Artigo / Article

Efficacy of a high-purity factor IX concentrate in hemophilia B patients undergoing surgery

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A plasma derived, high purity, solvent-detergent treated and subsequently nanofiltered factor IX concentrate (BEMOFIL) was evaluated in 19 hemophilia B patients, including four with severe, thirteen with mild or moderate type of disease and two hemophilia B carriers undergoing 31 surgical procedures. The mean in vivo recovery was 52 %, range 36 - 76 %. The mean preoperative plasma factor IX activity after the initial loading dose was 0.86 IU mL^{-1}, range 0.59 – 1.32 IU mL^{-1}. In eight major orthopedic procedures, the mean usage of factor IX was 44600 IU or 574 IU kg^{-1} during the hospital stay, mean 11.6 days. Thromboprophylaxis was not used. The hemostatic efficacy was evaluated good in all cases and there were no thromboembolic complications. In conclusion, BEMOFIL used as bolus dosing was found to be safe and effective in achieving hemostasis in subjects with hereditary F IX deficiency undergoing surgery.
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***Keywords**: Hemophilia B, factor IX, high-purity FIX, surgery, efficacy*

Introduction

Marked progress has recently been achieved in the purity and viral safety of plasma derived coagulation factor concentrates (1). In hemophilia, surgery provides the most demanding environment to test the efficacy of a hemostatic agent. We have retrospectively evaluated the hemostatic efficacy of a plasma derived, high purity, solvent-detergent treated and subsequently nanofiltered factor IX concentrate (BEMOFIL) in hemophilia B patients undergoing surgery. In this paper, we report on thirty one various surgical procedures, including nine major orthopedic operations and an aortofemoral vascular reconstruction carried out using intermittent intravenous injections of this factor IX concentrate. No viral seroconversions for either HBV, HCV or HIV have been detected in the users of this product (2).

Patients and Methods

Patients

In Finland, patients with bleeding disorders are centrally diagnosed and registered at the Department of Hemostasis of the Finnish Red Cross Blood Transfusion Service. At the end of 2001, there were a total of 63 patients with hemophilia B, thirteen of them with severe disease, in a population of 5.3 million. The senior medical staff of the Department of Hemostasis is normally consulted when a surgical procedure is planned in a patient with hemophilia.

Nineteen patients with hemophilia B underwent thirty-one surgical procedures between 1995 and end of 2001 using BEMOFIL as replacement therapy. The median age of the patients was 51 years, range 3 – 75 years, and the

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median weight 75 kg, range 9 – 93 kg. Two of the patients were female carriers of hemophilia B. All patients had been previously treated with a plasma derived FIX concentrate. All patients were HIV negative and none had a factor IX inhibitor in his or her history.

Factor IX concentrate

The factor IX concentrate, BEMOFIL (Finnish Red Cross Blood Transfusion Service, Helsinki, Finland) is a plasma derived (pFIX) high-purity product licensed in 1995. It is manufactured by ion exchange chromatography and affinity chromatography. The specific activity of BEMOFIL is > 110 IU mg^{-1} before albumin addition. It is virally inactivated with 0.3 % tri (N-butyl) phosphate (TNBP) and 1 % Tween 80. Since 1998, additional virus removal has been performed by nanofiltration with a 15 nm pore size filter to remove non-enveloped and unknown viruses. In the pre-registration clinical study, the biological (beta-phase) half-life of the product was 22 to 38 hours and *in vivo* recovery 57 to 76 %. So far, the total use of BEMOFIL exceeds 17 million units.

Treatment

Each patient was treated with a preoperative loading dose of pFXI determined by the consultant on the basis of the type of procedure, weight of the patient and on previous experience on the given subject. Also postoperatively pFIX was administered as intermittent injections. The hemostatic efficacy

Table 1. Surgical procedures in hemophilia B patients treated with BEMOFIL

Procedure	Major	Minor
Orthopedic surgery (n = 10)		
Total hip replacement	2	
Total knee replacement	2	
Revision knee operation	2	
Evacuation of iliac pseudocyst	1	
Ankle arthrodesis	1	
Rotator cuff repair	1	
Removal of external fixation		1
General surgery (n = 18)		
Inguinal hernia repair	3	
Endoscopy with biopsy	3	
Aortobifemoral reconstruction	1	
Appendectomy	1	
Cholecystectomy	1	
Fasciotomyof both calves	1	
Hypospadia repair	1	
Hysterectomy	1	
Removal of vertebral disc L5-S1	1	
Skin grafting	1	
Tonsillectomy	1	
Port-a-Cath insertion		2
Excision of multiple nevi		1
Dental procedures (n = 3)		
Dental extractions		3
Total procedures (n = 31)	24	7

was evaluated subjectively by the surgeon and, in the orthopedic patients, by the measured blood loss. The hemostatic response was rated good, moderate or poor. Tranexamic acid was used as adjunctive therapy in all orthopedic procedures. Medicinal thromboprophylaxis such as heparin was not used. Fibrin glue was not applied. The patients were observed clinically for blood loss, allergic complications and venous thromboembolism.

Laboratory analyses

In elective surgery, the response to the preoperative loading dose was determined from a blood sample taken fifteen minutes after the pFIX infusion. All factor measurements were centrally made at the Department of Hemostasis. The factor IX activity was measured using an one-stage partial thromboplastin time assay. Preoperative samples were not obtained from all patients, because some surgical and dental procedures were performed without formal recovery studies.

