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ORIGINAL ARTICLE *Inhibitors*

Experience of recombinant activated factor VII usage during surgery in patients with haemophilia with inhibitors

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Summary. Inhibitor development is one of the most challenging complications of haemophilia management. Haemostatic control in patients with haemophilia with inhibitors can be difficult, and is especially risky in those undergoing surgical interventions. Most haemophilia patients with inhibitors suffer from chronic joint disease requiring surgical correction due to recurrent bleeding episodes. The aim of this study was to assess the use of recombinant activated factor VII (rFVIIa) as haemostatic therapy during orthopaedic surgery in haemophilia patients with inhibitors. A series of case reports was retrospectively collected to describe clinical experience of rFVIIa use in inhibitor patients undergoing a range of orthopaedic surgical procedures at a single centre. All surgeries were performed using standard methods. All patients received rFVIIa at a starting dose of 120 μg kg^{-1} with the subsequent regimens depending on the type of surgery. rFVIIa provided effective haemostasis in 23 patients with haemophilia A and inhibitors (15 with high inhibitor titres) undergoing orthopaedic surgery. The majority (70%) of surgical procedures were major (joint and extra-articular surgery). The doses and intervals of rFVIIa treatment used varied depending on the severity of bleeding, and the type (major or minor) or site of surgery. In all cases, administration of rFVIIa achieved good haemostasis. In all 23 patients with haemophilia with inhibitors, rFVIIa treatment in orthopaedic interventions proved to be an efficient haemostatic agent, providing effective intra-operative and postoperative haemostasis.

Keywords: haemophilia, inhibitor, NovoSeven®, rFVIIa, surgery

Introduction

The development of inhibitors to factor VIII (FVIII) or FIX is one of the most challenging complications of managing patients with haemophilia A and B respectively. Inhibitor development occurs in 10–35% of patients with haemophilia A and 3–5% of patients with haemophilia B [1–5]. Infused deficient factor concentrates are rapidly inactivated by inhibitors. In addition, the infusion stimulates the synthesis of new antibodies, thereby increasing inhibitor titre and activity in the circulation. As a result, bleeding becomes uncontrolled, and may lead to tragic consequences, despite the current availability of haemostatic therapies.

The presence of inhibitors causes some inversion in the course of haemophilia disease, increasing its severity. The lack of appropriate prophylactic treatment and, in some instances, the low efficiency of haemostatic therapy can play an important role in this process [6]. Haemophilia patients with inhibitors frequently develop haemarthrosis, fractures, purulent infection and haematomas, which can transform into pseudotumours. Furthermore, the number of patients with inhibitors, including teenagers, that have multiple joint lesions requiring surgical or orthopaedic correction is increasing [7,8].

In patients with inhibitors undergoing orthopaedic surgery, a catabolic phase of wound healing is characterized by unstable homeostasis, tissue inflammation in the operational field and rapid consumption of coagulation factors [7]. Depending on the severity of the surgical intervention, this period usually lasts 3–5 days after surgery and requires intensive haemostatic therapy. It is, therefore, necessary to maintain good haemostasis throughout the catabolic phase in patients after major orthopaedic surgery.

Currently, different therapeutic approaches are used to achieve haemostasis during surgery in inhibitor patients [9–13]. One of the most effective haemostatic agents in patients with haemophilia with inhibitors undergoing orthopaedic surgery is the bypassing agent, recombinant activated factor VII (rFVIIa; NovoSeven®;

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1. rFVIIa provided effective haemostasis in 23 patients with haemophilia A and inhibitors (15 with hig... Anchor Name: Surgery with NovoSeven [Agency novoveeva@fcb.com]

2. rFVIIa provided effective haemostasis in 23 patients with haemophilia A and inhibitors (15 with hig... Anchor Name: Birçok çalışmada NovoSeven® ile 400'ün üzerinde başarılı cerrahinin gerçekleştirildiği raporlanmıştır. [Agency Turkey sibel.cakan@pitstop.com.tr]

