Prospective multi-center European randomized trial to evaluate PleuraSeal™ as an adjunct to standard closure techniques for control of visceral pleural air leaks following elective lobectomy via open thoracotomy

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Financial disclosure
Conflict of interest

• The study was funded by Covidien
• Dr. P. De Leyn has a consultancy agreement with Covidien

Product is not available for sale in the US.
Air leaks after lung resection

• Very common complication
• Intra-operative air leak: up to 70% after lobectomy
• Majority stop within 7 days
• Prolonged air leak (> 7 days): 15%

Wain et al., Ann Thorac Surg 2001;71:1623-9
Brunelli et al., Ann Thorac Surg 2004;77:1205-10
Prolonged air leaks

• Prolonged hospitalization
• Increased rate of empyema and pneumonia
  – Empyema: 11.9% vs 1%
  – Pneumonia: 11.9% vs 5.6%
• Increased cost and utilization of outpatient resources
• May necessitate pleurodesis and reoperation

*Brunelli et al., Chest 2006;1150-1156
**Brunelli et al., Ann Thorac Surg 2004;77:1205-10
***Liberman et al., Ann Thorac Surg 2010;89:891-8
Ideal lung sealant

• Adherent and strong
• Flexible and compliant
• Easy to store, prepare and apply
• Locally non-irritating, systemically non-toxic
• Resorbable
• Concerns about antigenicity and blood borne infections
Classification of Tissue Sealant

• Fibrin-based
  – Fluid glues, such as Tissucol®, Beriplast®, Quixil™, Vivostat®
  – Fleece-bound: Tachosil®

• Non-fibrin-based (synthetic)
  – Hydrogel (PleuraSeal™ lung sealant, Coseal®)
  – With photopolymerization i.e., acrylate
Synthetic Hydrogel: PleuraSeal™ Lung Sealant System

- **Two liquid components:**
  - Polyethylene glycol ester solution (PEG): blue precursor, improves visibility during application
  - Trilysine amine solution: clear precursor

- **When mixed, the liquids crosslink to form an absorbable gel**

When sprayed, liquid PleuraSeal™ diffuses into tissue surface. Hydrogel reaction *Mechanical interlock* with the tissue surface
Synthetic Hydrogel: PleuraSeal™ Lung Sealant System

- Short preparation time (< 2 min)
- Stored at room temperature
- Good adhesion to the pleura (5x as compared to liquid fibrin*)
- Expands with lung inflation
- Completely synthetic
- Absorbable (4-8 weeks)

*Proprietary Covidien data on file, # file 374991
Literature: Cochrane review
Belda-Sanchis et al, Cochrane database of systematic reviews 2010, Issue 1, Art. No: CD003051

- 1990-2008: Sixteen randomized trials (n=16)
- Reduction of post-op air leaks (n=6)
  - Porte; Wain; Fabian; Tansley; Marta; Droghetti
- Reduction of duration of chest drainage (n=3)
  - Fabian; Tansley; Anegg
- Reduction of duration of hospital stay (n=3)
  - Allen; Tansley; Anegg

Wain, Ann Thorac Surg, 2001
Tansley, J Thorac Cardiovasc Surg, 2006
Droghetti, J Thorac Cardiovasc Surg, 2008
Anegg, Europ J Cardiothorac Surg, 2007
Allen, Ann Thorac Surg, 2004
1990-2008: Sixteen randomized trials (n=16)

Multicenter trials: n=4
- Allen, Lang, Wain, Marta
- Reduction of duration of hospital stay: Allen

Inclusion: patients with air leaks: n=6
- Wong, Porte, Allen, Tansley, Anegg, Marta

Wain, Ann Thorac Surg, 2001
Tansley, J Thorac Cardiovasc Surg, 2006
Anegg, Europ J Cardiothorac Surg, 2007
Allen, Ann Thorac Surg, 2004
Lang, Europ J Cardiothorac Surg, 2003
Material and methods

- Prospective multicenter randomized study
- Air leak after lobectomy or anatomical segmentectomy (open thoracotomy)
- Adjunct to standard closure techniques
- 1/1 randomization pleuraseal™ vs control
Material and Methods

- **European academic tertiary thoracic units**
  - University Hospitals Leuven, Belgium
  - Otto Wagner Hospital, Vienna, Austria
  - VU Medical Centre Amsterdam, Netherlands
  - University Hospital Innsbruck, Austria
  - Papworth Hospital, Cambridge, UK
  - University Hospital Zurich, Switzerland
  - Free University Hospitals Brussels, Belgium
  - Medical centre Rotterdam Zuid, Rotterdam, Netherlands*

