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Simplifying surgery in haemophilia B: Low factor IX consumption and infrequent infusions in surgical procedures with rIX-FP

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ABSTRACT

Introduction: Long-acting recombinant factor IX (FIX) products may simplify the surgical treatment of haemophilia B patients. The impact of rIX-FP, a recombinant FIX fused to recombinant albumin, on FIX consumption and surgical management was assessed in patients with haemophilia B.

Materials and methods: Male patients, ≤65 years old with severe haemophilia B (FIX activity ≤2%) requiring non-emergency surgery were enrolled in the surgical substudy of PROLONG-9FP. Dosing was based on World Federation of Hemophilia guidelines and patients' pharmacokinetics. Haemostatic efficacy was assessed on a 4-point scale. rIX-FP consumption and safety were monitored throughout the perioperative period.

Results: This updated dataset reports on thirty (8 minor and 22 major) surgeries conducted in 21 patients. A single preoperative bolus was used in 96.7% (n = 29) of surgeries. After minor surgery, patients received a median (range) of 0 (0–3) infusions with a median (range) consumption of 0 (0–178.89) IU/kg in the 14-day postoperative period. In patients who underwent major surgery (including 15 patients undergoing joint replacement surgery), the median (range) number of infusions in the 14-day postoperative period was 5 (0 − 11) and median consumption was 221.7 (0–444.07) IU/kg. Haemostatic efficacy was rated as excellent or good in 87.5% (7/8) of minor surgeries and 95.5% (21/22) of major surgeries.

Conclusion: Surgical procedures can be performed using a single preoperative bolus of rIX-FP in nearly all patients. During postoperative care, use of rIX-FP necessitated infrequent infusions and low FIX consumption. Overall, data suggest rIX-FP simplifies perioperative care in patients with haemophilia B.

1. Introduction

Patients with haemophilia B undergoing surgery are at an increased risk of excessive or prolonged perioperative bleeding [1] and require comprehensive care, including monitoring of factor activity levels, administration of factor IX (FIX), and consultation with numerous specialists [1–4]. Surgeries that are usually performed as outpatient procedures can require overnight or longer-term hospital treatment for those with haemophilia B.

World Federation of Hemophilia (WFH) guidelines recommend that preoperative FIX levels are in range from 50 - 80 IU/dL for minor surgeries and 60–80 IU/dL for major surgeries. Patients undergoing minor surgery should maintain FIX activity levels of 30–80 IU/dL for up to five days postoperatively, depending on the type of procedure. Patients undergoing major surgery should be maintained at 40–60 IU/dL for postoperative days 1–3, 30–50 IU/dL for days 4–6 and 20–40 IU/dL for days 7–14 [1]. Achieving these high FIX activity levels can be challenging with standard recombinant FIX (rFIX), requiring frequent high doses or continuous infusion [5,6], and resulting in high FIX consumption. Surgery in patients with haemophilia can be costly, with a large part of these costs associated with the medical personnel required for patient care and the use of clotting factor concentrates [7,8]. Of note,

Abbreviations: CHO, Chinese hamster ovary; FIX, Factor IX; h, hours; IgG, immunoglobulin G; rFIX, recombinant factor IX; SD, standard deviation; WFH, World Federation of Hemophilia

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the cost of clotting factor concentrates has been highlighted as the limiting step in the number of surgical procedures that can be performed on patients with bleeding disorders [8]. With the potential implication of extended hospital stays, surgery in patients with haemophilia is a significant economic burden for a hospital [8].

Long-acting rFIX products may simplify the surgical treatment of patients with haemophilia B. Long-acting products could reduce the total number of infusions required during the peri- and postoperative periods, whilst maintaining high FIX activity levels and excellent haemostatic efficacy. rIX-FP is an albumin fusion protein linking rFIX to recombinant human albumin via a cleavable linker. rIX-FP has an extended half-life of 102 h, enabling dosing intervals of 7 to 14 days for prophylaxis [9,10], and maintains high, sustained trough levels that may provide additional protection during the postoperative period [11]. Preliminary experience with rIX-FP has shown that rIX-FP has excellent or good perioperative efficacy in patients undergoing major or minor surgery [12].

Here we investigated the impact of using rIX-FP on FIX consumption and infusion frequency in patients with haemophilia B undergoing surgery.

