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ORIGINAL ARTICLE

Management of surgery in persons with hemophilia A receiving emicizumab prophylaxis: data from a national hemophilia treatment center

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Abstract

Background: Persons with hemophilia A may require surgical procedures. Real-world data on invasive procedures in persons with hemophilia A receiving emicizumab prophylaxis are limited.

Objectives: To evaluate the safety of invasive procedures in persons with hemophilia A receiving emicizumab prophylaxis and their outcomes in a longitudinally followed cohort.

Methods: Data from medical records of persons with hemophilia A with and without factor VIII (FVIII) inhibitors longitudinally followed at our tertiary center, who received emicizumab prophylaxis and underwent all types of invasive procedures, were retrieved. Outcomes of interest were bleeding and thrombotic complications.

Results: Overall, 35 patients underwent 56 invasive procedures, 18 (32.1%) were major. The median age was 36.3 years (IQR, 8.8-55.9 years); 12 patients (34.3%) were younger than 18 years at the time of procedure; 17 (48.6%) were patients with FVIII inhibitors. Among major procedures, orthopedic surgeries prevailed. All patients who underwent major procedures received factor replacement with either recombinant activated factor VII (patients with inhibitors) or FVIII (patients without inhibitors). Factor concentrates were administered prior to 32 (84.2%) of the minor procedures. Repeated doses were given according to international expert opinion recommendations and patients' condition.There were 7 bleeding events in 6 patients, 5 were major bleeds, including 1 patient who underwent a minor procedure without factor replacement. None of the patients experienced a thrombotic complication.

Conclusion: Invasive procedures can be performed safely in patients receiving emicizumab prophylaxis with close surveillance after surgery. Factor concentrates may be advised in selected patients undergoing minor procedures.

KEYWORDS
emicizumab, hemophilia A, inhibitors, invasive procedures, surgery

Essentials

- Data are limited on the safety of surgical procedures in persons with hemophilia A receiving emicizumab prophylaxis.
- This was a tertiary center study on invasive procedures in persons with hemophilia A.
- It discusses safe invasive procedures with emicizumab prophylaxis and postsurgery surveillance.
- Factor concentrates are recommended for major procedures and advised for selected minors.

1 | INTRODUCTION

Persons with hemophilia A (HA) may require surgical procedures to treat conditions both related (eg, insertion and removal of central venous access devices [CVADs], orthopedic surgery for the treatment of joint damage) and unrelated to the hemophilia. During the perioperative period, enhanced hemostatic support is essential to prevent bleeding complications, inadequate wound healing, and infections [1].

Alloantibodies inhibiting factor VIII (FVIII) occur in approximately 30% of persons with severe HA, mostly within the first 20 exposures to exogenous FVIII concentrates early in life. These inhibitors render FVIII replacement ineffective, increase the risk of bleeding, resulting in short- and long-term morbidity, and mandate alternative strategies to achieve hemostatic control [2,3].

While representing a difficulty in all people with bleeding disorders, surgery in patients with HA with inhibitors is particularly challenging. In these patients, current strategies for hemostasis involve the intravenous administration of bypassing agents (recombinant activated factor FVII [rFVIIa] or activated prothrombin complex concentrate [APCC]), with or without concomitant antifibrinolytic agents [4]. A recent review outlined expert opinion recommendations for major orthopedic surgery in persons with HA with inhibitors, based on published evidence and clinical experience [5].

Emicizumab (Hemlibra, formerly ACE910; F Hoffmann-La Roche Ltd) is a bispecific, recombinant, humanized monoclonal antibody, which bridges activated factor IX and zymogen factor X and facilitates the activation of factor X to factor Xa, essentially replacing the function of activated FVIII, with resultant downstream thrombin generation (TG) and coagulation [6]. The safety and efficacy of emicizumab for hemostatic prophylaxis in 3 dosing regimens have been established through the HAVEN clinical trials program in adult and pediatric persons with HA with or without FVIII inhibitors [7–10], subsequently it was approved for prophylaxis in persons with HA with or without FVIII inhibitors by the *United States Food and Drug Administration* and *European Medicines Agency*.

Recently, pooled data from the HAVEN trials suggested that minor and major surgical procedures can be performed safely in persons with HA who receive emicizumab prophylaxis [11], yet data on real-world experience with management of patients undergoing surgery while receiving emicizumab are scarce. We aimed to evaluate the safety of invasive procedures in persons with HA receiving emicizumab prophylaxis and their outcomes in a longitudinally followed cohort.

