Recombinant Activated Factor VII as a Temporary Reversal Agent for Warfarin Anticoagulation: A Cautionary Report on an Off-Label Application

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Therapy with warfarin, a vitamin K antagonist, poses increased risks for bleeding during major orthopedic surgical procedures. Normalization of the prothrombin time after cessation of warfarin treatment is often delayed by several days.[1] Pharmacologic reversal with vitamin K or infusion of plasma products may be indicated in specific clinical situations. Although these treatments are effective, there are wide variations in doses, volumes, and rates of reversal, as well as potential complications such as anaphylaxis, fluid overload, transmission of infective agents, and thromboembolism.[2-4]

Recombinant activated factor VII (rFVIIa) is a genetically engineered coagulation protein that was approved by the US Food and Drug Administration (FDA) in 1999 for the treatment of bleeding in patients with hemophilia and antibodies against coagulation factor replacements. This medication was subsequently licensed for 2 additional indications: (1) bleeding prophylaxis for surgical procedures in patients with hemophilia and factor inhibitors and (2) control of bleeding in patients with congenital factor VII deficiency. Off-label administration rFVIIa has been reported as a potential novel means of rapidly and temporarily reversing the anticoagulation effects of warfarin.[3,5-8]

In this case report, we describe a patient on chronic warfarin therapy, considered at high risk for pulmonary emboli with cessation of warfarin anticoagulation, who was given rFVIIa to address the potential for excess bleeding during rotator cuff repair surgery. We also review other reported off-label applications of rFVIIa, the risks for thrombosis, and the need for further study.

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Case Report

A right-hand–dominant woman in her mid-40s presented with a 3-month history of pain in the right shoulder. Clinical examination findings were suggestive of rotator cuff pathology, with shoulder radiographs revealing mild degenerative arthritis localized to the acromioclavicular joint. The patient participated in a 6-week course of physical therapy and then in a home therapy program, but her condition improved only marginally. Magnetic resonance imaging of the shoulder then showed a full-thickness tear of the supraspinatus tendon.

The patient elected to have surgery to address the rotator cuff defect. She had been receiving long-term warfarin therapy for management of recurrent pulmonary emboli. A complete thrombophilia assessment, conducted 3 years earlier, revealed an elevated lipoprotein (a) level. Past medical history was otherwise notable for bilateral iliac vein narrowing, prominent lower extremity varicosities, recurring superficial thrombophlebitis in both legs, and uterine fibroid tumors.

The patient's treating hematologist recommended continuation of warfarin perioperatively with temporary reversal of the anticoagulation effects using rFVIIa (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark). The patient was considered at high risk for recurrent pulmonary emboli with cessation of warfarin anticoagulation. The hematologist reviewed the benefits and cost of rFVIIa use, and the patient agreed to proceed with treatment. The decision to administer rFVIIa was made before new information on potential thrombotic complications of this drug became available and before the hospital Pharmacy and Therapeutics Committee proposed specific guidelines.

Recombinant FVIIa was administered as an intravenous bolus at a dose of 40 µg/kg (3.6 mg) in the anesthesia preparation area 30 minutes before surgery. Before medication administration, international normalized ratio (INR) was 2.7 (normal range, 0.9-1.1), prothrombin time was 29.0 seconds (normal range, 12.3-14.3 seconds), and activated partial thromboplastin time was 41.1 seconds (normal range, 25.0-35.0 seconds). The operation, which proceeded uneventfully under general anesthesia, involved arthroscopic acromioplasty and mini-open rotator cuff repair. No excessive bleeding was encountered during surgery, and estimated blood loss was between 50 and 100 mL.

The patient was admitted to the hospital overnight for observation and released home the next morning. Sequential compression devices were used perioperatively, and warfarin was continued uninterrupted at a dose of 15 mg before bedtime. Hemoglobin level decreased from 13.6 g/dL before surgery to 12.0 g/dL the morning of discharge. Repeat measurement of prothrombin time was deemed unnecessary owing to the absence of unusual bleeding. In addition, the patient's hematologist was confident in the response to rFVIIa, as previously the patient had received the medication for a dental extraction procedure and had had no complications (at that time, INR had decreased from 2.9 to 1.2 within 10 minutes of administration of rFVIIa at a dose of 30 μg/kg). At routine measurement 2 days after the rotator cuff repair surgery, INR was 3.3, and prothrombin time was 43.1 seconds.

An arm sling was prescribed for postoperative comfort and support. Over 6 weeks, outpatient physical therapy progressed from passive to active shoulder motion, with no difficulties. Surgical wounds healed uneventfully, and there were no thrombotic complications. At latest follow-up (18 months after surgery), the patient reported no residual shoulder pain. Active shoulder forward flexion was 170°, and active shoulder external rotation with the arm adducted to the side was 65°. The patient was able to reach upward behind her back to the eighth thoracic vertebra. Strength with manual muscle testing was normal for all muscles around the right shoulder girdle.

