Haemophilia (2005), **11**, 2–4 DOI: 10.1111/j.1365-2516.2005.01051.x

REVIEW ARTICLE

Management of oral bleedings with recombinant factor VIIa in children with haemophilia A and inhibitor

P. LAGUNA and A. KLUKOWSKA
Department of Paediatrics, Haematology, and Oncology, Warsaw Medical University, Poland

Summary. Dental extraction in patients with haemophilia A and high-titre inhibitor is always a high-risk procedure, which often presents a lot of problems associated with bleeding. Prothrombin complex concentrates or recombinant activated factor VII (rFVIIa) has been used to control bleeding. rFVIIa was administered to five boys with severe haemophilia A complicated with inhibitor, who underwent seven dental extractions. The age of the patients ranged between 8 and 13 years (median 10 years). The concentrate was administered in doses of 90–100 μg kg^{-1} body weight. Duration in the therapy and intervals between rFVIIa doses depended on the severity of bleeding. rFVIIa was proven to be highly effective and no side-effects of the product were observed.

Keywords: dental extraction, factor VIII inhibitor, haemophilia A, recombinant factor VIIa, rFVIIa

Introduction

In spite of the increasing campaign on the prophylaxis of dental caries and the availability of oral-hygiene products, dental caries and parodontal diseases continue to be widespread problems in children in Poland [1,2]. These problems particularly affect children with inherited coagulation disorders. Because of the fear of bleeding, patients with coagulation disorders do not brush their teeth adequately or frequently, and their dentists are reluctant to undertake appropriate traditional treatment because of potential haemorrhagic complications. This results in severe dental caries and the necessity of dental extractions.

Since the early 1990s the increased availability of blood-derived products has enabled more effective dental care and treatment. Unfortunately, one of the most important complications of haemophilia treatment with plasma-derived coagulation factors, including factors VIII and IX, is the development of antibodies against these factors.

Correspondence: Pawel Laguna, Department of Paediatrics, Haematology, and Oncology, Warsaw Medical University, Poland. Tel.: +48 22 522 74 19; fax: +48 22 621 53 62; e-mail: skazy@litewska.edu.pl

Accepted after revision 4 October 2004

Factor VIII inhibitor occurs in 10–20% of patients, mostly in those with a severe type of haemophilia A [3]. Treatment of these patients is difficult and very expensive. Animal-derived coagulation factors and activated or non-activated prothrombin complex concentrates (APCC or PCC respectively) have been used to control bleeding in patients with a high titre of inhibitor.

Recently, there have been several reports on the use of rFVIIa (NovoNordisk, Bagsvaerd, Denmark) in the management of bleedings and cover of surgical procedures in haemophilia patients with inhibitor to factor VIII [4–10].

In our department, rFVIIa has been used in the management of joint, muscle, and central nervous system haemorrhages, as well as to cover minor surgical procedures including top-entry vascular access port insertion of an over the needle catheter for immune tolerance induction through regular factor VIII infusions. It has also been used in major surgical procedures, including hypospadia operations and appendectomy. In all these cases, rFVIIa was highly effective [11].

This report evaluates the haemostatic efficacy of rFVIIa in children with haemophilia A and inhibitor to factor VIII who underwent dental extractions and bleedings associated with eruption of teeth.

Cases

Recombinant factor VIIa (rFVIIa; NovoSeven®) was administered to five boys (median age 10 years) with haemophilia A and high titres of inhibitor to factor VIII ranging from 15 to 958 Bethesda Units per millilitre (BU ml^{-1}). Indications for rFVIIa administration included bleedings from the oral cavity or necessity of dental extraction. In total seven dental extractions were performed, including four extractions of rudimentary teeth (one canine tooth, three premolar teeth) and three extractions of permanent teeth (three molar teeth). Indications for extractions were as follows: dental caries complicated by toothache with no possibility of successful conservative treatment, bleeding from the region of mobile rudimentary teeth, and caries with recurrent periodontal inflammation and abscesses.

