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ORIGINAL ARTICLE

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Perioperative replacement therapy in haemophilia B: An appeal to "B" more precise

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Introduction: Haemophilia B is caused by a deficiency of coagulation factor IX (FIX) and characterized by bleeding in muscles and joints. In the perioperative setting, patients are treated with FIX replacement therapy to secure haemostasis. Targeting of specified FIX levels is challenging and requires frequent monitoring and adjustment of therapy.

Aim: To evaluate perioperative management in haemophilia B, including monitoring of FIX infusions and observed FIX levels, whereby predictors of low and high FIX levels were assessed.

Methods: In this international multicentre study, haemophilia B patients with FIX < 0.05 IU mL^{-1} undergoing elective, minor or major surgical procedures between 2000 and 2015 were included. Data were collected on patient, surgical and treatment characteristics. Observed FIX levels were compared to target levels as recommended by guidelines.

Results: A total of 255 surgical procedures were performed in 118 patients (median age 40 years, median body weight 79 kg). Sixty percent of FIX levels within 24 hours of surgery were below target with a median difference of 0.22 IU mL^{-1} [IQR 0.12-0.36]; while >6 days after surgery, 59% of FIX levels were above target with a median

difference of 0.19 IU mL^{-1} [IQR 0.10-0.39]. Clinically relevant bleeding complications (necessity of a second surgical intervention or red blood cell transfusion) occurred in 7 procedures (2.7%).

Conclusion: This study demonstrates that targeting of FIX levels in the perioperative setting is complex and suboptimal, but although this bleeding is minimal. Alternative dosing strategies taking patient and surgical characteristics as well as pharmacokinetic principles into account may help to optimize and individualize treatment.

KEYWORDS

clotting factor concentrates, haemophilia B, haemostasis, individualized treatment, perioperative replacement therapy, surgical procedures

1 | INTRODUCTION

Haemophilia B is an X-linked hereditary bleeding disorder characterized by a deficiency of coagulation factor IX (FIX). Treatment consists of prophylactic or on-demand replacement therapy with recombinant or plasma-derived FIX concentrates. However, replacement therapy with factor concentrates is costly. In the United Kingdom, 60 million international units of FIX concentrates are administered annually in 663 haemophilia B patients.[1] This will most probably increase further in the near future, due to the ageing haemophilia patient population and necessity of orthopaedic surgery for joint replacement.

In the perioperative setting, patients are generally treated with FIX concentrates for 7-10 consecutive days postoperatively. Efficacious perioperative treatment is of importance to prevent underdosing with a risk of bleeding and overdosing with a possible risk of thrombosis and waste of expensive concentrates. However, treatment is complex due to a large interpatient variability, which is not taken into account in National guidelines. Recently, we identified both underdosing and overdosing in perioperative haemophilia A patients and the need for optimization of treatment strategies.[2] Collected data were subsequently used to construct a population pharmacokinetic (PK) model, currently being validated in a randomized controlled trial.[3] Few studies have reported on safety and efficacy of perioperative management in haemophilia B.[4,5] Therefore, studies in these patients are vital to optimize treatment.

To evaluate current perioperative management in severe and moderate-severe haemophilia B patients and to identify predictive factors of low and high FIX levels, we conducted an international multicentre retrospective observational study to collect FIX levels after FIX concentrate administration during and after minor and major surgery as well as clinical outcome measures (FIX consumption and bleeding/thrombotic complications).

2 | METHODS

2.1 | Patients

In this international multicentre retrospective observational cohort study, patients were included with severe and moderate haemophilia B (FIX <0.05 IU mL^{-1}) who underwent elective minor or major surgical procedures with FIX replacement therapy between 1 January 2000 and 1 December 2015. The procedures were classified by surgical risk score as established by Koshy et al.[6] Patients attended one of ten Haemophilia Treatment Centres in the Netherlands and United Kingdom (Erasmus University Medical Centre Rotterdam; Academic Medical Centre Amsterdam; University Medical Centre Groningen; Leids University Medical Centre Leiden and Radboud university medical centre Nijmegen; Great Ormond Street Haemophilia Centre, London; Arthur Bloom Haemophilia Centre, Cardiff, Wales; Katharine Dormandy Haemophilia Centre, Royal Free London; Churchill Hospital, Oxford; The Royal London Hospital, London). Patients received recombinant or plasma-derived FIX concentrates to normalize FIX levels. Administered recombinant FIX concentrate was BeneFix (Pfizer Wyeth Pharmaceuticals Inc., Kent, UK). Plasma-derived FIX concentrates included the following: AlphaNine (Grifols Biologicals Inc. Los Angeles, USA), Replenine (BPL; Bio Products Laboratory, Hertfordshire, UK), Haemonine (Biotest Pharma GmbH, Dreieich, Germany), Mononine (CSL Behring GmbH, Marburg, Germany), Nonafact (Sanquin, Amsterdam, the Netherlands). Patients with possible disseminated intravascular coagulation due to sepsis and patients who developed FIX neutralizing antibodies during the perioperative period were excluded. The study was not subject to the Medical Research Involving Human Subjects Act and was approved by all Medical Ethics Committee in the Netherlands. In the United Kingdom, the study was approved by the Research Ethics Committee (NRES committee South Central—Berkshire, REC reference 15/SC/0367); an opt-out consent procedure was used to collect anonymized clinical data.

