

Case Reports

Management of Hemophilia in Colon and Rectal Surgery

Report of a Patient with Factor VIII Inhibitors and Review of the Literature

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With the introduction of Factor VIII concentrates, surgery on patients with hemophilia has become possible. The mortality in recent large series is zero. The morbidity has been variable, with postoperative hemorrhage the most common complication. There is a dramatic change in therapeutic strategy with the development of Factor VIII inhibitors. In reviewing the literature, there are no reports discussing this patient population with respect to the subspecialty of colon and rectal surgery. The authors present a report of a patient with hemophilia who, after hemorrhoidectomy, developed Factor VIII inhibitors and continued hemorrhage. This article also reviews the literature and centralizes the management of colon and rectal surgery patients with hemophilia. [Key words: Hemophilia A; Factor VIII inhibitors; Multidisciplinary approach]

THE INCIDENCE OF hemophilia in the United States is 1.05 per 10,000 males. Eighty percent of patients with the disorder have classic hemophilia (Hemophilia A). With the introduction of cryoprecipitates and the further development of concentrated preparations of both Factor VIII and Factor IX, surgery in this patient population has been accomplished with progressively less morbidity. A team approach is required between hematologist, surgeon, and blood bank for optimal care of these patients. However, there is a high percentage of hemophiliacs who hemorrhage in the postoperative period, who have received adequate doses of concentrate,

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and who have been maintained on adequate plasma levels of Factor VIII. The etiology of this postoperative hemorrhage is unknown.

In 10 to 15 percent of patients with hemophilia, Factor VIII inhibitors develop. These antibodies present a serious and often life-threatening complication in the management of these patients. The therapeutic approach and problems of a patient with an inhibitor are very different from those of patients without antiFactor VIII antibodies. The literature on management of patients with hemophilia in the perioperative period after colon and rectal surgery has not been centralized to one single article. A thorough search of the literature revealed only a few references specifically discussing that patient population.

This article presents a hemorrhoidectomy in a classic hemophiliac. The patient developed massive postoperative hemorrhage, Factor VIII inhibitors, and required multiple surgical procedures in order to control his hemorrhage.

Overview of Hemophilia

Hemophilia is a sex-linked recessive trait, carried by the female. About 30 percent of the patients affected have a negative family history. The Factor VIII molecule consists of two subunits—a procoagulant and a subunit

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for platelet function. The underlying coagulation defect results from the synthesis of a functionally inactive procoagulant Factor VIII. Hemophilia is classified into three types (Table 1). When Factor VIII levels greater than 25 percent normal, hemostasis is present.

Medical management of the hemophiliac has improved over the last 50 years. Before 1965, fresh frozen plasma and whole blood were used as the primary treatment modalities; however, the factor levels achieved often were too low and did not provide hemostasis. The surgical mortality rates were as high as 66 percent.¹ Pool and Hershgold² discovered cryoprecipitate and the operative care of the hemophiliac became possible. The operative mortality rate decreased to 2 percent. With the introduction of Factor VIII and IX concentrates in the early 1970s, elective surgery on the hemophiliac became possible.

Today the operative mortality in many studies is zero.³⁻⁵ The postoperative hemorrhage rate ranges from 6 to 23 percent. Factor VIII inhibitors develop in 10 to 15 percent of patients treated with factor VIII therapy.

The observation of postoperative hemorrhage in this patient population, even with therapeutic levels of Factor VIII, is a dilemma that faces any surgical team. Usually excessive intraoperative hemorrhage is not encountered. Kasper *et al.*⁶ had a 23 percent incidence of postoperative hemorrhage of moderate or severe degree in general surgical patients. Ninety-one percent of the hemorrhages began on postoperative days 1 to 11 with a peak incidence on postoperative days 6 and 7. Their rate in orthopedic patients was even higher. Brown *et al.*⁷ had an 18 percent postoperative hemorrhage rate in general surgical patients, but all patients were treated conservatively without the need for additional operations. Kitchens⁸ experienced only a 6 percent rate of hemorrhage complications. This variability in postoperative hemorrhage cannot be explained. It can be concluded, however, that circulating Factor VIII levels are not the only determinants of postoperative bleeding in this patient population. This hemorrhage may be due to anatomic and pathologic factors. In some series, the administration of aspirin or aspirin-containing compounds in the postoperative period has been indicated as the cause of hemorrhage.

