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REVIEW
Bilingual edition English/Spanish

Monitoring coagulation factors during surgery. A systematic review

Monitorización de factores de la coagulación en cirugía

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Abstract

Objective: The management of surgeries in patients with hemophilia is complex and requires adequate clotting factor adjustment to avoid bleeding complications and excessive factor consumption. The aim of this systematic review is to analyze the pharmacokinetic studies published on surgery in hemophilic patients, the methodologies used, the main pharmacokinetic covariates applied, and the recommendations made by clinical guidelines.

Method: A structured search was performed in Pubmed, the Cochrane Library, and the Database of Abstracts of Reviews of Effects using the search terms hemophilia (or haemophilia), surgery and pharmacokinetics (or PK). No date or language limits were established.

Results: The search yielded 186 results, from which 34 articles were selected. Many of these analyzed the use of continuous infusions with the aim of achieving stable factor VIII or IX levels and reducing overall factor consumption. However, continuous infusions have fallen into disuse. For decades, clinical guidelines have recommended the performance of comprehensive pharmacokinetic studies prior to surgery (9-11 samples). The clearance rate obtained is used to adjust the presurgical factor dose (or the infusion rate in case of continuous perfusion). Another approach is the use of population pharmacokinetic models, which allow adjustments to be made based on a more limited number of samples. However, the validity of these presurgical pharmacokinetic estimates ceases as soon as the surgical procedure is initiated, making it necessary to adjust the dose based on periodic peak and trough levels. In addition, depending on the

KEYWORDS
Surgery; Pharmacokinetics; Factor VIII; Factor IX; Bayesian inference.

Resumen

Objetivo: El manejo de las cirugías en pacientes hemofílicos es complejo y requiere de un ajuste adecuado de los factores de coagulación para evitar complicaciones hemorrágicas y un consumo elevado. El objetivo de esta revisión sistemática es analizar los estudios farmacocinéticos publicados en cirugía en pacientes con hemofilia, las metodologías empleadas, las principales covariables farmacocinéticas y las recomendaciones de las guías clínicas.

Método: Se ha realizado una búsqueda estructurada sin restricciones de fecha ni idioma en Pubmed, Cochrane y Database of Abstracts of Reviews of Effects empleado los mismos términos de búsqueda: (*hemophilia or haemophilia*), *surgery* y (*pharmacokinetics or PK*).

Resultados: La búsqueda sistemática obtuvo 186 resultados, de los que seleccionamos 34 artículos. Muchos estudios analizaban el uso de perfusiones continuas con el objetivo de lograr niveles estables de factor VIII o IX y reducir el consumo global, aunque su empleo ha caído en desuso. Durante décadas las guías clínicas recomendaban realizar estudios farmacocinéticos completos previos a la cirugía (9-11 muestras), según los cuales se ajusta la dosis prequirúrgica, así como la velocidad de infusión en caso de perfusión continua basándose en el aclaramiento calculado. Otra aproximación es el empleo de modelos poblacionales farmacocinéticos, ajustando con un número más limitado de muestras. Estas estimaciones farmacocinéticas prequirúrgicas pierden validez tan pronto como se inicia un procedimiento quirúrgico, y tienen que ajustarse con niveles pico y valle periódicos. Además, las guías clínicas recomiendan, en función del

PALABRAS CLAVE
Cirugía; Farmacocinética; Factor VIII; Factor IX; Estimación bayesiana.

type of surgery, clinical guidelines recommend maintaining factor VIII and IX levels above specific thresholds for certain periods of time, which makes it essential to use pharmacokinetics during the pre- and post-surgical process. In recent years, specific factor VIII and factor IX pharmacokinetic population models have been developed for surgery. The main covariates of these population pharmacokinetic models are age, blood type, and type of surgery for factor VIII; and age and body weight for factor IX.

Conclusions: Pharmacokinetic estimation could allow individual and standardized intraoperative dose adjustments to be conducted in patients with hemophilia. The development of specific population pharmacokinetic models for surgery, including those based on extended half-life factors, will allow an optimization of current treatments, potentially reducing factor consumption and hospital stays.

tipo de cirugía, mantener los niveles de factores VIII y IX por encima de los umbrales específicos durante periodos, por lo que resulta fundamental emplear la farmacocinética durante el proceso pre y postquirúrgico. En los últimos años se han desarrollado modelos poblacionales farmacocinéticos de factores VIII y IX específicos para cirugía. Las principales covariables de estos modelos son la edad, el grupo sanguíneo y el tipo de cirugía para el factor VIII, y la edad y el peso corporal para el factor IX.

