Outcome of Surgical Interventions in Patients with Haemophilia A and B Treated with Extended Half-Life (EHL) Factor Concentrates in a Single Centre

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Abstract

Background The prevention of intraoperative bleeding in patients with haemophilia is the key to a successful surgical procedure. Daily life of patients with haemophilia A and B significantly improved with prophylaxis with extended half-life factor concentrates (EHL-FVIII and EHL-FIX). The aim of this study was to investigate the efficacy and safety of EHL factor concentrates during surgery.

Methods In a retrospective chart review all surgical interventions in our hospital in patients with haemophilia A and B treated with EHL-FVIII or EHL-FIX undergoing surgery between 2016 and 2022 were included. Patients with inhibitors against FVIII or FIX were excluded.

Results A total of 88 surgical interventions (41 minor, 47 major) in 52 patients with haemophilia were performed. The interventions consisted of 70 surgeries in 42 patients with haemophilia A and 18 surgeries in 10 patients with haemophilia B. The replacement therapy during the surgeries was performed with four different EHL FVIII and three different EHL FIX concentrates. Bolus injections were performed directly before surgery and continued after surgery with variable intervals ranging from 8 to 48 hours. The median dose before major surgery was 32.31 IU/kg FVIII and 47.06 IU/kg FIX and before minor surgery was 27.78 IU/kg FVIII and 33.78 IU/kg factor IX. There were 11 complications including 4 bleeding complications during/after surgery. No thromboembolic event and no inhibitor against FVIII or FIX were detected during follow-up.

Summary The replacement therapy with EHL factor concentrates in surgical interventions in patients with haemophilia A and B is safe and effective.

Keywords
- surgery in haemophilia
- extended half-life concentrates
- haemophilia A and B

Introduction

Haemophilia A and B are rare congenital bleeding disorders with a risk for spontaneous bleeds, mainly into the joints, and with a need for intravenous replacement therapy with the missing clotting factor during bleeding episodes and surgical interventions. Historically surgical procedures in these patients have been considered a challenge due to the complicated control of haemostasis and were avoided if possible because of the risk of life-threatening bleeds.[1] In the last 50 years the development of replacement therapy with missing clotting factors has changed the surgical intervention to a routine

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procedure for haemophilia patients.[2] Through the development of haemophilia centres and with the collaboration of their multidisciplinary teams in pre- and postoperative care, the surgical interventions can be carried out safely for patients with haemophilia.[3] The half-life of standard FVIII replacement products is about 8 h, which requires frequent administrations of the missing clotting factor and laboratory monitoring of factor levels during surgery and in the post-surgical period. To achieve better control over targeted plasma levels and more efficient cover of haemostasis, a continuous infusion as an option was discussed but not widely used.[4] In the last decade the new developments in FVIII and FIX concentrates resulted in a longer half-life. Different methods like conjugating the factor molecule with the crystallizable (Fc) fragment of human immunoglobulin G1 or conjugation to recombinant albumin or conjugation to polyethylene glycol (PEG) led to extension of the half-life of factor concentrates.[5] Clinically EHL factor concentrates increased the effectiveness of prophylaxis and the management of bleeds for patients with haemophilia A and B with a lower burden of treatment and better quality of life.[6] During surgical interventions, replacement therapy with EHL products promises higher concentrations of FVIII or FIX in plasma and less frequent injections compared to standard half-life factor products. Real-world evidence about surgical interventions with EHL factor concentrates has been published mostly for single products. Due to the switch of haemophilia patients to EHL factor concentrates in the recent years more data about the clinical outcome in surgical interventions in a real-world setting are becoming available.[7]

The aim of this study was to assess the outcome of surgical interventions in patients with haemophilia A and B treated with EHL factor concentrates in a single haemophilia comprehensive care centre between 2016 and 2022. The study was approved by the institutional review board.

Methods

Patients with haemophilia A or B treated with EHL-FVIII or EHL-FIX concentrates undergoing surgical procedures between 2016 and 2022 at our hospital were included. Surgical procedures in patients with inhibitors against FVIII or FIX and outpatient invasive procedures were excluded. The severity of haemophilia was classified by measuring FVIII and FIX levels in plasma: FVIII <1 IU/dL as severe, 1 to 5 IU/dL as moderate, and >5 to 40 IU/dL as mild. The data on coagulation factor replacement therapy was collected from the records from 2016 onwards. In a retrospective chart review all surgical interventions at our hospital in patients with haemophilia A and B were analyzed. The data were collected from patient electronic health records.

