Use of recombinant activated Factor VII for refractory after lung transplant bleeding as an effective strategy to restrict blood transfusion and associated complications

Balu Bhaskar, Marc Zeigenfuss, Jivesh Choudhary, and John F. Fraser

BACKGROUND: Recombinant activated factor VIIa (rFVIIa) has been increasingly used to stop massive bleeding after cardiothoracic surgical procedures. However, the risk : benefit profile of such a potent hemostatic agent remains unclear in the postsurgical patient, and the cost benefit is even less clear. In patients after lung transplantation, volume of blood transfused is of major concern, and all attempts are made to minimize large blood transfusions in this cohort. We report our experience with rFVIIa in patients with refractory bleeding after lung transplant surgery.

STUDY DESIGN AND METHODS: All lung transplant patients who underwent single- or double-lung transplantation who received rFVIIa in the 5-year period, from January 2005 to June 2011, were included. A total of 15 patients were identified from a total of 95 lung transplant cases operated during this study period. Patient demographics, intra- and postoperative records were reviewed to assess the efficacy and safety of rFVIIa treatment.

RESULTS: Patients with major bleeding treated with rFVIIa showed improved hemostasis with rapid normalization of coagulation variables. rFVIIa treatment was not associated with an increase in mechanical ventilation time, length of intensive care unit stay, or hospital stay compared to other lung transplant patients. In addition, the use of rFVIIa was associated with reduction in transfusion requirements of red blood cells, fresh-frozen plasma, and platelets (all p < 0.001). No definite thromboembolic-related event was recorded in our cohort.

CONCLUSIONS: These data demonstrate that rFVIIa was associated with reduced blood loss, improvement of coagulation variables, and decreased need for transfusions. This reduction in losses led to a reduced requirement for blood transfusion, which may translate to a decrease in transfusion-related complications. Further investigation is needed to determine rFVIIa’s safety and its efficacy in improving postoperative morbidity and mortality specifically in the field of post–lung transplantation surgery.

Recombinant factor VIIa (rFVIIa; Novoseven) was introduced to control bleeding in persons with hemophilia with autoantibodies to Factor (F)VIII and F IX. Recent reports describe the use of rFVIIa in the context of refractory hemorrhage in trauma, neurosurgery, and cardiac surgery with success. However, there is ongoing concern regarding the safety, optimal dosage, and timing of rFVIIa administration.

Lung transplantation is the gold standard management for patients with end-stage lung disease. Since the early 1990s, more than 25,000 lung transplants have been performed at centers globally. The International Society for Heart and Lung Transplantation monitors lung transplantations throughout the world and keeps an ongoing registry, which is reported annually. A routine complication of lung transplantation is some perioperative bleeding. Postoperative hemorrhage can be divided into surgical bleeding and diffuse hemorrhage secondary to posttransplantation coagulopathy. Patients undergoing lung transplantation are often confronted with excessive intraoperative bleeding followed by large amounts of transfused blood. Surgical trauma is the most important etiologic factor, particularly in patients with severe chronic inflammatory changes and dense pleural and pericardial adhesions. Other important causes include

ABBREVIATIONS: APTT = activated partial thromboplastin time; ICU = intensive care unit.

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existing coagulation abnormalities and adverse hemostatic effects of cardiopulmonary bypass secondary to dilution, activation of clotting factors, thrombin generation, stimulation of fibrinolysis, heparin effects, and most importantly activation and degranulation of platelets (PLTs) in the bypass circuit. Accordingly, management must be directed to optimal surgical hemostasis and rapid correction of coagulopathy. In case of excessive and ongoing postoperative bleeding, surgical reexploration should be considered once the coagulation profile is optimized and normothermia is attained. However, rethoracotomy for diffuse hemorrhage can itself worsen bleeding through further tissue damage. When removal of the native lungs is difficult (e.g., in cystic fibrosis), diffuse bleeding from the inflamed pleural surface can be intractable.

