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ORIGINAL ARTICLE *Inhibitors*

Surgery in patients with haemophilia and high responding inhibitors: Izmir experience

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Summary. This report evaluates the haemostatic efficacy of recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrate (APCC) in patients with haemophilia and high responding inhibitors who underwent major and minor surgery. Data pertaining to surgeries from 2001 to 2009 at a single centre were retrospectively analysed. During this period, 53 surgical procedures were performed in 30 haemophiliacs with high responding inhibitors. Mean age was 16.2 ± 9.4 years. Eleven major surgeries in 4 patients, 41 radioisotope synovectomies (RS) and one circumcision classified as minor surgery in 28 patients were performed. Among the major surgery procedures, four were treated with rFVIIa, five with APCC and two with sequential use of APCC and rFVIIa. We used rFVIIa at the dosage of 80–120 μg kg^{-1} every 2 h and APCC 100 IU kg^{-1} every 12 h for the major surgery. When performing RS, we used rFVIIa in 18 patients with 26 target joints and APCC in 9 patients with 15 target joints. Three consecutive doses of rFVIIa (90 μg kg^{-1}) were used at 2-h intervals followed by additional three doses at 6-h intervals. The initial dose of APCC was 75 IU kg^{-1} followed by a second and third dose of 50 IU kg^{-1} at 12-h intervals. APCC and rFVIIa demonstrated excellent efficacy in our major and minor surgical interventions [100% (22/22) and 94% (31/33), respectively]. We had only two bleeding complications with rFVIIa. There were no thromboembolic complications. APCC and rFVIIa provide an effective and safe first line haemostatic therapy for inhibitor-positive haemophiliacs, allowing both major and minor surgery to be successfully performed.

Keywords: APCC, haemophilia A, haemostasis, inhibitor, rFVIIa, surgery

Introduction

The development of inhibitors against factor VIII (FVIII) or factor IX is one of the most serious complications in haemophilia therapy and is an important challenge in haemophilia care. The inhibitors occur in approximately 30% of patients with severe haemophilia A, less frequently in those with severe haemophilia B and render the treatment of bleeding episodes more difficult and surgery more hazardous [1,2]. The main short-term objective of the treatment in these patients is to control bleeding episodes. The frequency of bleeding is not increased in inhibitor patients. However, the presence of high-titre inhibitors may constitute a major obstacle in the control of haemostasis and severely jeopardize the outcome of the disease. In patients with low-responding inhibitors (≤5 BU mL^{-1}), successful haem ostasis may be achieved by saturating the inhibitor with higher doses of the deficient factor [3], but in patients with high responding inhibitors (>5 BU mL^{-1}) other treatment strategies are required. Additional by-passing agents are needed for surgical operations in these patients. There are several treatment options that appear to be sufficiently safe to assure haemostasis in different surgical procedures. Today, the alternative by-passing agents for the treatment of haemophilia A with inhibitors are prothrombin complex concentrates (PCC), activated prothrombin complex concentrate (APCC) and recombinant factor VIIa (rFVIIa). PCC and APCC

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have been the mainstay of by-passing treatment of inhibitor positive patients for decades [2–4]. Recently, rFVIIa has been added to the therapeutic armamentarium [5]. The haemostatic effect of rFVIIa is based on the activation of the extrinsic coagulation pathway and occurs by forming a complex with tissue factor at the site of bleeding. The risk of generalized hypercoagulability associated with the use of rFVIIa is very low because of the need for interaction of factor VIIa with tissue factor that is released locally only at the site of tissue injury [6]. The clinical use of these agents allowed surgeries to be successfully performed in haemophiliacs with high titre inhibitors and improved their quality of life [7–9].

This report describes the experience at a single Turkish centre over 8 years with by-passing agents as a first line treatment in severe haemophilia A patients with high responding inhibitors who required surgery. In this study, we present 53 surgical procedures (11 major, 42 minor) in 30 haemophilic patients with high responding inhibitors who were treated with APCC and/or rFVIIa. This is one of the largest single-centre series related to surgery in inhibitor positive haemophilia.