2.2 | Methods

The following information was extracted from the medical notes: patient characteristics, including age, body weight, baseline FIX level and history of FIX neutralizing inhibiting antibodies; and surgical and treatment characteristics that consisted of severity of surgical procedure (minor and major), mode of infusion (continuous and bolus infusion), type of product (recombinant and plasma-derived FIX concentrates), FIX concentrate infusion time and dose, and time of FIX level monitoring measured in IU mL^{-1}. FIX levels were monitored daily and

measured by one-stage assays in participating centres according to local protocol. Bleeding complications were defined as need of a second surgical intervention, haemoglobin decrease of >1.24 m molL^{-1} (>20 g L^{-1}) and/or red blood cell transfusion, or bleeding prolonging hospitalization, according to the International Society of Thrombosis and Haemostasis guidelines for major bleeding.[7] Clinically relevant bleeding complications were defined as bleeding complications requiring a second surgical intervention and/or necessity of a red blood cell transfusion. The duration of the perioperative period in the study was equivalent to duration of hospitalization (day of discharge minus day of surgery and start of infusion of FIX concentrates).

All patients received replacement therapy with FIX concentrate according to National and/or hospital guidelines with daily monitoring of FIX, while aiming for target FIX levels as prescribed (Table 1).[8] Perioperative treatment in severe and moderate haemophilia B patients consisted of FIX bolus infusion of approximately 100 IU kg^{-1}, followed by either continuous infusion or intermittent bolus infusions.[8] Only measured trough and steady-state FIX levels were compared to predefined FIX target ranges. Trough FIX levels were measured prior to next FIX bolus infusion, if treatment by bolus was performed. Steady-state FIX levels were defined as FIX levels measured when FIX concentrate substitution was equal to clearance in patients with treatment by continuous infusion. In general, it is assumed that steady state is reached after a loading dose is administered and continuous infusion is started. FIX peak levels after FIX bolus infusions were not included in analysis of this data set. Low FIX levels were defined as all FIX levels below lowest predefined target range level. High FIX levels were defined as all FIX levels above highest predefined target range level. FIX levels with a difference of ≥0.20 IU mL^{-1} above the highest FIX target range were defined as excessively high. This cut-off of 0.20 IU mL^{-1} was chosen arbitrarily to overcome inclusion of high FIX levels solely due to logistic delay of adjustment of treatment.

Potential predictors of FIX levels lower or higher than the target range were identified before analysis and based on the potential effects that they may have on PK parameters, eg clearance and/or volume of distribution of infused FIX concentrate. These consisted of age, body weight, history of FIX neutralizing inhibiting antibodies, type of product (recombinant or plasma-derived FIX), mode of infusion (continuous or bolus infusion), severity of surgical procedure. Also the influence of a clinically relevant bleeding complication was evaluated. In calculations of total perioperative FIX consumption, only FIX concentrate administered during the hospitalization period and during first surgical procedure in each individual patient was included.