The following parameters were recorded: demographics (age at the time of surgery), specific disease characteristics (haemophilia type and severity; ►**Table 1**), surgeries (divided into minor and major according to the type of surgery; ►**Table 2**), reported treatment complications (need for reoperations, bleeding postoperatively, wound healing), duration of hospitalization, and amounts of factor concentrates used during hospitalization.

Table 1 Patients characteristics

	Haemophilia A	Haemophilia B
Patients (*n*)	42	10
Patient age (median (range))	49 (1–76)	54 (30–76)
Severe (<1% FVIII/FIX IU/dL) (*n*)	23	3
Non-severe (>1% FVIII/FIX IU/dL) (*n*)	19	7
All surgeries (*n*)	70	18
Minor surgery (*n*)	34	7
Major surgery (*n*)	36	11

The trough level of factor VIII/factor IX was kept according to the recommendation in the World Federation of Haemophilia (WFH) Guidelines with higher-dose practise pattern (HDPP) in major surgeries in haemophilia A at 80 to 100 IU/dL pre-operatively and during 1 to 3 days post-operatively at 60 to 80 IU/dL and then deescalating to 40 to 60 IU/dL on 3 to 6 postoperative days and then in remaining days until day 14 post-operatively 30 to 50 IU/dL and in minor surgeries 50 to 80 IU/dL preoperatively and in remaining 5 days 30 to 80 IU/dL and in surgeries of haemophilia B patients at 60 to 80 IU/dL pre-operatively and during 1 to 3 days postoperatively at 40 to 60IU/dL and then deescalating to 30 to 50 IU/dL on 3 to 6 postoperative days and then in remaining days until day 14 post-operative 20 to 40 IU/dL and in minor surgeries 50 to 80 IU/dL preoperative and in remaining 5 days 30 to 80 IU/dL.[3]

Table 2 Characteristics of the 88 surgical procedures, classified as major or minor

Major surgery (47)	Minor surgery (41)
Arthroscopic joint surgery (7)	Tooth extraction (4)
Joint replacement (7)	Dermatologic, soft tissue surgery (6)
Arthrodesis (6)	Endoscopic surgical procedures like polypectomy in the GI and UG tract (14)
Bone fracture surgery (8)	Arterial angiographic interventions (coronary stenting, vascular embolization) (5)
Neurosurgery (6)	Prostate biopsy (4)
Abdominal surgery (5)	Port-a-Cath (3)
Prostatic surgery and urinary tract surgery (3)	Arterio-venous fistula creation (2)
ENT surgery (2)	Minor orthopaedic surgery (3)
Major soft tissue and muscle surgery (3)	

Abbreviations: ENT, ear nose and throat; GI, gastrointestinal; UG, urogenital.

The primary end point was the dose of EHL products in IU/kg used for surgery in patients with haemophilia A and B during the hospital stay. The secondary end points were efficacy and safety of EHL products. To assess safety and efficacy, we collected the following data: need for reoperation, blood loss during and after surgery, requirement for red cell transfusions, infection, and inhibitor development.

Statistical Methods

We performed only descriptive statistics reporting the median and the range.

Results

A total of 88 surgical interventions (41 minor and 47 major surgeries) in 52 patients with haemophilia were performed. Patient characteristics are shown in ►Table 1 and type of surgery in ►Table 2. The replacement therapy during the surgeries was performed with four different EHL FVIII factor concentrates, namely, efmoroctocog alfa,[8] rurioctocog alfa pegol,[9] damactocog alfa pegol,[10] and turoctocog alfa pegol,[11] and three different EHL FIX factor concentrates, namely, albutrepenonacog alfa,[12] nonacog beta pegol,[13] and eftrenonacog alfa.[14] The mean age of patients during hospitalization for surgery was 49.6 years with ages ranging from 1 to 76 years.

The interventions consisted of 70 surgeries conducted in 42 patients with haemophilia A and 18 surgeries in 10 patients with haemophilia B. In all 46 surgeries were performed in patients with severe haemophilia A and 6 in patients in severe haemophilia B (►Table 1).

Bolus injections were performed directly before surgery and continued after surgery with variable intervals ranging from 8 to 48 hours. The median dose before major surgery was 32.31 IU/kg FVIII (range 12.99–90.91) and 47.06 IU/kg FIX (range 32.26–70.59) and before minor surgery the median dose was 27.78 IU/kg FVIII (range 20.83–100.0) and 33.78 IU/kg (range 24.00–64.52) factor IX (►Table 3).

The median preoperative dose in severe haemophilia A for minor surgery was 28.17 IU/kg (range 21.79–100.00) and for major surgery 35.64 IU/kg (range 12.99–90.91) and in non-severe haemophilia A for minor surgery 22.47 IU/kg (range 20.83–54.35) and for major surgery 31.25 IU/kg (range 18.52–44.12).