Novo Nordisk A/S, Bagsværd, Denmark) [14–17]. This is a recombinant agent, free of human pathogens, that stops bleeding at the site of injury regardless of whether patients are deficient in FVIII (haemophilia A) or FIX (haemophilia B). rFVIIa acts by forming a complex with tissue factor on subendothelial cells, which provides fast and reliable haemostasis. Thus, rFVIIa treatment has a minimal risk of systemic activation of coagulation, and patients do not require additional treatment, such as plasmapheresis or immunosuppressive drugs to reduce inhibitor titre. The prescribing information for rFVIIa recommends that the therapy is given immediately before the intervention and then repeated at 2-h intervals during major or minor surgery, with different postsurgical regimens depending on whether the surgery is minor or major [17]. In our practice, the dose and frequency of rFVIIa administration therefore vary depending on the location, severity of bleeding and type of surgery.

This series of case reports presents our retrospective experience of using rFVIIa as haemostatic therapy in patients with haemophilia with inhibitors undergoing a range of orthopaedic surgical procedures in the Department of Reconstructive-Restorative Orthopaedics, Hematology Research Centre, Russian Academy of Medical Sciences, Moscow, Russia.

Materials and methods

All patients presented in this article required hospitalization and received haemostatic therapy as accepted in our medical institution and according to accepted reports for treating haemophilia patients in our country. All patients gave written informed consent to treatment.

rFVIIa was administered as a haemostatic agent in 23 patients with haemophilia A with inhibitors undergoing orthopaedic surgery: 16 major surgery and seven minor surgery (Table 1). Fifteen of the patients had a high inhibitor titre [>5 Bethesda units (BU)], among whom were six with knee endoprosthesis, three with pseudotumour removal, one with osteosynthesis of the left femur with a Dynamic Hip Screw (DHS), one with amputation of the leg and four with sinoviorthosis with rifampicin. All surgical procedures were performed by standard conventional methods [18]. All patients received rFVIIa at a starting dose of 120 μg kg^{-1} with the subsequent regimens depending on the type of surgery.

Table 1. The orthopaedic surgical interventions performed in haemophilia patients with inhibitors under haemostatic rFVIIa therapy.

	Number of cases		
Surgical indication	Major	Minor	Total
Knee endoprosthesis	6		6
Corrective hip osteotomy	2		2
Achilloplasty		1	1
Pseudotumour removal	4		4
Knee arthrolysis	1		1
Osteosynthesis	2		2
Sinoviorthosis with rifampicin		6	6
Amputation of the leg (up to the upper third of the thigh)	1		1
Total	16	7	23

The haemostatic efficacy of rFVIIa was evaluated based on clinical data (i.e. the volume of blood loss during the operation and in the postoperative period; development and volume of haematoma; and pain). In addition, inhibitor titre (BU) and FVIII concentration (%) were measured in all patients(Table 2).

In the early postoperative period, 17 patients received antibiotic therapy with broad-spectrum antibiotics to prevent surgical wound infection. Antifibrinolytic agents and heparin were not administered.

Six patients with chronic synovitis (knee $n = 5$, elbow $n = 1$) received intra-articular injections with rifampicin at a dose of 300 mg in the knee or 150 mg in the elbow. Treatment consisted of five injections at 7-day intervals.

Results and discussion

Two major types of musculoskeletal surgery were performed in the patients with haemophilia with inhibitors: joint surgery and extra-articular surgery (Table 1). Most (70%) of the surgeries conducted under rFVIIa haemostasis were major surgical procedures.

Treatment with rFVIIa

All the inhibitor patients in our centre received haemostatic therapy with rFVIIa immediately before and during orthopaedic surgery at 120 μg kg^{-1} every 2 h (Day 1). The rFVIIa dose was then reduced to 100 μg kg^{-1} every 3 h on Day 2 and 90 μg kg^{-1} every 3 h from Day 3 until the end of the catabolic phase. None of the patients experienced re-bleeding during this phase. During the anabolic phase (i.e. until major reparative processes in the damaged tissues were complete), patients who underwent high- and medium-risk surgical interventions received rFVIIa at a dose of 90 μg kg^{-1} every 4 h, with intervals gradually increasing to 6 h. In all cases, rFVIIa provided effective haemostasis.