TABLE 1 Specifications of perioperative replacement therapy according to guidelines, definition of bleeding complications and typical surgical procedures

Specified FIX target ranges in the perioperative period[a]		
Time		**FIX target level (IU mL^{-1})**
Day	**Hours**	
1	0-24	0.80-1.00
2-5	24-120	0.50-0.80
≥6	>120	0.30-0.50
Definition of bleeding complications[b]		**Definition of clinical relevant bleeding**
Re-operation		Re-operation
Red blood cell transfusion		Red blood cell transfusion
Haemoglobin drop >1.24 mmol L^{-1}		
Bleeding with prolonged hospitalization		
Examples of typical minor and major surgical procedures included in the study[c]		
Minor		**Major**
Dental procedures or surgery		Total knee/ hip and shoulder replacement
Excision of lipoma		Adenoid-tonsillectomy
Insertion/removal of intravenous catheters		Colorectal surgery
		Vascular surgery
		Maxillo-facial surgery (bimaxillary osteotomy)

IU mL^{-1}, International Units per milliliter.
[a]According to the National and/or hospital guidelines of the Netherlands and United Kingdom.
[b]According to the International Society of Thrombosis and Haemostasis.[6]
[c]According to the surgical risk score of Koshy et al[4]

2.3 | Statistical analysis

The nonparametric Mann-Whitney *U* test was used for comparison of FIX consumption between groups. To evaluate trends in FIX consumption, a "p for trend analysis by one-way ANOVA" was used. A stepwise forward and backward logistic regression analysis was performed to identify predictors of FIX levels lower or higher than target FIX levels with elimination of variables with $P > .10$. A Pearson chi-squared test was used for comparisons between proportions. General characteristics are presented as median and 25-75% interquartile range (IQR) and as number and percentages for respectively continuous and categorical variables. Data management and statistical analysis were performed with SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

A total of 118 severe and moderate haemophilia B patients who underwent a total of 255 surgical procedures were included. Of these, 85 (72%) were severe haemophilia B patients, of which 36 were on prophylactic treatment. Patient characteristics are shown in Table 2. Eighty-two adult patients underwent a total of 201 surgical procedures (median age 46 years; median body weight 85 kg), and 36 children underwent a

TABLE 2 General characteristics of study population

	Total cohort	Adults	Children
	No. (%); or Median [IQR]		
Patient characteristics			
No. of patients	118	82	36
Age (y)	40 [22-58]	46 [34-59]	6 [2-11]
Body weight (kg)	79 [65-92]	85 [73-95]	19 [13-39]
Severe haemophilia B (<0.01 IU mL^{-1})	85 (72)	57 (70)	28 (78)
On prophylaxis	36 (31)	28 (34)	8 (22)
Blood group O[a]	33 (28)	24 (29)	9 (25)
Neutralizing antibodies (historically)	6 (5)	5 (6)	1 (3)
Chronic hepatitis C	47 (40)	46 (56)	1 (3)
Surgical characteristics			
No. of surgical procedures	255	201	54
Total no. of patients undergoing			
1	55	33	22
2	31	21	10
≥3	42	28	4
Major surgical procedure	120 (47)	105 (52)	15 (28)
Type of surgical procedure			
General	19 (7)	16 (8)	3 (6)
Colo-rectal	16 (6)	14 (7)	2 (4)
Vascular	9 (4)	9 (4)	0 (0)
Cardio-thoracic	3 (1)	2 (1)	1 (2)
Orthopedic	99 (39)	92 (46)	7 (13)
Urological	11 (4)	11 (5)	0 (0)
Maxillofacial	1 (0)	1 (0)	0 (0)
Ear-Nose-Throat	9 (4)	5 (2)	4 (7)
Neurosurgery	1 (0)	1 (0)	0 (0)
Eye surgery	2 (1)	2 (1)	0 (0)
(Re)placement central intravenous catheters	27 (11)	2 (1)	25 (46)
Dental extractions	31 (12)	25 (12)	6 (11)
Miscellaneous	27 (11)	21 (10)	6 (11)
Replacement therapy with factor concentrate, hospitalization and blood loss			
Mode of infusion			
Continuous	56 (22)	54 (27)	2 (4)
Bolus	199 (78)	147 (73)	52 (96)
Product type			
Recombinant[b]	201 (79)	150 (75)	51 (91)
Plasma derived[c]	54 (21)	51 (25)	3 (6)
Duration of hospitalization (days)	4 [2-9]	5 [2-11]	4 [2-5]
Complications during perioperative period			
No. of patients suffering from a complication			
Bleeding			
Re-operation	2 (2)	2 (2)	0 (0)
Haemoglobin drop >1.24 mmol L^{-1}	23 (19)	17 (21)	6 (17)
Red blood cell transfusion	1 (1)	1 (1)	0 (0)
Thrombosis	0 (0)	0 (0)	0 (0)

