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Citation

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Perioperative pharmacokinetic-guided factor VIII concentrate dosing in haemophilia (OPTI-CLOT trial): an open-label, multicentre, randomised, controlled trial

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Summary

Background Dosing of replacement therapy with factor VIII concentrate in patients with haemophilia A in the perioperative setting is challenging. Underdosing and overdosing of factor VIII concentrate should be avoided to minimise risk of perioperative bleeding and treatment costs. We hypothesised that dosing of factor VIII concentrate on the basis of a patient's pharmacokinetic profile instead of bodyweight, which is standard treatment, would reduce factor VIII consumption and improve the accuracy of attained factor VIII levels.

Methods In this open-label, multicentre, randomised, controlled trial (OPTI-CLOT), patients were recruited from nine centres in Rotterdam, Groningen, Utrecht, Nijmegen, The Hague, Leiden, Amsterdam, Eindhoven, and Maastricht in The Netherlands. Eligible patients were aged 12 years or older with severe or moderate haemophilia A (severe haemophilia was defined as factor VIII concentrations of <0.01 IU/mL, and moderate haemophilia as 0.01 – 0.05 IU/mL), without factor VIII inhibitors, and planned for elective low or medium risk surgery as defined by surgical risk score. Patients were randomly assigned (1:1) using a web-based randomisation system and treatment minimisation, stratified by method of administration of factor VIII concentrate (continuous infusion vs bolus administration) and risk level of surgery (low and medium risk surgery), to the pharmacokinetic-guided or standard treatment group. The primary endpoint was total amount of infused factor VIII concentrate (IU per kg bodyweight) during perioperative period (from day of surgery up to 14 days after surgery). Analysis was by intention to treat and the safety analysis population comprised all participants who underwent surgery with factor VIII concentrate. This study is registered with the Netherlands Trial Registry, NL3955, and is now closed to accrual.

Findings Between May 1, 2014, and March 1, 2020, 98 patients were assessed for eligibility and 66 were enrolled in the trial and randomly assigned to the pharmacokinetic-guided treatment group (34 [52%]) or the standard treatment group (32 [48%]). Median age was 49.1 years (IQR 35.0 to 62.1) and all participants were male. No difference was seen in consumption of factor VIII concentrate during the perioperative period between groups (mean consumption of 365 IU/kg [SD 202] in pharmacokinetic-guided treatment group vs 379 IU/kg [202] in standard treatment group; adjusted difference -6 IU/kg [95% CI -88 to 100]). Postoperative bleeding occurred in six (18%) of 34 patients in the pharmacokinetic-guided treatment group and three (9%) of 32 in the standard treatment group. One grade 4 postoperative bleeding event occurred, which was in one (3%) patient in the standard treatment group. No treatment-related deaths occurred.

Interpretation Although perioperative pharmacokinetic-guided dosing is safe, it leads to similar perioperative factor VIII consumption when compared with standard treatment. However, pharmacokinetic-guided dosing showed an improvement in obtaining factor VIII concentrations within the desired perioperative factor VIII range. These findings provide support to further investigation of pharmacokinetic-guided dosing in perioperative haemophilia care.

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Introduction

Haemophilia A is an X-linked bleeding disorder, caused by a deficiency of coagulation factor VIII. Severity of disease is categorised according to residual factor VIII concentration. The clinical phenotype is characterised by severe bleeding, typically in muscles and joints. Replacement therapy with factor VIII concentrate is administered intravenously, both prophylactically to prevent bleeding

and on demand when bleeding occurs or when patients undergo medical interventions. Generally, factor VIII concentrate dosing is based on bodyweight, while aiming for factor VIII target ranges defined in clinical guidelines.^{1,2}

In the perioperative setting, high factor VIII concentrations are prescribed for longer time periods and are frequently monitored to assure sufficient factor VIII concentrate is administered. Previous studies have

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Research in context

Evidence before this study

We searched PubMed and the ClinicalTrials.gov on April 1, 2014, to find prospective studies in English investigating perioperative pharmacokinetic dosing in haemophilia A. We used the search terms “pharmacokinetics”, “hemophilia A”, “factor VIII concentrate”, “pharmacokinetic-guided dosing”, AND/OR “surgery”. We did not identify any studies investigating the effect of pharmacokinetic-guided dosing in patients with haemophilia A in the perioperative setting. By contrast, pharmacokinetic-guided dosing of factor VIII concentrate prophylaxis has been investigated in haemophilia A. However, this has only been investigated in cohorts with small patient numbers and never in a methodologically sound randomised controlled study design. Nevertheless, these two small studies showed promising results. Patients did not have increased bleeding events, treatment costs were reduced, and patients often obtained target factor VIII values to aid prevention of spontaneous bleeding. Therefore, we hypothesised that dosing based on an individual patient’s concentrations of factor VIII instead of bodyweight, which is standard treatment, would reduce perioperative consumption of factor VIII concentrate and improve the accuracy of attained factor VIII concentrations in a

setting in which reliability of these measurements is of utmost importance.

Added value of this study

To our knowledge, this is the first prospective randomised controlled trial to investigate the effect of perioperative pharmacokinetic-guided dosing in patients with haemophilia A, with randomisation stratified by method of administration of factor VIII concentrate and for risk level of surgery. We found that pharmacokinetic-guided dosing leads to similar perioperative factor VIII consumption as standard dosing, but more optimal obtainment of factor VIII target ranges.

Implications of all the available evidence

Our findings highlight the importance of investigating effects of pharmacokinetic-guided dosing in bleeding disorders and other rare diseases, for which quality of care is relevant and available treatment is expensive. Additionally, our findings also show that pharmacokinetic-guided dosing is feasible when a dedicated team is involved, even in haemostatically challenging situations such as a perioperative setting. Although more detailed research is needed, we advocate for the broad implementation of pharmacokinetic-guided dosing in bleeding disorders.

reported that standard perioperative dosing that is based on bodyweight results in most patients’ factor VIII concentrations being below or above predefined target ranges.^{3–7} Depending on postoperative day, 7–45% of patients have factor VIII concentrations under and 33–75% have factor VIII concentrations over target ranges.⁶ The reason for these variations between patients is probably the large interindividual differences in the pharmacokinetics of factor VIII concentrate, because these differences are not taken into account in dosing strategies.^{8,9} Decreasing this underdosing and overdosing of factor VIII concentrate is important to minimise perioperative risk of bleeding and additional treatment, which is associated with an increased risk of thrombosis and high medication costs.^{1,10–12}

Pharmacokinetic-guided iterative adaptive dosing of factor VIII concentrate is a promising innovative approach.^{9,13,14} However, effects on clinical and economic outcomes have yet to be established.^{15,16} Therefore, we did a randomised controlled trial in patients with severe and moderate haemophilia A to compare pharmacokinetic-guided perioperative treatment with standard bodyweight-guided factor VIII replacement therapy to assess the effect on factor VIII concentrate consumption and on attainment of target factor VIII concentrations.

