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Associated Risk of Recombinant Activated Factor VIIa Application

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ABSTRACT

Background: The recombinant human coagulation FVIIa was approved for the treatment of bleeding in hemophilia patients. The reports of a good hemostatic effect were followed by studies and applications without a regulatory extension of the therapeutic indication (off-label use). The aim of this retrospective study is the evaluation of thromboembolic adverse events and side effects in a large cohort of patients with FVIIa therapy.

Methods: In the period from January 2009 to March 2011, a total of 143/2453 (5.8%) cardiac surgical patients (69% male; age 67 ± 11 years; 39% thoracic aorta) were treated with different doses (mean, 6.1 mg; range, 1 to 27.2 mg) of factor VIIa. The administration of FVIIa was seen as a last therapeutic option and administered at the end of the treatment algorithm for severe bleeding.

Results: Due to an acute bleeding situation in 143 patients, 7.9 ± 5.8 units of packed red blood cells, 9.5 ± 6.1units of fresh frozen plasma, 1740 ± 1860 IU PPSB (Prothrombin-Proconvertin-Stuart Factor-Antihemophilic Factor B), 5.6 ± 4 g fibrinogen, and 7.9 ± 7.6 units of platelets were administered. A re-thoracotomy was necessary, despite maximal procoagulant therapy, in 55% of patients. The in-hospital mortality was 36% (51/2453 = 2%). Thrombotic complications occurred with a frequency of 16% (mesenteric infarction, n = 9; stroke/transient ischemic attack, n = 3; myocardial infarction, n = 3; other, n = 8).

Conclusion: The proof of direct causality of the events in relation to the administration of FVIIa is difficult because the temporal and therapeutic relationships with concomitant vasoconstrictive and procoagulant therapies were not obvious. However, there remains a suspicion that a higher rate of mesenteric infarctions may be provoked by the administration of FVIIa.

INTRODUCTION

Excessive bleeding after cardiac surgical procedures is a serious complication that results in treatment cascades of allogenic blood transfusions, blood products, and surgical measures. Blood transfusions at the time of the operation are associated with a significantly reduced survival time [Engoren 2002; Koch 2006a; Koch 2006b; Murphy 2007]. The administration of 5 units of allogenic blood increases the risk of death by a factor of 8 [Murphy 2007]. Despite progress in methods and surgical techniques by which loss of blood is controlled during and after cardiac surgeries, perioperative blood transfusions are still required in up to 80% of adult patients. Three to five percent of these patients require more than 10 red blood cell (RBC) units [Diprose 2005]. Mediastinal re-explorations due to increased amounts of drainage occur in 3% to 10% of the cases [Woodman 1990; McGill 2002]. Postoperative, treatment-resistant bleeding is usually due to a number of factors. Both the preoperative administration of platelet aggregation inhibitors and various causes of clotting disorders due to the operation itself may be responsible, such as the residual heparin effect after cardiopulmonary bypass (CPB), hypothermia, hemodilution, thrombocytopenia, dilution coagulopathy, the use of clotting factors, hyperfibrinolysis, and activation of the inflammation cascade, as well as platelet activation, use, and dysfunction [Nuttall 2000; Keogh 2004].

One possible treatment that has been critically discussed for years is the administration of recombinant factor VIIa (rFVIIa) (NovoSeven®; Novo Nordisk, Bagsvaerd, Denmark). rFVIIa is produced by means of in-vitro transfection of the human FVII gene into hamster kidney cells [Jurlander 2001]. This leads to the secretion of inactive rFVII in the culture medium, where it is subject to a chromatographic purification and then proteolytically converted through autocatalysis into active rFVIIa. rFVIIa was originally developed and described in 1983 by Hedner and Kisiel for the treatment of 2 patients with hemophilia A [Hedner 1983]. The FDA licensed rFVIIa in 1999 for the treatment of bleeding in patients with hemophilia A or B with inhibitors against Factor VIII or IX. Already early on, there was talk among surgeons about the fact that the preparation can also stop severe bleeding in other patients.

One case report in the Lancet was particularly impressive [Kenet 1999]: Vascular surgeons in Israel reported how life-threatening bleeding could be stopped within a short time after the infusion of the drug. In the following years, off-label use increased greatly. In the United States, the drug is currently used in 96% percent of cases beyond the indication limits. Finally, approval was extended in 2005 (use in surgical procedures in hemophilia A and B patients with inhibitors, congenital Factor VII deficiency, and Glanzmann

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thromboasthenia) [O'Connell 2006]. What must be considered, however, is that the off-label use of all drugs is not free of uncertainties, because there are no data from approval studies on secondary indications. Adverse events in rFVIIa therapy were, however, recorded in the first 5 years after approval by the FDA. Thromboembolic complications, including severe myocardial infarction, cerebral infarctions, and pulmonary embolisms occurred in 90% of these reports. Moreover, 72% of the reported deaths were judged to be the result of these thromboembolic events, and in 52% of these events there was a chronological association [O'Connell 2006]. In fact, over the past few years, there have been more and more reports of myocardial infarctions or ischemic strokes, which have dampened the original enthusiasm of many surgeons.