Corrective hip osteotomy

Two patients with low inhibitor titre and severe bony ankylosis of the knee underwent epicondylic osteotomy of the hips with good results. Both patients received haemostatic therapy with rFVIIa 120 μg kg^{-1} immediately before and after 2 h, then 90 μg kg^{-1} every 2 h during the first day. On Days 2 and 3 postsurgery, they received rFVIIa at a dose of 90 μg kg^{-1} every 4 h, after

Table 2. Characteristics of the patients.

Age (year)	Type of haemophilia	Inhibitor peak (BE)	Titre of inhibitor previous to the surgery (BE)	Type of the operation	Initial dose of rFVIIa (μg kg^{-1})	Number of doses of rFVIIa	Duration of treatment of rFVIIa (days)	Total dose of rFVIIa (μg kg^{-1})
16	A	3	2	Corrective hip osteotomy	120	38	7	3780
17	A	3	1,2	Corrective hip osteotomy	120	38	7	3780
21	A	5	5	Sinoviorthosis with rifampicin	120	15	10	1800
24	A	4	4	Sinoviorthosis with rifampicin	120	15	10	1800
27	A	40	23	Sinoviorthosis with rifampicin	120	15	10	1800
10	A	27	15	Sinoviorthosis with rifampicin	120	15	10	1800
28	A	60	18	Sinoviorthosis with rifampicin	120	15	10	1800
23	A	46	20	Sinoviorthosis with rifampicin	120	27	11	2880
21	A	40	23	Knee endoprosthesis	120	94	14	9180
23	A	17	8	Knee endoprosthesis	120	94	14	9180
24	A	17	12	Knee endoprosthesis	120	94	14	9180
47	A	25	11	Knee endoprosthesis	120	94	14	9180
22	A	19	18	Knee endoprosthesis	120	94	14	9180
37	A	27	25	Knee endoprosthesis	120	94	14	9180
23	A	12	2	Pseudotumour removal	120	56	8	5130
23	A	20	7	Pseudotumour removal	120	67	8	6090
32	A	27	6,7	Pseudotumour removal	120	67	8	6090
24	A	28	12	Pseudotumour removal	120	94	15	9060
20	A	18	12	Osteosynthesis	120	60	12	5430
24	A	5	4	Osteosynthesis	120	60	12	5430
39	A	5	2	Achilloplasty	120	45	14	4140
23	A	3	3	Knee arthrolysis	120	72	14	6480
25	A	28	20	Amputation of the leg	120	94	14	9180

which rFVIIa was administered at 6-h and then 8-h intervals. There was good haemostasis in both cases.

Sinoviorthosis with rifampicin

Currently, we use chemical synovectomy (sinoviorthosis) with repeated rifampicin injections in patients with chronic synovitis of large joints [19–22]. Rifampicin causes sclerosis of the synovial membrane and decreases its vascularization. Following sinoviorthosis, arthropathy does not usually progress. This method has several advantages: (i) it can be performed as an outpatient treatment, (ii) it has a lower requirement for haemostatic agents than open surgical interventions, and (iii) there is no deterioration of joint function after the end of the course of treatment.

In the six inhibitor patients with chronic synovitis, sinoviorthosis with intra-articular rifampicin injection was performed with concomitant rFVIIa administration. Two doses of rFVIIa (120 μg kg^{-1}) were administered immediately before and one dose 4 h after the first rifampicin injection. One patient developed an intermuscular haematoma in the lower third of the thigh at the site of the fourth rifampicin injection on Day 4. In all these cases of sinoviorthosis, rFVIIa treatment provided good results (i.e., cessation of haemarthrosis was achieved).

Knee endoprosthesis

In parallel with changes in the synovial membrane in haemophilic arthropathy, progressive destruction of cartilage and bone components of joints also occurs. Six patients with Stage IV–V haemophilic arthropathy underwent total knee joint replacement; one of these patients had bony ankylosis of the affected joint. One of the patients ('Patient P') underwent two-stage arthroplasty of both knee joints (Fig. 1). All patients had marked adhesions with fibro-vascularized scar tissue growth in the joint cavity. In Patient P, there was a gross deformation of the articulating surfaces, with formation of intra-osseous cysts, and the complete absence of cartilage (Fig. 2). Endoprosthesis in patients with marked joint changes is usually accompanied by increased bleeding from the scar tissue; in patients with haemophilia with inhibitors, this may lead to uncontrolled bleeding. However, blood loss in inhibitor patients who underwent arthroplasty of the knee with haemostatic rFVIIa therapy in our clinic was comparable to that in patients with classic haemophilia undergoing this type of intervention.

