

Performance of a Novel Sealant Film (TissuePatch™3) compared with commercially available Products in the resolution of Air Leaks during Lung Surgery.

David Mandley, Nick Woods
Tissuemed Ltd., Leeds, LS14 6UF

Summary

The literature surrounding treatment of intra-operative air leaks encountered during lung surgery is relatively inconclusive, being based on different products for different indications with different outcome measures. This short review attempts to isolate the clinically important features of the alternative products used for this purpose and draws some conclusions about their efficacy. Analysis is presented in the context of a recently undertaken clinical study¹ of a new product, TissuePatch3 (Tissuemed Ltd., Leeds, UK) and examines cessation of air leaks, duration of any post operative air leaks, chest drain removal and patient discharge. The common thread is that drain removal and patient discharge appear to be not entirely related to resolution of air leaks, which raises other clinical issues. In its resolution of air leaks TissuePatch3 appears to present a compelling alternative to the competitive products, especially when its comparative preparation and application time are significantly shorter.

Background

The incidence of intra-operative air leaks during lung surgery is reported to be as high as 70%². Persistent air leakage lasting longer than 7 days occurs in 15-25% of patients and is one of the primary factors influencing prolonged chest tube drainage³.

Standard practices for primary closure of lung wounds and prevention of gross air leaks during lung surgery include stapling, suturing and electrocautery. Adjunctive methods to resolve air leaks in number, intensity and duration include the use of sealant products based on fibrin⁴⁻⁶, synthetic polyethylene glycol (PEG) based materials^{2,7,8} and collagen patches coated with fibrinogen and thrombin⁹. The aim of this report is to compare the clinical performance of TissuePatch3, a new synthetic sealant film, with representatives from the other sealant product categories

TissuePatch3 is CE mark approved in Europe and has been designed to offer the surgeon effective sealing of air leaks in a user-friendly presentation with clinically advantageous characteristics including low material bulk, rapid delivery to the target tissues, zero preparation time and very short application time. This study attempts to characterise the performance of the product from a clinical perspective in a comparative context.

The recent Cochrane Review³ evaluating the effectiveness of sealants in preventing or reducing post operative air leaks in patients with lung cancer undergoing pulmonary resection concluded that while 'sealants' seem to reduce postoperative air leaks, their use had no effect on the length of hospitalisation. While this report comments only on the efficacy of the products in resolution of air leaks, it is clear that measures to improve treatment have the potential not only to improve the patient experience but also to optimise the patient treatment algorithm with the attendant clinical and economic benefits.

Figure 1. TissuePatch3 synthetic sealant film



Study design

In addition to the TissuePatch3 post-marketing surveillance (PMS) study, data from four earlier clinical studies involving two different fibrin sealants, Tisseel⁶, Vivostat¹⁰ (autologous/patient derived), Tachosil, a collagen patch coated with human fibrinogen and thrombin⁹ and PleuraSeal, a PEG-based two component liquid sealant¹¹, are presented in the proceeding sections of this review. The TissuePatch3 study was undertaken at two centres in the UK, St James's Hospital Leeds and Norfolk & Norwich (N&N) Hospital. Twenty patients were recruited, although five were older than 75 and outside the inclusion criteria for the study. Of the 15 patients included in the study there were 11 (73%) male and 4 (27%) female subjects. Age ranged from 49 to 75, with a mean age of 64.8. Of the 15 patients included in the data analysis, there were 14 lobectomies performed and 1 wedge resection. The study was managed and independently monitored by MedVance Ltd.

Results

Although there are similarities in the general design of each of these studies, there are differences in the manner in which the findings have been reported. Consequently, the performance of TissuePatch3 is compared individually (sometimes with different end points) against each of the four alternative sealants.

