Total Knee Arthroplasty Using Recombinant Factor VII in Hemophilia-A Patients with Inhibitors

A Report of Three Cases

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Elective orthopaedic surgery, including total joint arthroplasty, has become a safe and effective therapeutic option for most patients with hemophilic arthropathy and has been reported to reduce the rate of hemarthrosis and the clinical consequence of severe joint damage[1]. However, the 10% to 30% of patients with severe hemophilia who have development of neutralizing antibodies (inhibitors) to factor VIII (FVIII) or factor IX (FIX) do not fare as well[2]. The development of an inhibitor is one of the most serious complications associated with hemophilia because inhibitors may neutralize clotting factor concentrates. Patients with inhibitors often have substantially worse joint function secondary to inadequate treatment and traditionally have not been candidates for elective joint replacement surgery[3]. The orthopaedic literature regarding total knee arthroplasty in patients with hemophilia is limited, with little emphasis on patients with inhibitors[4-9]. Previous studies of total knee arthroplasty in patients with inhibitors, involving a variety of treatment regimens (including immune therapy, Factor VIIa, and Factor VIII), have been reported in the literature, but the duration of clinical follow-up has been limited and no consensus has been reached with regard to the appropriate dosing regimen[2,10-13]. Recombinant Factor VIIa has a short half-life but a high bioavailability when administered intravenously, and therefore the clinical impact has been difficult to predict in patients undergoing elective surgery[14,15]. In the present report, we describe three successful total knee arthroplasties that were performed with use of recombinant human factor VIIa (rFVIIa) in two patients who had different inhibitor characteristics and who were followed for more than two years.

Case Reports

Case 1. A forty-year-old man presented in 2000 with bilateral knee pain. He was born with severe Factor VIII deficiency and had development of a high-titer inhibitor to FVIII during childhood. Preoperatively, he had continuous moderate to severe bilateral knee pain and recurrent hemarthroses in both knees. He was essentially able to walk only in the home and used crutches to climb stairs. Physical examination demonstrated an anatomic axis of 11° of valgus of the right knee and 5° of varus of the left knee. The right knee had a range of motion of 5° to 80°, and the left knee had a 25° flexion contracture with flexion to 35°. The right knee had a 60° extensor lag. Radiographs demonstrated complete loss of joint space with bone loss in both knees. The preoperative Knee Society knee and function scores were 41 and 33 (of 100) points, respectively, for the right knee and 37 and 29 points, respectively, for the left knee.

A left total knee arthroplasty was performed through a standard medial parapatellar arthrotomy under tourniquet control. Before the incision, the patient was given a dose of rFVIIa (approximately 90 μg/kg). A synovectomy was performed. The tourniquet was released after cementing of the components and before closure. A second dose of rFVIIa (approximately 90 μg/kg) was given just before tourniquet release. Hemostasis was obtained before wound closure, and the measured intraoperative blood loss was <100 mL. An intra-articular drain was placed. rFVIIa was administered on the basis of protocols established at our institution. Physical therapy and continuous passive motion from 0° to 30° were gradually introduced beginning on the first postoperative day.

Eleven months after the left total knee arthroplasty, the patient underwent a right total knee arthroplasty. The measured intraoperative blood loss was <200 mL. An intra-articular drain was placed. In the first twenty-four hours postoperatively, there was evidence of bleeding as the drain output approached 250 mL over twenty-four hours, without notable tapering (90 mL over the previous eight-hour period). The dosage of rFVIIa was increased to approximately 120 μg/kg (9.6 mg) every two hours (compared with approximately 90 μg/kg every two hours during the previous operation). This resulted in good hemostasis as demonstrated by physical ex-

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amination and stabilization of the hemoglobin level. The drain was discontinued, and there were no further episodes of drainage. Physical therapy with limited weight-bearing was gradually introduced, but continuous passive motion was not started until the wound had stabilized. At thirty-five months of follow-up for the left knee, the range of motion was from 2° to 85°, there had been no further episodes of hemarthrosis, and the Knee Society knee and function scores were 88 and 70 points, respectively. At twenty-four months of follow-up for the right knee, there was no pain, the range of motion was from 5° to 85°, and the Knee Society knee and function scores were 82 and 70 points, respectively. At the time of the most recent follow-up, the patient no longer used the crutches and only occasionally used the cane to assist with walking.

CASE 2. A forty-four-year-old man with severe hemophilia presented in 2000 with bilateral knee pain. At the time of presentation, he had severe hemophilic arthropathy affecting multiple joints, most severely both knees. After the initiation of treatment in 1993, a high-titer FVIII inhibitor developed.