In all cases of knee endoprosthesis with haemostatic rFVIIa therapy, good haemostasis was achieved. An integrated rehabilitation programme, developed in our Hematology Research Centre to restore motion in the operated joint, was initiated 3–4 days after endoprosthesis, not 2–3 days as used in patients with classic haemophilia. One patient required removal of prosthesis 1 year after knee endoprosthesis due to reactivation of endogenous infection following unsuccessful treatment; compression arthrodesis of the knee was performed in this patient with good results.

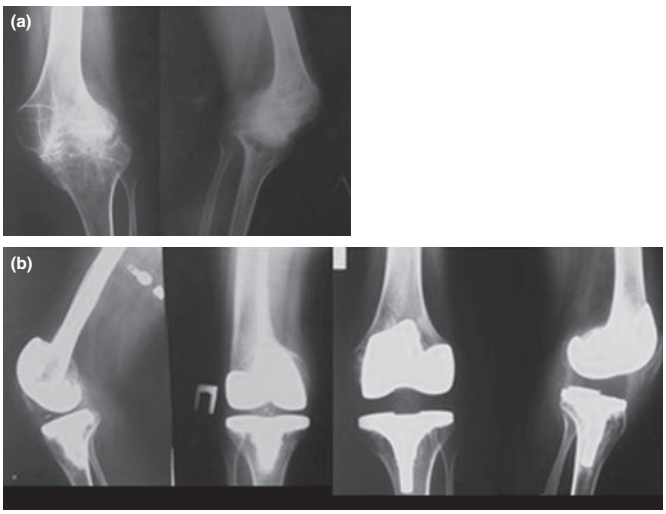

Fig. 1. X-rays of Patient P (a) prior to surgery, showing Stage IV haemophilic arthropathy of the knees, and (b) of the right and left knee joints after knee replacements showing that the extremity axis is correct and components of endoprosthesis are stable.

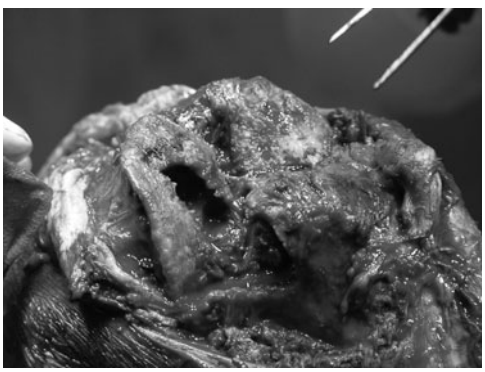

Fig. 2. Photograph of Patient P, showing Stage IV haemophilic arthropathy of the knee with marked deformity of the articular surfaces, destruction of the sliding zone with bone cysts formation and absence of cartilage.

Hip pseudotumour removal

Arthropathy is the main, but not the only, long-term manifestation of haemophilia. Haemorrhages in the musculoskeletal system and their consequences can be much more severe and more diverse. Pseudotumour development from a haematoma, with its inherent clinical and radiological symptoms, is pathognomonic only for severe haemophilia. Due to the current availability of haemostatic therapies, pseudotumours are extremely rare.

Pseudotumour complications can vary and depend on the localization of the pathological process. The following may occur in the affected limbs: fracture, lysis of bone fragments, internal capsule rupture with bleeding into the surrounding tissue and risk of limb ischaemia, and rupture of the necrotic pseudotumour contents out through the capsule and soft tissues. In addition, generalized infection and uncontrolled bleeding can develop. Without appropriate surgical treatment, the patient may die from haemorrhagic shock and sepsis.

