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Perioperative continuous infusions of factor VIII versus factor IX for patients with hemophilia A or B undergoing major surgery

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Abstract

Continuous factor VIII (FVIII) or factor IX (FIX) infusions are commonly used for patients with hemophilia A (HA) or B (HB) undergoing surgery to secure perioperative hemostasis. To describe differences between the initial recovery and subsequent FIX and FVIII levels, and describe clinical outcomes among HB and HA patients receiving perioperative continuous infusion (CI) of recombinant FVIII and FIX concentrates. Retrospective chart review was conducted on 8 consecutive patients with HB and 7 consecutive patients with HA who underwent major surgery between 2014 and 2018 and received continuous infusions of standard half-life factor concentrate. Median initial bolus dose per kilogram was higher for HB compared to HA patients [90.8 (IQR 78.0–98.7) vs. 52.1 (IQR 48.6–55.6) IU/kg], while initial CI dose-rates were similar [4.3 (IQR 3.8–4.6) vs. 4.2 (IQR 3.8–4.4) IU/kg/h]. Median post-bolus recovery was higher for FVIII compared to FIX [1.70 (IQR 1.23–1.75) vs. 0.88 (IQR 0.75–1.00) IU/mL]. Median factor levels also were higher for FVIII on post-operative days 1 to 3. HB patients had greater mean intraoperative estimated blood loss [285.7 (range 0–1000) vs. 142.8 (range 0–400) mL] and longer median length of hospital stay [9 (IQR 8–12) vs. 5 (IQR 4–6.5) days]. Our initial evidence suggests greater in vivo yield of rFVIII compared to rFIX in the perioperative setting. We identified poorer clinical outcomes in this small cohort of perioperative HB patients indicating that they may benefit from a higher CI rate for adequate surgical hemostatic coverage.

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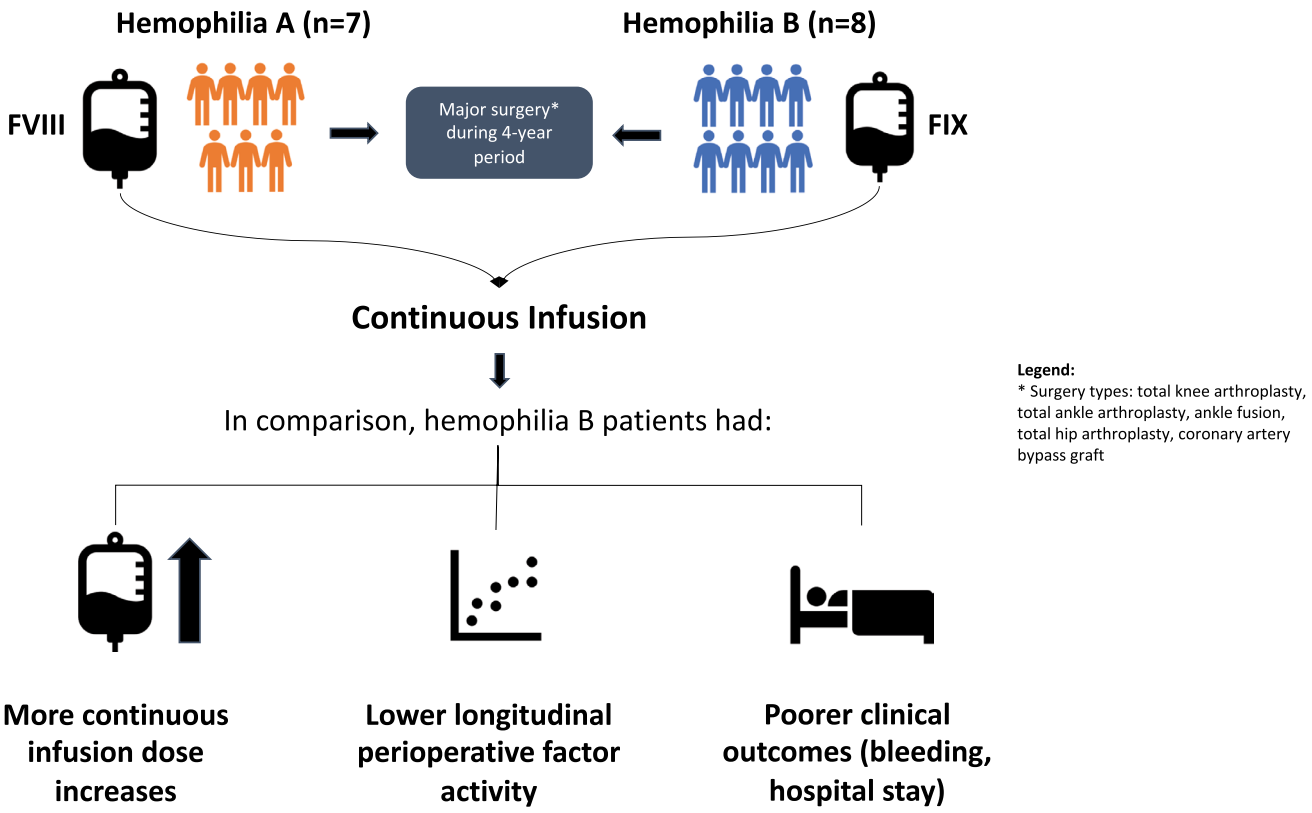
Graphical abstract