No., number; IQR, inter-quartile range; kg, kilogram; IU mL^{-1}, international units per milliliter.
[a]Blood group available in 80 patients.
[b]Including BeneFix (Pfizer Wyeth Pharmaceuticals Inc., Kent, UK)
[c]Including AlphaNine (Grifols Biologicals Inc. Los Angeles, USA); Replenine (Bio Products Laboratory, Hertfordshire, UK); Haemonine (Biotest Pharma GmbH, Dreierich, Germany); Mononine (CSL Behring GmbH, Marbourg, Germany); Nonafact (Sanquin, Amsterdam, the Netherlands).

total of 54 surgical procedures (median age 6 years; median body weight 19 kg). Twenty-six patients with 51 surgical procedures were included from Haemophilia Treatment Centres in the Netherlands and 92 patients with 204 surgical procedures from Haemophilia Treatment Centres in the United Kingdom. In children, 25 (46%) of all surgical procedures consisted of an insertion or removal of a central intravenous catheter; adult patients underwent an orthopaedic surgical procedure most frequently (n = 92; 46%). Most patients (n = 199; 78%) received their replacement therapy by bolus infusion therapy. In 201 (79%) surgical procedures, patients were treated with recombinant factor concentrates. Children had a higher FIX consumption than adults (children: 145 IU kg^{-1} day^{-1} [IQR 71-234 IU kg^{-1} day^{-1}]; adults: 68 IU kg^{-1} day^{-1} [IQR 34-97 IU kg^{-1} day^{-1}]; $P < .001$). In accordance with guidelines, FIX consumption was highest on day 1 in both adults and children. Strikingly, FIX consumption did not decrease as prescribed during hospitalization from day 2 until day 7 (P for trend = .92; Figure 1). Patients with a minor surgical procedure were admitted for a median of 3 days (IQR 25% and 75% range: 1-5 days) and with a major surgical procedure for a median of 8 days (IQR 3-13 days).

3.1 | Perioperative complications

In only 3 (1.2%) surgical procedures, clinically relevant bleeding complications were observed. Two of these 3 patients underwent total knee replacements followed by haemarthrosis requiring a second intervention. One of these 3 patients received a red blood cell

transfusion after surgery. No association between FIX levels and occurrence of a bleeding complication was found. However, FIX testing was limited during bleeding events. No predictors of clinically relevant bleeding complications could be established.

3.2 | Observed FIX levels and comparison to target ranges

No differences were observed between observed FIX levels between treatment centres and between countries. Daily monitoring of FIX levels revealed that most perioperative FIX levels were outside specified target ranges (Figure 2). More specifically, 60% of trough or steady-state FIX levels were below target range with a median difference of 0.22 IU mL^{-1} [IQR 0.12-0.36 IU mL^{-1}] within 24 hours of the surgical procedure. Relative underdosing decreased over time with only 9% of values under target range at 6 days after surgery (median difference 0.09 IU mL^{-1} [IQR 0.05-0.20 IU mL^{-1}]). Conversely, an increase in proportion of FIX levels above target range was observed over time, with 59% of FIX levels above target range with a median difference of 0.19 IU mL^{-1} [IQR 0.10-0.39 IU mL^{-1}] 6 days after surgery.

