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Activated prothrombin complex concentrate (FEIBA®) treatment during surgery in patients with inhibitors to FVIII/IX

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Summary. Non-activated and activated prothrombin complex concentrates (PCC/aPCC) have been used successfully to treat bleeds in haemophilia patients with inhibitors, but most physicians do not consider these products as effective as factor VIII/IX (FVIII/IX) concentrates in non-inhibitor patients. Thus, surgical procedures in inhibitor patients have been performed reluctantly. We have performed 14 minor and five major surgical and invasive diagnostic procedures in eight patients with congenital haemophilia A and inhibitors and in two patients with acquired haemophilia. When a loading dose of 100 U kg^{-1} of FEIBA® was given followed by 200 U kg^{-1} day^{-1} in three divided doses every 8 h for 3 days, and then, when the daily dose was tapered to 100–150 U kg^{-1}, no severe or unexpected bleeding complications were observed. However, one adverse event was observed. A 69-year-old man who suffered a myocardial infarction the third postoperative day following sigmoidectomy was managed safely with opiate analgesia, nitrates and diuretics, and the continued use of FEIBA®.

Keywords: activated prothrombin complex concentrates, haemophilia, inhibitors, myocardial infarction, surgery

Introduction

High titre inhibitors to factor VIII (FVIII), and less often to factor IX (FIX), represent a major obstacle in the treatment of haemophilia A and B [1,2]. These allo-antibodies, as well as auto-antibodies in acquired haemophilia, confer refractoriness to therapy with FVIII or FIX concentrates. Porcine FVIII, recombinant factor VIIa (rFVIIa), non-activated and activated prothrombin complex concentrates (PCC/aPCC) have been used successfully to treat bleeds in patients with inhibitors. Nevertheless, most physicians do not consider these products as effective as FVIII/FIX concentrates in non-inhibitor patients, and surgical procedures have been performed reluctantly in inhibitor patients [3–5].

For several years, porcine FVIII concentrates along with PCC to the patients whose inhibitors cross-reacted with porcine FVIII, were the mainstay in the management of bleeds in inhibitor patients in Norway. Shortness in supplies of porcine FVIII and the introduction of recombinant rFVIIa made us reconsider our treatment strategies for inhibitor patients and for patients with acquired haemophilia. Activated prothrombin complex concentrate (FEIBA®; Baxter BioScience, Vienna, Austria) which had been available in the Nordic countries from the early 1980s and rFVIIa (NovoSeven®; NovoNordisk, Copenhagen, Denmark) which became available to us in the early 1990s had both been used successfully in the management of bleeds in inhibitor patients [6,7]. In 1995, we decided to use FEIBA® as first line treatment in adult inhibitor patients presenting with bleeds. At that time, there were no studies reported that clearly indicated that rFVIIa or aPCC were more efficacious than the other in controlling bleeds in these patients. However, cost favoured the use of aPCC. As time went by, our experience with FEIBA® in the management of bleeds was excellent (Tjønnfjord, unpublished observations). Consequently, we were encouraged to use FEIBA® in patients with allo- or auto-antibodies to FVIII who were in need of surgery or invasive diagnostic procedures. The purpose of this report is to disseminate our experience

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with the use of FEIBA® during surgery in adult patients with high titre FVIII/FIX inhibitors.

Materials and methods

Patients

Elective surgery on patients with bleeding disorders from all of Norway is performed at Rikshospitalet University Hospital. All surgical and invasive diagnostic procedures performed at this hospital between January 1996 and March 2003 on patients with high titre inhibitors to FVIII/FIX have been included in this report. Altogether, we have had 16 patients (14 adults and two children) with high titre inhibitors in Norway during the study period. Patients with acquired haemophilia who have had surgery performed in our institution are also part of the study population. A total of 10 patients are included in the report, eight patients with severe haemophilia A complicated by inhibitors and two patients with acquired haemophilia. Patient characteristics are provided in Table 1.

Substitution therapy

FEIBA® was delivered by short time infusion (15–20 min) three times daily. A preoperative loading dose of 100 U kg^{-1} was given. The following doses were adjusted so that the total daily dose approximated to 200 U kg^{-1}. Following the third postoperative day, the dose of FEIBA® was tapered gradually to a daily dose of 100–150 U kg^{-1}.

Tranexamic acid was not administered systemically. However, we aimed at local application of tranexamic acid whenever possible. Tranexamic acid (solution containing 500 mg diluted in an equal volume of drinking water) was used as mouth-rinse four times daily for a week following tooth extraction (patients 2, 4 and 9). Dressings moistened with tranexamic acid were applied daily for a week following circumcision in patient 3.

Monitoring of treatment

Specific laboratory assesment of the haemostatic effect of FEIBA® was not available. We did, however, measure the prothrombin time (PT) immediately prior to and 15–20 min following the loading dose of FEIBA®. To address the development of disseminated intravascular coagulation PT, activated partial thromboplastin time (APTT), fibrinogen and D-dimer were assessed daily.