Discussion

Reported use of rFVIIa in orthopedic surgery has been primarily limited to FDA-licensed applications: control of bleeding in patients with hemophilia and factor inhibitors and congenital factor VII deficiency.[9-17] To our knowledge at the time of writing, the English-language literature includes only 1 case report of administering rFVIIa in orthopedic surgery to temporarily reverse the anticoagulation effects of warfarin: A 57-year-old woman with a history of renal failure and atrial fibrillation received 1 dose of rFVIIa off-label in preparation for surgical repair of a femoral neck fracture.[5] Numerous authors in other medical and surgical specialties have described unlabeled use of rFVIIa for the treatment of hemorrhages related to warfarin anticoagulation, thrombocytopenia, liver disease, child birth, intestinal disease, and trauma, for the treatment of spontaneous intracerebral bleeding, and for the control of bleeding during prostatectomy, liver transplantation, neurosurgical procedures, spine surgery, and open heart surgery.[3-9,18-28]

Recombinant FVIIa stimulates both tissue-factor-dependent and -independent pathways of coagulation, leading to an increase in thrombin generation on the surface of activated platelets.[5,29-31] The precise mechanism of action for reversal of warfarin anticoagulation has not been clarified. Although factor VII is replenished to a superphysiologic level and INR is reduced after medication administration, INR normalization does not automatically portend a prohemostatic response.[3] Nevertheless, cessation of warfarin-induced bleeding with rFVIIa administration has been demonstrated in an animal model and has been well documented clinically.[5,7,18-22,32]

The anticoagulation effects of warfarin are reestablished within hours after rFVIIa administration in a dose–time dependent fashion.[33] In a study of volunteers who received acenocoumarol to maintain INR above 2.0, 5 μg/kg of rFVIIa maintained INR at or below 1.0 for 2 to 4 hours, while doses of 80 to 320 μg/kg normalized INR for more than 6 hours.[34] Although continued warfarin dosing after rFVIIa administration can have an unfavorable effect on bleeding,[32] the clinical significance with intended restoration of anticoagulation is unclear.

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The enhancing effects of rFVIIa in hemostasis are thought to be localized to sites of vessel injury.[4,6,9,29-31,35-37] However, rFVIIa injection has potential thromboembolic complications, and, unfortunately, the degree of risk for pathologic clot formation is unknown.[3,19,28,30,31,34,38-49] Between March 25, 1999, and December 31, 2004, the FDA received 168 reports of 185 thrombotic adverse events (cerebral vascular accident, myocardial infarction, other arterial thromboses, pulmonary embolism, deep vein thrombosis, clotted devices).[45] Most of the events occurred after use of rFVIIa for unlabeled indications, and many resulted in serious morbidity and mortality. A recent meta-analysis of 17 rFVIIa clinical trials in nonhemophilic patients found a 4.4% incidence of significant thrombosis in medication recipients and a 3.7% incidence of significant thrombosis in control patients who received placebo.[39]

Clinical situations in which rFVIIa therapy is potentially unsafe include pregnancy, breast-feeding, prolonged immobilization, advanced age, obesity, cancer, disseminated intravascular coagulation, diabetes, hypertension, crush injury, sepsis, previous cerebrovascular accident, use of coagulation factor concentrates or other hemostatic agents, atherosclerotic disease, and organ failure.[3,29,31,39-49] Many of the patients in these situations are at increased risk for a thrombotic event because of circulating tissue factor or a predisposing coagulopathy. Recombinant FVIIa is contraindicated in patients with known hypersensitivities to mouse, hamster, or bovine proteins, as trace amounts of these substances are present from the manufacturing and purification processes.

In the future, in very select orthopedic patients who receive warfarin therapy, rFVIIa may prove useful as an alternative or adjunct to warfarin cessation, vitamin K, and plasma product infusion in normalizing prothrombin times. However, further research is needed to develop an effective monitoring assay for rFVIIa-induced hemostasis and an appropriate medication antidote. In addition, studies are needed to determine the precise mechanism of action, the ideal dosing regimen, the appropriate patient selection criteria, the cumulative and comparative costs (eg, comparison to bridge therapy with low-molecular-weight heparin), and the ultimate safety of rFVIIa as a temporary reversal agent for warfarin anticoagulation. We strongly advise against generalized off-label use of rFVIIa for moderating warfarin anticoagulation pending thorough supportive research and requisite FDA approval.

Authors' Disclosure Statement

Dr. Kalainov reports no actual or potential conflict of interest in relation to this article. Dr. Valentino wishes to note that he is a speaker and Advisory Board member for Novo Nordisk and has received an Investigation Research Grant from Novo Nordisk.

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