2 | METHODS

2.1 | Patients and treatments

The Israeli National Hemophilia Center at Sheba Medical Center, Ramat Gan, Israel, treats 638 patients with HA, of whom 162 receive emicizumab prophylaxis and are prospectively followed. Adult and pediatric emicizumab-treated persons with HA who underwent all types of elective invasive procedures between October 1, 2018, and November 30, 2022, were included in the current cohort. The demographic and clinical data from medical records, including surgery reports and follow-up notes during hospitalization, were accessed. The data were collected regarding the past and present FVIII inhibitor status and Bethesda titer, type of invasive procedure, use of FVIII and bypassing agents (BPAs), surgical outcomes, occurrence of bleeding or thrombotic complications, laboratory results, and length of hospital stay.

While alternative dosing regimens have been described [9,10], all patients included in the current study were treated according to the once weekly dosing schedule (1.5 mg/kg/dose). Perioperative hemostatic management at our center includes antifibrinolytics for all patients, excluding patients undergoing urological procedures involving the uroepithelium. Patients without FVIII inhibitors undergoing major surgery receive replacement therapy with short half-life FVIII concentrates (35-50 units/kg/dose). During the postoperative period, chromogenic FVIII levels are measured to ensure initial FVIII trough levels above 50%. Patients with inhibitors are treated with rFVIIa (75-90 mcg/kg/dose). Patients undergoing minor procedures receive replacement therapy at the discretion of the treating hematologist. Repeated doses are given according to international expert opinion recommendations and patients' condition. We avoid coadministration of emicizumab with APCC.

The study was approved by the Institutional Ethics Committee at Sheba Medical Center, adult patients provided written informed consent, and for participants aged <18 years, informed consent was provided by a parent or legally authorized representative.

2.2 | Definitions, measurements, and outcomes

The classification of the type of surgery (ie, major vs minor) was adopted from Santagostino et al. [12] (Supplementary Table). Outcomes of interest were length of hospital stay in days, the occurrence of bleeding of any severity, and thrombotic complication. The International Society on Thrombosis and Haemostasis definitions were used for classification of major and clinically relevant nonmajor bleeding (CRNMB) [13,14]; therefore, the data on hemoglobin levels before and after surgery and administration of blood components were retrieved.

2.3 | Laboratory methods

2.3.1 | Processing of blood samples

Blood samples were obtained during routine clinic visits. Blood samples were drawn in 0.109 M buffered citrate tubes. Platelet-poor plasma (PPP) was obtained at room temperature by centrifugation of blood at 2000 *g* for 10 minutes. Plasma was then aspirated into a plastic tube and residual platelets were removed following a further centrifugation at 14,000 *g* for 5 minutes. The double-spun PPP was stored in aliquots at −70°C and thawed prior to the assay.

Emicizumab concentration in patients' plasma was measured by a modified version of the traditional activated partial thromboplastin time–based FVIII one-stage clotting assay, which has been calibrated against emicizumab and includes a dedicated plasma emicizumab calibrator and a plasma-based control. Chromogenic Bethesda assay was tested with bovine reagents, as previously described [15].

2.3.2 | TG analysis

Prior to elective surgeries, TG analysis was performed in plasma samples of emicizumab-treated persons with HA and FVIII inhibitors, who gave their additional consent. *Ex vivo* spiking with rFVIIa of the emicizumab-treated plasma was performed in order to predict the optimal hemostatic response. When feasible, patients' TG was re-assessed postoperatively, following perioperative rFVIIa treatment.

TG was measured using a calibrated automated thrombogram method as previously described [16,17]. Eighty microliters of PPP samples were added to 20 μL of working buffer (PPP–Reagent LOW; Diagnostica Stago; final concentration ~1 pM tissue factor and ~4 μM phospholipid) and placed in round-bottom 96-well plates. TG was initiated by the addition of 20 μL of fluorogenic substrate/$CaCl_2$ buffer (FluCa-Kit; Stago Inc). Fluorescence intensity was measured, and endogenous thrombin potential (ETP [nM × min]) and thrombin peak height (nM) were calculated by a dedicated software attached to the fluorometer (version 3.0.0.29; Thrombinoscope BV). All experiments were performed at least in duplicates.

