PEDIATRIC DENTISTRY/Copyright © 1987 by
The American Academy of Pediatric Dentistry
Volume 9 Number 4

Activated prothrombin complex concentrates in the management of the hemophiliac with Factor VIII inhibitor: case report

Ann L. Griffen, DDS W. Keith Hoots, MD A. Bruce Carter, DDS

Abstract

This report describes the management of a bleeding episode following exodontia in a patient with severe hemophilia A and inhibitor to Factor VIII. For this patient activated prothrombin complex concentrates provided an effective method of controlling hemorrhage.

Maintaining hemostasis in the surgical patient who has hemophilia A and inhibitor to Factor VIII is a difficult challenge for dentists and physicians. This report describes management of a postextraction bleeding episode using activated prothrombin complex concentrates (activated PCCs), an effective therapeutic approach not previously reported in the pediatric dental literature. Of special interest is this patient's failure to respond to one of the available activated PCC products and his immediate response to the only other available product.

Background

Hemophilia A is a hereditary coagulation disorder characterized by a Factor VIII clotting activity deficiency. Affected patients may experience hemorrhagic episodes, the severity of which varies depending upon the Factor VIII activity level and the extent of the injury. Severely affected individuals may experience recurrent hemarthroses, hematomas, spontaneous central nervous system bleeding, and prolonged bleeding after exodontia, local anesthesia, or gingival trauma. With adequate Factor VIII replacement therapy these episodes can usually be managed. But a subset of hemophiliacs develops antibodies or inhibitors to Factor VIII. These inhibitors, which inactivate Factor VIII clotting activity, develop in about 15% of hemophiliac patients who receive replacement therapy. The inhibitors are most likely to occur in patients with severe hemophilia A, and there appears to be a genetic predisposition to their development (Roberts and Cromartie 1984).

Hemophiliacs with inhibitor can be divided into two groups with respect to their inhibitor titers. Patients whose levels remain below 10 Bethesda units (BU) despite repeated exposure to Factor VIII are considered low responders, and those whose inhibitor levels rise above 10 BU following exposure to Factor VIII are considered high responders. Patients with high responsive antibodies typically maintain a stable antibody titer for 5-7 days following antigen exposure and then show a rise to a peak in 8-15 days. This peak is followed by a slow fall over a period of weeks to months. Although the majority of inhibitor patients follow the high responsive pattern, it is unusual for low responders to become high responders (Allain and Verroust 1984).

The management of bleeding episodes in these two groups is by necessity different. Patients showing a low antibody response can be treated by neutralizing the inhibitor with large amounts of Factor VIII concentrate. But if the inhibitor is present at high enough levels, it cannot be overcome in this way, and the patient is likely not to respond to Factor VIII replacement therapy. This makes bleeding episodes in high responsive individuals more difficult to manage, and so morbidity is often greater. Infusion of activated PCCs may be an effective form of treatment for bleeding in these individuals.

The lack of a laboratory assessment that correlates with clinical response to activated PCCs has impeded the quantitative studies necessary to determine the efficacy of these products, but single infusions have been shown to be effective in controlling joint bleeds in approximately 50-65% of patients (Lusher et al. 1983; Sjamsoedin et al. 1981). Limited data have been published on their effectiveness for dental extractions. Dental treatment with the potential to produce hemorrhage has been avoided in high level inhibitor patients because of the potential for exsanguination[1], but the availability of activated PCCs has made elective exodontia for these patients an option advocated by some authors.[2]

[1] Berlocher and King 1979; Nelson et al. 1985; Redding and Stiegler 1983.

[2] Agrestini et al. 1982; Garehime et al. 1983; Zech and Strother 1983.

