Prevention of Air Leakage by Spraying Vivostat Fibrin Sealant After Lung Resection in Pigs*

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Study objectives: To evaluate Vivostat fibrin sealant in the prevention of air leakage after experimental lung resection in pigs.

Design: Randomized study.

Setting: University laboratory.

Methods: Six Landrace pigs were operated on in both lungs through a median sternotomy. Five different resection sites were created in each lung.

Intervention: Randomization was performed to either application of Vivostat fibrin sealant (ConvaTec; Skillman NJ) or human albumin 20% (control) at the resection sites. The lung parenchyma was occluded with a soft clamp for either 1, 2, 5, or 10 min in the treatment group and 10 min in the control group. After removal of the clamp, the lung was ventilated with an increasing intrabronchial pressure of 20, 30, and 45 cm H2O for 2 min at each step.

Results: At inspiratory pressures of 20 and 30 cm H2O air leaks were found in the control group but not in the Vivostat group (p < 0.001). At an inspiratory pressure of 45 cm H2O, there were two small air leaks in the Vivostat group at each clamping time (four at 5 min), compared with five small and seven large leaks in the control group. Analysis of the data after 10 min of clamping showed that the Vivostat group was superior to the human albumin group (p = 0.002).

Conclusions: This randomized study shows that Vivostat fibrin sealant is effective in preventing air leakage after small lung resections in pigs, even at high inspiratory pressures.

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Key words: autologous; complications; fibrin sealant; lung resection; pulmonary air leak

Postoperative air leakage is the most frequent complication after lung surgery, regardless of whether an operation is performed by thoracotomy or by use of endoscopic techniques. A persistent air leak increases the incidence of morbidity and prolongs patient hospitalization, incurring additional expenses.1 Therefore, expectations are high for the many new types of surgical sealants for pulmonary air leakage that have emerged in the last decade. The aim of this randomized study was to study the effectiveness of a new, autologous fibrin sealant, Vivostat (ConvaTec; Skillman NJ), on air leaks after experimental lung resection in pigs. In addition, the optimal conditions for use of the sealant were studied, as well as its efficacy during high positive ventilation pressure (to simulate coughing).

Materials and Methods

Fibrin Sealant Production

The Vivostat system is a medical device for the preparation of an autologous fibrin sealant from 120 mL of the patient’s blood in the operating theater.2 The system is fully automated and microprocessor-controlled, and is made up of three components: an automated processor unit, an automated applicator unit, and a disposable, single-patient-use unit, which includes a preparation set and a Spraypen applicator (Fig 1).

To produce the sealant, 120 mL of the patient’s blood is drawn into the preparation set and mixed with 17 mL of 4% trisodium citrate USP for anticoagulation. The preparation set is then placed into the processor, and the automated processing is begun. Rapid cycle centrifugation results in the isolation of...
approximately 60 mL of platelet-poor plasma, which is reacted with biotin-batroxobin for 10 min at 37°C. Biotin-batroxobin acts on fibrinogen in the patient’s plasma to catalyze the release of fibrinopeptide A, without activating factor XIII, resulting in the formation of an acid-soluble fibrin I polymer. This is isolated by further centrifugation and dissolved in 3.5 mL of 0.2 mol/L sodium acetate buffer (pH 4) containing calcium chloride. Avidin, covalently bound to agarose, is added to the solution, which complexes with the biotin-batroxobin. The biotin-batroxobin—avidin-agarose complexes are then separated from the fibrin I solution by filtration. The vial containing the purified concentrated fibrin I solution is then transferred to the applicator unit, which also houses a syringe containing 1.0 mL of 0.75 mol/L carbonate/bicarbonate buffer (pH 10). The two solutions are administered simultaneously and intimately mixed during the process in a 7:1 ratio (fibrin I to carbonate/bicarbonate buffer). In the presence of calcium ions at the resulting neutral pH, endogenous prothrombin is converted to thrombin, which causes fibrinopeptide B to be cleaved from fibrin I, forming fibrin II. This endogenous thrombin also activates endogenous factor XIII, which acts on the acid-soluble fibrin II polymer to form a chemically stable, cross-linked fibrin II polymer that is a clinically useful sealant.

**Study Design**

Six Danish Landrace pigs (weight, 35 to 41 kg) were anesthetized and intubated with a single-lumen tracheal tube (tiopental 250 mg/30 kg IV and halothane 1% inhalation endotracheal tube). After a median sternotomy, both pleural cavities were opened, and five different resection sites (each 4 × 2 cm) were created in each lung with scissors. A resection site was only included for study if there was significant air leakage. The central part of the relevant lobe of the lung was oozed with a soft tissue clamp, to stop ventilation and air leakage, and randomization was performed. Resection sites were randomized to one of five possible treatments: Vivostat fibrin sealant with clamp application for 1, 2, 5, or 10 min or human albumin 20% (control) with the clamp applied for 10 min. The Vivostat fibrin sealant used in this study was derived from human blood. After removal of the clamp, the resection line was ventilated with an increasing intrabronchial pressure at intervals of 20, 30, and 45 cm H2O for duration of 2 min for each interval. Animals were ventilated intermittently to peak pressure at a respiratory rate of 20 breaths per minute. The resection sites were tested for air leakage (±) under water. Statistical analysis was performed using McNemar’s test after the small and large air leaks were combined into a single air leak category. Exact binomial methods were used to compute the probability values.

