

ORIGINAL ARTICLE

Clinical haemophilia

Management of people with haemophilia A undergoing surgery while receiving emicizumab prophylaxis: Real-world experience from a large comprehensive treatment centre in the US

Magdalena Lewandowska  | Nicole Randall | Nihal Bakeer  | Jennifer Maahs |
Jeanne Sagar | Anne Greist | Amy D. Shapiro 

Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA

Correspondence

Magdalena Lewandowska, Indiana Hemophilia and Thrombosis Center, 8326 Naab Road, Indianapolis, IN, 46260, USA.
Email: mlewandowska@ihtc.org

Funding information

The development of this manuscript was funded by F. Hoffmann-La Roche Ltd.

Abstract

Introduction: Surgery is frequently required in persons with haemophilia A (PwHA). Emicizumab, a bispecific, humanized monoclonal antibody, bridges activated factor (F) IX and FX. Management of patients undergoing surgery while receiving emicizumab is of clinical interest due to paucity of data.

Aim: Review real-world experience of PwHA with/without FVIII inhibitors who required surgery while receiving emicizumab prophylaxis.

Methods: Data regarding peri-operative management, including type of surgery, haemostatic agent use and bleeding complications, were collected for PwHA receiving emicizumab undergoing surgery between 25/10/18 and 31/12/19 at the Indiana Hemophilia and Thrombosis Center. Analyses were exploratory and descriptive.

Results: Twenty minor and five major surgeries were performed in 17 and five patients, respectively. Overall, 9/20 minor surgeries were planned to occur with emicizumab as the sole haemostatic agent; of these, four required additional coagulation factor (2 due to haematomas following port removals, 1 due to oozing at port removal site, 1 due to bleeding following squamous cell carcinoma removal). Three of the 11 minor surgeries with planned additional coagulation factor resulted in non-major bleeds; all were safely managed with additional coagulation factor. All five major surgeries were planned with additional haemostatic agents; there was 1 bleed in a patient undergoing elbow synovectomy with nerve transposition, likely triggered by physical/occupational therapy. There were no major bleeds, thrombotic events or deaths.

Conclusions: Additional haemostatic agent use is safe in PwHA undergoing surgery while receiving emicizumab. Additional data are needed to determine the optimal dosing/length of treatment of additional haemostatic agents to lower bleeding risk.

KEYWORDS

emicizumab, haemophilia, real-world evidence, surgery

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. Haemophilia published by John Wiley & Sons Ltd

1 | INTRODUCTION

Surgery is frequently needed among people with haemophilia A (PwHA).¹ Orthopaedic surgery is often required to manage the sequelae of recurrent joint bleeds.²⁻⁴ In the era of emicizumab, central venous access device (CVAD) removal is common in the paediatric population.

Persons with haemophilia A are at increased risk of surgical complications, such as poor wound healing, infection and bleeding. Meticulous peri-operative monitoring with consideration of additional haemostatic agent use is essential to ensure optimal patient outcomes.^{1,5}

Emicizumab (Hemlibra[®]), a bispecific humanized monoclonal antibody, bridges activated factor (F) IX and FX and replaces the function of activated FVIII, with resultant downstream thrombin generation and coagulation.⁶ Emicizumab was approved by the United States Food and Drug Administration in 2017 and the European Medicines Agency in 2018, for prophylaxis in PwHA with or without FVIII inhibitors; in the EU, approval for use in persons without FVIII inhibitors is limited to those with severe HA.^{7,8} It is subcutaneously administered and is approved as 3 maintenance dosing regimens: 1.5 mg/kg once weekly (QW), 3 mg/kg once every 2 weeks and 6 mg/kg once every 4 weeks; each regimen follows a loading dose of emicizumab 3 mg/kg QW for 4 weeks.⁷ The safety and efficacy of emicizumab for the prophylaxis of bleeding events in PwHA with or without FVIII inhibitors were demonstrated in the HAVEN clinical trials programme.⁹⁻¹²

As emicizumab is a novel treatment option for PwHA, data are limited with respect to peri-operative management. The HAVEN trials were not designed to evaluate the peri-operative use of emicizumab. Although minor and unplanned major surgeries did occur, there was no standardized protocol and patients were managed at the investigator's discretion. The management and outcomes of PwHA who require surgery while receiving emicizumab prophylaxis are of significant clinical interest.

