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Case Reports

Dose Titration of Recombinant Factor VIIa Using Thromboelastograph Monitoring in a Child With Hemophilia and High Titer Inhibitors to Factor VIII: A Case Report and Brief Review

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Abstract: The administration of recombinant factor VIIa (rFVIIa) is complicated by a wide inter-subject variation in response, a short half-life, evolving indications for use, and the absence of a test that has been shown to correlate with clinical effect. This report describes a method used to titrate rFVIIa to thromboelastography (TEG) parameters in a difficult to manage hemophilic patient with high titer inhibition to factor VIII. The current concepts of monitoring rFVIIa administration in hemophiliacs and uncontrolled hemorrhage in cardiac surgery are briefly reviewed. **Keywords:** recombinant factor VIIa, thromboelastography, hemophilia A. *JECT. 2006;38:254–259*

Recombinant factor VIIa (rFVIIa; NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) is widely accepted as a treatment for hemophilia complicated by inhibitors, specifically inhibitors to factors VIII or IX (1). While this is the only indication approved by the US Food and Drug Administration, novel uses continue to emerge in the literature, including uncontrolled hemorrhage in surgery and trauma, platelet-related bleeding disorders, intracranial hemorrhage, liver disease, vitamin K antagonist anticoagulation, and factor VII disorders and deficiencies (2,3). Clinical evidence for these indications is rapidly accumulating but is hampered by the general absence of large-scale, randomized trials. Furthermore, controversy exists on the exact mechanisms by which rFVIIa enhances thrombin generation, and very little is known about which hemostatic components are most important for the different indications.

While clinical efficacy has been difficult to establish for off-label uses, rFVIIa is a good option for hemophiliacs (both A and B) with inhibitors. By inducing hemostasis through the activation of factor X, therapeutic levels of rFVIIa can avoid the need for either circulating factor VIII or factor IX, thus effectively "bypassing" the inhibited factor (4). The current rFVIIa preparation has also shown a good safety record for this indication (16 serious events/1957 treatments) with a low occurrence of thrombotic events (<1:11,300 in 170,000 doses) (4,5). However, optimal dosing regimens have not been identified (6). In part, this is because of a wide inter-subject variation in response (7). Furthermore, rFVIIa has the shortest half-life ($T_{1/2}$) of any bypassing agent, yet it is approved for only bolus infusions, not continuous infusion. Complicating the matter further, there is evidence suggesting that the $T_{1/2}$ is even shorter in children (1.32 vs. 2.72 hours) (8).

With the challenges of accurately identifying patients who will benefit from rFVIIa therapy and which dosing

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schedule will be safe and effective, a relevant monitoring system that correlates with clinical effect would be indispensable. Unfortunately, an accurate and precise test, which has been shown to correlate with clinical outcome, has yet to be identified. In the absence of such a test, rFVIIa is typically administered empirically, without considering the indication for use, individual patient response, or differential $T_{1/2}$. However, with empiric dosing, there exists a finite failure rate (i.e., continued bleeding) and a finite risk (i.e., thrombotic events) (9).

In cardiac surgery, our center has developed guidelines for the use of rFVIIa for uncontrolled hemorrhage after cardiotomy, with promising early results (10,11). The system uses thromboelastography (TEG; Haemoscope, Niles, IL), a potential improvement over traditional plasma-based systems that use the first evidence of clot formation as their endpoint. Because of this limitation, plasma based systems fail to show the effects of platelets on thrombin generation and fibrin structure, and information about fibrin formation and dissolution is lost. Others have reported on TEG use for rFVIIa administration in hemophilia with inhibitors (12,13). Their results contradict our results in cardiac surgery. Specifically, these groups have identified improvement in TEG parameters with rFVIIa administration lasting 6 hours, postulating a correlation with improved hemostasis (12,13). Our experience in cardiac surgery indicated the opposite—TEG parameters need to be normalized before administration of rFVIIa to achieve a hemostatic effect. The primary difference is that rFVIIa effect was being monitored for two quite disparate indications. In hemophilia with inhibitors, rFVIIa is given to bypass the need for FVIII, whereas in cardiac surgery, rFVIIa is given to provide a burst of thrombin generation at the site of bleeding (12–14).

