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“Hemophilia Clinical Consults: Therapeutic Decisions in the Perioperative Management of Patients With Hemophilia A Undergoing Surgery”

Louis M. Aledort, MD, MACP, and Johanna McCarthy, RN
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Introduction

Individuals with hemophilia are living extended lives, up from 7.8 years in the 1930s to 74 years (for HIV-negative patients) between 1990 and 2001,¹ as a result of advances in care over the past 40 years. According to recent CDC estimates, individuals aged between 45 and 65+ years comprise 14.2% of the total population of patients with hemophilia A.²

Hemostatic therapy has evolved from whole blood to highly purified, virally inactive plasma-derived and recombinant factor VIII (FVIII) and factor IX (FIX) products.³ Immune tolerance induction therapy and other therapeutic innovations in the form of home therapy and prophylactic treatment regimens have added to the hemophilia patient’s quality of life.^{4,5}

Surgery, once considered prohibitive for this population, especially for patients with high-titer inhibitors, has become routine, with procedures such as radiosynovectomy further improving quality of life for affected individuals due to the advent of factor concentrates and the bypassing agents.⁶⁻¹⁰

Despite improvements in care for hemophilia patients, challenges remain. The perioperative management of this population is complicated due to the need to attend to hemostatic control, which requires the establishment and maintenance of appropriate target FVIII levels to prevent bleeding during the operative, postoperative, and rehabilitative phases³; however, for inhibitor patients, there are no guidelines to specify the proper marker for monitoring coagulation factor plasma levels and how to use concentrates effectively during surgery.¹¹ Inhibitor patients also pose a challenge, as it is difficult to predict hemostatic outcome in this cohort.² While surgery in inhibitor

patients has become more commonplace in the past 10 years due to the development of the activated prothrombin complex concentrates (aPCCs; FEIBA) and recombinant factor VIIa (rFVIIa), such procedures are still difficult, given both the lack of solid, evidence-based dosage recommendations and routine perisurgical patient drug administration.¹⁰

Moreover, while patients with hemophilia have an extended life expectancy thanks to the development of factor concentrates and the bypassing agents, patients have also had to cope with the common comorbidities of older age: cardiovascular disease,^{5,12-14} joint disease and musculoskeletal disorders,^{5,14} neoplasia, renal disorders, and hepatic, prostate, and other cancers.^{13,14} Hepatocellular cancer is an increasingly important cause of mortality, with a reported standardized mortality ratio of 17.2.⁵

In the following 3 case scenarios, all depicting older hemophilia patients, 2 with inhibitors and 1 without, surgical challenges are presented and ultimately overcome, based on therapeutic decisions made perioperatively to maintain hemostatic control.

Case 1: William M.

William M. is a 50-year-old male with mild hemophilia who has experienced almost no spontaneous bleeds in his lifetime. He has tested negative for HIV and HCV. Recently, he was diagnosed with prostate cancer and will undergo surgery for the robotic removal of his prostate. His preoperative FVIII level is 12% and his inhibitor titer, 0 BU. He is given IV desmopressin 0.3 µg/kg, which increases his FVIII level to 42%. On the day of his surgery, desmopressin + vW-containing FVIII concentrate are administered to raise FVIII levels to 100%. The concentrate is adjusted thereafter to maintain a level >50% for the first week postsurgery, and daily desmopressin is administered as well. This surgical treatment plan is to be followed for 7 days postoperatively unless there is a reduction in the patient's serum sodium, a possible symptom of desmopressin-associated hyponatremia. Should this occur, the desmopressin will be discontinued. As part of the patient's surgical recovery program, the goals are to reduce exposure to FVIII to decrease inhibitor reduction, and to use vW-containing FVIII concentrate for reduced inhibitor incidence.

Clinical Discussion

Perioperative Management of Hemophilia A Patients With No Inhibitors

A goal for the management of hemostasis in noninhibitor patients is to establish and maintain appropriate FVIII levels to prevent bleeding during the intraoperative, postoperative, and rehabilitative phases.^{3,15} Desmopressin and the FVIII concentrates are therapeutic options for the achievement of hemostatic control in this cohort of patients. While the former agent is ineffective in patients with severe hemophilia,¹⁶ for most patients with mild hemophilia, it is effective, resulting in a 2- to 6-fold increase of FVIII levels over baseline.¹⁷ Desmopressin should be used whenever possible in patients with mild hemophilia A to minimize the exposure to exogenous FVIII and the risk for inhibitor development¹⁷; however, because the agent has an antidiuretic effect, patients are at risk for hyponatremia and water intoxication¹⁸ and should be carefully monitored.