The purpose of this manuscript is to review the real-world experience of PwHA with or without FVIII inhibitors who underwent surgery while receiving prophylactic treatment with emicizumab prophylaxis at the Indiana Hemophilia and Thrombosis Center (IHTC) in Indianapolis, USA.

2 | MATERIALS AND METHODS

2.1 | Setting, participants and design

Data were collected for all PwHA receiving emicizumab prophylaxis and undergoing surgery between 25 October 2018 and 31 December 2019 at the IHTC. All interventions and treatments during this time were made at the discretion of the treating physician. Individual informed consent was not required as the study involved only retrospective data collection. Institutional Review

Board approval was obtained for chart mining review and data reporting.

2.2 | Data collection and outcomes measured

Demographic data and medical histories were collected from participants' medical records. Patient and disease characteristics included age, FVIII inhibitor status and severity of FVIII deficiency.

Data on the pre-, intra- and post-operative management and treatment of PwHA were collected, including: emicizumab dose and frequency, type of surgical procedure, planned and unplanned use of haemostatic agents for the peri-operative treatment plan (including product, dose and number of infusions), as well as any treatment plan modifications.

Information regarding procedure-related bleeding was also collected, including the number of major and clinically relevant non-major bleeds. Major bleeds were defined according to International Society on Thrombosis and Haemostasis (ISTH) Control of Anticoagulation Subcommittee recommendations.¹³ Adverse events and hospitalizations were also recorded. When clinically appropriate, FVIII activity levels were obtained using a bovine chromogenic assay for measurement of FVIII replacement levels.

Surgical procedures were classified as major or minor, as defined by Santagostino et al.² Major surgery was defined as an invasive operative procedure where 1 or more of the following occurred: a body cavity was entered, a mesenchymal barrier was crossed, a fascial plane was opened, an organ was removed, and/or normal anatomy was operatively altered. Minor surgery was defined as an invasive operative procedure in which only skin, mucous membranes or superficial connective tissue was manipulated.

2.3 | Data analyses

All data were analysed retrospectively and all analyses were regarded as exploratory and descriptive, and were not designed to make confirmatory claims.

3 | RESULTS

3.1 | Patient characteristics and surgery overview

Overall, 25 surgeries took place in 22 patients (Table 1A,B), with 20 minor procedures in 17 patients and five major procedures in five patients. Patient age ranged from 2 to 66 (median 15) years. The majority (19/22; 86%) of patients had severe (<1% activity) FVIII deficiency and 4/22 (18%) had active FVIII inhibitors at the time of surgery. Two patients (Table 1A, #1 and #9) had a concomitant diagnosis of Type I von Willebrand disease (VWD).



TABLE 1 Patient and surgical information for patients undergoing minor (A) and major (B) surgeries.

Pt #	Age range (yrs)	FVIII inhibitor (yes/no/historical)	Disease severity (% FVIII activity)	Time on emicizumab ^a (days)	Emicizumab dose	Surgery type
A. Patients undergoing minor surgery						
Port removal						
1	>2-12	Yes (peak: 160 BU; 2 months pre-operatively: 80.4 BU)	Severe (<1%)	73	1.5 mg/kg weekly	Port removal
2	>2-12	Yes (chromogenic FVIII Bethesda titre 1 month pre-op: 0.6; increased to 13 on chromogenic assay)	Severe (<1%)	314	1.5 mg/kg weekly	Port removal
3	>2-12	Historical ^b	Severe (<1%)	243	1.5 mg/kg weekly	Port removal
4	>2-12	Historical ^b	Severe (<1%)	266	3 mg/kg Q2 W	Port removal
5	>12-18	No	Severe (<1%)	163	1.5 mg/kg	Port removal
6	>2-12	No	Severe (<1%)	297	6 mg/kg Q4 W	Port removal
7	>2-12	No	Severe (<1%)	224	1.5 mg/kg weekly	Port removal
8	≤2	No	Severe (<1%)	265	3 mg/kg Q2 W	Port removal
9	>2-12	No	Severe (<1%)	193	3 mg/kg Q2 W	Port removal
Dental						
10	>2-12	Yes (peak:165 BU; 1 month pre-operatively: 6.7 BU)	Severe (<1%)	122	1.5 mg/kg weekly	Dental extractions: 5 primary teeth with abscesses
9	>2-12	No	Severe (<1%)	372	3 mg/kg Q2 W	Dental crowns placed in or under general anaesthesia
11	>18-65	No	Severe (<1%)	122	6 mg/kg Q4 W	Buccal mucosa biopsy
Endoscopic						
12	>18-65	No	Severe (<1%)	92	3 mg/kg Q2 W	EGD
13	≥65	No	Severe (<1%)	155	1.5 mg/kg weekly	Colonoscopy +polypectomy
14	>18-65	No	Severe (<1%)	202	6 mg/kg Q4 W	Endoscopy +colonoscopy
Orthopaedic						
15	>12-18	No	Severe (<1%)	394	6 mg/kg Q4 W	Right ankle foreign body
16	>18-65	No	Severe (<1%)	114	1.5 mg/kg weekly	Microlumbar discectomy