Keywords Hemophilia A · Hemophilia B · Pharmacokinetics · Perioperative care · Factor VIII · Factor IX

Highlights

- Continuous infusion (CI) is safe and effective for perioperative hemostasis in hemophilia A/B
- Pharmacokinetics of Factor VIII and IX CI perioperatively are not well described
- We present a retrospective review of 15 perioperative patients with hemophilia A and B
- Perioperative hemostasis was more difficult to achieve in hemophilia B patients on CI

Introduction

Patients with hemophilia undergoing major surgery require factor replacement to maintain adequate levels and secure hemostasis perioperatively. While bolus injections (BI) are commonly used, these are costly and can result in trough levels of factor VIII or IX that may increase bleeding risk [1]. Continuous infusion (CI) of factor concentrate products, a strategy that avoids peak and trough levels, has been proven safe and effective in patients with both hemophilia A (HA) and B (HB) for surgery and severe bleeding episodes [2, 3]. Some studies found that CI of factor VIII (FVIII) and factor IX (FIX) concentrates led to improved safety and clinical outcomes (including fewer transfusions and bleeding complications), economic benefit, and reduced factor consumption compared to BI for major surgery [1, 4, 5]. A recent randomized trial showed comparable outcomes with CI and BI in HA [6]. When feasible, it is standard at many hemophilia treatment centres for patients with moderate to severe hemophilia undergoing major surgery to receive an initial bolus injection of factor to achieve a target level of 80–100%, followed by CI at a rate of 2–4 mg/kg/h [7, 8].

Although both are proven effective in the setting of CI, there are known differences in the inherent pharmacokinetics of standard half-life unmodified recombinant FVIII versus FIX concentrates. The plasma half-life of infused FVIII, 8–12 h, is shorter than that of FIX, 18–24 h [9–11]. Also, the expected in vivo factor activity increase in response to FVIII replacement is approximately 2% per IU/kg, while FIX has a yield of 0.5 to 1% per IU/kg [12]. In contrast to

the one-compartment model of FVIII distribution [13], an initial study of FIX infusion in baboons provided evidence that a substantial proportion of infused FIX may be distributed extravascularly [14]. This prompted further studies that confirmed a two-compartment pharmacokinetic model of FIX, demonstrating that most injected FIX does not remain in circulation, but is found in the extravascular compartment [15–17]. Assuming that extravascular FIX is hemostatically active, the plasma levels of FIX following infusion may therefore not accurately reflect hemostatic function and bleeding risk. There is additional evidence that extravascular FIX retains its procoagulant function, as infused FIX has provided bleed protection much longer than predicted based on its plasma half-life [16, 18]. Furthermore, some studies demonstrate increased clinical severity of severe HA compared to HB (defined on the basis of baseline FVIII or FIX level < 1%), which may be in part explained by hemostatically active extravascular FIX in patients with HB [18–20].

To our knowledge, no studies have directly described the differences between the pharmacokinetics of recombinant FVIII and FIX in patients receiving CI for surgery. As CI is commonly used for perioperative factor replacement, it is important to better understand the differences between FVIII and FIX to guide treatment. As the extravascular compartment of FIX may contribute to hemostasis, HB patients may respond differently to CI from both a laboratory and clinical perspective. We therefore aimed to primarily describe the recovery and subsequent maintenance of FIX and FVIII levels, and to secondarily describe clinical outcomes amongst HB and HA patients receiving continuous FIX or FVIII infusion perioperatively.