The median preoperative dose administered to patients with severe haemophilia B was 48.39 IU/kg (range 32.26–50.00) for minor surgical procedures and 47.22 IU/kg (range 32.26–64.5) for major surgical procedures. In patients with non-severe haemophilia B, a median dose of 31.93 IU/kg (range 24.00–57.14) was used for minor surgeries, while 47.06 IU/kg (range 34.09–70.59) was administered for major surgeries. The target level for factor VIII and FIX was >80 IU/dL according to local practice and the WFH recommendation.

The median duration of hospitalization following minor surgeries was 2.0 days and for major surgeries it was 5.0 days, with an overall range of 1 to 42 days for all surgeries. The median amount of EHL FVIII concentrate administered was 146.67 IU/kg (range 27.78–2,727.28) for major surgeries and 73.17 IU/kg (range 21.74–2,608) for minor surgeries. The median amount of EHL FIX concentrate used was 140.28 IU/kg (range 90.91–354.84) in major surgeries and 78.57 IU/kg (range 28.57–257.14) in minor surgeries.

A total of 11 complications during the hospitalization for surgery were reported (►Table 4). In all surgeries the desired target level of the factor VIII or IX was achieved before surgery with the recommended one-stage clotting assay for the specific product according to the recommendations of the laboratory commission of the German Society of Thrombosis and Haemostasis research. Revision surgery was needed in seven cases. Bleeding was the reason for revision surgery in four cases. Major bleeding was described in two neurosurgical surgeries due to subdural haematoma necessitating reoperation—once 5 hours post-surgery in patient 1 and 2 days post-surgery in patient 4 (►Table 4). In four cases, a haematoma occurred between the 17th and 23rd days after surgery, necessitating the removal of excess fluid due to infection and wound healing complications in patients 3, 9, and 10. In patient 11 the repeated surgery was required due to an incomplete removal of a malignant skin tumour. In four cases, bleeding was considered as minor and did not necessitate intervention, and the complication was mainly related to technical aspects of the surgical procedure (►Table 4). Blood transfusion of red cells was needed in two patients; in patient 3 the transfusion was administered during the revision surgery period, more than 17 days after the first surgery. In patient 6 transfusion of red cells and fresh frozen plasma (FFP) took place during an emergency surgery after femoral fracture because of chronic anaemia. No postoperative prophylaxis against venous thrombosis with antithrombotic agents was administered after surgery, and there was no occurrence of venous thromboembolism

Table 3 Dosing and consumption of clotting factor during the hospital stay for surgery

	Haemophilia A major surgery	Haemophilia A minor surgery	Haemophilia B major surgery	Haemophilia B minor surgery
Pre-dosing IU/kg (median) (range)	32.31 (12.99–90.91)	27.78 (20.83–100.00)	47.06 (32.26–70.59)	33.78 (24.00–64.58)
Amount of factor concentrate during hospital stay, IU/kg (median) (range)	146.67 (27.28–2,727.8)	73.17 (21.74–2,608)	140.28 (90.91–35.84)	78.57 (28.57–257.14)

Note: The recovery profiles and pharmacokinetic properties of EHL factor IX products differ from those of EHL factor VIII products.

Table 4 Characteristics of complications in patients treated with EHL products during operations and postoperative periods in 2016–2023 where in 11 operations out of 88 operations a postoperative complication was described

Patient	Age	Baseline FVIII/FIX activity (IU/dL)	Surgery	Complication	Time interval to the onset of complication	FVIII/FIX activity at the time of complication (IU/dL)	Treatment of complication	Days in hospital
1	68	6 (FVIII)	Craniectomy for decompression	Subdural haematoma*	5 hours	70	EHL-FVIII, FXIII, and desmopressin	18
2	25	1 (FVIII)	Bladder biopsy	Bleeding	17 days	10	EHL-FVIII and tranexamic acid	5
3	72	<1 (FVIII)	Hernia surgery, herniotomy	Haematoma and retardation of wound healing	3 days	58	Surgical revision and transfusion of 1 unit red cells	42
4	0.8	<1 (FVIII)	Craniectomy	Bleeding*	2 days	119	Revision surgery	33
5	37	<1 (FVIII)	Ankle arthrodesis	Bleeding after drain removal*	1–2 days	108	Local compression	4
6	68	<1 (FIX)	Femur fractur open reduction and internal fixation (ORIF)	Emergency surgery with preexisting anaemia and moderate blood loss during surgery	Intraoperative	80	Transfusion of 1 unit red cells and FFP	14
7	61	27 (FVIII)	Knee replacement (TEP)	Local wound bleeding	4 days	115	Local compression	7
8	53	4 (FVIII)	Polypectomy	GI bleeding*	2 days	68	Endoscopy and local treatment	3
9	45	5 (FVIII)	Correction of the nasal septum with resection	Surgical complication	23 days	5	Revision surgery (FESS)	4 + 1
10	51	1 (FVIII)	Ulnar neurolysis	Infection	22 days	50	Antibiotics and revision surgery	2 + 6
11	75	6 (FIX)	Basal cell carcinoma excision	Prolonged wound healing due to incomplete removal	17 days	6	Revision surgery	1

