Sequential bypassing agents during major orthopedic surgery: a new approach to hemostasis

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Key Points

- Sequential bypassing agents may be a safe and effective treatment during major orthopedic surgery in hemophilia patients with inhibitors.

Introduction

Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of factor VIII (FVIII) and characterized by spontaneous or traumatic bleeding into joints, muscles, and body cavities. Clotting factor concentrate, recombinant FVIII (rFVIII), is necessary to treat and prevent bleeding, but its use is limited in the approximately 30% who develop FVIII alloantibody (inhibitor), most of whom have severe disease (FVIII < 0.01 IU/mL).¹ Inhibitor development, one of the most severe and challenging complications of hemophilia, is associated with a 2-fold increase in hospitalizations, 10-fold increase in cost, and 3.5-fold increase in mortality.²⁻⁴

For these reasons, as recently as the early to mid-1990s, elective surgery was contraindicated in inhibitor patients because of the risk of uncontrolled bleeding and death.⁵ But over the past decade, with the use of bypassing agents (BPAs), recombinant activated factor VII (rFVIIa), and activated prothrombin complex concentrate (APCC), surgery has become more commonplace.⁶ Yet orthopedic surgery, often necessary because of advanced arthropathy from repeated hemarthrosis, is frequently avoided in inhibitor patients, despite a 2.5-fold decrease in joint mobility and a negative association between health-related quality of life and orthopedic condition.^{7,8} Nevertheless, several published reports have demonstrated the feasibility of orthopedic surgery with BPAs in this cohort, and consensus recommendations have been developed detailing their use.⁹⁻¹¹

With that said, BPAs are not as effective as rFVIII in achieving and maintaining hemostasis, and 10% to 20% of bleeding events in hemophilia patients with high-titer inhibitors cannot be controlled.¹² We experienced this at our institution after a 58-year-old male with severe hemophilia A and a high-titer inhibitor underwent total knee arthroplasty for advanced arthropathy. Despite maximal dosing with either rFVIIa 90 mcg/kg every 2 hours or APCC 5000 units every 6 hours (not exceeding 20 000 units in any 24-hour period), hemostasis was poor. Ultimately, an above-the-knee amputation was necessary. As a last resort to avoid similar complications in the future, we initiated a novel approach alternating rFVIIa and APCC, referred to as sequential BPA therapy; however, the risk of thrombosis is a chief concern, especially in high-risk situations, such as orthopedic surgery.

Thrombotic events have been documented with the use of rFVIIa and APCC, albeit uncommonly when used in the appropriate clinical situation. The use of rFVIIa in hemophilia patients with inhibitors in clinical trials was associated with only a 0.2% incidence of thrombosis.¹³ An analysis of the US Food and Drug Administration's Adverse Event Reporting System database identified 185 thrombotic events with rFVIIa; however, only 17 occurred in patients with hemophilia.¹⁴ An analysis of Baxter's Pharmacovigilance database described 16 thrombotic events with APCC (4 per 100 000 infusions), 8 of which occurred when APCC was given at a higher-than-recommended amount.¹⁵

Case description

In this report, we describe the use of sequential BPA therapy to prevent surgical bleeding in a patient with moderately severe hemophilia A (FVIII = 0.03 IU/mL) and a high-titer inhibitor. Institutional review

board (IRB) approval was obtained from the University of Pittsburgh IRB, and the study was done in accordance with the Declaration of Helsinki.

Methods

Our patient is a 52-year-old male with moderately severe hemophilia A and a high-titer inhibitor (current titer, 44.8 Bethesda units). His comorbidities include advanced arthropathy of multiple joints and previous left total hip and knee arthroplasty. He has a severe bleeding phenotype characterized by recurrent hemarthrosis and soft tissue bleeds. The incidence and severity of bleeding has worsened with aging and joint degeneration, and the frequency of clotting factor concentrate infusion (CFC) has necessitated central venous catheter (CVC) placement. Episodes of bleeding have been unresponsive to either rFVIIa or APCC. This has prompted treatment with sequential BPA therapy to control bleeding. With this regimen, he has had a reduction in the frequency and severity of bleeds.

