

ORIGINAL ARTICLE

Major orthopaedic surgeries for haemophilia with inhibitors using rFVIIa

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Summary. Between 2000 and 2008, 11 major orthopaedic surgeries for 7 congenital haemophilia patients with inhibitors were performed by the first author as the primary doctor using recombinant activated factor VII (rFVIIa). Orthopaedic surgical treatments were performed for six surgeries for four high-responder haemophilia A patients, three surgeries for two high-responder haemophilia B patients and two surgeries for one low-responder haemophilia B patient. This low-responder patient is allergic to factor IX products, so he usually uses rFVIIa as a haemostatic agent. All of the surgeries were major, such as joint arthroplasty, arthroscopic synovectomy, and a combination of both, and excellent surgical results were achieved. Seven cases were controlled by bolus infusion of rFVIIa, and the other four cases were controlled by combined bolus

and continuous infusion of rFVIIa. An anti-fibrolytic agent was used for all cases. There were no thrombotic adverse effects, only two bleeding episodes. As for haemostatic control, nine surgeries were excellent, one was good and one was fair. This report is the largest clinical report on major orthopaedic surgeries at a single institute. We have concluded that the combination of bolus and continuous infusion of rFVIIa is safe and effective, and more convenient to administer than simple bolus infusion therapy to achieve haemostasis at peri-operative periods. In addition, our data also concurs with the data of several previous reports which showed that orthopaedic surgery for haemophilia patients with inhibitors by means of rFVIIa is safe and effective.

Keywords: inhibitor, orthopaedic surgery, rFVIIa

Introduction

For haemophilia patients without inhibitors, orthopaedic surgery is becoming popular. However, for haemophilia patients with antibodies for the deficient factor VIII or IX (inhibitor), this surgery is an elective treatment [1,2], because there is still no guideline, based on surgical case studies, which specifies a proper monitoring marker to monitor the coagula-

tion factor plasma levels and how to effectively use concentrates to control bleeding during surgery. However, many haemophilia patients with inhibitors also complain about joint dysfunction and seek out orthopaedic surgical treatments. Surgical results were reported for some surgeries that were performed using bypassing agents, such as activated prothrombin complex concentrate (aPCC) and activated recombinant factor VII (rFVIIa). Most of these results were of minor surgeries such as radioactive synovectomy or tooth extraction. In some multicentre studies [1,3–6], the results of more than 10 major orthopaedic surgeries were reported, but there is no large report from a single treatment centre. This report includes the results of 11 major surgeries that were performed for 7 haemophilia patients by one orthopaedic surgeon as the primary doctor who is

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sufficiently knowledgeable in matters related to haemostasis and an experienced and active surgeon at two hospitals.

Patients

Between 2000 and 2008, the first author as the primary doctor performed 16 orthopaedic surgeries at 2 hospitals for 10 haemophilia patients with inhibitors. During 11 orthopaedic surgeries and postoperative periods for 7 patients, rFVIIa was used to control bleeding. Seven surgeries were performed at the first hospital between 2000 and 2006, and four surgeries were performed at the second hospital between 2007 and 2008. All surgeries were performed by one primary doctor, knowledgeable in haemostasis and an active surgeon, thus, making this the largest clinical report based on major orthopaedic surgeries at a single institute. For Case 1, there was a pseudotumour (20 × 10 cm) in the left femoral region with two skin ulcers. For Case 2, the abduction of both shoulders was less than 80° and flexion was less than 60° owing to osteophytic impingement. Total knee arthroplasty and bipolar hip arthroplasty (Cases 3 and 7) were indicated for end-stage arthropathy with severe pain and recurrent bleeding. Arthroscopic synovectomy (Cases 4, 5 and 6) was indicated for early or progressive arthropathy with recurrent bleeding.