Methods

Study design and participants

The peri-Operative Pharmacokinetic-guided dosing of CLOTting factor in hemophilia (OPTI-CLOT) trial is an

open-label, multicentre, randomised, controlled trial comparing pharmacokinetic-guided perioperative dosing of standard half-life factor VIII concentrates with routine dosing based on bodyweight in patients with severe and moderate haemophilia A.¹⁷

Patients were recruited from nine Dutch academic and non-academic haemophilia treatment centres in Rotterdam, Groningen, Utrecht, Nijmegen, The Hague, Leiden, Amsterdam, Eindhoven, and Maastricht in The Netherlands (appendix p 11). One patient per participating haemophilia treatment centre (not including the primary treatment site, Erasmus MC), was allocated to the pharmacokinetic-guided treatment group as part of a training cohort to test the logistics involved with iterative pharmacokinetic guidance of dosing to test the feasibility and safety of this approach. These patients were analysed for secondary endpoints only (figure 1).

Eligible patients had severe and moderate haemophilia A, with severe haemophilia defined as factor VIII concentrations of less than 0·01 IU/mL, and moderate haemophilia as concentrations of 0·01–0·05 IU/mL; were aged 12 years or older; planned for elective low or medium risk surgery as defined by the International Classification of Diseases, 9th revision, diagnosis codes for procedures on the basis of the complexity of the planned surgery;¹⁸ had no detectable factor VIII inhibiting antibodies (<0·2 Bethesda units) at inclusion, and provided written informed consent. Written informed consent was obtained from both parents or the legal guardian of participants aged 12–18 years. Patients could

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See Online for appendix

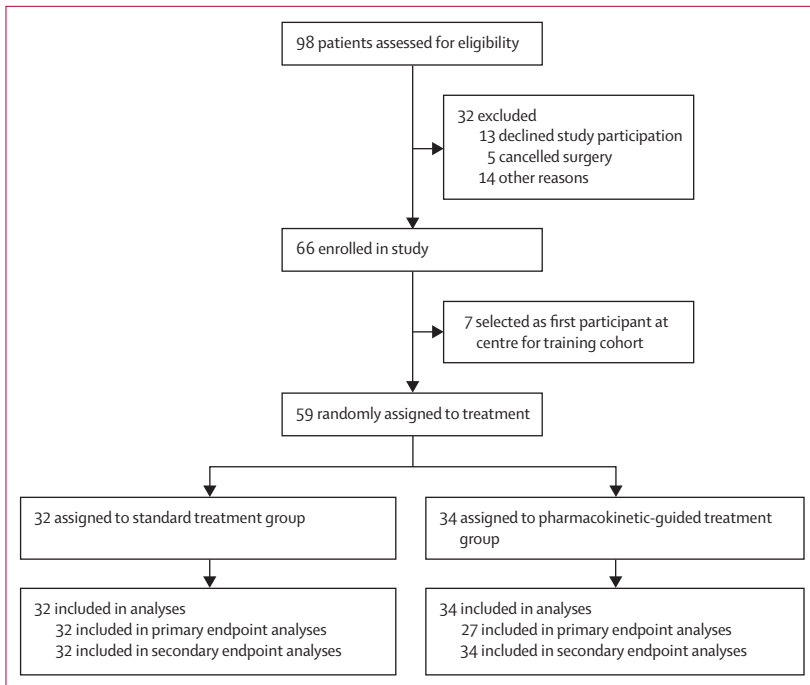


Figure 1: Trial profile

Medical ethical approval required addition of one pharmacokinetic-guided patient into a training cohort per participating centre to test the logistics of pharmacokinetic-guided dosing. These pilot patients were not randomly selected and therefore not included in primary endpoint analyses, but were included in secondary endpoint analyses.

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be enrolled up to 1 year before planned surgery. Patients were excluded if they had other congenital or acquired haemostatic abnormalities, had factor VIII inhibitors, if no written informed consent was acquired, if the planned surgery was high risk, and if they were having an acute medical intervention. Detailed information on inclusion and exclusion criteria is in the appendix (p 5) and has been published elsewhere.¹⁷

In our protocol, we planned to recruit across all age groups; however, due to anticipated difficulties regarding medical ethical approval of the study protocol, because pharmacokinetic-guided dosing of factor concentrates in the perioperative setting was quite innovative at initiation of the OPTI-CLOT randomised controlled trial, we initially included only individuals aged 12 years and older (included in this analysis). When pharmacokinetic guidance was deemed safe and reliable, the OPTI-CLOT kids observational trial was opened without a randomised controlled trial design. To date, only one child younger than 12 years has undergone surgery under pharmacokinetic guidance of bolus infusions.

The study was approved by the Medical Ethical Committee of Erasmus University Medical Center Rotterdam, the Netherlands, and by the boards of participating hospitals. Medical ethical approval required addition of one patient as a training cohort to the pharmacokinetic-guided treatment group per participating centre to test logistics of pharmacokinetic-guided dosing. Due to slow patient inclusion, the protocol was amended and approved

to include three extra haemophilia treatment centres in the study (approved June 28, 2016, in two centres and Feb 1, 2019, in one centre). The study protocol is available in the appendix (pp 13–70).

Randomisation and masking

Using the Trans European Network for Clinical Trials Services (TENALEA), a web-based registration and randomisation system, remaining patients were randomly assigned (1:1) using minimisation, stratified by perioperative method of administration of factor VIII concentrate (ie, intermittent bolus *vs* continuous infusion) and risk level of surgery (ie, low risk *vs* medium risk surgery), because these factors are known to influence consumption of factor VIII concentrate.^{16,18,19} Patients, guardians, treatment teams, and statisticians were unmasked to treatment assignment. Treating haematologists and paediatric haematologists and haemophilia teams were masked to all preoperative individual pharmacokinetic profiles to ensure no indication of patients' factor VIII pharmacokinetic profiles, but were not masked to factor VIII doses. In the pharmacokinetic-guided treatment group, the treatment team was also masked to all perioperative factor VIII measurements, but in the standard treatment group, treating haematologists were not masked to these measurements because they needed them for adjustment of dosing. Unmasking occurred 10 weeks after surgery.

