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The effect of recombinant factor VIIa (NovoSeven®) on peri-operative bleeding during total knee replacement in a non-hemophiliac patient

Ocena wpływu rekombinowanego czynnika VIIa (NovoSeven®) na śródoperacyjne krwawienie podczas operacji rekonstrukcyjnej kolana z totalną endoprotezą u pacjenta bez hemofilii

Key words: *total knee arthroplasty, blood loss, thrombolysis, rheumatoid arthritis, hemostasis*
Słowa kluczowe: *artroplastyka kolana, utrata krwi, rozpuszczenie skrzepliny, reumatoidalne zapalenie stawu (RZS), hemostaza*

SUMMARY

Background. *Recombinant factor VIIa has been in use for some time to control bleeding in persons with hemophilia. In the present study we describe our experience with the use of a commercial form of recombinant factor VIIa, NovoSeven® (Novo Nordisk, Denmark), to control perioperative bleeding in the course of total knee replacement on a patient who, though not hemophiliac, had a very low tolerance for blood loss.*

Case report. *A 44-year-old patient with anemia and rheumatoid arthritis, with a history of significant peri-operative blood loss was referred for total knee replacement. The employment of two relatively small doses of NovoSeven® caused a considerable decrease in peri-operative surgical site bleeding, and post-operative blood loss from the surgical wound within the first 20 hours after the procedure was easily controlled. No complications were encountered.*

Conclusions. *NovoSeven® can be used safely and successively to control perioperative bleeding even in non-hemophiliac patients.*

STRESZCZENIE

Wstęp. *Czynnik rekombinowanego VIIa stosuje się od paru lat w celu hamowania krwienia u osób z hemofilią. W niniejszej pracy autorzy przedstawiają doświadczenie własne w zakresie stosowania komercyjnej postaci czynnika rekombinowanego VIIa NovoSeven® (Novo Nordisk, Dania) w celu hamowania śródoperacyjnego krwawienia w przebiegu artroplastyki z totalną endoprotezą kolana u pacjentki, która, choć nie miała hemofilii, jednak posiadała bardzo niską tolerancję krwawienia.*

Historia przypadku. *U pacjentki l. 44 z niedokrwistością oraz reumatoidalnym zapaleniem stawu kolanowego, u której podczas poprzedniego zabiegu chirurgicznego doszło do poważnej utraty krwi, wykonano ope-*

rację rekonstrukcyjną kolana z totalną endoprotezą. Po zastosowaniu dwóch stosunkowo niewielkich dawek NovoSeven® nastąpiło znaczne zmniejszenie krwawienie w polu operacyjnym, natomiast utratę krwi z rany chirurgicznej w ciągu pierwszych 20 godzin po zabiegu z łatwością zahamowano, przy braku powikłań.

Wnioski. *NovoSeven® można stosować bezpiecznie i z powodzeniem w celu hamowania śródoperacyjnego krwawienia, nawet u chorych bez cech hemofilii.*

INTRODUCTION

Blood loss during total knee replacement remains a major problem [1-3], complicated by the fact that venous thromboembolism is one of the more serious and most common post-operative complications [4,5]. The difficulties are caused by a clinical dilemma: measures taken to retard perioperative bleeding may well increase the risk of clot formation, while conversely, preventive administration of thrombolytic agents may in some cases lead to increased blood loss during surgery [6,7]. Balancing these countervailing risks is a major challenge for the surgeon, often prompting the decision not to operate in cases where concomitant illnesses (especially hemophilia) increase the risk of perioperative hemorrhage [8,9].