2.4 | Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics (version 23.0; IBM Corp). Continuous variables were presented as median, range, or IQR, as indicated. Categorical variables were presented as counts, proportions, and/or percentages. The Mann–Whitney U-test was used to compare 2 patient subgroups for continuous variables, and the Fisher's exact test was used to compare 2 patient subgroups for categorical variables. Correlation was assessed by Spearman's rank correlation coefficient (r_s). Two-tailed *P* values of less than .05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Overall, 35 patients underwent 56 invasive procedures. Eighteen major surgeries (32.1%) were performed in 13 patients (37.1%), and 38 minor procedures (67.9%) were performed in 25 patients (71.4%). Median age at the time of invasive procedure was 36.3 (IQR, 8.8-55.9] years; 12 of 35 (34.3%) were patients younger than 18 years, and 2 of 35 were children younger than 2 years of age.

Of the 35 patients, 17 (48.6%) had a history of FVIII inhibitors. Immune tolerance induction was attempted in 9 patients and was successful in 4 patients. Patients with active and historic FVIII inhibitors were younger at the time of emicizumab initiation (median age, 12.3 [IQR, 2.8-39.9] years vs 49.8 [IQR, 33.1-60.9] years; *P* = .010) as well as at the time of the first invasive procedure (median age, 13.1 [IQR, 5.2-41.6] years vs 50.5 [IQR, 33.3-62.3] years; *P* = .014). Median time on emicizumab prophylaxis was 9 (IQR, 5-21) months, which did not differ between patients with and without FVIII inhibitors. Patients with FVIII inhibitors had higher median emicizumab concentration (47.5 [IQR, 39.8-63.0] μg/mL vs 37.5 [IQR, 28.5-45.3] μg/mL; *P* = .028). Patients' characteristics are presented in Table 1.

3.2 | Invasive procedures

Among major procedures, most were orthopedic surgeries (*n* = 11, 61.1%), followed by general surgeries (*n* = 4, 22.2%). The most common minor procedures were dental (*n* = 8, 21%), endoscopies (*n* = 8, 21%), and minor orthopedic interventions (*n* = 7, 18.4%).

Characteristics of the invasive procedures are presented in Table 2.

3.3 | Hemostatic management

All patients who underwent major procedures received factor replacement either with rFVIIa 75 to 90 μg/kg/dose (patients with

TABLE 1 Patients' demographic and clinical characteristics.

Characteristics	Patients with FVIII inhibitors	Patients without FVIII inhibitors
Number of patients, n (%)	17 (48.6%)	18 (54.4%)
ITI attempted	9	–
Successful ITI	4	–
Inhibitor level (BU), median (IQR)	21 (12-80)	–
Age at first procedure (y), median (IQR)	13.1 (5.2-41.6)	50.5 (33.3-62.3)[a]
Age at emicizumab initiation (y), median (IQR)	12.3 (2.8-39.9)	49.8 (33.1-60.9)[b]
Time on emicizumab (mo), median (IQR)	10 (4.5-37.5)	9 (4.8-15.5)
Emicizumab concentration (μg/mL), median (IQR)	47.5 (39.8-63.0)	37.5 (28.5-45.3)[c]
Number of minor procedures	17 (12)	21 (13)
Number of major procedures (number of patients)	8 (5)	10 (8)

All patients included in this study were Israeli Jews and Arabs.

BU, Bethesda units; FVIII, factor VIII; ITI, immune tolerance induction therapy.

[a]P = .014.

[b]P = .01.

[c]P = .028.

inhibitors, n = 5) or FVIII 35 to 50 IU/kg/dose (patients without inhibitors, n = 8). Median duration of rFVIIa treatment was 5 days (range, 3-26 days), dosed 4 times daily on the first day, 3 times daily on postoperative days 1 and 2, and twice daily thereafter. Median duration of FVIII treatment was 6 days (range, 3-18 days), dosed twice daily on the first day and once daily thereafter.

A single dose of factor concentrates was administered prior to 32 (84.2%) of the minor procedures, with rFVIIa 90 μg/kg/dose (patients with inhibitors, n = 7, 8 procedures) or FVIII 35 to 50 IU/kg/dose (patients without inhibitors, n = 15, 24 procedures). A median of 3 (range, 2-6) repeated doses of rFVIIa were given to 3 patients following 3 distinct procedures; major orthopedic surgeries, major abdominal surgeries, and removal of CVAD. A median of 2 (range, 2-5) repeated doses of FVIII were administered to 8 patients after 8 procedures, in 1 case due to excess bleeding classified as CRNMB after an elective tympanoplasty.