This report describes a method used to titrate rFVIIa dosing in a patient with severe hemophilia A and high titer inhibitors to FVIII. The report is used to highlight the effects of rFVIIa administration on TEG parameters when used for an indication other than uncontrolled hemorrhage in cardiac surgery.

DESCRIPTION

A 12-year-old, 43-kg boy with severe hemophilia A and high titer inhibitors to FVIII was admitted to the Pediatric Intensive Care Unit with gross hematuria complicated by clot passage and severe loin pain. The child had a history of recurrent severe renal bleeds, degenerative destruction of multiple joints, and osteopenia. After the child had received 27 doses of rFVIIa (90 μg/kg every 6 hours [Q6]) without resolution of his symptoms, Pharmacy Services consulted the Department of Perfusion Services. After discussing the past experience with TEG and rFVIIa administration in cardiac surgery with the hematologist and the pharmacist, a decision was made to set up a dose titration of rFVIIa using the TEG to determine the effect of different concentrations of rFVIIa (rFVIIa:C) on several TEG parameters.

METHODS

A total of six TEG channels were used (Table 1). All were drawn from citrated blood collection tubes and activated with kaolin vials. Baseline 1 was drawn before any rFVIIa was given, and Baseline 2 was drawn 1 hour after the 27th dose of rFVIIa (90 μg/kg Q6 hours). The same blood sample used for Baseline 2 was used for Channels 1, 2, 3, and 4, with additional rFVIIa added to achieve the equivalent of one (Channel 1), two (Channel 2), four (Channel 3) and eight (Channel 4) additional 90 μg/kg doses, assuming a volume of distribution of 105% and a circulating blood volume of 75 mL/kg. The last two assumptions are based on commonly published values and the product insert. To uniformly account for hemodilution, identical volumes of rFVIIa were added to each channel, with 0.9% normal saline (NS) substituted for Baseline 1 and Baseline 2 (Table 2). The most limited reagent was rFVIIa, because only a small aliquot of leftover was available. Opening a new vial for this purpose represented a significant expense. To achieve the desired concentrations, avoid excessive dilution of the samples, and use the limited amount of rFVIIa available, the original aliquot was diluted to 184 μg/mL for a total volume of 400 μL. After delivering 20 μL of 184 μg/mL rFVIIa to Channel 4, the aliquot was diluted with 380 μL of 0.9% NS to achieve an rFVIIa:C of 92 μg/mL rFVIIa and a total volume of 760 μL. Twenty microliters of 92 μg/mL rFVIIa was delivered to Channel 3, and the aliquot was further diluted with 740 μL of 0.9% NS to achieve an rFVIIa:C of 46 μg/mL and total volume of 1480 μL. Twenty microliters of 46 μg/mL rFVIIa was delivered to Channel 2, and the aliquot was further diluted with 1460 μL of 0.9% NS to achieve an rFVIIa:C of 23 μg/mL and total volume of 2920 μL. Twenty microliters of 23 μg/mL rFVIIa was delivered to Channel 1.

Table 1. Recombinant FVIIa doses and resulting circulating concentration.

	Baseline 1	Baseline 2	Channel 1	Channel 2	Channel 3	Channel 4
Dose	No rFVIIa	90 μg/kg Q6 (X)	X + 90 μg/kg	X + 180 μg/kg	X + 360 μg/kg	X + 720 μg/kg
rFVIIa:C	0.00 μg/mL	Y μg/mL	Y + 1.28 μg/mL	Y + 2.56 μg/mL	Y + 5.12 μg/mL	Y + 10.24 μg/mL

X, starting dose; Y, starting concentration.

Table 2. Reagents added to the individual thromboelastograph channels.

	Baseline 1	Baseline 2	Channel 1	Channel 2	Channel 3	Channel 4
Blood	320 μL	320 μL	320 μL	320 μL	320 μL	320 μL
0.2 mol/L $CaCl_2$	20 μL	20 μL	20 μL	20 μL	20 μL	20 μL
0.9% NS	20 μL	20 μL	0 μL	0 μL	0 μL	0 μL
rFVIIa:V	0 μL	0 μL	20 μL	20 μL	20 μL	20 μL
rFVIIa:C	—	—	23 μg/mL	46 μg/mL	92 μg/mL	184 μg/mL
rFVIIa	—	—	0.46 μg	0.92 μg	1.84 μg	3.69 μg