The development of Factor VIII inhibitors in the postoperative setting represents a turning point in the management of the hemophiliac. Factor VIII inhibitors are most commonly observed in patients with hemophilia A. With very few exceptions, inhibitors have appeared in patients with Factor VIII deficiency only after transfusion therapy. The circulating anticoagulants are IgG immunoglobulins. The inhibitory activity resides in the Fab fragment of the antibody. These antibodies form soluble, nonprecipitating complexes

TABLE 1. *Classification of Hemophilia*

Type	F VIII*	Common Sign	APTT†
Severe	< 1%	Severe spontaneous bleeding	Prolonged
Moderate	1-5%	Marked bleeding from minor trauma Spontaneous bleeding uncommon	Prolonged
Mild	5-24%	Serious bleeding from surgery or trauma Spontaneous bleeding rare	Variable
Subclinical	25-50%	Moderate bleeding from surgery or trauma Diagnosis frequently missed	Often normal

*Factor VIII activity

†Activated partial thromboplastin time

with Factor VIII and inhibit its "coagulant activity." The immune response to Factor VIII is variable. Some patients develop low levels of inhibitors (low responders) while others develop high levels of inhibitors (high responders). The latter group shows sharp induction of inhibitor after Factor VIII exposure. This leads to an amnestic response to the inhibitor that begins 2 to 4 days after Factor VIII therapy. The plasma inhibitor level gradually falls over several months to several years, in the absence of further Factor VIII therapy.

Report of a Case

A 22-year-old black man was admitted in July 1986 to the Georgia Baptist Medical Center for his third episode of gastrointestinal hemorrhage. Hemoglobin was 8.5 gm/dl and APTT was 42 sec over the control of 30 sec. Hematologic workup, at that time, revealed a Factor VIII level of 5 to 7 percent of normal. Physical examination was significant for actively bleeding grade III internal hemorrhoids.

The patient was not diagnosed with Hemophilia A before this hospitalization. He denied a family history of congenital coagulopathies. He lived an active life with only one episode of bleeding problems after a dental extraction several years before admission. The patient was managed conservatively until the end of September but, because of continued hematochezia (hemoglobins between 7 to 8 mg/dl), an elective hemorrhoidectomy was performed.

His admission Factor VIII level was 7 percent of control; this was raised to greater than 100 percent of normal preoperatively. Hemorrhoidectomy was performed without intraoperative hemorrhage. His Factor VIII level was maintained greater than 100 percent for the first 5 postoperative days, then greater than 50 percent of normal for the next 2 postoperative days. The patient was discharged on the eighth postoperative morning, but returned to the emergency room on the ninth postoperative day with massive hematochezia. He was diaphoretic, hypotensive, and tachycardic. His hematologic profile showed a hemoglobin of 6.0 gm/dl and serum Factor VIII level of 50 percent of control. He was returned to the operating room where large amounts of clots were evacuated from the rectal ampulla. The hemorrhoidectomy site was actively oozing; suture ligation was required. He was transferred to the surgical intensive care unit. He required transfusion of multiple units of packed red blood cells and his Factor VIII level was maintained at 100 percent of normal.

On the third hospital admission day, his Factor VIII level began to fall in the face of the continued Factor VIII replacement. He tested positive for Factor VIII antibodies. His Factor VIII level fell to 11 percent of normal. He required several return trips to the operating

TABLE 2. *Factor VIII Deficiency and Ulcerative Colitis*

Surgical Procedure	Diagnosis	Transfusion
Emergency laparotomy	Spontaneous retroperitoneal hemotoma	Massive amounts of whole blood were required. Then transferred to another hospital. He then received Factor VIII concentrates. (3,000 units/q8hrs for 10 days).
Percutaneous drainage of abscess 1 month later	Intra-abdominal abscess	Infusion of 1750 units Factor VIII q8hrs. Factor VIII level 42% normal. No perioperative hemorrhage.
Required second percutaneous drainage 1 month later	Necrotic material	Infusion of 800 units Factor VIII q8hrs. Factor VIII level 86% of normal. No perioperative hemorrhage.
Laparotomy (3 months later) Resultant development of enterocutaneous fistula	Drainage of interloop Proximal jejunal abscess	Infusion of 1750 units Factor VIII q8hrs. Factor VIII level 80% of normal. No perioperative hemorrhage.
Colonoscopy (4 months later)	Ulcerative colitis severe	Infusion 900 units of Factor VIII q8hrs for 3 days. No perioperative hemorrhage.
Total abdominal colectomy end ileostomy	Severe ulcerative colitis	Infusion 2,000 units Factor VIII q8hrs for 17 days. No perioperative hemorrhage.

room for application of topical thrombin and rectal packing. At this point, overwhelming dosages of Factor VIII were used to override the antibodies. Combining this regime with Factor IX concentrates, we were able to maintain the Factor VIII level between 100 to 200 percent of normal.