Patients and methods

Ege Hemophilia Center is among the biggest centres, which serves all regions in Turkey. This is a retrospective study in haemophilic patients with inhibitor who required major or minor surgery between June 2001 and October 2009. During this period, 53 surgical operations were performed in 30 haemophilic patients with high responding inhibitors (>5 BU mL^{-1}), including scheduled and emergency minor and major surgery. Eleven major surgeries in 4 patients and 42 minor surgeries (41 radioisotope synovectomies, RS; 1 circumcision) in 28 patients were evaluated. All patients had severe type haemophilia A (FVIII≤0.01 IU mL^{-1} in 17; 0.01–0.02 IU mL^{-1} in 13), and their mean age was 16.2 ± 9.4 years (range: 3–40 years).

Regarding the group of major surgeries, 4 patients (range: 3–16 years) underwent 11 surgical operations: one brain operation + ventriculo-peritoneal (V/P) shunt placement for subdural haematoma (developed after cranial trauma), one V/P shunt revision operation, two open surgical synovectomy, six antegrad oesophageal dilatation operation after corrosive liquid intake and one molar teeth extraction. Two major products were used during preoperative and postoperative period of major procedures to maintain haemostasis. We used rFVIIa (NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) at the dosage of 80–120 μg kg^{-1} every 2 h and APCC (FEIBA®, Baxter AG, Vienna, Austria) 100 IU kg^{-1} every 12 h. Four procedures (two patients) were treated with rFVIIa, five procedures (one patient) with APCC and two procedures (two patients) with sequential use of APCC and rFVIIa.

The laboratory tests carried out prior to operation were platelet count, prothrombin activity, activated partial thromboplastin time (APTT), fibrinogen level, d-dimer and level of inhibitor. The initial dose of by-passing agent was given 1 h before the operation. APTT does not return to normal by using these agents. Shortening of prothrombin time was accepted as significant considering the efficacy of the products. Postoperative control tests carried out at least 24–72 h were platelet count, prothrombin activity, APTT, fibrinogen level and d-dimer.

Regarding the RS, 19 knees, 9 elbows, 10 ankles and 3 shoulders were injected in 27 haemophilic patients (range: 3–40 years). All patients had Grade II (permanent synovitis) or Grade III (chronic haemophilic arthropathy) synovitis according to the clinical classification developed by Fernandez-Palazzi [10]. In our centre, we prefer to use yttrium-90 (Y^{90}) for knees and rhenium-186 (Re^{186}) for other joints (elbow, ankle, shoulder) as the colloidal solution of radioactive agents. Between 2001 and 2005, we used Y^{90} as radioisotopic agent for all joints with chronical synovitis. After January 2005, we started using Re^{186} in elbow, ankle and shoulder as Re^{186} has a shorter half-life and a lower tissue penetration range compared with Y^{90}. Y^{90} was injected 5 mCi (4 mCi for ages below 10 years) by orthopaedist intra-articularly for knees and 2 mCi for elbow, ankle and shoulders. Isotope was injected into the joint in a volume of 1 mL, using a separate syringe, prepared by radiochemist. After 2005, 2 mCi Re^{186} was injected for medium-sized joints as elbow, ankle and shoulder. Our RS protocol is described in detail in our previous reports [11,12].

We used rFVIIa in 26 target joints of 18 patients. Three consecutive doses of rFVIIa (90 μg kg^{-1}) were used at 2-h intervals followed by additional three doses at 6-h intervals. APCC was used in 15 target joints of 9 patients. The initial dose of APCC was 75 IU kg^{-1} followed by a second and third dose of 50 IU kg^{-1} at 12-h intervals. The initial doses of both agents were given 1 h before the RS procedures.

Evaluation of haemostatic efficacy

Haemostatic efficacy was assessed on the basis of transfusion requirements. Major and minor surgical interventions reported in this study do not require

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blood transfusions when sufficient haemostasis is achieved in haemophilia patients. The response to treatment was evaluated in two groups: (i) the response to by-passing agents is defined as *good* when there is no need for transfusion of red blood cell concentrates, and (ii) the response to by-passing agents is defined as *poor* when there is a need for transfusion during or after the operation (haemoglobin <7 g dL^{-1}).

