The Clinical and Laboratory Response to Recombinant Factor VIIa in Trauma and Surgical Patients with Acquired Coagulopathy

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OBJECTIVE: In bleeding patients who are coagulopathic, the clinical response to administration of recombinant factor VIIa (rFVIIa) relates to the changes in prothrombin time (PT).

DESIGN: Retrospective review of all surgical and trauma patients who were coagulopathic and received factor VIIa at the authors' institution over the past 27 months.

SETTING: Academic tertiary referral facility and level I trauma center.

PARTICIPANTS: Eighteen patients met inclusion criteria, 10 trauma and 8 surgical. Mean age 50 years (range, 17-84).

RESULTS: Overall mortality was 39%. All but 1 patient (17/18) had resolution of coagulopathic bleeding with rFVIIa, and all clinical responders (n = 17) (defined as clinical cessation of bleeding within 24 hours determined by either attending surgeon or chief resident progress note) had a decrease in PT to normal range. In contrast, the single clinical nonresponder had an insignificant PT decrease (19 to 18 seconds). Prothrombin time decreased from 20 ± 4 seconds to 12 ± 2 seconds, $p < 0.05$ (n = 17). International Normalized Ratio (INR) decreased from 1.59 to 0.86, $p < 0.05$ (n = 17). Fibrinogen before administration was 299.73 (range, 105-564) (n = 15). pH before administration was 7.25 (±0.18) (n = 10). Patient temperature was 98.64 (±2.06). Effect in partial thromboplastin time (PTT) was inconsistent (50 ± 49 seconds to 34 ± 6 seconds, $p > 0.05$). Transfusion requirements for red blood cells (14 to 3 units) and plasma (12 to 3 units) were significantly reduced after rFVIIa. There were no significant differences in percentage PT decrease between dose ≥100 mcg/kg vs <100 mcg/kg, surgical vs trauma patients, survivors vs nonsurvivors, and those with pretreatment platelet count ≥100 K vs <100 K.

CONCLUSIONS: The administration of rFVIIa caused a decrease in the PT in nearly all patients. There were an insufficient number of patients to support the use of PT as a clinical predictor of response; however, the data are suggestive of such utility. If the PT does not correct, then it is likely that there is a deficiency of other factors of the coagulation cascade. (Curr Surg 63:246-251. © 2006 by the Association of Program Directors in Surgery.)

KEYWORDS: coagulopathy, hemorrhage, trauma, recombinant factor VIIa, thromboembolism

INTRODUCTION

The "lethal triad" of hypothermia, acidosis, and coagulopathy poses a significant problem in the care of critically ill surgical patients. The sequential and additive effect of these 3 conditions perpetuates a vicious cycle associated with increased mortality.[1] Once this downward spiral has initiated, it is difficult, if not impossible, to interrupt. Standard transfusion therapy is often inadequate to deal with the challenges of the progression of acquired coagulopathy.

In 1990, recombinant factor VIIa (rFVIIa, Novoseven; Novo Nordisk, Bagsvaerd, Denmark) was introduced for the treatment of hemophilia. The use of rFVIIa for the correction of acquired coagulopathy and treatment of traumatic hemorrhage was first reported in 1999.[2] Since then, the off-label use of rFVIIa for the treatment of coagulopathic hemorrhage secondary to major surgery and trauma has been the subject of limited retrospective series.[3-5] The agent has also shown promise in experimental animal models of severe traumatic hemorrhage.[6-10] A recent multicenter study of rFVIIa demonstrated decreased blood product usage in blunt-trauma patients with traumatic hemorrhage.[11]

The above studies of the efficacy of rFVIIa in treating coagu-

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lopathy have primarily examined surrogate endpoints such as blood product usage and the response of laboratory tests of coagulation to drug administration. There are few published data regarding the clinical response to the drug. Clinically relevant endpoints are the cessation of bleeding, restoration of hemodynamic stability, and survival. There is little discussion in the literature relating the laboratory response to the clinical response. The relationship of laboratory response to clinical outcomes has not been addressed. The elucidation of these relationships will allow for further refinement of the use of this expensive but promising agent in various patient populations.

The data were retrospectively analyzed on the use of rFVIIa in trauma and surgical patients with acquired coagulopathy at the authors' institution to examine the relationship between the clinical and laboratory responses to the drug. It was hypothesized that the laboratory response to a dose of rFVIIa in a bleeding, coagulopathic patient could be used to predict a clinical response.