Procedures

Factor VIII activity levels were measured with the factor VIII one-stage assay and the inhibitor status was determined with the Nijmegen Bethesda assay.^{20,21}

In all patients, regardless of treatment group, a preoperative pharmacokinetic profile was obtained in a steady non-bleeding state after an intravenous bolus infusion of approximately 50 IU/kg of various standard half-life factor VIII concentrates. Factor VIII activity one-stage assay measurements were done approximately 4 h, 24 h, and 48 h after bolus infusion.¹⁴ Factor VIII concentrations were measured locally and results were sent to the clinical pharmacologist for analyses (Amsterdam UMC, Amsterdam, Netherlands). Pharmacokinetic profiling was done a maximum of 1 year before surgery. Blood samples were taken before surgery to determine the factor VIII peak concentration, and directly after surgery and daily at the clinic every morning thereafter if possible, up to a maximum of 14 days after surgery. During the perioperative period, factor VIII concentrate was administered intravenously as bolus administrations or continuous infusion, or both. Adjustments in patients given continuous infusions were done by infusion of an additional bolus factor VIII dose or by adjusting the infusion rate. In most patients, treatment with factor VIII concentrate was continued after discharge from hospital with bolus infusions. Factor VIII trough levels were determined if

possible and when indicated by the haematologist. Patients were always allowed to stop study participation if requested. Dosing of factor VIII concentrate and factor VIII levels were monitored until 14 days after surgery.

In the standard treatment group, factor VIII dosing regimens were based on bodyweight and established by the treating haematologist according to clinical guidelines, aiming to reach target prespecified factor VIII target levels (appendix p 8).¹

In the pharmacokinetic-guided treatment group, the factor VIII concentrate loading dose was calculated using the patient's preoperative individual pharmacokinetic profile.^{8,9} Consecutive factor VIII doses were then also iteratively adjusted after application of maximum a posteriori Bayesian forecasting that estimated individual pharmacokinetic parameters to calculate the required dosing regimen to obtain target factor VIII concentrations.¹⁶ Iterative dosing is described as integrating all previous factor VIII doses and factor VIII measurements when modelling to calculate a consecutive factor VIII concentrate dose. All factor VIII doses were rounded to vial size, in which 250 IU was the smallest amount available for most factor concentrates.

After successful inclusion, dosing strategy around surgery, and logistics of one pilot patient in each centre, other patients at each centre were included as part of the main cohort.

No difference was observed between advised dose of factor VIII concentrate and actual dose based on vial size because dosing was prescribed according to available complete vial sizes or when administered continuously according to mL/h.

The haematologist was allowed to deviate from factor VIII target ranges if clinically indicated. The middle of the prespecified target range was used to assess how accurate factor VIII concentrations were. Perioperative bleeding was defined as clinically relevant bleeding on the basis of the International Society of Thrombosis and Haemostasis definition.²² Additionally, for our analyses, this definition specifically included bleeding complications involving a haemoglobin decrease of 1·24 mmol/L or more, or necessitating additional factor VIII concentrate treatment, red blood cell transfusion, a second surgical intervention, or extension of hospital stay, or a combination of these events. Bleeding events were recorded up to 10 weeks after surgery. Grading of bleeding events was done according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). Bleeding events were recorded via the patients' (electronic) log book. Additionally, participants were asked to inform their treating haematologist if a bleeding event occurred.

Outcomes

The primary endpoint was factor VIII concentrate consumption during the total perioperative period, defined as all factor VIII concentrate doses (IU per kg

bodyweight) from 72 h before surgery up to 14 days after initiation of surgery. However, in the perioperative consumption analyses, we report the perioperative period as the day of surgery until 14 days after surgery to exclude the influence of prophylactic factor VIII concentrate dosages on total perioperative consumption.

Secondary endpoints were perioperative haemostasis quantified by haemoglobin concentrations before and after surgery, safety (eg, bleeding and thrombosis), the duration of hospital stay, the effect of baseline von Willebrand factor (VWF), VWF propeptide values,

	Pharmacokinetic-guided treatment group (n=34)	Standard treatment group (n=32)	Total (n=66)
Age, years	49·8 (36·3–63·7)	47·6 (34·8–59·1)	49·1 (35·0–62·1)
Sex			
Female	0	0	0
Male	34 (100%)	32 (100%)	66 (100%)
Bodyweight, kg	83·0 (74·1–95·0)	88·2 (73·3–96·6)	86·7 (73·9–95·4)
Blood group			
O	21 (62%)	19 (59%)	40 (61%)
Not O	13 (38%)	13 (41%)	26 (39%)
Haemophilia severity			
Severe	22 (65%)	22 (69%)	44 (67%)
Moderate	12 (35%)	10 (31%)	22 (33%)
Factor concentrate			
Octocog alfa (Kogenate)	8 (24%)	10 (31%)	18 (27%)
Octocog alfa (Advate)	11 (32%)	9 (28%)	20 (30%)
Morococog alfa	3 (9%)	1 (3%)	4 (6%)
Plasma-derived factor VIII concentrate	2 (6%)	1 (3%)	3 (5%)
Turoctocog alfa	10 (29%)	11 (34%)	21 (32%)
Mode of administration			
Bolus	19 (56%)	16 (50%)	35 (53%)
Continuous	15 (44%)	16 (50%)	31 (47%)
Risk level of surgery			
Low	17 (50%)	17 (53%)	34 (52%)
Medium	17 (50%)	15 (47%)	32 (48%)
Type of surgical procedure			
General	1 (3%)	1 (3%)	2 (3%)
Colorectal	2 (6%)	1 (3%)	3 (5%)
Neurological	3 (9%)	0	3 (5%)
Orthopaedic	12 (35%)	19 (59%)	31 (47%)
Urology	3 (9%)	1 (3%)	4 (6%)
Ear-nose-throat	1 (3%)	1 (3%)	2 (3%)
Eye	2 (6%)	0	2 (3%)
Miscellaneous	10 (29%)	9 (28%)	19 (29%)
Length of stay in hospital, days	3·0 (0·0–8·0)	4·5 (0·3–10·5)	3·5 (0·0–9·0)
Days of treatment required	10·5 (5·8–11·0)	10·0 (7·3–13·0)	10·0 (6·8–11·3)
Complications			
Bleeding	6 (18%)	3 (9%)	9 (14%)
Thrombosis	0	0	0
Number of factor VIII measurements	6·0 (3·3–10·0)	7·5 (3·8–10·0)	6·5 (3·3–10·0)

Data are n (%) or median (IQR).