One possible solution for this dilemma is recombinant factor VIIa (rFVIIa), obtained in usable form by culturing renal cells from newborn hamsters. The successful application of rFVIIa to prevent uncontrolled hemorrhages in hemophilia [10-12], and in particular to reduce perioperative bleeding in these patients [8,13,14], motivated us to apply a commercial form of rFVIIa, NovoSeven® (Novo Nordisk, Denmark), in the course of total knee replacement in a 44-year-old patient with anemia and rheumatoid arthritis who, though not hemophiliac, had a very low tolerance for blood loss. The purpose of the present study, then, is to present this case and the results achieved by applying rFVIIa to achieve hemostasis without incurring an undue risk of thrombosis.

CASE HISTORY

The patient (initials RT), female, weight 53 kg, was 44 years old at the moment of operation. Between September 23 and October 5, 2001, RT was hospitalized in our Department (patient history no. 2524) for diagnosis and treatment of severe degenerative disease of the knee (cf. Fig. 1).

There were several concomitant conditions that gave grounds for concern about the possible consequences of blood loss during surgery. RT suffered from renal insufficiency and anemia associated with

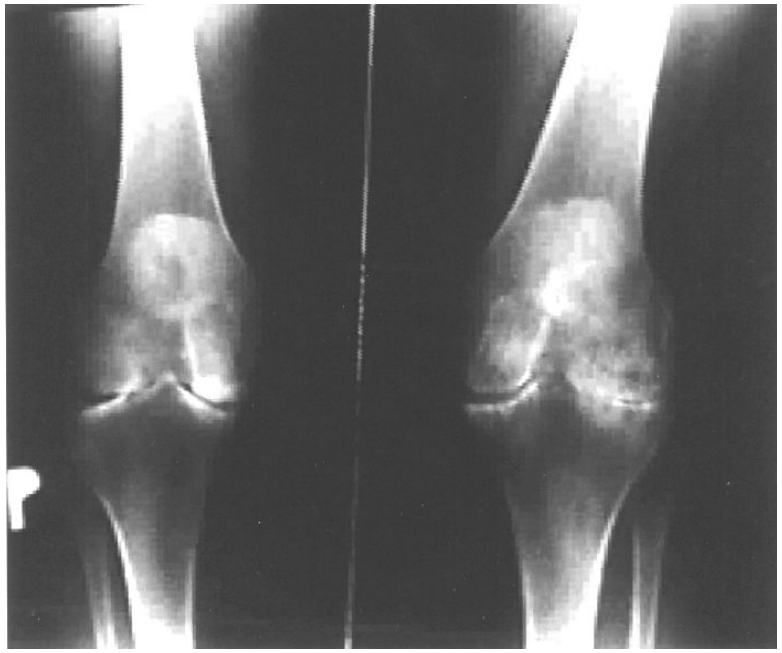

Fig. 1. Pre-operative x-rays of the left knee of patient RT (female, age 44), showing extensive degeneration of the joint, justifying total knee arthroplasty

Ryc. 1. Zdjęcie rentgenowskie lewego kolana pacjentki RT l. 44. Widoczne rozległe zwyrodnienia stawu uzasadniające operację rekonstrukcyjną kolana z totalną endoprotezą

amyloidosis secondary to rheumatoid arthritis, and from hypertension (grade II according to WHO criteria). On the one hand, then, the blood loss expected to occur peri- and postoperatively could be dangerous in view of her anemia; on the other, her immunocompromised condition made it essential to keep allogenic transfusions to a minimum. Upon weighing all these factors, we made the decision to proceed with surgery, and administer recombinant factor VIIa (NovoSeven®) as needed to maintain hemostasis.

OPERATION

The procedure was performed in the typical manner, with the patient under epidural anesthesia. Due to the possibility of complications associated with arteriosclerosis, the operation was not performed in ischemia. Forty-five minutes into the procedure, the volume of blood loss had reached 350 ml, prompting the decision to administer the first dose of NovoSeven®, at a dosage of 30 g/kg of body mass. The tibial and femoral bone cuts were then made. At that point in time, i.e. approximately 15 minutes after administration of NovoSeven®, bleeding from the surgical site diminished markedly. Surgery was completed after 105 minutes.