Recently, a review in the *New England Journal of Medicine* [Levi 2010] documented an increased incidence of arterial thromboembolic events that appeared in 5.5% of patients (versus 3.2% in the placebo group; odds ratio 1.68; 95% confidence interval 1.20-2.36). Older patients were at particular risk: In those over 65 years of age, an arterial thromboembolic event occurred in 9.0% (versus 3.8%). In those over 75 years of age, the figure was even higher, at 10.8% (versus 4.1%). However, the manufacturer-sponsored study gave the impression that the risk-benefit ratio is, in the end, positive.

On the other hand, a meta-analysis in the *Annals of Internal Medicine* [Yank 2011] comes to the conclusion that the risks in various off-label uses can outweigh the benefits. Yank et al incorporated 16 randomized controlled studies, 26 comparative observational studies, and 22 non-comparative observational studies in their calculations and differentiated among the most frequent off-label uses. In cardiac surgery, according to Yank, there is no advantage with respect to mortality, but the rate of arterial thromboembolisms increases by 5 percentage points.

The use of rFVIIa in cardiac surgery remains a volatile and much-discussed subject. This explains our motivation to subject our own data to a retrospective analysis. Our endpoint, in addition to the recording of postoperative complications (safety), was the efficacy of rFVIIa in adult cardiac surgery patients.

MATERIALS AND METHODS

Sample

A retrospective data analysis was performed for quarters January 2008 to March 2010. The identification and search criterion within the clinical hospital information system was the OPS code 8-810.6 for the administration of genetically-produced clotting factors. In 143 of a total of 2,453 patients (5.8%), the administration of rFVIIa was confirmed from examination of the files. Only patients who underwent a cardiac operation at the Hospital of the Johann Wolfgang Goethe University were included. In addition to the demographic information, the database included all serious adverse effects (SAEs), mortality, use of blood and blood products, and the dosage of rFVIIa.

In-Hospital Coagulation Management

Before cardiac surgical procedures, it is essential to record a detailed bleeding history in order to determine primary hemostasis disorders. Prophylactic antifibrinolytic therapy should currently be carried out with tranexamic acid. In the case of persistent diffuse bleeding after the heparin antagonization and surgical hemostasis, PPSB (Prothrombin-Proconvertin-Stuart Factor-Antihemophilic Factor B) or possibly GFP (Gefrorenes Frischplasma) (Cave TRALI) are to be applied. In the event of a fibrinogen concentration below 1 g/L or clinical suspicion of fibrinogen deficiency or fibrin polymerization disorder in the event of continued bleeding, fibrinogen is substituted. For a platelet count under 80/nL or the suspicion of thrombopathy, platelet concentrates are to be administered. For primary hemostasis disorders within the scope of known kidney or liver insufficiency or long-term medication with ASA (asprin), the infusion of desmopressin may be helpful. The use of rFVIIa should be limited for treatment-resistant bleeding, despite adequate substrate substitution. For more targeted diagnosis and treatment of diffuse, non-surgical bleeding, the ROTEM® and Multiplate® analyses represent promising methods (Tem International GmbH, Munich, Germany).

Statistics

Continuous variables (e.g., age, ejection fraction) were calculated and presented as the mean ± standard deviation (SD) or median and range. Nominal data are presented as a percentage. Comparisons between groups for quantitative variables were performed by student t-test. Ordinal variables were not calculated. SPSS 20.0 (IBM, Chicago, IL, USA) was used for the data calculation.

RESULTS

Description of the Patient Cohort

Table 1 describes the preoperative characteristics of the patients studied. The patients, with an average age of

Table 1. Preoperative Demographics and Risk Profile

	n	%
Male	99 (143)	69
Diabetes	33 (143)	23
Dyslipidemia	54 (143)	38
Pulmonary hypertension	36 (143)	25
Hypertension	100 (143)	70
Atrial fibrillation	49 (143)	34
Smoker	30 (122)	24
	Mean ± Standard Deviation	Minimum–Maximum
Age, y	66 ± 11	29–90
Weight, kg	78 ± 15	50–130
Height, cm	172 ± 9	148–193
BMI	26 ± 3.7	17–38
Euroscore	7.6 ± 4.1	0–21

Table 2. Surgical Procedures

	n	%
Re-do	67	47
Combination procedure	77	54
Double valve procedure	29	20
Aortic surgery	55	39
CABG single	51	36

66 ± 11 years, were primarily male (69%) and exhibited a typical risk profile (EuroSCORE 7.6 ± 4.1). What differed were the types of operations performed (Table 2). The patients treated required more complex surgical treatments. With a ratio of 47% reoperations, 39% thoracic vessel surgery, and 54% combination procedures, it is clear that there is an indication for administration of rFVIIa in patients with more major and more complex procedures. A congenital clotting defect was present in 4 of 143 patients. In 2 patients with hemophilia, the indication for administration of rFVIIa was within the approval provisions. Up to the time of the operation, 28 of 143 patients had dual platelet inhibition.