Methods

This is a retrospective case series carried out at St. Michael's Hospital in Toronto, Canada, an academic tertiary care institution with the largest Canadian Hemophilia Treatment Center. This program cares for approximately 360 patients with HA and 100 patients with HB. All patients who underwent major surgery and received perioperative CI with FIX or FVIII from January 1, 2014 to December 31, 2018 were eligible for this study. Eight consecutive patients with HB and seven consecutive patients with HA were included (no patients who met criteria were excluded). Eligible patients were identified via electronic chart review.

Data were retrospectively collected and included baseline patient and disease characteristics, surgical details, dosing of bolus and continuous factor infusions, and clinical outcomes during admission (i.e., bleeding, thromboembolic events, length of hospital stay). Baseline characteristics were obtained through consultation reports and initial transcriptions. Data regarding perioperative CI rates were obtained from transfusion records and anaesthesia reports. Clinical outcomes were determined using medical notes, imaging reports, and discharge summaries. Perioperative factor activity was collected at various timepoints, including pre-bolus, post-bolus, post-operative, and at the first three post-operative days (POD 1, 2 and 3). Doses of bolus and CI were chosen based on best available evidence and guidelines for patients with HA and HB at the time [21, 22]. We used a one-stage PTT-based assay to measure FVIII and FIX (Precision Biologic FVIII/FIX deficient plasma reagent, Instrumentation Laboratory ACL TOP Family 50 Series). As this was a retrospective study, some patient data were not available for every variable and missing data were reported when necessary.

Informed consent was waived due to lack of feasibility based on the retrospective nature of the study. Institutional research ethics board approval was obtained.

Statistical analysis

All analyses were stratified by hemophilia type. Factor levels were described as mean (standard deviation), median (interquartile range), and range at each perioperative time point.

Results

Patient population

While the patient population was not selected nor controlled, the HB and HA groups had remarkably similar characteristics (Table 1). There was a similar distribution of blood groups; 4 patients with both HB and HA were group O. Target joints were also similar across both groups. The HB patients were slightly younger (median age 40 years, IQR 35.2–56.2 years) compared to the HA patients (median 54 years, IQR 42.0–65.0 years). Median BMI was slightly higher in the HA group (30.2 vs. 26.3). In addition, a slightly greater proportion of HB patients had severe disease (75% vs. 57%). 1 HB patient and 2 HA patients had a history of inhibitors, however no patients in either group had active inhibitors at the time of surgery or developed inhibitors following surgery. The majority of patients in both group were on prophylactic factor replacement, as only 1 HB patient and 1 HA patient were being replaced on-demand. Pre-operative hemoglobin levels were similar between both groups; 2 HA patients and 3 HB patients had mild pre-operative anemia (hemoglobin < 130 g/L). The two groups also had a similar distribution of surgery types, with all but one patient undergoing orthopedic surgery (one HB patient underwent cardiac surgery). In HA patients, 3 underwent total knee arthroplasty, 2 total hip arthroplasty, 1 ankle arthroplasty, and 1 subtalar ankle fusion. In HB patients, there were 4 total knee

Table 1 Clinico-demographic features of study population

Variable	Hemophilia A (n = 7)	Hemophilia B (n = 8)
Median Age, years (IQR)	54 (42–65)	40 (35.2–56.2)
Median Body mass Index (IQR)	30.2 (28.6–31.6)	26.3 (18.8–30.6)
Disease severity[a] (%)		
Severe	4 (57)	6 (75)
Moderate	1 (14)	2 (25)
Mild	2 (28)	0 (0)
Type of therapy (%)		
Prophylactic	6 (86)	7 (88)
On Demand	1 (14)	1 (12)
Target Joints (%)		
Ankle	4 (57)	5 (62)
Knee	5 (71)	5 (62)
Elbow	3 (43)	5 (62)
Surgery type (%)		
Orthopedic	7 (100)	7 (88)
Cardiac[b]	0 (0)	1 (12)
Median preoperative hemoglobin, g/L (IQR)	140 (134.0–148.5)	139 (129.8–146.2)
Planned intraoperative tranexamic acid (TXA), n (%)	6 (86)	5 (62)
Median dose of intraoperative TXA, mg/kg (IQR)	20.2 (19.5, 20.8)	19.7 (18.2, 20.0)
Pharmacologic thromboprophylaxis		
LMWH (%)	5 (71)	5 (62)
UFH (%)	0 (0)	1 (12)
Blood group (%)[c]		
A	1 (14)	2 (25)
B	1 (14)	0 (0)
AB	1 (14)	1 (12)
O	4 (57)	4 (50)
History of inhibitor (%)	2 (28)	1 (12)