2. Materials and methods

2.1. Study conduct

All trials were approved by independent ethics committees or institutional review boards of all participating sites. Patients or their legal guardians provided written, informed consent. Trials were conducted in accordance with the declaration of Helsinki (2008) and in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines. All studies contributing data were registered at www.clinicaltrials.gov (NCT01496274, NCT01662531 and NCT02053792).

2.2. Patients

Eligible patients were male, aged 0–65 years old, with severe haemophilia B (FIX activity ≤2%) and no history of FIX inhibitors. Patients were enrolled in the surgical substudy if they required non-emergency minor or major surgery. Major surgery was defined as any elective or emergent surgical procedure that involved general anaesthesia and/or respiratory assistance. Patients could directly enrol in the surgical substudy, or were enrolled from the phase III PROLONG-9FP clinical study programme (NCT01496274 and NCT01662531).

2.3. Trial design

Dosing was based on WFH surgical guidelines and patients' available pharmacokinetic data. The trial design has been previously described [12]. Patients adhered to their normal treatment regimen prior to surgery; where possible, FIX activity was monitored prior to receiving a preoperative dose. Patients received a single preoperative bolus dose of rIX-FP approximately 3 h prior to surgery to target a FIX activity level of 50–80 IU/dL for minor surgeries and 80–100 IU/dL for major surgeries. Intraoperative dosing was based on FIX activity and surgery type. Postoperative dosing (from wound closure up to 14 days) was based on local laboratory results and was dependent on the type of surgery and local standard of care. FIX activity levels were monitored following preoperative dosing, immediately after surgery, and 24, 48, and 72 h postoperatively; additional monitoring was undertaken as required.

2.4. Concomitant medications

The use of blood products (packed red blood cells, whole blood, fresh frozen plasma or platelets) was allowed, if needed, during the perioperative period. Prior to surgery, the investigator determined if blood products were likely to be required, these were documented as planned transfusions. Any unplanned transfusions used during surgery were also documented by the investigator. Heparin was allowed during the study to maintain patency of intravenous lines but was limited to 200 IU/day. The following additional concomitant medications were allowed during the study: antifibrinolytic agents (e.g. tranexamic acid or epsilon aminocaproic acid); antibiotics and antiviral agents; local haemostatic measures (e.g. oxidized cellulose, fibrin glue); standard thrombosis prophylaxis. Postoperative pain was managed initially through intravenous morphine or other narcotic analgesics, followed by oral opioids. As pain decreased, paracetamol or acetaminophen was allowed.

2.5. Outcomes

Haemostatic efficacy was measured by the investigator based on a 4-point scale, as described in Négrier et al [12]. Investigators were asked to rate efficacy immediately after surgery and every 24 h, up until 72 h, at discharge and to provide an overall efficacy assessment. The haemostatic efficacy rating assigned to a surgery was the lowest efficacy recorded at any timepoint. The predicted and actual blood loss during surgery was determined by the surgeon and investigator. Unplanned transfusions, the number of re-bleeding events at the surgical site occurring within the first 72 h following surgery and the number of rIX-FP infusions were recorded. rIX-FP consumption was calculated for the preoperative, intraoperative and postoperative periods. For major surgeries, after the 14-day postoperative period, patients began 7-day prophylaxis treatment with rIX-FP; those already enrolled in the clinical programme resumed their previous regimen. At the investigators' discretion, patients could initiate prophylaxis prior to the end of the 14-day period these doses were included in consumption calculations. For minor surgery, prophylaxis could begin on postoperative day 1. Postoperative consumption was calculated based on rIX-FP doses administered after wound closure in the 14-day postoperative period. Patients who underwent surgery during the extension study were followed up for 28 days following surgery; however, overall consumption reported here was based only on the pre-, intra- and postoperative rIX-FP doses administered in the 14-day assessment period. Safety and adverse events were assessed by the investigator. Prior to surgery and after the surgery study period, patients were assessed for development of inhibitors to FIX using the Nijmegen modified Bethesda method. Additionally, enzyme-linked immunosorbent assays were used to assess patients for antibodies against rIX-FP and CHO cell proteins. Throughout the perioperative period, vital signs and haematology parameters were monitored.