The second dose of NovoSeven®, in the same dose as the first, was given at 2 hours and 45 minutes after the first dose, 1 hour and 50 minutes after the completion of the surgical procedure. A tourniquet had not been used, and the total perioperative blood loss came to 400 ml. Between the completion of the procedure and the administration of the second dose of NovoSeven®, the total volume of blood loss reached 800 ml. Following the administration of the second dose, the volume of lost blood diminished considerably over the next 18 hours, amounting to 290 ml. In total, the patient lost 1090 ml of blood over 20 hours. In spite of the low initial blood cell count values, it proved necessary to give only two units of packed erythrocytes, with no hemodynamic abnormalities. Pre- and postoperative laboratory findings are presented in Table 1. Fig. 2 shows the percentage changes in laboratory parameters, taking the baseline value as zero.

Tab. 1. Laboratory findings determined pre-, peri- and postoperatively before and after administration of first and second dose of NovoSeven®

Tab. 1. Wyniki badań laboratoryjnych wykonanych przed, podczas i po zabiegu, przed i po podaniu pierwszej i drugiej dawki NovoSeven®

Parameter	T_0 – baseline	T_1 - commencement of surgery	T_2 –after 10-15 min	T_3 - before second dose	T_4 -10-15 min. after second dose	T_5 - 4 h	T_6 – 20 h
WBC	14.2	6.1	9.3	12.9	14.7	13.0	18.4
RBC	2.83	2.65	2.53	2.21	2.05	2.81	2.61
HGB	9.3	8.3	7.9	7.0	6.4	8.8	8.0
HCT	26.0	24.4	23.4	20.4	19.0	25.5	23.5
PLT	238	187	207	203	180	159	117
PT	11.4	11.4	7.5	8.6	7.5	8.6	13.6
INR	0.82	0.83	0.54	0.62	0.54	0.62	0.99
ATTP	29.8	34.5	31.1	31.5	30.4	30.3	43.1
Fibrinogen	3.52	3.16	3.07	2.77	2.36	2.09	2.81
D-dimers	<0.5	<0.5	0.5-3.0	0.5-3.0	0.5-3.0	>3.0	

