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Successful Use of Recombinant Factor VIIa for Emergency Fasciotomy in a Patient With Hemophilia A and High-Titer Inhibitor Unresponsive to Factor VIII Inhibitor Bypassing Activity

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We report a patient with hemophilia A and high-titer factor VIII inhibitor who developed compartment syndrome of his forearm following trauma. Emergency fasciotomy was performed. Initial hemostatic treatment with factor VIII inhibitor bypassing activity (FEIBA) was unsuccessful. Bleeding was controlled with recombinant factor VIIa. Am. J. Hematol. 79:58–60, 2005. © 2005 Wiley-Liss, Inc.

Key words: hemophilia A; inhibitor; compartment syndrome; FEIBA; factor VIIa; hemorrhage

INTRODUCTION

The treatment of bleeding episodes in hemophilia patients with inhibitors remains a challenge [1–3]. In patients with low-titer inhibitors [4], therapeutic choices may include higher doses of factor VIII or factor IX as well as inhibitor bypassing agents. In contrast, in patients with high-titer inhibitors, options are limited to inhibitor bypassing agents, namely, either activated prothrombin complex concentrates or recombinant factor VIIa [5,6].

We report a patient with severe hemophilia A with high-titer inhibitor who sustained an injury resulting in compartment syndrome requiring emergency fasciotomy. Treatment with factor VIII inhibitor bypassing agent (FEIBA) was unsuccessful in controlling bleeding. Recombinant factor VIIa was utilized to obtain hemostasis, allow further surgical repair, and facilitate complete healing of the injury and surgical wounds. This case emphasizes the importance of individualized care for patients with hemophilia and high-titer inhibitors.

CASE REPORT

An 8-year-old African-American male with severe hemophilia A and high-titer inhibitor injured his right forearm on a metal basketball goal 2 days before admission. He received 2 doses of factor VIII inhibitor bypassing activity (FEIBA) at 50 units/kg body weight at a 12-hr interval by a home health care agency following the injury. He awoke the day of admission with numbness of and inability to move the fingers of his right hand. He was evaluated in a local emergency department, and a diagnosis of compartment syndrome was made. He received an additional dose of FEIBA, 100 units/kg body weight, and was transferred to the Children's Hospital of Alabama for surgical and hematologic management.

His past medical history was pertinent for a diagnosis of severe factor VIII deficiency (baseline level less than 1%) in infancy. He was initially treated on demand with recombinant factor VIII concentrate. At age 4 years, at the time of a routine screen, he was noted to develop a factor VIII inhibitor. Over time, the titer increased to a peak of 54 Bethesda units (BU). He received inhibitor bypassing treatment with FEIBA on demand. At the

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time of presentation with compartment syndrome, his factor VIII inhibitor titer was 10 BU.

On arrival at the Childrens' Hospital, he was found to have severe swelling of his right forearm. He had poor, active movement of his fingers but brisk capillary refill of the fingers. The decision was made to perform an emergency fasciotomy. Hematologic preparation consisted of 100 units of FEIBA/kg body weight. The procedure was completed without complication except for bleeding. By intraoperative measurement using a compartment pressure monitoring device, the right forearm superficial and deep volar and dorsal compartment pressures were all markedly elevated prior to surgery and normalized following fasciotomy. During the operation, the patient required transfusion of 20 mL of packed red blood cells (PRBC)/kg to match blood loss.

In the 8 hr following surgery, blood loss continued despite continued dosing of FEIBA 100 units/kg every 12 hr (200 units/kg/day). Measured blood loss by weight of bandage was 60–90 mL/hr. The patient required an additional 20 cc PRBC/kg transfusion in the post-operative period. Due to poor hemostasis with FEIBA, the decision was made to initiate recombinant factor VIIa therapy. The patient received 90 μg/kg every 2 hr for two doses then to 90 μg/kg every 6 hr. In the 8 hr following the first dose of recombinant factor VIIa, the measured blood loss fell to a total of 10 mL. No further PRBC transfusions were necessary.

Hemostasis was maintained with recombinant factor VIIa 90 μg/kg every 6 hr. On the third hospital day, the patient underwent a further surgical procedure with irrigation and debridement of the wound and application of a split-thickness skin graft without complication. Hemostasis was controlled with recombinant factor VIIa. Replacement therapy was continued at an interval of 6–24 hr over the next 3 weeks until healing was complete.