3. Results

A total of 30 surgeries have been conducted in 21 patients, including four surgeries in four paediatric patients. Previously, data on 21 surgeries in 19 patients has been reported [12]. Data here includes an additional 8 major surgeries (including six additional orthopaedic surgeries) and one minor surgery [12]. Patient demographics are shown in Table 1.

Seven patients were recruited into the surgery substudy and subsequently began prophylaxis with rIX-FP. All other patients were already receiving prophylaxis with rIX-FP prior to surgery. In total there were 22 major surgeries, of which 15 were orthopaedic joint replacement surgeries, and eight minor surgeries. Orthopaedic surgeries included: knee replacement (n = 12); ankle replacement (n = 1); hip replacement (n = 1); and revision of hip replacement (n = 1). Non-orthopaedic major surgeries included: double mastectomy liposuction (n = 1); haemorrhoidectomy (n = 2); rhinoplasty, submucosal resection and inferior turbinectomy (n = 1); circumcision (n = 2); and umbilical hernia and circumcision (n = 1). Minor surgeries included teeth extractions (n = 5), embolism of scrotal variceal (n = 1), excision of pigmented nevus (n = 1) and endoscopic mucosal resection (n = 1). No patients received thromboprophylaxis treatment.

Table 1
Baseline demographics for all patients.

	Patients (n = 21)
Patient age at time of surgery[a]	
Mean (SD)	37.2 (18.40)
Median (range)	43 (5–59)
Race, N (%)	
White	15 (71.4)
Asian	4 (19.1)
Black or African American	2 (9.5)
Surgery type, n (%)	N = 30
Major	22 (73.3)
Minor	8 (26.7)

SD, standard deviation
[a] Calculated for each surgery. Multiple ages were recorded for patients undergoing multiple surgeries.

3.1. Efficacy

Haemostatic efficacy was assessed in all surgeries and was rated as excellent (n = 6) or good (n = 1) or moderate (n = 1) in all minor surgeries and excellent (n = 16), good (n = 5) or moderate (n = 1) in all major surgeries. All assessed minor surgeries (n = 4) were conducted with expected or less than expected blood loss. During 21 major surgeries, blood loss was assessed and was as expected or less than expected in 90.5% (n = 19/21) of surgeries. One patient was undergoing total knee endoprosthesis and had a predicted blood loss of 400 mL but an actual blood loss of 500 mL. In one patient undergoing a circumcision, the investigator predicted a blood loss of 0 mL, but 3 mL was measured. In six joint replacement surgeries in five patients, red blood cell or whole blood transfusions were required. In surgeries where blood transfusions were required, significant blood loss was predicted. One patient undergoing minor surgery and three patients undergoing major surgery experienced re-bleeding events in the first 72 h after surgery. Of the three patients undergoing major surgery with postoperative re-bleeding events, one of these was an orthopaedic procedure (right knee arthroplasty). The bleeding event occurred in the right knee, 48 h post-surgery. The bleed was treated with 3200 IU of rIX-FP and the bleed resolved. The FIX activity level as measured 1 day prior to the event was 72.9 IU/dL. The second re-bleeding event occurred following a circumcision. Post-surgical bleeding at the circumcised site was reported within 24 h of surgery and was treated with 500 mg tranexamic acid every 8 h for 72 h. This was not classified as a major bleed and no rIX-FP was administered. Additional bleeding events occurred in a patient undergoing a knee endoprosthesis 7 and 12 days following surgery; his most recent FIX activity measurement recorded 3 days post-surgery was 90.5 IU/dL (3.9 and 9.0 days prior to the bleeding events, respectively). No additional drugs were used to treat these bleeding events.

3.2. Pre- and intraoperative period

Patients adhered to their normal treatment regimen prior to surgery; where possible, FIX activity was monitored prior to the pre-operative dose in order to ensure that target FIX levels were achieved. The last prophylaxis dose prior to surgery was administered mean (SD) 9.4 (7.0) and 6.8 (3.8) days prior to the preoperative dose, respectively. Patients received a mean (SD) preoperative dose of 94.0 (25.15) and 55.8 (22.04) IU/kg rIX-FP, in major and minor surgeries, respectively (Table 2).

