: standard surgical lobectomy. Autologous fibrin sealant was applied. B) Control group: Standard lobectomy with no additional interventions
Outcomes	Rate of air leak on the day of the operation and daily thereafter until chest drains were removed, time to chest tube removal, 24-h and chest-tube drainage (bleeding/exudation) volume at removal of chest tube, duration of thoracic epidural analgesia treatment and postoperative length of the hospital stay. All patients had lung tumours limited to one lobe
Notes	All patients had air leaks before randomization

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The patients were assigned to either the control or Vivostat groups by opening a sealed envelope that contained the randomisation code (allocated by a computer general random sequence)".
Allocation concealment?	Low risk	The patients were randomized intraoperatively by opening a sealed envelope. Investigators enrolling patients could not foresee assignment.
Blinding? All outcomes	Low risk	Quote: "The personnel recording these parameters were blinded to the intervention received".
Incomplete outcome data addressed? All outcomes	Low risk	Quote: "No patients were withdrawn from the study".

Droghetti 2008

Methods	Randomized, prospective, controlled parallel-group trial
Participants	Forty patients were randomized. Twenty were assigned to the treatment group. Twenty were assigned to standard treatment group.
Interventions	Interventions A) Intervention group: electrocautery surgical dissection of interlobar fissures plus a collagen patch with human fibrinogen and human thrombin. B) Control group: routine surgical procedure with staplers with no additional treatments
Outcomes	Primary: Percentage of demonstrated intraoperative alveolar air leak effectively sealed after application of the sealant and to compare the proportion of patients in the sealant and control groups who were free of air leaks throughout hospitalization. Secondary: Postoperative air leaks, the moment of chest tube removal, length of hospitalization. Costs of the procedure and hospitalization, safety of the sealant treatment by surveillance of the incidence and severity of complications
Notes	All the randomized patients had early-stage non-small cell lung cancer. This was a pilot study, and no attempts were made to calculate a sample size to provide statistical power sufficient for confident evaluation of the results.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Randomization was performed intraoperatively using closed envelopes containing notes reading either ‘‘ES’’ for electrocautery and sealant or ‘‘ST’’ for conventional treatment with staplers".
Allocation concealment?	Low risk	Randomization was performed using closed envelopes
Blinding? All outcomes	Unclear risk	The study did not address this outcome
Incomplete outcome data addressed? All outcomes	Low risk	No missing outcome data. Quote: "One and 3 months after surgery the treated patients underwent a clinical examination and chest radiography"

Fabian 2003

Methods	A prospective randomized blinded study
Participants	One hundred and thirteen patients undergoing planned open anatomic resection or wedge resection. Thirteen were withdrawn intraoperatively. The remaining 100 patients were randomized. Fifty patients were assigned to treatment group and 50 to control group
Interventions	A) Intervention group: At the end of the procedure patients were treated with an application of fibrin glue. B) Control Group: received no additional treatments
Outcomes	The incidence and duration of air leaks, prolonged alveolar air leaks, the volume of pleural drainage, the time to tube removal and the postoperative length of stay and any complications related to treatment
Notes	

Risk of bias

Fabian 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Patients were randomly assigned in the operating room to control or treatment groups in a 1:1 ratio by opening a sealed envelop"
Allocation concealment?	Low risk	Randomization was done by opening a sealed envelop
Blinding? All outcomes	Low risk	The presence or absence of air leak and the volume of chest tube drainage were assessed by a blinded observer
Incomplete outcome data addressed? All outcomes	Low risk	Excluded patients and outcomes were well reported

Fleisher 1990

Methods	Randomized controlled clinical trial
Participants	Twenty-eight patients undergoing uncomplicated lobectomy. Fourteen (9 male and 5 female with a mean age of 63.8 years) were included in the fibrin group. Fourteen (8 male and 6 female of 59.0 years of mean age) were controls
Interventions	A) Intervention group: Division of lung fissures with stapling devices; two millilitres of fibrin glue were applied to staple lines and any cut surfaces of the lung regardless of the presence or absence of air leaks. B) Control group: Division of lung fissures with stapling devices, without additional fibrin glue
Outcomes	Duration of postoperative air leaks, chest tube drainage and postoperative hospitalization
Notes	Patients were randomized by their hospital record number

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Sequence was generated by their hospital record number
Allocation concealment?	High risk	Assignement of either group was made before thoracotomy by the surgeon according the hospital record number
Blinding? All outcomes	Unclear risk	No information reported about this domain
Incomplete outcome data addressed? All outcomes	Low risk	No missing outcome data in the study