DISCUSSION

The development of neutralizing auto-antibodies which inhibit the activity of infused coagulation factors in patients with hemophilia, an inhibitor, is one of the most feared complications of hemophilia care. Inhibitors develop in up to 20% of patients with factor VIII deficiency [7] and in 5% or less of patients with factor IX deficiency [8]. Once identified, inhibitors are classified as low-titer (inhibitor titers < 5 BU/mL) or high-titer (inhibitor titers > 5 BU) [4]. Patients with high-titer inhibitors are especially difficult to manage because they typically do not respond to infused factor VIII or IX at any dose and, with titers above 10 BU, are less responsive to immune tolerance induction [9].

Treatment options for patients with high-titer inhibitors are primarily limited to use of a factor bypassing agent, either activated prothrombin complex concentrates or recombinant factor VIIa. Multiple studies with these products document efficacy of approximately 80% with either choice [5,10–12]. However, hemostasis is not assured with any one bleeding episode with any one agent. Therefore, response to any prescribed treatment must be closely monitored for efficacy. Laboratory monitoring is typically a poor surrogate for determining clinical response in hemophiliac patients with inhibitors [13,14]. Clinical evaluation and/or measurement of blood loss are a better measure of hemostasis in this setting.

Luckily, compartment syndrome is an uncommon bleeding manifestation in hemophilia patients with inhibitors [15,16]. However, once present, the clinical challenges posed by compartment syndrome are significant and complex [17]. Should the patient undergo fasciotomy with the resultant risk of uncontrollable hemorrhage, or should therapy be directed at lowering compartment pressures with nonsurgical treatment at the potential risk of loss of function? These questions are difficult, and treatment decisions must be made on a case-by-case basis. In our patient, the decision was made to proceed with surgical fasciotomy with the assumption that FEIBA therapy would provide intraoperative and postoperative hemostasis. The patient had responded to FEIBA therapy for the prior 4 years when individual joint and soft tissue bleeds were treated on demand. However, despite high-dose FEIBA therapy, our patient continued to bleed, and the decision was made to switch to recombinant factor VIIa therapy. Following one dose of recombinant factor VIIa, the bleeding resolved and hemostasis was maintained. The patient had no complications of concurrent FEIBA and recombinant factor VIIa therapy during the transition period of a few hours.

It is unclear why our patient failed to respond to FEIBA during the surgical period, when, prior to this event and following this event, he had demonstrated a clinical response to FEIBA therapy. Perhaps the degree of bleeding, tissue damage, and trauma resulting from the compartment syndrome and fasciotomy overwhelmed the ability of FEIBA to induce and maintain a clot. In contrast, the tissue factor exposed by this series of events may have provided the foundation for successful therapy with recombinant factor VIIa.

A contrasting explanation of the patient's clinical response is that the initial FEIBA therapy provided synergy with recombinant factor VIIa and resulted in hemostasis. Under this interpretation of events, the FEIBA therapy was not a failure but instead provided the framework for successful treatment with factor VIIa. Such a synergistic effect between factor

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VIIa and prothrombin complex concentrates has been proposed [18]. The initial report by Key and associates was based on clinical observations and supported by in vitro data demonstrating an enhanced clotting time response to factor VIIa in blood samples pretreated with prothrombin complex concentrates. One explanation of such a synergistic effect is that the prothrombin complex concentrates provide increased levels of prothrombin and or factor X that serve to enhance thrombin generation by factor VIIa [19,20]. Because the half-life of factor X in humans is as long as 30 hr [21], ongoing treatment with prothrombin complex concentrates may be unnecessary to obtain this synergistic response.

Whether the child we describe obtained hemostasis via factor VIIa alone or by synergy with FEIBA is uncertain. In the initial bleeding episode, synergy is certainly possible because FEIBA therapy preceded factor VIIa therapy. However, the second surgical procedure 3 days later was performed with factor VIIa alone, arguing for the primacy of factor VIIa for hemostasis in the second surgery. Currently, the child is receiving on demand therapy with FEIBA while a trial of immune tolerance is contemplated. To this point, social issues have prevented immune tolerance therapy.