The activated PCCs were developed from PCCs which are partially purified concentrates of clotting Factors II, VII, IX, and X originally developed for the treatment of Factor IX deficiency (hemophilia B). When the PCCs were found to slow bleeding in Factor VIII-deficient patients with inhibitor, an attempt was made to increase their effectiveness for these patients by activation. The precise mechanism of action is not known, but the activated PCCs probably contain traces of the activated forms of clotting Factors VII and X which bypass the need for Factor VIII (Zech and Strother 1983). Despite their relatively greater efficacy, activated PCCs are generally reserved for serious bleeding because of their high cost. There are currently two activated PCC products available which are prepared by slightly different processes.[a]

Case Report

A 3-year-old Hispanic male with severe hemophilia A had a family history of hemophilia involving three generations and including a brother who died of hemorrhagic complications. He was the product of an accidental pregnancy and was carried to term with a normal vaginal delivery. He was not circumcised. The child was diagnosed as having severe Factor VIII deficiency during a routine screening at the age of six months and was followed and treated from that time at the Gulf States Regional Hemophilia Center. An effort was made to involve the family in a preventive management program, but little cooperation was obtained. Medical care was in effect limited to crisis management and no dental care was provided. During the first three years of his life he received a total of 20 exposures to cryoprecipitate or Factor VIII concentrate to control various joint and oral bleeding episodes.

Three months prior to dental treatment a routine screening test first indicated the presence of inhibitor to Factor VIII. Two months later, during infusions to control a shoulder bleed, inhibitor levels and in vivo survival of Factor VIII were measured (Table 1). Twelve days after this the patient presented with a facial cellulitis with labial, nasal, and periorbital swelling. He was afebrile. His behavior was extremely uncooperative, but an oral examination revealed four severely carious primary maxillary incisors. The infection was ameliorated with oral penicillin V and a decision was made to extract the teeth.

Three days later the patient presented to the hemophilia clinic for treatment. He was sedated with oral meperidine (0.4 mg/kg) and promethazine (0.2 mg/kg) and infused with 1080 units of Factor VIII concentrate, a dose calculated to bring his Factor VIII level to 70% of normal based on his weight (15 kg) and most recent postinfusion survival rate. Using infiltration anesthesia the teeth were extracted. The sockets were packed with absorbable gelatin sponge[b] and an acrylic splint was placed. Oozing from the extraction sites persisted, so after two hr the sockets were cleansed and packed with microfibrillar collagen hemostat.[c] After three hr the patient was given 1.25 g epsilon amino caproic acid (EACA)[d] orally. Oozing from the extraction sites increased despite measures to control bleeding, and after five hr the patient was admitted and infused with 1500 units of Autoplex without response. He was sedated with chloral hydrate (25 mg/kg) to make it possible to continue with local attempts to achieve hemostasis. Laboratory results returned at this time indicated his inhibitor level at the time of the initial infusion was 24 BU. After 13 hr of hemorrhage the patient was infused with 1500 units of Feiba, and hemostasis was achieved immediately. The patient was started on oral iron supplements to treat the resulting anemia and antifibrinolytic therapy with oral EACA (1.25 g every 6 hr) to maintain clot stability. The EACA therapy was continued for the subsequent 10 days. Further oozing from the extraction sites occurred two days later and hemostasis was again achieved with a single additional infusion of 1750 units of Feiba.

Eight weeks postoperatively he presented to the outpatient clinic with persistent bleeding from a minor oral laceration unrelated to the extractions. Hemostasis was once more achieved following three daily infusions of 1200 units of Feiba and oral EACA therapy.

Following this episode, moderately successful attempts were made to involve the patient in a dental prevention program consisting of regular oral hygiene, diet control, and topical and systemic fluorides.

TABLE 1. Inhibitor and Post-Infusion Factor VIII Levels

Time Prior to Exodontia	*Inhibitor Level*	*Per Cent Predicted Factor VIII Level**
3 months	†	not measured
25 days	4 BU	60
17 days	5 BU	50
0 days	24 BU	< 2

* Observed factor level 30 min post-infusion.
† *Factor level predicted in absence of inhibitor.*

[a] Autoplex (Travenol Laboratories; Glendale, CA) and Feiba (Immuno; Vienna, Austria).