Results

Six orthopaedic surgical treatments were performed for four high-responder haemophilia A patients, three surgeries for two high-responder haemophilia B patients and two surgeries for one low-responder haemophilia B patient. This low-responder patient is allergic to FIX products, so he usually uses rFVIIa as a haemostatic agent (Table 1). The average age at

operation was 26 years (11–52 years old) and the average body weight was 56 kg (43–80 kg). The preoperative inhibitor titres were 1–54.3 Bethesda Units (BU) mL⁻¹ and the plasma-deficient factor levels in all cases were less than 1%, except one (1.7%). All of the surgeries were major, such as joint arthroplasties, arthroscopic synovectomy and a combination of both (Table 2). Four arthroscopic knee synovectomies and two total knee arthroplasties were performed using a tourniquet. There was very little bleeding during the surgeries except for the one that was combined with septoplasty. The blood loss volumes for five orthopaedic surgeries performed for haemophilia patients with inhibitors, without the use of a tourniquet, were comparatively the same with the blood loss volumes for orthopaedic surgeries for haemophilia patients without inhibitors. The average operation period was 125.3 min (69–193 min).

The average of one bolus infusion dose per body weight was 113.6 mcg kg⁻¹ (range 95.2–39.5 mcg kg⁻¹) (Table 3). For the first case (Case 1), which was our first experience, we administered the first bolus infusion before general anaesthesia, and then the second bolus infusion after bleeding occurred following the first incision. For cases that followed, we administered the first bolus infusion before general anaesthesia, and then the second bolus infusion just before the first incision. The average total period for peri-operative bleeding control using rFVIIa was 11.5 days (range 6–23 days). This period, compared with the first two cases (Cases 1 and 2-1), was longer than that of the other cases and the total dose per body weight was also gradually decreased. Bleeding complications during seven surgeries were controlled by bolus infusions of rFVIIa (bolus group) and the other four surgeries were controlled by combined bolus and continuous infusions of rFVIIa (combined group). The total period for peri-operative bleeding control of the bolus group

Case	Age (years)	Body weight (kg)	Deficient factor	Deficient factor level (%)	Inhibitor titre (BU mL ⁻¹)	Anamnestic response
1	52	58	VIII	1.70	17.5	Yes
2-1	29	51	VIII	<1	2.3	Yes
3-1	38	60	VIII	<1	6.5	Yes
4-1	11	43	IX	<1	28.8	Yes
5	27	48	VIII	<1	1	Yes
3-2	39	60	VIII	<1	5.8	
6	13	45	IX	<1	54.3	Yes
4-2	13	47	IX	<1	29	
2-2	33	80	VIII	<1	13	
7-1	16	63	IX	<1	1	No
7-2	17	60	IX	<1	1	No

BU, Bethesda Unit.

Table 1. Patient demographics and clinical characteristics: 11 major orthopaedic surgeries were performed for 7 congenital haemophilic patients with inhibitors.

Table 2. Surgical data: seven surgeries from Cases 1 to 6 were performed at the former hospital and the others from Cases 4-2 to 7-2 were performed at the present hospital.

Case	Operation	Operation time (min)	Blood loss (mL)	Tourniquet
1	Removal of pseudotumour	193	1608	No
2-1	Removal of osteophytes and manipulation of right shoulder	107	57	No
3-1	Right total knee arthroplasty	146	120	Yes
4-1	Arthroscopic synovectomy for right knee	119	Little	Yes
5	Arthroscopic synovectomy for right knee and removal of osteophytes of left ankle	163	Little	Yes
3-2	Left total knee arthroplasty and septoplasty	160	610	Yes
6	Arthroscopic synovectomy for right knee	116	Little	Yes
4-2	Arthroscopic synovectomy for left knee	95	Little	Yes
2-2	Removal of osteophytes of left shoulder	106	53	No
7-1	Left bipolar hip arthroplasty	104	1056	No
7-2	Right bipolar hip arthroplasty	69	519	No

