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Successful use of activated recombinant factor VII in life-threatening bleeding after thoracic surgery

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Summary

We present three patients in whom life-threatening haemorrhage following lung resection was successfully managed using activated recombinant factor VII (NovoSeven®).

In one case, activated recombinant factor VII was the only therapy administered to manage bleeding, and in the two remaining cases, activated recombinant factor VII was administered after patients failed to respond to conventional therapy. All patients demonstrated effective haemostasis and improved coagulation parameters as a result of treatment with activated recombinant factor VII.

Our experience with the clinical use of rFVIIa suggests that this agent may provide effective hemostasis following lifethreatening postoperative bleeding after major thoracic surgery. Despite these favorable results, randomized, placebo – controlled trials are needed to identify optimal treatment strategy, patient selection, and safety of treatment in patients with massive bleeding following major thoracic surgery.

Key words: haemorrhage; recombinant factor VII; NovoSeven; lung resection

Introduction

Thoracic surgery belongs to the category of major surgical procedures associated with a high risk of massive, life-threatening postoperative haemorrhage. Postoperative bleeding complicates approximately 3% of thoracotomies, and the rate of mortality in such patients is approx. 23% [1]. The most common causes of profuse postoperative haemorrhage in thoracic surgery include slippage of ligatures from major pulmonary arteries and veins, diffuse bleeding from large, vulnerable surfaces and systemic arterial haemorrhage from bronchial and intercostal arteries.

Patients who undergo surgery to remove thoracic malignancies often present with different comorbidities [2]. The underlying malignancy places these patients in the high-risk group for development of thromboembolic complications, necessitating perioperative thromboembolic prophylaxis [3]. The situation may be complicated further by the use of anticoagulant medication or drugs that reduce platelet aggregation (e.g. aspirin) to treat such underlying comorbidities as myocardial infarction, ischaemic heart disease, arrhythmia, diabetes mellitus, or COPD.

As a result, the control of massive postoperative bleeding in thoracic surgery patients is a highly complex procedure.

Recombinant activated factor VII (rFVIIa; NovoSeven®, NovoNordisk, Bagsværd, Denmark) was originally developed for the treatment of patients with haemophilia A or B with inhibitory antibodies against factor VIII or factor IX. It has recently been approved in Europe for the treatment of haemorrhage in FVII deficiency and Glanzmann's thrombasthenia. Thus far rFVIIa has has shown itself highly efficacious with a favourable safety profile across a variety of indications and a wide range of doses [4, 5].

The efficacy and safety of off-label use of rFVIIa in securing haemostasis after surgery [6–8] has been demonstrated in only a few prospective randomised trials.

A recent report in the literature suggests that postoperative bleeding following cardiac surgery

may be successfully managed by the use of recombinant factor VIIa [9]. To the best of our knowledge there are no data in the literature on the use of recombinant FVIIa for bleeding control after major thoracic surgery.

We report favourable results obtained with rFVIIa for the management of massive postoperative haemorrhage in three patients undergoing major thoracic surgery.

Case reports

Patient 1

A 71-year-old male Jehovah's Witness with a history of diabetes mellitus, hypertension, myocardial infarction and pulmonary embolism underwent right upper lobectomy for planocelullar lung cancer (stage IIB; T2N1M0). Discontinuation of warfarin on admission resulted in normalisation of the PT and INR after 4 days.

3500 IU of reviparin was administered 12 hours before surgery in accordance with perioperative thromboembolic prophylaxis protocols.