Conclusiones: La farmacocinética puede permitir ajustar de forma individual y protocolizada las cirugías en pacientes hemofílicos. El desarrollo de modelos farmacocinéticos poblacionales específicos para cirugía, incluyendo los factores de vida media extendida, permitirá optimizar estos tratamientos, con potencial reducción del consumo y las estancias hospitalarias.

Introduction

Hemophilia is an unusual hereditary hemorrhagic disorder caused by a deficiency in coagulation factor VIII (FVIII) in the case of hemophilia A or factor IX (FIX) in the case of hemophilia B. It is associated with the appearance of often recurrent joint bleeds which, in the long term, tend to result in a disabling degenerative arthropathy[1]. The standard of care for severe or moderate hemophilia with a hemorrhagic phenotype is regular and continuous prophylactic administration of the deficient factor to prevent the appearance of joint bleeds and preserve quality of life[2,3].

Use of any of the techniques available to measure post-infusion FVIII/FIX activity in plasma can be considered a basic pharmacokinetic (PK) application in the treatment of hemophilia. Such techniques are typically applied in three different scenarios: (i) to measure peak and trough levels during prophylaxis; (ii) to measure peak and trough levels intraoperatively; or (iii) to measure in vivo recovery (IVR) and the plasma half-life ($t_{1/2}$) of FVIII/FIX to assess immune tolerance in patients with inhibitors[4].

Despite the widespread use of prophylaxis, especially those patients with advanced age who did not receive primary prophylaxis at the appropriate time and therefore developed hemophilic arthropathy, often require orthopedic surgery[3]. Management of these surgeries is often complex and requires titrating the replacement therapy to prevent hemorrhagic complications. Titration of the dose is advisable both from a therapeutic and an economic standpoint given the high intraoperative consumption of the replacement clotting factors and their high cost[4].

Historically, different approaches have been used for PK adjustments during surgery. The purpose of this systematic review is to analyze the PK-based adjustment studies published on operated patients with hemophilia A and B, as well as the methodologies applied, the main covariates used, and the recommendations made by clinical guidelines.

Methods

Search for and selection of studies

The search was conducted by two independent reviewers (JEMV and SBB) based on the criteria used by the systematic reviews and meta-analyses of the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[5]. A structured search with no date or language restrictions was carried out in Pubmed, the Cochrane Library and the Database of Abstracts of Reviews of Effects (DARE). Moreover, a manual search was performed of the tables of contents of the leading scientific journals in the field of coagulopathies. A secondary search was also conducted, based on the references listed in the articles selected during the first literature search. It was not necessary to contact experts to identify articles not retrieved during the review. The last literature search was carried out on 13 April 2021. Additionally, a review was conducted of the latest clinical guidelines of the International Society on Thrombosis and Haemostasis (ISTH) and the World Federation of Hemophilia (WFH) to establish the criteria currently used in PK studies on hemophilic patients undergoing surgery.

The reviewers carried out the selection of studies independently. In case of disagreement, a third reviewer (MRM) was consulted. The same search terms were used across all databases: *(hemophilia or haemophilia), (surgery) and (pharmacokinetics or PK).*

Inclusion criteria were as follows:

- Studies analyzing population PK modeling (PopPK) software or medical devices specific to surgical procedures where replacement FVIII or FIX were used.
- Studies analyzing a certain type of FVIII or FIX replacement therapy during surgery where dosages were titrated based on previous PK measurements.
- Studies analyzing the effect of the covariates on the PK of FVIII or FIX replacement therapies during surgery.

Exclusion criteria were as follows:

- Studies analyzing the use of a certain type of FVIII or FIX during surgery, but without stating whether PK information was used for dose titration.
- Studies analyzing patients in special situations (patients with inhibitors).
- Studies analyzing other clotting factors (Von Willlebrand factor, activated factor VII, factor XI, factor XIII, fibrinogen, etc.).
- Studies analyzing non-factor replacement therapies (emicizumab).

The results of the primary search were used to select articles that met the inclusion criteria based on their title and abstract. Subsequently, a secondary selection was made based on the full articles.

Results

The systematic search performed produced a total of 181 hits from the above mentioned databases; five hits were also obtained from the additional sources (Figure 1). As a result of the primary selection, a total of 41 citations were selected for full reading, with 34 of those eventually meeting the selection criteria. Concordance between the reviewers was excellent (*kappa* = 0.98). The most significant data from the different studies is summarized in table 1.

Main types of PK studies

Traditional (individual) PK analyses

Traditional PK estimates individual parameters on the basis of the concentrations of the drug obtained at different sequential sample collections following administration of one dose of the replacement factor. No population-based models are used. According to the ISTH, measuring the individual pharmacokinetic profile of FVIII and FIX requires 9-11 adult patient samples (4 collected during the distribution phase and 5-7 during the excretion phase) and at least five samples in children[6]. A washout period of five $t_{1/2}$ is also needed. The procedure also requires a firm commitment from the patient and their family given the large number of samples and the amount of time necessary, which makes its application difficult in clinical practice. These kinds of analyses are normally restricted to clinical trials that include small and homogeneous groups of hemophilic patients, where the reference technique selected must be subject to a low intrinsic error rate.