In 1994, the patient underwent a left total knee arthroplasty at an outside institution without the use of rFVIIa, which at the time had not been approved by the United States Food and Drug Administration. Postoperatively, a compartment syndrome developed in the left leg. The patient was managed with rFVIIa, which was available on a compassionate-use basis, and underwent a two-incision fasciotomy. He was left with a partial motor and sensory deficit, including a foot drop. At the time of evaluation at our institution, he had almost complete resolution of the foot drop but had a mild sensory deficit over the dorsum of the left foot. The patient reported a ten-year history of moderate continuous pain in the right knee, the need for a cane, and an inability to walk more than one-half block. Physical examination of the right knee showed quadriceps atrophy, neutral alignment, and a range of motion from a 10° flexion contracture to 70° of flexion. Preoperatively, the Knee Society knee and function scores for the right knee were 44 and 40 points, respectively. Despite the neurologic deficit involving the left leg, he preferred to use the left leg over the right.

We performed a right total knee arthroplasty through a medial parapatellar approach under tourniquet control. Prior to the incision, the patient was given a dose of rFVIIa (approximately 90 μg/kg). Following implantation of the prosthesis, rFVIIa was administered before tourniquet deflation. Hemostasis was obtained. The estimated blood loss was <100 mL, and an intra-articular drain was placed. Postoperatively, rFVIIa was administered on the basis of our institutional protocols. Physical therapy, including continuous passive motion, was initiated on the first postoperative day and gradually progressed. At two years postoperatively, the right knee had excellent stability, an absence of pain, a range of motion from 5° to 85° of flexion, and Knee Society knee and function scores of 84 and 80 points, respectively. The patient no longer used an assistive device to walk.

Discussion

Patients with hemophilia in whom inhibitors have developed pose a particularly challenging problem. They often have substantially worse joint function than do patients without inhibitors[16] because they have had more severe, uncontrolled bleeding episodes. Eradication of inhibitors with use of immune tolerance therapy is not always successful[11]. Prothrombin complex concentrates, the alternative to rFVIIa for the treatment of bleeding in patients with high-titer inhibitors, may produce disseminated intravascular coagulation, particularly if given frequently or at high doses. For this reason, they have not been used commonly to allow major elective surgical procedures[3].

Currently, rFVIIa is approved by the United States Food and Drug Administration for the treatment of bleeding in patients with hemophilia A or B and inhibitors. The initial recommended dose of 90 μg/kg is administered by bolus injection, with additional doses given at intervals of every two to three hours for severe bleeding. Whether this is the optimal dose or route of administration is unknown. rFVIIa has been shown to increase Factor VII-coagulant activity within ten minutes after administration of high doses (120 μg/kg)[15,17]. Factor VII-coagulant activity rapidly decreases and returns to baseline within twenty-four hours after a single intravenous administration of rFVIIa. Of note, the efficacy of rFVIIa has been shown to be greater when a bleeding episode is treated within three hours than it is when a bleeding episode is treated after longer intervals[15]. While our experience is not sufficient to support the routine use of a larger dose, following the second total knee arthroplasty in one of our patients (Case 1), the standard dose of rFVIIa did not lead to effective hemostasis, whereas a larger dose did. In light of the short half-life of rFVIIa, we believe that frequent dosing is important in order to maintain the coagulant activity level in both the serum as well as the bone. Compared with previous investigators who have used dosages of 400 to 800 μg/kg/day of rFVIIa in the perioperative period, we used an average dosage of 1050 μg/kg/day for one patient (Case 1) and of 1200 μg/kg/day for the other (Case 2)[2,7,10-12,18]. Emphasis was placed on the administration of higher doses earlier and more frequently in the preoperative and postoperative periods, including in the period before tourniquet deflation. Furthermore, early intervention with the administration of bolus doses of rFVIIa was initiated when bleeding was suspected.

The optimal rFVIIa protocol remains to be established. Our protocol typically involves the administration of rFVIIa at a dosage of approximately 90 μg/kg beginning just before surgery and continuing every two hours for the first seventy-two hours, followed by every three hours for an additional forty-eight hours, and then decreasing to every four hours for a total of fourteen days. Furthermore, we routinely administer one dose of rFVIIa (approximately 90 μg/kg) just before tourniquet deflation. Recently, we have used an increased dose (120 to 180 μg/kg) and an increased interval (every six hours) to allow for more manageable home therapy after discharge. Epsilon-aminocaproic acid is also given for the first few postoperative days to decrease fibrinolysis. Our other recommendations include placing an

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intra-articular drain before closure, controlling bleeding by releasing the tourniquet before wound closure, and removing the drain when the output is <30 mL over eight hours. We place greater priority on the condition of the wound than on the early range of motion. Therefore, the knee is initially placed in a knee immobilizer, and physical therapy and continuous passive motion between 0° and 30° are typically started twenty-four to forty-eight hours postoperatively, depending on the condition of the wound.

On the basis of our early experience, total knee arthroplasty has been safe and effective for greatly improving joint function and mobility in patients with hemophilia and inhibitors. Therefore, we believe that further evaluation of elective and emergent orthopaedic surgical procedures in this population of patients may be reasonable after carefully evaluating the risks and benefits and providing the patient with appropriate informed consent. ■

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