Results

In total, thirty-one surgical procedures including ten orthopedic operations, eighteen other operations and three dental procedures are reported here (Table 1). Twenty-four procedures were evaluated as major ones on the basis of extent of operation, duration of factor concentrate use and risk of an internal bleeding complication.

The preoperative loading dose ranged from 500 to 6000 IU, median 5000 IU, or 47 to 79, median 64 IU kg^{-1}. The achieved preoperative F IX activity 15 minutes after the loading dose ranged from 0.59 to 1.32 mL^{-1}, mean 0.86 IU mL^{-1} (n = 17). The *in vivo* recoveries in individual patients ranged from 36 to 76 %, mean 52 %. The hemostatic responses to the studied pFIX were rated good in all cases. No thromboembolic or allergic complications were registered.

Six patients underwent nine major orthopedic operations, eight of which could be

***Table 2**. Major orthopedic operations in hemophilia B patients treated with BEMOFIL*

Procedure	***Weight (kg)***	***Post-infusion* FIX activity (%)***	***Recovery (%)***	***Blood loss (ml)*****	***Total dose IU***
Ankle arthrodesis	93	72	51	0	33000
Evacuation of pseudocyst	76	127	60	4000 + 1900	68000
Revision knee operation	78	74	43	150 + 500	42000
Revision knee operation	85	132	76	50 + 300	40000
Total hip replacement	76	93	55	650 + 1700	48000
Total hip replacement	75	99	n.a.	n.a.	54500
Total knee replacement	71	118	66	300 + 1500	31500
Total knee replacement	67	102	52	400 + 630	39500

** loading dose, ** perioperative and drainage, n.a. = not available*

analysed in detail (Table 2.). The mean preoperative F IX activity achieved in these patients was 1.02 IU mL^{-1}. The mean hospital stay was 11.6 days, range 8 - 16 days. The mean use of pFIX during hospitalization was 44600 IU, or 574 IU kg^{-1}. In the joint replacements, the mean perioperative blood loss ranged from 50 to 650 mL and the postoperative blood loss from 300 to 1700 mL. The mean use of pIX during hospitalization was 565 IU kg^{-1} in the joint replacements.

The mean *in vivo* recoveries of the original and nanofiltered pFIX were 50 % (n = 10) and 53 % (n = 7), respectively. The difference was not significant.

Discussion

The purpose of this study was to evaluate the hemostatic efficacy and safety of a high-purity plasma derived FIX concentrate in surgical procedures in patients with hemophilia B. Thirty-one operations of various nature were performed using pFIX as the sole factor replacement. Intermittent bolus dosing was used. Tranexamic acid was used as adjuvant therapy in orthopedic surgery. The hemostatic response was rated good, and the peri- and post-operative blood losses were estimated similar to those in non-hemophilic subjects. The recovery of the nanofiltered BEMOFIL did not differ from that of the original non-filtered form of the product. There were no adverse reactions and no thromboembolic complications.

In the absence of randomised trials, comparison of the present pFIX to other plasma derived or recombinant products is hampered by differences in study design. In orthopedic surgery, the mean usage of BEMOFIL in joint replacements was less (565 IU kg^{-1} versus 663 IU kg^{-1}, respectively) than reported for a comparable pFIX (3). Continuous infusion was used in the latter study but recoveries were not reported. The mean *in vivo* recovery of BEMOFIL was clearly better than that of a recombinant FIX product (52 % and 34 %, respectively) used in hemophilia surgery (4). The product usage was not reported in the last mentioned study.

Our material included two unusually large operations. The evacuation in a ten-hour operation of a giant pseudocyst invading the right iliac bone required bone grafting and microvascular techniques, which explain the considerable perioperative bleeding. An uneventful aortobifemoral vascular reconstruction with prosthesis in a 71-year-old man suffering from advanced atherosclerosis and angina pectoris speaks for minimal thrombogenic potential of the pFIX used.

In conclusion, BEMOFIL was found to be safe and effective in achieving hemostasis in subjects with hereditary factor IX deficiency undergoing surgery. Our results compare favorably with previous studies.

Eficácia do concentrado de alta pureza do fator IX em pacientes cirúrgicos portadores de hemofilia B

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Sumário

O concentrado de fator IX (Bemofil) , um derivado plasmático de alta pureza tratado com solventes-detergente e nano-filtrado , foi avaliado em 19 pacientes portadores de Hemofilia B .Quatro pacientes apresentavam a forma grave da moléstia, 13 a forma leve e moderada e dois portadores em um total de 31 atos cirúrgicos.A recuperação média "in vivo" foi de 52% (36-76%).

A atividade plasmática média pré-operatória do fator IX após a dose inicial foi de 0,86 UI ml^{-1}, média de 0,59 – 1,32 UI ml^{-1}. Em oito procedimentos ortopédicos extensos , a média de utilização do fator IX foi de 44.600 UI ou 574 UI kg –1 durante a hospitalização que teve a média de 11,6 dias. A tromboprofilaxia não foi utilizada. A eficácia hemostática avaliada em todos os casos foi boa ,e não ocorreu nenhum tipo de complicação tromboembólica .Concluímos que o Bemofil em bolus foi considerado seguro e eficaz para a hemostasia em pacientes portadores de hemofilia B que necessitam de um procedimento cirúrgico.

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***Palavras-chave**: Hemofilia B, fator IX, cirurgia, eficácia*

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