Session IV:
Clinical Experience with NovoSeven (rFVIIa)

Hæmostasis

Haemostasis 1996;26(suppl 1):118–123

Major Surgery in Haemophilic Patients with Inhibitors Using Recombinant Factor VIIa

J. Ingerslev[a]
D. Freidman[b]
D. Gastineau[c]
G. Gilchrist[c]
H. Johnsson[d]
G. Lucas[e]
J. McPherson[f]
E. Preston[g]
E. Scheibel[h]
M. Shuman[i]

[a] Coagulation Laboratory and Haemophilia Centre, University Hospital Aarhus/Skejby, Denmark;
[b] Childrens Hospital, Philadelphia, Pa.,
[c] Mayo Foundation Hemophilia Center and Mayo Medical Center, Rochester, Minn., USA;
[d] Karolinska Hospital, Stockholm, Sweden;
[e] Manchester Royal Infirmary, Manchester, UK;
[f] Newcastle University Hospital, Newcastle, Australia;
[g] Royal Hallamshire Hospital, Sheffield, UK;
[h] Haemophilia Centre, University Hospital Copenhagen, Denmark;
[i] University of California, San Francisco, Calif., USA

Key Words
Haemophilia
Factor VIII inhibitors
Surgery
Factor VIIa
Recombinant factor VIIa

Abstract

In the haemophilic patient, development of antibodies that inhibit the function of the missing coagulation factor causes several delicate problems. Most importantly, antibodies will block the function of the specific coagulation factor, and often the antibody activity is so fierce that effective substitution therapy is outruled. In consequence, alternative measures must be adopted to control bleeding. Amongst those most commonly employed, like factor IX concentrates, activated prothrombin complex concentrates, and factor VIII of porcine origin, a new recombinant activated factor VII molecule has been evaluated clinically for some years with promising results. The aim of the present paper was to present a series of patients suffering from haemophilia A or B in whom inhibitors have complicated the clinical picture, and in whom a surgical procedure was indicated. As part of a compassionate use program devised by the producer of this genetically engineered factor VIIa, 12 patients underwent life-saving or essential surgery where the recombinant factor VIIa product was used to promote haemostasis in 13 surgical procedures. Due to a short in vivo half-life of activated factor VIIa, frequent administration was scheduled, injecting factor VIIa every 2–3 h for up to 2 days after which dosage intervals were prolonged. In one case, a global evaluation of the end treatment result was not reported, but in all of the other 12 cases the end result were considered excellent (n = 11) or efficient (n = 1). In none of the cases was other types of coagulation factor treatment modalities necessary. In conclusion, recombinant factor VIIa seems a tempting alternative to traditional treatment of the haemophilic patient with inhibitors, in whom surgery is called for. With other types of haemostatic agents, surgery in haemophilic inhibitor patients has only been studied rarely, and operations have generally been restricted to life-threatening situations.

Introduction

As deduced from recent and historical long-term studies of the previously unexposed child suffering from a severe haemophilia A, it has been appreciated that a significant proportion of patients are at risk of developing inhibiting antibodies directed against the treatment factor. The frequency has been anticipated to be around 25%, but it may be as

KARGER
E-Mail karger@karger.ch
Fax + 41 61 306 12 34

0301–0147/96/0267–0118$10.00/0

J. Ingerslev, MD, DMSc
Haemophilia Centre Director
University Hospital Skejby
DK–8200 Aarhus N (Denmark)

1. **12 pat ients underwent life-saving o r essential surgery where the recombinant factor Vlia product ...**
Anchor Name: Cerrahi uygulanan inhibit.rlü hemofili hastalarında kanıtlanmış etkililik
[Agency Turkey sibel.cakan@pitstop.com.tr]

2. **in all of the other 12 cases the end result were considered excellent (n = 11) or efficient (n = l...**
Anchor Name: Cerrahi uygulanan inhibit.rlü hemofili hastalarında kanıtlanmış etkililik
[Agency Turkey sibel.cakan@pitstop.com.tr]

