Management of traumatic oral-facial injury in the hemophiliac patient with inhibitor: case report

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Abstract

This report describes identification of Factor VIII inhibitor in a patient who then received immune tolerance therapy. The precipitating event was a traumatic orofacial injury that was nonresponsive to traditional factor-replacement therapies. An inhibitor complicates medical and dental management of the hemophiliac patient because it counteracts usual techniques of hemorrhage control using coagulation agents derived from Factor VIII (Monoclate—Armour, Blue Bell, PA). Successful identification and management of the inhibitor patient require communication and consultation between the physician and dentist, up-to-date knowledge regarding the hemophiliac patient’s bleeding and infusion history and aggressive application of local adjunctive hemostatic therapies. (Pediatr Dent 15:282–87, 1993)

Introduction

Hemophilia A (classical hemophilia) is a rare blood clotting disorder affecting Factor VIII and having a recessive X-linked inheritance. Approximately 1:10,000 persons are affected by this disorder. Managing bleeding episodes or preparing elective surgery often requires infusion of factor replacement products. These products have contributed to increased longevity and quality of life for the hemophiliac patient, but they are not without limitations, including blood-borne pathogens. Approximately 10–15% of patients with severe hemophilia A (< 1% Factor VIII) also develop antibodies to Factor VIII (inhibitors) rendering the product less effective. Inhibitors increase morbidity and mortality for this patient population as well as health care costs. The current case report a traumatic oral-facial injury to a 4-year-old child with severe hemophilia in which Factor VIII inhibitor was diagnosed and immune tolerance therapy successfully implemented. A brief review of hemophilia and inhibitors and management and treatment strategies for traumatic oral injuries in inhibitor patients are discussed.

Literature review

As a cofactor in the intrinsic pathway, Factor VIII facilitates activation of Factor X of the common pathway (Fig 1). In hemophilia A, the absence or deficiency of this factor impairs blood clotting and results in persistent and prolonged hemorrhage—primarily into muscle tissue and joint spaces. Mild, moderate, and severe forms of the disease are exhibited and have been well described in the literature (Table). Treatment for the hemophiliac patient has undergone drastic changes in the last 30 years, with the advent of fresh frozen plasma, cryoprecipitate, and self-infusion at home. The use of porcine Factor VIII, genetically engineered Factor VIII, and DDAVP (desmopressin) has further advanced treatment options. Although these advances have resulted in a more normal and productive life, they also have resulted in complications. The fresh frozen plasma, cryoprecipitate, and fractionated human factor concentrates are obtained from pooled blood sources that have the potential to carry blood-borne pathogens such as hepatitis viruses, EBV, CMV, and HIV. Infusion therapy also can lead to hypervolemia, hemolytic anemia, allergic reactions, and development of inhibitors to Factor VIII.

Patients with inhibitors are classified as low responders (< 5 BU/ml), intermediate responders (5–10 BU/ml), and high responders (> 10 BU/ml). The inhibitor presentation varies considerably for these patients. Low responders may retain low titers or become high responders with repeated Factor VIII exposure. In other patients, the inhibitor may disappear without recurrence when challenged with factor. Unless specifically treated for elimination of the inhibitor, high responders rarely lose their inhibitor spontaneously. Some high responders show a brisk elevation in inhibitor titers (anamnestic response) following exposure to any Factor VIII material and are the most difficult inhibitor patients to manage. About two-thirds of these patients develop inhibitor before the age of 20 years, but inhibitor may develop at any age without regard to the number of previous exposures to Factor VIII. While severe hemophiliacs are at greatest risk for inhibitor development, cases have been reported in mild hemophiliacs. Evidence also suggests a genetic predisposition for inhibitor development.

The approach to the hemophiliac with suspected circu-
Fig 1. Coagulation cascade with associated Factor VIII deficiency and pathways of hemostasis management.

lating inhibitors who has an acute bleeding episode is to first identify and quantitate the inhibitor activity to both human and porcine Factor VIII in Bethesda units (BU). A Bethesda unit is the amount of antibody that will neutralize half the Factor VIII in 1 cc of plasma. After the antibody is quantified; high-dose human Factor VIII may be effective if the antihuman titer is less than 10 BU. For patients with antibody titers greater than 10 BU, porcine factor may be used. Unfortunately, many inhibitors cross-react with porcine factor. Control of bleeding in patients with high-titer (> 10 BUs) inhibitors is almost impossible to obtain with human Factor VIII.