TABLE 2 Invasive procedures in persons with hemophilia A receiving emicizumab prophylaxis.

Surgery type	Number of procedures	Number of patients	Age (y), median (IQR)[a]	Number of patients with FVIII inhibitors	Time on emicizumab prophylaxis (mo), median (IQR)
Major procedures					
Orthopedic surgery	11	9	36 (25.5-54.5)	4	9 (3.5-39)
General surgery	4	4	32 (16-50.5)	0	10 (5-20.5)
Neurosurgery	2	1	3	1	7
Urological surgery	1	1	37	0	2
Minor procedures					
Endoscopies	8	7	52 (38-62)	2	24.5 (9-35)
Dental procedures	8	6	44 (4.5-59.5)	3	18 (10.5-28.5)
Orthopedic procedures	7	6	41.5 (17-49)	3	19 (9-28)
Vascular access	5	5	6 (3-12.5)	4	5 (1.5-8)
Plastic surgery	5	5	63 (27.5-72)	2	28 (10-34)
Vascular surgery	2	2	44, 62	0	27, 28
Urological procedures	1	1	0.25	1	0.5
Ophthalmology	1	1	6	0	43
Otolaryngology	1	1	62	0	27

FVIII, factor VIII; IQR, interquartile range.

3.4 | Clinical outcomes

None of the included patients experienced intraoperative bleeding during any of the procedures. There were 7 events of postoperative bleeding in 6 patients (2/6 with FVIII inhibitors), of which 5 were major bleeds. In all but one case, excessive bleeding was noted within the first 2 postoperative days. Among the bleeding persons with severe HA and FVIII inhibitors, 1 infant presented after a minor procedure (circumcision), performed without preoperative factor replacement. This patient was described thoroughly in a previous publication by our group [17]. An elderly patient with FVIII inhibitor experienced 2 bleeding episodes. The first occurred following a complex major surgery which involved drainage of an epidural abscess, spinal fusion, and internal fixation. Due to the nature of the infection, the patient required a prolonged hospitalization for intravenous antibiotic treatment, and subsequently experienced another bleeding episode following a second procedure for incision and drainage of a spinal hematoma. Of note, this patient had relatively low emicizumab plasma levels measured at the time of events. He was treated with rFVIIa, yet at reduced dosing (76 μg/kg/dose) and increased intervals (3-4 times daily instead of every 3 hours postoperatively), taking into account his age, comorbidities, and potential thrombotic risk. Another person with severe HA experienced a major bleeding of gastrointestinal origin, following a laparoscopic single-anastomosis bariatric gastric bypass. Postoperative anticoagulant prophylaxis was attempted; however, treatment was halted after a single dose of low molecular weight heparin due to bleeding. Lastly, bleeding beyond 48 hours following surgery was observed in a single patient without FVIII inhibitor who underwent a total hip replacement. This patient experienced major bleeding 1 week after the surgery and required continued home treatment with daily FVIII for a total of 11 days. Characteristics of patients who experienced bleeding complications and their subsequent treatments are presented in Table 3.

The median length of hospital stay for all procedures was 2 (IQR, 0-3) days, which did not differ between patients with FVIII inhibitors and patients without a history of FVIII inhibitors (2 [IQR, 0.5-4] days vs 2 [IQR, 0-2.25] days, respectively; $P = .347$). There was no correlation between the length of hospital stay and emicizumab concentrations. None of the patients experienced a thrombotic complication or a thrombotic microangiopathy following replacement therapy with either FVIII or rFVIIa, and no patient died.

Nine patients underwent 11 major orthopedic surgeries, of which 5 were joint replacement and 2 were surgical fracture repair. Four of these patients had FVIII inhibitors. Factor replacement with either rFVIIa 90 μg/kg ($n = 3$, of the patients with FVIII inhibitors, one patient with a low-titer inhibitor was treated with FVIII) or FVIII 50 IU/kg ($n = 8$) was given for a median of 11 (IQR, 3-17) days. Median length of hospital stay was 9 (IQR, 3-11) days. Notably, 5 patients were discharged to continue home treatment with FVIII. Two patients experienced 3 bleeding episodes, including the patient who underwent drainage of an epidural abscess, spinal fusion, and internal fixation, and the patient who underwent a total hip replacement.