Elective/urgent	Inpatient/outpatient	Pre-operative factor treatment	Post-operative factor treatment	Adjunctive antifibrinolytics (yes/no)	Bleeding episode (yes/no)
Urgent (due to sepsis)	Inpatient	rFVIIa 90 µg/kg × 1 pre-operatively	rFVIIa 90 µg/kg every 2 h × 2; then every 4 h for × 2; then every 6 h × 1 (total: 5 doses)	No	Yes
Elective	Inpatient	None	None	Yes, for nosebleeds: aminocaproic acid 95 mg/kg 1950 mg suspension orally every 6 h through POD 3	No
Elective	Inpatient	None	None	No	No
Elective	Inpatient	None	EHL rFVIII 50 IU/kg on POD 1, 2, and 4 due to chest wall haematoma	No	Yes
Elective	Inpatient	None	None	No	No
Elective	Inpatient	None	None	No	No
Elective	Inpatient	None	None	No	No
Elective	Inpatient	None	EHL rFVIII 50 IU/kg on POD 1–4, 6	No	Yes
Elective	Inpatient	None	EHL rFVIII 26 IU/kg, von Willebrand factor/ FVIII concentrate (Humate-P) 26 IU/kg on POD 8 and 15	No	Yes
Elective	Outpatient	rFVIIa 200 µ/kg × 1 dose	rFVIIa 200 µ/kg × 2 (3 and 6 h post-operatively), rFVIIa 90 µ/kg × 1 dose on POD 1 (total: 3 doses)	Aminocaproic acid 100 mg/kg orally QID from extraction until POD 10	Yes
Elective	Outpatient	Humate-P FVIII 50 IU/kg 1 h pre-operatively	None	Plan for aminocaproic acid 100 mg/kg orally from time awake after anaesthesia: QID for 5–7 days; stopped on POD 2 due to GI upset	No
Elective	Outpatient	EHL rFVIII 40 IU/kg ^c	EHL rFVIII 40 IU/kg on POD 1 and 20 IU/kg on POD 5	Aminocaproic acid 3000 mg/kg orally QID for 5–7 days	Yes
Elective	Outpatient	EHL rFVIII 40 IU/kg 2–3 h pre-operatively	None	No	No
Elective	Outpatient	EHL rFVIII 40 IU/kg 2–3 h pre-operatively	Polypectomy: EHL rFVIII 40 IU/kg through POD 3	Polypectomy: TA 1300 mg orally TID through POD 10	No
Elective	Outpatient	EHL rFVIII 22 IU/kg 2 h pre-operatively	None	TA 1300 mg orally TID through POD 5	No
Elective	Inpatient	EHL rFVIII 50 IU/kg 2–3 h pre-op	EHL rFVIII 50 IU/kg on POD 1	No	No
Elective	Inpatient	rFVIII 50 IU/kg before surgery then rFVIII 4 IU/kg continuous infusion	rFVIII continuous infusion 4 IU/kg/hr throughout hospitalization, and 50 IU/kg through POD 7	No	No

(Continues)



TABLE 1 (Continued)