Results

All patients operated with by-passing agents and the treatments that they received are indicated in Table 1.

Major surgeries

Patients who had major surgery are summarized in Table 2. One of the patients was a 4-year-old haemophiliac who had a posttraumatic intracranial haemorrhagia. Evacuation of subdural haematoma and V/P shunt operation were performed with rFVIIa supplementation. The protocol for rFVIIa supplementation was 90–120 μg kg^{-1}, at 2-h intervals for the first 3 days, at 4-h intervals on the 4th and 5th days and at 6-h intervals between 6th and 10th days. This patient was re-operated because of disfunctional V/P shunt. For this procedure, rFVIIa (120 IU kg^{-1}) was given at 2-h intervals for the first 2 days, at 4-h intervals on the 3rd and 4th days and at 8-h intervals between 5th and 7th days.

Open surgical synovectomy operation was performed in left knee and elbow joints of a 16-year-old patient. The initial dose of rFVIIa (160 μg kg^{-1}) was administered 1 h before the operation. Following doses (80 μg kg^{-1}) were administered at 2-h intervals during the first 24 h, at 3-h intervals on the 2nd and 3rd days, at 4-h intervals between the 4th and 7th days and at 6-h intervals between 8th and 10th days.

Another 3-year-old patient had oesophageal stricture that developed after corrosive liquid intake. During the antegrade oesophageal dilatation operation, APCC (100 IU kg^{-1}) was administered at 12-h intervals for three consecutive doses in five different sessions. Fourth dose of APCC was required in only second session.

In two cases, sequential therapy with APCC and rFVIIa was obligatory. One of the patients (3 years old) with an antegrade oesophageal dilatation was administered a single dose of APCC (100 IU kg^{-1}). After an initial dose of APCC, patient received rFVIIa because of the temporary unavailability of APCC in our hospital. rFVIIa (90 μg kg^{-1}) was administered at 2-h intervals for six consecutive doses. The other patient (10 years old) with a problematic molar teeth extraction was administered APCC, rFVIIa and fibrin glue sequentially. Following the administration of rFVIIa (90 μg kg^{-1}) to the patient, extraction of two molar teeth was performed. Same dose of rFVIIa was given at 2-h intervals for four consecutive doses after the extraction procedure. Additionally, tranexamic acid therapy was started. Despite this therapy, bleeding continued. Therefore, the patient received a total of 47 doses of rFVIIa (90 μg kg^{-1}) at 3–4-h intervals between the 2nd and 6th day. As the haemoglobin decreased to 7 g dL^{-1}, 3 units of red blood cells were given to the patient. At days 7 and 8, the patient received APCC (100 IU kg^{-1}) at 8-h intervals for six consecutive doses, and fibrin glue was applied twice. The bleeding completely ceased after these interventions.

Minor surgeries

Circumcision operation was performed in an 8-year-old patient. First, three doses of rFVIIa (90 μg kg^{-1}) were administered at 2-h intervals. The remaining doses were administered at 4-h intervals for 2 days and 6-h intervals on the 3rd and 4th days. According to our circumcision protocol [13], fibrin glue and tranexamic acid (10 mg kg^{-1}, three times per day, 7 days) were used as supportive agents to maintain haemostasis. However, at the end of the 7th day, the patient traumatized the surgical wound and bleeding restarted. This bleeding episode was resistant to intensive rFVIIa therapy. Two units of red blood cells were given to the patient. Between postoperative 7th and 15th days, a total of 36 doses of rFVIIa (90–120 μg kg^{-1}) were used, and additionally, fibrin glue was applied once on the 14th day. Bleeding episode was controlled completely on the 15th day.