The patient presented to the hospital with severe left knee pain, and he was diagnosed with septic arthritis and bacteremia. The infectious agent was identified as *Klebsiella oxytoca*. Antibiotic therapy was initiated with cefazolin. Orthopedic surgery recommended urgent left knee arthrotomy, synovectomy, and excisional debridement of soft tissue to bone. Unfortunately, bleeding had complicated previous surgeries with single-agent BPA therapy; therefore, we chose to proceed with surgery utilizing sequential BPA therapy.

The patient received rFVIIa 180 mcg/kg preoperatively. Postoperatively, rFVIIa 90 mcg/kg and APCC 5000 units were alternated every 3 hours (Table 1). This dosing schedule was continued until postoperative day (POD) 14. CFC taper was planned to begin at that time; however, the patient underwent surgery for CVC placement. Again, rFVIIa 180 mcg/kg was given preoperatively. Subsequently, sequential BPA therapy was resumed as detailed above. On POD 14, rFVIIa and APCC were changed to alternate every 4 hours. This was continued until POD 28 when BPA therapies were changed to alternate every 6 hours. On POD 42, BPA agents were changed to alternate every 12 hours. This was continued until POD 56, when regular BPA prophylaxis schedule was resumed. We administered CFC longer than typically recommended postoperatively because of the patient's history of refractory bleeding.

Results and discussion

Perioperative sequential BPA therapy was effective in maintaining hemostasis without adverse events. Minimal blood loss occurred intraoperatively. A Jackson Pratt drain was placed at the time of surgery and drainage monitored postoperatively. Serosanguinous drainage was present without any evidence of overt bleeding. The Jackson Pratt drain was removed on POD 8. Normal postoperative pain and swelling was present, but there was no evidence of overt hemarthrosis and hemoglobin remained stable without significant decrease. There was no evidence of deep venous thrombosis, pulmonary embolism, or other thrombotic event. No other adverse events were experienced.

Our case report is the first to describe the use of sequential BPA therapy in a patient with moderately severe hemophilia and a high-

Table 1. Sequential BPA treatment regimen

Time	3-h interval*	4-h interval	6-h interval	12-h interval
12 AM	rFVIIa	rFVIIa	rFVIIa	rVIIa
1 AM				
2 AM				
3 AM	APCC			
4 AM		APCC		
5 AM				
6 AM	rFVIIa		APCC	
7 AM				
8 AM		rFVIIa		
9 AM	APCC			
10 AM				
11 AM				
12 PM	rFVIIa	APCC	rFVIIa	APCC
1 PM				
2 PM				
3 PM	APCC			
4 PM		rFVIIa		
5 PM				
6 PM	rFVIIa		APCC	
7 PM				
8 PM		APCC		
9 PM	APCC			
10 PM				
11 PM				

*The duration of each interval is 14 days.

titer inhibitor undergoing major orthopedic surgery. Previous reports have documented the effectiveness of sequential BPA therapy for acute bleeding, but not for surgery, during which the risk of thrombosis is of greater concern, especially with major orthopedic surgery.¹⁶ Van Veen et al described the safe use of a hybrid regimen in inhibitor patients undergoing major surgery; however, rFVIIa and APCC were alternated once, which differs from the sequential therapy we describe here.¹⁷ The effectiveness of sequential BPA therapy is probably related to the differing effect of each drug on the coagulation cascade. APCC converts prothrombin in the prothrombinase complex to thrombin, and rFVIIa binds to and directly activates factor X on activated platelet surfaces, which then converts prothrombin to thrombin. These distinct actions probably have a synergistic effect on hemostasis.¹⁸

In conclusion, the outcome of our patient suggests that sequential BPA therapy is a safe and effective salvage therapy to prevent surgical bleeding in hemophilia patients with inhibitors unresponsive to single-agent BPA treatment. Whether alternating BPA agents is hemostatically more effective than single-agent BPA treatment will require a clinical trial; however, our experience suggests the use of sequential BPA therapy should be considered. Given the prevalence of advanced arthropathy, pain, and disability in inhibitor patients, this treatment option may provide an approach to

achieving hemostasis not previously possible in surgical settings and thereby improve the quality of life of such patients.

Authorship

Contribution: C.D.S. and M.V.R. designed and completed the research, analyzed the data, formulated the conclusions, and wrote the paper.

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