In treating bleeding in the high responder, Factor VIII may be bypassed using nonactivated (PCC; Konyne-Miles Cutter) or activated prothrombin complex concentrates (APCC; Autoplex-Hyland Division, FEIBA Immuno-US Inc.). These activate Factor X directly, bypassing the intrinsic pathway, which is dependent upon the deficient Factor VIII (Fig 1). These concentrates are effective in controlling bleeding in most patients. The use of activated prothrombin concentrates is complicated by high cost and potential inappropriate activation of the coagulation system. This can result in disseminated intravascular coagulation (DIC) or thrombotic complications such as myocardial infarction when multiple doses are given. Their efficacy cannot be measured by the usual coagulation tests and the lots may vary in effectiveness. As a result, while these products generally are effective in controlling most bleeding episodes, they may not be reliable in elective surgeries or for serious major bleeds. Factor VIIA also has been demonstrated to activate Factor X directly. This agent currently is undergoing clinical trials and may be a substitute for activated prothrombin complex concentrates in the future.

In the nonhemophiliac patient with acquired inhibitor to Factor VIII, immunosuppression with cyclophosphamide or prednisone has been successful in decreasing the inhibitor titer. However, attempts to suppress inhibitor titers with immunosuppressants have not been consistently successful in hemophiliacs. If the inhibitor is successfully suppressed, contributing host factors have included: low inhibitor (<10 BU), initiation of immunosuppressive therapy at first sign of inhibitor development, and little or no exposure to Factor VIII after the inhibitor was detected. The use of intravenous gamma globulin (IVIG) has shown varied results in inhibitor suppression.
change plasmapheresis has also been applied to reduce inhibitor levels allowing for use of Factor VIII. This process may take several hours and is not practical for managing serious bleeds.\textsuperscript{11}

In the patient with a newly diagnosed inhibitor, immune tolerance regimens have been derived using porcine and human Factor VIII as a toleragen.\textsuperscript{5, 8, 10, 20, 21} These studies have shown promising results, and newly diagnosed patients should be considered for treatment. First introduced in 1974 by Brackmann, this therapy is designed to overwhelm the immune system with high doses of Factor VIII in an attempt to achieve immune tolerance in a manner analogous to treating allergies.\textsuperscript{6, 10} This initial protocol has since undergone variation and may involve high-, intermediate- or low-dose regimens. All regimens require good venous access via an indwelling catheter and patient compliance.\textsuperscript{8, 10} The best results are obtained in patients with peak levels of 100 BU, with recent inhibitor development or when therapy is initiated without recent exposure to Factor VIII. Patients will likely receive continued prophylactic doses of factor to suppress inhibitor development. Response to therapy may range from one to 12 months depending on the regimen used. In addition, the high-dose regimen involves the use of immunosuppressants and is not recommended for children.\textsuperscript{8, 10}

**Case report**

A 4-year-old male with severe classic hemophilia presented to his local emergency room after falling on his right cheek. A hematoma was present in the buccal space extending from the zygomatic area to the mandibular border. Factor VIII (Monoclate\textsuperscript{8}—Armour, Blue Bell, PA) was administered at 50 μ/kg initially, 50 μ/kg the following morning, and 25 μ/kg in the evening. Over the next four days, the hematoma decreased extraorally and increased intraorally. The patient was readmitted to the local hospital after developing intraoral bleeding through the right buccal mucosa. Upon admission, the patient’s hemoglobin was 5.1 and two units of packed red cells were administered to raise the hemoglobin to 12. After unsuccessful attempts to control the oral bleeding, the patient was transferred to the University of Nebraska Medical Center (UNMC) for care. Transfer medications included: Monoclate 1000 units q 12 hr, Claforan\textsuperscript{8} (Hoeschst-Roussel, Somerville, NJ) 500 mg IV 6 hr and epsilon aminocaproic acid (Amicar\textsuperscript{8}—Lederle, Wayne, NJ) 3 ml q 6 hr.