Lang 2003

Methods	Multicenter randomized and prospective study
Participants	One hundred and eighty-nine patients undergoing lobectomy or bilobectomy for lung cancer were enrolled in this trial. Ninety-six patients were assigned to treatment group and 93 to control group

Lang 2003 *(Continued)*

Interventions	A) Treatment group: standard surgical resection plus absorbable patch consisting of an equine-collagen fleece coated with human fibrinogen and human thrombin. B) Control Group: Surgical standard procedures with no additional treatments
Outcomes	Primary: incidence of air leakage 48 h after lobectomy. Secondary: reduction of intraoperative air leakage intensity after the first test treatment, intensity and duration of postoperative air leakage up to postoperative day 9, postoperative mortality and morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Insufficient information about the sequence generation
Allocation concealment?	Unclear risk	There is not sufficient information about the allocation concealment
Blinding? All outcomes	Unclear risk	The study did not address this outcome
Incomplete outcome data addressed? All outcomes	Low risk	Patients included and excluded are well reported, outcomes were recorded in all patients until a final follow-up control 1 month postoperatively

Macchiarini 1999

Methods	Randomized controlled trial
Participants	Thirty patients requiring pulmonary resection other than pneumonectomy. Four were ineligible because they eventually required pneumonectomy. Two were pilot patients. Thirteen (9 male and 4 female of 61 years mean age) were assigned to the treatment group. Eleven (9 male and 2 female of 59 years mean age) were controls
Interventions	A) Intervention group: standard bronchial closure and suture; a synthetic sealant was applied to all identified surgical sites (staple lines, suture lines, areas of dissection or adhesiolysis), excluding bronchial stump, regardless of the presence of air leaks. Additional sealant was applied if leaks persisted or new leaks were identified. B) Control group: standard bronchial closure and suture, with no addition of sealant
Outcomes	Primary: persistence of air leaks during operation and duration of chest tube air leaks. Secondary: time from operation to chest tube removal and hospital discharge, hospitalization time and costs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "the randomization for each patient was maintained in a sealed envelope"
Allocation concealment?	Low risk	Quote: "The envelopes were sequentially opened"

Macchiarini 1999 *(Continued)*

Blinding? All outcomes	Unclear risk	The study did not address this outcome
Incomplete outcome data addressed? All outcomes	Low risk	No missing outcome data in the study

Marta 2008

Methods	Open, randomized, prospective, multicenter, parallel-group trial
Participants	Three hundred and one patients requiring pulmonary lobectomy. One hundred and forty-nine were assigned to the treatment group. One hundred and fifty were assigned to standard treatment group
Interventions	A) Intervention group: standard surgical resection plus absorbable patch consisting of human fibrinogen and human thrombin. B) Control group: surgical standard procedures with no additional treatments
Outcomes	Primary: Duration of postoperative air leak. Secondary: reduction of intraoperative air leakage intensity after treatment, number of days after removal of last chest tubes, adverse effects
Notes	All patients randomized had lung cancer. Only patients with grade one or two air leakage evaluated by water submersion test were randomized

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Quote: "patients were randomized by means of an interactive voice response system"
Allocation concealment?	Unclear risk	Insufficient information about the allocation concealment
Blinding? All outcomes	Unclear risk	The study did not address this outcome
Incomplete outcome data addressed? All outcomes	Low risk	No missing outcome data is reported

Mouritzen 1993

Methods	Randomized controlled clinical trial
Participants	One hundred and fifteen patients undergoing pulmonary resections including pneumonectomy. One patient was withdrawn because more than one surgical procedure was required. Fifty-five were assigned to the fibrin glue group and 59 to the control group. Seventy-seven patients were male and 37 female; their mean age was 59 years
Interventions	A) Intervention group: standard surgical treatment; fibrin glue was applied to bronchial stumps and lung surfaces. B) Control group: standard surgical treatment with no additional fibrin glue

Mouritzen 1993 *(Continued)*

Outcomes	Primary: difference in air-tolerance-pressure before and after fibrin glueing; rate of patients with post-operative bronchopleural or pulmonary leakages; number of days with persistent air leakage, only for patients who presented an air leak on the first postoperative day. Secondary: length of stay in the intensive care unit; length of hospital stay; duration of intubation after surgery; number of days with chest tubes; rate of complications; daily amount of secretion from chest tubes; general condition of the patient
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Patients were randomized by a close-envelope system
Allocation concealment?	Low risk	Closed envelopes were sequentially opened after pulmonary resection
Blinding? All outcomes	Unclear risk	Insufficient information about this item
Incomplete outcome data addressed? All outcomes	Low risk	No missing outcome data