Pt #	Age range (yrs)	FVIII inhibitor (yes/no/historical)	Disease severity (% FVIII activity)	Time on emicizumab ^a (days)	Emicizumab dose	Surgery type
Other						
17	>18-65	No	Mild (7%)	182	6 mg/kg Q4 W	Sacral ulcer (excision and closure)
13	≥65	No	Severe (<1%)	195	1.5 mg/kg weekly	Facial squamous cell carcinoma excision
5	>12-18	No	Severe (<1%)	164	1.5 mg/kg weekly	Cardiac catheterization for removal of central line fragment
Pt ID	Age (yrs)	FVIII inhibitor (yes/no/historical)	Disease severity (% FVIII activity)	Time on emicizumab* (weeks +days)	Emicizumab dosing	Surgery type
B. Patients undergoing major surgery						
18	>18-65	Yes (recurrent; peak: 5 BU; 2 weeks pre-operatively: 3 BU)	Severe (<1%)	18	3 mg/kg weekly loading doses (received 3 doses)	Laparoscopic appendectomy
19	>12-18	No	Mild (8%)	143	3 mg/kg Q2 W	Right medial patellofemoral ligament reconstruction
20	>12-18	No	Severe (<1%)	138	1.5 mg/kg weekly	Open reduction and internal fixation 5 th phalangeal
21	>18-65	No	Moderate (2%)	195	6 mg/kg Q4 W	Elbow arthroscopic synovectomy with nerve transposition
22	>18-65	No	Severe (<1%)	27	6 mg/kg Q4 W	Screw fixation; femoral neck fracture

Abbreviations: EGD, oesophagogastroduodenoscopy; EHL, extended half-life; GI, gastrointestinal; ITI, immune tolerance induction; POD, post-operative day; Q2 W, once every 2 weeks; Q4 W, once every 4 weeks; QID, 4 times a day; rFVIIa, activated recombinant factor VII; rFVIII, recombinant factor VIII; TA, tranexamic acid; TID, 3 times a day.

^aPrior to surgery.

^beradicated with ITI.

^cPatient did not administer this dose due to confusion over consultation and actual procedure date.

Elective/urgent	Inpatient/ outpatient	Pre-operative factor treatment	Post-operative factor treatment	Adjunctive antifibrinolytics (yes/no)	Bleeding episode (yes/no)
Elective	Inpatient	rFVIII 30 IU/kg 2 h pre- operatively; rFVIII continuous infusion 4 units/kg x 24 h	rFVIII continuous infusion 4 units/kg x 24 h (adjust for goal FVIII activity ~100%), followed by rFVIII 40 IU/kg daily through POD 5	No	No
Elective	Outpatient	None	EHL rFVIII 25 IU/kg on POD 1 and EHL rFVIII 50 IU/kg on POD 9	No	Yes
Urgent	Inpatient	EHL rFVIII 40 IU/kg 1 h pre-operatively	None	No	No

Elective/urgent / emergent	Inpatient/ outpatient	Pre-operative treatment	Post-operative treatment	Adjunctive antifibrinolytics (yes/no)	Bleeding episode (yes/no)
Emergent	Inpatient	rFVIIa 90 µg/kg x 1 30 mins pre- operatively	rFVIIa 90 µg/kg every 2 h x 9 doses; then EHL rFVIII 200 IU/kg on POD 1-2. Instructed to restart ITI regimen on discharge (EHL rFVIII 100 IU/kg) 3x per week; plan for last loading dose of emicizumab 3 mg/ kg, then 1.5 mg/kg weekly	TA 1300 mg orally TID x 5 days	No
Elective	Inpatient	EHL rFVIII 50 IU/kg x 1	EHL rFVIII 40 IU/kg every 8 h x 3 doses; EHL rFVIII 40 IU/kg every 12 h x 2; EHL rFVIII 40 IU/kg daily through POD 5	No	No
Elective	Inpatient	EHL rFVIII 50 IU/ kg 2-3 h pre-operatively	EHL rFVIII 50 IU/kg every 12 h x 2 doses	No	No
Elective	Inpatient	rFVIII 50 IU/kg 1.5 h pre-operatively	rFVIII 50 IU/kg through POD 5	No	Yes
Elective	Inpatient	EHL rFVIII 50 IU/kg 1 h pre-operatively	EHL rFVIII 32 IU/kg on POD 1-7 then EHL rFVIII 38 IU/kg on POD 9	No	No



3.2 | Management of surgeries and bleeding episodes

3.2.1 | Minor procedures

Of 20 minor procedures, there were nine port removals, three dental surgeries, three endoscopic surgeries, two orthopaedic surgeries and three other surgeries (1 sacral wound closure, one facial squamous cell carcinoma [SCC] resection and one right heart catheterization) (Table 1A).