The preoperative dose was administered approximately 3 h prior to surgery and achieved mean (SD) FIX activity levels of 107.5 (21.1) and 61.6 (11.84) IU/dL for major and minor surgeries, respectively. Additionally, major orthopaedic and major non-orthopaedic surgeries achieved a mean (SD) FIX activity level of 112.3 (17.8) and 97.3 (25.1) IU/dL, respectively. FIX activity levels during the perioperative period are shown in Fig. 1.

Table 2
Pre- and intraoperative consumption.

	Preoperative dose (IU/kg)	Intraoperative dose (IU/kg)	FIX activity (IU/dL)[c]
Minor surgery (n = 8)			
Mean (SD)	55.8 (22.04)[a]	NA[b]	61.6 (11.8)
Median (range)	57.4 (14.29–82.29)[a]	NA[b]	59.5 (46.5, 78.9)[d]
Major surgery (n = 22)			
Mean (SD)	94.0 (25.15)	1.9 (8.83)[b]	107.5 (21.1)
Median (range)	90.9 (45.95–139.87)	0 (0–41.4)[b]	109.8 (54.8, 145.1)[d]

SD, standard deviation.
[a] One patient did not require a preoperative dose as he was covered by his regular prophylaxis infusion; however, his prophylaxis dose is included in the calculated values for preoperative consumption.
[b] Only one patient required an intraoperative dose.
[c] Following preoperative dose.
[d] Median (min, max).

A single bolus was required in 96.7% (n = 29/30) of surgeries; one minor surgery (wisdom tooth extraction) was performed under prophylaxis (this was included in the pre-operative dose and overall consumption calculations) and one patient undergoing a total knee endoprosthesis had one additional intraoperative dose of 41.4 IU/kg rIX-FP (Table 2).

3.3. Postoperative period

After minor surgery 62.5% (n = 5) of patients did not require postoperative infusions of rIX-FP. These patients were able to maintain adequate haemostasis or begin their normal prophylactic regimen within 72 h postoperatively. Overall, 33% of surgeries required additional rIX-FP dosing up to 24 h postoperatively. In the 14-day postoperative period, patients received a median (range) of 0 (0–3) infusions of rIX-FP. Mean consumption in the postoperative period was 41.3 (67.80) IU/kg. Further information on consumption in the postoperative period is shown in Table 3. Prophylaxis was restarted at a mean (SD) of 36.0 (29.7) and 7.8 (6.1) days following major and minor surgeries, respectively. Additionally, prophylaxis was restarted at a mean (SD) of 44.4 (31.6) and 17.7 (13.7) days following major orthopaedic and non-orthopaedic surgeries.

Total mean (SD) rIX-FP consumption during minor surgery from the preoperative dose to the end of the 14-day postoperative period was 97.1 (83.67) IU/kg with a median (range) of 60.1 (14.29–253.8) IU/kg (Table 4).

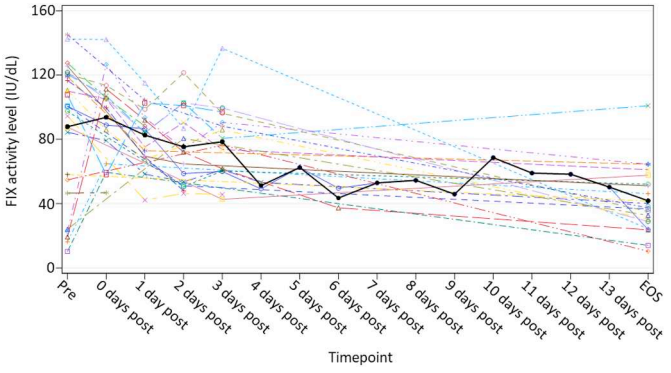

Fig. 1. FIX activity relative to surgery time.
*Thick black line represents mean FIX activity (IU/dL) across all surgeries; EOS, end of study.

Table 3
Consumption during the postoperative period in minor and major surgeries.