Discussion

As a general rule, it is advisable to obtain inhibitor levels within a few hours of a contemplated surgical procedure. In this case it was decided, perhaps imprudently, to forego the routine presurgical measurement, because postinfusion Factor VIII and inhibitor levels had both been measured twice in the preceding month and had been in close agreement. It was assumed that

[b] Gelfoam - Upjohn; Kalamazoo, MI
[c] Avitene - Avicon; Fort Worth, TX.
[d] Amicar - Lederle; Pearl River, NY.

the patient would continue to maintain the constant inhibitor level characteristic of a low responder when challenged with Factor VIII. In retrospect it is clear that the patient developed a high level of antibodies to Factor VIII in response to the infusions he received 12 and 20 days before the teeth were extracted, with peak antibody levels occurring at the time the teeth were extracted. This represents an insidious pattern of onset of a high responsive inhibitor in a previously low responsive patient, and might be attributed to the young age of this individual (Allain and Verroust 1984). If inhibitor levels had been measured immediately prior to the surgical procedure, the initial five hr of hemorrhage which occurred while attempting to treat the patient with Factor VIII concentrate could have been avoided. When the initial high dose of Factor VIII did not maintain hemostasis, it was assumed, and later corroborated by laboratory results, that inhibitor levels had risen. It was decided that infusing additional Factor VIII would likely be futile, and therefore an alternative approach to achieving hemostasis was sought. Due to the progressively morbid nature of the bleeding episode, it was decided to try activated PCCs immediately, rather than beginning with less expensive PCC therapy.

The fact that the patient responded to Feiba and not to Autoplex is interesting because it suggests that when a patient does not respond to one product it may be useful to try another. Although this is an accepted practice among hematologists, there is little if any information in the medical literature to suggest which of the two available activated PCCs is most likely to be effective initially. There appears to be significant variability between individual patients and, on occasion, even from episode to episode in a single patient (Roberts et al. 1982). The diminished response this patient demonstrated during his last course of activated PCC may be indicative of just such varying reliability.

Although many clinicians and investigators use antifibrinolytic agents such as EACA and tranexamic acid (a recently approved drug likely to replace EACA because of its greater potency, longer half-life, and lower toxicity) in combination with PCC or aPCC to reduce the amount of concentrate required to maintain hemostasis, it should be noted that this may increase the risk of thrombotic complications. Patients with compromised liver function may be especially prone to these problems, and all patients should be monitored for signs or symptoms of disseminated intravascular coagulation.

There are other therapeutic options available for treating patients with inhibitors. Long periods of time during which there is no exposure to the Factor VIII protein often result in a gradual fall in antibody titer. This may allow short-term Factor VIII therapy at high doses to be used for life-threatening or major hemorrhage. Other options include chronic Factor VIII antigen immune tolerance induction (an exceedingly prolonged and costly regimen), plasma exchange, or porcine Factor VIII (Roberts et al. 1982).

For this patient the necessity for exodontia could have been avoided had he participated in a dental prevention program such as the one described by Goepferd (1986). This type of program is ideal for the hemophiliac or other medically compromised patient, but it involves a high level of parental commitment which in this case was not present.

The dental management of the hemophiliac with high level inhibitor is a complicated problem that must be solved in conjunction with the patient's hematologist. Ideally, dental treatment will consist of a rigorous program designed to prevent dental disease and avoid possible hemorrhagic episodes. However, in those cases where this has not been achieved and treatment is necessary, activated PCCs can provide an effective method of controlling bleeding.

At the time this patient was treated, Dr. Griffen was a resident and Dr. Carter was an assistant professor and director of the University of Texas pediatric dental graduate program. Currently Dr. Griffen is an assistant professor, pediatric dentistry, The Ohio State University; and Dr. Carter is chief of the Texas Children's Hospital dental clinic and is in private practice in Houston, Texas. Dr. Hoots is an associate professor, pediatrics, University of Texas System Cancer Center, M.D. Anderson Hospital; pediatrics and internal medicine, University of Texas Medical School; adjunct clinical assistant professor, pediatric dentistry, University of Texas Health Sciences Center at Houston; and director, Gulf States Regional Hemophilia Center in Houston. Reprint requests should be sent to: Dr. Ann Griffen, Dept. of Pediatric Dentistry, The Ohio State University, College of Dentistry, 305 W. 12th Ave., Columbus, OH 43210.