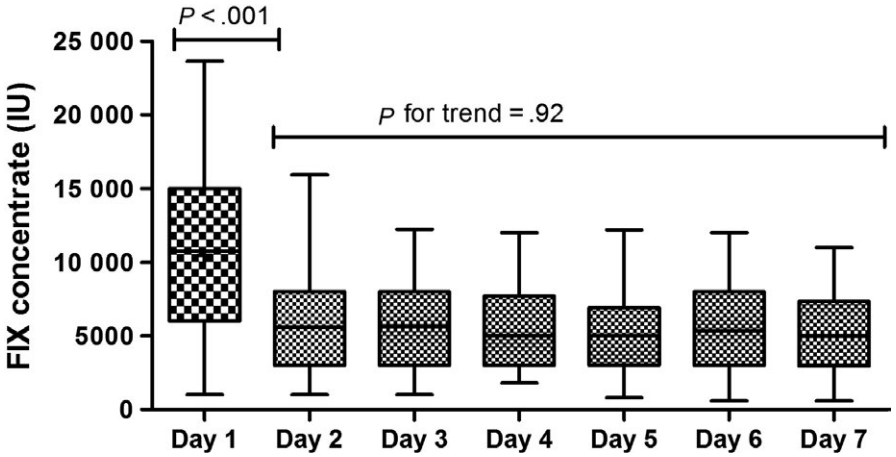
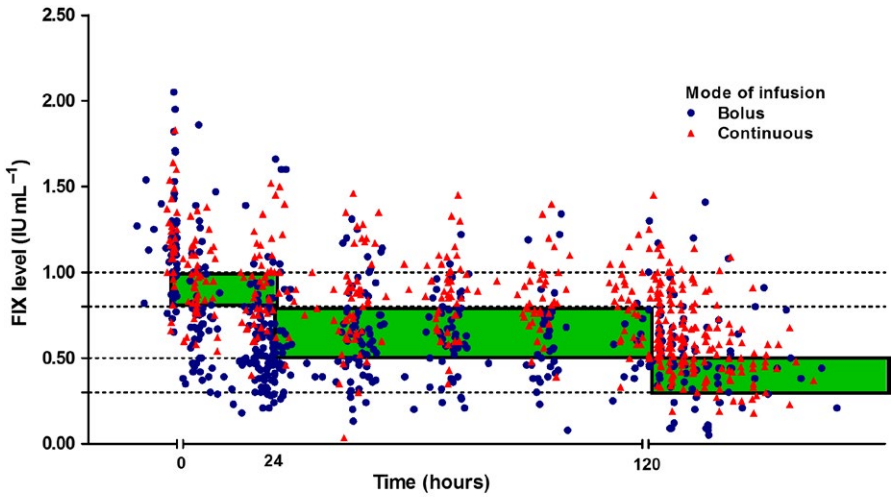


FIGURE 1 Perioperative FIX consumption on consecutive days. Overview of FIX consumption on consecutive postoperative days postoperatively. The amount of FIX administered factor concentrates was higher on day 1 in comparison with following days. *P* for trend analysis using one-way ANOVA showed no differences between amounts of FIX concentrates administered postoperatively



Frequency of lower and higher FIX levels than target range and median difference of target range

	0-24 h		24-120 h		>120 h	
		Median difference (IU mL^{-1}) [IQR]		Median difference (IU mL^{-1}) [IQR]		Median difference (IU mL^{-1}) [IQR]
Total no. of samples	232		381		273	
Lower FIX levels	140 (60)	0.22 [0.12-0.36]	81 (21)	0.11 [0.05-0.19]	25 (9)	0.09 [0.05-0.20]
Higher FIX levels	41 (18)	0.15 [0.08-0.26]	148 (39)	0.16 [0.09-0.32]	162 (59)	0.19 [0.10-0.39]

FIGURE 2 Achieved trough and steady-state FIX levels in the perioperative period. Achieved trough and steady-state FIX levels are shown for both patients treated by bolus infusion replacement therapy (blue) and by continuous infusion (red). Bolus infusion therapy was predictive of lower levels in the first 24 h after surgery in comparison with replacement therapy by continuous infusion. Frequency of lower and higher FIX levels than target range with median difference in IU mL^{-1} and corresponding 25-75% interquartile range (IQR) during the perioperative period is shown corresponding to specified target ranges (green) as defined by National and/or hospital guidelines

3.3 | Predictors of lower and higher FIX levels than target range

When analysing the complete perioperative period in the total study population, both treatments by bolus infusion and minor surgical procedures were predictive of lower FIX levels than required by guidelines (respectively, OR = 5.4 95% CI 3.5-8.3, OR = 2.0 95% CI 1.2-3.2). During the first 24 hours after surgery, only bolus infusion was predictive of lower FIX levels in comparison with continuous infusion (OR = 6.1 95% CI 2.8-13.4; Table 3). Occurrence of a clinically relevant bleeding complication and treatment with continuous infusion were associated with excessively high FIX levels (≥0.20 IU mL^{-1} above target). No differences were observed between achieved FIX levels between treatment centres or between countries and/or between product type (plasma derived versus recombinant) (data not shown).

4 | DISCUSSION AND CONCLUSION

This is the largest cohort of perioperative haemophilia B patients described to date with a total of 255 surgical procedures in 118 patients. This study demonstrates the challenges of perioperative FIX concentrate dosing as most perioperative FIX levels were outside the predefined target ranges recommended by National and/or hospital guidelines. Importantly, 60% of trough and steady-state FIX levels were below the target level in the first 24 hours after surgery, while 59% of FIX levels were above target more than 6 days after surgery. Despite the lower FIX levels, clinically relevant bleeding complications were uncommon (3/255, 1.2%).