For patients unresponsive to desmopressin, or if long-term correction of FVIII levels is mandatory in major surgery, FVIII concentrates are considered the treatment of choice.¹⁷ FVIII replacement provides optimal hemostatic coverage for patients with hemophilia A because near-normal levels are the best protection against bleeding. However, they should be used only when inhibitor titers are <1-2 BU.¹⁹

Surgical Guidelines

There are few guidelines for the management of surgery in hemophilia patients.²⁰ Similarly, the management of cancer in this population is supported by a paucity of data,¹⁴ despite the fact that its incidence is increasing as the hemophilia population ages.¹³

Although the optimal level and duration of replacement therapy required to prevent surgical bleeding complications in hemophilia patients have not been established conclusively,²⁰ a recently conducted literature review offers a consensus of opinion.²⁰ Hermans and investigators conducted a review of 35 clinical studies that included 1328 total surgical procedures, 707 orthopedic procedures among them, and 1114 patients with mild to severe hemophilia A or B.²⁰ For 26 of 31 studies, the preoperative target FVIII or FIX level was >80 U/dL, and among 27 studies that addressed postoperative trough level, 19 targeted troughs of >50 U/dL in the first postoperative week.²⁰ While the study provides a comprehensive review and survey of replacement therapy in hemophilia patients undergoing surgery, it also points to the need for more studies to define minimal hemostatic levels and optimal durations of treatment.

In all surgical situations, the patient's inhibitor status and risk for venous thromboembolism should be taken into account,⁵ especially for major orthopedic procedures in older patients. For procedures necessitating anticoagulation, such as cardiopulmonary bypass and valve replacement, special management may be required for older patients who receive intensive replacement therapy or bypassing agents. Such patients may be at risk for thrombotic events and appropriate anticoagulation therapy may need to be considered.¹³

Careful preoperative planning is essential for every type of surgery.¹⁵ This includes a patient/family medical history, a detailed plan for preoperative, intraoperative, and postoperative patient management, inhibitor screening, availability of clotting factor replacement, and cooperation of the hemophilia care team.^{8,9,15,21} Lab support and monitoring of the FVIII dose to maintain FVIII-C level are important intraoperatively, as is meticulous monitoring of FVIII replacement postoperatively, because prolonged doses may be required to foster healing at the surgical site and to facilitate postoperative physical therapy.²²

Tables 1 and 2 provide recommended replacement therapy dosing guidelines for major and minor surgical procedures in hemophilia.^{20,21}

Table 1. Recommended* Plasma Factor Level and Duration of Administration for Patients With Hemophilia A		
Type of Hemorrhage	Desired Level	Duration (days)
Surgery (major) [†]		
• Preop	80%-100%	
• Postop	60%-80%	1-3
	40%-60%	4-6
	30%-50%	7-14

*World Federation of Hemophilia.

[†]An appropriate factor level should be maintained for 5-7 days or until wound healing after minor surgery and for 10-14 days after major surgery.

Adapted from World Federation of Hemophilia.

Table 2. European Survey of Replacement Therapy for Invasive Procedures in Hemophilia

Procedure	Duration of Treatment (days)	Replacement therapy Target FVIII levels in %			No Treatment (%)
		80%-100%	40%-70%	20%-40%	
Circumcision					
Preoperative		81	19		0
Postoperative	1-3	19	75	6	0
	4-7		44	31	25
	>7			6	94
CVAD insertion					
Preoperative		81	19		0
Postoperative	1-3	25	62.50		12.50
	4-7	6	31	12.50	
	>7			6	94
Dental extraction					
Preoperative		32	59	9	0
Knee arthroplasty					
Preoperative		100			
Postoperative	1-5 (bolus)	85	15	0	0
	6-14 (bolus)	7	71	22	0
	1-5 (CI)	66	34	0	0
	6-14 (CI)	0	58	42	0
Liver biopsy					
Preoperative		77	14	9	0
Postoperative		45.50	45.50	9	0
Surgical synovectomy					
Preoperative		87.50	12.50		0
Postoperative	1-3	50	50		0
	4-7	19	69	12.00	0
	>7		50	25	25
Tonsillectomy					
Preoperative		100			0
Postoperative	1-3	69	31		0
	4-7	25	75		0
	>7		25	25	50

CVAD=central venous access device; CI=continuous infusion.

Adapted from Hermans C, et al, for the European Haemophilia Therapy Standardisation Board. *Haemophilia*. 2009;15:639-658.

Case 2: Marcus J.