[a]Severe: < 1% factor activity; moderate: 1–5%; mild: > 5–50%

[b]HB cardiac patient underwent coronary artery bypass grafting

[c]Group and screen for one HB patient was not available

arthroplasties, 1 total hip arthroplasty, and 2 subtalar ankle fusions, and one coronary artery bypass graft (CABG). Surgery types per patient are also displayed in Table 2. Five HB patients and six HA patients received planned intraoperative tranexamic acid; median total doses were 19.7 mg/kg (IQR 18.2, 20.0 mg/kg) and 20.2 mg/kg (IQR 19.5, 20.8 mg/kg) respectively.

Factor replacement

All patients received an initial bolus dose prior to initiating CI, as per usual care. All patients received CI with standard half-life products. Table 2 describes the characteristics of perioperative treatment with factor replacement. The median initial bolus dose was higher for HB compared to HA (90.8 vs. 51.0 IU/kg), while the initial CI dose-rate was similar for both groups (4.3 vs. 4.2 IU/kg/h). HB patients had a longer median duration of CI treatment (6.5 vs. 4.5 days). Four HA patients received Advate (Shire), while two received Xyntha (Pfizer) and one received Kovaltry (Bayer). All HB patients received Benefix (Pfizer).

Five patients with HB were given a second bolus infusion (median dose 52.6 IU/kg) because of suboptimal factor IX levels on CI, three of them within 24 h of the surgery. No HA patients required a second bolus. 5 HB patients had a dose-rate escalation of CI compared to 1 HA patient during the first 48 h post-operatively; the relative increase in dose was much higher for HB patients compared to the HA patient (median 2.0 fold vs. 1.1 fold). The CI infusion rate was reduced in 3 HA patients and in no HB patients over the course of their hospital admission.

Perioperative factor activity

Figure 1 illustrates measured FIX and FVIII levels for individual HB and HA patients in the perioperative period.

Table 2 Type of surgery and characteristics of perioperative factor replacement

Subject #	Initial bolus dose, IU/kg	Initial CI dose, IU/kg/h	Factor product used	Duration of CI, days	Second bolus dose, IU/kg	CI dose increase, fold	Type of surgery
1—HA	47.3	3.5	Advate	4	No	1.1	TKA
2—HA	58.0	4.2	Advate	5	No	No	TKA (revision)
3—HA	58.2	4.4	Advate	6	No	No	TKA
4—HA	52.1	3.1	Advate	5	No	No	AF
5—HA	53.3	4.3	Xyntha	3	No	No	AF
6—HA	50.0	4.1	Xyntha	7	No	No	TKA
7—HA	33.7	4.4	Kovaltry	3	No	No	THA
Median (IQR)	52.1 (48.6, 55.6)	4.2 (3.8, 4.4)	N/A	5 (3.5, 5.5)	N/A	1.1 (N/A)	N/A
9—HB	103.4	4.1	Benefix	3	34.5	No	AF
10—HB	97.1	3.9	Benefix	4	No	No	TAA
11—HB	96.2	4.9	Benefix	7	54.9	1.9	TKA
12—HB	133.1	4.5	Benefix	8	No	2.4	THA
13—HB	78.2	3.1	Benefix	14	15.6	1.6	CABG
14—HB	85.5	3.3	Benefix	8	52.6	2.8	TKA
15—HB	54.5	4.5	Benefix	6	54.5	2.0	TKA
16—HB	77.2	4.9	Benefix	6	No	No	THA
Median (IQR)	90.8 (78.0, 98.7)	4.3 (3.8, 4.6)	N/A	6.5 (5.5, 8.0)	52.6 (34.5, 54.5)	2.0 (1.9, 2.4)	N/A

TKA total knee arthroplasty, *AF* ankle fusion, *THA* total hip arthroplasty, *TAA* total ankle arthroplasty, *CABG* coronary artery bypass graft