	Postoperative days			Total (0–14 days)
	0–3 days	4–7 days	8–14 days	
Minor surgery (n = 8)				
Consumption (IU/kg)				
Mean (SD)	6.9 (19.48)	13.4 (24.78)	21.0 (45.15)	41.3 (67.80)
Median (range)	0 (0–55.10)	0 (0–55.10)	0 (0–126.90)	0 (0–178.79)
Infusions, n				
Mean (SD)	0.1 (0.35)	0.3 (0.46)	0.4 (0.74)	0.8 (1.16)
Median (range)	0 (0–1)	0 (0–1)	0 (0–2)	0 (0–3)
Major surgery (n = 22)				
Consumption (IU/kg)				
Mean (SD)	58.4 (40.28)	63.9 (37.62)	87.6 (78.77)	209.9 (131.16)
Median (range)	53.8 (0–121.98)	55.7 (0 − 120)	98.3 (0–240)	221.7 (0–444.07)
Infusions, n				
Mean (SD)	1.3 (1.08)	1.5 (0.96)	1.8 (1.60)	4.5 (3.00)
Median (range)	1 (0–4)	1 (0–4)	1.5 (0–5)	5 (0–11)

SD, standard deviation.

Table 4
Total FIX consumption (including pre-, intra- and postoperative consumption) by type of surgery.

Surgery type	N	FIX consumption (IU/kg) median (range)
Minor surgery	8	60.9 (14.29–253.79)
Embolisation of left scrotal varicoele	1	14.3
Endoscopic mucosal resection	1	70.4
Excision of pigmental nevus - lumbal area	1	192.5
Teeth extraction	5	49.8 (40.34–253.79)
Major surgery	22	317.5 (78.33–550.00)
Circumcision	2	104.9 (78.33–131.50)
Double mastectomy liposuction	1	178.8
Haemorrhoidectomy	2	288.6 (180.75–396.5)
Orthopaedic joint replacement	15	353.5 (191.49–550.00)
Rhinoplasty, submucosal resection and inferior turbinectomy	1	130.2
Umbilical hernia and circumcision	1	230.9
All surgeries	30	233.1 (14.29–550.00)

Range not shown for an n of 1. All doses of rIX-FP were included, including all doses administered up until the end of the 14-day post-operative period.

In patients who underwent major surgery, the median (range) number of postoperative infusions was 5 (0–11). For postoperative days 0–3, patients received a median (range) of 1 (0–4) infusion. Mean (SD) consumption in the postoperative period was 209.9 (131.16) IU/kg with patients requiring a mean (SD) of 58.4 (40.28) IU/kg in the first 72 h postoperatively (Table 3). The total mean (SD) consumption from the preoperative dose until the end of the 14-day postoperative period was 250.1 (152.3) IU/kg and median (range) consumption was 233.1 (14.3–550.0) IU/kg. Data on total consumption for different surgery types is shown in Table 4.

No patients developed inhibitors to FIX during the study period and no patients developed antibodies to rIX-FP or CHO proteins. No patient experienced an adverse event related to rIX-FP administration.

4. Discussion

In both minor and major surgeries a majority of patients experienced excellent or good haemostatic efficacy with a single preoperative bolus of rIX-FP. On average, for minor surgeries, FIX activity levels were maintained at WFH recommended guidelines; patients were well managed at these levels, with no additional intraoperative doses required. Perioperative consumption over the 14-day period (including preoperative and intraoperative infusions) was low with rIX-FP, with a mean of 97.1 IU/kg in 8 minor surgeries and 305.8 IU/kg in 22 major surgeries (including 15 orthopaedic joint replacement surgeries). There were no safety concerns from rIX-FP administration in the study period.

rIX-FP modifies standard practice during surgery by reducing the burden on patients and healthcare resources. Nearly all surgeries were managed with a single preoperative bolus and patients required few postoperative infusions. This would be easier for a nursing team to manage than surgery requiring frequent or continuous infusions. The low consumption of rIX-FP may lead to reductions in the costs of surgery in haemophilia B patients. Fewer FIX units may be used compared with standard rFIX/plasma-derived FIX and fewer complications may enable shorter stays in hospital following surgery.