(average 12.3 days) was longer than that of the combined group (6.5 days), and the total dose per body weight of the bolus group (7.66 g kg^{-1}) was also more than that of the combined group (3.65 g kg^{-1}), but statistically speaking there were no real differences between the two groups. An anti-fibrolitic agent (tranexamic acid) was used during peri-operative bleeding control periods for all patients except three who complained of nausea induced by the agent. Excellent surgical results were achieved for all surgeries. The pseudotumour was removed *en bloc*. After both shoulder osteophytes were removed and the right shoulder was manipulated, the abduction and flexion of both shoulders improved to around 90° . After joint arthroplasties, pain was relieved and bleeding did not recur. After synovectomy, bleeding gradually stopped and did not recur.

However, haemostatic evaluations differed. Nine surgeries had been controlled without unexpected massive bleeding or bleeding complications (excellent), and one of the two performed pseudotumour removals had expected massive bleeding with bleeding complications (good), and another performed bipolar hip arthroplasty had unexpected massive bleeding with bleeding complications (fair).

Complications

There were no thrombogenic adverse effects, only two bleeding episodes. One episode was re-bleeding on day 9 after the operation. This bleeding was controlled with a shortened bolus infusion interval from 6 to 4.5 h. The second episode was continued bleeding from the operative day, despite good haemostasis in the operation room. We continued

Table 3. Overview of dose and periods of recombinant activated factor VII for bleeding control at peri-operative periods and complications.

Case	One dose per body weight (mcg kg^{-1})	Total dose per body weight (g kg^{-1})	Total infusion periods (days)	Bolus infusion periods (days)	Continuous infusion periods (days)	Tranexamic acid (days)	Complications
1	103.4	9.9	19	19	0	18	Bleeding
2-1	117.6	13.9	22	22	0	21	
3-1	120.0	8.5	12	12	0	13	
4-1	139.5	5.3	7	7	0	2	Nausea
5	125.0	4.5	8	8	0	7	
3-2	120.0	8.4	12	12	0	14	
6	106.7	3.1	6	6	0	6	
4-2	102.1	3.5	5	2	3	2	Nausea
2-2	120.0	2.4	5	2	3	2	Nausea
7-1	95.2	3.8	7	1	6	8	
7-2	100.0	4.9	9	2	7	8	Bleeding

to administer rFVIIa by bolus injection, 15 times at 2-h intervals, until the bleeding started to ooze and then we changed to continuous infusion. The bleeding stopped on day 3 after the operation.

Discussion

There are two major limitations to performing surgery for haemophilia patients in Japan. First, general insurance in Japan does not permit chemical or radioactive synoviorthesis for any arthropathies or synovitis. The clinical results show that these synoviorthesis procedures are safe and effective. Internationally, these procedures are first-line therapies for haemophilic synovitis, especially for inhibitor patients. However, as we are not able to choose these procedures, arthroscopic synovectomy is the first-line therapy for haemophilic synovitis in Japan. This is the reason why we have many arthroscopic synovectomies for haemophilia with inhibitors. Another limitation concerns the use of aPCC. Until the end of March 2008, we were not permitted to use aPCC over 3 days serially and we were required to change from aPCC to other concentrates on the fourth day even if aPCC had been effective. Most of the cases in this report were performed before April 2008 and they were controlled using rFVIIa.

Orthopaedic surgery had been impossible for haemophilia with inhibitors for the past two decades. The development of bypassing agents, such as aPCC and rFVIIa made orthopaedic surgery possible, and the results of the first operation using rFVIIa was published in 1988 [7]. After this case report, orthopaedic surgery started to be performed internationally for haemophilia with inhibitors, but as an elective surgery performed only by an expert medical haemophilia team. Most of the surgical results were of minor surgeries and major surgical results were mainly reported as case reports. In terms of large major orthopaedic surgical results for haemophilia with inhibitors under rFVIIa cover, Obergfell *et al.* [4] reviewed the orthopaedic surgical results published up until 2006. According to this review, the surgical results of two to six major orthopaedic surgeries were reported among five articles from single institutes. After 2006, Harberman *et al.* [8] reported the surgical results of six surgeries, which was the largest study from a single institute. However, some multicentre studies had reported 6–18 major orthopaedic surgical results [5,9,10]. This report has 11 major orthopaedic surgical results and is the largest study from a single institute.