Coagulation factor levels for both HA and HB patients were descriptively analyzed at each timepoint, and are shown in Table 3. HA patients had higher median factor activity post-bolus [1.70 (IQR 1.28–1.92) vs. 1.07 (IQR 0.80–1.25) IU/mL] and post-operation [1.54 (IQR 1.14–1.65) vs. 0.99 (IQR 0.86–1.14) IU/mL] compared to HB. In addition, HA patients maintained higher median clotting factor activity throughout the first three post-operative days; POD 1 [1.44 (IQR 1.19–1.67) vs. 0.81 (IQR 0.76–0.91) IU/mL], POD 2 [1.63 (IQR 1.48–1.86) vs. 0.94 (0.88–1.10) IU/mL], and POD 3 [1.43 (IQR 1.37–1.55) vs. 1.03 (IQR 0.94–1.20) IU/mL]. To account for differences in baseline factor levels, Fig. 2 describes the FVIII and FIX levels as a delta from pre-bolus levels in a boxplot. The median initial post-bolus recovery (post-bolus—pre-bolus factor activity) was higher for FVIII than FIX [1.70 (IQR 1.23–1.75) vs. 0.88 (IQR 0.75–1.00) IU/mL] and this pattern was also seen longitudinally for the other timepoints.

Clinical outcomes

Table 4 outlines various clinical outcomes for the two groups. HB patients had a greater mean intraoperative estimated blood loss [285.7 (range 0–1000) vs. 142.8 (range 0–400) mL]. In addition, 2 HB patients received post-op transfusion with other blood components; one received red blood cells and platelets following total hip arthroplasty, and the other received red blood cells following CABG.

The median length of hospital stay was longer for HB patients compared to HA [9 (IQR 8–12) vs. 5 (IQR 4–6.5) days]. Decisions surrounding patient length of hospital stay were made jointly by the hematologist and surgeon based on perioperative bleeding and clinical complexity. One patient with HB developed an infection and died of sepsis following cardiac surgery. No other patients had post-operative infectious complications. Six HB and five HA patients received pharmacologic thromboprophylaxis during their CI, mostly with low molecular-weight heparin at standard doses. One HB patient received unfractionated heparin thromboprophylaxis. No patients in either group experienced an arterial or venous thromboembolic event nor post-operative bleeding requiring re-operation during their hospital stay. All but one patient survived until hospital discharge. The one patient who died had HB and died post-CABG of infection.

Discussion

We provide preliminary evidence suggesting poorer laboratory and clinical outcomes for patients with HB on continuous infusion of FIX than patients with HA on FVIII around the time of major surgery. FIX levels appeared to be more difficult to maintain with CI in this setting; HB patients were on CI for longer, required more dose increases and despite this demonstrated lower longitudinal clotting factor activity in the perioperative period. Although our sample size is small, postoperative clinical outcomes in HB patients