Radioisotope synovectomy was performed in 27 inhibitor positive patients to treat 41 target joints. During radioisotope synovectomy procedure, $Yttrium^{90}$ was used in 26 target joints (19 knees, 4 ankles, 2 elbows, 1 shoulder) and $Rhenium^{186}$ in 15 target joints (7 elbows, 6 ankles, 2 shoulders). We did not observe any bleeding problem during and after procedures. rFVIIa (90 μg kg^{-1}) was used successfully in 18 patients for the treatment of 26 target joints (11 knees, 6 elbows, 7 ankles and 2 shoulders) at 2-h intervals for three consecutive doses and at 6-h intervals for the following three doses. However, three of these patients required three more doses of rFVIIa at 6-h intervals. APCC was success-

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Table 1. Major and minor surgeries performed in inhibitor-positive haemophilic patients and the therapy modalities applied for haemostasis.

No	Surgery	Age (years)	Inhibitor (BU mL^{-1})	Initial dose* (μg kg^{-1} or IU kg^{-1})	No. doses	Total dose* (μg kg^{-1} or IU kg^{-1})	Response
With rFVIIa							
1	Brain + V/P shunt	4	5.4	120	68	8160	Good
	V/P shunt revision	4	5.4	120	45	5400	Good
2	Open surgical synovectomy in two joints	16	11.5	160	64	5200	Good
	RS (knee + elbow)	14	16	90	6	576	Good
3	Circumcision**	8	16	90	23	2070	Poor
4	RS (knee)	3	65	90	6	544	Good
5	RS (two knees)	10	14.4	90	6	480	Good
6	RS (knee + ankle)	16	19.5	90	6	523	Good
7	RS (two knees)	19	174	90	9	720	Good
8	RS (elbow)	8	8.2	90	6	576	Good
9	RS (elbow + shoulder)	14	9.4	90	6	600	Good
10	RS (knee)	18	131.8	90	9	745	Good
11	RS (shoulder)	14	8.8	90	6	626	Good
12	RS (ankle)	7	5.2	90	6	626	Good
13	RS (ankle)	40	32	90	6	545	Good
	RS (ankle)	39	36	90	6	545	Good
14	RS (knee + elbow)	19	23	90	6	514	Good
15	RS (ankle)	17	14.3	90	6	530	Good
16	RS (ankle)	21	12.8	90	6	496	Good
17	RS (knee + ankle)	16	57.6	90	9	830	Good
18	RS (elbow)	17	9.8	90	6	514	Good
19	RS (knee)	13	28	90	6	600	Good
20	RS (elbow)	22	32	90	6	480	Good
With APCC							
21	Oesophageal dilatation-**1**	3	5.7	100	3	300	Good
	Oesophageal dilatation-**2**	3	5.7	100	4	400	Good
	Oesophageal dilatation-**3**	3	5.7	100	3	300	Good
	Oesophageal dilatation-**4**	3	5.7	100	3	300	Good
	Oesophageal dilatation-**5**	3	5.7	100	3	300	Good
19	RS (two elbows)	12	32	75	3	230	Good
22	RS (knee)	12	8	75	2	175	Good
23	RS (knee + ankle)	14	8.7	75	3	240	Good
24	RS (two knees)	16	6.5	75	3	225	Good
25	RS (knee)	24	37.5	75	2	162	Good
26	RS (knee + ankle)	13	11.2	75	3	240	Good
27	RS (knee + elbow)	26	18.5	75	3	227	Good
28	RS (shoulder)	22	16.8	75	3	230	Good
29	RS (knee + ankle)	40	93	75	3	232	Good
Sequental use of rFVIIa and APCC							
21	Oesophageal dilatation-**6**	3	5.7	100	APCC (1)	100	Good
				90	rFVIIa (6)	600	Good
30	Molar teeth extraction**	**10**	**23**	**90**	**rFVIIa (47)**	**4338**	Poor
				100	#APCC (6)	**600**	Good

V/P, ventriculo-peritoneal; RS, radioisotope synovectomy; rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrate.

*μg refers to rFVIIa, IU refers to APCC.