Five patients underwent removal of a CVAD (median age, 6 [range, 1-13] years). Four patients had FVIII inhibitors. These patients received factor replacement with either rFVIIa 90 μg/kg ($n = 3$) or FVIII 50 IU/kg ($n = 2$) for a median of 2 (range, 1-3) days. Median length of hospital stay was 2 (range, 1-3) days. None of these patients experienced postprocedural bleeding.

3.5 | TG and recombinant FVII dosing

A representation of the hemostatic impact of rFVIIa upon TG peak height and ETP in a plasma sample of a person with severe HA and a high responding inhibitor receiving once weekly emicizumab prophylaxis is illustrated in Figure A. A plasma sample from this patient was studied in our laboratory prior to an elective knee procedure. The patient was later managed successfully with perioperative rFVIIa. Emicizumab steady-state level was 39 μg/mL at the time of sampling. The sample was spiked by increasing concentrations of rFVIIa from 0.62 up to 2.5 μg/mL, corresponding to rFVIIa doses of 22.5, 45, and 90 μg/kg, respectively. Notably, hemostatic response, as reflected by peak height above 100 nM × min, was achieved following *ex vivo* spiking with rFVIIa at concentrations of either 45 or 90 μg/kg. The peak height and ETP reference values of normal controls in our laboratory are 313 ± 93.5 nM and 1998 ± 405 nM × min, respectively.

Figure B demonstrates TG of plasma obtained from a second emicizumab-treated patient with a high responding inhibitor, before surgery, and postoperatively, following perioperative treatment with rFVIIa 66 μg/kg. The patient's hemostasis was well maintained, without any periprocedural bleeding.

4 | DISCUSSION

We described the safety of invasive procedures in a longitudinally followed cohort of adult and pediatric persons with HA, with and without FVIII inhibitors, and receiving emicizumab prophylaxis.

Notably, with a predetermined factor replacement plan, none of these patients experienced an intraoperative bleeding during any of the procedures. However, 6 patients had postprocedural bleeding that were generally managed by continuing factor replacement, and their length of hospital stay was mostly not affected.

In a subanalysis of the HAVEN 1-4 studies, Kruse-Jarres et al. [11] reported 215 minor surgical procedures, of which about 18% of patients experienced postoperative bleeding complications, whereas among our cohort, bleeding was observed only among 2 of 35 (5.7%) patients with minor interventions. This low incidence of hemostatic derangement may be attributed to the preoperative administration of a single dose of factor concentrate in the vast majority of our patients. A subanalysis of the HAVEN studies and real-world cohorts from the United States and Italy reported that among minor surgeries of emicizumab-treated patients, dental procedures and CVAD removals prevailed [11,18,19]. In a phase IV, multicenter, open-label study, Escobar et al. [20] reported on 14 persons with HA who underwent

TABLE 3 Bleeding complications in persons with hemophilia A who underwent invasive procedures.

Patient	Age at the time of procedure (y)	Comorbidities	Time on emicizumab (mo)	FVIII inhibitor status and level at procedure (BU)	Emicizumab level (μ/mL)	Type of procedure	Procedure	Factor replacement therapy prophylaxis	Duration of treatment (d)	Bleeding severity	Length of hospital stay (d)
1	0.25	None	1	4	54	Minor urology	Circumcision	None	3	Major bleeding	4
2	27	NASH	7	No inhibitor	45	Major general surgery	Laparoscopic single-anastomosis gastric bypass	Recombinant FVIII	9	Major bleeding	9
3	36	None	9	No inhibitor	76	Major orthopedic	Total hip replacement	Recombinant FVIII	11[a]	Major bleeding	4
4	37	None	24	No inhibitor	45	Major urology	Retrograde intrarenal surgery with stent insertion	Recombinant FVIII	1[b]	CRNMB	2
5	62	IHD, s/p PCI, diabetes, HCV, HIV carrier, lymphoma	27	No inhibitor	28	Minor otolaryngology	Tympanoplasty	Recombinant FVIII	2	CRNMB	2
6	79	Diabetes, Adenocarcinoma of pancreas, s/p Whipple	51	7.2	29	Major orthopedic	Epidural abscess drainage, spinal fusion, and internal fixation	Recombinant FVIIa	11	Major bleeding	45
			51.5	7.2	29	Major orthopedic	Incision and drainage of spinal hematoma	Recombinant FVIIa	26	Major bleeding	30

BU, Bethesda units; CRNMB, clinically relevant nonmajor bleeding; FVIIa, activated factor VII; FVIII, factor VIII; HCV, hepatitis C virus carrier; IHD, ischemic heart disease, NASH, nonalcoholic steatohepatitis; PCI, percutaneous coronary intervention; s/p, status post.