This case report highlights the importance of individual decision making and continuous monitoring of response to therapy in patients with high-titer inhibitors and hemophilia. Treatment options require ongoing modification to ensure hemostasis and optimize patient outcomes. A history of prior response to a given agent does not guarantee response with a new bleeding episode. Fasciotomy for compartment syndrome is safe in hemophilia patients with inhibitors, but only in experienced hands and with close coordination between the surgeon and hematologist.

REFERENCES

1. Kulkarni R, Aledort LM, Bertrop E, et al. Therapeutic choices for patients with hemophilia and high titer inhibitors. Am J Hematol 2001;67:240–246.
2. Tarantino M, Aledort L. On the treatment of hemorrhage in patients with hemophilia and associated inhibitors. Transfusion 2001; 41:1628.
3. Aledort LM. Unsolved problems in hemophilia. Hemophilia 1998; 4:341–345.
4. Brackmann HH, Lenk H, Scharrer G, Auerswald G, Kreuz W. German recommendations for immune tolerance therapy in type A haemophiliacs with antibodies. Haemophilia 1999;5:203–206.
5. Hilgartner MW, Knatterud GL. The use of factor eight inhibitor by-passing activity (FEIBA immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors. Blood 1983;61: 36–40.
6. Ingerslev J. Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilia patients with factor VIII and factor IX inhibitors. Semin Thromb Hemost 2000;26:425–432.
7. Scharrer I, Bray GL, Neutzling O. Incidence of inhibitors in hemophilia A patients—a review of recent studies of recombinant and plasma-derived factor VIII concentrates. Haemophilia 1999; 5:145–154.
8. Ehrenforth S, Kreuz W, Scharrer I, et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet 1992;339:594–598.
9. DiMichele DM. Immune tolerance: a synopsis of the international experience. Hemophilia 1998;4:568.
10. Lusher J, Ingersleve J, Roberts H, Hedner V. Clinical experience with recombinant factor VIIa. Blood Coagul Fibrinolysis 1998; 9:119–128.
11. Key NS, Aledort LM, Beardsley D, et al. Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (NovoSeven) in haemophiliacs with inhibitors. Thromb Haemost 1998;80:912–918.
12. Negrier C, Goudemand J, Sultan Y, et al. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. Thromb Haemost 1997;77:1113–1119.
13. Turecek PL, Varadi K, Keil B, et al. Factor VIII inhibitor-bypassing agents act by inducing thrombin generation and can be monitored by a thrombin generation assay. Pathophysiol Haemost Thromb 2003;33:16–22.
14. Ingerslev J, Christiansen K, Calatzis A, Holm M, Ebbesen LS. Management and monitoring of recombinant activated factor VII. Blood Coagul Fibrinolysis 2000;11(Suppl 1):25–29.
15. Rahimtoola ZO, van Baal SG. Two cases of acute carpal tunnel syndrome in classic haemophilia. Scand J Plast Reconstr Surg Hand Surg 2002;36:186–188.
16. Bruggers CS, Bleak S. Successful treatment of acquired factor VIII deficiency in a child using activated factor VII concentrates: case report and review of the literature. J Pediatr Hematol/Oncol 2003;25:578–580
17. Naranja RJ, Chan PS, High K, Esterhai JL, Heppenstall RB. Treatment of considerations in patients with compartment syndrome and an inherited bleeding disorder. Orthopedics 1997;20: 706–711.
18. Key NS, Christie B, Henderson N, Nelsestuen GL. Possible synergy between recombinant factor VIIa and prothrombin complex concentrate in hemophilia therapy. Thromb Haemost 2002; 88:60–65.
19. Allen GA, Monroe DM, Roberts HR, Hoffman M. The effect of factor X level on thrombin generation and the procoagulant effect of activated factor VII in a cell-based model of coagulation. Blood Coagul Fibrinolysis 2000;1(Suppl):3–7.
20. Tomokiyo K, Nakatomi Y, Araki T, et al. A novel therapeutic approach combining human plasma-derived factors VIIa and X for haemophiliacs with inhibitors: evidence of a higher thrombin generation rate in vitro and more sustained haemostatic activity in vivo than obtained with Factor VIIa alone. Vox Sang 2003; 85:290–299.
21. Girolami A, Molaro G, De Marco L. Factor X survival and therapeutic factor X levels in the abnormal factor X (factor X Friuli) coagulation disorder. Acta Haematol 1974;52:223–231.

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