Agrestini F, Solinas S, Marinelli M, Avvisati G, Badia D, Mazzucconi MG: Activated prothrombin complex concentrates in dental extractions and oral and minor surgery in hemophiliacs with high-titer inhibitor, in Activated Prothrombin Complex Concentrates: Managing Hemophilia with Factor VIII Inhibitor, Mariani G, Russo MA, Mandelli F, eds. New York; Praeger, 1982 pp 168-75.

Allain JP, Verroust I: The response to Factor VIII infusion in inhibitor patients, in Factor VIII Inhibitors, Hoyer LW, ed. New York; Alan R. Liss, Inc, 1984 pp 99-108.

Berlocher WC, King DL: Considerations in the dental management of the Factor VIII-deficient child with inhibitors. Pediatr Dent 1:188-91, 1979.

Garehime WJ, Pecaro BC, Green D: Use of activated prothrombin complex concentrate in a severely hemophilic patient with Factor VIII inhibitor. J Oral Maxillofac Surg 41:262-64, 1983.

Goepferd SJ: Infant oral health: a protocol. J Dent Child 53:261-66, 1986.

Lusher JM, Blatt PM, Penner JA, Aledort LM, Levine PH, White GC, Warrier AI, Whitehurst DA: Autoplex vs Proplex: a controlled,

double-blind study of effectiveness in acute hemarthrosis in hemophiliacs with inhibitors to Factor VIII. Blood 62:1135-38, 1983.

Nelson L, Elfman J, Cohen A: Management of Ludwig's angina in a patient with severe hemophilia A with Factor VIII inhibitors: report of a case. J Dent Child 52:306-11, 1985.

Redding SW, Stiegler KE: Dental management of the classic hemophiliac with inhibitors. Oral Surg 56:145-48, 1983.

Roberts HR, Cromartie R: Overview of inhibitors to Factor VIII and IX, in Factor VIII Inhibitors, Hoyer LW, ed. New York; Alan R. Liss, Inc, 1984 pp 1-18.

Roberts HR, White GC, McMillan CW, Braunstein KM, Blatt PM: Current approaches to the treatment of patients with anti-Factor VIII antibodies, in Activated Prothrombin Complex Concentrates: Managing Hemophilia with Factor VIII Inhibitor, Mariani G, Russo MA, Mandelli F, eds. New York; Praeger, 1982 pp 39-44.

Sjamsoedin LJ, Heijnen L, Mauser-Bunschoten EP, van Geijlswijk JL, van Houwelingen H, van Asten P, Sixma JJ: The effect of activated prothrombin complex concentrate (Feiba) on joint and muscle bleeding in patients with hemophilia A and antibodies to Factor VIII. N Engl J Med 305:717-21, 1981.

Zech R, Strother SV: Maintenance ot hemostasis during exodontia in two hemophiliacs with Factor VIII inhibitors. J Oral Maxillofac Surg 41:53-56, 1983.

Forensics and dental remains

One of the problems faced by forensic scientists who are presented with the remains of more than one individual is the commingling of body parts. What may appear to be the remains of seven individuals may actually turn out to be the remains of only four individuals...or of nine individuals, as reported in a study using dental remains and a computer to verify the identity of a group of U.S. servicemen killed during the Vietnam War and whose remains were returned by the North Vietnamese.

Perhaps the most durable and distinctive body parts available to forensic scientists are the teeth. When the dental remains of this group of servicemen were examined, inconsistencies were detected, eventually indicating that the remains identified by the North Vietnamese as a single individual, actually represented the remains of three different individuals, none of which could be associated with the remains of the other six servicemen. The identity of the two additional individuals was established with the aid of a computer-assisted postmortem identification system that matched certain features of the "mystery" teeth with the dental records of more than 2400 missing-in-action personnel from the Vietnam War.

Dailey JC: Computer-assisted identification of Vietnam War dental remains
Military Medicine 152:179-82, 1987