Significant advances in perioperative management and surgical techniques have both contributed to decreasing the incidence of severe bleeding in patients undergoing transplant surgery. Patients with uncontrolled critical bleeding and coagulopathy have significant morbidity and mortality, despite standard replacement of coagulation factors and surgical intervention. Blood product transfusion correlates with increased morbidity, including multiorgan failure, acute respiratory distress syndrome, transfusion-related acute lung injury (TRALI), transfusion-related immune modulation, transfusion-related fluid overload, infection, and death. Blood loss and resultant cardiovascular compromise predispose to poor outcomes with regard to the health and quality of life of the solid-organ recipient. In immunosuppressed transplant recipients, transfusion poses a unique set of challenges as it may be associated with infectious complications, an increased risk of acute lung injury, and transfusion-associated graft-versus-host-disease (GVHD) due to donor lymphocytes. Increased transfusion also carries a risk of the recipient developing anti–human leukocyte antigen (anti-HLA) antibodies and thus increased rates of acute and chronic graft rejection. This cohort of patients is often associated with increased costs to the health care system in the form of excessive blood and blood product requirements and extended stays in the intensive care unit (ICU) and hospital.

Although the disturbance of clotting and fibrinolysis during cardiac operations and use of rFVIIa has been widely investigated, little is known about its occurrence and prevention during lung transplantation. We describe the use of rFVIIa in patients with diffuse bleeding after lung transplantation at our hospital, need of blood and blood product transfusion, and also complications after use of rFVIIa to stop bleeding in the postoperative period.

MATERIALS AND METHODS

From the operating room, pharmacy, and ICU databases we retrospectively identified all consecutive lung transplant recipients at The Prince Charles Hospital, Brisbane. All lung transplant patients who underwent single- or double-lung transplantation who received rFVIIa in the 5-year period, from January 2005 to June 2011, were included. From this cohort, we identified a subset who had received rFVIIa either intraoperatively or postoperatively for intractable bleeding. The study was approved by the human ethics committee of our hospital. Consent was waived as this was a retrospective analysis of data and patients were not identified. Use of rFVIIa was cross-checked against the cardiac surgery department, intensive care, hospital pharmacy, and hospital blood bank databases. Demographic, procedural, and hematologic data were abstracted from the medical record. Altogether, 15 such patients who were operated on during the study period were identified from a total of 95 lung transplant cases operated on during the same time period. Patient records and operating room and ICU databases were reviewed to assess the efficacy and safety of rFVIIa treatment. To assess efficacy, hourly bleeding volumes and data of blood products and other hemostatic agents administered 6 hours before and 12 hours after rFVIIa administration were registered. The clinical outcome and any reported thromboembolic complications were registered. Hematologic data included international normalized ratio, activated partial thromboplastin time (APTT), fibrinogen, and PLT count. Use of red blood cells (RBCs), fresh-frozen plasma (FFP), PLTs, and cryoprecipitate were monitored before and after rFVIIa infusion.

rFVIIa administration

The decision to use rFVIIa was a combined decision made by the surgical team and intensive care specialist, after exhaustive exclusion of surgical causes of bleeding and failure of traditional hemostatic measures that included non-RBC support (FFP, PLTs, cryoprecipitate), desmopressin (DDAVP), and antifibrinolytics. To ensure adequate elements for hemostasis, blood product administration preceded the standard rFVIIa dose of 40 to 120 μg/kg. When rFVIIa was used during the primary operation it was administered in the operating room after heparin reversal and loading of blood products but before sternal closure. This allowed the surgeon to assess for large surgical bleeding causes, when the coagulopathic bleeding settled. Some patients had their rFVIIa administered in the ICU and after reexploration for bleeding. It was difficult to quantify the exact amount of bleeding in the operating theater; however, there was accurate measurement of chest tube drainage over the first 24 postoperative hours in ICU.

Statistical analysis

Data were analyzed using computer software (Statistical Package for the Social Sciences [SPSS], Version 15.0, SPSS,
Inc., Chicago, IL). Data are presented as mean ± SD (range), median (quartiles), or number (%). Differences in pre- and post-rFVIIa administration were assessed using paired-samples t test when differences between scores met assumptions of normality or the Wilcoxon signed-rank test when normality assumptions were violated. A two-sided p value of less than 0.05 was considered significant.