Marcus J. is a 57-year-old Hispanic male with hemophilia A and inhibitors. His FVIII level is <1%, and for many years, he has had an inhibitor titer of 80 BU. On-demand treatment for bleeding has consisted of FEIBA 75 U/kg q12h. He has never been on prophylaxis and, in fact, for many months has not had a need for on-demand treatment. Recently, the patient fell and fractured his right femur, which caused major bleeding. He was given rFVIIa 90 µg/kg q2h, which arrested the bleed. It was determined that he needed a cast and surgery. A repeat Bethesda assay done preoperatively indicated an inhibitor titer of 5 BU. On the day of his surgery, the patient received high-dose FVIII concentrate until evidence of anamnesis. The FVIII concentrate is continued for 5 days postoperatively, with normal FVIII levels. By days 5-10, his inhibitor titer increased, and the decision was made to switch from FVIII concentrate, which was no longer effective, to FEIBA 75 U/kg q12h. There was no postoperative bleeding. On day 10, the patient's platelet count decreased to 90,000; his D-dimers were >20, and there was no evidence of clinical clotting. As a result, the decision was made to alternatively administer rFVIIa 90 µg/kg q2h, increasing the dosing interval to q4h and ultimately q6h for the remainder of the postoperative period. The patient was discharged on hospital day 15.

Clinical Discussion

The bypassing agents aPCC (FEIBA) and rFVIIa have made orthopedic and other types of surgery possible for hemophilia patients with inhibitors,^{10,11} and both are able to maintain hemostasis in patients with high-responding inhibitors; however, product choice should be dependent on which agent leads to the best treatment response for acute bleeding.²³ Since the introduction of the bypassing agents, no hemostatic problems have been reported in surgical interventions, but the risk remains for thrombotic complications, especially when they are combined with antifibrinolytic drugs.²⁴ Although more data are being generated regarding aPCC and rFVIIa for surgical use, there is a lack of solid evidence-based dosage recommendations and little objective evidence regarding differences in the relative efficacy and safety.^{10,19} What is known about them is based largely on anecdotal evidence: retrospective analyses, chart reviews, and case reports.^{7,10,25}

Balkan and investigators recently conducted a retrospective analysis to determine the efficacy of aPCC and rFVIIa.²⁵ Twenty-nine patients with hemophilia A and high-responding inhibitors were evaluated. The surgical procedures (10 major, 38 minor) were performed at one hemophilia

treatment center (HTC). Among the major surgical procedures, 3 were treated with rFVIIa, 5 with aPCC, and 2 with sequential use of aPCC and rFVIIa. Of the minor procedures, radiosynovectomy was performed in 25 patients, 16 of whom received rFVIIa and 9 of whom received aPCC. No bleeding complications were observed. Both agents demonstrated excellent efficacy, with results indicating that it is possible to perform surgical procedures safely with separate or sequential use of rFVIIa and aPCC in patients with high-titer inhibitors.

Similarly, Rodriguez-Merchan and colleagues conducted a case series of 90 inhibitor patients who underwent 92 major or minor surgical procedures, 42 with aPCC and 47 with rFVIIa. Results indicate that, despite the type of surgery performed, both agents achieved satisfactory hemostatic control (Tables 3 and 4).¹⁰

Table 3. Main Data and Results of Orthopedic Procedures

Procedure	No. procedures	Hematological treatment	Result	Complications	Comments
Ankle arthrodesis, removal of hardware (M)	2	2 with FEIBA	Good	None	None
Knee arthrodesis (M)	1	rFVIIa	Good	None	None
Fixation of femoral neck fracture (M)	1	rFVIIa	Good	None	None
Radiosynovectomies (m)	27	20 with FEIBA, 7 with rFVIIa	19 good, 1 fair	1 postinjection bleeding	Yttrium-90 and Rhenium-186
Total hip arthroplasty (M)	1	rFVIIa	Good	None	None
Total knee arthroplasty (M)	3	2 with FEIBA, 1 with rFVIIa	2 good, 1 fair	1 postoperative bleeding	Required arterial embolization to be resolved

M=major procedure; m=minor procedure.

Adapted from Rodriguez-Merchan EC, et al. *Haemophilia*. 2010;16:84-88.

Table 4. Main Data and Results of Non-Orthopedic Procedures

Procedure	No. procedures	Hematological treatment	Result	Complications	Comments
Appendectomy (M)	1	FEIBA	Good	None	None
Cataract (m)	1	FEIBA	Good	None	None
Central catheter placements (m)	37	17 FEIBA, 20 rFVIIa	All good	None	None
Corneal transplant (M)	1	FEIBA	Good	None	None
Craniotomy (M)	1	rFVIIa	Good	None	None
Dental extractions (m)	10	2 FEIBA, 8 rFVIIa	All good	None	None
Hydrocele (m)	1	rFVIIa	Good	None	None
Inguinal hernia (m)	2	2 rFVIIa	2 good	None	None
Lipoma (m)	1	FEIBA	Good	None	None
Pyloroplasty (M)	1	rFVIIa	Good	None	None
Thoracotomy (lobectomy) (M)	1	rFVIIa	Poor	Death (pulmonary complications)	None

M=major procedure; m=minor procedure.