**Tranexamic acid was administered.

#Fibrin glue was applied twice with APCC.

fully used in 9 patients for the treatment of 15 target joints (8 knees, 3 elbows, 3 ankles and 1 shoulder). The initial dose of APCC was 75 IU kg^{-1} followed by a second and third dose of 50 IU kg^{-1} at 12-h intervals (Table 3).

Haemostatic efficacy and complications

General analyses of our treatment approaches in surgery procedures with by-passing agents were given in Table 4. APCC and rFVIIa demonstrated

Table 2. Major surgery in inhibitor-positive haemophilic patients with by-passing agents.

Product	Type of operation	Age	Treatment
rFVIIa	Open surgical synovectomy in two joints	16	After an initial dose of 160 μg kg^{-1}, following doses (80 μg kg^{-1}) were administered at 2-h intervals during the first 24-h, at 3-h intervals on the 2–3 days, at 4-h intervals between the 4–7 days and at 6-h intervals between 8–10 days.
rFVIIa	Brain operation for subdural haematoma + V/P shunt	4	120 μg kg^{-1}, at 2-h intervals during first 3 days, at 4-h intervals during 4–5 days and at 6-h intervals during 6–10 days.
rFVIIa	V/P shunt revision	4	120 μg kg^{-1}, at 2-h intervals during first 2 days, at 4-h intervals during 3–4 days and at 8-h intervals during 5–7 days.
APCC	*Oesophageal dilatation (five sessions)*	*3*	100 IU kg^{-1}, 3 doses were given at 12-h intervals in every session.
rFVIIa and APCC	Molar teeth extraction	10	47 doses of rFVIIa in 8 days + 6 doses of APCC in last 2 days + fibrin glue was applied twice on the 8th day + tranexamic acid was given for 8 days.

V/P, ventriculo-peritoneal shunt; rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrate.

Table 3. Radioisotope synovectomy in inhibitor positive haemophilic patients with by-passing agents.

Product	Patients (n)	Joints (n) (knee, elbow, ankle, shoulder)	Mean age (range)	Treatment regimen
rFVIIa	18	26	17.2 (3–40)	90 μg kg^{-1}, three consecutive doses at 2-h intervals followed by additional three doses at 6-hour intervals (9 doses were required in 3 patients)
APCC	9	15	19.8 (12–40)	Initial dose of 75 IU kg^{-1} followed by 2nd and 3rd doses of 50 IU kg^{-1} every 12-h

rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrate.

Table 4. General analyses of our surgery procedures treated with by-passing agents.

Product	Patients (n)*	No of episodes* (major+minor)	Response	Complication (n)
rFVIIa	22	33	Good (94%) (31/33)	Bleeding (2)
APCC	12	22	Good (100%) (22/22)	-

rFVIIa, recombinant factor VIIa; APCC, activated prothrombin complex concentrate.
*rFVIIa and APCC were used sequentially in two episodes in two patients.

excellent efficacy in our major and minor surgical interventions [100% (22/22) and 94% (31/33), respectively]. Poor response was observed only in two patients. One of these patients had molar teeth extraction and the other circumcision operation. Transfusion of red blood cells was required after these two procedures. We did not observe any thromboembolic events when using both by-passing agents.

Discussion

Until recently, the decision for surgery in inhibitor positive haemophilic patients was made when it was an absolute necessity, i.e. in emergency situations. However, in reality, elective surgery is often advisable in haemophilic patients with inhibitors because it may lead to an improved quality of life [14]. Currently, several by-passing agents (mainly rFVIIa and APCC) allow haemophilic patients with inhibitors to undergo all types of surgery [15]. Rodriguez-Merchan *et al.* reported a series of 108 elective orthopaedic surgical procedures, suggesting that haemophilic patients with inhibitors requiring elective orthopaedic surgery can undergo such procedures with high expectation of success [16]. In a study by Astermark *et al.*, rFVIIa was routinely used in all participating centres for both children and adults at dosages ranging from 90 to 250 μg kg mL^{-1} at an interval of 2–4 h [17]. APCC is used in 85% of the centres in adults and in 25% of the centres in children with haemophilia A at dosages of 50–100 IU kg^{-1} every 6–12 h [17]. Higher dosages of both agents are considered in the case of life-threatening bleeds.