The lower FIX levels observed immediately after surgery in our study are most likely due to increased clearance of FIX concentrate during and directly after surgery [4] as well as increased consumption of FIX due to activation of haemostasis by tissue damage and blood loss. Bolus infusion therapy was predictive of FIX levels lower than target range, most prominently in the first 24 hours after surgery. This is in accordance with pharmacokinetic principles as bolus infusions generally lead to overall lower trough levels when frequency of dosing is not sufficient. In addition, the somewhat higher FIX levels in patients treated by continuous infusion may be attributed to overall lower FIX clearance rates due to saturation of FIX binding sites and additional extravascular localization of FIX.[5] Moreover, it should be considered that clinicians may have neglected to adapt continuous infusion rates and may have tolerated or aimed for higher FIX levels in patients undergoing major surgical procedures. This is further supported by the observation, although not remarkable, that minor surgical procedures were predictive of underdosing, when the total perioperative period was evaluated. Minor surgical procedures are often treated for a shorter period of time, with possible acceptance of lower FIX levels. Also, guidelines do not distinguish between severity of surgical procedure in haemophilia.[8] Furthermore, as may be expected, patients with a clinically relevant bleeding complication were excessively overdosed, due to repetitive bolus infusions and/or increased infusion rates in cases of continuous infusion.

TABLE 3 Predictors of lower and (excessively) higher FIX levels than target range[a]

	OR	95% CI
Lower FIX levels (0-24 h)		
Bolus infusion (vs continuous)	6.1	2.8-13.4
Age (increasing per year)	1.0	1.00-1.03
Lower FIX levels (total perioperative period)		
Minor surgical procedure (vs major)	2.0	1.2-3.2
Bolus infusion (vs continuous)	5.4	3.5-8.3
Age (increasing per year)	1.0	1.00-1.02
Higher FIX levels		
Continuous infusion (vs bolus)	3.1	2.2-4.5
Age (decreasing per year)	1.0	1.0-1.0
Excessively higher FIX levels		
Continuous infusion (vs bolus)	1.6	1.03-2.5
Bleeding complication (vs not present)	2.8	1.4-5.8

OR, odds ratio; CI, confidence interval.
[a]Stepwise forward and backward logistic regression analysis.

4.1 | Study strengths and limitations

The large number of patients, 118 patients, and variety of surgical procedures, in total 255 from ten Academic Haemophilia Treatment Centres in two countries, make this study representative for perioperative management in high-income countries in severe and moderate-severe haemophilia B. Moreover, no differences were observed between observed FIX levels and FIX consumption between these treatment centres and between countries. Haemophilia B patients were treated in hospitals specialized in the treatment of patients with bleeding disorders. As such, there is experience of treating patients in the perioperative period with clotting factor concentrates. Moreover, these centres collaborate in international clinical and research networks and treat patients according to latest developments and standards. This study is one of the few studies evaluating perioperative management in haemophilia B with identification of predictors of FIX levels lower and higher than target ranges specified by guidelines. Study limitations include the retrospective nature of the data. However, treatment characteristics, including FIX timing and dosing and timing of FIX sampling, were collected thoroughly, and complications were extensively documented. Yet, documentation of blood loss remained difficult, although we do feel that clinically relevant bleeding defined as necessity of a second surgical intervention and/or necessity of a red blood cell transfusion depicts noteworthy bleeding in this cohort of perioperative patients. Patients with an established neutralizing antibody to FIX were excluded from analysis as these influence FIX clearance due to other immunological mechanisms. This study may lead to both refinements

of current guidelines with regard to target ranges as well as towards implementation of alternative dosing strategies based on more specific criteria than body weight and crude estimations of clearance, as the high proportion of FIX levels within 24 hours after surgery was not associated with a bleeding risk.

4.2 | Perioperative bleeding

Overall in our study population, perioperative bleeding in haemophilia B in both countries was rare (1.2%) and was not correlated with low FIX levels. However, FIX testing was limited during bleeding events. In literature, in 2 case series consisting of 36 and 25 surgical procedures respectively,[4,5] higher percentages of clinically relevant bleeding events as defined in our study have been reported (4-8.3%). In addition, most of these included patients underwent an orthopaedic surgical procedure. Contrastingly, in a cohort of 74 haemophilia B patients undergoing 81 surgical procedures, no red blood cell transfusions were reported and haemostatic efficacy was rated as excellent by surgical teams.[9] In this study, also different minor and major surgical procedures were included, which was similar compared to our cohort. Exceptions are made for certain surgical procedures as a recent report by Kapadia et al showed that lower extremity total joint arthroplasty leads to significantly more red blood cell transfusions in haemophilia patients (15.1%) in comparison with a large matched cohort without a known bleeding history (9.8%); OR 1.60 (95% CI 1.11-2.31).[10]