Because almost none of the variables measured conformed to normal distributions, nonparametric statistics were used throughout for consistency of reporting and analysis. Coagulation indicators and blood product usage before and after rFVIIa dose were compared in individuals by using Wilcoxon matched-pairs signed-ranks tests. Univariate and multivariate analyses were performed to assess the relationship between the outcomes of interest (response and mortality or both) and age, sex, patient weight, size of dose, temperature, pH, hemoglobin (Hb), hematocrit (Hct), PLT, and fibrinogen levels; prothrombin time/international normalized ratio; APTT; type of operation; and number of RBC, FFP, cryoprecipitate, and PLT units before and after the dose of rFVIIa.

RESULTS

Demographics

A total of 95 patients underwent lung transplantation in our institution during the study period, of which 15 patients received FVIIa. Most patients who received FVIIa were male (73.33%). The median age of patients was 38 years (range, 14-58 years). Most of the patients had bilateral sequential lung transplant compared to single-lung transplant (Table 1). Major indication was chronic obstructive airway disease (COPD) or emphysema. The majority of the patients underwent bilateral sequential lung transplant (81, 85.26%). Eleven patients had single-lung transplant and four had heart–lung transplant. Fifteen patients had pleurodesis in the past before the transplant of which eight had rFVIIa postoperatively. The rFVIIa was administered in the operating theater in five patients and 10 patients received rFVIIa in the ICU. In all patients treated in the operating theater who received rFVIIa no surgical cause of bleeding was found; it was mostly diffuse bleeding. Temperature was corrected to more than 37°C in all patients who received rFVIIa.

TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Lung transplant patients (n = 95)</th>
<th>Patients who received rFVIIa (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSSLTx</td>
<td>81</td>
<td>14</td>
</tr>
<tr>
<td>SLTx</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>HLT</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sex, male</td>
<td>65 (68.4)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (14-62)</td>
<td>38 (14-58)</td>
</tr>
<tr>
<td>Patients on anti-PLT medication who received rVIIa</td>
<td>60 (63.2)</td>
<td>10 (66.7)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.60 ± 1.8 (1.3-1.96)</td>
<td>1.62 ± 2.0 (1.30-1.96)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>46.9 ± 8.8 (38-92)</td>
<td>48.1 ± 9.6 (38-80)</td>
</tr>
<tr>
<td>BMI</td>
<td>22.3 ± 2.8 (15.8-32.3)</td>
<td>20.2 ± 2.8 (15.8-28.1)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin &lt;7 days</td>
<td>40 (42.1)</td>
<td>7 (46.7)</td>
</tr>
<tr>
<td>Corticosteroids &lt;7 days</td>
<td>40 (42.1)</td>
<td>6 (40.0)</td>
</tr>
<tr>
<td>Previous thoracotomy status</td>
<td>5 (5.3)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema or COPD</td>
<td>30 (31.6)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>20 (21.1)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
<td>18 (21.2)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>4 (4.2)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Primary pulmonary hypertension</td>
<td>4 (4.2)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Retransplant or graft failure</td>
<td>1 (1.05)</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.1)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Ventilator days</td>
<td>1.8 (0-18)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>18 (9-37)</td>
<td>20 (9-35)</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>4 (2-20)</td>
<td>4.4 (2-18)</td>
</tr>
</tbody>
</table>

* Data are reported as number (%), median (quartile), or mean ± SD (range).
BSSLTx = bilateral sequential single-lung transplantation; COPD = chronic obstructive airway disease; HLT = heart–lung transplant; SLTx = left single-lung transplantation.

Dose

In the 15 patients who received 20 doses of rFVIIa, five patients received two consecutive doses and the remaining patients received a single dose. The median dose was 88.6 μg/kg (interquartile range, 82-103 μg/kg; range, 9-141 μg/kg). The median time from onset of bleeding to dose administration was 4 hours (interquartile range, 1-8 hr; range, 0-36 hr). Before treatment with rFVIIa, 90% of patients were returned to the operating theater in an attempt to control blood loss, including eight patients who were returned more than once before treatment with
rFVIIa. After treatment with an initial dose of rFVIIa one patient was returned to the operating theater for removal of a large lung apical pleural clot (apical cap) rather than active bleeding.