high as 50% [1]. An inhibiting antibody adds seriously to the risk of the haemophilic individual with regard to uncontrollable bleeding, disability, and premature death. Due to unpredictable haemostasis and final outcome, it has generally been advised that surgery in the person with inhibitor antibodies should be carried out only if absolutely necessary [2]. The major problems related to surgery in the inhibitor carrying individual consist of insufficient haemostasis, serious side effects, or both. When a low titer inhibitor is present, human factor VIII or porcine factor VIII concentrates seem favourable because a measurable factor VIII level may be reached. In some centres, extensive plasmapheresis or immune adsorption of IgG molecules to protein A sepharose has been performed preoperatively to reduce the level of an inhibitor. However, an anamnestic response must always be encountered, and a preoperative assessment of recovery of factor VIII may seriously shorten the time span available for treatment before anamnesis and, as a consequence, failure of treatment occurs. Porcine factor VIII in some patients seems less immunogenic compared to human factor VIII, but immediate-type allergic reactions due to non-factor VIII porcine protein constituents and thrombocytopenia can occur. A retrospect analysis of surgery in haemophilic inhibitor patients using porcine factor VIII has been reported on more occasions [2–6]. In high-titred patients, a coagulation-active principle called the factor VIII by-passing activity (Feiba, Autoplex) can be utilised to assist haemostasis. Although its specific action has not been clarified in detail, this phenomenon can be found to a minor degree in various types of less purified factor IX concentrates, but quite vigorously in the so-called activated prothrombin complex concentrates (aPCC) that constitute side products of factor IX production. Due to the existence of several putative activated coagulation factors, biochemical signs of DIC may occur in the recipient, and severe thrombotic complications like deep-vein thrombosis and myocardial infarction have been reported [7]. The ability of aPCC to give sufficient haemostasis during surgery has been reported in a retrospective manner in several publications [8–13]. In some of these, however, treatment by aPCC was introduced only following postoperative inhibitor anamnesis induced by an initial treatment with high doses of factor VIII, and the number of patients reported is quite small. Recently, a factor VII molecule in the activated form has been produced by recombinant DNA cell technology (recombinant factor, rFVIIa), and an immunopurified, virally inactivated product has been tested clinically in patients suffering from allogenic and autologous antibodies against factor VIII and IX, where it has demonstrated a substantial degree of haemostatic efficacy. A clinical study program has been devised, in which patients with bleeding were enrolled for compassionate treatment with rFVIIa if other treatment modalities had been unsuccessful or inadequate. A compilation of clinical data from the first segment of this clinical study has recently been published [14]. We present data on major surgeries from segments II and III of the Compassionate Use Program (October 1991 to September 1994) carried out in several centres.

Material and Patients

Material

The diagnosis and inhibitor results for each patient were based on standard laboratory procedures of each participating centre. Likewise, recordings of factor VII:C, activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen, antithrombin-III, fibrin D-dimers and platelet counts were performed at the investigational sites. rF VIIa (NovoSeven, Niastase) for treatment was kindly provided by Novo Nordisk A/S (Gentofte, Denmark) for all treatments after

[no notes on this page]

Table 1. Demographic patient data and surgeries performed

Patient	Age, years	Inhibitor titre Bethesda units/ml	Surgery
1	35	56	knee joint synovectomy
2	27	5.4	knee joint arthroplasty
3	43	1,000	bilateral knee joint arthroplasty
4	41	22	amputation of lower limb
5	15	20	knee joint synovectomy
6	27	3.5	knee joint osteotomy and arthroplasty
7	35	570	herniotomy
8	41	30	liver biopsy, two courses
9	36	20	herniotomy
10	40	121	extirpation of eye
11	6	120	removal of epidural haematoma, craniotomy
12	n.a.	46	surgical removal of haemophilic pseudotumour

n.a. = Not available.

consultation and approval. The product was delivered as sterile, bottled freeze-dried aliquots of 1.2 mg (in some instances 1.9 mg) to be dissolved with pyrogen-free sterile water immediately before use. rFVIIa dosages were administered as single bolus injections in all cases. Doses selected were significantly higher (mean 99 μg/kg, range 89–118 μg/kg) as compared to treatments given under segment I of this investigation [14].

Patients

In total, 12 patients aged 6–43 years (median 35 years) of whom 11 cases had haemophilia A, and 1 case haemophilia B, underwent major surgery. Although no detailed historical documentation was available for all cases at the time of this publication, the median age of this group points to the likelihood that most inhibitors had been present for a long time. As assessed from inhibitor levels recorded in context with or close to surgery, a median inhibitor titre of 46 Bethesda units/ml (range 3.5–1,000), was found. The key criteria to obtain permission of the sponsor to use recombinant factor VIIa had been a lacking efficacy of alternative treatment modalities closely linked with the present condition requiring surgery. Six subjects had not previously been exposed to rVIIa, whereas the other 6 patients had received rFVIIa treatment on 2–25 occasions. Five of these 6 patients had previously undergone other minor or major surgery using factor VIIa. Approval by respective national authorities was obtained in each case, and written and spoken informed consent was received from all patients. A list of the surgeries carried out is shown in table 1.