RESULTS

The TEG results are summarized on Figure 1. After 65.9 minutes, no clot had been detected by the TEG for the Baseline 1 sample (no rFVIIa; R-time = 65.9 minutes, K-time = no endpoint [NEP], α angle = NEP; maximum amplitude = NEP, coagulation index = NEP, 30 minutes lysis = NEP). One hour after the 27th 90 μg/kg Q6 dose of rFVIIa had been administered (Baseline 2), clot was detected, but nearly every TEG parameter was outside of normal range (R-time = 34.6 minutes, K-time = 9.8 minutes, α angle = 31.8°, maximum amplitude = 76.9 mm, coagulation index = –22.2, 30 minutes lysis = 0.0%). After an additional equivalent dose was added to Baseline 2, R-time returned to normal range, improving the overall coagulation index (Channel 1: R-time = 6.9 minutes, K-time = 11.8 minutes, α angle = 30.2°, maximum amplitude = 79.8 mm, coagulation index = –4.7, 30 minutes lysis = 1.0%). With the addition of the equivalent of a double dose of rFVIIa to Baseline 2 (Channel 2), K-time and α angle were also normalized (R-time = 9.0 minutes, K-time = 2.2 minutes, α angle = 60.7°, maximum amplitude = 67.5 mm, coagulation index = –1.6, 30 minutes lysis = 1.0%). The addition of the equivalent of a four-fold increase (Channel 3) and an eight-fold increase (Channel 4) in rFVIIa:C resulted in little further improvement of TEG parameters (Channel 3: R-time = 8.7 minutes, K-time = 2.3 minutes, α angle = 61.1°, maximum amplitude = 67.7 mm, coagulation index = -1.4, 30 minutes lysis = 1.3%; Channel 4: R-time = 6.8 minutes, K-time = 1.8 minutes, α angle = 66.1°, maximum amplitude = 70.5 mm, coagulation index = 0.8, 30 minutes lysis = 0.7%).

COMMENT

The results provided by the TEG rFVIIa titration suggested that this child required a doubling of the circulating rFVIIa concentration (Channel 1) to improve the measured parameters and to potentially achieve adequate hemostasis. The addition of the equivalent of a double dose (Channel 2) would likely result in further improvement. Little benefit would be achieved with even larger increases in rFVIIa:C (Channels 3 and 4), and it could not be determined if the patient would be more susceptible to a hypercoagulable state or if the TEG was not sensitive to this potential. Therefore, a recommendation was made to either double the dose, or given the short $T_{1/2}$ of rFVIIa, to increase the frequency of dosing. The orders were rewritten for 90 μg/kg Q2 instead of 90 μg/kg Q6. Almost immediately, visible bleeding discontinued, with a gradual