*This center was not able to enroll patients*
Material and Methods

• **Primary end-point:**
  Proportion of patients remaining air leak free from the time of skin closure to hospital discharge

• **Secondary endpoints:**
  1. Proportion of patients for whom intraoperative air leak sealing success is achieved
  2. Duration of air leak (hours)
  3. Duration of chest drainage (hours)
  4. Duration of hospitalization (hours)

• **Statistics:**
  – Estimated success rates for primary end-point:
    Pleuraseal group: 40%; Control group: 15%
  – 112 patients
# Material and Methods

## Air leak risk score assessment

### Pre-operative criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score = 0</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD 1 (FEV1≥80)</td>
<td>Not present</td>
<td>Present = 1</td>
</tr>
<tr>
<td>COPD 2 (FEV1 50-80)</td>
<td>Not present</td>
<td>Present = 2</td>
</tr>
<tr>
<td>COPD 3 (FEV1&lt;30-50)</td>
<td>Not present</td>
<td>Present = 3</td>
</tr>
<tr>
<td>COPD 4 (FEV1&lt;30)</td>
<td>Not present</td>
<td>Present = 4</td>
</tr>
<tr>
<td>FEV1/FVC%&lt;65%</td>
<td>Not present</td>
<td>Present = 1</td>
</tr>
<tr>
<td>Smoking (ever as habit)</td>
<td>Not present</td>
<td>Present = 1</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Not present</td>
<td>Present = 1</td>
</tr>
<tr>
<td>Pre-op chemotherapy</td>
<td>Not present</td>
<td>Present = 1</td>
</tr>
<tr>
<td>Pre-op radiation therapy</td>
<td>Not present</td>
<td>Present = 1</td>
</tr>
</tbody>
</table>

### Intra-operative criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score = 0</th>
<th>Score = 1</th>
<th>Score = 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adhesions</td>
<td>Absent</td>
<td>Present (any)</td>
<td>N/A</td>
</tr>
<tr>
<td>Tissue</td>
<td>Normal</td>
<td>Fragile</td>
<td>N/A</td>
</tr>
<tr>
<td>Extent of surgery</td>
<td>Typical</td>
<td>Extensive</td>
<td>N/A</td>
</tr>
<tr>
<td># Leak Sites</td>
<td>1-2</td>
<td>3-6</td>
<td>&gt; 6</td>
</tr>
</tbody>
</table>

Stratification into low-risk or high-risk strata based on pre-op and intra-op factors.
Intra-operative air leak classification

- Grade 0: No air leak
- Grade 1: Countable bubbles
- Grade 2: Stream of bubbles
- Grade 3: Coalescent bubbles

Chest tube management

- Two chest tubes
- Suction 18 h, then water seal
- Evaluated by trained staff/12 h; visual control
- Removal: no air leaks and drainage level < 300ml/24 h
## Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pleuraseal ™ group (n=62)</th>
<th>Control group (n=59)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>61.5</td>
<td>62.8</td>
<td>0.463</td>
</tr>
<tr>
<td>Nicotine use</td>
<td></td>
<td></td>
<td>0.719</td>
</tr>
<tr>
<td>• History</td>
<td>31 (50%)</td>
<td>34 (58)</td>
<td></td>
</tr>
<tr>
<td>• Current</td>
<td>22 (36%)</td>
<td>17 (29)</td>
<td></td>
</tr>
<tr>
<td>Concomitant Pulmonary disease</td>
<td>35 (56%)</td>
<td>25 (42.%)</td>
<td>0.147</td>
</tr>
<tr>
<td>Indication for operation</td>
<td></td>
<td></td>
<td>0.236</td>
</tr>
<tr>
<td>• Primary lung cancer</td>
<td>62 (100%)</td>
<td>57 (97%)</td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td>0</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Type of procedure</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>• Lobectomy</td>
<td>61 (98%)</td>
<td>58 (98%)</td>
<td></td>
</tr>
<tr>
<td>• Segmentectomy</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Total Risk score (pre- and intra-op)</td>
<td>3.9 ±2.0</td>
<td>3.4 ±1.6</td>
<td>0.160</td>
</tr>
<tr>
<td>Risk stratification</td>
<td></td>
<td></td>
<td>0.298</td>
</tr>
<tr>
<td>• Low risk (score 1-5)</td>
<td>51 (82.3%)</td>
<td>53 (89.8%)</td>
<td></td>
</tr>
<tr>
<td>• High Risk (score 6-11)</td>
<td>11 (17.7%)</td>
<td>6 (10.2%)</td>
<td></td>
</tr>
</tbody>
</table>
Secondary end-point
Percentage of patients with intra-operative air leak sealing