Results

Procedures performed

Nineteen surgical and invasive diagnostic procedures, 14 minor and five major procedures, were performed in eight patients with severe haemophilia and in two patients with acquired haemophilia (Tables 2 and 3). We did not cancel any scheduled procedure because of lack of shortening of PT, and a shortening of PT of 4–8 s following the loading dose of FEIBA® was observed in all patients.

Haemostatic efficacy

The haemostatic efficacy was excellent with no blood loss following all minor procedures. This was also the case following two of the major procedures. The haemostatic efficacy has been rated as good following three major procedures. Patient 6, who had a left-sided nephrectomy performed as a result of a renal carcinoma, became haemodynamically unstable during the first postoperative day.

Table 1. Patient characteristics.

Patient no.	Age (years)	Weight (kg)	Haemophilia A	Max. inhibitor titre (BU)	Current inhibitor titre (BU)
1	58	72	Acquired (anti-FIX)	37	37
2	64	130	Acquired (anti-FVIII)	1350	1350
3	71	75	Congenital	488	186
4	64	87	Congenital	100	4
5	48	85	Congenital	76	43
6	41	105	Congenital	28	28
7	69	87	Congenital	13	5
8	26	55	Congenital	270	97
9	79	77	Congenital	77	33
10	22	50	Congenital	124	124

Table 2. Main characteristics of minor surgical procedures.

Patient no.	Procedure	No. of infusions	Duration (days)	Total dose (U)	Dose (U $kg^{-1}day^{-1}$)	Complications	Haemostatic outcome
1	Trephine biopsy	1	1	4000	55	No	Excellent
2	Insertion of Hickman-line	3	1	33 000	253	No	Excellent
2	Tooth extraction	3	1	15 000	115	No	Excellent
3	Cataract and intraocular lens implantation	3	1	20 000	267	No	Excellent
3	Cataract and intraocular lens implantation	3	1	14 000	186	No	Excellent
3	Circumcision (phimosis)	3	1	14 000	186	No	Excellent
3	Teleangiectasia of the tongue/laser	1	1	4000	50	No	Excellent
4	Cataract and intraocular lens implantation	3	1	14 000	162	No	Excellent
4	Tooth extraction	10	3	28 000	112	No	Excellent
5	Cystoscopy/pyelography	1	1	4000	47	No	Excellent
8	Extirpation of prepatellar bursa	10	5	39 000	132	No	Excellent
9	Tooth extraction	12	3	48 000	212	No	Excellent
9	Tooth extraction	3	1	11 000	146	No	Excellent
10	Paronychia/bil.nail resection	14	5	39 000	156	No	Excellent

Table 3. Main characteristics of major surgical procedures.

Patient no.	Procedure	No. of infusions	Duration (days)	Total dose (10^3 U)	Dose (U $kg^{-1}day^{-1}$)	Complications	Haemostatic outcome
5	Arthroplasty (knee)	20	9	127	167	Drainage 750 mL Hgb ↓ 45 g L^{-1}	Good
6	Nephrectomy/ splenectomy	53	17	227	127	Yes, splenic haemorrhage	Good
6	Wound rupture revision	17	5†	82	156	No	Excellent
7	Sigmoidectomy	23	13	118	104	Yes, myocardial infarction	Excellent
8	Arthroplasty (knee)	32	14	98	127	Hgb ↓ 62 g L^{-1} 2PRC	Good

†As a result of shortness in supplies, FEIBA® was followed by rVIIa (NovoSeven®) for an additional 3 days; a total dose of 57.6 mg rFVIIa was administered.

This was caused by a subcapsular splenic haemorrhage. A splenectomy was performed following which the haemostasis was excellent. The subcapsular haemorrhage was judged by the surgeons primarily to be a consequence of trauma to the spleen during the nephrectomy. Following a total knee arthroplasty, 750 ml of blood was recovered from the suction drain in patient 5. He experienced a drop in haemoglobin concentration from 128 g L^{-1} to 83 g L^{-1}, but he did not require any transfusion of red cells. Patient 8 had a drop in haemoglobin concentration from 137 g L^{-1} to 75 g L^{-1} following a total knee arthroplasty and required transfusion of two units of packed red cells.

Adverse effects

The tolerance to FEIBA® during infusion was excellent. None of the patients reported chills, fever or rash. However, following a sigmoidectomy a non-ST-elevation myocardial infarction (NSTEMI) was diagnosed in patient 7, a 69-year-old man with no previous history of coronary heart disease. He had been bound to a wheelchair for several years because of haemophilic arthropathy. The possibility that this patient suffered from significant subclinical coronary atheromatosis cannot be excluded. A coronary angiography was never performed. He was a previous smoker. Unfortunately, we have no information on triglyceride or cholesterol levels. He complained of

chest pain and dyspnoea the third postoperative day following the ninth dose of FEIBA®. He was stabilized by opiate analgesia, nitrates and diuretics. We considered to stop the administration of FEIBA® and switch on to rVIIa, but we actually continued with FEIBA®. There was nothing to indicate a progression of his NSTEMI to a STEMI, and the patient had recovered completely without clinical signs of heart failure.