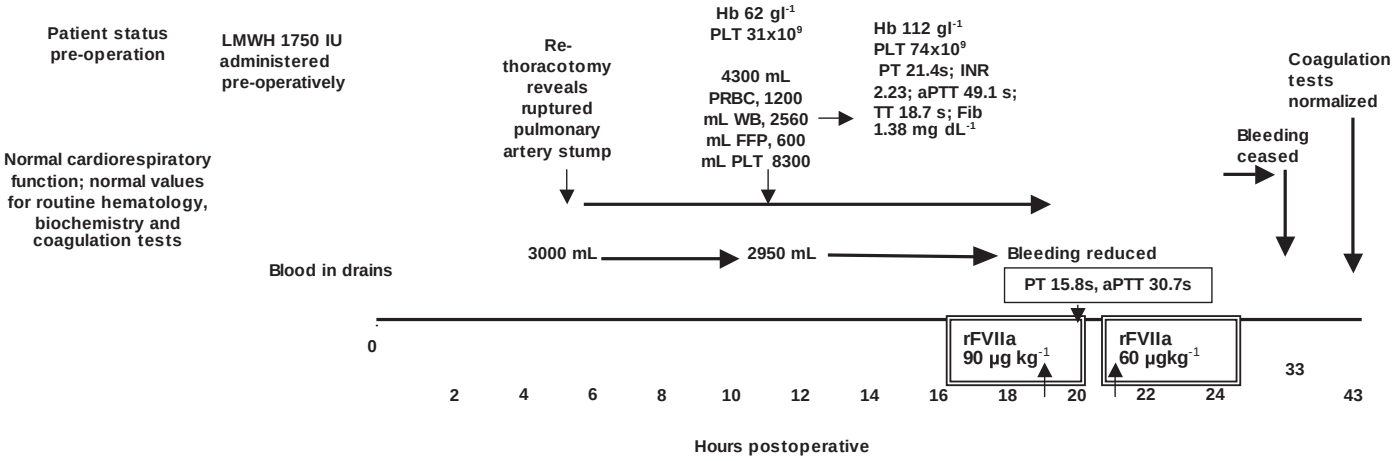

Figure 1

Case 2 – Course of treatment following admission.
aPTT, activated partial thromboplastin time; ATIII, antithrombin III; CP, coagulation parameters; CS, crystalloid solution; FFP, fresh frozen plasma; Fib, Fibrinogen; Hb, Haemoglobin; Htc, haematocrit; INR, international normalised ratio; LMWH, low-molecular weight heparin; PLT, platelet concentrates; PRBC, packed red blood cells; PT, prothrombin time; rFVIIa, recombinant factor VIIa; Time 0 = end of surgery; TT, thrombin time; vit K, vitamin K; WB, whole blood.