Population PK (PopPK) analyses. Bayesian estimation

Bayesian analysis is a statistical procedure used to adjust patient data to a previously proposed general model. It uses the experimental information obtained from the individual (individual information) plus the information known ex ante about a drug's performance in a given population (population-

Figure 1. *Systematic review search process followed in this study. FVIII: factor VIII; FIX: factor FIX; PK: pharmacokinetics.*

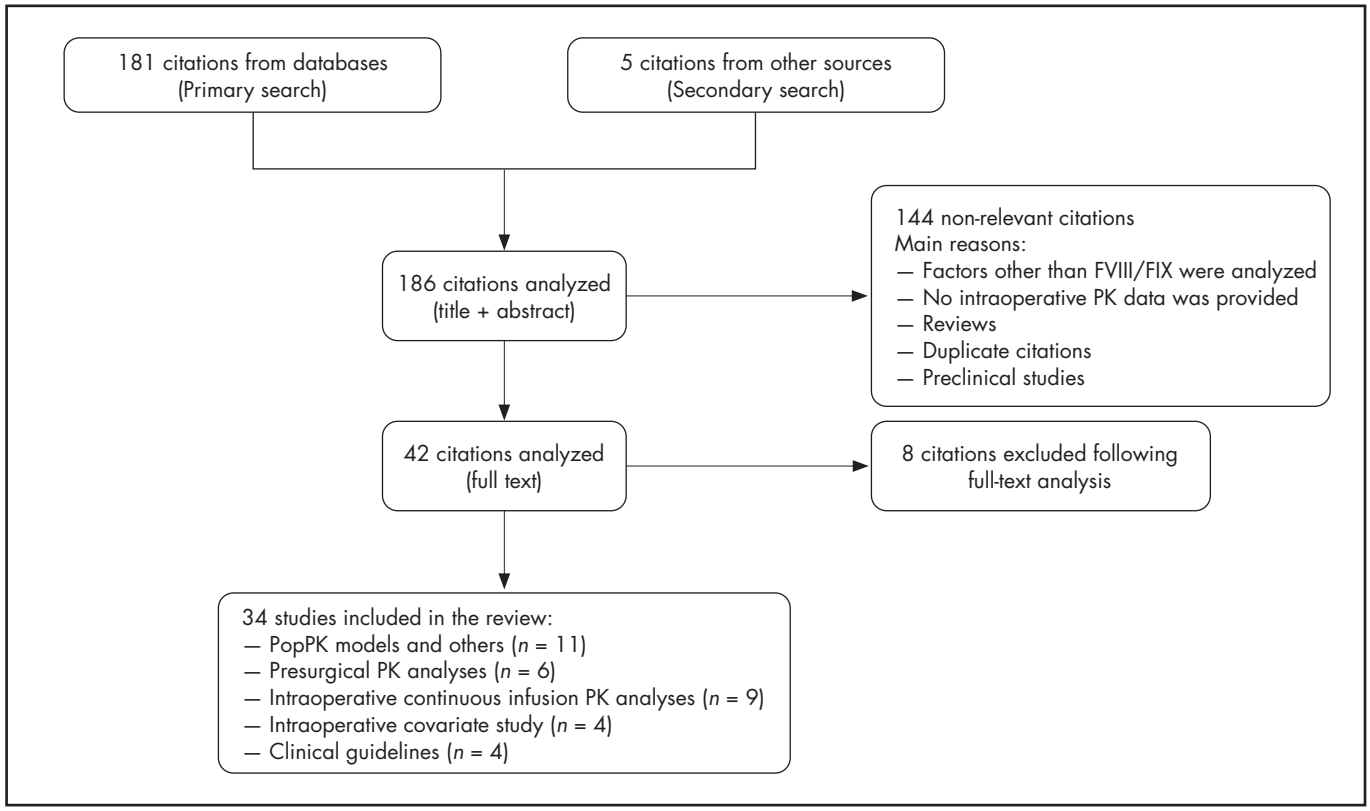


Table 1. Pharmacokinetic studies on hemophilic patients undergoing surgery included in the systematic review