[a]This was the only patient in whom bleeding occurred beyond 48 hours following surgery. The patients continued home treatment with daily FVIII.

[b]The patient experienced hematuria, treatment with additional FVIII doses was avoided.

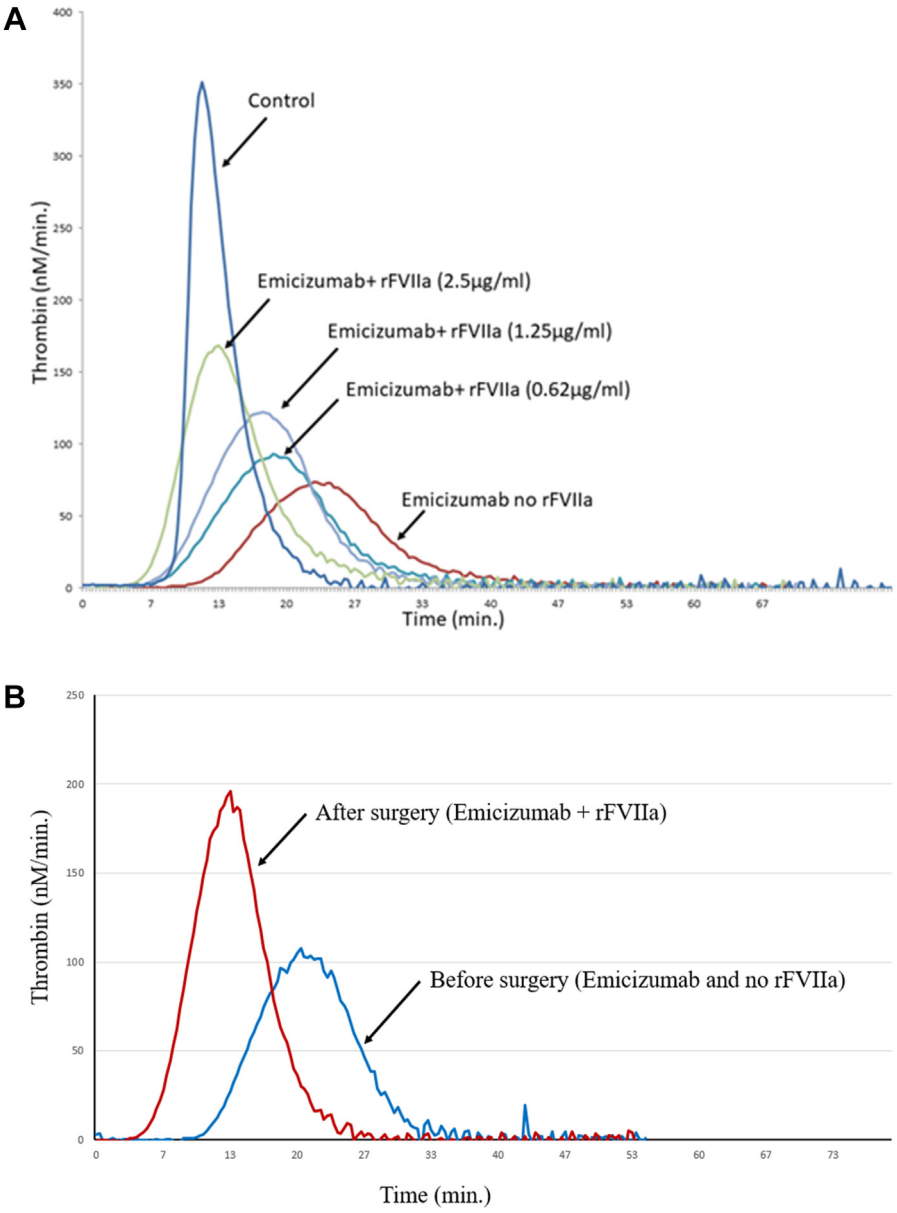

FIGURE Hemostatic impact of recombinant activated factor FVII (rFVIIa) concentrate on thrombin generation (TG) peak height and endogenous thrombin potential in plasma samples of persons with severe hemophilia A receiving once weekly emicizumab prophylaxis. (A) The hemostatic impact of rFVIIa concentrate on TG peak height and endogenous thrombin potential in a plasma sample of a person with severe hemophilia A and a high responding inhibitor receiving once weekly emicizumab prophylaxis, in the presence of 1 pM tissue factor, as compared with a control (healthy subject). (B) TG of plasma obtained from an emicizumab-treated patient with a high responding inhibitor, before and after surgery, 30 minutes after perioperative administration of 66 µg/kg of rFVIIa concentrate.

minor surgeries, where bleeding complications were noted following dental procedures as well as some CVAD extractions, necessitating intra or postoperative administration of factor concentrates. In contrast to reports by other groups, the majority of patients (with the exception of one patient who underwent a urological procedure involving the uroepithelium) received tranexamic acid, and all patients in our cohort received preprocedural treatment with either FVIII or rFVIIa. Importantly, none of them experienced surgical bleeding. Notably, all dental procedures were performed in an expert clinic located at our tertiary referral center that specializes in treating patients with bleeding disorders.

The changing treatment paradigm for persons with hemophilia after approval of emicizumab reduces the need for a suitable venous access. Therefore, many patients, including children with FVIII inhibitors, undergo CVAD removal. In a study from Ireland, 10 pediatric persons with HA underwent a successful CVAD removal without planned administration of FVIII or BPA, and no bleeding events were reported [21]. However, in the HAVEN trials, there were 2 bleeding events among the 27 patients who underwent CVAD removal without prophylactic coagulation factor administration [11]. Similarly, in a case series from a large tertiary United States center, removal of CVAD without adequate factor replacement was associated with periprocedural bleeding [22]. We managed patients who underwent CVAD removal with a short course of factor replacement (usually 1-2 doses) and tranexamic acid. None of these patients experienced bleeding, and all had a short-term hospitalization.