Porte 2001

Methods	Randomized controlled clinical trial
Participants	One hundred and twenty four patients requiring pulmonary lobectomy or bilobectomy. Four patients were withdrawn because they died. Fifty-nine patients were assigned to the treatment group. Sixty-one patients were controls
Interventions	A) Intervention group: A synthetic sealant was applied to all identified surgical sites leaking air or at risk of leaking air. B) Control group: After standard surgical treatment patients underwent no further procedures
Outcomes	Primary: Safety of surgical lung sealant by surveillance for unexpected adverse events during follow-up. Secondary: percentage of alveolar air leaks effectively sealed at operation after sealant application, durability of alveolar air leaks sealing and potential effect of sealant on the in-hospital stay
Notes	Randomized patients only included those judged intraoperatively to have moderate to severe alveolar air leaks

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	No information reported about this domain
Allocation concealment?	Unclear risk	No information reported about this domain
Blinding? All outcomes	Unclear risk	No information reported about this domain

Porte 2001 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Outcomes and patients that could not be evaluated according to the study protocol were reported

Tansley 2006

Methods	Prospective, randomized, single-blind, controlled study
Participants	Fifty-two patients were randomized. Twenty-five were assigned to the treatment arm. Twenty-seven were assigned to the non-interventional arm
Interventions	A) Intervention group: parenchymal suturing or stapling plus a mixture of bovine serum albumin and glutaraldehyde. B) Control group: standard surgical procedure (parenchymal suturing and stapling) with no additional treatments
Outcomes	Primary: Duration of air leak, duration of intercostal drainage, and duration of hospital stay. Secondary: Postoperative complications other than air leaks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Quote: "Randomization was undertaken with sequential closed envelopes..."
Allocation concealment?	Low risk	Close envelopes were opened sequentially
Blinding? All outcomes	Unclear risk	Insufficient information about this item
Incomplete outcome data addressed? All outcomes	Low risk	Criteria of exclusion and outcomes were reported

Wain 2001

Methods	Randomized controlled clinical study
Participants	One hundred and eighty patients undergoing lobectomy, wedge and segmental resections by open thoracotomy. Eight patients were excluded because they were pilot patients. One hundred and seventeen were assigned to the treatment group. Fifty-five patients were assigned to the control group
Interventions	A) Interventional group: Standard surgical treatment ; a synthetic sealant (Focal Seal) was applied to all sites of surgical manipulation. B) Control group: standard surgical treatment with no additional fibrin glue
Outcomes	Primary: Percentage of patients free of air leakage throughout hospitalization. Secondary: control of air leaks intraoperatively, time to postoperative air leak cessation, time to chest tube removal, time to hospital discharge and safety outcomes
Notes	

Wain 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Quote: "The patients were then randomized within their risk stratum by opening one or two sealed envelopes.The envelopes were randomly sequenced by computer"
Allocation concealment?	Low risk	Quote: "The patients were then randomized within their risk stratum by opening one or two sealed envelopes"
Blinding? All outcomes	Low risk	Quote: "Evaluation and recording of chest tube output was handled by the nursing and physician staff at the bedside who were blinded to the randomization status of the subject"
Incomplete outcome data addressed? All outcomes	Low risk	Criteria of exclusion and outcomes were reported

Wong 1997

Methods	Randomized controlled clinical trial
Participants	Sixty-six patients undergoing lobectomy segmentectomy or decortication, and presented moderate to severe alveolar air leaks after treating it with measures such as suturing or electrocautering. Thirty-three (22 male and 11 female of 62 years of median age) were assigned to the control group. Thirty-three (24 male and 9 female of 55.3 years of median age) were assigned to the fibrin glue group
Interventions	A) Intervention group: standard procedures to control air leaks; fibrin glue was applied to leaking areas while ventilation was suspended for a maximum of 2 minutes. B) Control group: Standard procedures to control air leaks with no additional fibrin glue
Outcomes	Days of postoperative air leaks, days of intercostal drainage, and of in-hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "Patients were randomized by a close envelope"
Allocation concealment?	Low risk	A closed envelope was opened after lung resection
Blinding? All outcomes	Unclear risk	There is not sufficient information about the blinding of participants and outcome assessors
Incomplete outcome data addressed? All outcomes	Low risk	Criteria of exclusion and outcomes were reported