All patients received rFVIIa in doses of 90–100 μg kg^{-1} and antifibrynolytic agents (Exacyl 20 mg kg^{-1} $dose^{-1}$ every 6 h). Two patients had initially received factor eight inhibitor bypassing activity (FEIBA) (APCC) and PCC because of the temporary unavailability of rFVIIa in their district hospitals. After the extractions had been completed or bleeding stopped the patients were given a cool liquid diet followed by a semi-solid diet for 2–3 days.

Patient 1 (O.T.) underwent a molar-tooth extraction under the cover of FEIBA and a two-component fibrin sealant (Tissucol Kit, IMMUNO, Austria). Six hours after the extraction bleeding occurred, which did not stop in spite of FEIBA administration. Therefore, rFVIIa was administered. Because rFVIIa is known to be active for only a short time and there was a danger of repeated bleeding, another dose was given after 2 h and a third dose after 3 h.

Two years later, the same patient was admitted to hospital due to haemorrhage following extraction of his molar tooth, with gangrenous pulp and mild bleeding from the alveolar process region. One dose of rFVIIa was given before extraction and I dose 2 h after extraction. The next four doses were administered every 3 h and the last two doses every 4 h (in total eight doses).

Patient 2 (B.P.) was a 10-year-old boy, who experienced severe haemorrhage from the gum as a result of the eruption of the right inferior molar tooth. The patient had been hospitalized in a district hospital for 2 weeks and multiple doses of PCC and FEIBA had failed to improve his haemostasis. He received five red-blood-cell transfusions because of anaemia. Adjunctive treatment including dental dressing and local laser therapy had not provided any therapeutic effects. After admission to our department, three doses of rFVIIa were given in 2-h intervals. The bleeding stopped. His inhibitor level was later found to be 958 BU ml^{-1}.

Table 1. Teeth extractions in patients with haemophilia A and inhibitor.

			Extraction			Bleeding		
No	Initials	Date of birth	Date	Number of teeth	Pyogenic paradontitis	Before extracions	After VIIa administration	
1	O T	22.11.90	18.07.98	5*	+	++		After extraction, bleeding was observed despite FEIBA administration Two doses of VIIa secured haemostasis
			20.01.00	6	+			Eight doses of VIIa was administered at 2–4 h intervals
2	B P	8.07.88	20.08.98	6		+++		Prolonged bleeding following the tooth extraction was observed for 2 weeks despite administration of the factor IX and FEIBA. Blood transfusions (PRBC) because of anaemia after bleeding were administered five times. Administration of VIIa secured haemostasis (three doses)
3	P M	31.08.86	3.08. 99	6	+		+	VIIa at 2–3 h intervals for 2 days (seven doses). Bleeding occurred between second and third dose
4	H M	4.10.91	28.02.01	5*				One dose of VIIa before and one dose after extraction
			7.06.01	5*				One dose before
5	K J	29.01.91	12.04.02	3*				One dose of VIIa before and one dose after extraction

*Milk-tooth

Patient 3 (P.M.) had a molar tooth extraction under the cover of rFVIIa. The next three doses were given every 2 h, then two doses every 3 h and the last dose after 4 h. (in total seven doses). Between the second and the third doses mild bleeding occurred, which stopped after rFVIIa and application of an absorbable gelatin sponge (Spongostan, Johnson-Johnson, UK) and pressure dressing.

The other two patients (H.M. and K.J.), who underwent, in total, three rudimentary tooth extractions (canine teeth, premolar and molar), were given rFVIIa just before and 2 h after the procedure. No bleeding was observed.

No adverse effects related to rFVIIa were seen in any of the patients (Table 1).

Discussion

Recombinant factor VIIa was first used in Stockholm in 1988 during synovectomy of knee joint [12]. The haemostatic effect of rFVIIa is based on activation of the extrinsic coagulation pathway and occurs by forming a complex with tissue factor at the site of bleeding [11]. Unlike APCC, the risk of generalized hypercoagulability associated with the use of rFVIIa is very low because of the need for interaction of FVIIa with tissue factor that is released locally only at the site of tissue injury [13].