Abbreviations: EHL, extended life product factor; FESS, functional endoscopic sinus surgery; FFP, fresh frozen plasma; ORIF, open reduction and internal fixation; TEP, total endoprosthesis.
Note: *Bleeding occurred in four patients during the first 72 hours after surgery. Bleeding was not related to the product used; the bleeding occurred regardless of replacement therapy.

observed postoperatively. No inhibitors against FVIII or FIX were detected during the 3-month follow-up period after surgery.

Discussion

We explored the efficacy and safety of EHL replacement therapy during surgery for haemophilia patients retrospectively in our haemophilia centre. To achieve this, we analyzed the electronic health records of all patients with haemophilia A and B who had undergone surgery at our haemophilia comprehensive care centre from 2016 to 2022, and 52 patients undergoing 88 surgical interventions were evaluated. In our heterogenous real-world cohort, we found EHL replacement therapy during surgery to be effective and safe following the proposed factor levels of the WFH recommendations, despite the fact preoperative dosing with factors VIII and IX per body weight was lower than suggested in other clinical studies. No thrombosis or FVIII/FIX inhibitor formation was observed during the 30-day postoperative period. In our cohort 11 complications (12.5%) were reported following surgical interventions: 7 patients (7.95%) required repeated surgery, wound healing complications occurred in 3 patients (3.41%), surgery-related bleeding was observed in 4 patients (4.55%), and 2 patients (2.27%) required red cell transfusions. Notably in all patients with bleeding complications, the factor levels during surgery were in the recommended range and the factor dose before surgery was higher than the median dose for the entire cohort. We can only speculate if higher doses of factor concentrates could have avoided these complications but bleeding complications can occur in patients without haemophilia after surgery too, even assuming a predisposition to postoperative hypercoagulability.[15]

Surgical management of patients with bleeding disorders requires careful planning of dosing of replacement therapy and the selection of an appropriate factor concentrate.[16] Replacement therapy with EHL factor concentrates has the potential to enhance both the feasibility and outcome of surgical procedures.[17] This improvement can be attributed to higher factor levels due the improved pharmacokinetic profile of EHL products and the prolonged circulation in the blood.[18] Consequently, factor levels remain elevated at higher levels on the first postoperative days compared to those achieved with standard half-life (SHL) factor concentrates.[17]

The classification of surgical procedures into major and minor surgeries is common, but not universally established.[19,20] This classification may vary depending on the chosen perspective—whether based on the extent of surgical [21] or haemostatic requirements,[19] making it largely subjective and specific to individual studies. From the perspective of a coagulation factor laboratory testing, best practice guidelines recommend maintaining target factor levels of 80 to 100 IU/dL for major surgeries, both preoperatively and on the first postoperative day.[22] However, the severity of a patient's bleeding tendency is influenced by multiple factors, not just FVIII or FIX laboratory measurements alone.[1,23,24] Standard laboratory tests vary between centres, and discrepancies in assays for EHL products further complicate clinical decision-making, given the complexity of both analysis and interpretation.[25]

Preoperative pharmacokinetic studies may serve a valuable role in optimizing replacement factor calculations for planned surgical procedures.[26] However, given the associated laboratory challenges, effective collaboration and clear communication between laboratory specialists and clinicians are also crucial to achieve optimal patient management.

Complications during and after surgery may arise either from the surgeon's technique or insufficient levels of clotting factors with impact on wound healing or inflammation.[24] In our cohort, bleeding complications were observed in 4 (4.5%) cases, a lower number than reported in other studies—12% in a Nordic cohort treated with EHL[7] and 30% in a U.S. cohort undergoing orthopaedic surgery with an unspecified replacement factor.[27] Postoperative bleeding may result from inhibitor development following intensive replacement therapy[28] or from inadequate patient adherence and understanding of the continued need for replacement therapy.