Study, year	Purpose of the study	N	Hemophilia	PK parameters	Covariates	Sampling times	Type of pharmacokinetics
Kasper *et al.* (1985)[7]	Retrospective PK study	350	HA	$t_{1/2}$, IVR	NA	2: pre-dose & 10 min post-dose	Semilogarithmic role
Ruffo *et al.* (1986)[8]	Development of PopPK & limited sampling method	NA	HA	$t_{1/2}$, Vd, clearance	Weight, age and baseline FVIII level	2: 3 & 9 h post-dose	Single-compartment PopPK
Longo *et al.* (1985)[9]	Development of nomogram for 3 target FVIII concentrations	20	HA	$t_{1/2}$, Vd	Weight	1: 10 h post-dose	Single-compartment PopPK[8]
Durisová *et al.* (1998)[11]	Development of PK estimation method	18	HA	Clearance, AUC	Weight	9 (ISTH): pre-dose, 15, 30 min, 1, 3, 6, 9, 12, 24 h post-dose	Frequency-response method
Bolon-Larger *et al.* (2007)[11]	Development of PopPK & limited sampling method	33	HA	$t_{1/2}$, Vd, clearance	Weight, body area and FVIII baseline level	2: 0,5 & 6-8 h post-dose	Two-compartment PopPK
Martinowitz *et al.* (1992)[13]	Continuous infusion PK study	24	HA	Clearance	NA	9 (ISTH): pre-dose, 15, 30 min, 1, 3, 6, 9, 12, 24 h post-dose	Single-compartment PopPK[9]
Hay *et al.* (1996)[14]	Continuous infusion PK study	24	HA	$t_{1/2}$, clearance, clearance rate	Nav	NAv	Single-compartment PopPK
Rochat *et al.* (1999)[15]	Continuous infusion PK study	*5*	HA	$t_{1/2}$, Vd, clearance, MRT	Weight	9 (ISTH): pre-dose, 15, 30 min, 1, 3, 6, 9, 12, 24 h post-dose	Individual PK
Martinowitz *et al.* (2009)[16]	Continuous infusion PK phase II trial	14	HA	$t_{1/2}$, Vd, clearance, MRT, IVR, AUC	Nav	9 (ISTH): pre-dose, 15, 30 min, 1, 3, 6, 9, 12, 24 h post-dose	Individual PK
Suzuki *et al.* (2017)[17]	Continuous infusion PK study	34	HA	IVR, clearance	Body mass index and type of FVIII	1: 70 h post-dose	Use of IVR & clearance formulas

Table 1 *(cont.).* Pharmacokinetic studies on hemophilic patients undergoing surgery included in the systematic review

Study, year	Purpose of the study	N	Hemophilia	PK parameters	Covariates	Sampling times	Type of pharmacokinetics
Kremer Hovinga *et al.* (2018)[18]	Case study on continuous infusion of EHL FVIII products	1	HA	$t_{1/2}$	NA	NAv	PopPK (WAPPS-Hemo)
Schulman *et al.* (1999)[19]	Continuous infusion PK study	10	HB	Clearance	NA	NAv	Individual PK and clearance formula
Hoots *et al.* (2003)[20]	Continuous infusion PK study	28	HB	$t_{1/2}$, Vd, clearance, MRT, IVR, AUC	NA	10: pre-dose, 15 min, 1, 4, 8, 24, 48, 52, 72, 76 h post-dose	Individual PK
Suzuki *et al.* (2015)[22]	Comparison of 5 different methods to calculate clearance	7	HB	$t_{1/2}$, clearance, IVR	NA	NAv	PopPK, Individual PK and formulas based on AUC, $t_{1/2}$ distribution and terminal $t_{1/2}$
Mahlangu *et al.* (2016)[23]	Pre-surgical PK study on EHL FVIII (rFVIIIFc)	21	HA	NAv	NA	NAv	Individual PK
Brand *et al.* (2016)[24]	Pre-surgical PK study on EHL FVIII (BAX 855)	15	HA	$t_{1/2}$, Vd, clearance, MRT, IVR, AUC	NA	NAv	Individual PK
Gruppo *et al.* (2019)[25]	Pre-surgical PK study on EHL FVIII (BAX 855)	21	HA	$t_{1/2}$, Vd, clearance, MRT, IVR, AUC	NA	10: pre-dose, 15 min, 3, 9, 32, 56, 96 h post-dose	Individual PK
Négrier *et al.* (2016)[26]	Pre-surgical PK study on EHL FVIII (rIX-FP)	19	HB	NAv	NA	Nav	Individual PK
Curtin *et al.* (2020)[27]	Pre-surgical PK study on EHL FVIII (rIX-FP)	21	HB	NAv	NA	Nav	Individual PK
Powell *et al.* (2015)[28]	Pre-surgical PK study on EHL FVIII (rFIXFc) & comparison with PopPK	12	HB	$t_{1/2}$, clearance, IVR, time up to 1%	NAv	NAv	Three-compartment PopPK[29] (not surgery-specific)
Hazendonk *et al.* (2015)[30]	Protocol of the OPTI-CLOT trial	NA	HA	NAv	NA	NA	PopPK vs standard dosing
Hazendonk *et al.* (2016)[31]	Development of PopPK	75 ADU 44 PED	HA	$t_{1/2}$, Vd, clearance	Age, blood type and type of surgery	NAv	Two-compartment PopPK
Preijers *et al.* (2021)[32]	Validation & readjustment of PopPK[31] in PED	87 PED (206 total)	HA	$t_{1/2}$, Vd, clearance	Weight & age	NAV	Two-compartment PopPK[31]
Preijers *et al.* (2018)[33]	Desarrollo PopPK	82 AD 32 PED	HB	$t_{1/2}$, Vd, clearance	Weight, age & type of FIX	NAV	Three-compartment PopPK
Collins *et al.* (2012)[34]	Development, validation of PopPK N9-GP and comparison of PK of rFIX, pdFIX & N9-GP	NA	HB	$t_{1/2}$, Vd, clearance, peak level, trough level at 3 & 7 days	NAv	NAV	Two-compartment PopPK (not surgery-specific)
Simpson *et al.* (2019)[36]	Comparison of PK of rFIXFc & N9-GP	15	HB	NAv	NAv	14: pre-dose, 10, 30 min, 1, 3, 6, 8, 24, 48, 96, 144, 168, 192 & 240 h post-dose	Single-compartment PopPK (N9-GP) & three-compartment (rFIXFc)
Preijers *et al.* (2019)[38]	Case report on obese patient	1	HA	Vd, clearance	Ideal weight	8 samples (NAv)	Two-compartment PopPK[31]
Van Moort *et al.* (2019)[39]	Case report on patient with extreme weight loss	1	HA	$t_{1/2}$, clearance, IVR, time up to 1%	Ideal weight	NAv	Ideal weight-adjusted PopPK
White *et al.* (1995)[40]	Influence of covariates on IVR	72	HB	IVR	Weight, age and type of pdFIX	NAv	Use of IVR formulas
Hazendonk *et al.* (2016)[41]	Analysis of FVIII under- and overdosing predictors	119	HA	Vd, clearance	Age, blood type, type of surgery, of FVIII and of perfusion	NAv	Individual PK