**Results**

A total of 60 resection sites were made, 48 of which were treated with Vivostat fibrin sealant and 12 with human albumin (controls). Results are summarized in Table 1. At an inspiratory pressure of 20 cm H2O, no air leaks were found in the Vivostat group regardless of the clamping time, compared with seven small and five large air leaks in the human albumin group (p < 0.001). At an inspiratory pressure of 30 cm H2O, no air leaks were found in the Vivostat group, whereas five small and seven large air leaks were found in the human albumin group (p < 0.001). At an inspiratory pressure of 45 cm H2O, there were two small air leaks in the Vivostat group at each clamping time, with the exception of 5

**Table 1—Number and Size of Air Leak in Each Treatment Group by Peak Ventilator Pressure**

<table>
<thead>
<tr>
<th>Group</th>
<th>Clamp Time, min</th>
<th>Air Leak Size</th>
<th>Peak Ventilator Pressure, cm H2O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Vivostat sealant</td>
<td>1</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Human albumin</td>
<td>10</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>

*+ = small air leak; ++ = large air leak.
min, for which there were four leaks (three small and one large). All Vivostat groups with two small air leaks at this inspiratory pressure were found to be superior to the human albumin group (seven small and five large air leaks) (p = 0.002). The Vivostat group with four air leaks (three small and one large) was also superior to the human albumin group (p = 0.008). Overall, only a single large air leak was observed in the Vivostat group compared with a total of 19 in the control group. Statistical analysis was not performed on large air leaks alone, inasmuch as all air leaks were deemed to be of clinical relevance. However, this difference would appear to be significant.

**Discussion**

The use of fibrin sealant to control pulmonary air leakage is controversial. Most surgical groups have reported a beneficial effect of fibrin sealant, but others have come to the opposite conclusion. However, when studying these reports carefully, it is clear that the studies differ in a number of respects. There are differences in the type of sealant used; the application technique (spray or double-barreled syringe, air leakage or bleeding or dry surface when sealant is applied); the operative procedures performed; the number of patients included; the clinical end points used; the presence of underlying pulmonary disease; and lastly, the origin of air leakage (from the bronchial stump, parenchyma, or both).

Bearing in mind these variations in study design, it is not surprising that the results differ considerably. The conclusion from the literature seems to be that fibrin sealant may reduce a small pulmonary air leakage if it is properly applied with a spray system to a dry lung surface, without bleeding or air leakage, at the time of the application. This means that the lung should not be ventilated for 1 to 2 min while the sealant is allowed to cross-link. Major air leaks from bronchi should be sown or stapled before gluing; otherwise, the sealant will detach from the lung. The application method is crucial, and recently a sequential technique has been described in which fibrinogen solution is first rubbed into the lung parenchyma, followed by spraying the fibrin sealant at the lung surface. The fibrinogen in the lung parenchyma is converted to fibrin, and the sealant covers the surface of the lung and enhances the sealing efficacy.

An operation on a patient with a major air leak cannot be salvaged through the use of fibrin sealant alone. The surgeon must reduce any air leakage by careful suturing, stapling, electrocautery, and so forth. The advantage of using fibrin sealant in lung surgery is clear if a small to moderate air leak can be closed, and the lung expands fully and adheres to the chest wall, thereby preventing collapse. This is the immediate goal of any successful lung resection. A disadvantage of the traditional repair of surgical defects in the lung parenchyma by use of sutures and stapling devices is the concomitant damage to adjacent healthy lung parenchyma. One advantage of repairing the lung parenchyma with fibrin sealant is the conservation of the lung tissue, which is important both for patients undergoing large or multiple resections, and for patients with marginal pulmonary reserve. Fibrin sealant is a biodegradable product that may enhance healing and stimulate fibroblast growth, and decrease the number of adhesions. To date, no other biological or synthetic adhesive materials have been as successful in terms of lack of toxicity and clinical benefits.

Vivostat is a totally autologous fibrin sealant with fine elasticity and biocompatibility. This was a preliminary study in a short-term animal model, involving only a small number of animals. Human albumin was chosen as a control because of its similarities with Vivostat; like Vivostat, it is translucent and of high viscosity, containing human proteins. The test circumstances were clearly experimental because the central part of the relevant lobe of the lung was occluded with a soft clamp for up to 10 min to stop ventilation and air leakage from the resection site. This may represent a limitation of this model, as lung clamps are not routinely used during lung resection in humans. Our results showed that Vivostat, when sprayed at the lung surface, was an efficient pneumostat even at high inspiratory pressures, suggesting that it is also likely to be effective under physiologic conditions such as coughing.

The efficacy of Vivostat in the comparable human clinical setting remains to be determined, but it seems likely to be good providing air leakage and lung movements can be stopped while the sealant is allowed to harden. We are currently working on such a technique. A randomized study in patients undergoing lung resections has been initiated, in which the lung clamp will not be used. In this study, patients will instead be intubated with a double-lumen tube, allowing selective occlusion of ventilation to the relevant lung. This will allow the lung to be kept in a neutral position with lung tissue expanded but without positive intrabronchial pressure. This will ensure that there is no active leakage of air from the lung or movement of the lung surface, enabling the sealant to be applied and harden before ventilation is slowly restarted. The biocompatibility and physical properties of Vivostat (elasticity, adhesion to tissue, and internal strength), coupled with the findings of
this preliminary trial, lead us to believe that Vivostat can become an important aid in lung surgery.

REFERENCES
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