In our cohort, neurosurgical procedures following spontaneous subdural haemorrhage were complicated by severe bleeding, necessitating revision surgery due to major bleeding.[29] Additionally, two elderly patients with comorbidities required red cell transfusions. The occurrence of bleeding and the need for transfusion in these cases could not be prevented by factor replacement therapy and were associated with disease severity and comorbid conditions.

Although delayed wound healing in patients with inherited bleeding disorder is recognized, it remains rather uncommon.[30] Studies based on using haemophilia mouse model suggest that maintaining factor levels with prolonged replacement therapy after surgery supports wound healing by promoting angiogenesis and thereby preventing re-bleeding.[31] These models demonstrate the superior effectiveness of extended half-life factor products in enhancing wound healing and reducing bleeding compared to standard half-life concentrates.[32] In our cohort, wound healing complications occurred in three patients (3.4% of surgeries), two of whom were over 70 years of age. A study from Tokyo[33] has identified advanced age as a risk factor for impaired wound healing alongside other factors such as diabetes, infection, and smoking, all of which influence the healing process.[30]

Surgical procedures, excessive replacement factor dosing, and the postoperative recovery period can disrupt coagulation balance, inducing a hypercoagulable state and increasing the risk of thrombosis.[34] Although thromboprophylaxis is a standard component of postoperative care in patients without bleeding disorders,[34] patients with haemophilia A and B are generally considered to have a lower risk of venous thrombosis.[35–37] However, a European survey of haemophilia specialists revealed differing practices, with 30% identifying surgery as a high thrombosis risk.[38] Current guidelines recommend an individualized approach to

thromboprophylaxis for high-risk cases for venous thrombosis (e.g., obesity, comorbidities, surgery type).[3] In contrast patients with mild haemophilia or FVIII trough levels exceeding >20 IU/dl may follow general thromboprophylaxis guidelines.[39] Haemophilia B has also been associated with a higher incidence of venous thromboembolism.[40]

In our cohort, no cases of postoperative thrombosis were observed despite the presence of high-risk factors such as cancer, obesity, and advanced age. Excessive clotting factor dosing may contribute to thrombosis risk, as noted in WFH guidelines, which recommended careful consideration of replacement therapy strategies in surgical settings. These guidelines establish target peak plasma factor levels to align with common clinical practice with no reported safety concerns.[3] The WFH guidelines propose both low- and high-dose practice patterns based on peak factor levels (IU/dL). In surgical studies, the higher-dose WFH replacement strategy has been applied to EHL concentrates, as reflected in the Summary of Product Characteristics (SPCs). In our cohort the preoperative dosing and overall median consumption of EHL concentrates during surgical replacement therapy were lower than reported in studies specified in SPCs of the EHL products.[8–14] The lower dose could be related to the duration of calculated days of replacement therapy.

A key limitation of our study is its retrospective design and the absence of a direct comparison with SHL products, which have been in clinical use for decades. Ideally, a parallel study involving SHL products within the same centre or another institution would provide a more comprehensive evaluation. However, given the rarity of haemophilia A and B, assembling comparable patient cohorts undergoing identical surgeries within the same timeframe presents significant challenges. Previous studies have calculated total consumption based on different criteria, making direct comparison with our data difficult.[7] Furthermore, complications were assessed only during hospitalization or in cases requiring rehospitalization and reoperation. This limitation arises from the study's retrospective nature, which relies on real-world electronic data rather than prospective patient-reported outcomes.

Conclusion

The peak factor level (IU/dL) recommended by WFH guidelines, along with regular monitoring of factor levels during the pre- and postoperative periods ensures the safe and effective use of the EHL concentrates in haemophilia patients through individual dosing and dosing intervals. The results of our study support the feasibility of individualized dosing for safe replacement therapy during surgery in haemophilia centres. No inhibitors were detected during the 3-month postsurgical follow-up and no thromboembolic events occurred without pharmacological thromboprophylaxis in our cohort. Complications were in line with other publications about surgery in haemophilia. In conclusion replacement therapy with EHL factor concentrates during surgery is safe and effective.

What is Known About this Topic?

1. Extended half-life concentrates improve prophylaxis for patients with haemophilia.
2. Surgery in patients with haemophilia requires replacement therapy.
3. Data on extended half-life concentrates used during surgery are limited.

What Does this Paper Add?

1. Safety and efficacy of EHL concentrates in patients with haemophilia during surgery.
2. Real-world single-centre experience with EHL in surgery.

Conflict of Interest

Robert Klamroth declares Grants from 'Bayer, CSL Behring, Leo Pharma, Octapharma' and Consulting fees from 'Bayer, Biomarin, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Sanofi, Sobi, Takeda'; Ines Vaide declares all support for the present manuscript from 'Novo Nordisk Grand 2019'.

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