Safety Endpoints

The patient outcome is described in Table 3. Mortality in the rFVIIa group was 36%. With respect to the overall cohort of 2,453 patients, the mortality is 2%. The most frequent cause of death was a septic event, cardiac low output syndrome, or multi-organ failure. The average hospital stay for all patients was 22 ± 27 days.

Thromboembolic complications over the course of the inpatient stay occurred in 16% of the patients who received rFVIIa therapy, but not directly intra-operatively. Adverse events (AE) are described after admission to the intensive care unit, and up to the tenth postoperative day. Thus no direct causal connection between administration of rFVIIa and AE can be directly proven. A re-thoracotomy was necessary in 55% of the patients during inpatient hospitalization, despite the maximized procoagulant therapy. The indication was a drainage quantity of > 200 mL/h for more than 2 hours.

Efficacy Endpoints

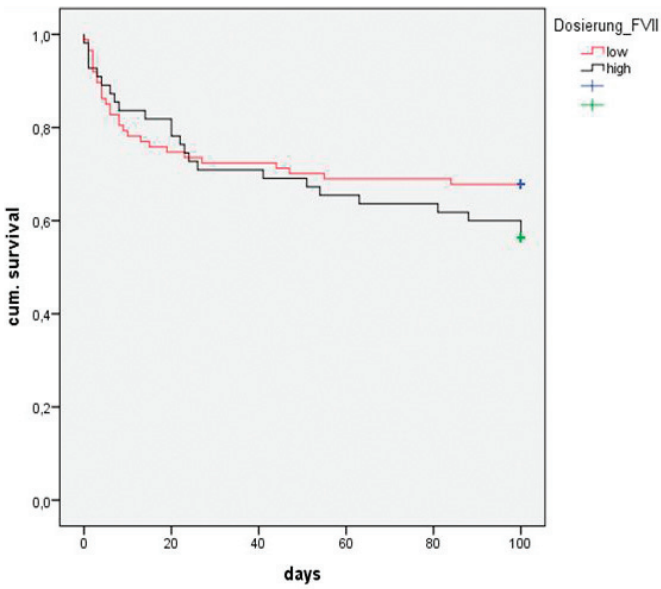
Patients received a total dose of between 1 and 27 mg rFVIIa (mean 6.1 ± 4.7 mg; 308 ± 235 KIU / 50 KIU = 1 mg rFVIIa). The application of rFVIIa in each case was performed after standard therapy was unsuccessful (RBC concentration, 7.9 ± 5.8 units; fresh frozen plasma, 9.5 ± 6.1 units; PBSP, 1740 ± 1860 IU; fibrinogen, 5.6 ± 4 g; thrombocytes, 7.9 ± 7.6 units). The majority of patients received a single dose of rFVII. However, in several patients, repeated application was documented.

According to the physician information, an initial dose of 90 µg/kg is recommended. For an average body weight of 78 ± 15 kg, a mean dose of 7 mg is to be expected. From this, one can infer that the patients were undertreated by an average of 1 mg.

Statistics calculated for various rFVII dosages (low, < 6 g / high > 6 g) showed no significant differences in the incidence of SAEs and mortality (Figure 1).

Table 3. Postoperative Complications and Serious Adverse Events (SAE)

	n	%
Renal replacement therapy	53 (125)	37
CPR	24 (143)	19
Mortality	52 (143)	36
Septic shock	19 (52)	36
Multi-organ failure	12 (52)	23
Low output syndrome	14 (52)	27
Hemorrhagic shock	4 (52)	8
Thrombotic SAE	23 (143)	16
Mesenterial infarction	9 (23)	39
Cerebral infarction	3 (23)	13
Myocardial infarction	3 (23)	13
Other	8 (23)	35
Re-thoracotomy	82 (143)	55
	Mean ± Standard Deviation	Minimum–Maximum
Length of hospital stay, d	22 ± 27	0–142



Kaplan-Meyer survival curve for patients with a high or low dose of rFVIIa (> 6 mg or < –6 mg).