**Blood products**

Administration of rFVIIa was associated with a significant reduction of transfusion of all blood products. A comparison of the units of RBCs received before and after the initial dose of rFVIIa in each individual showed a significant reduction (p < 0.001) in the group of patients who received rFVIIa. Lung transplant patients during the study period received a mean of 6.876 ± 5.97 units of RBCs, 6.97 ± 4.42 units of FFP, 10.1 ± 4.75 units of PLTs, and 20.1 ± 15.3 units of cryoprecipitate before dosing of rFVIIa but only 2.53 ± 1.86, 2.36 ± 1.54, 2.1 ± 3.8, and 3.75 ± 8.32 respective units of these blood products after administration (all p < 0.001; Table 2). After the administration of rFVIIa, most patients (88%) received less than 3 units of RBCs. No patients were identified as receiving rFVIIa prophylactically.

**Blood loss**

Blood loss was measured for each patient from the initiation of surgery and before and for at least 12 hours after administration of rFVIIa. The blood loss before administration of rFVIIa was a mean of 808 ± 290 mL/hr (median, 664 mL/hr). This blood loss dropped significantly to 180 ± 140 mL/hr (p = 0.001; median, 142 mL/hr) for the first 6 hours and 132 ± 120 mL/hr (p < 0.001; median, 100 mL/hr) for 12 hours immediately after administration of the drug.

**Table 2. Blood products**

<table>
<thead>
<tr>
<th>Blood product (units)*</th>
<th>Before rFVIIa administration</th>
<th>After rFVIIa administration</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBCs</td>
<td>6.876 ± 5.97</td>
<td>2.53 ± 1.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFP</td>
<td>6.97 ± 4.42</td>
<td>2.36 ± 1.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PLTs</td>
<td>10.1 ± 4.75</td>
<td>2.1 ± 3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>20.1 ± 15.3</td>
<td>3.75 ± 8.32</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Cryoprecipitate, 10 mL/U; FFP, 250 mL/U; PLTs, 50 mL/U; RBCs, 250 mL/U.

**Temperature and pH**

Temperature was recorded in all patients at the time of the initial rFVIIa dose. Only two patients had a temperature less than 36°C when rFVIIa was administered. The pH was documented for patients at the time of the initial rFVIIa dose: five patients had a pH of less than 7.34 at the time of rFVIIa administration and only one patient was acidic with a pH value of less than 7.20.

**Laboratory indicators**

Details of coagulation indicators before and after the initial dose of rFVIIa are provided in Table 3. Prothrombin time was prolonged (>15.5 sec) in 12 of the 15 patients before administration of rFVIIa. Similarly, APTT was prolonged (>46) in 8 of 15 patients before administration of rFVIIa. Most coagulation indicators exhibited significant changes after the initial dose of rFVIIa compared to before the administration of rFVIIa (Table 3) but did not reach significance. PLT levels did not exhibit a significant change; PLT count before rFVIIa was 140.1 ± 80.1 and after was 200.1 ± 96.7 (p = 0.026). The Hb levels 10.2 ± 1.3 significantly improved after rFVIIa to 12.8 ± 2.1 (p = 0.001) and Hct levels, which were 29.6 ± 4.6 before and 35.2 ± 4.2 after rFVIIa (p = 0.001), also increased significantly (Table 3), reflecting decrease in bleeding and stabilization of Hb and Hct.

**Response and outcome**

rFVIIa was considered to have decreased or stopped bleeding in all the patients where efficacy was reported. The observed mortality for all patients who underwent lung transplant at 28 days was 2 of 95 patients, and sur-
vival rate for all transplant patients was 87% after 1 year. There was no mortality recorded at 28 days for any of the patients who received rFVIIa and 1-year survival for these patients at 1 year was 95%.

**Adverse events**

No patients were considered to have died of adverse events related to the use of rFVIIa. No adverse effect secondary to rFVIIa was recorded in the notes.

**DISCUSSION**

Lung transplantation as a vital therapeutic option for patients with end-stage lung disease has benefited from multiple improvements over the years and achieved better short- and intermediate-term outcomes. The perioperative reduction of use of blood products appears to be a very important strategy that should start with the preoperative identification of patients at risk of massive blood loss.