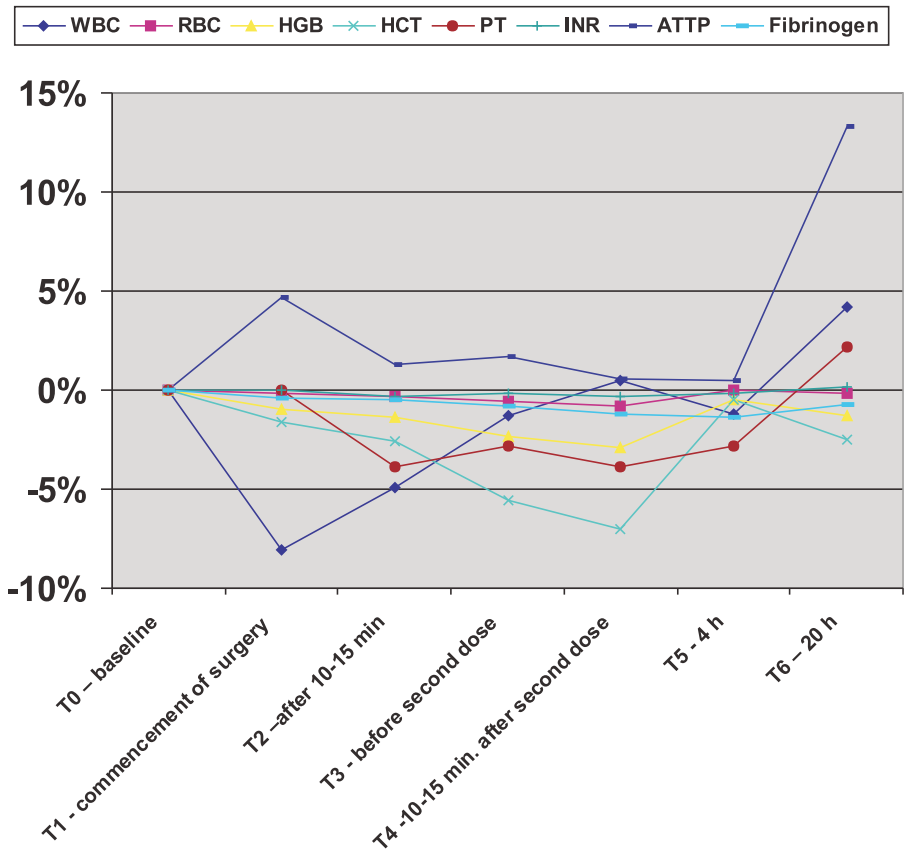

Fig. 2. Changes in laboratory results at the established time points
Ryc. 2. Zmiany wyników badań laboratoryjnych w określonych punktach czasowych

The effect of decreased intraoperative bleeding from the surgical site is illustrated in Figure 3a (initial phase of the procedure) and 3b (30 minutes following the administration of NovoSeven®).

Suction drainage of the surgical wound was maintained for 20 hours. The wound healed quickly and without complication. Throughout her hospitalization RT received a complete program of rehabilitation to promote healing and restore mobility. She was discharged 12 days after surgery. On discharge her general and local condition was good: she was capable of walking unassisted using elbow crutches and

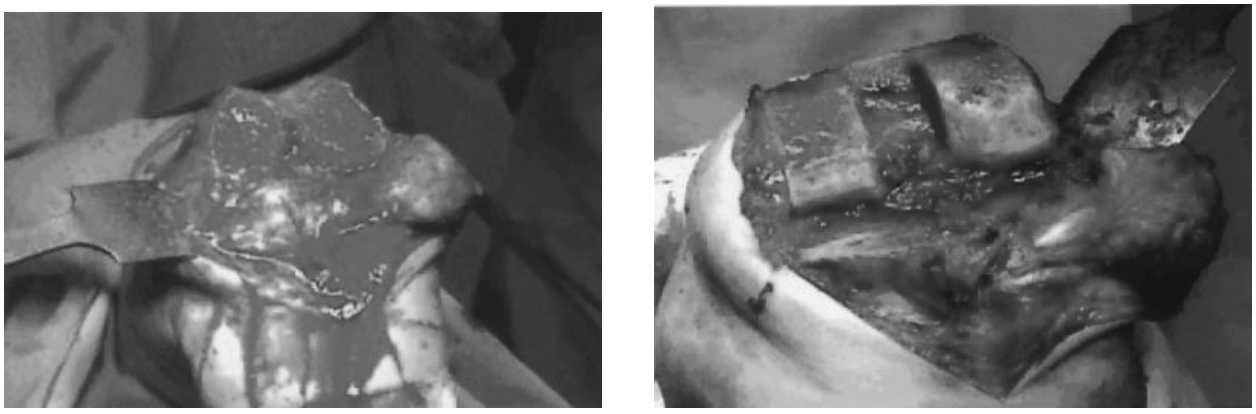

Fig. 3. Peri-operative photographs (patient RT). a) at the conclusion of the initial phase; surgical field inundated, significant blood loss; b) 30 minutes after the administration of NovoSeven®; bleeding has diminished considerably
Ryc. 3. Zdjęcie śródoperacyjne pacjentki RT. a) zdjęcie wykonane tuż po zakończeniu I fazy. Pole chirurgiczne zalane krwią, znaczna utrata krwi. b) zdjęcie wykonane 30 min. po podaniu NovoSeven®, krwawienie znacznie zmniejszone

with full loading on the affected extremity. In the course of 11 months of follow-up she reported no complaints and achieved a fully satisfactory outcome in rehabilitation. Presently the patient is awaiting another operation, i.e. total knee replacement on the right side.