Among major surgeries reported within the HAVEN trials, bleeding occurred in 3 of 15 pretreated cases [11], comparable to our 4 of 18 bleeds in patients undergoing major surgeries. In a recently published case series from Italy, Castaman et al. [19] reported a total

of 27 major surgeries, most of which were orthopedic procedures. Bleeding complications were noted in 4 of 21 procedures of persons with HA and FVIII inhibitors, of whom one patient died, whereas none of the noninhibitor patients experienced excessive bleeding [19]. Similar to the cumulative data from the HAVEN studies [11], no fatalities occurred among any of our patients with bleeding complications.

For major surgeries, our patients received factor concentrates and tranexamic acid during their hospital stay and were discharged following a relatively short course of therapy, after which emicizumab treatment was continued. This aligns with the report by Castaman et al. [19], who demonstrated a reduction of approximately 40% in factor concentrate consumption among hospitalized patients.

Among our patients who experienced major bleeding or CRNMB, 2 of 6 had perioperative emicizumab plasma levels <30 μg/mL. This finding is consistent with data previously published by our group, suggesting that low emicizumab plasma levels may correlate with bleeding risk [16,23]. Two patients who experienced postoperative bleeding received inadequate preprocedural coagulation factor treatment (Table 2), where patient 1 received lower than recommended rFVIIa dosing regimens and patient 5 received no rFVIIa. One patient (patient 2) experienced a gastrointestinal bleeding following a gastric bypass bariatric surgery, a complication that may be observed in 1.5% of individuals undergoing this procedure [24]. Likewise, bleeding following a hip replacement (patient 4) is not uncommon, occurring in roughly 50/1000 patient years [25].

None of our patients had thrombosis or thrombotic microangiopathy, which is reassuring, as such complications have been previously reported among adult and adolescent persons with HA when concomitant BPA treatment with APCC was administered during emicizumab prophylaxis [26,27]. It is noteworthy that no thrombotic complications were documented in any of the recently published manuscripts addressing surgeries among patients with HA receiving emicizumab prophylaxis [11,18–22]. Indeed, results of our TG studies conducted *ex vivo* and *in vivo* regarding coadministration of emicizumab and rFVIIa at doses between 45 and 90 μg/kg are encouraging, as neither peak height nor ETP exceed hemostatic values observed among normal controls. TG monitoring of emicizumab-treated patients has been suggested as an ancillary tool for fine-tuning of additional hemostatic therapy [28], and applied for bleeding prediction in the surgical setting [29].