Tisseel⁶ versus TissuePatch3

The Tisseel randomised trial published in 1997 by Goldstraw et al involved 66 patients (73% male, 27% female) with alveolar air leaks. The percentage of lobectomies undertaken was 70%. All surgery was undertaken at the Royal Brompton Hospital, London. A summary of the comparative findings is presented in Table 1. Data from the TissuePatch3 PMS study are provided by study centre

Table 1. Duration of air leak, chest drain and discharge *

Variable (all days)	Tisseel	TissuePatch3	
		Leeds	N&N
Air leak duration	5 (0.08-22)	2 (0-5)	0 (0-3)
Chest drain time	6 (2-23)	9 (2-21)	3 (1-23)
Time to discharge	8 (4-35)	8 (3-21)	12 (5-24)

* Values are expressed as median (range)

It can be seen from the data presented in Table 1 that the time to cessation of air leak was consistently shorter for TissuePatch3 treated

patients when compared to those receiving Tisseel. However this did not lead to a reduction in the time to chest drain removal or hospital discharge. The median time to chest drain removal for TissuePatch3 treated patients from Leeds and the Norfolk & Norwich hospitals was 9 and 3 days respectively compared to 6 for Tisseel treated subjects. The median time to hospital discharge for TissuePatch3 treated patients from Leeds and the Norfolk & Norwich hospitals was 8 and 12 days respectively compared to 8 for Tisseel treated subjects.

When comparing the data for Tisseel treated patients with control subjects, Goldstraw was unable to show any advantage in the intraoperative use of Tisseel. However in one of the TissuePatch3 study centres there was a statistically significant reduction in air leak duration compared with the control group. In both Leeds and Norfolk & Norwich studies there was an indicative reduction in time to chest drain removal and in Leeds a two day reduction in patient stay, again not statistically significant due to patient numbers.

Vivostat¹⁰ versus TissuePatch3

In their 2004 publication, Belboul *et al* presented the findings of a prospective randomised study involving Vivostat, an autologous fibrin sealant. This study included 20 patients treated with Vivostat and an equivalent number of control subjects. 45% of all patients treated with Vivostat were male, with the remaining 55% female.

In contrast to the TissuePatch3 PMS study, in which the device was used to eliminate definite air leaks, in the Vivostat study air leaks were surgically corrected in both treatment and control group using conventional techniques prior to patients then being randomly selected for additional treatment with Vivostat. Assessment of Vivostat therefore was in prevention of potential future air leaks rather than treating those already identified.

A summary of the findings of the Vivostat study compared with TissuePatch3 is presented in Table 2.

Table 2. % of patients air leak free, chest drain and discharge data *

Variable (all days)	Vivostat	TissuePatch3	
		Leeds	N&N
% air leak free t=0	60%	100%	57%
Chest drain time*	1	9	3
Time to discharge*	4	8	12

*values are expressed as median

The Vivostat study did not report the time to cessation of air leaks, preferring to record the % of patients that were air leak free at the time of chest closure. It can be seen from the data presented in Table 2 that for the 20 Vivostat treated patients, 16 (60%) were air leak free. This compares to 100% and 57% for patients receiving TissuePatch3 treatment at Leeds and Norfolk & Norwich hospitals respectively.

The use of Vivostat in this study as a preventative treatment for potential future air leaks is reflected in the markedly shorter times for the removal of chest drains (median=1) and patient discharge (median=4) when compared to TissuePatch3 and Tisseel⁵. As a consequence of the use of Vivostat over the entire area at risk of air leak or bleeding to

prevent potential air leaks and blood losses, the findings of this single centre study (Gothenburg, Sweden) are not directly comparable with the findings of the TissuePatch3 PMS study.

When comparing the data of Vivostat treated patients with subjects receiving no further treatment, Belboul reported that although median durations of chest tube drainage and hospitalisation times were shorter in the Vivostat group (by 1 and 0.5 days respectively, the differences were not statistically significant.

Tachosil⁹ versus TissuePatch3

The 2007 clinical paper detailing the use of 'sealants' for the treatment of air leaks in lung surgery concerns the use of Tachosil. In a 152 patient single centre (Graz, Austria) prospective randomised study, 75 patients were treated with Tachosil, whilst the remaining 77 were controls. 72% of all patients treated with Tachosil were male, with the remaining 28% female. The percentage of lobectomies undertaken was 86%.

The criteria for the use of Tachosil in the aforementioned study was comparable with those defined in the TissuePatch3 PMS study. Namely that only Grade 1 or 2 air leaks were treated with the experimental device. A summary of the findings of the Tachosil study compared with TissuePatch3 are presented in Tables 3 and 4.