Table 1 *(cont.).* Pharmacokinetic studies on hemophilic patients undergoing surgery included in the systematic review

Study, year	Purpose of the study	N	Hemophilia	PK parameters	Covariates	Sampling times	Type of pharmacokinetics
WFH *et al.* (2005)[35]	WFH 2005 Clinical Guidelines: target FVIII/FIX levels during surgery	NA	HA-HB	NA	NA	NA	NA
Srivastava *et al.* (2013)[37]	WFH 2013 Clinical Guidelines: target FVIII/FIX levels during surgery	NA	HA-HB	NA	NA	NA	NA
Srivastava *et al.* (2020)[3]	WFH 2020 Clinical Guidelines: target FVIII/FIX levels during surgery	NA	HA-HB	NA	NA	NA	NA
Iorio *et al.* (2017)[43]	Delphi Consensus for defining target FVIII levels	NA	HA	NA	NA	NA	NA

ADU: adult patients; AUC: area under the curve; BAX 855: rurioctocog alfa pegol; EHL: extended half-life; FVIII: factor VIII; FIX: factor FIX; HA: hemophilia A; IVR: *in vivo* recovery index; N9-GP: nonacog beta pegol; NA: not applicable; NAv: not available; pdFIX: plasma-.derived FIX; PED: pediatric patients; PK: pharmacokinetics; PopPK: population PK models; rFIX: recombinant FIX; rFIXFc: eftrenonacog alfa; rFVIIIFc: efmoroctocog alfa; rIX-FP: albutrepenonacog alfa; $t^{1/2}$: half-life; MRT: mean residence time; Vd: distribution volume; WFH: World Federation of Haemophilia.

based information) whose physiopathological characteristics are similar to those of the patient under analysis. If experimental information is limited, the influence of population-based values will be high. However, the influence of population-based values decreases as more experimental data become available. PopPK is capable of estimating individual parameters without the need of the exhaustive sample collection required by traditional PK[4].

Initial studies analyzing the methodology used to estimate the FVIII/FIX PK profile during surgery

The first few PK studies on hemophilic patients undergoing surgery were published in the 1980's[7-9]. At that time, a retrospective study analyzed the PK values obtained in 350 surgical procedures in patients with hemophilia A[7]. A pre-infusion sample was collected at baseline, followed by a post-infusion one al 10 minutes to calculate the $t_{1/2}$ and IVR of the replacement factor. In 1986, Ruffo *et al.* published the first software ever based on a PopPK model applied to surgery[8], modifying previous models used for prophylaxis[10]. The new PopPK, based on FVIII, used a non-linear single-compartment strategy that assumed that the $t_{1/2}$ of FVIII peaked immediately after surgery and gradually decreased over the next few days. The model suggested obtaining two samples, one at 3 hours and the other at 9 hours post-infusion. Sometime later, a nomogram was put together based on the PK data from 20 patients with hemophilia A undergoing surgery, which allowed determination of the required maintenance dose on the basis of the FVIII concentration observed 10 hours after application of the loading dose for three target FVIII steady-state concentrations (30, 60 or 90 IU/dL)[9].