Table 1: Baseline demographic and clinical characteristics and perioperative clinical characteristics

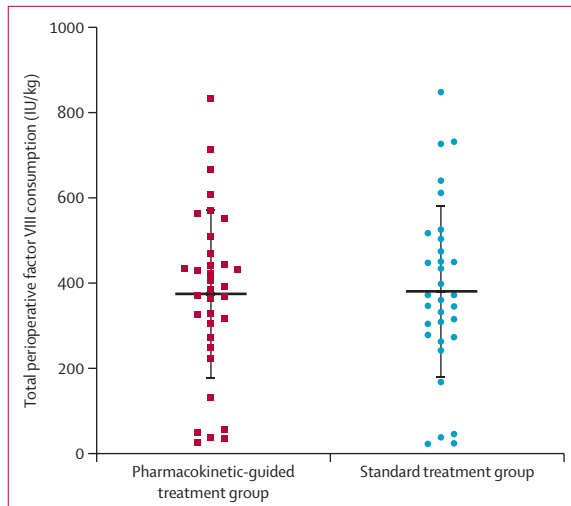


Figure 2: Total perioperative consumption of factor VIII concentrate
Whiskers show the SD of the data and the middle horizontal line shows the overall mean. Each datapoint shows the total factor VIII consumption per patient over the perioperative period. The perioperative period was defined as time from day of surgery until 14 days after surgery.

and blood type on factor VIII clearance, achieved factor VIII levels after factor VIII infusion (IU/mL), and economic evaluation. The influence of VWF on factor VIII clearance has already been investigated²³ and is not included in the analyses presented here. A complete cost-effectiveness analyses is ongoing and will be reported elsewhere.

Statistical analysis

We hypothesised that a reduction in consumption of factor VIII concentrate of 25% was feasible when applying pharmacokinetic-guided dosing. This hypothesis was based on our retrospective study on perioperative consumption of factor VIII concentrate in patients with haemophilia A.⁶ In this previous study, we calculated that the actual achievement of target factor VIII concentrations would lead to a cost reduction of up to 44% on expensive factor VIII concentrate consumption. For the current study, we calculated that a sample size of 60 patients, 30 patients in each treatment group, stratified for method of administration of factor VIII concentrate in the perioperative period and risk level of surgery, was needed to detect a 25% reduction in consumption of FVIII concentrate with a power of 80% and a two-sided α of 0.05.

The patients in the training cohort were not randomly assigned to treatment, and therefore were not included in the primary endpoint analyses, but were included in the secondary endpoint analyses. All analyses were done by intention to treat. Our safety population included all patients who underwent surgery with factor VIII concentrate. Measurements are reported as mean (SD), unless otherwise specified.

We analysed the primary study endpoint using a multivariable linear regression model. We adjusted

analyses for the possible confounders of age, bodyweight, blood group, method of administration of factor VIII concentrate, and risk level of surgery. We did post-hoc analyses to assess the association between factor VIII concentrate consumption and demographic and clinical characteristics.

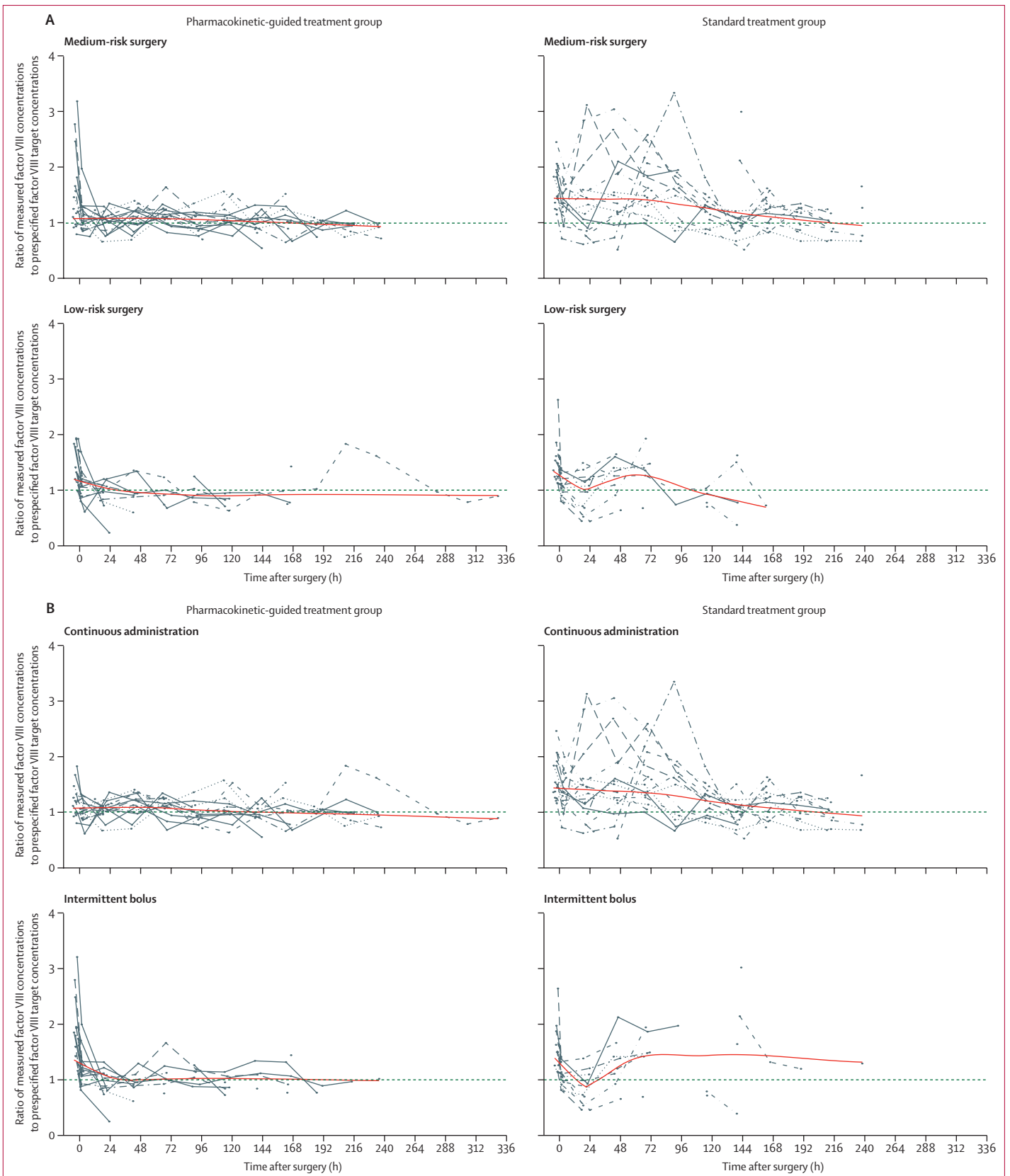
We did post-hoc analyses of the primary outcome in patients who received continuous infusion and for different postsurgical time periods because previous studies have shown underdosing with factor VIII concentrate mostly in the first 24 h after surgery and overdosing in the period 24–120 h, and beyond 120 h after surgery.¹ We did sensitivity analyses of the primary endpoint using three different cutoffs for the perioperative period—ie, until 24 h after surgery, all consumption of factor VIII concentrates from 24 h until 120 h after surgery, and all consumption beyond 120 h after surgery.