Standard rFIX concentrates achieve similar haemostatic efficacy to rIX-FP during the perioperative period; however, multiple infusions are required during and after surgical procedures [5,13]. For example, the haemostatic efficacy of BAX326 (RIXUBIS®, Shire) was rated as excellent in all 14 surgeries evaluated; however, the overall mean (range) dose administered was 291 (55–601) IU/kg for minor surgery and 1265 (415–2965) IU/kg for major surgery [5]. The study period ranged from 4–28 days for minor surgery and 16–93 days for major surgery. In a study in 28 patients (13 minor and 23 major surgeries) clinical efficacy of nonacog alfa (BeneFIX®, Pfizer) was rated as excellent or good in 34 out of 35 evaluated surgeries. In this study, the preoperative bolus (25–155 IU/kg) was followed by either regular infusions (in 14 major and 13 minor procedures) or continuous infusion (nine major surgeries) and patients required treatment for 10–52 or 25–78 exposure days, respectively [6,13]. In contrast, surgery with rIX-FP was performed with a single bolus in most surgeries (with a dose of 14.29–139.87 IU/kg) and few infusions were required in the postoperative period. Only 3 patients undergoing minor surgery required postoperative infusions prior to resuming normal prophylaxis. These patients restarted prophylaxis at the investigators discretion because the high FIX activity levels provided by rIX-FP prophylaxis were sufficient for the late postoperative period. This is a significant reduction in dosing frequency and surgical treatment duration therefore a reduction in the burden for hospital staff. Additionally, FIX activity monitoring to guide dosing was conducted in the local laboratories at participating centres (alongside central laboratory assays) with no issues noted by any of the centres.

Studies with other long-acting recombinant products have shown similar results. Refixia® (nonacog beta pegol; N9-GP, Novo Nordisk) is a glycopegylated rFIX and ALPROLIX® (rFIXFc, Bioverativ) is an rFIX fused to the Fc portion of the IgG receptor [14,15]. Both products showed similar surgical haemostatic efficacy to rIX-FP. Surgeries were

conducted with a single bolus and few postoperative infusions were required [14–16].

It is challenging to compare rIX-FP with other long-acting products. This is due to the large differences in surgery types and local practices. However, rIX-FP demonstrated excellent or good efficacy with a single bolus. Mean postoperative consumption in minor surgeries was low (41.3 IU/kg). Mean postoperative consumption in major surgeries (209.9 IU/kg) was higher than that reported for N9-GP (126.1 IU/kg); however, this included both orthopaedic surgeries and some non-orthopaedic surgeries that could be considered minor [16]. Median postoperative consumption in all surgeries reported for rFIXFc (432.3 IU/kg) [15] is higher than reported here with rIX-FP. Patients had a low median number of postoperative infusions within each time point assessed (0–3 days, 4–7 days and 8–14 days post-surgery), in both minor and major surgery.

FIX activity levels achieved preoperatively were adequate to manage bleeding during surgery with only one procedure requiring an additional intraoperative dose. Several bleeding events were reported during this study, with recent FIX activity measurements suggesting that FIX levels should have been adequate to prevent spontaneous bleeding. However, without FIX activity measurements taken at the time of bleeding, or pharmacokinetic data enabling a robust prediction of FIX activity at the time of bleeding, these conclusions should be interpreted with caution. The relatively low volume of distribution of rIX-FP has previously been suggested as a potential explanation for unexpected bleeding events [17]. It should be noted, however, there is no clinical evidence to show that extravascular distribution correlates with efficacy or bleeding events clinically or in the surgical context. In agreement with Negriér et al. 2016, this study demonstrates that rIX-FP provides adequate FIX activity levels for perioperative management [12].

As previously mentioned, a limitation of this study is the small study size and the wide variety of surgical procedures; however, this limitation applies to all surgical studies in patients with haemophilia B. The small, varied study populations mean that comparisons between studies are challenging. Additionally, as the surgery types varied, it is challenging to understand if rIX-FP reduced the hospital length-of-stay for patients undergoing major surgery. Real-world data on the use of rIX-FP in surgery may provide valuable information on hospital length-of-stay and the impact of rIX-FP on the cost of surgery.

5. Conclusions

Surgical procedures can be performed using rIX-FP with low FIX consumption and low infusion frequency. Outpatient treatment may be possible for some minor surgeries in haemophilia B patients when treating with rIX-FP. Reduced dosing frequency and FIX consumption, greater protection from postoperative bleeding complications enabling a better recovery and a shorter hospital stay could reduce both demands on medical personnel and could significantly reduce costs associated with surgery in patients with haemophilia B. Overall, data suggests rIX-FP simplifies perioperative care in patients with haemophilia B.

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Declaration of competing interest

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