In total, 9/20 (45%) minor procedures were planned to occur with emicizumab as the sole haemostatic agent, of which 8 (89%) were port removals and 1 was an excision of a facial SCC. Five port removals were successfully performed without additional haemostatic agent use. Four minor procedures required additional coagulation factor, 2 of which were port removals that resulted in haematoma formation. Patient #4 (Table 1A) required extended half-life (EHL) rFVIII 50 IU/kg on post-operative days 1, 2 and 4 due to a chest wall haematoma and patient #8 (Table 1A) required EHL rFVIII 50 IU/kg on post-operative days 1–4 and 6 for a suspected chest wall haematoma that was later determined to be a seroma. Additionally, a paediatric patient with a concomitant diagnosis of Type I VWD (Table 1A, #9), undergoing a port removal, experienced a minor bleed described as blood on steri strips and erythema around the port site that resolved spontaneously without additional haemostatic factor administration. Thereafter, the patient reported oozing from the excised port site and poor wound healing was noted. He was managed with EHL rFVIII 26 IU/kg and von Willebrand factor/FVIII concentrate (Humate-P) 26 IU/kg infusions on post-operative days 8 and 15 and eventually healed by secondary intention with keloid scar formation. Patient #13 (Table 1A) who underwent excision of SCC required additional coagulation factor with EHL rFVIII 25 IU/kg on post-operative day 1 due to oozing; he subsequently required EHL rFVIII 50 IU/kg on post-operative day 9, due to bleeding through steri strips after suture removal.

Eleven minor procedures were managed with planned additional peri-operative haemostatic agents, 3 (27%) of which experienced bleeding. A paediatric patient (Table 1A; #1) with a FVIII inhibitor and concomitant Type I VWD underwent urgent port removal for a fungal infection. The patient received a pre-operative dose of rFVIIa 90 µg/kg and required rFVIIa 90 µg/kg intra-operatively due to excess oozing from the incision site. In the post-operative period, he required only 5/13 planned post-operative doses of rFVIIa over the course of the next 24 h. Additional doses were not administered as the patient showed no evidence of post-operative bleeding. This patient was hospitalized for 4 days awaiting sterilization of blood cultures.

Two bleeding episodes occurred in patients undergoing dental surgeries. Patient #11 underwent a buccal mucosa biopsy, prior to which he was to infuse EHL rFVIII 20 IU/kg. However, due to patient confusion over the actual procedure date, rFVIII was not administered pre-operatively. He subsequently developed oozing and liver clot formation at the biopsy site and received EHL rFVIII 40 IU/kg

on post-operative day 1 and 20 IU/kg on post-operative day 5. The patient was also prescribed aminocaproic acid 3 g 4 times per day for 5 days, with which he was not adherent. The other dental surgery bleed occurred in a paediatric patient (Table 1A, #10) with an active FVIII inhibitor at the time he underwent five extractions for extensive dental decay and a dental abscess. The patient had received rFVIIa 200 µg/kg pre-operatively. The patient awoke on post-operative day 1, pale, faint and with blood on his face and a liver clot at the extraction site. He was instructed to infuse rFVIIa 200 µg/kg prior to evaluation and re-suturing by oral surgery. The patient was admitted and received: IV tranexamic acid 10 mg/kg every 8 h and rFVIIa 90 µg/kg every 4 h on post-operative day 1; and rFVIIa 90 µg/kg every 8 h on post-operative day 2. He was discharged on post-operative day 3 and instructed to administer rFVIIa 90 µg/kg every 12 h until the morning of post-operative day 6, and take aminocaproic acid through post-operative day 10. The patient developed delayed bleeding at the extraction site, requiring 8 additional doses of rFVIIa (90–140 µg/kg) on post-operative days 10–15.