Emergency angiography revealed an arteriovenous fistula from a small branch of the left pudendal artery. This area was embolized with gel foam. The patient continued to hemorrhage from the anal canal and lower one third of the rectum. The area was granular and friable, with small punctuate ulcerations. Attempts at rectal packing, with and without proximal diversion, were of no consequence. The use of epinephrine and prothrombin-soaked gauze and a 30-ml Foley catheter balloon did not stop the hemorrhage for extended periods of time. He was receiving massive doses of Factor VIII concentrates, platelets, and fresh frozen plasma in order to prevent coagulopathy.

By the fifth week of intensive care monitoring, the patient continued to hemorrhage and an abdominoperineal resection was performed without blood loss. Five days postoperatively, despite a normal blood profile, he began to hemorrhage again and was returned to the operating room where packing was placed in the pelvis and the perineal wound.

On the ninth week of hospitalization, hemorrhaging stopped and the patient improved rapidly. He was discharged in good health and there has been no bleeding for two years. During his hospital stay, he received 119 units of packed red blood cells, 260 units of cryoprecipitate, 80 units of fresh frozen plasma, 70 units of platelets, and 2.7 million units of Factor VIII concentrates.

Discussion

Using a team approach to the management of the hemophiliac in the perioperative period has lowered the mortality rate to zero. The morbidity rate of this population varies from 6 to 23 percent. Postoperative hemorrhage is the leading cause of postoperative morbidity. In reviewing the surgical literature on hemophiliacs, there are two major headings—orthopedic and general surgical procedures, including colon and rectal cases. To further complicate the search for literature, hemophiliac patients are also categorized under congenital coagulopathies. Most of the cases that

are listed are those with postoperative complications and only a few uncomplicated surgeries are listed. Because of the overall small number of patients and the other factors mentioned, a statistical analysis is impossible. There is also some criticism of individual case reports from multiple institutions because they tend to minimize fatalities and maximize the spectacular cases.⁹

Kitchens⁸ reviewed 100 consecutive procedures on patients with congenital coagulopathies, of which 80 had hemophilia. Only 30 of the cases were general surgical—20 major and 10 minor cases. One particularly interesting case was a 34-year-old male with severe hemophilia (less than 1 percent of normal Factor VIII) and ulcerative colitis. This patient had a particularly protracted course including multiple hospitalizations, surgical procedures, high doses of prednisone, malnutrition, poor wound healing, and excessive postoperative hemorrhaging (Table 2).

In a second case report on a patient with hemophilia and ulcerative colitis, the problems inherent in managing this difficult combination became evident.¹⁰ A 21-year-old male with mild hemophilia (3 to 4 percent Factor VIII) developed ulcerative colitis. His illness progressed over 4 months, leading to malnutrition and passage of increasing amount of blood per rectum. Despite several hospitalizations and high doses of oral and intravenous steroids, he continued to deteriorate and underwent an emergent total proctocolectomy with end ileostomy without complications. These two case reports indicate the difficulty in managing a patient with hemophilia and inflammatory bowel disease. It must first be determined whether the patient is bleeding from deficient Factor VIII levels or from the activity

TABLE 3. Other Cases Specifically Relating to Patients Under Colon and Rectal Specialty

Procedure	Complication
Minor	
Colonoscopy polypectomy	None
Colonoscopy polypectomy	Postprocedure hemorrhage
Colonoscopy (ulcerative colitis)	None
Pilonidal cyst excision (outpatient)	None
Fistulectomy	Postoperative hemorrhage
Major	
Take down of colovesical fistula Secondary to diverticulosis	None
Duhamel procedure for Hirschsprung's disease	None
Laparotomy lysis of adhesions	Postoperative hemorrhage secondary to nasogastric tube

of bowel pathology. In this particular case, despite adequate levels of Factor VIII and continued maximal medical therapy for ulcerative colitis, life-threatening bleeding occurred and emergent surgery was required. This is a rare combination and the estimated prevalence is approximately 4-8 per 1×10^8 patient. In reviewing this combination of illnesses, it may indicate earlier surgical intervention in this population.