DISCUSSION

For almost twenty years now, rFVIIa has been successfully used to control bleeding in hemophiliac patients, including persons with acquired hemophilia (inhibitors against factors VIII and IX) [15-19]. It has been used successfully to control bleeding in hemophiliacs who have incurred accidental overdoses of oral anticoagulants or traumatic injuries [20,21], which for these patients are of course life-threatening situations. NovoSeven® is particularly recommended for hemophiliac patients undergoing surgery, e.g. in the course of transplantation [17,18,22,23], cardiac valve replacement [24], aneurysm repair [25,26], and especially orthopedic surgery [27-31]. Thus surgical treatment can now be applied in many cases which until a few years ago were simply ruled out for patients with hemophilia.

The use of rFVIIa to control bleeding in patients who do not have hemophilia, on the other hand, is a very recent development [32]. In one of the few group studies as yet performed on this question, Friederich et al. used various doses of rFVIIa in non-hemophiliac patients undergoing transabdominal retropubic prostatectomy, an operation associated with a high risk of substantial blood loss, and achieved highly satisfactory results with no thrombotic complications [33]. Sobieszczyk et al. recently reported on the successful use of rFVIIa to stop a life-threatening hemorrhage during a cesarean section with hysterectomy [34]. Langer et al. used rFVIIa to control bleeding from a subcapsular renal hematoma caused by extracorporeal shockwave lithotripsy in a patient who did not present with any abnormalities of coagulation [35].

In the case reported here, the fact that our patient did not have hemophilia may account for the fact that the dosage necessary to control bleeding was somewhat lower than would be necessary in a hemophiliac patient. Negrier and Lienhart [36] recommend a dosage from 60 to 120 g/kg of body weight, with 90 g/kg of body weight as a generally accepted minimum initial dose [23], administered either as bolus injections at intervals of 2-6 hours or as a continuous infusion. Carr et al. [27] controlled bleeding in a hemophiliac patient undergoing a total knee replacement by applying a series of relatively large doses (85 g/kg of body weight), beginning just before surgery and continuing every two hours until 48 hours after surgery was completed, and then at 4-hour intervals for another 48 hours. Tourniquet ischemia was also necessary, though release was possible immediately after surgery.

In the case reported here, however, two doses of 30 g/kg of body weight were sufficient to keep blood loss within acceptable limits. This was a difficult challenge, since on the one hand the patient was anemic, and on the other, immunocompromised. Thus the fact that only two units of packed RBCs were necessary to maintain hemodynamic parameters within acceptable limits should be regarded as a significant advantage. On the other hand, the lack of subsequent thrombotic complications despite achieving hemostasis at the wound site is noteworthy. This is doubtless explained, as Erhardtsen suggests, by the fact that rFVIIa's hemostatic effect is limited to the site of injury and does not cause a system-wide activation of the coagulation cascade [15].

The outcome we achieved is consistent with the findings reported by Al Douri [32] regarding the use of NovoSeven® to control peri-operative bleeding in non-hemophiliac patients, and with the recommendations of Cooper et al. [29] that the dose of rFVIIa be kept as low as necessary in each case to prevent hemorrhages. In our case, we did not administer NovoSeven® initially, but only after it became apparent that blood loss was approaching dangerous levels at a fairly early stage in surgery. The effects were apparent within 15 minutes after both of the two doses, and the outcome was fully satisfactory.

As in any case study, there are obvious limits to the extent to which the success achieved in this operation can be generalized. In the authors' opinion, however, further study is clearly warranted on the use of NovoSeven® for non-hemophiliac patients during orthopedic surgery to control bleeding without incurring an unacceptable risk of thrombosis. It seems particularly important to call more attention among orthopedic surgeons to the possibility of using NovoSeven® to control bleeding in knee and hip replacements for non-hemophiliac patients, since to date most of the existing literature on this topic has appeared in hematological journals.

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