To assess the likelihood of factor VIII measurements being within the target ranges over the perioperative period while accounting for the correlation between repeated measurements for each patient, we used a mixed-effect logistic regression model using adaptive Gaussian Quadrature. In the fixed-effects part, we corrected for age, bodyweight, blood group, method of administration of factor VIII concentrate, and risk level of surgery. We also analysed the attainment of factor VIII concentrations within the prespecified target range by calculating the ratio of measured versus target concentrations and compared both treatment groups. We did post-hoc subanalyses for surgical risk and method of administration (appendix p 4). We analysed occurrence of bleeding and thrombotic events in the perioperative period using Fisher's exact test. We compared the duration of hospital stay between treatment groups using multivariable linear regression. We log-transformed the number of days of hospital stay because data were not normally distributed. We also adjusted length of hospital stay for confounders (age, bodyweight, blood group, method of administration of factor VIII concentrate, and risk level of surgery). We used trough levels in all analyses, except for the analyses of the number of factor VIII levels above 1.50 or 2.50 IU/mL, for which we used trough, peak, and all levels in between.

All statistical analyses were two-sided. We used R (version 3.6.1) and SPSS Statistics (version 25.0) for all analyses. This study is registered in the Netherlands Trial Registry, as NL3955.

Figure 3: Ratio of measured factor VIII to prespecified target factor VIII in perioperative period by risk level of surgery (A) and method of administration of factor concentrate (B)

Each datapoint represents a participant at specific timepoints and these datapoints are connected and represented by grey lines of different dot and dash patterns to represent the different participants. The red line indicates the local regression line, which follows the densest part of the data. The green dotted line is at $y=1$, and shows the most ideal situation in which measured factor VIII levels are equal to targeted factor VIII level.



Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 1, 2014, and March 1, 2020, 98 patients were assessed for eligibility, of whom 66 (67%) were enrolled in the study. One centre (Maastricht) did not recruit any participants. 34 (52%) patients were assigned to the intervention group and 32 (48%) to the standard treatment group (figure 1). The Medical Ethical Committee of Erasmus University Medical Center permitted dispensation for the 67th patient and study finalisation during the COVID-19 pandemic. The two groups were well balanced at baseline (table 1), and all 66 patients completed the entire study and were eligible for their respective analyses. Furthermore, no loss to follow-up occurred, such that the follow-up time for every patient amounted to data until 14 days after surgery with complete follow-up for safety outcomes.

No logistical challenges occurred within the training cohort, therefore the results of the training cohort were integrated into the main cohort results for the secondary endpoints.

In the total perioperative period (time from day of surgery until 14 days after surgery), we found no difference in the consumption of factor VIII concentrate between the pharmacokinetic-guided treatment group (mean consumption 365 IU/kg [SD 202]) and the standard treatment group (379 IU/kg [202]; adjusted difference -6 IU/kg [95% CI -88 to 100]; figure 2). In post-hoc analyses, increasing age was associated with increasing consumption of factor VIII concentrate, with an increase of 1 year in age being associated with a total

decrease of 4 IU/kg (95% CI -7 to -1) in consumption of factor VIII concentrate in the perioperative period ($p=0.018$; appendix p 9). Patients having low-risk surgeries had a non-significantly lower mean total consumption of factor VIII concentrate (310 IU/kg [SD 231]) than patients having medium-risk surgeries (443 IU/kg [132]; adjusted difference 119 IU/kg [95% CI -1 to 239]; $p=0.052$; appendix p 9). There was also no association between consumption and bodyweight or blood group. The mean factor VIII consumption in surgeries with intermittent bolus infusions were non-significantly lower than in surgeries with continuous infusion (mean 302 IU/kg [SD 210] vs 452 IU/kg [159]; adjusted difference 112 [95% CI -3 to 228]; $p=0.057$; appendix p 9). 25 (81%) of 31 surgeries with continuous infusion of factor VIII concentrate were categorised as medium-risk surgeries, and 28 (80%) of 35 surgeries with bolus infusions were categorised as low-risk surgeries. However, post-hoc analysis of only patients who had continuous infusion found no differences in consumption of factor VIII concentrate consumption between the standard treatment group (mean 448 IU/kg [SD 180]) and the pharmacokinetic-guided treatment group (461 IU/kg [128]; adjusted difference 1.5 IU/kg [95% CI -103 to 106]; $p=0.98$).

In post-hoc analyses, no association between pharmacokinetic-guided dosing and factor VIII consumption was found during the first 24 h after surgery (adjusted difference -4 IU/kg [95% CI -31 to 24]; $p=0.79$), during 24–120 h after surgery (-5 IU/kg [-45 to 35]; $p=0.82$), and beyond 120 h after surgery (14 IU/kg [-29 to 58]; $p=0.51$).