All lung transplantations may be complicated by perioperative and/or postoperative hemorrhage, which is associated with the need for transfusions and additional surgical procedures. In our study, we analyzed the use of rFVIIa in lung transplant patients; the blood product usage of RBCs, FFP, cryoprecipitate, and PLT in lung transplantation before and after infusing rFVIIa; and the complications secondary to use of rFVIIa.

The results of our retrospective study demonstrate that the use of rFVIIa in posttransplant patients is not only safe but a very effective strategy to prevent severe diffuse and nonsurgical bleed. The use of rFVIIa not only stops bleeding but also prevents excessive use of blood and blood products and indirectly prevents complications secondary to massive blood transfusion in these post-lung transplant patients. rFVIIa significantly reduced perioperative transfusion requirement and postoperative bleeding during lung transplant surgeries.

The use of rFVIIa as a hemostatic agent is attractive for several reasons. Because it is cloned and expressed in hamster kidney cells and purified without use of human serum or other proteins, there is minimal risk of virus transmission. Further, the use of rFVIIa may be associated with decreased blood product transfusions and the associated risks of infection, TRALI, volume overload (transfusion-associated fluid overload), immune complications (transfusion-related immune modulation), and transfusion reactions. Finally, rFVIIa may be safer than other coagulation factor products because it is active at the site of injury, thereby decreasing the risk of systemic thromboembolic events. The hemostatic process is not systemic but confined to the surface of the thrombin-activated PLTs and the tissue factor-bearing cells at the site of vascular injury. The local activation of hemostasis constitutes the rationale for the use of rFVIIa in disseminated intravascular coagulation–associated severe bleeding. However, definitive data demonstrating efficacy are lacking, and it is very expensive (approx. $9400 for a standard 90 µg/kg dose for a 70-kg patient). Further, thromboembolic adverse events have been reported with its use in patients with and without hemophilia. A major concern when using activated coagulation factors such as rFVIIa is the possible induction of disseminated intravascular coagulation or thromboembolism. However, in the many studies performed so far, rFVIIa was not associated with systemic activation of the coagulation cascade. In a recently published study of a large and comprehensive cohort of patients in placebo-controlled trials of rFVIIa, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events, especially among the elderly. The effect of rFVIIa on plasmatic coagulation derives from its interaction with tissue factor. Thus, the procoagulatory effect is predominantly located in regions where tissues or vessels are injured. This intriguing characteristic might be an explanation for the relatively low incidence of thromboembolic events (1%-2%) after the use of rFVIIa. In our cohort of patients no thrombotic complications were noted but this may be limited by the small number of patients and by the fact that this was a retrospective chart analysis.

Clinicians must become increasingly aware of the potential for bleeding complications and risks associated with transfusion of blood products. In particular, TRALI may exacerbate or contribute to the primary graft dysfunction associated with severe ischemia–reperfusion injury. In patients undergoing transplantation, transfusion may result in the development of alloantibodies that may increase the risk of rejection or induce microchimerism or GVHD. Transfusion support remains a critical component during lung transplantation. Our data should help surgeons and transfusion medicine specialists establish guidelines for transfusion requirement during the operation.

In conclusion, in our retrospective review of patients undergoing lung transplantation, we found that rFVIIa appeared to be effective in reducing life-threatening bleeding refractory to conventional hemostatic blood component therapy. We also found that administration of rFVIIa may be associated with significant decrease in blood loss and blood component use and associated complications. None of our patients had thromboembolic events. Our data thus add to the growing literature regarding the use of rFVIIa in treatment of refractory coagulopathy associated with noncoronary complex cardiac surgeries. However, additional randomized investigations to study the optimal timing, dosing, and associated thromboembolic risks of rFVIIa are needed. In summary it can be concluded that rFVIIa administration
can be helpful in the treatment of patients with life-threatening bleeding after lung transplantation.

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CONFLICT OF INTEREST

The authors certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in this manuscript (e.g., employment, consultancies, board membership, stock ownership, honoraria).

REFERENCES