Signs of disseminated intravascular coagulation and venous thromboembolism were not observed in any of the patients.

Discussion

Inhibitory allo- and auto-antibodies to FVIII/IX render replacement therapy with FVIII/IX concentrates ineffective. However, several therapeutic options are available to control bleedings in patients with inhibitors [3–7]. Our report underscores that minor and major surgical procedures may be performed with a low risk of bleeding complications using an aPCC (FEIBA®) as the sole substitution product. No haemostatic failure was observed. Admittedly, one patient became haemodynamically unstable following nephrectomy. This was because of a subcapsular splenic haemorrhage, which was judged by the surgeons primarily to be a result of trauma to the spleen during nephrectomy and not ineffective haemostasis. The blood loss following the two total knee replacements is within the range reported in non-inhibitor patients [8], although, somewhat in excess of the blood loss we usually see in non-inhibitor patients in our institution (Tjønnfjord, unpublished observations). Our results are in line with those reported by the French FEIBA study group [9].

Cataract removal and intraocular lens implantation are mostly performed through avascular structures of the eyeball with a very low risk of bleeding complications in normal individuals. Therefore, one might argue that such procedures could be performed without the prophylactic use of coagulation factor concentrates in haemophiliacs. Sometimes an iridectomy may be needed and even a small amount of postoperative bleeding would jeopardize the outcome of the procedure. Thus, we chose to give FEIBA® preoperatively followed by two postoperative doses.

We usually treat haemophiliacs with coagulation factor concentrates for 3 days following tooth extractions and combine it with mouth-rinse with tranexamic acid for a week. On two occasions, we gave FEIBA® for only 1 day (three doses) because the surgical trauma was judged to be minor in these particular cases. Following major surgery, coagulation factor concentrates was given for 9–17 days. Prevention of per-operative and postoperative bleeding has been accomplished with aPCC at a broad range of doses and frequency [9–13]. Total doses per day in these studies ranged from 50–400 U kg^{-1}, and postoperative dosing tended to cluster around 150 U kg^{-1}. We aimed at providing a preoperative loading dose of 100 U kg^{-1} followed by a postoperative dose of 200 U kg^{-1} day^{-1} in three divided doses every 8 h for the first three postoperative days. Thereafter, we tapered the dose in line with our practice in non-inhibitor patients [14]. Our treatment schedule turned out to be effective in preventing postoperative bleeding, but we do not know whether our treatment schedule provided a minimum effective dose and frequency of aPCC. We used a shortening of PT as an indication of procoagulant activity provided by the infusion of aPCC, but we do not consider measurements of PT as a useful tool to assess the minimum effective dose and frequency of aPCC in preventing postoperative bleeding. The thrombin generation assay show some promise as an indicator of haemostatic efficacy of aPCC, but its definitive role has to be established in controlled trials. The lack of a reliable laboratory assay to assess haemostatic efficacy of aPCC and rFVIIa in the patients with inhibitors is a major disadvantage in the care of these patients. Establishing a minimum effective dose and frequency to prevent postoperative bleeding would help to reduce hospital costs. We have previously shown that coagulation factor concentrates have a major impact on the total cost of surgery in haemophiliacs [14]. Taking total knee arthroplasty as an example using our treatment schedule, the coagulation factor concentrate costs in the patients with inhibitors are four to five times higher than in non-inhibitor patients.

Establishing a minimum effective dose and frequency would also be helpful in avoiding overdose and the risk of life-threatening thrombotic complications. It has been recognized for many years that thrombotic complications may be associated with the use of PCCs and aPCCs, and it is noteworthy that in inhibitor patients, the major clinical manifestation is myocardial infarction (MI) [15, reviewed in 16]. One of our patients, a 69-year-old man, developed a NSTEMI on the third postoperative day following sigmoidectomy. Hough *et al.* have safely used rFVIIa to treat bleeds in the immediate and long-term period following aPCC-related MI [16]. Based on their two cases, they recommend that the immediate management of aPCC-related MI should include stopping the administration of the concentrate. Their report

was not published when we were faced with our patient with an aPCC-related MI. Obviously, we considered to stop the treatment with FEIBA® and switch on to rFVIIa. However, for practical reasons this did not turn out to be an option, and we continued treatment with FEIBA ® as scheduled just as safely as reported by Hough *et al.* switching to rFVIIa [16].

In summary, minor and major surgery is feasible with a low risk of severe bleeding complications in haemophilia patients with inhibitors and patients with acquired haemophilia using aPCC (FEIBA®). Laboratory assays to guide establishing a minimum effective dose and frequency of aPCC are badly needed to reduce the high cost of coagulation factor concentrates and the risk of aPCC-related thrombotic complications.

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