Pharmacokinetic-guided treatment was associated with a higher number of patients having factor VIII concentrations within the prespecified target range during

	Treatment group	Time since surgery, h	Grade of bleeding event	Blood group	Description
1	Pharmacokinetic-guided treatment	72	2	O	Postoperative haemorrhage in knee 3 days after total knee replacement, consequently additional surgery was necessary; bleeding stopped after second surgery
2	Pharmacokinetic-guided treatment	384	2	O	Postoperative haemorrhage in knee 16 days after total knee replacement
3	Standard treatment	24	4	Non-O (B)	Postoperative haemorrhage around site of incision 1 day after tonsillectomy, leading to admission to intensive care
4	Standard	168	2	O	Central line insertion; 7 days after placement, mild blood leakage from insertion site
5	Pharmacokinetic-guided treatment	384	2	Non-O (A)	Postoperative haemorrhage; haematuria 16 days after transurethral prostate resection
6	Pharmacokinetic-guided treatment	216	1	O	Postoperative haemorrhage in lower arm 9 days after ulnar nerve release surgery under factor VIII prophylaxis
7	Pharmacokinetic-guided treatment	336	2	Non-O (AB)	Haematuria, 14 days after trigger finger surgery, bleed not related to surgery
8	Standard	Immediately after surgery	1	O	After revision of a total knee replacement, leakage of the surgical wound occurred
9	Pharmacokinetic-guided treatment	7	1	O	Postoperative haemorrhage, subcutaneous bleed in lower leg 7 days after total knee replacement

Table 2: Description of postoperative bleeding events

follow-up than was standard treatment (appendix pp 6–7, 10). The number of factor VIII measurements was lower at the end of the perioperative period than at the start (appendix p 7). The number of factor VIII measurements during the perioperative period that were within the target range were 113 (68%) of 166 for patients in the pharmacokinetic-guided treatment group and 58 (37%) of 158 in the standard treatment group. The median time that factor VIII measurements were taken was between 96 h and 120 h hours. Mixed-effects logistic regression analysis showed that pharmacokinetic-guided dosing was associated with an increased likelihood of factor VIII concentration being within the target range compared with standard dosing, while keeping random effect values and other variables constant (odds ratio [OR] 4.6 [95% CI 2.5–8.4]). Similarly, standard dosing was associated with an increased likelihood of dosing above the prespecified factor VIII range compared with pharmacokinetic-guided dosing (OR 4.5 [2.4–8.6]). No differences were found between the pharmacokinetic-guided treatment group and standard dosing treatment group in the number of factor VIII measurements being below the prespecified target range (OR 0.7 [0.3–1.5]).

When analysing the ratio of measured factor VIII concentrations to the prespecified target factor VIII concentrations, pharmacokinetic-guided dosing was associated with improved attainment of prespecified factor VIII levels compared with standard dosing based on bodyweight (figure 3). The overall ratio of measured factor VIII concentrations divided by prespecified target levels was calculated as mean 1.10 (SD 0.33) for the pharmacokinetic-guided treatment group and 1.31 [0.50] for the standard treatment group (adjusted difference 0.85 [95% CI 0.77–0.93]; $p < 0.0001$).

Bleedings were documented until 10 weeks after surgery. Nine (14%) of 66 patients had a clinically relevant bleed at a median of 7.0 days (IQR 1.5–15.5) after surgery (table 2). Six (18%) of 34 patients in the pharmacokinetic-guided treatment group and three (9%) of 32 in the standard treatment group had bleeds ($p = 0.48$). Most bleeds occurred when perioperative treatment ended and prophylactic treatment was continued. No patients had thrombosis and no deaths were reported. Because increased factor VIII levels are associated with thrombosis, we also analysed factor VIII measurements above 1.50 IU/mL or above 2.50 IU/mL. In the standard treatment group, 22 (10%) of 221 factor VIII measurements were above 1.50 IU/mL whereas only 13 (6%) of 236 in the pharmacokinetic-guided treatment group were above this cutoff. The median duration of hospital stay was 3.0 days (IQR 0.0–8.0) in the pharmacokinetic-guided treatment group and 4.5 days (0.3–10.5) in the standard treatment group. The adjusted duration of hospital stay was associated with method of concentrate administration (adjusted between-group difference 2.45 days [95% CI 1.63–3.77]; $p < 0.001$).

Discussion

To our knowledge, this is the first randomised controlled trial to assess the efficacy of pharmacokinetic-guided replacement therapy compared with standard bodyweight-guided replacement therapy in patients with severe and moderate haemophilia A undergoing surgery. We found no difference between pharmacokinetic-guided treatment and standard treatment with regards to the primary endpoint of consumption of factor VIII concentrate; however, in secondary endpoint analyses we found an improvement in obtaining factor VIII concentration within the desired range. Therefore, we believe that pharmacokinetic-guided treatment could optimise and personalise haemophilia treatment in patients undergoing surgery.

In a previous retrospective study,⁶ we assessed perioperative data from 119 patients with severe and moderate haemophilia A who had 198 surgeries in total, and we found that 45% of measured factor VIII concentrations were below the target range during the first 24 h after surgery and that 75% were above the target range 120 h after surgery. On the basis of these data, we assumed that patient safety and quality of care would improve with attainment of factor VIII concentrations within target ranges via implementation of pharmacokinetic-guided dosing. Moreover, in a previous study⁶ we calculated that the achievement of target factor VIII concentrations would lead to a cost reduction of up to 44% that would otherwise be spent on expensive factor VIII concentrate medication. However, in the current randomised controlled trial, we found that consumption is similar and not reduced with pharmacokinetic-guided dosing compared with standard bodyweight-guided dosing, whereas factor VIII concentrations are more often within the prespecified target range with pharmacokinetic-guided dosing than with standard bodyweight-guided dosing.