Table 3. Pre-treatment air leak grades

Grade	Tachosil	TissuePatch3		
		Leeds	N&N	Both
Grade 1	17%	100%	0%	66.6%
Grade 2	83%	0%	100%	33.3%

The grade of air leak treated with Tachosil was higher than those treated with TissuePatch3 in Leeds and lower than Norfolk and Norwich. The assessment of air leak grade as either "all 1" or "all 2" may indicate a variation in methodology or judgement.

Table 4. Post treatment air leak analysis- % Patients with air leaks detected

Grade	Tachosil	TissuePatch3		
		Leeds	N&N	Both
Day 1	63%	69%	29%	48%
Day 2	30%	54%	14%	33%
> 2 Days	31%	46%	7%	26%
> 7 Days	24%	8%	0%	4%

Considering each TissuePatch3 study centre independently, throughout the first three assessment periods the percentage of treated patients in whom air leaks were detected was consistently lower at the Norfolk & Norwich hospital than either Leeds or the Tachosil study. In Leeds the proportion of air leaks was marginally higher than the 75 Tachosil treated patients over the same period. The percentage of patients with persistent air leakage (> 7 days) was consistently higher for patients treated with Tachosil compared to those subjects receiving TissuePatch3. The reduction in air leaks by TissuePatch3 as summarised in Table 4 and Figure 2 (overleaf) suggests that performance is at least comparable with that of Tachosil, with an indication that TissuePatch may be more effective over time.

Figure 2. Post treatment air leak analysis- % Patients with air leaks detected. Tachosil vs TissuePatch3(combined data)

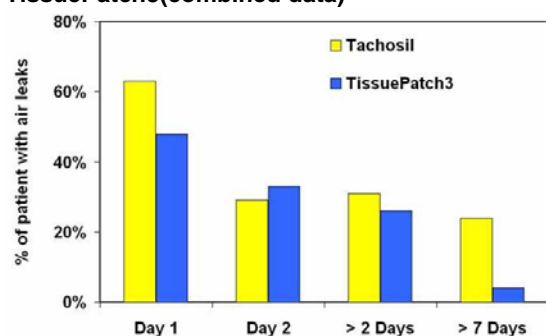


Table 5. Chest drain and discharge data *

Variable (all days)	Tachosil	TissuePatch3	
		Leeds	N&N
Chest drain time*	5.1	9.5	5.4
Time to discharge*	6.2	8.4	12.1

*values are expressed as means

As discussed in the 'Tisseel versus TissuePatch3' section of this report, the ability of TissuePatch3 to reduce air leak duration is not reflected in similar chest drain duration and times to discharge which appear to be almost independent of air leak data. The mean time to chest drain removal for TissuePatch3 treated patients from Leeds and the Norfolk & Norwich hospitals was 9.5 and 5.4 days respectively compared to 5.1 for Tachosil treated subjects. The mean time to hospital discharge for TissuePatch3 treated patients from Leeds and the Norfolk & Norwich hospitals was 8.4 and 12 days respectively compared to 6.2 for Tisseel treated subjects.

Comparing the data generated from the 75 patients treated with Tachosil with the 66 patients treated with Tisseel, the fibrin sealant delivered as a 3-D matrix, Tachosil may have outperformed the conventional liquid sealant Tisseel in respect of time to chest drain removal and stay in hospital.

PleuraSeal¹¹ versus TissuePatch3

During the period that Tissuemed has been developing TissuePatch3, Covidien has evaluated the PEG based liquid sealant, PleuraSeal for use in lung surgery. In a 140 patient study undertaken from May 2006-May 2007, the sealant was routinely applied to most lung resections. While not clear from the information available it is likely that treatment with PleuraSeal was preventative for potential air leaks as in the Vivostat study rather than used to eliminate definite gradeable air leaks as in the TissuePatch3, Tachosil and Tisseel studies. 54% of patients treated with PleuraSeal were male, with the remaining 46% female. The percentage of lobectomies undertaken was 46%, and it is the analysis of the limited amount of data from these patients that is compared with TissuePatch3 treated patients in Table 6.