3.2.2 | Major procedures

All five major surgeries were planned to be managed with haemostatic agents in addition to emicizumab prophylaxis (Table 1B). There was 1 bleed in an adult patient (Table 1B, #21) with moderate FVIII deficiency (2% activity) undergoing left elbow arthroscopic synovectomy with nerve transposition. The patient was initially treated with rFVIII 50 IU/kg 1.5 h pre-operatively and continued with this dose once daily until post-operative day 5. He subsequently experienced post-operative bleeding into the soft tissue/muscles of his left forearm on post-operative day 8, likely provoked by physical therapy/occupational therapy. This was managed with 6 additional daily doses of rFVIII 40 IU/kg on post-operative days 8–13.

3.3 | Modifications to management plans

Overall, only 1 pre-operative management plan was not followed. As highlighted above, this was in the patient (Table 1A, #11) undergoing a buccal mucosa biopsy whereby the patient did not administer the planned EHL rFVIII 20 IU/kg pre-operatively.

In terms of post-operative management plans, 12/25 (48.0%) were modified, 7 of which were due to non-major bleeding episodes. The remainder was modified for other reasons, such as in the patient undergoing microlumbar discectomy (Table 1A, #16) who was discharged early due to family obligations and was started on bolus infusions on post-operative day 1 instead of 2. A patient (Table 1A, #15) undergoing minor surgery to remove a foreign body from their right ankle had their plan modified as the surgery was more extensive than anticipated; he required an additional dose of EHL rFVIII 50 IU/kg on post-operative day 2 due to peroneal tendon dissection/peroneal retinaculum repair. Furthermore, a patient (Table 1B, #19) with mild FVIII deficiency (8%), undergoing right medial patellofemoral

ligament reconstruction (a major procedure), exhibited higher FVIII activity trough than expected, likely due to a stress response (208%; Table S1), so the final dose of EHL rFVIII 40 IU/kg was omitted; the patient was hospitalized for 3 days.

3.4 | Hospitalization

Ten patients were observed for 23 h, and 8 patients required inpatient stays. Of these, only 1 patient (Table 1B, #22) required a prolonged post-operative hospital stay (>7 days) secondary to rehabilitation facility placement issues following screw fixation of a right femoral neck fracture. The patient remained hospitalized for 15 days. Sepsis was reported in a paediatric patient (Table 1A, #1) with FVIII inhibitors (80.4 BU 2 months pre-operatively) and concomitant Type 1 VWD. The patient underwent urgent port removal due to infection and was hospitalized for 4 days. In a patient undergoing a port removal (Table 1A, #5), the catheter fractured during removal and was lodged in the subclavian vein. The patient required urgent right heart cardiac catheterization for retrieval of the central line fragment and received EHL rFVIII 40 IU/kg 1 h pre-operatively. The patient did not experience bleeding from either procedure and was discharged 2 days post-operatively. Also, a patient undergoing laparoscopic appendectomy (Table 1B, #18) developed a wound infection which required treatment with oral antibiotics. This patient also had a FVIII inhibitor (3.0 BU 2 weeks pre-operatively), was in the loading phase of emicizumab, and had been on ITI (100 IU/kg 3 times per week) prior to the development of acute appendicitis. Despite this, the patient only required 23-h observation and did not experience bleeding complications.

3.5 | Adverse events of interest

No thrombotic events, thrombotic microangiopathies or deaths were reported in any patient undergoing surgery. Administration of additional haemostatic agents did not result in thrombotic complications.

4 | DISCUSSION

In general, there is a lack of evidence-based data for the peri-operative management of PwHA; this is particularly true of those who are receiving emicizumab prophylaxis. Our data demonstrate that a wide variety of surgeries can be safely performed in PwHA receiving emicizumab prophylaxis. There were no thrombotic events reported in patients treated with additional haemostatic agents while receiving emicizumab prophylaxis. The ability to safely monitor FVIII activity post-operatively using a bovine chromogenic assay allowed for adjustment of rFVIII dosing, thus preventing complications and lowering thrombosis risk.

Overall, 5/9 port removals were performed without additional haemostatic agents, and without bleeding complications. Collectively, 4/9 patients received additional haemostatic therapy for non-major bleeding with CVAD removal. Three of these were not administered pre-operative haemostatic therapy: 1 with parent-reported delayed minor oozing from the surgical incision, 1 with swelling at the port removal site later confirmed to be a seroma and 1 who developed a chest wall haematoma. Only 1 of 4 patients who bled had received pre-operative additional haemostatic therapy: this patient had a high titre FVIII inhibitor, concomitant mild type 1 VWD and sepsis; he developed excessive oozing from port site intra-operatively. Overall, 2/4 bleeding episodes were confirmed by a physician.