Possible explanations why no difference was found in the consumption of factor VIII concentrate between the groups are diverse. First, when assessing the overall perioperative period the use of higher factor VIII doses to obtain factor VIII concentrations closer to target levels in the first 24 h after surgery in the pharmacokinetic-guided treatment group might have counterbalanced reduced consumption beyond 120 h after surgery. We were not able to investigate this hypothesis because of the small number of factor VIII measurements at the end of the perioperative period. More specifically, the median number of factor VIII measurements per patient (6.5 overall, 6.0 in the pharmacokinetic-guided treatment group, and 7.5 in the standard treatment group) in the total study corresponds with a median of only 96–120 h after surgery. Second, the difference in the median length of hospital stay was 3.5 days (IQR 0.0–9.0); however, in our retrospective study⁶ the median length of hospital stay was 9 days (5.0–12.0), a difference that might explain the absence of reduction of consumption of factor VIII

concentrate over time in the intervention group. This decrease in duration of hospital stay seems to be due to a general trend of shorter stay in hospital than during our retrospective study, because no difference in surgical risk was observed between treatment groups. No association was found between earlier discharge from hospital with concomitant switch to intermittent bolus infusion and increased consumption of factor VIII concentrate at the end of the 14-day study period (data not shown). Finally, use of different concentrates between patients and use of different on-site assays and reagents to measure factor VIII levels between centres might have led to differences in factor VIII consumption. However, earlier results on which the perioperative population pharmacokinetic model was constructed showed no differences were present between the perioperative pharmacokinetic characteristics of the various factor VIII concentrates or between treatment centres.¹⁶ Therefore, we do not expect that the variability in the pharmacokinetics of the factor VIII concentrates is the reason why we did not observe a difference in consumption of factor VIII concentrates. Furthermore, our study resembles the real-world situation in which multiple standard half-life factor VIII concentrates are administered at the same centre to various patients, which makes translation of our study findings to the (outpatient) clinic easier. To our knowledge, our study is the first to show the effect of pharmacokinetic-guided treatment in a perioperative setting in a methodologically sound design. Previously, these effects were investigated in two prophylaxis studies with small patient numbers.^{24,25}

Our study has several limitations, many of which are because of the real-world setting of the study. First, standard dosing was done by haematologists and paediatric haematologists who were not masked to factor VIII doses and factor VIII measurements. Therefore, stricter and more precise dosing might have occurred in the standard treatment group than in the pharmacokinetic-guided treatment group simply because the haematologists knew these measurements were of importance, and, because primarily excessive factor VIII dosing was found in the previous retrospective study⁶ and the same centres participated in that study and the current study, researchers might have been affected by a desire to obtain better and more precise factor VIII levels than in the previous study (a phenomenon known as the Hawthorne effect²⁶). In our previous study,⁶ which was done without such a performance bias, only 22% of all factor VIII measurements were within the prespecified factor VIII target range during the perioperative period. Therefore, the fact that within the current trial this proportion increased to 68% in the pharmacokinetic-guided treatment group versus 37% in the standard treatment group suggests that pharmacokinetic-guided dosing allows more accurate obtainment of target factor VIII levels. Second, the absence of consecutive factor VIII

measurements at the end of a patient's hospital stay is a limitation. We assume that due to real-life patient-related and doctor-related factors, factor VIII monitoring was less proactive at the end of the perioperative period than directly after surgery to unburden both the patient and organisation of the intensive intravenous blood sampling required at the beginning of each perioperative period. Third, although pharmacokinetic-guided treatment resulted in more optimal achievement of factor VIII target ranges than standard bodyweight-guided treatment, the non-significantly shorter length of hospital stay in the pharmacokinetic-guided treatment group might have caused bias. A shorter stay with more factor VIII measurements might indicate less time between the measurements and more opportunity to adapt dosing schedules than during a longer stay. However, factor VIII measurements were scheduled to take place daily and the pharmacokinetic-guided treatment group only included two additional patients compared with the standard treatment group. Taking these factors into account, time periods are similar between factor VIII measurements and factor VIII measurements per patient and therefore comparable, such that this bias was not present. Fourth, no cost-effectiveness analysis has been done. In this Article, we only focus on consumption of factor VIII concentrate, which is generally accepted to be the main driver of costs.¹² However, a cost-effectiveness analysis would take more variables into account, such as the costs per h of involved health-care professionals. Therefore, such a cost-effectiveness analysis would provide an estimation of real-life costs of pharmacokinetic-guided dosing as an intervention. Finally, the frequency of bolus administrations per day and subsequent factor VIII doses are considerably affected by practical issues and cannot be endlessly adapted. Infrequent dosing leads to increased doses when aiming for prespecified target ranges, and high frequency dosing with lower doses is often logistically difficult.

Hypothetically, our outcomes could have been more robust. First, treatment heterogeneity might be present in our trial. If more medium-risk surgeries and fewer lower-risk surgeries had occurred, our findings might have been different. Second, VWF was not yet part of our perioperative pharmacokinetic model, which might have resulted in less precise pharmacokinetic estimations than had it been included. However, VWF concentrations were collected prospectively in the OPTI-CLOT study and will be used to enrich future models.²³ Unexpectedly, VWF levels only minimally affected factor VIII pharmacokinetics.²³ This finding was most probably because VWF concentrations were all excessively high due to the perioperative setting and therefore not low enough to lead to increased factor VIII clearance. Therefore, looking back, inclusion of VWF in the perioperative population pharmacokinetic model might not have changed our results.

Bleeding events occurred in six (18%) patients in the pharmacokinetic-guided treatment group and three (9%) patients in the standard treatment group. We are confident that pharmacokinetic-guidance during the surgical procedures was not causally related to the late bleeding events occurring in this study because bleeding generally developed when patients were back on regular factor VIII prophylaxis. However, reflecting critically on the study monitored, factor VIII prophylactic trough levels might have been too low to prevent spontaneous bleeding. However, factor VIII trough levels above 0.01 IU/mL are the current target standard in clinical care. For both the prophylactic and the perioperative setting in patients with haemophilia, more detailed research is needed to provide more insight into the association between factor levels and bleeding phenotype—eg, by population pharmacokinetic-pharmacodynamic modelling.

In summary, although this trial showed no differences between interventions, pharmacokinetic-guided treatment could decrease overdosing of patients with haemophilia while using similar amounts of factor VIII replacement therapy compared with standard treatment. Importantly, we found that pharmacokinetic-guided treatment results in more optimal achievement of prespecified factor VIII ranges with more accurate perioperative dosing than standard bodyweight-guided dosing and hence optimisation of treatment for patients.