4.3 | Current guidelines and possible refinements

Although target ranges in most National and/or hospital guidelines do not differ between haemophilia A and B,[8,11-13] other international guidelines such as set by the World Federation of Haemophilia (WFH) prescribe lower FIX levels in the perioperative setting.[14] In contrast, in developing countries with scarce resources, even lower FIX levels are advised (FIX levels of 0.20-0.50 for 1-5 days postoperatively).[14] A low frequency of perioperative bleeding under replacement therapy with lower FVIII and FIX target levels was reported by Srivastava et al in a single-centre respective study of 11 haemophilia A and 7 haemophilia B patients.[15] In this study, FIX trough levels were set at 0.15-0.30 IU mL^{-1} on day 1-3 postoperatively and at 0.10-0.20 IU mL^{-1} more than 4 days postoperatively, until the wound had healed and sutures had been removed. Only one of these 7 haemophilia B patients experienced postoperative bleeds due to surgical reasons as verified by the surgeon. Our study supports these last findings, as in only 7 of 259 surgical procedures (2.7%) a clinically relevant bleeding complication was documented despite underdosing within 24 hours after surgery in 60% of FIX levels. We conclude that there may be growing evidence that it may be possible to maintain lower FIX target ranges in the perioperative setting.

4.4 | Perioperative FIX consumption and individualization of therapy

Although a significant proportion of the study population were underdosed without bleeding, a significant proportion was overdosed, especially >6 days after surgery with 59% of trough and steady-state FIX levels above target. Current costs of health care for society warrant avoidance of excessive dosing without a clinical effect. Overdosing may be prevented by more individualized dosing strategies that take patient, and surgical characteristics as well as individual pharmacokinetics of concentrates into account.

Children had a higher FIX consumption when compared to adults, which is explained by a large volume of distribution and higher clearance.[16]

In prophylactic treatment, it has been proven that FIX consumption can be significantly reduced by individualization of dosing based on pharmacokinetic modelling.[17-20] Several studies have also shown that preoperative dosing based on an individual pharmacokinetic profile is safe, effective and applicable.[5,21] However, the actual challenge is to implement iterative pharmacokinetic-guided FIX concentrate dosing during the perioperative period. This has not been possible to date, as a reliable perioperative population pharmacokinetic model has been lacking. Widespread application of such a model will help to implement individualization of dosing, thereby increasing the proportion of patients with FIX levels within the target range.

This study shows that targeting of FIX levels in the perioperative setting is complex and results are suboptimal as both lower and higher levels than targeted are observed. Individualization of dosing by identification of predictors of volume of distribution and clearance of FIX concentrate may improve *these* outcomes. In addition, a critical assessment of current FIX target ranges seems warranted as few bleeding complications occurred in patients with lower levels than prescribed by National and/or hospital guidelines. Pharmacokinetic-guided dosing may help attain this goal, as lowering of FIX target ranges as *set in such a study could* be achieved reliably. Moreover, *PK guidance* may also decrease overdosing in the last days of the perioperative period. Therefore, we suggest that construction of population pharmacokinetic models and dosing according to these models will lead to *more exact dosing in order to achieve FIX target ranges. Moreover, PK-guided dosing may be able to support studies aiming to refine and possibly lower* current target ranges in haemophilia B, *thus leading* towards overall optimization of perioperative management *in haemophilia B*.

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AUTHORSHIP CONTRIBUTIONS

MC, PWC, RL and HH were responsible for protocol development. HH was responsible for the implementation of the study protocol, data collection and analysis. RL, PC, DH, DK, BL, FM, KM, KF, FL, PWC and MC monitored patient inclusion. MC, PWC and RL supervised the study, with FL and KF giving critical guidance during the project. HH and MC are main authors of the manuscript. All authors substantially contributed to the writing and critically revised the manuscript, with approval of the final draft.