The only other cases specifically relating to patients under the colon and rectal specialty are shown in Table 3.

There cannot be any conclusions drawn from these cases, but they are important to the overall fund of knowledge. The current hematologic management of the hemophilic patient without inhibitors during the perioperative period has decreased the postoperative incidence of hemorrhage. The etiology of postoperative hemorrhage in the hemophiliac has been theorized to be an anatomic and/or physiologic problem. As yet there may be an undetermined "factor" in the coagulation cascade that is not replaced in large enough quantities with the current products used.

In a particularly important report, Kasper *et al.*⁶ reviewed 350 consecutive emergency and elective surgical operations on 163 different patients with classic hemophilia A without inhibitors. Doses were given every 8 to 12 hours in order to maintain a desired minimum (trough) factor level for a minimal healing period of 10 to 14 days. The observed *in vivo* recovery was calculated by multiplying the increase in plasma Factor VIII levels (units/milliliter) by the estimated plasma volume (weight in pounds times 20, not covered for hematocrit). A very interesting fact came to light

TABLE 4. Relationship Between Factor VIII and Incidence of Postoperative Hemorrhage

Time	Trough Level of F VIII	Duration	Dose/Operation
1967-1972	> 30%	10 days	600 Units/Kg
1973-1974	> 50%	14 days	1,000 Units/Kg
1975-1979	> 50%	14 days	1,300 Units/Kg
1980's	> 50%	14 days	2,000 Units/Kg

*The amount of Factor VIII given for minor operations was about one-half that used for major operations. This was due to a shorter duration of therapy.

in this study. The dosage of Factor VIII given to these patients increased over the study period, but the incidence of postoperative hemorrhage remained unchanged (Table 4).

Brown *et al.*⁷ reviewed 23 surgical procedures on 22 patients. Their protocol was to increase the plasma Factor VIII level to 100 percent of normal immediately before surgery, and then to maintain a level of 50 to 100 percent unit/ml of normal for the first 5 to 7 postoperative days. Then the amount or frequency of Factor VIII infusions would be decreased in order to maintain a plasma level of 0.25 to 0.50 units/ml for the remaining postoperative period. The interval of infusions were every 8 to 12 hours. The incidence of postoperative hemorrhage was still 18 percent.

Our approach to the hematologic management of our patient was similar to that of Brown *et al.*⁷ Before elective hemorrhoidectomy, the patient's Factor VIII level was increased to 100 percent of normal and maintained at this level for 5 days. The last 2 days, the Factor VIII level was decreased to 50 percent of normal. Upon discharge from the hospital, the patient returned with massive hematochezia. Figure 1 shows that the amount of Factor VIII consumed for attempted control of the multiple procedures and episodes of hemorrhage was considerable.

After development of Factor VIII inhibitors, the therapeutic approach to this patient becomes very different from the patient without Factor VIII inhibitors. The three different approaches are conservative management without parenteral therapy, prothrombin complex infusion therapy, and Factor VIII concentrate infusion therapy. Conservative management is only for simple lacerations, mild hemarthrosis, or low-grade mucosal bleeding. The use of prothrombin complex concentrates (PCC) has been shown to be an effective method of replacement therapy in hemophiliacs with Factor VIII antibodies. The PCCs contain the vitamin-K-dependent Factors (II, VIII, IX, X). These concentrates "by pass" the Factor VIII reaction during coagulation, by an as yet unknown mechanism. The more commonly

FACTOR CONCENTRATE USED DURING VARIOUS BLEEDING EPISODES (UNITS CONSUMED)

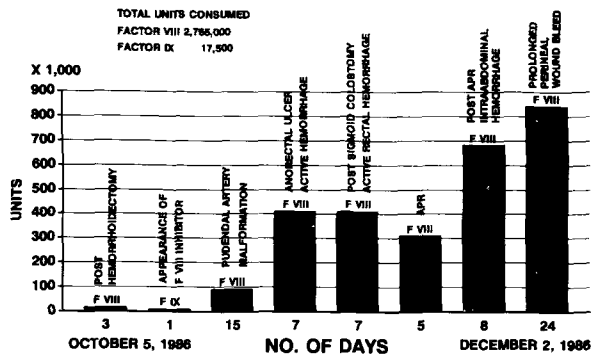


FIG. 1. Factor concentrate used during various bleeding episodes (units consumed).