It is important for bleeding control using rFVIIa to increase plasma rFVIIa levels. Hoffman *et al.* [11]

concluded that the doses of rFVIIa required for efficacy produce plasma levels that are several orders of magnitude greater than the K_d for binding of FVIIa to tissue factor, and a platelet surface mechanism is better able to explain the clinical efficacy of high-dose FVIIa therapy. In a report that included the experiences of seven European haemophilia centres, it was concluded that high doses of rFVIIa are safe and effective for the treatment and prevention of bleeding [12]. Also Salaj *et al.* [13] concluded that initial high doses of rFVIIa were associated with a decline in total rFVIIa consumption, because the rate of thrombin generation is important for fibrin clots that form in the presence of high amounts of rFVIIa and are more resistant to proteolysis, which might be of great importance in the context of joint inflammation where elevated enzyme levels exacerbate proteolysis and the destruction of synovium, cartilage and bone. In two recently published papers in which the sole aim was to establish a consensus protocol, bolus infusion was recommended as routine haemostasis therapy for haemophilia with inhibitors and continuous infusion was not recommended because more clinical studies are required for this mode of administration [6,14]. Giangrade [14] recommended that 120–180 mcg kg⁻¹ be injected at the start of surgery, just prior to the first incision. Then, follow-up doses of 90 mcg kg⁻¹ are given at 2–6-h intervals during the peri-operative periods.

In our experiences, the first bolus infusion was given before general anaesthesia and the second bolus infusion was given just before the first incision. The interval between the first and second infusions was shorter than 2 h. This administration mode achieved higher plasma rFVIIa levels without changing the dose and prevented bleeding incidents for unconscious patients.

However, rFVIIa has a short half-life and requires frequent administrations to keep the plasma levels of FVIIa above that required to maintain haemostasis for haemophilia with inhibitors. Therefore, there were some reports that already confirmed the stability and microbiological safety *in vitro* and *in vivo* of rFVIIa after being reconstituted [15–17]; also, the good surgical results noted in the clinical reports [15,18–20] were increased by the continuous infusion of rFVIIa as an economical mode of administration. Continuous infusion was started after initial bolus infusion. The bolus dose range was from 90 to 104 mcg kg⁻¹. The continuous infusion rate range at the start was from 16.5 to 50 mcg kg⁻¹ h⁻¹, and the duration range was from 1 to 26 days. In terms of the continuous infusion rate, Schulman [15] concluded that it was possible to use 10 IU mL⁻¹ as a

maintenance level for most situations provided that precautions are taken to avoid the risk factors for hemorrhagic complications. This 10 IU mL^{-1} was calculated to be $660 \text{ IU kg}^{-1} \text{ h}^{-1}$ or $13.2 \text{ mcg kg}^{-1} \text{ h}^{-1}$. In all the reports, the continuous infusion rates were more than $13.2 \text{ mcg kg}^{-1} \text{ h}^{-1}$ and achieved good haemostasis, except one. This continuous infusion rate at the start was $16.5 \text{ mcg kg}^{-1} \text{ h}^{-1}$. To achieve good haemostasis during surgery and just after operation, the rFVIIa plasma levels must be higher than 10 IU mL^{-1} as a maintenance level.