Results

The surgical end result of all operations was satisfactory, and postoperative haemostasis was achieved in all patients. Importantly, all of these patients were treated in-hospital from before the initiation of surgery until the risk of rebleeds could be ruled out with rFVIIa as haemostatic agent. In no case uncontrollable bleeding that demanded a change in treatment modality occurred. Thus, in these cases there was no additional or subsequent treatment with aPCC or porcine factor VIII.

[no notes on this page]

Table 2. Data concerning single dose, number of doses and accumulated administration of the haemostatic agent rFVIIa pre- and postoperatively in 12 patients undergoing 13 surgical interventions

Patient	First dose rFVIIa µg/kg	Accumulated doses of rFVIIa	rFVIIa used mg	Days of treatment
1	95	122	654	43
2	115	144	735	35
3	97	191	1,306	42
4	118	160	862	21
5	97	59	495	9
6	90	63	529	10
7	100	66	475	10
8	95	45	270	5.5
8	95	51	306	6
9	118	92	558	12
10	94	69	455	9.6
11	89	102	185	10
12	94	95	1,026	10.7

The initial dose of rFVIIa selected and the number of doses and days of treatment as well as the accumulated consumption of rFVIIa administered during and after surgery is given in table 2. Clinicians were asked to perform an overall end of treatment assesment of efficacy. The results of this are given in table 3. In 1 patient this information is not available at present, whereas in all others the efficiency rate was 100%, and the rate of an excellent overall result was 92%.

Table 3. Global end of treatment evaluation results as assessed by the physician responsible

Efficacy score	Number of surgeries
Excellent	11 (92)
Efficient	1 (8)
Not available	1
Total	13

Figures in parentheses represent percentage.

Laboratory Monitoring

The platelet counts were monitored in all patients in this study. As compared to preoperative values, only very small reductions in platelet numbers could be identified as one may expect in a patient undergoing major surgery. The PT results from various centers are not directly comparable but significantly shortened PT have been found in postdosage samples following rFVIIa infusion. Likewise, the APTT was shortened, with one exception, in all patients in response to treatment with rFVIIa. In those responding, the mean shortening of the APTT was 36% (range 33–55%) of preinfusion times. The levels of postinfusion factor VII:C had been determined in 8 of the cases. The highest VII:C level recorded in each individual ranged from 8.4 to 84 U/ml (mean 39 U/ml). These differences may be ascribed to differences in the recovery of rFVIIa as well as differences in assay methods for estimation of VII:C activity. Only insignificant changes in fibrinogen levels were seen with no specific trend. Only one sample from 1 patient revealed a fibrin D-dimer level

[no notes on this page]

above the reference limit set by the local laboratory, whereas all other samples from the same patient and all other patient samples monitored for D-dimers gave results below the limits of specified abnormality. Antithrombin III values did not display any tendency to decrease.

Discussion

Major surgery is a rare event in the haemophilic patient with inhibitors, and most often surgical intervention has been performed only on very strict indications. In the series of 12 patients reported here, essential or life-saving surgery has been performed with a high degree of success and no serious side effects. It is worth mentioning that 6 patients had previously undergone minor surgery haemostatically assisted by rFVIIa which probably explains why elective surgery apparently had been selected by some of the participating investigators. In this segment of the compassionate use clinical program, doses of rFVIIa were somewhat increased (89–118 μg/kg) compared to those adopted in the first segment (70–100 μg/kg), which may explain the higher efficacy rate obtained (91 vs. 71%). It may be speculated whether an improved clinical experience with rFVIIa in general has influenced the clinical result. Since the in vivo half-life of rFVIIa is only 2.5–3 h, frequent dosing seems very important to maintain haemostasis in the postoperative period. Further, rFVIIa has been dispensed with no protein stabilisers added, and it has been recommended that this agent should not be administered from a drip container, but rather that each dose should be injected as a bolus injection. An unsuccessful result of hernioplasty has recently been published [15] in detail, explaining three serious recurrent bleeding episodes in the postoperative period. In the present series, two herniotomies were performed with no bleeding complications. The doses selected here were higher, 100 versus 75 μg/kg, than those selected in the described case with treatment failure, and the dosage intervals here were kept at 2 h for at least the first 24 h postoperatively. The combined effect of these measures presumably accounts for maintenance of haemostasis in this critical part of the postoperative period. Further, quite substantial experience of the haemostatic efficacy of rFVIIa in the surgical patient was obtained in the present series, since advanced orthopaedic surgeries were performed including amputation and two total condylar knee joint arthroplasties. In these, the postoperative bleeding pattern was similar to that of the non-haemophilic patient or the fully substitued non-inhibitor haemophilic patient presenting with gradually reducing amounts of blood in the suction catheter bags during the first 1–2 postoperative days. Hence, it appears that rFVIIa is efficacious in controlling pre- and postoperative bleeding in the haemophilic patient with inhibitors to factor VIII or IX. As assessed by variables like platelet count, fibrinogen, fibrin D-dimers and antithrombin-IIII there seems to be no systemic activation of coagulation raising suspicion of DIC even after prolonged and frequent exposure of patients to doses of rFVIIa at 89–118 μg/kg. In the present series, patients with variable titres of inhibitors have demonstrated equally efficient haemostasis during and after surgery, illustrating that the action of rFVIIa most likely is independent of the actual level of the inhibitors.

