Coagulopathy as a result of factor V inhibitor after exposure to bovine topical thrombin

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We describe a case of severe coagulopathy after mesenteric revascularization. Laboratory investigation results revealed the presence of plasma inhibitors of factor V believed to result from exposure to bovine thrombin used for intraoperative hemostasis. Vascular and cardiothoracic surgeons commonly use topical thrombin for surgical hemostasis, and many patients undergo multiple exposure. More patients likely have factor V inhibitors develop than has previously been realized, and this may account for some otherwise unexplained postoperative coagulation disorders. This report may alert surgeons to coagulation disturbances that can result from exposure to bovine thrombin and provide guidelines for diagnosis and management. (J Vasc Surg 2002;35:400-2.)

Postoperative coagulopathy is not unusual. Causes include supratherapeutic levels of heparin or warfarin sodium, malnutrition, sepsis, and hypothermia.[1] A less known cause of postoperative coagulopathy is the development of inhibitors to factor V, first described by Ferguson, Johnson, and Howell[2] in 1958. More recently, Zehnder and Leung[3] showed the development of antibodies to factor V in a patient who underwent repeated exposures to topical bovine thrombin. The authors identified the presence of factor V in commercial bovine thrombin and suggested that antibodies to bovine factor V interacted with human factor V and were likely responsible for the patient's postoperative coagulopathy.

CASE REPORT

A 75-year-old woman, who had undergone multiple lower extremity revascularization procedures in the past, underwent mesenteric revascularization with a bifurcated polytetrafluoroethylene graft from the supraceliac aorta. Approximately 5000 units of bovine thrombin was used as a topical hemostatic agent in the form of soaked gelatin sponges.

The patient's postoperative course was initially uncomplicated. The daily coagulation study results routinely obtained in our intensive care unit revealed marked elevation in the patient's prothrombin time (PT) and activated partial thromboplastin time (aPTT) on the 9th postoperative day, which peaked on postoperative day 11 (aPTT, 102 seconds; PT, 46.9 seconds; international normalized ratio, 13.2; Fig). The fibrinogen level was 363 mg/dL (normal level, 193 to 383 mg/dL). The abnormal coagulation parameters did not improve with the administration of vitamin K or fresh frozen plasma (FFP). The patient did not undergo heparin or warfarin therapy during the postoperative period, and there was no clinical or serologic evidence of hepatic dysfunction.

The thrombin time with human thrombin was 22.5 seconds (upper limits of normal, 19.3 seconds). Incubation of a 1:1 mixture of normal and patient plasma at 37°C for 1 hour prolonged both the aPTT and PT of the normal plasma, indicating the presence of a circulating inhibitor in the patient's plasma. The fact that both the PT and aPTT were prolonged suggested that the inhibitor was against one of the coagulation factors of the common pathway (factor V, X, or II). Factor II activity was 78% (normal activity, 70% to 130%), factor X activity was 35% (normal activity, 60% to 130%), but the factor V activity was less than 2% (normal activity, 60% to 130%). The moderate decrease in factor X activity was thought to reflect nonspecific interference of a factor V inhibitor with the endpoint of the one stage coagulation factor assays. These coagulation study results revealed that the patient had circulating inhibitors of human factor V stimulated most probably by the patient's prior exposure to bovine thrombin. There was little cross reactivity of the antibody with human thrombin as evidenced by the mild elevation of the thrombin time with human thrombin in the assay. There was, however, marked cross reactivity with human factor V that resulted in a profound inhibition of factor V activity.

The patient did not exhibit any clinical signs of bleeding, and at the time of discharge on postoperative day 20, the aPTT decreased to 53 seconds and the PT decreased to 24.1 seconds (Fig). At the 5-month follow-up examination, the patient was doing well with a PT of 12.0 seconds, an international normalized ratio of 1.1, a PTT of 29 seconds, and a factor V level of 94%.

DISCUSSION

Topical thrombin preparations are widely used in the form of sprays, paste, fibrin glue, or other dry procoagulant materials that have been soaked in the topical thrombin. Most of these preparations in use in the United States are prepared from bovine thrombin.[4] It is now recognized that patients exposed to any of these preparations may have antibodies develop to bovine thrombin, factor V, or any other proteins that may be found in the preparations. However, the precise clinical effects of this immunogenic response are unclear.

Patients with repeat exposures to bovine thrombin may have antibodies develop to the coagulation proteins in these compounds.[4] Flaherty, Henderson, and Wener[5]

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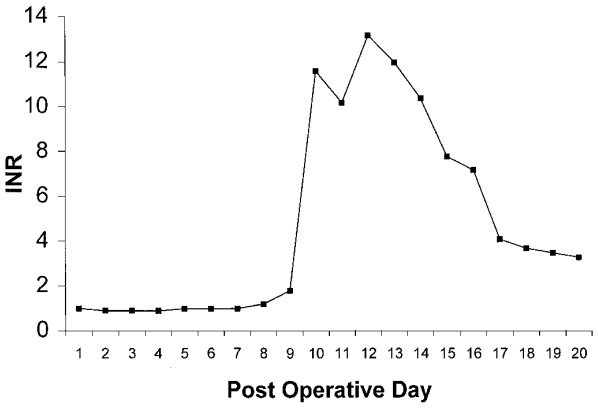
reported four patients with prolonged thrombin times after surgical procedures during which topical thrombin was used.[5] Substitution of human thrombin (for the bovine thrombin normally used in performing the thrombin times) normalized the clotting times, which indicated that the inhibitor activity was directed against bovine thrombin. Other coagulation parameters were normal in these patients, and there were no bleeding complications. Bleeding complications associated with antibodies to bovine thrombin alone have not been described and are rarely detected as thrombin times are now rarely performed.