FACTOR VIII LEVEL MAINTAINED DURING PATIENT MANAGEMENT

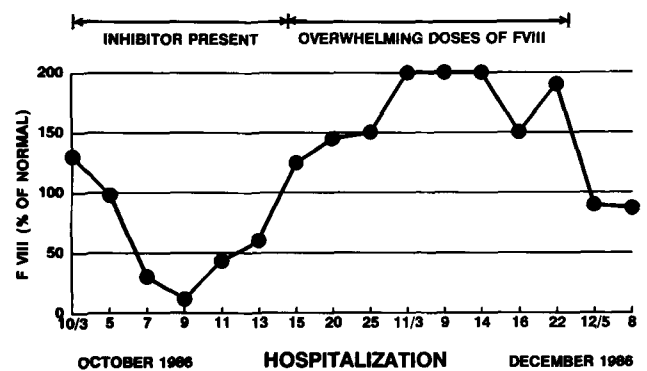


FIG. 2. Factor VIII level maintained during patient management.

used Auto Plex (Anti-inhibitor Coagulant Complex) and FEIBA (Factor Eight Inhibitor by Passing Activity) Immuno have shown varied success in clinical trials.¹¹⁻¹⁴ These concentrates have specific indications and should be used only for spontaneous hemorrhage, traumatic hemorrhage, and hemorrhage during surgical procedures in patients with inhibitors. There is no method of titrating the effect of these agents; therefore, too little may not alter hemorrhage and too much is thrombogenic.¹⁵ The most common approach to patients with inhibitors is Factor VIII concentrates. The doses are much larger than the normal amount transfused. The mechanism of action is that the initial dose of Factor VIII neutralizes the plasma inhibitor, whereas the next doses are used for coagulation. Other therapeutic modalities have been used with varying success. Plasmapheresis or exchange transfusion has been used to reduce the circulating titers of antibodies and total immunoglobulin content; the remaining antibodies are then neutralized by infusion of Factor VIII concentrates.¹⁶ The use of epsilon aminocaproic acid (DACA) and 1-des-amino-8d-arginine (DDAVP) has been studied. The first is a fibrinolytic activator and has arrested bleeding. The latter is a synthetic vasopressin analogue that increases Factor VIII levels without the pressor effect.¹⁷⁻²⁰

When our patient developed Factor VIII inhibitors, we used overwhelming doses of Factor VIII to override the inhibitors. Because of continued hemorrhage, we used Factor IX concentrates. This patient continued to hemorrhage in spite of the Factor VIII levels that were achieved (Fig. 2). During the management of this patient, multiple methods for local control of hemorrhage were used with varied response. The use of rectal packing in the early stages was of little effect; in fact, it caused edema and mucosal damage that added to

the hemorrhagic problem. Attempts at using epinephrine-soaked gauze, prothrombin-soaked gauze, and a 30 ml Foley catheter balloon induced the defecation response and did not stop the hemorrhage. With diversion of the fecal stream and again attempting rectal packing, a similar response occurred. We do not recommend this approach for management of anal canal or lower rectal hemorrhage.

The most beneficial approach in the early stages was angiography with intra-arterial vasopressin (Pitressin®, Parke-Davis, Morris Plains, NJ) and embolization in the short term. This also caused low-grade ischemia of the rectum, which eventually led to increased hemorrhage. There was an impressive response to topical thrombin for immediate but short-term cessation of hemorrhage in the anal canal. Overall this patient was salvaged because of continued aggressive combined medical and surgical treatment.

Summary

Major advances have been made for surgery since the development of cryoprecipitates and factor concentrates. The mortality is acceptably low but the morbidity remains variable. The centralization of this patient population under the category of colon and rectal surgery is very important, especially the anorectal procedures. We believe that more publications, whether single case reports or series, will continue to add to the understanding of the perioperative care of this patient population in the specialty of colon and rectal surgery.

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Weight on the elbows and the knees,
The greatest of indignities,
To find oneself up-ended there,
With elevated derrière.

Indeed, this posture is unique,
It's keyed to medical technique;
The doctor clarifies the scene.
"A test," he says, "it's just routine."

With no adieu he starts to spy,
On parts that never meet the eye,
And carefully, with no time to waste,
The patient's "innards" must be cased.

In like procedures do we learn,
To know ourselves from stem to stern;
For sure, it's not a parlor topic,
This basic test—the proctoscopic.

Julia L. Stoker