From the data presented here, it appears that rFVIIa, being a new haemostatic tool, has opened some entirely new perspectives for the patient with classical haemophilia complicated by the presence of inhibitors, since a variety of acute and elective surgeries have been enabled under circumstances of controlled bleeding with this drug.

[no notes on this page]

References

1 Ehrenfort S, Kreuz W, Scharrer I, Linde R, Funk M, Güngör T, Krackhardt B, Kornhuber B: Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet 1992;339:594–598.

2 Brettler DB: Inhibitors of factor VIII and IX. Haemophilia 1995;1 (suppl 1):35–39.

3 Gatti L, Mannucci PM: Use of porcine factor VIII in the management of seventeen patients with factor VIII antibodies. Thromb Haemost 1984;51:379–384.

4 Brettler DB, Forsberg AD, Levine PH, Aledort LM. Hilgartner MW, Kasper CK, Lusher JM, McMillan C, Roberts HR, Cooperating investigators: The use of porcine factor VIII concentrate (Hyate:C) in the treatment of patients with inhibitor antibodies to factor VIII. Arch Intern Med 1989;149:1381–1385.

5 Lozier JN, Santagostini E, Kasper CK, Teitel JM, Hay CR: Use of porcine factor VIII for surgical procedures in hemophilia A patients with inhibitors Semin Hematol 1993;30/2 (suppl 1):10–21.

6 Warrier I, Kueffler S, Pfaffmann L, Lusher J: Use of porcine F VIII Hyate:C) for hemostasis during surgery in children with factor VIII inhibitor (abstract 71). 21st International Congress of the World Federation of Hemophilia, Mexico City, 1994.

7 Lusher JM: Thrombogenicity associated with factor IX complex concentrates. Semin Hematol 1991;28/3(suppl 6):3–5.

8 Penner JA: Treatment of inhibitor patients with activated prothrombin complex concentrates; in Hoyer LW (ed): Factor VIII Inhibitors. Prog Clin Biochem Res New York, Liss, 1984, vol 170, pp 291–307.

9 Hutchinson RJ, Penner JA, Hensinger RN: Anti-inhibitor coagulant complex (Autoplex) in hemophilia inhibitor patients undergoing synovectomy. Pediatrics 1983;71: 631–633.

10 Negrier C, French Feiba Study Group: Multicenter retrospective study on the utilization of Feiba in France in patients with factor VIII and factor IX inhibitors (Abstract 23). 2nd International Symposium on Inhibitors to Coagulation Factors, University of North Carolina at Chapel Hill, 1993.

11 Lauroroa P, Barbier F, Dieu P, Dumora D, Mouliner J: Prothèse bilaterale genou chez un hémophilie A avec inhibiteur. Ann Fr Anesth Reanim 1986;5:154–156.

12 Christiansen SE, Ingerslev J, Wallevik K, Farsø F, Helmig O, Stenbjerg S: Management of anterior compartment syndrome in two high responder factor VIII inhibitor patients with activated prothrombin complex concentrate. Thromb Res 1986;42:707–712.

13 Sindet-Petersen S, Stenbjerg S, Ingerslev J: Treatment of bilateral fracture of the mandible in a hemophilic patients with inhibitor to factor VIII. J Oral Maxillofac Surg 1987;45:537–540.

14 Glazer S, Hedner U, Falch J: Pathologic inhibitors: Management with factor VIIa; in Green D (ed): Anticoagulants, Physiologic, Pathologic and Pharmacologic, Boca Raton, CRC Press, 1994, pp 131–141.

15 Gringeri A, Santagostini E, Mannucci PM: Failure of recombinant activated factor VII during surgery in a haemophiliac with high-titer factor VIII antibody. Haemostasis 1991;21:1–4.

[no notes on this page]