The cohort of longitudinally followed patients with HA and robust data represent study's strengths. However, the retrospective nature of the study design introduces inherent limitations, and it is also limited by a relatively small number of patients with HA undergoing major surgeries. The exclusive inclusion of Israeli Jews and Arabs may restrict the therapeutic strategy, particularly in the context of minor surgical procedures, imposes a limitation as there may have been slight variations in treatment strategy within our cohort.

In conclusion, our study demonstrates the safety of concomitant treatment with emicizumab and factor concentrates in a cohort of longitudinally followed persons with HA undergoing surgery. Our findings support the administration of either rFVIIa or FVIII concentrates for all patients undergoing major surgeries, whereas for minor surgeries, hemostatic support with factor concentrates may be also advised in selected patients. Further prospective studies are suggested to evaluate the role of perisurgical emicizumab plasma levels and TG assessments for bleeding prediction and individual treatment tailoring strategies.

FUNDING

The authors received no funding for this study.

ETHICS STATEMENT

The study was approved by the Institutional Ethics Committee at Sheba Medical Center; adult patients provided written informed consent, and for participants aged <18 years, informed consent was provided by a parent or legally authorized representative.

AUTHOR CONTRIBUTIONS

O.C., T.L., G.K., and A.A.B. developed the study concept and design. O.C., N.L., S.K.L., S.L., and M.M. acquired the data. E.A. performed the laboratory studies. T.L. performed the thrombin generation analyses. I.B. and O.E. performed the statistical analysis. A.L. performed the data safety and analysis monitoring. T.B.-B. was the study coordinator. O.C., A.A.B., and G.K. drafted the manuscript. All authors interpreted the data, critically revised the manuscript and provided final approval of the manuscript.

RELATIONSHIP DISCLOSURE

O.C. reports Investigator Initiated Study grants from Pfizer and personal fees from PlasFree, outside the submitted work. S.L.-M. reports grants from Pfizer and Novo Nordisk and personal fees from Pfizer, outside the submitted work. G.K. reports grants from Pfizer and Roche; other support from ASC Therapeutics, Bayer, Novo Nordisk, Pfizer, Roche, and Sanofi Genzyme; and personal fees from Bayer, BioMarine, BPL, CSL, Pfizer, Novo Nordisk, Roche, Sanofi Genzyme, Sobi, Spark, Takeda, and uniQuore, outside the submitted work. M.M. reports honoraria for lectures from Roche. A.A.B. reports honoraria for lectures from Roche. All other authors declare no competing financial interests.

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SUPPLEMENTARY TABLE: Definitions for major and minor surgery.

Major surgery*	Minor surgery
• An invasive operative procedure where one 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 • Normal anatomy was operatively altered • Expected duration of surgery-related FVIII treatment at least 7 days including the day of surgery**	• An invasive procedure in which only skin, mucous membranes, or superficial connective tissue was manipulated, and none of the criteria of 'major surgery' were met.

Abbreviations: F, Factor.

Adapted from Santagostino E, Lentz SR, Misgav M, et al. Safety and efficacy of turoctocog alfa (NovoEight®) during surgery in patients with haemophilia A: results from the multinational guardian™ clinical trials. Haemophilia. 2015 Jan;21(1):34-40. https://doi.org/10.1111/hae.12518 Epub 2014 Oct 2. PMID: 25273984; PMCID: PMC4309503.

*The decision on whether a surgery was a minor or a major surgery was taken before the surgery was performed, and hemostatic management was planned accordingly: Peri-operative hemostatic management at our center includes antifibrinolytics for all patients, excluding patients undergoing urological procedures involving the uroepithelium. Patients undergoing major surgery receive replacement therapy either with FVIII (patients without inhibitors) or rFVIIa (patients with inhibitors). Patients undergoing minor procedures receive replacement therapy at the discretion of the treating physician. Repeated doses are given according to international expert opinion recommendations and patients' condition.

**Patients receiving bolus injections could be discharged before day 7 post surgery, but were to have daily assessments at least until that day.