The patient was admitted to the Pediatric Hematology and Oncology service to manage his acute bleeding episode. The patient’s factor replacement history revealed a factor VIII and inhibitor assay were obtained.

levels were 1%. The patient was dosed with 2000 units of Monoclate and was taken to the operating room.

Surgical exploration of the area revealed a 5.5x5.5-cm coagulum covering a 3.5x4-cm dehiscence in the right buccal mucosa. A diagnosis of traumatic dissecting hematoma was made. A thrombin-soaked microfibrilar collagen pad was placed over the area for 5 min. A second 5-min application was completed followed by placing two horizontal mattress sutures (Fig 3). A mixture of cryoprecipitate and thrombin was placed over the wound site. The hemostatic patch was secured into position through incorporation into the final tie of the most posterior horizontal mattress suture. A Jobst (Jobst, Toledo, OH) head dressing was applied.

The presence of postoperative swelling and difficulty with intubation dictated that the patient remain intubated until control of bleeding was assured. Oozing was observed in the buccal mucosa and intraoral gauze packing was positioned in the buccal vestibule. A postoperative Factor VIII and inhibitor assay were obtained.
The patient’s factor level was 1% with an inhibitor level of 85 BU. Activated prothrombin complex concentrate (Autoplex®—Hyland Division—Baxter, Glendale, CA) was given at 50 μ/kg q 6h for management of hemostasis. Subsequent development of fever and bilateral consolidations in the lung suggested aspiration of secretions resulting in administration of 220 mg Clindamycin IV q 8 hr for anaerobic coverage. Coagulation was monitored with DIC screens and prothrombin fragments 1:2 prior to and 2 hr after infusion. Autoplex was decreased to 50 μ/kg q 12 hr and eventually to q 24 hr as the patient’s condition continued to improve.

Due to the recent development of inhibitor and the patient’s age, it was felt that the patient was a good candidate for immune tolerance therapy. Parental permission was obtained for initiation of therapy. A Hickman catheter® (CR Bard Inc.—Davol Inc., Cranston, RI) was placed on day nine of the hospitalization for central venous access during factor administration. By day 14, the patient’s coagulation was stabilized, intraoral healing was progressing normally, and there were no signs of continued bleeding. The patient continued with immune tolerance therapy using 2000 units (100 units/kg) of Monoclate IV daily on an outpatient basis. After six months of immune therapy and tapered dosing of Monoclate, the inhibitor was undetectable.

Discussion

Many pediatric dentists participate in and have pioneered hemophilia care as members of comprehensive care teams at hemophilia treatment centers. In addition, dentofacial trauma is a common area of consultation and treatment efforts for pediatric dentists. The interaction between the physician (hematologist) and dentist is an essential part of hemophilia management with or without the presence of trauma. The dentist’s role in hemophilia care involves maintaining accurate knowledge of the patient’s factor level, bleeding history, type of factor product used, and the number of required infusions per year. This information is beneficial in routine dental management, but equally valuable when confronted with a patient who is not responsive to traditional hemophilia management strategies. Unusual bleeding episodes in the presence of proper replacement therapy may signal the development of inhibitors. As in the present case, recent onset, limited factor exposure, and patient age and compliance allowed for successful inhibitor suppression with immune tolerance therapy. The use of immune tolerance therapy has shown favorable results in reducing antibody titers and can reduce future health care cost, morbidity, and mortality.

With a suspicious bleeding episode, assessment must be made as to baseline factor levels followed by a factor challenge and a second factor assay. An abnormal response to the challenge would dictate an inhibitor assay. If ordered stat, a factor level may be received in one to two hours. In an emergency situation, depending upon the location of the bleed, its rate of progression, and its impact on systemic function, systemic and local management may need to proceed while factor levels are pending.

Once an inhibitor is identified, combinations of local and systemic therapies will be necessary to manage bleeding episodes. The coordination of systemic therapies is handled by the physician, but local management often remains in the hands of the dentist. With the use of PCC of APCC products in the inhibitor patient, monitoring involves observation of coagulation through the use of DIC screens and prothrombin fragments. These tests provide the hematologist with information regarding fibrin activity, platelet levels, and prothrombin activity, and may signal inappropriate activation of coagulation cascade leading to potential thrombotic events.