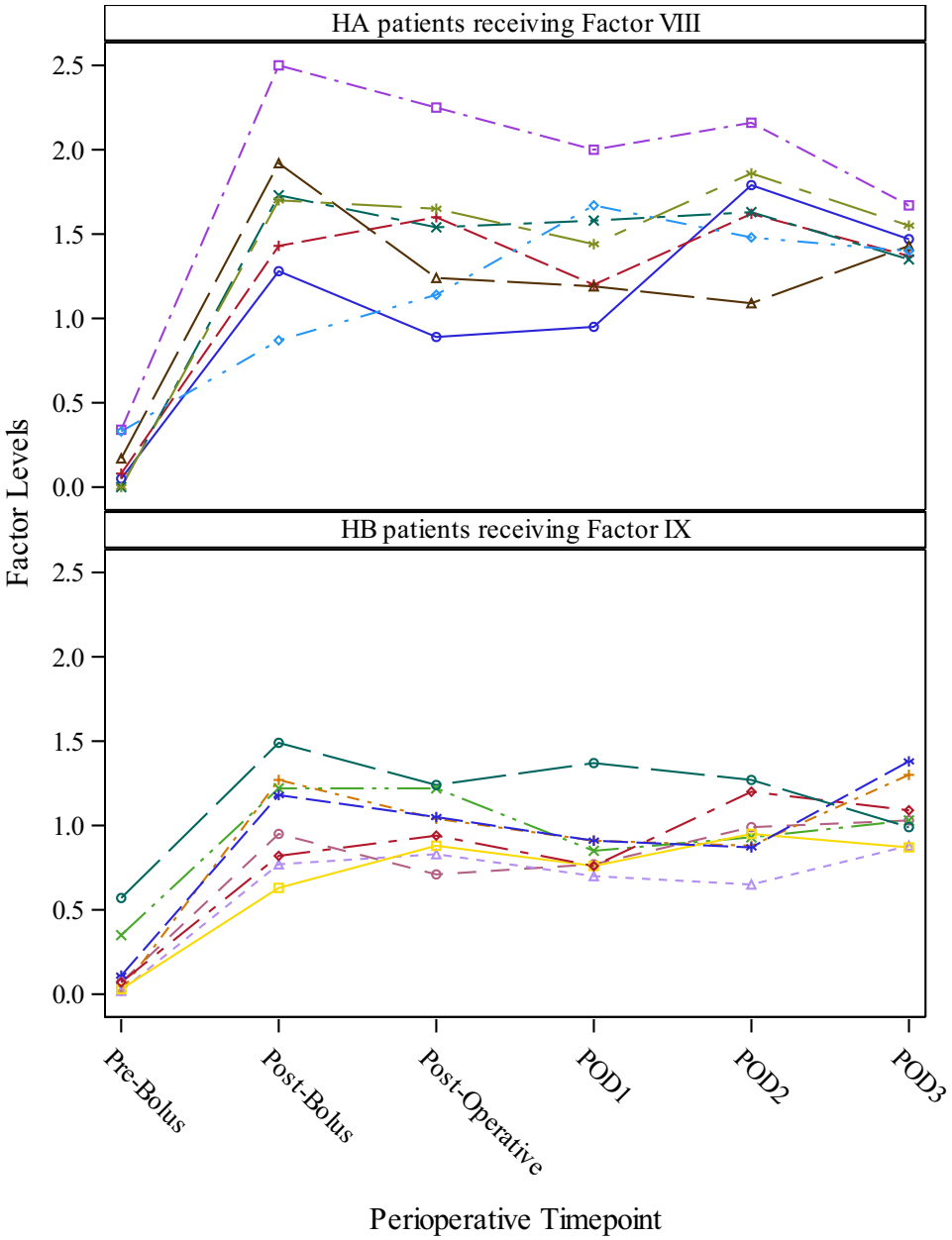


Fig. 1 Individual factor IX and factor VIII activity for HB and HA patients respectively at different perioperative timepoints. Factor IX activity levels were those before additional boluses, where applicable. HA patients overall had higher factor activity levels longitudinally throughout the perioperative period, compared to HB. *POD* postoperative day, *HA* hemophilia A, *HB* hemophilia B

Table 3 Descriptive statistics of factor VIII and IX levels at various peri-operative timepoints

Perioperative Timepoint	Hemophilia A (Factor VIII), n = 7			Hemophilia B (Factor IX)[a], n = 8		
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
Pre-Bolus	0.14 (0.15)	0.08 (0.00–0.33)	0.00–0.34	0.16 (0.20)	0.07 (0.03–0.23)	0.02–0.57
Post-Bolus	1.63 (0.52)	1.70 (1.28–1.92)	0.87–2.50	1.04 (0.29)	1.07 (0.80–1.25)	0.63–1.49
Post-Operative	1.47 (0.44)	1.54 (1.14–1.65)	0.89–2.25	0.99 (0.19)	0.99 (0.86–1.14)	0.71–1.24
POD1	1.43 (0.35)	1.44 (1.19–1.67)	0.95–2.00	0.88 (0.21)	0.81 (0.76–0.91)	0.70–1.37
POD2	1.66 (0.33)	1.63 (1.48–1.86)	1.09–2.16	0.97 (0.19)	0.94 (0.88–1.10)	0.65–1.27
POD3	1.46 (0.11)	1.43 (1.37–1.55)	1.35–1.67	1.07 (0.18)	1.03 (0.94–1.20)	0.87–1.38