Durisová *et al.* estimated the PK of FVIII intraoperatively by using the "frequency-response" method, based not only on post-surgical FVIII levels as previous models, but also considering pre-surgical FVIII concentrations[11]. The sheer complexity of the model combined with the lack of a software that facilitated its application and the failure to titer the dose in some patients meant that the model was soon neglected.

Bolon-Larger *et al.* developed a two-compartment PopPK model using a non-linear mixed effects modeling (NONMEM) strategy based on data from 33 patients with hemophilia A[12]. Of the different samples analyzed, the ones exhibiting the greatest accuracy and the fewest biases were those obtained at 0.5 and at 6-8 hours post infusion. Body weight, body surface area, and the baseline FVIII concentration were the covariates with the greatest influence on the distribution volume (Vd).

PK studies in patients on continuous infusion undergoing surgery

Intraoperative use of continuous infusion (CI) of coagulation products was for some time promoted over intermittent injections with a view to achieving more stable levels of FVIII/FIX and reducing overall factor consumption. However, continuous infusion has lately fallen into disuse. The literature search performed as part of this study detected 8 studies on the use of CI during surgery, 6 of which with FVIII[13-18] and 2 with FIX[19,20]. These studies usually included a preoperative individual PK analysis with nine sample collections and using non-compartmental models to titer the dosage of the clotting factors, following the recommendations of the ISTH[6]. These studies confirmed that clearance decreases over the first five days post-op, making it possible to adjust the dosing schedule and reduce factor consumption. Use of CI with extended $t_{1/2}$ factor (EHL) products during surgery was only reported in the case of one patient, who was being treated with efmoroctocog alfa[18]. In that case, WAPPS-Hemo® was used to analyze previous PK values[21].

A study by Suzuki *et al.* compared five different methods for calculating the clearance of nonacog alfa in patients on CI[22]. The method, based on IVR and $t_{1/2}$ distribution, obtained similar clearance rates as direct CI calculations, while clearance calculations using terminal $t_{1/2}$ and AUC values underestimated the clearance rate. The simulated single-compartment model also obtained good correlations.

PK analyses of the new FVIII/FIX products used intraoperatively

The advent of the new EHL factor products has resulted in the performance of new research into the intraoperative behavior of PK, both for EHL FVIII[23-25] and FIX[26-28]. Most of these studies carry out a preoperative individual non-compartmental PK analysis to estimate the PK parameters. The exception is a study on eftrenonacog alfa (rFIXFc) that used the PopPK model in patients on prophylaxis[29] and compared the estimated levels with the real-life levels, obtaining an excellent correlation between them[28].

Use of new PopPK models during surgery

The OPTICLOT trial was designed to create a FVIII PopPK model for surgical use and compare it to the results of standard dosing[30]. A bicompartmental surgical model was developed using the NONMEM technique with data from 140 procedures on 75 adult patients and 58 procedures on 44 children with hemophilia A[31]. Covariates in this PopPK analysis included age, blood type and type of surgery. The model was validated through a cohort of 87 pediatric patients, and a new model comprising a total of 206 patients was generated[32]. This new model significantly improved the available predictions, with the estimation accuracy improving from a median underestimation of 17 IU/dL to a median overestimation of 2 IU/dL. Similarly, a three-compartment surgical PopPK analysis was developed using the NONMEM technique, with data from 255 procedures on 118 patients with hemophilia B[33]. Body weight, age and type of FIX were the main covariates.

Few studies have compared the PK values of the new EHL factors with those of standard $t_{1/2}$ (SHL) factors or other EHL factors during surgery.

Noteworthy among them is a study on nonacog beta pegol (N9-GP). The authors developed a specific bicompartmental PopPK and analyzed its performance in different scenarios against recombinant FIX (rFIX) and plasma-derived FIX (pdFIX)[34]. Intraoperative simulations were carried out to compare the dosing regimens of N9-GP, rFIX and pdFIX needed to achieve the target FIX levels established by the WFH (100-120 IU/dL pre-op, 40 IU/dL at days 1-3; 30 IU/dL at days 4-6; and 20 IU/dL at 7-14 post-op)[35]. Use of N9-GP, as measured in IUs/kg, was 80% lower than that of rFIX and pdFIX; the number of infusions required was also lower (2 vs.16).