- Control (n=59): 23.7%
- PleuraSeal™ (n=62): 71%

p < 0.001
Primary end-point
Percentage of patients that remained air leak free until discharge

• Overall : 41.9% (P group) vs 30.5% (C group), p=0.257

• Significant effect in patients with grade II-III air leaks
  43.5% (P group) vs 15.2% (C group), p=0.013
Primary endpoint
Percentage of patients remaining air leak free (until discharge)

- Grade 1: PleuraSeal™ (n=62) 37.5%, Control (n=59) 50%
  - p=0.530
- Grade 2 or 3: PleuraSeal™ 43.5%, Control 15.2%
  - p=0.013
## Results

<table>
<thead>
<tr>
<th></th>
<th>PleuraSeal™ group (n=62)</th>
<th>Control group (n=59)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-op air leak sealing success (%)</strong></td>
<td>71.0%</td>
<td>23.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Post-op air leak free (%)</strong></td>
<td>41.9%</td>
<td>30.5%</td>
<td>0.257</td>
</tr>
<tr>
<td><strong>Duration of air leak (hours)</strong></td>
<td>6 (0-630)</td>
<td>30 (0-312)</td>
<td>0.790</td>
</tr>
<tr>
<td><strong>Duration of chest tube drainage (h)</strong></td>
<td>94 (23-838)</td>
<td>94 (18-479)</td>
<td>0.339</td>
</tr>
<tr>
<td><strong>Amount of chest tube drainage (ml)</strong></td>
<td>1816 (500-7825)</td>
<td>1642 (400-5145)</td>
<td>0.559</td>
</tr>
<tr>
<td><strong>Length of hospitalization (h)</strong></td>
<td>312 (144-3144)</td>
<td>288 (120-2040)</td>
<td>0.292</td>
</tr>
</tbody>
</table>

Values are presented as median (range)
Results: adverse events

- No hospital mortality
- Similar incidence of complications:
  35.5% (P group) vs 23.7% (C group), p=0.170
- No adverse events attributable to use of sealant
- No effect on renal or liver function (laboratory)
- No differences in lung expansion or pneumothorax
## Results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Statistic</th>
<th>Pleuraseal (n=62)</th>
<th>Control (n=59)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>n (%)</td>
<td>5 (8.1)</td>
<td>3 (5.1)</td>
<td>0.718</td>
</tr>
<tr>
<td>Empyema</td>
<td>n (%)</td>
<td>2 (3.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>n (%)</td>
<td>2 (3.2)</td>
<td>2 (3.4)</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>n (%)</td>
<td>1 (1.6)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>n (%)</td>
<td>9 (14.5)</td>
<td>5 (8.5)</td>
<td>0.397</td>
</tr>
<tr>
<td>ARDS</td>
<td>n (%)</td>
<td>1 (1.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>BP fistula</td>
<td>n (%)</td>
<td>1 (1.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>n (%)</td>
<td>0</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>n (%)</td>
<td>1 (1.6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>n (%)</td>
<td>6 (9.7)</td>
<td>3 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>n (%)</td>
<td>0</td>
<td>1 (1.7)</td>
<td></td>
</tr>
</tbody>
</table>
• Pleuraseal™ had no effect in grade I air leaks.

• Pleuraseal™ had a significant effect on grade II-III air leaks
Control group: results better than expected

- Primary end-point control 30.5% (expected 15%)

Differences in air leaks before randomization in P and C group?
Grade of air leaks (before randomization)

- **PleuraSeal™ (n=62):**
  - Grade 1: 25.8%
  - Grade 2: 67.7%
  - Grade 3: 6.5%

- **Control (n=59):**
  - Grade 1: 44.1%
  - Grade 2: 54.2%
  - Grade 3: 1.7%

p-value: 0.077
In this study, hospitalization time after lobectomy was significantly longer compared to duration of air leak and chest tube drainage.

We observed a high variability in length of hospitalization by site.
Conclusions

• In this multicenter trial, PleuraSeal™ significantly reduced intra-op air leaks after lobectomy
• In patients with grade 2-3 air leaks, significant more patients remained air leak free
• PleuraSeal™ is safe and effective
• In Europe, hospitalization time after lobectomy is (not yet) determined by duration of air leak