Surgical treatment of a pseudotumour should include total removal of its capsule and non-viable tissue, thus avoiding re-bleeding. Effective local haemostasis is an important step in pseudotumour extirpation. During the operation, we used local haemostatic therapies, such as fibrin glue (Tissucol®; Baxter AG, Vienna, Austria).

In our department of reconstructive-restorative orthopaedics, four inhibitor patients with a pseudotumour of the lower extremities (hip $n = 3$, knee $n = 1$) underwent surgical pseudotumour extirpation with haemostatic rFVIIa therapy. Three patients had a high inhibitor titre (>5 BU). One patient (inhibitor titre 3 BU), with pseudotumour and pathological fracture in the middle third of the femur, underwent simultaneous pseudotumour extirpation and intramedullary fixation with an unreamed femoral nail (UFN). In all cases, after pseudotumour extirpation, postoperative wounds were treated by a semi-open method through cavity squeezing with gauze tissue and antiseptic solution. The gauze was removed from the wound according to residual cavity reduction. In all cases of pseudotumour extirpation with haemostatic rFVIIa therapy, good haemostasis was achieved. All patients were free from re-bleeding, and maintained function in the operated limb.

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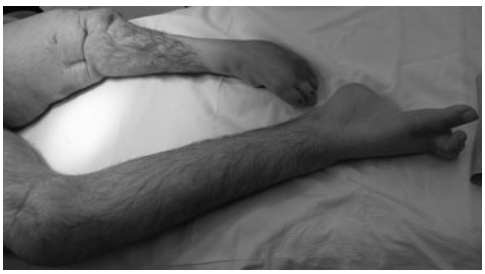

Fig. 3. Photograph of Patient T, showing ischaemic contracture with limb hypoplasia following extensive pseudotumour, resulting in a dysfunctional left leg.

Fig. 4. Photograph of Patient T, showing suppurating and spontaneous rupture of the left foot pseudotumour.

Amputation of the leg

In 1995, one patient with inhibitors ('Patient T') had an extensive pseudotumour in the left thigh and knee. As a result, the patient developed necrosis of the soft tissues and femur, with neurovascular bundle compression, and a pseudotumour infection that had a spontaneous rupture accompanied by massive bleeding. The patient's life was saved at that time. However, ischaemic contracture with limb hypoplasia (shortening of the leg by 20 cm) and marked femur defect subsequently developed, and the limb became completely dysfunctional (Fig. 3). In addition, he experienced recurrent pseudotumours of the left foot accompanied by massive life-threatening bleeding episodes (Fig. 4). Therefore, the patient's left leg was amputated up to the upper third of the thigh. Haemostatic therapy with rFVIIa was administered during surgery and the postoperative period. Good haemostasis was achieved and the patient did not have further bleeding. The wound healed well without inflammation or necrosis and a good stump formed that in current conditions allows limb prosthetics, with an external prosthesis, to be used.

Osteosynthesis

One patient with a high inhibitor titre (12 BU) underwent osteosynthesis with a DHS plate because of an intertrochanteric fracture of the left femur. Another patient undergoing osteosynthesis also had an intertrochanteric fracture of the left femur, but had a low inhibitor titre (4 BU). In both cases there were no bleeding complications during surgery or in the postoperative period. After 1.5–2.0 months, the patients experienced complete consolidation of the bone fragments and currently have an active life and are in employment.

Achilloplasty

One patient with an equinus deformation of the left foot and haemophilia with low titre inhibitor (2 BU) underwent achilloplasty with a good outcome. After the operation, the foot was fixed in a plaster bandage for 6 weeks.

Knee arthrolysis

One patient with Stage III-IV haemophilic arthropathy, which was accompanied by pain and restricted movement, had declined total knee joint replacement. This patient underwent arthrolysis of the target joint; there were no complications during the operation or in the postoperative period.

Conclusion

In all 23 patients with haemophilia with inhibitors, rFVIIa treatment in orthopaedic interventions proved to be an efficient haemostatic agent, providing effective intra-operative and postoperative haemostasis.

Author contributions

T. Polyanskaya, V. Zorenko, E Karpov, M Sampiev, G Mishin and D Vasiliev all took part in the treatment of patients. T. Polyanskaya and V. Zorenko analysed the data and T. Polyanskaya wrote the manuscript. All authors have reviewed drafts of the manuscript and approved the final submitted version. Editorial assistance was provided by Sharon Rayner and Anne Stirland (medical writers, PAREXEL) in compliance with international guidelines for good publication practice.