Table 6. Chest drain and discharge data *

Variable (all days)	PleuraSeal	TissuePatch3	
		Leeds	N&N
Chest drain time	1	9	3
Time to discharge	4	8	12

*values are expressed as median

The particularly short times to chest drain removal and time to patient discharge - 1 and 4 days respectively, values comparable to those reported from the aforementioned Vivostat study (see table 2), suggests that the PleuraSeal study presented involved this sealant as a preventative treatment for air leaks. As a consequence the findings of this study cannot be compared directly with the findings of the TissuePatch3 PMS study.

Conclusions

This paper compares the clinical performance of TissuePatch3, with four 'sealant' products that are currently available to thoracic surgeons; three liquids and one impregnated matrix. The design of clinical studies involving Tisseel and Tachosil were similar to the post market study involving TissuePatch3, enabling a direct comparison of each of these products. 'Duration of air leak' data from each of these studies indicates that the ability of TissuePatch3 to prevent/reduce air leaks was at least as good as if not better than both Tisseel and Tachosil. The air leak duration of TissuePatch3 treated patients was a maximum of 2 days compared to 5 days for subjects receiving Tisseel (both median). Furthermore, comparing the incidence of post operative air leaks between TissuePatch3 and Tachosil, the latter's performance was comparable with the exception that a higher proportion of patients treated with Tachosil presented 'persistent' > 7 days air leaks.

Despite the early cessation of air leaks following application of TissuePatch3, this has not consistently lead to a reduction in the time to chest drain removal and discharge from hospital in the small patient cohort. The occurrence of early cessation of air leaks (e.g. within 48 hours) but prolonged time to chest drain removal (>>5 days) and prolonged delay between drain removal and discharge are numerous in TissuePatch3 treated patients and a similar population of 'control' patients selected for retrospective analysis. This feature is consistent with other studies and is indicative of other factors including patient treatment algorithm that have a more significant influence on post operative events such as drain removal and patient discharge.

The method of use of Vivostat and PleuraSeal in studies available to date, where both products appear to have been used as a general prophylactic preventative treatment for air leaks as opposed to targeting definite Grade 1 or 2 air leaks dictates that direct comparison with TissuePatch3, Tisseel and Tachosil is not possible. Certainly the very short time to chest drain removal (1 day) and patient discharge (4 days) data presented in the Vivostat and PleuraSeal studies is indicative of low grade if any air leak being present at time of treatment.

Why TissuePatch3?

When comparing the range of sealants available to thoracic surgeons, the performance data, while interesting and indicative of differences is inconclusive either because data sets are low or because experimental methodologies are too variable to be meaningful. However there are clear differences in the format, mode of use, composition, time for preparation and strength¹² of the available products. Of the physical barrier-type products included in this review TissuePatch3 is uniquely dedicated to its purpose, Tachosil being a haemostatic "felt" that has found its way into use as

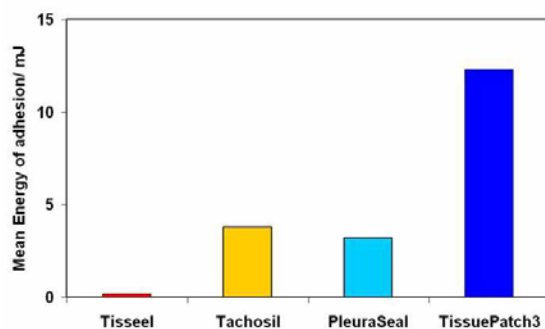
a lung sealant. TissuePatch3 is significantly thinner (<0.05mm) compared to the Tachosil fleece and unlike Tachosil can be used 'straight out of the packet' with a short time for application (30 seconds) compared to 3-5 minutes for Tachosil.

Of the liquid products, preparation time of fibrin sealants has been reported to take approximately 10-14 minutes depending on the experience of the technician. PleuraSeal is significantly quicker to prepare, but unless used in its spray-applicator configuration shares the feature with other liquids that it may be prone to 'run off'. Furthermore like all liquid sealants it is prone to applicator blockage to the extent that spare tips are provided by the manufacturer. The format of TissuePatch3 enables the user to direct the product precisely to the site requiring treatment

The clinical data presented in this summary suggest that all products perform well in the acute phase, namely the immediate intra-operative resolution of air leaks. However the post-operative performance may well vary based on factors such as how adherent the sealant is to its target tissue. *In vitro* studies comparing the energy of adhesion of this range of sealants revealed that TissuePatch3 adhered to target tissue at a level significantly above Tachosil, PleuraSeal and Tisseel with the latter's surface adherence in the model being on average 35 times lower than TissuePatch3. This performance advantage can be explained by the generation of covalent bonds between the polymeric compounds on the contact surface of TissuePatch3 with amine groups on the tissue surface. The fibrin-based products are effectively haemostats and therefore while they have undoubted cohesive strength they possess lower adhesive capability.