With the help of the results of a cross-sectional clinical trial comparing the PK of EHL FIX products with that of N9-GP and rFIXFc, specific PopPK (single- and three-compartment, respectively) models were designed for surgical and on-demand applications[36]. The model was used to make estimations on the basis of the recommendations of the WFH for factor administration during surgery[37], with N9-GP requiring the lowest number of infusions (67% and 55% in major and minor surgery, respectively) and the lowest product consumption (67% and 58% in major and minor surgery, respectively).

Effect of co-variables on PopPK values during surgery

The FVIII PopPK model developed under the OPTICLOT trial showed that clearance decreased with age and was 26% higher in patients with blood type 0[31]. Moreover, a 7% decrease in clearance was observed in major surgeries as compared with minor ones. Two case reports on PK-based FVIII dose titration during surgery concluded that the recommended weight is the ideal body weight both for obese patients[38] and in cases of extreme weight loss[39].

FIX PopPK showed that clearance and the distribution volume in the central compartment (V1) grew gradually with age and increasing body weight until the age of 20[33]. Patients treated with pdFIX showed lower clearance and V1 levels than those treated with rFIX (11% and 17%, respectively). Similarly, V1 in patients with moderate hemophilia B was 10% lower than in those with severe hemophilia B.

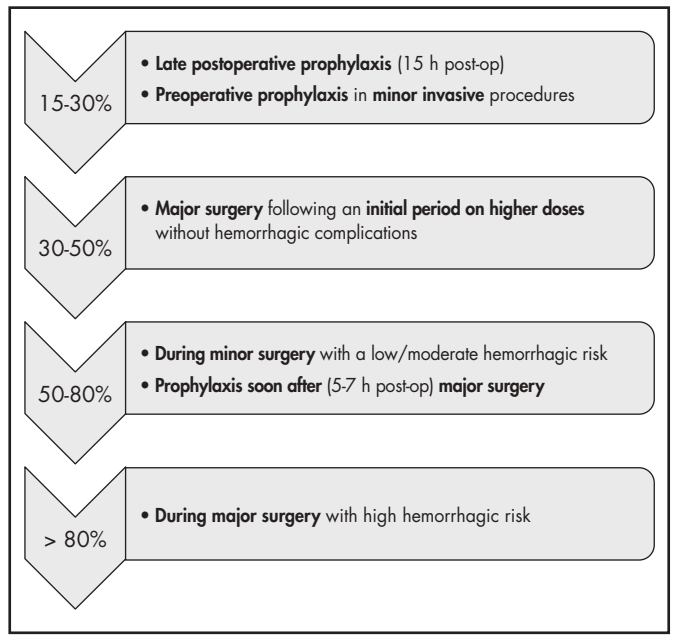
Other studies analyzed the influence of the covariates on PK during surgery. A study on pdFIX compared IVR before and after surgery and demonstrated an age, weight and pdFIX type-dependent effect on dosing[40]. A retrospective study analyzed the variables that influenced IVR and clearance in patients on CI of FVIII during surgery and detected differences in the clearance rate depending on the subjects' body mass index and the type of FVIII used[17].

Another study analyzed the factors capable of predicting FVIII under- and overdosing in 198 surgeries on 119 patients[41]. Blood type 0 and major surgery turned out to be predictors of overdosing, while underdosing was associated with increasing age, plasma-derived FVIII and intermittent infusion. Blood type 0 was also associated with an increased bleeding rate.

Intraoperative factor concentrations recommended by clinical guidelines

To ensure bleeding control during surgery, the clinical guidelines recommend maintaining FVIII/FIX levels above specific thresholds for specific time periods. Exact target levels will depend on the type of surgery performed. These recommendations have undergone certain changes over time[3,35,37]. Table 2 contains the recommendations of the latest WFH guidelines[3].

Figure 2. *Target intraoperative FVIII plasma levels. Adapted from Iorio* et al. *2017*[43].



Another approach is the one followed by the Delphi expert consensus, which redefined the target plasma levels of FVIII, replacing the traditional target level of 1 IU/dL by 8 different target levels[42]. Four of these target levels are related to surgery, with thresholds being established depending on the different surgical stages and the complexity of the surgery (Figure 2).