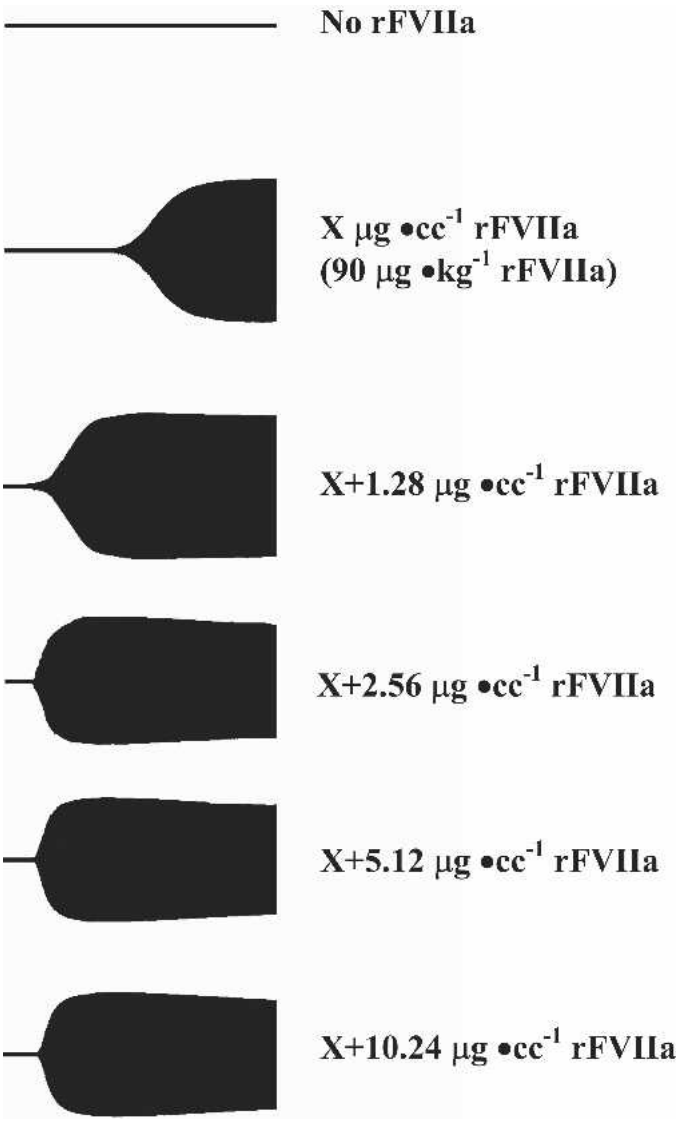

Figure 1. Thromboelastographic profiles with different rFVIIa concentrations.

resolution of the hematuria. The child was discharged 3 days later in satisfactory condition.

Recombinant factor VIIa is not the only therapeutic option for inhibitor complicated hemophilia, but the other available options such as high-dose factor VIII, porcine factor VIII, prothrombin complex concentrates (PCCs), and activated prothrombin complex concentrates (aPCCs) are also plagued by dosing and monitoring challenges (7). The disadvantage of the shorter $T_{1/2}$ of rFVIIa may be off set by significant advantages over the alternatives. Recombinant FVIIa is effective regardless of the inhibitor titer (unlike FVIII preparations), does not produce an amnestic response (unlike FVIII, PCCs, and aPCCs), and does not have the strong association with disseminated intravascular coagulation, deep vein thrombosis, pulmonary embolism, and myocardial infarction (unlike PCCs and aPCCs) (7).

The need for an adequate monitoring system for rFVIIa administration cannot be denied. In hemophiliacs with inhibitors, it is difficult to predict which dose will be effective. In a prospective, double-blind, randomized trial study of 29 patients, a dose as low as 35 μg/kg controlled bleeding in a proportion of the population, but doses of 90 μg/kg or higher were required in others (15). In addition, the effective dose may be altered by the timing of the intervention, with significant benefit being reported with early intervention vs. delayed intervention, but the bulk of the data guiding empiric dosing originates from studies of delayed intervention (16). Furthermore, inter-subject variation in $T_{1/2}$ exists, especially between adults and children (8). In the absence of a monitoring system capable of identifying which patients could benefit from rFVIIa, which dose should be used, and how often the dose should be administered, the drug is administered empirically even for the approved indication. Such administration carries a finite potential for failing to establish effective hemostasis, which has been reported in up to 40% of the patient population (7). Empiric dosing may also increases the risk for thrombotic complications and can result in significant waste (17). With a very expensive drug such as rFVIIa, fiscal responsibility could mandate tailoring the dose to the need.

The monitoring challenges posed by rFVIIa administration are compounded when it is used outside of the approved indication. Multiple off-label uses have been reported, encompassing bleeding episodes ranging from surgery, trauma, platelet disorders, and anticoagulation therapy. The body of evidence for efficacy and safety is expanding rapidly, but is still primarily limited to small, non-randomized trials (2,7). Issues related to monitoring rFVIIa effect(s) have barely been addressed for these indications. Gabriel et al. (13) had shown that the TEG profile of hemophiliac patients improved with administration of rFVIIa, an effect that persisted for 6 hours after administration. On the other hand, our group has shown that, in uncontrolled hemorrhage in cardiac surgery, rFVIIa had no effect on TEG parameters (10,11). The discrepancy between the two results was of concern to our group, especially when the child in this report was presented. A careful examination of the proposed mechanisms of action of rFVIIa, however, may account for the differential monitoring results.