[a]Factor IX activities taken before additional boluses, where applicable

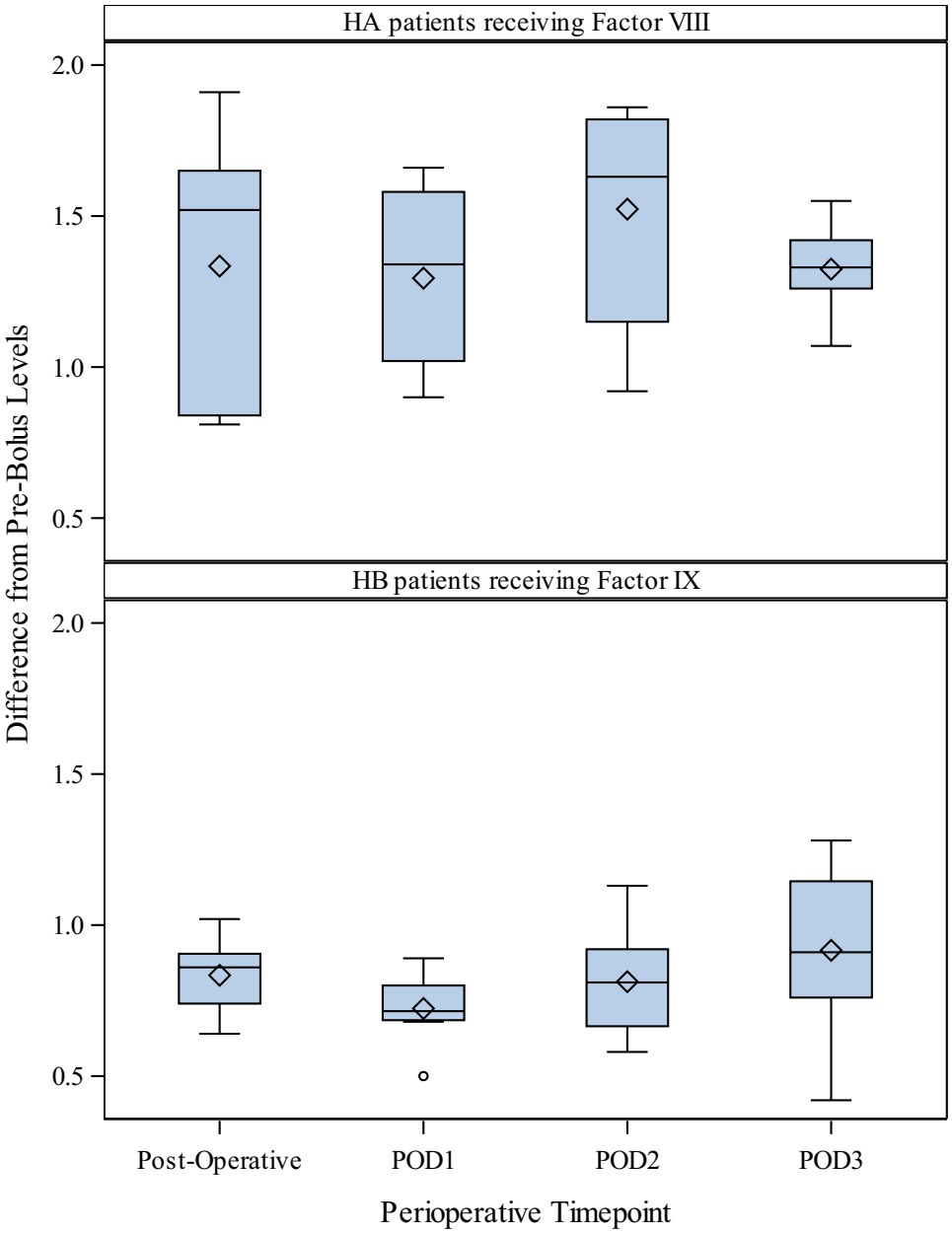


Fig. 2 Boxplot of factor VIII and IX activity at various perioperative timepoints shown as delta from pre-bolus levels to account for baseline factor activity. Factor IX activity levels were those before additional boluses, where applicable. The median initial post-bolus recovery (post-bolus—pre-bolus factor activity) was higher for factor VIII than factor IX, and this pattern was also seen longitudinally for the other timepoints. *POD* post-operative day, *HA* hemophilia A, *HB* hemophilia B

were consistently poorer compared to HA; HB patients experienced greater intraoperative blood loss and longer length of hospital stay which did not appear to be due to the underlying nature of the surgery (as the types of surgeries were essentially similar amongst the two hemophilia study cohorts), thus plausibly could be attributed in part to lower FIX levels requiring more dosing adjustments. However, other differences pertaining to surgical complexity, anatomy, baseline fitness and pre-operative optimization likely also contributed to outcomes.