Against this background, hemophilic patients undergoing surgery should have their peak levels measured 15-30 minutes after the replacement factor has been infused; trough levels should also be regularly measured. It has also been suggested that a full preoperative PK or a PopPK analysis be conducted. The former would require a larger number of samples (9-11) than the latter to adjust the preoperative dose and, if needed, the continuous infusion rate, based on the calculated clearance rate[3]. These preoperative PK estimations must be adjusted during surgery by regularly measuring peak and trough factor concentrations. Several studies have shown that the FVIII/FIX concentrations obtained with this method tend to fall outside the established

Table 2. Recommended peak FVIII/FIX levels and length of treatment depending on type of surgery. Adapted from Srivastava *et al.* 2020[3]

Type of surgery	Hemophilia A				Hemophilia B			
	Low-dose pattern		High-dose pattern		Low-dose pattern		High-dose pattern	
	Peak level (IU/dL)	Length of treatment (days)	Peak level (IU/dL)	Length of treatment (days)	Peak level (IU/dL)	Length of treatment (days)	Peak level (IU/dL)	Length of treatment (days)
Major surgery								
Preoperative	60-80		80-100		50-70		60-80	
Postoperative	30-40	1-3	60-80	1-3	30-40	1-3	40-60	1-3
	20-30	4-6	40-60	4-6	20-30	4-6	30-50	4-6
	10-20	7-14	30-50	7-14	10-20	7-14	20-40	7-14
Minor surgery								
Preoperative	40-80		50-80		40-80		50-80	
Postoperative	20-50	1-5	30-80	1-5	20-50	1-5	30-80	1-5

target range, leading to under- or overdosing[41,43]. This is the reason why the OPTICLOT group is promoting the use of surgery-specific PopPK models to make these kinds of adjustments[31,33].

Discussion

PK has become a new tool to adjust prophylactic treatment in hemophilic patients. Thanks to the fact that PopPK, unlike traditional direct calculation and multiple sampling methods, requires only 2-3 samples[3,4], PK has now become widely used, among other things, to manage changes between SHL clotting factors[44] or between SHL factors and the new EHL ones[45,46]. Nonetheless, while clear recommendations have been published concerning the sampling times required to estimate the PK of FVIII and FIX used prophylactically[47], there is still no standard concerning the optimal number of samples required for PK analyses performed during surgery.

CI is commonly used in major surgery given the convenience it provides by preventing peaks and troughs. However, its drawbacks include the high level of expertise required to appropriately design the required dose, the need to use specifically designed pumps, and the need to determine the stability of FVIII or FIX concentrations after reconstitution within the infusion device[3]. Use of CI has been associated with lower clearance rates, which allow a reduction of the dose and of factor consumption as a whole[3]. Nevertheless, stability issues may require changes every 12 hours or additional bolus injections to ensure effective circulating clotting factor levels. The technique is nowadays only considered useful in patients with severe hemophilia A or B, as in patients with milder phenotypes dosage titration tends to be more difficult. Moreover, CI has been related with a higher risk of inhibitor development in these patients[48,49].

Although the role of covariates of FVIII and FIX PK in prophylaxis is well understood, many knowledge gaps still exist regarding their influence during surgery. The uncertainty is even greater when it comes to EHL factors, for which few PopPK models are available for the surgical setting. The role of the extravascular space may be particularly important as that space is the site at which FIX accumulates and binds to collagen. The strength of this bond is believed to vary across the different types of FIX[50], which leads to a higher Vd for rFIXFc given its broad extravascular distribution and to a lower Vd for N9-GP, depending on the PK model employed; Vd is three-compartmental for rFIXFc[29] and single-compartmental for N9-GP[51].

As is the case with all regression models, a PopPK model's predictive precision depends on it being used in the same conditions as it was developed. For that reason, studies using PopPK models developed in the context of prophylaxis are only valid for the preoperative dose and fail when it comes to making estimations during the procedure[41,43]. The OPTICLOT group has in the last few years developed surgery-specific PopPK models for FVIII and FIX[31,33]. They are furthermore conducting a randomized clinical trial in order to show that PopPK models provide more precise estimations than traditional approaches, permitting more effective dosing and minimizing hemorrhagic complications and overall factor consumption[30]. Prophylaxis-specific collaborative models such as WAPPS-Hemo could in the near future incorporate these surgery-based approaches and facilitate their use in clinical practice[21].

In short, la PK may allow an individualized and standardized adjustment not only of the design of replacement factor prophylaxis but also of the surgical administration of clotting factors during surgery. There still remains to define the best suited PopPK model for each case as well as the most appropriate sampling times for PK analyses. In addition, the recent development of EHL clotting factors may result in the design of surgical protocols with fewer infusions, which would allow a reduction in the bleeding risk associated to peak and trough levels, in the consumption of clotting factors and thereby in the overall cost of surgical procedures and in the patients' hospital stay. Significant as it already is, the contribution of pharmacists to multidisciplinary teams dedicated to the management of PK within the Congenital Coagulopathies Unit will become even more decisive thanks to the new developments discussed in this study. Indeed, pharmacists could become a key figure in the management of these patients.

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Conflict of interests

No conflicto of interests.

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