DISCLOSURES

All authors have completed the Competing Interest form and have no financial or personal relationships that could inappropriately influence the study. With regard to other projects and travel grants: KM has received unrestricted research grants from Baxter, Bayer, Pfizer and Sanquin; travel support from Baxter, Bayer, Pfizer and Sanquin; speaker fees from Bayer, BMS, Boehringer Ingelheim and Sanquin. BL has received unrestricted educational grants from Baxter and CSL Behring. FL has received unrestricted research grants from CSL Behring and Baxter and is a consultant for uniQure. KF has received unrestricted educational grants from CSL Behring, Novo Nordisk and Bayer and is member of the European Haemophilia Treatment and Standardization Board sponsored by Baxter. MC has received unrestricted research/educational funding for various projects and other "OPTI-CLOT" studies as well as travel funding from the following companies: Pfizer, Baxter, Bayer Schering Pharma, Novo Nordisk, Novartis, CSL Behring and Roche. The remaining authors declare no competing financial interests.

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REFERENCES

1. UKHCDO. Bleeding disorder Statistics for April 2014 to March 2015; A report from the National Haemophilia Database. 2015, 1-77.
2. Hazendonk HC, Lock J, Mathot RA, et al. Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications. *J Thromb Haemost*. 2016;14:468-478.
3. Hazendonk H, Fijnvandraat K, Lock J, et al. A population pharmacokinetic model for perioperative dosing of factor VIII in hemophilia A patients. *Haematologica*. 2016;101:1159-1169.
4. Hoots WK, Leissinger C, Stabler S, et al. Continuous intravenous infusion of a plasma-derived factor IX concentrate (Mononine) in haemophilia B. *Haemophilia*. 2003;9:164-172.
5. Ragni MV, Pasi KJ, White GC, et al. Use of recombinant factor IX in subjects with haemophilia B undergoing surgery. *Haemophilia*. 2002;8:91-97.
6. Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. Cooperative Study of Sickle Cell Diseases. *Blood*. 1995;86:3676-3684.
7. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202-204.
8. Leebeek FWG, Mauser-Bunschoten EP. Richtlijn Diagnostiek en behandeling van hemofilie en aanverwante hemostasestoornissen. *Van Zuiden Communications BV* 2009;Netherlands:1-197.
9. Shapiro AD, White Ii GC, Kim HC, Lusher JM, Bergman GE. Efficacy and safety of monoclonal antibody purified factor IX concentrate in haemophilia B patients undergoing surgical procedures. *Haemophilia*. Netherlands: Van Zuiden Communications BV; 2009.
10. Kapadia BH, Boylan MR, Elmallah RK, Krebs VE, Paulino CB, Mont MA. Does hemophilia increase the risk of postoperative blood transfusion after lower extremity total joint arthroplasty? *J Arthroplasty*. 2016;31:1578-1582.
11. AHCDO. *Guideline for the management of patients with haemophilia undergoing surgical procedures*. AHCDO; 2010:1-13.
12. Armstrong E, Astermark J, Baghaei F, et al. *Nordic Hemophilia Guidelines*. Nordic Hemophilia Council; 2015.
13. Santagostino E, Mannucci PM, Bianchi Bonomi A. Guidelines on replacement therapy for haemophilia and inherited coagulation disorders in Italy. *Haemophilia*. 2000;6:1-10.
14. Srivastava A, Brewer AK, Mauser Bunschoten EP, et al. *Guidelines for the management of hemophilia*. Montréal, Canada: Blackwell Publishing; 2012.
15. Srivastava A, Chandy M, Sunderaj GD, et al. Low-dose intermittent factor replacement for post-operative haemostasis in haemophilia. *Haemophilia*. 1998;4:799-801.
16. Bjorkman S. Comparative pharmacokinetics of factor VIII and recombinant factor IX: for which coagulation factors should half-life change with age? *Haemophilia*. 2013;19:882-886.
17. Bjorkman S, Shapiro AD, Berntorp E. Pharmacokinetics of recombinant factor IX in relation to age of the patient: implications for dosing in prophylaxis. *Haemophilia*. 2001;7:133-139.
18. Bjorkman S. A commentary on the differences in pharmacokinetics between recombinant and plasma-derived factor IX and their implications for dosing. *Haemophilia*. 2011;17:179-184.
19. Kisker CT, Eisberg A, Schwartz B; Mononine Study G. Prophylaxis in factor IX deficiency product and patient variation. *Haemophilia*. 2003;9:279-284.
20. Carlsson M, Bjorkman S, Berntorp E. Multidose pharmacokinetics of factor IX: implications for dosing in prophylaxis. *Haemophilia*. 1998;4:83-88.
21. Zakarija A. Factor IX replacement in surgery and prophylaxis. *Blood Coagul Fibrinolysis*. 2004;15(Suppl 2):S5-S7.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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