In all above-mentioned cases, rFVIIa provided effective haemostasis in oral bleedings in patients with severe haemophilia A and high titre of inhibitor. FEIBA and PCC administered prior to rFVIIa in two patients had failed to ensure efficient haemostasis and one of these cases was complicated by severe anaemia with necessity of repeated blood transfusions.

Administration of rFVIIa in doses of 90–100 $\mu g\ kg^{-1}$ body weight immediately before and 2 h after the procedure of rudimentary tooth extraction should be sufficient for effective haemostasis.

As regards permanent tooth extraction, administration of more than one dose of rFVIIa after the procedure might be required in certain circumstances depending on the extent of the inflammatory process, the extent of the procedure and the severity of parodontal lesions.

Antifibrinolytic agents are recommended and a cool liquid diet should be given [14,15].

Conclusions

Recombinant factor VIIa is safe and effective in the management of oral bleedings in children with haemophilia and a high titre of inhibitor.

References

1 Jańczuk Z, Banach J. Health problems of the stomatognathic system in the Polish population covered by stomatological health care place of residence and work. *Czas Stomat* 1990; **43**: 1–6.

2 Szpringer-Nodzak M, Tawczyńska A, Moszczeńska-Cieślikowska B. Masticatory organ condition evaluation in children with blood coagulation defects. *Czas Stomat* 1992; **XLV 3**: 127–32.

3 Klukowska A, Zieleniewska B. The results of bleedings treatment in haemophilia A children with factor VIII inhibitor. *Acta Haematol Pol* 1994; **25**: 349–54.

4 Ingerslev J, Freidman D, Gastineau D. Major surgery in haemophilic patients with inhibitors using recombinant factor VIIa. *Haemostasis* 1996; **26**: 118–23.

5 Knet G. The use of Novoseven for profuse bleedings in surgical patients. Abstract presented at the 6th Novo Nordisk Symposium on Treatment of Bleeding and Thrombotic Disorders. Copenhagen, Denmark, May 3–4, 2001.

6 Hay CR, Negrier C, Ludlam CA. The treatment of bleeding in acquired haemophilia with recombinant factor VIIa: a multicentre study. *Thromb Haemost* 1997; **78**: 1463–7.

7 Gastinean DA, Pruthi RK, Moir CR, Bolander B. Kgilchrist GS. The May Clinic surgical experience with congenital hemophilia and high titer inhibitors. *Thromb Haemost* 1997; **1**(Suppl. 51).

8 Lusher IM. Recombinant factor VIIa (Novoseven) in the treatment of internal bleeding in patients with factor VII and IX inhibitors. *Haemostasis* 1996; **26** (Suppl. 1): 124–30.

9 Trangeborn L, Kjellman B, Elfstrand PO, Bagenholm T. Recombinant factor VIIa in an infant with hemophilia a and inhibitors. *Acta Paediatr* 1992; **81**: 566–7.

10 O'Connell N, Mc Mahon C, Smith J *et al.* Recombinant factor VIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high responding inhibitors. *Br J Haematol* 2002; **116**: 632–5.

11 Klukowska A, Laguna P, Obitko-Pludowska A, Rokicka-Milewska R. Use of activated recombinant factor VII (rFVIIa) in the treatment of hemofilia A children with high-titer inhibitor. *Acta Haemat Pol* 1998; **29**: 401–6.

12 Hedner U, Glazer S, Pingel K *et al.* Successful use of recombinant factor VIIa in patient with severe haemophilia A during synovectomy. *Lancet* 1988; **2**: 1193.

13 Rao L, Rapaport SI. Cells and the activation of factor VII. *Haemostasis* 1996; **26** (Suppl. 1): 1–5.

14 Rokicka-Milewska R, Krajewska-Martel A, Dyszy-Laube B. Epsilon-aminocaproic Acid for oral mucosal bleeding in hemophiliacs. *Pol Arch Med Wewn* 1966; **37**: 445–50.

15 Dyszy-Laube B, Jastrzębski S, Szumilewicz-Serocka B, Kamińska D. Teeth extraction in haemophilic children. *Czas Stom* 1975; **28**: 715–23.