Recombinant FVIIa has no direct effect on the formation of a hemostatic plug; instead, it enhances the generation of thrombin at the site of injury (18). Early theories centered on a tissue factor (TF)–dependent pathway by which rFVIIa combines with TF, up-regulating the activation of factors X and IX, thus accelerating the flow through the coagulation cascade (19). The action thus eliminates the need for the factor VIII pathway. Because of the relatively high plasma rFVIIa:C required, however, a TF-dependent mechanism is probably not the only mechanism responsible for the establishment of hemostasis (5). Indeed, a partially TF-independent generation of thrombin, on the activated platelets at the site of injury, seems to better suit the kinetics of the therapeutic effect (20). Indeed, Butenas et al. (21) has shown that the TF-dependent pathway is essential and that the platelets that accumulate (five times native blood levels) enhance the rFVIIa thrombin formation at the site of vascular injury through the TF-independent pathway. The amount of thrombin generated through the TF-dependent (extrinsic pathway) is likely small, but is sufficient to release factor VIII from von Willebrand factor (vWF) and activate factors V and XI. More importantly, the small amount of original thrombin can activate platelets, providing a surface for the prothrombinase complex and consolidation of the coagulation cascade.

It is equally plausible that additional rFVIIa mechanisms may contribute to the formation of a more stable hemostatic plug. There may be an enhancement in the activation of thrombin activatable fibrinolysis inhibitor, improved physical properties of the fibrin clot, enhanced platelet activation, and enhanced factor XII activation (18,22–24).

With such a complex array of interactions at work, it should not be surprising that traditional plasma-based systems have failed to correlate with clinical effects. An ideal coagulation assay would reflect the interaction between all blood components, because levels of TF, factor X, and platelets are all essential for rFVIIa to enhance thrombin generation, with white blood cells and fibrinogen also essential for the final establishment of effective hemostasis (12). The implications of using TF as an activator for TEG analysis of rFVIIa are unknown, so kaolin-based tests were used in this case. There are two additional, but related, requirements of a monitoring system for rFVIIa administration. First, it should be able to predict which in-

dividuals will not respond to recommended dosing schedules, and second, it should identify a variable that correlates with both hemostasis and thrombosis (9). To accomplish these goals, the method should be relatively easy to perform, relevant to clinical outcome(s), affordable, readily available, highly accurate and precise, require small amounts of blood, and contain a rapid turnaround time (9). Traditional plasma assays have failed to accommodate these requirements. For prothrombin time (PT), maximal shortening occurs at a rFVIIa:C of 5 U/mL, whereas standard doses reach a peak effect at concentrations 10 times this amount (25). In fact, even direct measurement of rFVIIa:C has failed to correlate with clinical outcome (26).

The TEG has shown promise as a monitoring tool for rFVIIa administration (11–13). As shown by this report and others, however, the interpretation of the results and target effect may be dependent on the indication for administration, and the key components of the mechanism(s) of rFVIIa should be considered (10–13). For example, in bleeding caused by hemophilia with inhibitors, the goal is to bypass the need for the inhibited agent (factor VIII or IX). Under these circumstances, a TEG performed before administration of rFVIIa would be expected to be very poor, because FVIII is essentially missing, and no endpoint (prolonged or infinite r-time) would be expected (12,13). When rFVIIa is administered in therapeutic doses, the need for FVIII should be effectively eliminated, and a normalization of TEG parameters would be expected (12,13).

A completely different use of rFVIIa is for uncontrolled hemorrhage in cardiac surgery. Under these circumstances, FVIII would be expected to be present in concentrations relative to the concentration of other coagulation elements. If a poor TEG is obtained before rFVIIa, this would not reflect the absence of FVIII but the absence of several components of coagulation. If the key elements for rFVIIa action, especially platelets and factor X, are low, one would expect a poor TEG and the administration of rFVIIa to be ineffective in establishing hemostasis or normalizing the TEG parameters. In part, this is one reason our group and others have advocated the correction of any coagulation deficit before the administration of rFVIIa, and thus a normalized TEG should be required (10,11,14). The other reasons for correcting any coagulation abnormalities under these circumstances are more obvious and compelling. First, all traditional means for controlling hemorrhage (i.e., transfusions) should be exhausted before the administration of an off-label drug. Second, rFVIIa is an exceedingly expensive therapeutic option, and the appropriate use should be fiscally mandated.

To date, no adequate coagulation test for the use of rFVIIa has been identified in a sufficiently large patient sample. Such a test would be able to accurately identify which patients will benefit from rFVIIa administration, it would correlate to clinical outcome, and it would be able to preempt adverse events related to inappropriate use/overdose. Whereas the TEG has shown promise in filling this void, larger trials are needed to establish its effectiveness. When the TEG is used, it seems to be critical to consider the mechanisms of action in concert with the indication for administration before interpretation.

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