The Utility of Thromboelastography for Guiding Recombinant Activated Factor VII Therapy for Refractory Hemorrhage After Cardiac Surgery

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Objective: **Recombinant activated factor VII (rFVIIa) is being increasingly used in cardiac surgical patients with refractory hemorrhage. In this study, the authors assessed the ability of thromboelastography (TEG) in guiding rFVIIa therapy in this setting.**

Design: **Retrospective study.**

Setting: **Tertiary care university hospital.**

Participants: **Thirty-eight consecutive patients who received rFVIIa for refractory hemorrhage after cardiac surgery and had a complete coagulation profile including TEG within 30 minutes before and after rFVIIa.**

Interventions: **Standard coagulation (prothrombin time, partial thromboplastin time, platelet number, and fibrinogen) and TEG measurements (r time, k time, α angle, and maximum amplitude) before and after rFVIIa therapy were compared between responders and nonresponders (determined retrospectively based on clinical records).**

Measurements and Results: **Twenty-eight patients (74%) were classified as responders. There were no consistent changes in standard coagulation and TEG measurements before and after rFVIIa therapy. The number of abnormalities in pretreatment coagulation tests was related to response rates; odds of response were 11-fold (95% confidence interval [CI]) and 33-fold (95% CI) greater among patients with 0 or 1 abnormality in standard coagulation tests and TEG measures, respectively, than those with 2 or more abnormalities.**

Conclusions: **TEG may be a useful tool for predicting response to rFVIIa in the setting of refractory hemorrhage after cardiac surgery.**

KEY WORDS: recombinant factor VIIa, cardiac surgery, thromboelastography

EXCESSIVE BLEEDING IS A common complication of on-pump cardiac surgery that is independently linked to serious postoperative complications.[1] In a subset of patients, standard hemostatic interventions, which include the use of antifibrinolytic drugs, surgical re-exploration, and blood component therapy, fail to stop or reduce the blood loss in a timely manner. Physicians are increasingly treating these cases of refractory hemorrhage with recombinant activated factor VII (rFVIIa),[2-4] which constitutes an off-label use of a hemostatic drug that is currently approved primarily for hemophiliac patients with inhibitors.

Although the overall risk-benefit profile of the off-label use of rFVIIa in this setting has not yet been elucidated fully, there is increasing evidence that its benefits outweigh its (mainly thrombotic) risks in selected cases.[4-6] A substantial proportion of patients with refractory hemorrhage, however, do not respond to rFVIIa.[7] Given that rFVIIa therapy is not risk free, the ability to predict and monitor response to rFVIIa would confer important benefits. Previous studies have identified several patient-related factors and laboratory tests that are associated with a lack of response. Examples of the former include acidosis and hypothermia,[8,9] and examples of the latter include thrombocytopenia ($<80 \times 10^6$) and elevated prothrombin time (PT >2.0).[7,10-12] The predictive value of these factors for lack of response, however, is relatively modest. Similarly, there are no reliable means of monitoring the effects of rFVIIa.

It has been proposed that thromboelastography (TEG), which, unlike standard tests of coagulation that are performed on platelet-poor plasma, is performed on whole blood and provides information on the entire clotting process, including initiation and speed of clot formation, clot strength, and fibrinolysis, may be more useful for predicting and monitoring the effects of rFVIIa.[13,14] In bleeding hemophiliac patients with inhibitors, TEG was found to be useful for monitoring the effects of rFVIIa.[14-16] There are also 2 recent case reports describing the ability of TEG to guide rFVIIa therapy in hemophiliacs undergoing surgery.[17,18] Authors of these studies noticed that rFVIIa increased the clot strength in a dose-dependent manner as measured by TEG. However, whether TEG is similarly useful in bleeding cardiac surgical patients without hemophilia is not known.

Consequently, the authors performed this retrospective study in nonhemophiliac patients who received rFVIIa for refractory hemorrhage after cardiac surgery to determine if TEG could identify coagulation defects that are undetected by standard coagulation tests or be used to guide rFVIIa therapy.

METHODS

After approval of the institutional research ethics board, detailed perioperative data, including patient demographics, surgical information, timing and number of blood product transfusions, perioperative medications including drugs affecting coagulation, laboratory tests, and postoperative outcomes, were retrospectively obtained on consecutive patients who received rFVIIa (Novo Nordisk, Bagsaerd, Denmark) for refractory hemorrhage after cardiac surgery from 2005 to 2007 and in whom coagulation tests, including TEG, were performed within 30 minutes before and after rFVIIa therapy. Data were obtained from prospectively collected clinical databases that include detailed perioperative information on all cardiac surgery patients.

