First Major Elective Orthopaedic Surgery, Despite Limited Financial Resources, in a Patient with Severe Haemophilia A and Factor VIII Inhibitors in Macedonia: A Case Report

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Abstract

Orthopaedic surgery in patients with haemophilia and inhibitors is not straightforward due to the increased bleeding risk compared with patients without inhibitors during the surgical procedure. We describe the use of rFVIIa using the Giangrande protocol for the first elective orthopaedic surgery in a patient with severe haemophilia A and inhibitors performed in Macedonia, a country with limited resources.

Keywords: Elective Orthopaedic Surgery; Severe Haemophilia A; Inhibitor; rFVIIa

Introduction

Plasma-derived factor VIII (FVIII) concentrates and the subsequent development of recombinant FVIII (rFVIII) products have advanced care and contributed to better outcomes in patients with haemophilia A [1-3]. An adverse consequence of exposure to FVIII replacement therapy is the risk of developing anti-FVIII neutralising antibodies (inhibitors) that markedly reduce the effectiveness of treatment, with consequent bleeding events [3]. Inhibitor incidence rates of up to 30% have been reported in patients with severe haemophilia A [3].

Repeated bleeding into joints may lead to synovitis, joint instability and progressive arthropathy in people with haemophilia [4-7]. Patients with inhibitors have a greater incidence of joint abnormalities and more rapid progression of arthropathy than those without inhibitors and experience a greater range of joint motion limitations and joint pain at an earlier age [8]. Furthermore, patients with high-titres of inhibitors have substantially worse clinical and radiological joint scores than patients without inhibitors, and a three-fold increased risk of disability due to joint disease progressing more rapidly [8,9].

Corrective orthopaedic surgery may be the best option to improve quality of life for some patients with haemophilic arthropathy [4]. However, orthopaedic surgery in patients with inhibitors is not straightforward due to an increased bleeding risk compared with patients without inhibitors [4,10]. The presence of inhibitors in patients with haemophilia was previously considered as a contraindication to elective surgery [4]. However, bypassing agents (i.e. rFVIIa or plasma-derived activated prothrombin complex concentrate [pd-aPCC]) have been shown to be effective in haemostatic control in surgery and wound healing [4,10].

A consensus protocol was published in 2009 (Giangrande protocol) for elective orthopaedic surgery (EOS) in patients with haemophilia with inhibitors using rFVIIa as initial treatment to control haemostasis during surgery [4]. Guidance on the planning of surgery
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and pre-operative testing were outlined, in addition to recommendations for the bolus schedule for rFVIIa pre-surgery and 2-h follow-up doses of rFVIIa throughout surgery; advice was also provided on administration of rFVIIa following surgery and dosing prior to removal of sutures, as well as on the concomitant use of antifibrinolytic agents and fibrin sealants.

Financial resources in Macedonia are limited; therefore, it is important to secure an excellent outcome that minimises costs when planning for and embarking on a major EOS procedure in a patient with inhibitors. Here we report a case study of the first EOS procedure performed in Macedonia using the Giangrande protocol on a patient with severe haemophilia A and inhibitors.

Case Report

The patient was a 53-year-old man with severe haemophilia A and a history of FVIII inhibitors. His body weight was 78 kg and height was 170 cm. He was hepatitis C antibody positive. The FVIII genetic mutation status was not known for this patient.

The patient presented with pain, decreased range of motion and instability in his left knee. This joint had been affected by numerous bleeding episodes over 30 years. In the last 2 years, the patient had experienced difficulty walking and climbing stairs because of a fixed flexed deformity of the left knee (flexion contracture with -25° extension) but walked without aid and only occasionally used crutches.

Until the patient developed inhibitors, his haemophilia had been mainly treated with plasma cryoprecipitate and, sometimes, depending on availability, plasma-derived FVIII. Twenty years ago, he had an episode of bleeding from the oesophagus and developed inhibitors against FVIII during this episode. The bleeding was stopped with abdominal surgery and use of rFVIIa (eptacog alfa, NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark). After the development of inhibitors, the patient was treated on-demand with bypassing therapy with rFVIIa, to which he had a good response.

Six months prior to EOS on his left knee, the patient’s inhibitor titre was 12 Bethesda Units (BU). He received advice to minimise risk for bleeding episodes during this period, including more frequent use of crutches, performing minimal household activities and abstinence from alcohol. He was also advised on how to manage bleeding episodes but there were none during this period.