DISCUSSION

Under the assumption that all the thromboembolic events described in the results are connected to the administration of rFVIIa, this would indicate a very high incidence, as compared to that cited in the literature to date. After more than 170,000 administered standard doses of rFVIIa (hemophilia patients with inhibitors), thromboembolic events were described in fewer than 1:11.300 cases [Hay 1997]. In a systematic review of the rFVIIa applications in non-hemophiliacs with bleeding complications published up to 2005, Levi

et al estimate an incidence of 1.4% for thromboembolic side effects [Levi 2010]. For administration of rFVIIa to healthy subjects—with unimpaired thrombogenesis—no serious side effects could be proven [Friedrich 2001]. One of the reasons for the postulated safety of rFVIIa is the hypothesis that the hemostatic effect remains limited by the locally-expressed tissue factor (TF) and the local activation of platelets to the site of the injury to the vessel [Hoffman 2001]. The FDA listing of all serious rFVIIa side effects over 5.5 years showed 185 thromboembolic events; among them 39 cerebrovascular complications, 34 myocardial infarctions, 26 arterial and 42 venous thromboses, and 32 pulmonary embolisms [O'Connell 2006]. No calculation of incidence was possible within this framework. In 36 patients, the thromboembolic event was the probable cause of death. The authors suspected a causal connection with the administration of rFVIIa in 75% of all cases reported. They confirmed a close chronological relationship between the application of the rFVIIa and the occurrence of the side effect. In the majority of the published cases with serious side effects, however, no direct chronological connection between the thromboembolic event and the administration of rFVIIa could be proven. For example, some patients with myocardial infarctions had predisposing risk factors, or the events occurred 7 to 14 or even up to 18 days after the administration of rFVIIa [Koch 2006b]. The question of the safety of haemostatic therapy is of particular significance in cardiac surgery. Coronary surgical patients, due to their underlying arteriosclerosis, are at risk for plaque rupture and thromboembolisms and for this reason were primarily excluded from several studies of the use of rFVIIa [Diprose 2005]. For this reason, Diprose et al also excluded patients with coronary surgical procedures. Goodnough et al found arteriosclerotic diseases to be contraindicated for the administration of rFVIIa [Goodnough 2004]. By means of the thrombin-generating effect of rFVIIa, the activation of the plasmatic and cellular components of hemostasis that, according to Dietrich et al, is comparable to a disseminated intravascular coagulation (DIC), was increased even more, possibly during the extracorporeal circulation [Dietrich 2002]. Furthermore, optimal anticoagulation for the prevention of increased clotting activation during extracorporeal circulation (ECC) is subject to therapeutic and methodical limitations. In the controlled cardiac surgery studies on the use of rFVIIa, Diprose et al detected no side effects, although they excluded coronary surgical patients [Diprose 2005]. Karkouti et al, in their first trial, were not able to differentiate whether the increased morbidity (renal insufficiency and length of hospital stay) of the rFVIIa group was associated with the greater blood loss or the administration of rFVIIa [Karkouti 2005]. In an expanded controlled study of 114 patients treated with rFVIIa, no differences in the rate of side effects as compared to the control group were found, but the rate of side effects increased with the later start of rFVIIa therapy. Potentially, there is also the risk of thromboembolic side effects with the simultaneous administration of rFVIIa and prothrombin complex concentrates through intensification of the thrombogenic effect [Levi 2010]. Commercial PPSB concentrate is standardized only with respect to the Factor IX content. Its thrombogenic potential can be caused by too-high prothrombin concentrations or the content of activated clotting factors, although for modern preparations, this is judged to only be a slight risk overall. In this analysis, all patients in the study group received PPSB, but PPSB and rFVIIa were not administered simultaneously. Bui et al reported on 1 patient with a fatal thrombosis on (extracorporeal membrane oxygenation (ECMO) therapy, who had received activated prothrombin complex 6 hours after 2 administrations of rFVIIa [Bui 2002]. Further statements on the direct comparison between thrombogenic side effects of rFVIIa and clotting factor concentrates are not possible in the absence of clinical studies.

CONCLUSION

The evaluation of this retrospective analysis is difficult and is limited by various factors. The efficacy of rFVIIa is difficult to describe in the absence of a control group. Since according to our algorithm, treatment with rFVIIa is the last remaining option in the therapy concept for a catastrophic bleeding situation after cardiac surgical procedures, there are few bases for comparison. With a re-thoracotomy rate of 55%, however, there are still doubts as to its efficacy. The high mortality rate in this patient cohort is most certainly an expression of the complexity of the procedures and the difficult postoperative care. The thromboembolic complications that occurred cannot be placed in a close chronological connection with the administration of rFVIIa and from a pathophysiological perspective, they can certainly also have other causes. The suspicion remains, however, that the administration of rFVIIa can give rise to an increased rate of thromboembolisms (mesenteric infarctions). The application should remain a therapy of last resort in patients with a hard-to-control bleeding situation.

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