Adapted from Rodríguez-Merchan EC, et al. *Arthroscopy*. 2010;16:84-88.

Case 3: Frank P.

Frank P. is a 50-year-old African American male with a known, long-standing FVIII inhibitor, who treats his bleeds on demand. He experiences a spontaneous bleed in his right arm, with pain and expanding mass. He allows too much time to elapse before checking into the ED, at which point he has numbness and tingling in the fingers of his right hand. rFVIIa 90 µg/kg q2h decreases the pain, but space pressures are such that the compartment syndrome necessitates surgery to save the nerves. The patient undergoes surgery with rFVIIa coverage and has excellent hemostasis for 3 to 4 days, with increasing intervals of rFVIIa. New bleeding and pain suddenly manifest at the surgical site, and FEIBA 75 U/kg is now administered, with no response. A decision is made to administer rFVIIa 90 µg/kg and FEIBA 75 U/kg simultaneously. This results in definite hemostasis. The plan for the remainder of the course is to continue rFVIIa q6h until discharge. No residual neuropathy exists.

Clinical Discussion

The differential patient response to the bypassing agents has been well documented. Approximately 10% to 20% of bleeds in inhibitor patients cannot be controlled by initial use of aPCC or rFVIIa.^{26,27} Such patients may become refractory to one or the other agent.²⁸ Although both products involve induction and facilitation of thrombin generation (TG), neither agent completely normalizes TG.²⁹ Because these preparations have a differing composition and mode of action, combined therapy, either sequential or simultaneous, recently has been used for achieving hemostasis during bleeding episodes in patients who became refractory to FEIBA or rFVIIa when each was given alone.^{27,28,30}

Livnat and colleagues conducted an in vitro study to illustrate by a sensitive assay of TG that phospholipids present in FEIBA and other procoagulants contribute to FEIBA's activity and that exogenous phospholipids are essential for the activity of rFVIIa. Relevant to the dosing of the 2 agents, investigators also demonstrated that the combination of FEIBA and rFVIIa has a marked synergistic effect on TG in the plasma of high-titer hemophilia A patients. Demonstrating this latter point, investigators determined that while FEIBA or rFVIIa each had a small effect on TG in platelet-rich plasma of the study patients, adding both agents yielded a dramatic increase in TG.³⁰

The investigators' study suggests that patients with an inhibitor who become refractory to FEIBA or rFVIIa therapy might benefit from administration of a mixture of low concentrations of both preparations. Additional studies are warranted to determine more fully whether simultaneous or alternative administration of both preparations will be more effective and safe.

Surgical Considerations for Inhibitor Patients

Whenever possible, surgery should be performed in an HTC, where all members of the team can participate in patient management.¹⁹ Table 5 presents a checklist of factors that should be taken into account before surgery is undertaken in this patient cohort.

Table 5. Surgery in the Patient With Inhibitors: Factors to Consider

Age of patient
Availability of multidisciplinary team of experts experienced in perioperative management of hemophilia (hemophilia treatment center)
Cost of replacement and bypassing products to national blood system, patient, or third-part insurer
Experience of surgeon
Indication for surgery
Inhibitor titer and anamnestic response
Patient and family preferences
Relevant comorbidities
Risk factors for thrombosis (age, type of procedure, thrombophilic genotypes)
Sufficiency of supply of replacement and bypassing products
Type of surgical procedure
Urgency of the surgical procedure

Adapted from Teitel JM, et al. *Hemophilia*, 2009;15:227-239.

Patient age gets first listing in the checklist because it generally exerts a strong influence on surgical decisions.¹⁹ For example, surgery deferred for years may result in soft-tissue contractures, reduced muscle strength, and damage to multiple other joints, ultimately compromising the surgical outcome.¹⁹

Summary

As the hemophilia population ages, a concomitant increase in age-related comorbidities is likely. These comorbidities may require complex treatment, such as surgery. However, due to advances in hemophilia care and clinicians' increasing knowledge of the safety and efficacy of factor replacement concentrates and the bypassing agents, surgery is now an option for many patients who, decades earlier, would have had to endure the debilitating consequences of this disease.

Additional information on radiosynovectomy can be found by participating in the following Blood CME Center programs:

“Radiosynovectomy in Hemophilia,” a vodcast activity copresented by James V. Luck, MD, and Mauricio Silva, MD

[Enter Program](#)

“Safe Use of Radiosynovectomy for Chronic Hemophilic Synovitis,” a Clinical Insights activity featuring expert commentary by James V. Luck, MD, and Mauricio Silva, MD

[Enter Program](#)

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