As the patient had no inhibitors (0 BU) on admission to hospital, it was decided that this would be the appropriate time for him to undergo his EOS, which was a cruciate-retaining total knee endoprosthesis (cemented) to the left knee.

Although the patient had no inhibitors at this stage, the Giangrande protocol with rFVIIa, rather than FVIII, was used prior to, during and also after the procedure [4] in order to reduce the risk of postsurgery haematoma or an anamnestic response. The re-occurrence of inhibitors to FVIII therapy was a particular concern because of the anamnestic response the patient had experienced twenty years ago. Another factor influencing the choice of rFVIIa was the patient’s history of gastrointestinal bleeding. Furthermore, although the centre had excellent clinical experience with rFVIIa, it had restricted quantities of rFVIIa to manage any potential inhibitor recurrence and insufficient was available to provide coverage for rehabilitation after the patient was discharged from the hospital. The limited amount of rFVIIa was to be used over the period when the patient was receiving physical therapy in hospital and during the removal of sutures, and given to the patient for home use in the event of a bleed. Therefore, a modification was made to the Giangrande protocol (i.e. a higher dose of rFVIIa during and after surgery), with the hope of reducing the overall amount of haemostatic therapy.

Five minutes before the surgical incision, 120 µg/kg rFVIIa was administered. Tranexamic acid (antifibrinolytic agent) was administered (750 mg every 8h). During and after surgery rFVIIa (120 µg/kg) was administered at 2-h intervals to obtain and maintain good haemostasis. The duration of surgery was 2h 5 min (110 min to skin closure and 125 min to extubation). In the first 2 days after surgery, rFVIIa (120 µg/kg) was given every 2h; on the third and fourth day, it was given every 4h. On the fifth day, rFVIIa (120 µg/kg) was given with a 6-h regimen with the interval increasing until discharge (day 10).
Physical therapy was started on the fourth postoperative day with only slight exercises (as tolerated by the patient) and was closely monitored by the surgeon for signs of bleeding. Antibiotic prophylaxis with ceftriaxone (2g per day) was used for the first 4 days. There was no thromboprophylactic treatment.

Pre- and postsurgery images (6 weeks after surgery) of the patient’s left knee are shown in figure 1. Pre- and postsurgery X-ray images (a day after surgery) of the patient’s left knee are shown in figure 2.

**Figure 1**: Presurgery (A) and 6 weeks postsurgery (B and C) images of the patient’s left knee.
The patient made an uneventful recovery after the operation. He is walking without aid and with no pain; by 1 year postsurgery, he has had no bleeding episodes in his left knee. The range of motion in the knee was 95° of flexion with full extension.

**Figure 2:** X-ray Images of the left knee presurgery (A and B) and 1 day postsurgery (C and D).
Discussion

Orthopaedic surgery in patients with haemophilia complicated by inhibitors is challenging and it is recommended that such procedures should only be carried out in comprehensive care centres with the requisite multidisciplinary experience and facilities [4]. The advent of pdaPCPs and rFVIIa as bypassing treatments to control haemostasis has made major orthopaedic surgery possible for patients with haemophilia with inhibitors [11,12]. Studies in major surgery, including orthopaedic procedures, have found that rFVIIa provides consistently high haemostatic efficacy rates. Importantly, the data do not raise any unexpected safety concerns surrounding rFVIIa use. Use of rFVIIa has been a major step towards narrowing the gap in outcomes between those patients with or without inhibitors [13].

Cruciate-retaining total knee endoprosthesis was successfully carried out in this case using the Giangrande consensus protocol recommendations for use of rFVIIa to control of haemostasis. An exception from the Giangrande protocol [4] was the use of a higher-dose regimen of rFVIIa (120 µg/kg rather than 90 µg/kg) during and after surgery. Due to limited resources in the centre, there was little rFVIIa available for post-hospital rehabilitation. Therefore, the higher dose was used to maximise haemostasis and wound healing thereby shortening the time to full mobility while in hospital. We considered that reducing the likelihood of a bleed with the higher dose during postoperative rehabilitation would potentially reduce the amount of haemostatic therapy required, as a bleed with a lower rFVIIa dose would necessitate an immediate dose increase and return to a decreased dosing interval.

Conclusion

The implantation of a total knee endoprosthesis as an elective surgery was performed for the first time in the country. The success of this first EOS procedure carried out in Macedonia in the setting of limited resources opens the way for improved care for patients with haemophilia who have arthropathy in this country.

Disclosures

No conflicts of interest.

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