Zehnder and Leung[3] reported a patient whose condition became severely coagulopathic and who had bleeding complications after reoperative cardiac surgery with reexposure to topical bovine thrombin. This patient had marked prolongation of the PT and PTT and the thrombin time that did not respond to administration of vitamin K and FFP therapy. Study results of their patient revealed the presence of an inhibitor to human factor V in addition to the inhibitor of bovine thrombin. These investigators were subsequently able to identify bovine factor V within the thrombin preparations studied. The bovine factor V was believed to stimulate the development of antibodies that cross-reacted with human factor V and produced the coagulopathy in their patient.

Subsequently, a number of cases of factor V inhibitors have been described after exposure to bovine thrombin.[6-8] Banninger et al[6] noted the development of thrombin inhibitors after primary exposure to bovine thrombin in 11 of 24 patients after cardiac surgery and in two of 10 patients after neurosurgical procedures. All 13 patients with thrombin inhibitor also had significantly reduced factor V activity levels (10% to 60% of normal levels). These authors also noted a relationship between the amount of fibrin glue (bovine thrombin) used and the likelihood of sensitization.

In an attempt to clarify the prevalence of these antibodies, Ortel et al[4] performed a prospective analysis of 151 patients who underwent cardiac surgical procedures. They observed a 33% incidence rate of antibodies to two or more bovine antigens in patients with likely prior exposure to topical thrombin. In addition, in the postoperative period, more than 95% of the patients had a seropositive response to bovine coagulation proteins develop, and 51% manifested elevated antibody levels to the corresponding human coagulation proteins after bovine thrombin exposure. The authors also found that patients with established antibody levels to multiple bovine proteins before their surgical procedure were more likely to have an adverse clinical outcome after surgery.

The development of antibodies to bovine thrombin after exposure to these products is predictable and perhaps little more than a laboratory curiosity because thrombin times are rarely used today. In contrast, the development of antibodies that cross react with human factor V will result in prolongation of both the PT and the aPTT as seen in the case presented here. It appears that in some



Patient international normalized ratio *(INR)* after surgery. Patient was undergoing no heparin therapy in any form and no warfarin sodium therapy and had normal hepatic function.

cases this finding may not simply represent a confounding laboratory value but may be associated with a significant clinical risk of hemorrhage. Patients who undergo vascular surgical procedures are at higher risk for these events because many have had prior vascular or cardiac procedures in which bovine thrombin may have been used. Appropriate mixing study and factor assay results will identify the presence of clinically significant factor V inhibitors. The delay in the rise in coagulation times (9 days in our patient) is caused by the time required to develop an immune response and is consistent with other reports.[3,6] In a patient with a factor V inhibitor, invasive procedures should be avoided because of the risk of hemorrhage, especially when factor V activity is less than 10%, as in our patient. The titer of factor V inhibitors usually falls rapidly during weeks to months in the absence of further exposure to bovine thrombin with normalization of the PT and aPTT.[6] Although the presence of lupus-anticoagulant activity has been identified in some patients with thromboembolic complications associated with the development of anti–factor V antibodies,[9] dramatic elevations of coagulation times cannot be attributed to lupus anticoagulant alone. We recommend checking for evidence of antiphospholipid antibodies in the event of thrombotic complications.

Patients with factor V inhibitors, who have bleeding complications and whose conditions fail to respond to FFP administration, may undergo treatment with platelet transfusions, intravenous gammaglobulins, and plasmapheresis to achieve hemostasis.[3] Unfortunately, controlled studies are lacking and the best methods of treatment remain unclear.

Whether the incidence rate of factor V inhibitors varies with the manufacturer of thrombin or with the delivery technique is unclear at this time. Alternative commercial hemostatic agents that use human thrombin and human fibrin as fibrin glue are available. Although these products would avoid the use of bovine thrombin, some contain

bovine aprotinin as a fibrinolysis inhibitor and are contraindicated in individuals known to be hypersensitive to bovine protein.

Although the magnitude of risk associated with the presence of factor V inhibitors has been uncertain, it is probably best that anticoagulation therapy be avoided because factor V inhibition interferes with the PT and aPTT assays used to monitor both warfarin sodium and heparin anticoagulation therapy. When anticoagulation therapy is required (eg, in patients with prosthetic heart cardiac valves), Zumberg et al[8] have suggested withholding treatment until there is a diminution in the effect of the acquired inhibitors.

Vascular surgeons should be alerted to the possibility of factor V inhibitors in their patients as a possible cause of postoperative coagulopathies. Aberrations in the PT or aPTT produced by factor V inhibitors may occur more often than has been previously recognized. In addition, secondary exposure in patients with unrecognized, preestablished antibody levels has been associated with an increased risk of surgical complication.[4] Future prospective study in patients for vascular surgery may be warranted to establish the prevalence of significant factor V inhibitors in patients who undergo noncardiac vascular surgical procedures. The reconsideration of the routine use of these products in our surgical procedures may also be prudent.

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