Recombinant Factor VIIa in the Management of Surgery and Acute Bleeding Episodes in Children with Haemophilia and High-Responding Inhibitors

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Key Words

Children · Inhibitors · Surgery · Bleeding episodes

Abstract

The development of inhibitors to therapeutic factor concentrates in children with haemophilia A or B is a troublesome complication of factor replacement therapy. Immune tolerance protocols have been developed to eliminate the inhibitors, and these are successful in approximately 80% of children. However, acute bleeding episodes require treatment with a factor (F)VIII or FIX bypassing agent to prevent an anamnestic rise in the inhibitor level before starting immune tolerance. In addition, central venous access is necessary to help parents administer frequent, high dose factor concentrate. In view of the benefits of rFVIIa seen in adults, a study has been carried out on the use of this agent as haemostatic cover in children with severe FVIII or FIX deficiency with high responding inhibitors. Information was obtained retrospectively from the National Children's Hospital, Dublin and Great Ormond Street Hospital, London. Twelve children aged 1–16 years were treated successfully with rFVIIa to prevent surgical bleeding in 20 surgical procedures. Minor post-operative haematomata developed in 2 of 20 cases after regular rFVIIa therapy had

been discontinued. In both cases, resolution of bleeding occurred after a short course of rFVIIa. Three children experienced a total of six life- or limb-threatening bleeds. All bleeding episodes resolved with regular rFVIIa treatment, although topical fibrin glue was needed in one child with a frenulum tear. The rFVIIa therapy was well tolerated and there was no evidence of any treatment-related complications. In conclusion, rFVIIa is the treatment of choice for the management of surgery and acute life- or limb-threatening bleeding in children with haemophilia and high responding inhibitors.

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Introduction

Inhibitor formation is a serious complication of haemophilia therapy as it impairs the efficacy of factor replacement treatment. Patients with high titre inhibitors fail to respond to factor concentrates even if high doses of the treatment are used. Patients most at risk of inhibitor development are those with previously untreated haemophilia, usually children with severe haemophilia A. The incidence of inhibitors approaches 33% in patients with FVIII deficiency and 3% of those with FIX deficiency [1].

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Several publications have shown that immune tolerance therapy (ITT) can ablate the inhibitors in 80% of children who develop them [2–5]. Immune tolerance is more likely to succeed if the patient has an inhibitor titre less than 10 Bethesda Units (BU). However, acute bleeding episodes continue to require adequate haemostatic cover with a FVIII- or FIX-bypassing agent to prevent an anamnestic rise in the inhibitor level before starting ITT. In addition, young children require the insertion of a central venous access catheter, again with haemostatic cover, to help parents administer frequent high dose factor concentrate and acute treatment. The provision of this haemostatic cover can be achieved with rFVIIa. To date, the use of rFVIIa has been predominantly in adults with severe FVIII-deficiency and inhibitors who are undergoing surgery [6]. The agent has also become established as the treatment of choice for acute life-threatening bleeding episodes in adult haemophilia patients with inhibitors.

In the light of the experience with rFVIIa in adults, there has been much interest over the past few years in the use of this agent in paediatric patients who have severe FVIII- or FIX-deficiency with inhibitors. A study has therefore been carried out to investigate the use of rFVIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high responding inhibitors [7].

Study Design

The study was a retrospective chart review by the National Children's Hospital in Dublin and the Great Ormond Street Hospital for Children in London. The review included children with haemophilia and inhibitors who received rFVIIa between December 1995 and December 2000. During this time, 12 children received rFVIIa for the prevention of bleeding during a total of 20 surgical procedures (table 1). Additionally, rFVIIa treatment was given to 3 children among whom there were 6 acute life- or limb-threatening bleeding episodes.

Regimen

For the surgical cover, the dose of rFVIIa used in the Dublin centre was 90 µg/kg every 2 h during the first 24 h and then every 4 h during the following 24 h. At Great Ormond Street, the dose used for surgical cover was 90 µg/kg 2-hourly for the first day, 3-hourly for the second day and 4-hourly for the third day. The acute bleeding episodes were treated with a dose of rFVIIa of 90 µg/kg every 2–4 h until the bleeding stopped. All these patients

Table 1. Study design for the two-centre investigation of the use of rFVIIa in the management of surgery and acute bleeds in children with haemophilia and inhibitors