Wurtz 1990

Methods	Prospective randomized study
Participants	Fifty patients undergoing a pulmonary resection except pneumonectomy
Interventions	A) Intervention group: at the end of the procedure patients were treated with fibrin glue. B) Control group: No additional interventions
Outcomes	Quality of aerostasis, post-operative drainage, persistence of residual collection or faulty re-expansion after removal of drains, the necessity for repeated drainage and length of post-operative hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Sequence generation was made by the method of coin tossing
Allocation concealment?	Unclear risk	Insufficient information to permit judgement
Blinding? All outcomes	Unclear risk	No information reported about this domain
Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were reported

Wurtz 1992

Methods	Prospective randomized study
Participants	Fifty patients undergoing a pulmonary resection except pneumonectomy
Interventions	A) Intervention group: at the end of the procedure patients were treated with fibrin glue. B) Control group: No additional interventions
Outcomes	Post-operative amount of drainage, persistence of residual collection or faulty re-expansion after removal of drains and length of post-operative hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Sequence generation was made by the method of coin tossing
Allocation concealment?	Unclear risk	Insufficient information to permit judgement
Blinding? All outcomes	Unclear risk	No information reported about this domain

Wurtz 1992 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Outcome data were reported

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brega Massone 2003	Case control study
Gagarine 2003	Case control study
Grunenwald 1989	Case control study
Gundogdu 2006	Non-randomized comparative study
Ito 2003	Non-randomized comparative study
Izbiki 1994	Animal case series
Kiaergard 2000	Randomized animal study
Kobayashi 2001	Non-randomized comparative study in rats
Massone 2002	Case control study
Matsumura 2004	Non-randomized comparative study
McCarthy 1988	Randomized animal study
Miyamoto 2003	Clinical case series
Nomori 2000	Non-randomized comparative study
Omote 1994	Non-randomized comparative study
Potaris 2003	Case control study
Ranger 1997	Randomized animal study
Sabanathan 1993	Clinical case series
Ueda 2007	Case control study

ADDITIONAL TABLES

Table 1. Randomized studies of sealants in lung surgery

Authors	Sealant	N° patients	Air leaks duration	Days chest tube	Prolonged air leaks	Days hospitalization	Empyema
Fleisher	Fibrin glue	Treatment: 14	3.2	6.1	14%*	9.8	0%
		Control: 14	3.3	5.9	7%	11.5	0%
		Signif.	NS	NS	NS	NS	
Wong	Fibrin glue	Treatment: 33	5	6		8	0%
		Control: 33	4	6		9	3%
		Signif.	NS	NS		NS	
Mouritzen	Fibrin glue	Treatment: 55	4	3		9	
		Control: 59	5	4		10	
		Signif.	NS	NS		NS	
Macchiarini	Advaseal	Treatment: 13	1.9	6.1		13	3,8%
		Control: 11	2.4	6.4		14	0%
		Signif.	NS	NS		NS	
Porte	Advaseal	Treatment: 59	33.7 h		13%	9.2	6.78%
		Control: 61	63.22 h		22%	8.59	0%
		Signif.	S		NS	NS	NS
Wain	Focal Seal	Treatment: 117	30.9 h	4.5	2.5%	7.4	3%
		Control: 55	52.3 h	5.2	7%	10.1	0%
		Signif.	S	NS	NS	NS	NS
Allen	Bioglue	Treatment: 95	2	6.8		6	0%
		Control: 53	2	6.2		7	0%

Table 1. Randomized studies of sealants in lung surgery *(Continued)*

		Signif.	NS	NS		S	
Fabian	Fibrin glue	Treatment: 50	1.1	3.5	2%	4.6	0%
		Control: 50	3.1	5	16%	4.9	0%
		Signif.	S	S	S	NS	
Lang	TachoComb	Treatment: 96	1.7				
		Control: 93	2				
		Signif.	NS				
Belboul	Vivostat	Treatment 20		1		4	
		Control 20		3		4.5	
		Signif.		NS		NS	
Wurtz	Fibrin glue	Treatment 25				11,4	0%
		Control 25				13	0%
		Signif.				NS	
Wurtz	Fibrin glue	Treatment 25				9,9	0%
		Control 25				10,6	0%
		Signif.				NS	
Marta	TachoSil	Treatment 149	-	4.9			
		Control 150	-	5.5			
		Signif.	S	NS			
Droghetti	TachoSil	Treatment 20	1.7	7.6	5%	14.3	0%
		Control 20	3.7	10.2	20%	11.0	0%