Although CI has been proven safe and effective in both HA and HB, few comparisons have been made between the two patient populations [7, 23]. In fact, we are aware of only one prospective study which described CI in both groups of patients in major/minor surgery and bleeding events [24]. Otherwise, the literature consists of largely case reports describing the successful use of CI in the perioperative management of a range of different surgical procedures [25–27]. Our study describes the differences between groups of HA and HB patients with similar baseline clinical characteristics, and presents relevant data comparing their perioperative hemostasis with CI.

Some studies suggest that plasma activity of FIX is a misleading predictor of bleeding risk because of the large pool of extravascular FIX [16, 18]. We found both lower FIX activity levels and poorer postoperative clinical outcomes in patients with HB compared to HA. This calls into question whether the current CI dosing strategy is

Table 4 Clinical outcomes during hospital admission

Outcome	Hemophilia B (n = 8)	Hemophilia A (n = 7)
Mean intraoperative estimated blood loss, mL (range)	285.7 (0–1000)	142.8 (0–400)
Post-operative transfusion with other blood components, n (%)	2 (25)	0 (0)
Median length of hospital stay, days (IQR)	9 (8–12)	5 (4–6.5)
Post-operative infection (%)	1 (12)	0 (0)
Survival to discharge (%)	7 (88)	7 (100)

hemostatically sufficient for HB patients undergoing surgery, and if extravascular distribution in this setting is hemostatically protective, a concept supported by a Korean study that showed lower global hemostatic activity with a standard bolus dose of FIX compared to FVIII [28].

The main limitation of this study is its small sample size and lack of randomization. The retrospective nature of the study also led to some missing data, especially laboratory parameters including individual pharmacokinetic parameters and von Willebrand factor levels. However, all data were available to allow for evaluation of our primary study objective. In addition, there was lack of uniform treatment across the two groups; all HB patients received Benefix, however the HA patients received three different products, including two full-length (Advate, Kovaltry) and one B domain-deleted (Xyntha) FVIII. While we recognize that the field is turning towards preparations with longer half-lives (including PEGylated, Fc receptor bound, and non-clotting factor products), we aimed to highlight the experience with CI, which typically uses standard half-life factor concentrate products. At the time of data collection, we focused on the contemporary strategy for major surgeries where tight hemostatic control was warranted with the use of boluses and CIs; however, with newer agents such as emicizumab [29], the treatment paradigm around surgery (especially minor procedures) has since changed for patients with severe hemophilia A. Our findings however, remain relevant for patients with moderate hemophilia and for patients with hemophilia B undergoing major surgery.

We demonstrate, in this small cohort, that perioperative hemostasis was more difficult to achieve with CI in HB than in HA patients. Furthermore, their poorer clinical outcomes suggest that the extravascular stores of FIX may not be as protective as hypothesized by other groups. HB patients may therefore benefit from a higher CI rate compared to their HA counterparts (i.e., 8 IU/kg/h vs. 4 IU/kg/h), which accounts for the known discrepancy in factor recovery per unit per kilogram for these two clotting factors. Due to general as well as individualized differences in FIX and FVIII pharmacokinetics, it may be beneficial to conduct individualized pharmacokinetic evaluations prior to surgery to most effectively tailor CI dosing. Based on our observations, use of standard half-life products with CI remains an option for perioperative management, along with the further advancement in longer-acting products for patients with HB. This initial evidence highlights the need for larger prospective studies to minimize bias and allow for more robust statistical analysis.

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Author contributions BT, JT, and MS contributed to the design of the study. BT and GF collected the data. RN, BT, and MS analyzed the data, in consultation with all authors. All authors (BT, RN, GF, AJ, JT, MS) were involved in the writing and review of the manuscript. MS conceptualized and supervised the study.

Data Availability All relevant data are presented within the paper. Requests to access any additional data should be directed to the corresponding author.

Declarations

Conflict of interest MS has received unrestricted research funding from Takeda and Octapharma. She has previously received honoraria for advisory boards from Takeda, Octapharma, Bayer and NovoNordisk. JT has been a paid consultant and and Advisory Board member for Bayer, Takeda, Novo Nordisk, and Pfizer. He has received research support from Pfizer, Bayer, and Takeda. BT, RN, GF, and AJ have no conflicts to disclose.

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