There were bleeding episodes in eight patients, including one in a patient undergoing major surgery; all were treated with additional haemostatic agents and were managed safely. Five major surgeries were managed with planned pre- and post-operative coagulation factor, of which one patient experienced delayed post-operative bleeding into soft tissue/muscles of the left forearm after starting physical/occupational therapy that required additional treatment. In hindsight, this patient may have benefited from additional haemostatic agent administration prior to starting physical/occupational therapy given his underlying arthropathy. Risk of bleeding may also have been impacted by age (e.g. due to an inability to self-restrict activity in younger children), FVIII inhibitor status and other coagulopathies (e.g. VWD).

In PwHA, peri-operative management should focus on patient safety, with the ultimate goal of preventing excessive bleeding and its associated complications, such as impaired wound healing, infection risk and prolonged hospitalization. In our experience, only 1 patient required prolonged (>7 days) hospitalization following their surgery, which was due to placement issues for post-operative rehabilitation purposes.

No major bleeding episodes occurred in patients undergoing surgeries, and none of our patients required red blood cell transfusion. There were no reports of thrombosis, thrombotic microangiopathy or death, including in those with FVIII inhibitors treated with rFVIIa or those without FVIII inhibitors treated with a variety of rFVIII products. No activated prothrombin complex concentrate was utilized in any patient undergoing surgery.

Our results along with the growing evidence base support the safety of other haemostatic agents in addition to emicizumab, with a number of case reports and observational studies showing similar outcomes to those presented here. In a review of medical records from PwHA treated with emicizumab at a single centre in the United States, 15 surgeries were undertaken in 10 PwHA (six with FVIII inhibitors). The surgeries were well tolerated with no bleeding in 11/15 (73%) procedures. Six surgeries were managed with additional pre-operative coagulation replacement, 4 of which led to post-operative bleeding (three were in PwHA with FVIII inhibitors).¹⁴ Furthermore, in an observational study, 19 surgical procedures were performed in 19 PwHA (regardless of FVIII inhibitor status) being treated with emicizumab prophylaxis. Of 14 port removals carried

out, five did not require additional pre-procedural haemostatic agent; 7/14 received rVIIa or FVIII pre-procedure and 2/14 of these PwHA received a subsequent dose as part of their plan. Overall, 3/14 PwHA that underwent port removal had swelling and haematoma at the surgical site 1–2 days post-operatively and subsequently received 1–2 doses of FVIII concentrate to treat these bleeding events. One patient underwent a major procedure (intracranial shunt revision) and received multiple doses of FVIII with no bleeding complications. No thrombotic complications were reported in any patients.¹⁵

While the overall rate of breakthrough bleeding was considered higher than desired, the authors believe that outcomes in PwHA receiving emicizumab prophylaxis can be optimized in the future, based upon a different treatment approach. Although this and other studies show that some minor procedures may be done without administration of additional haemostatic agents without resultant bleeding, this is not predictable and may increase patient risk. As such, the decision for additional haemostatic agent use should be based on individual bleeding risk (including FVIII inhibitor status, additional concomitant diagnoses, pre-existing arthropathy, and other medical conditions that may delay wound healing) and physician judgment. The authors suggest it may be prudent to follow treatment guidelines for patients with mild HA not on emicizumab; this follows the understanding that emicizumab converts patients with severe HA to a mild phenotype. Persons with mild HA receive additional haemostatic agents prior to most procedures, which the authors would recommend as a reasonable approach for patients with HA on emicizumab. Accordingly, it might be possible to reduce the dose of additional haemostatic agents; however, protocols are needed to help determine the optimal dosing/length of treatment of additional haemostatic agents required to ensure adequate haemostasis with a low bleeding risk. With further experience regarding the safety of utilizing additional haemostatic agents, we expect a decrease in post-operative bleeding. For example, the optimal peri-operative timing and dosing of bypassing agents (e.g. rFVIIa) in patients with FVIII inhibitors on emicizumab are unknown, as there is difficulty monitoring haemostatic levels in these individuals. It is certainly reassuring that PwHA and FVIII inhibitors in our study appeared to do well with rFVIIa dosing without severe bleeding and with no evidence of thrombosis. The impact of FVIII inhibitor status on surgical outcomes is an area of future interest as the number of surgery cases accumulate. While PwHA with an increased risk of bleeding due to arthropathy and tissue inflammation continue to require additional haemostatic agent support, it is possible that lower doses may be utilized and the course of treatment may be shorter than in the pre-emicizumab era.