- rFVIIa usage in children with sFVIII/IX and inhibitors Dec 1995 to Dec 2000.
- Retrospective via chart review
- rFVIIa dosage used for acute bleeds:
 - 90 µg/kg 2–4 h until bleeding stopped (TxA 15 mg/kg, topical fibrin glue in 1 patient)
- rFVIIa dosage for surgical cover:
 - 90 µg/kg, 2 h × 24 h, 4 h × 24 h (NCH)
 - 90 µg/kg, 2 h × 24 h, 3 h × 24 h, 4 h × 24 h (GOS) (TxA 15 mg/kg i.v. or p.o. × 1 week)
- Efficacy – clinical assessment/shortening of PT

Table 2. Patient characteristics of participants in the London/Dublin study

Median age, years	2.5
Range	1–16
FVIII	12
FIX	1
Max. historical BU	
Median	120
Range	2–712
BU at time of rFVIIa	
Median	12
Range	<1–100

also received tranexamic acid in a dose of 15 mg/kg either intravenously or orally for 1 week.

Efficacy was measured by clinical assessment of haemostasis. Shortening of the prothrombin time was also measured.

Patient Characteristics

The patients in this study had a median age of 2.5 years, ranging from 1 to 16 years (table 2). Of the patients, 12 were FVIII-deficient and one was FIX-deficient. The patients' records showed that their median maximum historical inhibitor titre was 120 BU with a range of 2–712 BU. At the time of rFVIIa treatment, the median inhibitor level was 12 BU with a range of 1–100 BU.

Surgery

The operations included 19 procedures for insertion or removal of a central venous access device (CVAD) and

Table 3. Surgical procedures

Number of patients	12
Total number of procedures	20
CVAD insertion or removal	19
Multiple dental extractions	1
Duration of cover, h	
Median	48
Range	12–72
Total dose rFVIIa, mg	
Median	43.2
Range	19.2–124.8

Table 4. Acute life-threatening bleeding episodes

Number of patients	3
Total number of bleeds	6
Mouth bleed	3
Port bleed	2
Forearm bleed/neuro \$ms	1
Duration of cover, h	
Median	20
Range	4–96
Total dose rFVIIa, mg	
Median	43.2
Range	2.4–46.8

one multiple dental extraction (table 3). The median duration of surgical cover with rFVIIa was 48 h, ranging from 12–72 h. The median total dose of rFVIIa for surgery was 43 mg with a range of 19–125 mg.

All the surgical patients were treated successfully with rFVIIa. Two of the patients had minor bleeding 3 days after insertion of their CVAD, at which time both had discontinued their rFVIIa treatment. Re-treatment with 2–3 doses of rFVIIa resolved the bleeding.

Acute Bleeding

The 6 acute bleeds that occurred in 3 patients included mouth bleeds in 3 patients and port bleeds in 2 patients following insertion of a needle. One child had a forearm bleed with neurological symptoms. Three of the 6 bleeding episodes were associated with significant anaemia, haemoglobin levels dropping below 8 g/dl. Transfusion of red blood cells was required in 2 of the bleeding episodes.

Patients in the acute bleed group received rFVIIa treatment over a median of 20 h, ranging from 4–96 h (table 4). The median total dose of rFVIIa in these patients was 43 mg, ranging from 2–47 mg. All the bleeding episodes resolved with rFVIIa treatment, except one case involving a frenulum tear, which was brought under control by application of topical fibrin glue.

Prothrombin Time

Prothrombin time (PT) was measured in all 20 surgical procedures and in 1 of the patients with acute bleeds. In all 21 occasions, the PT shortened to the lower limit of normal following rFVIIa treatment. It was assumed this confirmed that a haemostatic level of FVII:C had been reached.

Side Effects

Treatment with rFVIIa was well tolerated. No treatment-related complications were seen in any of these surgical or acute bleed cases. There was no evidence of systemic activation of coagulation as indicated by activation markers including a D-Dimer.

Conclusion

We concluded from this series that rFVIIa was shown to be extremely effective and reliable in the management of acute bleeding episodes and in the prevention of surgical bleeding in children with FVIII- or FIX-deficiency with inhibitors.

Further research is required to determine the optimum therapeutic dose of rFVIIa in the paediatric setting. As the half-life of rFVIIa in children is only half that in adults, it could be that a lower bolus dose of rFVIIa would be effective. In assessing the best dose regimen, it may be necessary to examine more closely the kinetics of FVII:C in haemophiliac children with inhibitors during rFVIIa treatment. In this study, we noted that increasing the dosing intervals to 4-hourly was associated with a drop in the FVII:C levels which no longer exceeded the threshold believed to be necessary for haemostasis.

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