One of the therapeutic options for inhibitor positive patients to control haemostasis during surgery is APCC. In the first prospective clinical study that was focused on efficacy of APCC in controlling joint and muscle haemorrhages during surgical procedures, bleeding was controlled in 86% of the cases by the use of the product at a dose of 75 IU kg^{-1} every 12 h for a maximum of three doses [18]. However, this study included a small number of surgical procedures. In a multicentre retrospective study by Negrier *et al.*, 19 minor and 4 major surgical procedures were performed using APCC as sole treatment without any bleeding complication [19]. The dose of APCC used during minor and major surgeries was 78–210 IU kg^{-1} and 210 IU kg^{-1}, respectively. Regarding dental extractions, doses of APCC between 150 and 210 IU kg^{-1} were used, and good clinical response was achieved in all cases. A Norwegian study by Tjonnfjord *et al.* [20] also reported their experience on a series of 5 major and 14 minor surgical procedures. In this study, APCC doses ranged between 47 and 267 IU kg^{-1} in minor surgery and 104–267 IU kg^{-1} in major surgery. Bollard [21] and Morado [22] also reported successful central venous catheter insertion procedures performed with APCC.

In our study, the initial dose of APCC used in minor surgeries was 75 IU kg^{-1} with a maintenance dose of 50 IU kg^{-1}, and APCC dose used in major surgeries was 100 IU kg^{-1} at 12-h intervals. The efficacy we obtained with APCC is excellent in 100% of the cases described. We had no haemorrhagical complication in the 22 procedures (7 major and 15 minor surgeries). Our results are consistent with other studies in the literature [7,8,19]. The optimal dose and duration of APCC treatment during surgery have yet to be established. In 2004, a consensus summary from an international workshop on surgery in haemophilia patients with inhibitors recommended that dosage be based on the major vs. minor nature of procedure [23]. The recommended preoperative dosage was 50–70 IU kg^{-1} for minor procedures and 75–100 IU kg^{-1} for major. We obtained good results with the APCC protocol used in RS at our centre (50–75 IU kg^{-1}, at 12-h intervals, for 2–3 doses). Although we used a lower dose of APCC when compared with the literature, we obtained similar results [7,19,20]. Because of the potential for thrombosis, the maximum daily dose of APCC recommended in the past has been 200 IU kg^{-1} [24] and 250 IU kg^{-1} [23]. Overall, APCC has been associated with an extremely low risk of thrombotic events [24,25]. Thromboembolic complications related to APCC were not observed in our study.

The other therapeutic option is rFVIIa. The prospective study by Ingerslev *et al.* reported the data of 12 patients undergoing major surgery by the use of rFVIIa to promote haemostasis where the mean dose used was 99 μg kg^{-1} (89–118 μg kg^{-1}) [26]. In this report, overall efficacy was reported as excellent in 92% of cases, and no adverse effects were described. Lusher *et al.* [27] subsequently reported a total of 103 surgical procedures. In this study, patients received an initial dose of 90 μg kg^{-1} (range 60–120 μg kg^{-1}) with excellent/effective results in 81% of major procedures, 86% of minor procedures and 92% of dental procedures. In the third prospective study, Scharrer *et al.* [28] reported a total of 67 surgical procedures in 28 patients with haemophilia. rFVIIa was used successfully at a dose of 90 μg kg^{-1}. In this study, the most important adverse effect observed in two patients is three episodes of thrombophlebitis. Similar results were reported by DiMichele *et al.* in inhibitor-positive haemophilia patients with central venous catheter insertion [29]. In another prospective randomized study, Shapiro *et al.* [30] presented 29 episodes (18 minor, 11 major) comparing two doses of rFVIIa (35 μg kg^{-1} and 90 μg kg^{-1}). The response to the treatment was good in 93% of the episodes treated with high doses and 67% of the episodes treated with low doses. Kenet *et al.* [31] evaluated 149 episodes treated with three different protocols: two protocols on continuous infusion with standard and high doses and the third protocol with high doses of rFVIIa as a single dose. Greater efficacy was obtained with high dose protocols (either as continuous infusion or single dose) vs. continuous infusion at low doses.