Local measures to control hemorrhage typically take one of three forms: antifibrinolytics, topical thrombin, and hemostatic pads. Such local measures, used individually or in combination, also must be coupled with basic hemostatic principles of primary wound closure, pressure, and careful tissue management during intraoral procedures. Combination therapies support clot formation from different points along the clotting cascade increasing the likelihood of success in problematic cases (Fig 1). Clot maintenance is essential in hemophilia care, and this need is amplified when inhibitor is present. Early break-down or insufficient clot stabilization will lead to continued bleeding. These local measures allow for maturity of the clot and the initial phases of wound healing. Aggressive application of these local adjunctive measures is advocated in the inhibitor patient in order to reduce the need for additional infusions of factor products or PCC / APCC.

Antifibrinolytic agents delay fibrin dissolution by inhibiting plasminogen activator substances. While both Amicar and tranexamic acid (Cyklokapron®—Kabivitrum, Franklin, OH) can be used systemically, only tranexamic acid has been successfully applied locally at the bleeding sites. The liquid form can be used as an oral rinse or may be applied via a spray bottle or atomizer. Ten ml of a
In the case of severe oral bleeding, a circumferential head dressing (Jobst's) can be used to achieve these objectives. If the airway is threatened during intubation, intubation can be maintained until hemostasis is assured. These recommendations for the patient with inhibitor are based on the clinical objective of reducing the elective need of PCC/APCC or other alternative hematologic management techniques and avoiding additional exposure to Factor VIII products resulting in an undesired inhibitor response.

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Other techniques that may be helpful in wound management are oral or biological adhesives, periodontal dressings, or stents. Successful application is based upon the patient's ability to comply and cooperate and the doctor's ability to gain adequate access to the bleeding site. Sedation or general anesthesia may be necessary in order to achieve these objectives. If the airway is threatened during the traumatic event or by postoperative swelling, oral intubation can be maintained until hemostasis is assured. Local management of a serious oral bleed also can be assisted by immobilization to prevent dislodging the clot and initiating renewed bleeding. In the present case, immobilization and sustained pressure was achieved through application of a circumferential head dressing (Jobst's), which supported local wound management. General dental management of patients with inhibitors should include extended appointments in order to provide as much dental therapy as possible and aggressive application of preventive care. These recommendations for the patient with inhibitor are based on the clinical objective of reducing the elective need of PCC/APCC or other alternative hematologic management techniques and avoiding additional exposure to Factor VIII products resulting in an undesired inhibitor response.

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Gender affects long-term outcome of angina pectoris

Women live longer and have lower risk for this warning sign of a heart attack

Compared with men, women diagnosed with angina pectoris (pain that is a warning sign of coronary heart disease) live longer and are at lower risk for heart attack, according to a study published in this week’s Journal of the American Medical Association.

“Women with angina pectoris as an initial diagnosis... have longer survival and lower risk of subsequent myocardial infarction/cardiac death than do men of similar age in this population,” writes Anthony Orencia, MD, PhD, from the Division of Biostatistics, Mayo Clinic, Rochester, Minn., with colleagues.

The authors conducted a follow-up of all Rochester, Minnesota, residents (1,140 women and 1,501 men) first diagnosed with angina pectoris or myocardial infarction/sudden unexpected death between January 1, 1960, and December 31, 1979.

“Angina pectoris was the initial diagnosis for 529 women and 504 men,” they report. “The average age of patient diagnosed with angina pectoris was 67 years for women and 60 years for men.”

Without stratifying for age, 70.4% of women survived 10 years after their initial diagnosis, while only 59.2% of men did. “Controlling for differences in age and calendar year of diagnosis... women presenting with angina pectoris had a risk of dying that was only 0.45 times that of men,” they say.

They say that women who had myocardial infarction/sudden unexpected death had survival rates and risks of subsequent heart attacks/coronary death that were similar to men of the same age.

“Developing better strategies to diagnose and treat coronary heart disease in women must include careful study of the prodromal [warning] symptoms of women with myocardial infarction and sudden unexpected death to determine whether the symptoms differ from those of men and whether physicians have overlooked important clues to diagnosis,” they write.

The researchers continue: “There is some indication that women admitted to the hospital with a diagnosis of acute myocardial infarction or unstable angina pectoris are more likely than men to have symptoms that can be easily misinterpreted as gastrointestinal in origin.”