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The effects of recombinant activated factor VII dose on the incidence of thromboembolic events in patients with coagulopathic bleeding☆,☆☆

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ABSTRACT

Introduction: Previous studies have suggested the used of off-label recombinant factor VII (rFVIIa) increases the risk of thromboembolic events, but the effect of the dose of rFVIIa is not well described in the literature.
Materials and Methods: All adult patients that received off-label rFVIIa from 2005-2012 were included in this single-center, retrospective cohort study. The primary endpoint was the incidence of a thromboembolic event in the low dose (<50 mcg/kg) compared to the high dose (≥50 mcg/kg) cohort. Secondary endpoints compared time to thromboembolic event, incidence of arterial compared to venous events, and mortality.
Results: There were 152 patients that received rFVIIa during the study period with 66 in the low dose cohort and 86 in the high dose cohort. Mean total dose of rFVIIa was 30.2 mcg/kg (SD ± 9.5 mcg/kg) in the low dose and 99.8 mcg/kg (SD ± 64.7 mcg/kg) in the high dose cohort ($p = 0.0001$). The overall incidence of thromboembolic events was 12.5%. There were 12 (14%) events in the low dose cohort and seven (10.6%) in the high dose cohort, RR = 0.76 (95% CI 0.31-1.82). There were no differences in any of the secondary outcomes. A higher incidence of thromboembolic events in cardiothoracic surgery (20.8%) and penetrating trauma patients (21.4%) was seen compared to the remaining cohort (6.7%).
Conclusions: No significant difference in the incidence of thromboembolic events was seen between low dose versus high dose rFVIIa over a seven year period at our institution. However, due to the relatively low overall incidence and a small sample size, type II error may be present.

Introduction

Coagulopathy occurs in patients with a significant hemorrhage where clotting factors are consumed rapidly. When this occurs, bleeding can be more severe and prolonged. Several surgical services including trauma, transplant, cardiothoracic, and vascular surgery perform complex cases with significant blood loss both during surgery and in the postoperative period. Preventing or controlling coagulopathic bleeding is often performed with massive blood product transfusions and additional surgical intervention if required for hemorrhage control. Transfusion strategies are controversial and may vary between institutions [1]. Control of coagulopathic bleeding is time sensitive and concentrated factor products such as recombinant activated factor VII (rFVIIa) have been used off-label for this indication among these surgical services since its approval in 1999. Recombinant activated factor VII is currently approved in the United States for the prevention and treatment of bleeding in hemophilia A or B with inhibitors, congenital factor VII deficiency, and acquired hemophilia [2]. Over the past 10 years, additional research has been focused on the potential use of rFVIIa to manage uncontrolled coagulopathic bleeding and reduce transfusion requirements in patients with hemorrhage.

Due to increased usage of off-label rFVIIa, increasing safety concerns, high acquisition cost, and new literature suggesting efficacy with lower doses, a rFVIIa guideline for coagulopathic bleeding was approved within our institution in 2008. Prior to the implementation of the guideline, physicians were using rFVIIa without criteria for use or off-label dose guidance. The package insert dose of 90 mcg/kg was often used and many patients died shortly after administration of rFVIIa. The guideline also emphasized a lower dose of 20-45 mcg/kg, which had been shown

Abbreviations: rFVIIa, recombinant activated factor VII; VTE, venous thromboembolism; PE, pulmonary embolism; MI, myocardial infarction; CNS, central nervous system.

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to be effective in reversing INR in patients with warfarin-induced intracranial hemorrhage [3,4]. The new guideline also emphasized inclusion and exclusion criteria that selected patients that were most likely to benefit from rFVIIa and excluded patients that were likely to expire within a few hours.

There are two proposed mechanisms of action for rFVIIa effects in coagulopathic bleeding. The first is that rFVIIa binds to exposed tissue factor and activates coagulation factors IX and X resulting in thrombin production. The other is that rFVIIa binds directly to factor Xa on the activated platelet surface, and subsequently causes a thrombin burst at the site of injury, which results in local hemostasis. Although it is proposed that the action of rFVIIa is at the site of injury, there is still concern for systemic clot formation. Based on these proposed mechanisms of action, one would expect rFVIIa to increase the risk of thromboembolic events such as venous thromboembolism (VTE), pulmonary embolism (PE), peripheral arterial thromboembolism, ischemic stroke, or ischemic cardiovascular events such as myocardial ischemia or infarction (MI). Thromboembolism has been seen in clinical practice, and there have been retrospective cohort studies [5,6] as well as a meta-analysis [7] conducted evaluating the incidence of these events.

This single-center, retrospective cohort study was an evaluation of thromboembolic events throughout a seven year period, both before and after implementation of the institutional guideline, which provided a high dose and low dose cohort for comparison. The purpose of our study was to determine if the dose of rFVIIa administered in patients with uncontrolled coagulopathic bleeding affected the incidence of thromboembolic events.