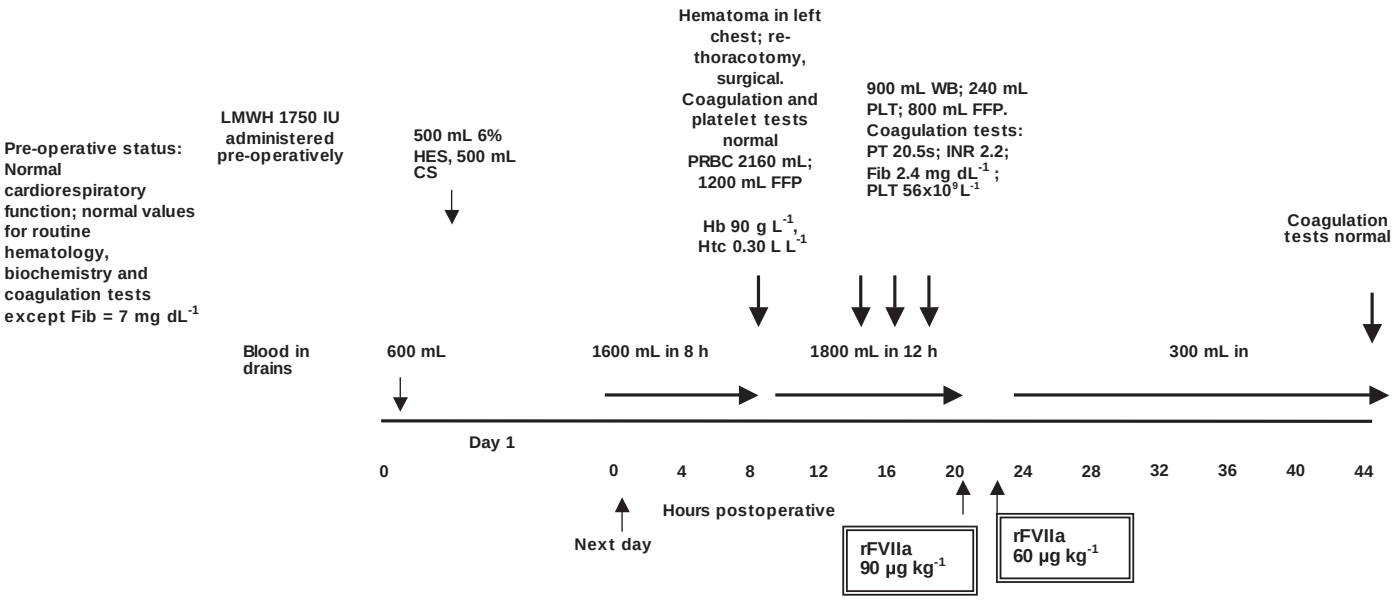

Figure 2

Case 3 – Course of treatment following admission.
CS, crystalloid solution; FFP, fresh frozen plasma; Fib, fibrinogen; Hb, haemoglobin; Htc, haematocrit; HES, hydroxyethyl starch; INR, international normalised ratio; LMWH, low-molecular weight heparin; PRBC, packed red blood cells; PLT, platelet concentrates; PT, prothrombin time; rFVIIa, recombinant factor VIIa; Time 0 = end of surgery; WB, whole blood.

Surgery was uneventful and haemostasis was good. Two hours after surgery excessive bleeding through the chest tube (500 mL over a 2-hour period) was observed. The patient's religious beliefs precluded the use of blood products. Accordingly, the patient received vitamin K, 1000 mL crystalloid solution, and 500 mL 6% HES. Coagulation parameters were all within normal ranges.

Despite the normal coagulation screen, a bolus dose of 90 μg kg^{-1} rFVIIa was administered, resulting in prompt cessation of bleeding.

The subsequent postoperative course was uneventful. Warfarin was reintroduced into the patient's therapeutic regimen upon full remobilisation. The patient was discharged from hospital two weeks after surgery.

Patient 2

Right lung resection was performed for adenocarcinoma (stage IIB; T3N0M0) in a 70-year-old male. Haematology, biochemistry and coagulation tests were normal at admission. Two hours prior to surgery the patient received 1750 IU of reviparin.

The patient suddenly developed haemorrhagic shock 5 hours after surgery, with massive blood loss of 3000 mL through the chest tube. Reexploration of the thorax showed a ruptured right pulmonary artery stump which underwent immediate surgical repair.

During the next 14 hours the patient lost a further 2950 mL of blood. Coagulation parameter values are shown in Figure 1. The patient received 4300 mL packed red blood cells (PRBC), 1200 mL whole blood, 2560 mL fresh frozen plasma (FFP), 600 mL platelet concentrate, and 8300 mL crystalloid solution. AT III and vitamin K were administered as bolus doses (fig. 1).

Due to continuous haemorrhage and haemodynamic instability, rFVIIa was administered as a bolus dose of 90 μg kg^{-1}. After one hour bleeding was reduced. After two hours the patient was given a second bolus dose of 60 μg kg^{-1} rFVIIa. Over the next 12 hours the haemorrhage ceased completely and the coagulation test normalised within 24 hours.

Patient 3

Left pneumonectomy was performed in a 50-year-old male for adenocarcinoma of the left upper lobe (stage IIB; T2N1M0). All laboratory tests were normal on admission. The patient received 1750 IU reviparin two hours before surgery. The perioperative course was uneventful. Next day massive bleeding through the chest tube occurred, involving a loss of 1600 mL blood over 8 hours. Reexploration of the thorax showed diffuse haemorrhage. Haemostasis was achieved surgically by clamping and ligation of small blood vessels and the haematoma was evacuated. The coagulation and platelet tests were all within normal limits.

Over the next 12 hours, 1800 mL of sanguineous content was drained despite transfusions of whole blood, platelet concentrate and FFP. Coagulation tests performed during the 12-hour period are shown in figure 2. The patient was given a single bolus dose of 90 μg kg^{-1} rFVIIa 12 hours after reexploration of the thorax, followed by a repeat bolus dose of 60 μg kg^{-1} rFVIIa 2 hours later (Fig. 2). Blood loss diminished considerably, to 300 mL of sanguinolent content over the next 24 hours, and coagulation parameters normalised. The subsequent postoperative course was unremarkable and the patient was discharged 17 days after surgery.