Contributors

MHC, IvM, and HCAMH were responsible for protocol design and study implementation. IvM enrolled patients, did blood sampling for pharmacokinetic analysis, collected data, did statistical analyses, and, together with MHC, is the main author of the manuscript. TP and LHB did the population pharmacokinetic calculations. REGS, BAPL-vG, LN, FJMvdM, KF, FWGL, PY, EAMB, MC, and KM monitored patient inclusion. MHC, RAAM, FWGL, KF, and KM gave critical guidance during the project. MHC and RAAM supervised the study. RAAM and LHB had access to and verified the underlying data. JGvdB provided statistical and methodological support, contributed to the writing, critically revised the manuscript, and approved the final draft. All authors substantially contributed to the writing, critically revised the manuscript, and approved the final draft. All the authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Requests to access the data collected in the OPTI-CLOT trial should be sent to the corresponding author. Decisions on whether access will be granted will be made through a data access committee, comprising the principal investigators from the OPTI-CLOT steering committee. No identifiable data will be shared and should not be requested. For each data sharing request, a data access form should be completed, describing the purpose, scope, data items requested, and analysis plan. Requestors who are granted access to the data will be required to complete a data sharing agreement that will be signed by the requester, and principal investigator or investigators, and should confirm that the OPTI-CLOT steering committee acknowledge the agreement.

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References

- Leebeek FWG, Mause-Bunschoten EP. Richtlijn diagnostiek en behandeling van hemofilie en aanverwante hemostase stoornissen. Utrecht: Van Zuiden Communications BV, 2009: 1–197. <https://hematologienederland.nl/wp-content/uploads/2021/02/Richtlijn-Diagnostiek-en-Behandeling-van-Hemofilie-2020-geautoriseerde-versie-20210206-2.pdf> (accessed May 27, 2021; in Dutch).
- Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 2020; 26 (suppl 6): 1–158.
- Batorova A, Martinowitz U. Intermittent injections vs. continuous infusion of factor VIII in haemophilia patients undergoing major surgery. *Br J Haematol* 2000; 110: 715–20.
- Dingli D, Gastineau DA, Gilchrist GS, Nichols WL, Wilke JL. Continuous factor VIII infusion therapy in patients with haemophilia A undergoing surgical procedures with plasma-derived or recombinant factor VIII concentrates. *Haemophilia* 2002; 8: 629–34.
- Bidlingmaier C, Deml MM, Kurnik K. Continuous infusion of factor concentrates in children with haemophilia A in comparison with bolus injections. *Haemophilia* 2006; 12: 212–17.
- Hazendonk HC, Lock J, Mathôt RA, et al. Perioperative treatment of hemophilia A patients: blood group O patients are at risk of bleeding complications. *J Thromb Haemost* 2016; 14: 468–78.
- Schütte LM, de Rooij N, Hazendonk HCAM, et al. Current dosing practices for perioperative factor VIII concentrate treatment in mild haemophilia A patients result in FVIII levels above target. *Haemophilia* 2019; 25: 960–68.
- Björkman S, Folkesson A, Jönsson S. Pharmacokinetics and dose requirements of factor VIII over the age range 3–74 years: a population analysis based on 50 patients with long-term prophylactic treatment for haemophilia A. *Eur J Clin Pharmacol* 2009; 65: 989–98.

- 9 Björkman S, Oh M, Spotts G, et al. Population pharmacokinetics of recombinant factor VIII: the relationships of pharmacokinetics to age and body weight. *Blood* 2012; **119**: 612–18.
- 10 Johnson KA, Zhou ZY. Costs of care in hemophilia and possible implications of health care reform. *Hematology Am Soc Hematol Educ Program* 2011; **2011**: 413–18.
- 11 Shrestha A, Eldar-Lissai A, Hou N, Lakdawalla DN, Batt K. Real-world resource use and costs of haemophilia A-related bleeding. *Haemophilia* 2017; **23**: e267–75.
- 12 Zhou ZY, Koerper MA, Johnson KA, et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. *J Med Econ* 2015; **18**: 457–65.
- 13 Hazendonk HCAM, van Moort I, Mathôt RAA, et al. Setting the stage for individualized therapy in hemophilia: what role can pharmacokinetics play? *Blood Rev* 2018; **32**: 265–71.
- 14 Björkman S. Limited blood sampling for pharmacokinetic dose tailoring of FVIII in the prophylactic treatment of haemophilia A. *Haemophilia* 2010; **16**: 597–605.
- 15 Sheiner LB. The population approach to pharmacokinetic data analysis: rationale and standard data analysis methods. *Drug Metab Rev* 1984; **15**: 153–71.
- 16 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**: 1159–69.
- 17 Hazendonk HC, van Moort I, Fijnvandraat K, et al. The “OPTI-CLOT” trial. A randomised controlled trial on periOperative Pharmacokinetic-guided dosing of CLOTting factor concentrate in haemophilia A. *Thromb Haemost* 2015; **114**: 639–44.
- 18 Koshy M, Weiner SJ, Miller ST, et al. Surgery and anesthesia in sickle cell disease. *Blood* 1995; **86**: 3676–84.
- 19 Mulcahy R, Walsh M, Scully MF. Retrospective audit of a continuous infusion protocol for haemophilia A at a single haemophilia treatment centre. *Haemophilia* 2005; **11**: 208–15.
- 20 Over J. Methodology of the one-stage assay of Factor VIII (VIII:C). *Scand J Haematol* 1984; **41**: 13–24.
- 21 Verbruggen B, Novakova I, Wessels H, Boezeman J, van den Berg M, Mauser-Bunschoten E. The Nijmegen modification of the Bethesda assay for factor VIII:C inhibitors: improved specificity and reliability. *Thromb Haemost* 1995; **73**: 247–51.
- 22 Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015; **13**: 2119–26.
- 23 van Moort I, Bukkems LH, Heijdra JM, et al. von Willebrand factor and factor VIII clearance in perioperative hemophilia A patients. *Thromb Haemost* 2020; **120**: 1056–65.
- 24 Carlsson M, Berntorp E, Björkman S, Lethagen S, Ljung R. Improved cost-effectiveness by pharmacokinetic dosing of factor VIII in prophylactic treatment of haemophilia A. *Haemophilia* 1997; **3**: 96–101.
- 25 Valentino LA, Mamonov V, Hellmann A, et al. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia A management. *J Thromb Haemost* 2012; **10**: 359–67.
- 26 Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *BMJ* 2015; **351**: h4672.