Table 1. Randomized studies of sealants in lung surgery *(Continued)*

		Signif.	S	NS	NS	NS	
Anegg	TachoSil	Treatment 75		5.1	24%	6.2	0%
		Control 77		6.3	32.46%	7.7	0%
		Signif.		S	S	S	
Tansley	Bio glue	Treatment 27	1	4	11%	6	0%
		Control 25	4	5	8%	7	0%
		Signif.	S	S		S	

APPENDICES

Appendix 1. Search strategy for MEDLINE and EMBASE

MEDLINE

#1 (("Lung Neoplasms"[Mesh] OR "Carcinoma, Small Cell"[Mesh]) OR "Carcinoma, Squamous Cell"[Mesh]) OR "Carcinoma, Non-Small-Cell Lung"[Mesh]

#2 (lung[tiab]) AND (cancer[tiab] OR neoplasm*[tiab] OR adenocarcinoma*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR squamous[tiab])

#3 (pulmon*[tiab]) AND (cancer[tiab] OR neoplasm*[tiab] OR adenocarcinoma*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR squamous[tiab])

#4 NSCLC[tiab] OR nonsmall cell lung[tiab] OR non small cell lung[tiab] OR sclc[tiab] OR small cell[tiab]

#5 (((#1) OR (#2)) OR (#3)) OR (#4)

#6 resect*[tiab] OR lobectom*[tiab] OR excision[tiab]

#7 (#5) AND (#6)

#8 Pneumonectomy[mh]

#9 pneumonectom*[tiab]

#10 (pleurectom* OR parietectom* OR segmentectom*).ti,ab.

#11 air leak*[tw]

#12 ((((#7) OR (#8)) OR (#9)) OR (#10)) OR (#11)

#13 "Suture Techniques"[Mesh]

#14 sutur*[tw] OR closur*[tw] OR stapl*[tw]

#15 Surgery[subheading]

#16 ((#13) OR (#14)) OR (#15)

#17 "Tissue Adhesives"[Mesh] OR "Fibrin Tissue Adhesive"[Mesh]

#18 adhesiv*[tw] OR seal*[tw] OR glue*[tw]

#19 (#17) OR (#18)

#20 (#16) AND (#19)

#21 (#12) AND (#20)

EMBASE

1 exp Lung Tumor/

2 exp Small Cell Carcinoma/

3 exp Squamous Cell Carcinoma/

4 exp Lung non Small Cell Cancer/

5 (lung adj10 (cancer or neoplasm* or adenocarcinoma* or carcinoma* or tumor* or tumour* or squamous)).ti,ab.

6 (pulmon* adj10 (cancer or neoplasm* or adenocarcinoma* or carcinoma* or tumor* or tumour* or squamous)).ti,ab.

7 (NSCLC or nonsmall cell lung or non small cell lung or sclc or small cell).ti,ab.

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 (resect* or lobectom* or excision).ti,ab.

10 8 and 9

11 exp Lung Resection/

12 pneumonectom*.ti,ab.

13 (pleurectom* or parietectom* or segmentectom*).ti,ab.

14 air leak*.ti,ab.

15 11 or 13 or 10 or 12 or 14

16 exp Suturing Method/

17 (sutur* or closur* or stapl*).mp.

18 16 or 17

19 exp Tissue Adhesive/

20 exp Fibrin Glue/

21 (adhesiv* or seal* or glue*).tw.

WHAT'S NEW

Date	Event	Description
14 January 2010	Amended	Several edits were done, mainly in risk of bias tables

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 4, 2001

Date	Event	Description
17 September 2009	New citation required but conclusions have not changed	Contact author changed
22 August 2009	New search has been performed	This is an update of the 2005 review. Searches were run and four new published papers were identified but conclusions did not change.

CONTRIBUTIONS OF AUTHORS

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Writing to authors of papers for additional information: None

Providing additional data about papers: None

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Other statistical analysis not using RevMan: None

Double entry of data: None

Interpretation of data: JBS, MSM, MIS, RRP

Statistical inferences: JBS

Writing the review: JBS

Guarantor for the review: JBS

Person responsible for reading and checking review before submission: JBS, RRP

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Air; Chest Tubes; Device Removal; Length of Stay; Lung Neoplasms [*surgery]; Postoperative Complications [*prevention & control]; Randomized Controlled Trials as Topic; Tissue Adhesives [*therapeutic use]

MeSH check words

Humans