Discussion

The control of massive postoperative bleeding in thoracic surgery patients is a highly complex procedure. At our institution, the University Hospital for Lung Diseases 'Jordanovac' (teaching centre for Zagreb University Medical School), we conduct some 500 major thoracic operations per year, chiefly for lung cancer. Occurrence of massive, life-threatening postoperative bleeding, one of the leading causes of mortality, at our institution is less than 1%. We describe three patients with massive postoperative bleeding arrested by FVIIa. A bolus dose of 90 μg kg^{-1} rFVIIa was selected on the basis of the literature on the use of rFVIIa. In Patients 2 and 3 administration of FVIIA was repeated after two hours after initial administration in slightly reduced dose (60 μg kg^{-1}). The recommended dose is 90 μg kg^{-1}, but the optimal dose and dosing intervals of FVIIa have not been established.

In Patients 1 and 3 the most likely cause of massive, life-threatening postoperative haemorrhage was diffuse bleeding from small blood vessels over a large area of the lung, with subsequent fast-onset consumption coagulopathy. Rapid development of consumption coagulopathy is due to the attempted restoration of haemostasis through activation of the coagulation cascade and the binding of tissue factor (TF) to FVIIa over a broad area of vulnerable tissue surface. This resulted in activation of the fibrinolytic system. It is likely that in our patients the coagulation process induced by bleeding over the extensive area of surgical injury caused a clinical situation similar to disseminated intravascular coagulation.

In Patient 2 the massive perioperative bleeding was caused by rupture of the pulmonary artery.

In our patients bleeding was successfully arrested by rFVII. A clinical response to rFVIIa was observed in the first few hours after administration, and appropriate haemostasis was achieved without induction of hypercoagulability.

No thromboembolic or other adverse events were observed in our patients. Thus far, rFVIIa has shown itself highly efficacious with a favourable safety profile across a variety of indications and a wide range of doses, an observation possibly explicable by the agent's mode of action [10].

Several possible mechanisms of action for rFVIIa have been suggested in the literature. According to one mechanism, rFVIIa forms a complex with TF locally over the wide area of vessel injury. Formation of TF-rFVIIa complex generates activation of factor X, which results in conversion of prothrombin to thrombin. Recent theories suggest that rFVIIa may act by binding to activated platelets and thus improving thrombin formation

independently of tissue factor [10]. Such localisation of rFVIIa activity explains its haemostatic efficacy and ensures that systemic activation of coagulation – and the subsequent risk of thrombotic events – is reduced.

Our modest experience of clinical use of rFVIIa suggests that this agent may provide effective haemostasis following lifethreatening postoperative bleeding after major thoracic surgery. Despite these favourable results, randomised, placebo-controlled trials are needed to identify the best possible treatment strategy, patient selection, and treatment safety in patients with massive bleeding following major thoracic surgery.

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References

1 Benumof JL. Major hemorrage. In: Benumof JL. Anaesthesia for thoracic surgery. Philadelphia, USA: WB Saunders Company, 1995: 699–700.
2 Lopez-Encuentra A. Bronchogenic Carcinoma Co-operative Group. Comorbidity in operable lung cancer: a multicenter descriptive study on 2992 patients. Lung Cancer. 2002;35:263–4.
3 Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. Lancet. 1998;351:1077–80.
4 Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood. 2004;104:3858–64.
5 Levi M, Peters M, Buller HR. Efficacy and safety of recombinant factor VIIa for treatment of severe bleeding: a systematic review. Crit Care Med. 2005;33:883–90.
6 Friedrich PW, Henny C, Messelink EJ, Geerdink MG, Keller T, Kurth KH . Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. Lancet. 2003;361:201–5.
7 Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, et al. for the NovoSeven Trauma Study Group. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double blind clinical trials. J Trauma. 2005;59(1):8–18.
8 Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Recombinant Activated Factor VII Intracerebral Haemorrhage Trial Investigators. Recombinant activated factor VIIa for acute intracerebral haemorrhage. N Engl J Med. 2005;352(8):777–85.
9 Warren O, Mandal K, Hadjianastassiou V, Knowlton L, Panesar S, John K, Darzi A, Athanasiou T. Recombinant activated factor VII in cardiac surgery: a systematic review. Ann Thorac Surg. 2007;83:707–14.
10 Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood. 2004;104:3858–64.

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