While this may not be borne out in the clinical data the typically small sample sizes and the fact that assessment of post operative air leak was also variable, may suggest further study is needed in this area.

Figure 3. Adhesive strength of 'sealants'



When deciding whether to use a sealant product and if so which one the available clinical evidence is inconclusive. This review suggests that while all sealants may well be effective in the acute intra-operative phase some studies measured efficacy when no air leak was present. Additionally there is some indication of different levels of efficacy, but few statistically significant conclusions. Furthermore it is unclear from the data whether sealant use should be restricted to treatment of

specific types or grades of air leak nor what the longevity of effect and clinical economic impact is in different groups of patients. The surgeon's choice therefore is one based on features such as easy availability at point of need, handling and cost. In this context TissuePatch3 represents a compelling offering. Notably the liquid sealants appear to be more complicated to use and require management of run-off on uneven surfaces. Additionally some of the liquid sealants necessitate application with the lung deflated, while TissuePatch3 can be applied with the lung ¾ inflated.

References

- Mandley DJ, Woods NP. Evaluation of a novel sealant film for sealing air leaks during lung surgery. Tissuemed Ltd, 2008.
- Wain JC, Kaiser LR, Johnstone DW, Yang SC, Wright CD, Friedberg JS, Feins RH, Heitmiller RF, Mathisen DJ, Selwyn MR. Trial of a novel synthetic sealant in preventing air leaks after lobectomy. *Ann Thorac Surg* 2001; **75**:1623-9
- Serra-Mitjans M, Belda-Sanchis J, Rami-Porta R. Surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancer. *The Cochrane Database of Systematic Reviews* 2005. Issue 3. Art No.: CD003051. pub2.
- Fabian T, Federico JA, Ponn RB. Fibrin glue in pulmonary resection: a prospective randomized blinded study. *Ann Thorac Surg* 2003; **75**: 1587-92.
- Fleisher AG, Evans KG, Nelems B, Finley RJ. Effect of routine fibrin glue use on the duration of air leaks after lobectomy. *Ann Thorac Surg* 1990; **49**(1): 133-4.
- Wong K, Goldstraw P. Effect of fibrin glue in the reduction of post thoracotomy alveolar air leak. *Ann Thorac Surg* 1997; **64**:979-81.
- Macchiarini P, Wain J, Almy S, Dartevelle P. Experimental and clinical evaluation of a new synthetic, absorbable sealant to reduce air leaks in thoracic operations. *J Thorac Cardiovasc Surg* 1999; **117**: 751-8.
- Porte HL, Jany T, Akhad R, Conti M, Gillet PA, Guidat A, Wurtz AJ. Randomised controlled trial of a synthetic sealant for preventing alveolar air leaks after lobectomy. *Ann Thorac Surg* 2001; **71**: 1618-22.
- Anegg U, Lindenmann J, Matzi V, Smolle J, Maier A, Smolle-Juttner F. Efficacy of fleece-bound sealing (Tachosil) of air leaks in lung surgery: a prospective randomised trial. *Eur J Cardio-Thorac Surg* 2007; **31**: 198-202.
- Belboul A, Dernevik L, Aljassim O, Skrbic B, Radberg G, Roberts D. The effect of autologous fibrin sealant (Vivostat) on morbidity after pulmonary lobectomy: a prospective randomised, blinded study. *Eur J Cardio-Thorac Surg* 2004; **26**: 1187-91.
- PleuraSeal clinical findings May 2006-2007. Covidien marketing presentation.
- Campbell PK, Bennett SL, Driscoll A, Sawhney AS. Evaluation of Absorbable Surgical Sealants: *In vitro* testing. Confluent Surgical 'White paper'.