METHODS

After approval from the Brooke Army Medical Center IRB, all patients who had received rFVIIa at this institution between January 1, 2002 and March 31, 2005 were identified. A total of 34 charts were reviewed. Patients who had received the drug for intracranial hemorrhage (n = 3), known hemophiliacs (n = 1), patients with pharmacologic anticoagulation (warfarin, heparin) at the time of rFVIIa administration (n = 3), those without coagulopathy (n = 2), burn patients (n = 1), and patients whose charts had incomplete data (n = 8) were excluded. The result was a population of 18 patients. Demographic data, laboratory results, blood product usage, and physician's notes were examined.

A guideline was used for the administration of rFVIIa to patients without a known inherited coagulopathy. The medication can be given as an adjunct to resuscitation at the request of an attending physician to a patient that has continued coagulopathy with clinical evidence of hemorrhage despite massive resuscitation as defined by greater than 10 units of red blood cells, 8 units of fresh frozen plasma, and an apheresis pack of platelets. In this series, there was 1 patient, who because of religious constraints, declined all blood products. Recombinant FVIIa was given on a "compassionate use" basis where no blood products were administered. A clinical response was defined as occurring in those patients who were deemed by the chief surgical resident or attending surgeon to be without evidence of continued hemorrhage and to be hemodynamically stable within 24 hours of their dose of rFVIIa. Prothrombin Time and partial thromboplastin time (PTT) (normal range, 12.0-14.3 and 24.2-37.2 seconds, respectively) were measured by the hospital laboratory using standard assays.

Data from patient records were compiled in a database (Excel; Microsoft, Redmond, WA). Statistical analysis was carried out using SigmaStat Statistical Software version 2.0 (SPSS, Inc, Chicago, IL). Means were compared using the Student *t*-test for normally distributed data and the Mann–Whitney rank sum test for non-normally distributed data. Statistical significance was defined as $p < 0.05$ throughout.

TABLE 1. Laboratory Response (mean ± SD) to rFVIIa in Patients with Acquired Coagulopathy

	PT (seconds)	PTT (seconds)
Pre-rFVIIa	20 ± 4	50 ± 49
Post-rFVIIa	12 ± 2*	34 ± 6
Absolute change	8 ± 4	16 ± 49
Percent change	38	10

*$p < 0.05$ compared with pre-rFVIIa.

RESULTS

A total of 18 patients met inclusion criteria and were included in the analysis. Their mean age was 50 years (range, 17-80). There were 10 trauma patients with a mean Injury Severity Score of 29 ± 10. Eight trauma patients had sustained blunt trauma, and 2 had penetrating trauma. Of particular note, 1 blunt trauma patient was a Jehova's Witness who refused all blood transfusion. He had sustained a severe pelvic fracture with arterial hemorrhage. Recombinant factor VIIa was administered after angiography with arterial embolization was performed. The surgical patients either had hemodynamically significant gastrointestinal bleeding requiring surgery or had undergone a major surgical procedure. Procedures performed included pancreaticoduodenectomy with portal vein reconstruction, abdominal aortic aneurism repair, abdominoperineal resection, and retroperitoneal placement of a central venous access device.

The mean dose of rFVIIa was 100 ± 20 mcg/kg. The overall mortality was 7/18 (39%). No complications were attributable to the administration of rFVIIa. All but 1 patient in this series was determined to be free of continued hemorrhage and became hemodynamically stable after the administration of rFVIIa. The overall mortality of the responders was 35%. As a note of interest, the Jehova's Witness patient was a responder and ultimately a survivor. The single nonresponder was a 74-year-old woman who had undergone a significant small bowel resection for infarcted bowel. This patient did not survive. Because of the existence in this series of only a single nonresponder, direct comparisons could not be performed between those patients who responded clinically and those that did not.

All patients were coagulopathic, exhibiting abnormal PT at the time of administration of rFVIIa. Pre- and post-dose laboratory coagulation parameters are presented in Table 1. The PT decreased an average of 38% with the administration of rFVIIa ($p < 0.05$), and all but the 1 patient who failed to respond clinically experienced a decrease into the normal range as defined by the authors' institution (12-14.3 seconds). The nonresponder experienced only a marginal decrease in the PT (19-18 seconds) and remained above the normal range. The effect of rFVIIa on PTT was more variable, and 3 patients experienced