Materials and Methods

This was a retrospective cohort study evaluating patients treated at a large academic medical center from 2005-2012. Patients were included in the study if they were 18 years or older and received off-label rFVIIa for coagulopathic bleeding during the study period. No patients were excluded from the study. Potentially eligible patients were captured from a quality assurance database containing all patients treated with off-label rFVIIa. Patients are captured for this database from daily billing reports for high cost medications and a pharmacist verifies the administration of all doses through the electronic medication administration record. This database includes patient demographics, blood products administered prior to rFVIIa administration, arterial lactate and pH, platelet count, fibrinogen level, and detailed information regarding the dose of rFVIIa and the time administered. Medical record numbers and admission dates from the database were cross-referenced with ICD-9 codes to identify patients who had a thromboembolic event anytime during the admission when rFVIIa was administered. Subjects were categorized into one of two cohorts based on the total cumulative dose of rFVIIa that was administered within 24 hours. The high dose cohort received a cumulative dose of 50 mcg/kg or more, and the low dose cohort received less than 50 mcg/kg. The 50 mcg/kg dose was chosen *a priori* as a separation point because the institutional guideline recommended doses of 20-45 mcg/kg, as this lower dose has been shown to effective in reversing INR in warfarin-induced hemorrhage [3,4]. We also wanted to allow room for rounding to the nearest vial size, as that is our institutional practice. Baseline characteristics collected from the two groups included age, sex, indication for rFVIIa, dose of rFVIIa, number of doses, arterial lactate, and arterial pH.

The primary outcome was the incidence of a thromboembolic event prior to discharge from hospital after receiving rFVIIa. A thromboembolic event was defined as a composite of venous thromboembolism (deep vein thrombosis, pulmonary embolism), thromboembolic stroke, myocardial ischemia or infarction, mesenteric infarction, or peripheral arterial thromboembolism. Secondary endpoints were type of thromboembolic event, time to thromboembolic event, early (≤72 hours after first dose) or late (>72 hours after first dose) thromboembolic event, thromboembolic event by indication, and mortality. These data were collected based on documentation in the medical record or quality assurance database.

Relative risk was calculated for the primary endpoint with 95% confidence intervals. For the baseline characteristics and secondary outcomes, Chi-Squared analysis or Fisher's exact tests were used for nominal data and Mann Whitney U analysis or Student's t-test were used for ordinal or continuous data as appropriate. All tests were two sided, and an alpha level of <0.05 was considered significant. This study was approved by the University of Rochester Medical Center Institutional Review Board.

Table 1
Baseline Characteristics.

Baseline Characteristics	Low Dose (n = 86)	High Dose (n = 66)	p-value
Age, years, median (IQR)	59 (42.25-67.75)	55 (45.3-66.5)	0.48[a]
Male Sex, n (%)	55 (63.9)	40 (60.6)	0.74[b]
Lactate, mg/dL, mean (SD)	6.5 (5)	9.2 (7.7)	0.046[c]
pH, mean (SD)	7.33 (0.13)	7.31 (0.10)	0.27[c]
Location of Administration			
Operating Room, n (%)	57 (66.3)	33 (50)	0.048[b]
Intensive Care Unit, n (%)	23 (26.7)	16 (24.2)	0.85[b]
Emergency Department, n (%)	1 (1.2)	0 (0)	1[b]
Unknown, n (%)	5 (5.8)	17 (25.8)	0.0008[b]
Indication for rFVIIa			
Cardiothoracic surgery, n (%)	30 (34.9)	18 (27.3)	0.38[b]
Blunt trauma, n (%)	13 (15.1)	9 (13.6)	0.82[b]
Penetrating trauma, n (%)	11 (12.8)	3 (4.5)	0.1[b]
Transplant, n (%)	13 (15.1)	18 (27.3)	0.07[b]
Neurosurgery, n (%)	5 (5.8)	4 (6.1)	1[b]
Vascular surgery, n (%)	12 (14)	11 (16.7)	0.66[b]
Medical, n (%)	2 (2.3)	3 (4.5)	0.65[b]
Units of Blood Products Prior to rFVIIa			
PRBC, median (IQR)	16 (7-28)	15.5 (7.8-24)	0.56[a]
FFP, median (IQR)	12 (6-20)	12 (6-19)	0.65[a]
Platelets, median (IQR)	2 (1-3)	2.5 (2-4)	0.46[a]
Cryoprecipitate, median (IQR)	1 (1-2)	1 (0-2)	0.45[a]

PRBC = packed red blood cells.
FFP = fresh frozen plasma.
a = Mann Whitney U Test.
b = Fisher's Exact Test.
c = Student's Paired T-Test.

Results

A total of 152 patients received rFVIIa from 2005-2012, and all were included in the study. Eighty-six patients received a dose of less than 50 mcg/kg and 66 patients received a dose of 50 mcg/kg or more. The only difference in baseline characteristics between the two groups was lactate levels prior to administration of rFVIIa and location of administration. (Table 1) There were more cardiothoracic surgery patients in the low dose group and more transplant patients in the high dose group, but neither of these were statistically significant.

A total of 207 doses were given to 152 patients with 101 doses given in the low dose group and 106 doses in the high dose group. Mean total dose of rFVIIa 30.2 mcg/kg (±9.5 mcg/kg) in the low dose and 99.8 mcg/kg (±64.7 mcg/kg) in the high dose cohort ($p = 0.0001$). The median number of doses was one for both groups, however, there was a wider range of number of doses in the high dose group (1-10 vs. 1-2; $p = 0.013$), which was statistically significant.

The overall incidence of thromboembolic events was 12.5%. There were 12 (14%) thromboembolic events in the low dose group and 7 (10.6%) in the high dose group, RR = 0.76 (95% CI 0.31-1.82). There was also no difference in the secondary outcomes of type of thromboembolic event, time to thromboembolic event, or mortality. (Table 2)