Disclosures

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References

1 McMillan CW, Shapiro SS, Whitehurst D, Hoyer LW, Rao AV, Lazerson J. The natural history of factor VIII:C inhibitors in patients with hemophilia A. a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors. *Blood* 1988; **71**: 344–8.

2 Ehrenforth S, Kreuz W, Scharrer I *et al.* Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet* 1992; **339**: 594–8.

3 Hay CR, Baglin TP, Collins PW, Hill FG, Keeling DM. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors' Organization (UKHCDO). *Br J Haematol* 2000; **111**: 78–90.

4 Ljung R, Petrini P, Tengborn L, Sjörin E. Haemophilia B mutations in Sweden: a population-based study of mutational heterogeneity. *Br J Haematol* 2001; **113**: 81–6.

5 Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia* 2003; **9**: 418–35.

6 Kulkarni R, Aledort LM, Berntorp E *et al.* Therapeutic choices for patients with hemophilia and high-titer inhibitors. *Am J Hematol* 2001; **67**: 240–6.

7 Andreev YN. Many-sided hemophilia. Monography. Moscow, Njudiamed, 2006: 215.

8 Yu Polyanskaya T, Khametova RN, Yu Andreev N. Development and clinical course of hemophilia complicated by the presence of an inhibitor. *Haematol Transfusiol* 2002; **47**: 9–12.

9 Nilsson IM, Berntorp E, Freiburghaus C. Treatment of patients with factor VIII and IX inhibitors. *Thromb Haemost* 1993; **70**: 56–9.

10 White GC 2nd, Taylor RE, Blatt PM, Roberts HR. Treatment of a high titer anti-factor-VIII antibody by continuous factor VIII administration: report of a case. *Blood* 1983; **62**: 141–5.

11 Abildgaard CF, Penner JA, Watson-Williams EJ. Anti-inhibitor coagulant complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia. *Blood* 1980; **56**: 978–84.

12 Lozier JN, Santagostino 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.

13 Hvid I, Soballe K, Ingerslev J. Elective orthopaedic surgery in haemophilia patients with high-responding inhibitors. In: Rodriguez-Merchan EC, Lee CA eds. Inhibitors in Patients with Haemophilia. Part 6. Musculoskeletal issues. Oxford, UK: Blackwell Science Ltd., 2002: 169–78.

14 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.

15 Faradji A, Bonnomet F, Lecocq J *et al.* Knee joint arthroplasty in a patient with haemophilia A and high inhibitor titre using recombinant factor VIIa (NovoSeven): a new case report and review of the literature. *Haemophilia* 2001; **7**: 321–6.

16 Saba HI, Morelli GA, Azam RR, Klein CJ, Letson GD. Efficacy of NovoSeven during surgery on a haemophiliac with previous history of inhibitors. *Haemophilia* 2003; **9**: 131–6.

17 NovoSeven® RT Prescribing Information. Available at http://www.novosevenrt.com/pdfs/PI_novosevenrt.pdf. Accessed November 23, 2011.

18 Mironov S, Kotelnikov G. A national management. Moscow, 2008.

19 Fernandez-Palazzi F, Rivas S, Viso R, de Bosch NB, de Saez AR, Boadas A. Synovectomy with rifampicine in haemophilic haemarthrosis. *Haemophilia* 2000; **6**: 562–5.

20 Chemis AG. Synoviorthesis with rifampicin in the treatment of chronic synovitis in hemophiliacs. *Haematol Transfusiol* 2002; **47**: 18–9.

21 Sadykova NV, Chemis AG, Mamonov VE, Zorenko VY, Ryashencev MM. The direct and remote results sinovectomy with rifampicin in the patients with hemophilia. *Hematol Blood Transfusion Prob* 2005; **1**: 7–11.

22 Rodríguez-Merchán EC. Management of the orthopaedic complications of haemophilia. *J Bone Joint Surg Br* 1998; **80**: 191–6.

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