We also obtained good results with rFVIIa in 94% of 33 surgery procedures. After an initial dose of 90 μg kg^{-1}, following doses (90 μg kg^{-1}) were administered at 2–6-h intervals in minor surgeries. In major surgeries, the initial dose was 90–160 μg kg^{-1} and the following doses were 80–120 μg kg^{-1} at 2–6-h intervals. Two patients with molar teeth extraction and circumcision operation developed haemorrhagical complications and received red blood cell transfusions.

The optimal dose of rFVIIa, which has to be administered during different surgical operations is still under investigation. Use of insufficient rFVIIa doses may explain some of the postoperative bleedings observed in some of the studies [22]. rFVIIa does not produce anamnestic response, as it does not contain FVIII. However, two serious side-effects are described: episodes of disseminated intravascular coagulation and thrombosis. In our study, we report no thrombotic phenomena, whereas DiMichele [29]

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and Shapiro [30] observed some major thrombotic episodes (central vein thrombosis and thrombosis of retina).

Antifibrinolytic agents and fibrin glue are suggested in addition to by-passing agents during molar teeth extraction and circumcision [13,32]. The studies demonstrate that tranexamic acid significantly improves the clot stability in patients with haemophilia [33]. Use of tranexamic acid in combination with factor concentrates in all haemophilia patients with and without inhibitors undergoing surgery increases the efficacy of haemostasis and decreases the treatment costs [13,19,32].

Both APCC and rFVIIa have generally demonstrated good efficacy in treating bleeds in inhibitor patients. However, there is inter-patient and inter-episode variability and, in some cases, either therapeutic intervention may even fail. As demonstrated in a recent randomized comparison of APCC and rFVIIa, some patients may respond better to one of the by-passing agents than to the other [34]. Therefore, an important consideration when approaching surgery in an inhibitor patient is past history of responsiveness to a particular by-passing agent.

In some inhibitor positive patients, haemostasis may not be achieved by either rFVIIa or APCC alone. Although *in vitro* studies [35] proposed a potential synergy between rFVIIa and APCC, until recently, treatment of refractory bleeding with rFVIIa and APCC combination therapy was avoided primarily because of the concern for increased risk of thromboembolic complications [36]. However, Schneiderman, in a recent study, reported that combination therapy with sequential administration of standard doses of APCC and rFVIIa was safe and effective in 35 refractory bleeding episodes in four young haemophilia patients [37]. Sequential administration of the by-passing agents was mandatory in our two patients. Efficient haemostasis was achieved in both cases. In another study, Martinowitz also showed that concomitant infusion of low-dose rFVIIa and low-dose APCC is safe, efficient and economical in patients' refractory to rFVIIa [38].

Conclusion

Our results show that major and minor surgical procedures can be performed safely in haemophilic patients with inhibitors using rFVIIa and/or APCC. In our study, we used standard doses of rFVIIa and APCC in surgery procedures without any serious complications. However, different doses of these by-passing agents are used in different surgical studies. Further research is required to delineate the optimal by-passing agent regimen for each type of surgery.

Disclosures

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

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1. **Our results show that major and minor surgical procedures can be performed safely in haemophilic pa...**
Anchor Name: kanıtlanmış etkililik cerrahi uygulanan inhibitörlü hemofili
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2. **Our results show that major and minor surgical procedures can be performed safely in haemophilic pa...**
Anchor Name: NovoSeven® inhibitörlü hemofili hastalarının klinik tablosunda tutarlı olarak yüksek etkililikle hızlı kanama kontrolü sağlar
[Agency Turkey sibel.cakan@pitstop.com.tr]

3. **Our results show that major and minor surgical procedures can be performed safely in haemophilic ...**
Anchor Name: NovoSeven® cerrahide kanamanın önlenmesinde etkili ve iyi tolere edilen ilk basamak tedavidir
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[no notes on this page]