5 | CONCLUSIONS

These real-world data support preliminary clinical study evidence which demonstrate that surgical procedures can be managed safely in PwHA who are receiving emicizumab prophylaxis, regardless of FVIII inhibitor status, age and other risk factors.¹⁶

ACKNOWLEDGMENTS

Editorial assistance for the development of this manuscript, under the direction of the authors, was provided by Alex Coulthard, BSc, of Gardiner-Caldwell Communications, and funded by F. Hoffmann-La Roche Ltd.


CONFLICT OF INTERESTS

All authors report funding from F. Hoffmann-La Roche Ltd for writing support for the development of this manuscript; JM reports funding for consultation/advisory role for Novo Nordisk and Takeda and speakers' bureaus for Genentech, Inc., and Novo Nordisk; JS reports research funding from Genentech, Inc.; ADS reports speakers' bureau and research funding from Genentech, Inc.

AUTHOR CONTRIBUTIONS

All authors were involved in data collection, analysis and interpretation, and all authors critically reviewed the manuscript, approved the final version and support this publication.

ORCID

Magdalena Lewandowska  <https://orcid.org/0000-0003-2581-1478>

Nihal Bakeer  <https://orcid.org/0000-0002-3370-8166>

Amy D. Shapiro  <https://orcid.org/0000-0003-2821-7159>

REFERENCES

- Coppola A, Windyga J, Tufano A, Yeung C, Di Minno MN. Treatment for preventing bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgery. *Cochrane Database Syst Rev*. 2015.
- Santagostino E, Lentz SR, Misgav M, et al. Safety and efficacy of turoctocog alfa (NovoEight(R)) during surgery in patients with haemophilia A: results from the multinational guardian clinical trials. *Haemophilia*. 2015;21(1):34–40.
- Luck JV Jr, Kasper CK. Surgical management of advanced hemophilic arthropathy. An overview of 20 years' experience. *Clin Orthop Relat Res*. 1989;242:60–82.
- Chevalier Y, Dargaud Y, Lienhart A, Chamouard V, Negrier C. Seventy-two total knee arthroplasties performed in patients with haemophilia using continuous infusion. *Vox Sang*. 2013;104(2):135–143.
- Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19(1):e1–e47.
- Kitazawa T, Igawa T, Sampei Z, et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. *Nat Med*. 2012;18(10):1570–1574.
- Roche FH-L. Hemlibra® summary of product characteristics. 2019; https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf. Accessed October 2019.
- Genentech. HEMLIBRA® (emicizumab-kxwh) injection for subcutaneous use, prescribing information. 2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761083s002s004bl.pdf. Accessed October, 2019.
- Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;377(9):809–818.
- Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med*. 2018;379(9):811–822.

11. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol*. 2019;6(6):e295-e305.
12. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood*. 2019;134(24):2127-2138.
13. Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8(1):202-204.
14. Ebbert PT, Xavier F, Seaman CD, Ragni MV. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. *Haemophilia*. 2020;26(1):41-46.
15. McCary I, Guelcher C, Kuhn J, et al. Peri-procedural management and outcomes of patients with hemophilia on emicizumab prophylaxis. *Blood*. 2019;134:2396.
16. Santagostino E. Surgical experience from four phase III studies (HAVEN 1-4) of emicizumab in persons with haemophilia A (PwHA) with or without FVIII inhibitors. *ISTH*. 2019;2019.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Lewandowska M, Randall N, Bakeer N, et al. Management of people with haemophilia A undergoing surgery while receiving emicizumab prophylaxis: Real-world experience from a large comprehensive treatment centre in the US. *Haemophilia*. 2021;27:90-99. <https://doi.org/10.1111/hae.14212>