Furthermore, we have another administration mode that is a combination of bolus and continuous infusion and had already been reported as continuous infusion [21–24], but here we refer to this mode as combination infusion because it consists of several bolus infusions as opposed to one bolus infusion prior to continuous infusion [18,20,25]. As for continuous infusion, Ludlam *et al.* [18] reported nine major orthopaedic surgeries in which rFVIIa was infused at a rate of $50 \text{ mcg kg}^{-1} \text{ h}^{-1}$ for 7–20 days after an initial preoperative bolus of 90 mcg kg^{-1} . Postoperatively, there were bleeds in six patients. Santagostino *et al.* [20] reported 11 major orthopaedic surgeries in which rFVIIa was infused at a rate of $20 \text{ mcg kg}^{-1} \text{ h}^{-1}$ for 3–14 days after an initial preoperative bolus of $90\text{--}135 \text{ mcg kg}^{-1}$. Postoperatively, there were bleeds in two patients. Smith *et al.* [25] also reported eight elective surgeries in which rFVIIa was infused at a rate of $16.5 \text{ mcg kg}^{-1} \text{ h}^{-1}$ for 1–26 days after an initial preoperative bolus of 90 mcg kg^{-1} , and they concluded that the $16.5 \text{ mcg kg}^{-1} \text{ h}^{-1}$ infusion rate reliably achieves plasma FVII activity levels of 10 IU mL^{-1} , but this level does not provide reliable haemostasis. However, for case studies related to the administration mode we referred to as combination infusion, Tagariello *et al.* [24] reported two cases in which rFVIIa was infused at a rate of $11\text{--}42 \text{ mcg kg}^{-1} \text{ h}^{-1}$ for 12–29 days after bolus infusion of 120 mcg kg^{-1} for 2–3 days. In both cases, bleeding complications occurred on days 8 and 14 after surgery, respectively. He also reported another successful case in which rFVIIa was infused five times at 2-h intervals prior to continuous infusion [23]. Peppez *et al.* [22] reported one case of a total hip arthroplasty in which rFVIIa was infused at a rate of $7\text{--}15 \text{ mcg kg}^{-1} \text{ h}^{-1}$ for 12 days after bolus infusion of $90\text{--}150 \text{ mcg kg}^{-1}$ for 5 days, and no bleeding complications occurred. Lorenzo *et al.* [21] reported one case of an open evacuation of a large knee haemarthrosis in which rFVIIa was infused at a rate of $20 \text{ mcg kg}^{-1} \text{ h}^{-1}$ for 7 days after bolus infusion of 120 mcg kg^{-1} for 3 days, and they concluded that

FVIIa plasma levels of $6\text{--}10 \text{ IU mL}^{-1}$ were safe and effective at preventing postoperative haemorrhaging in this patient.

Based on published articles, we thought that the continuous infusion rate of $16.5 \text{ mcg kg}^{-1} \text{ h}^{-1}$, which reliably achieves plasma FVII activity levels of 10 IU mL^{-1} , is good enough to maintain a haemostatic condition, but not to achieve good haemostasis. A higher rate of continuous infusion might achieve good haemostasis, however, two recent reports [6,14] concluded that bolus infusion is more reliable to achieve good haemostasis than continuous infusion. We believe it is most important for peri-operative haemostasis to achieve a good haemostatic condition just after surgery, and also believe that the administration of bolus infusion during surgery is more effective at stopping bleeding than continuous infusion. However, theoretically the total dose of bolus infusion administered during the peri-operative period is more than that of continuous infusion, so from an economical point of view it is also important to change from bolus infusion to continuous infusion once all bleeding has stopped. We recommend the administration of the referred to combination infusion that consists of two parts: a bolus infusion (i.e. several bolus infusions) to achieve good haemostasis and a continuous infusion to maintain a good haemostatic condition. We also believe that this combination infusion mode is the most effective and economical mode to administer.

We have performed numerous major orthopaedic surgeries for haemophilia patients with inhibitors and have achieved good haemostasis. Based on those results, we have concluded that the combination of bolus and continuous infusions of rFVIIa is safe and effective, and more convenient to administer than simple bolus infusion therapy to achieve haemostasis at peri-operative periods. In addition, our data also concurs with the data of several previous reports which showed that orthopaedic surgery for haemophilia patients with inhibitors by means of rFVIIa is safe and effective.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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