As has been described in detail elsewhere,[4] institutional guidelines required that patients meet all of the following criteria before rFVIIa

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Table 1. TEG Parameters and Ranges

Parameter	Short Description	Native	Kaolin	Tissue Factor
r time (min)	Measures initial clot formation (coagulation factors involved)	9-29	2-8	3-8
k time (min)	Measures the rate of clot formation (fibrin binding and interlinking)	2-9	1-3	0-5
Alpha angle (°)	The same as k time	22-58	55-78	52-82
Maximum amplitude (mm)	Provides measurement of clot strength (influenced mainly by platelet function and/or number)	44-64	51-69	46-72

NOTE. Normal ranges are institutional values for recalcified citrated blood without activators (native) and with activators (kaolin and tissue factor).[19]

was to be considered: (1) at least 4 units of red blood cells were transfused or blood loss exceeded 2,000 mL or was brisk enough to preclude sternal closure in the operating room, (2) a surgical source of bleeding was excluded by at least 2 hours of surgical re-exploration after the termination of CPB and reversal of heparin or by returning to the operating room for re-exploration, (3) antifibrinolytics were given, (4) patients had received at least 4 units of fresh frozen plasma and 5 units of platelets, (5) standard coagulation parameters were within 50% of the limits of normal, and (6) hematocrit concentration was at least 24%. The recommended dosage of rFVIIa was 35 μg/kg, rounded to the nearest ampoule size (1.2, 2.4, or 4.8 mg), repeated as necessary.

Table 2. Patient Characteristics

Variable	Responders (n = 28)	Nonresponders (n = 10)
Age (y)	65 (20-82)	64 (20-76)
Female sex	8 (29)	6 (60)
COPD/asthma	7 (25)	2 (20)
Renal dysfunction	12 (43)	2 (20)
Liver dysfunction	2 (7)	0 (0)
Congestive heart failure	16 (57)	7 (70)
Active endocarditis	1 (4)	1 (10)
Surgery type		
Single valve/ACB	11 (39)	1 (20)
Ascending aorta/arch	4 (14)	2 (20)
Congenital	3 (10)	0 (0)
Other	10 (36)	5 (5)
Redo surgery	6 (21)	6 (60)
Circulatory arrest	1 (3)	1 (10)
Received aprotinin	7 (25)	5 (50)
Cardiopulmonary bypass (min)	145 (61-294)	138 (69-279)
Cross-clamp (min)	102 (37-195)	92 (52-192)
Medications affecting coagulation		
Aspirin	9 (32)	6 (60)
Thienopyridines	2 (7)	1 (10)
Warfarin	10 (35)	2 (20)
GPIIb/IIIa inhibitors	1 (4)	1 (10)

NOTE. All variables are presented as n (%) or median (range). Liver dysfunction, defined as aspartate aminotransferase >40 IU/L or alanine aminotransferase >42 IU/L.

Abbreviations: rFVIIa, recombinant factor VIIa; renal dysfunction, calculated creatinine clearance <60 mL/min; ascending aorta/arch, surgery on ascending aorta or aortic arch; congenital, surgery for complex adult cardiac congenital disease; single valve/ACB, isolated coronary artery bypass grafting or single valve surgery; other, other cardiac surgical procedure; received aprotinin, all others received tranexamic acid.

Table 3. Blood Products Transfusions, Blood Loss, and Re-exploration Before and After rFVIIa Therapy

	Responders (n = 28)	Nonresponders (n = 10)	*p* Value
Transfusions before first dose of rFVIIa			
RBC	5.5 (3.5, 7)	7 (4, 10)	0.13
FFP	6.5 (4, 9)	8 (6, 10)	0.19
Platelets	10 (5, 10)	10 (10, 15)	0.027
Transfusions from first dose to 24 h after rFVIIIa			
RBC	2 (1, 3)	2 (1, 5)	0.19
FFP	0 (0, 0)	2 (1, 4)	0.002
Platelets	0 (0, 0)	5 (0, 10)	<0.0001
Chest tube loss before rFVIIa	248 (0, 618)	470 (100, 1,000)	0.27
Chest tube loss after rFVIIa (12 h)	433 (260, 545)	1,063 (505, 1275)	0.006
Re-exploration before 1st dose rFVIIa	10 (36%)	2 (20%)	0.45
Re-exploration after 1st dose rFVIIa	0 (0%)	3 (33%)	0.01

NOTE. Variables describing blood products transfusions and blood loss presented as median (25th and 75th percentile).

Abbreviations: rFVIIa, recombinant factor VIIa; RBC, units of packed red blood cells transfused; FFP, units of fresh frozen plasma transfused; platelets, units of platelets transfused; chest tube loss, chest tubes blood loss in the 6 hours before administration of rFVIIa (before rFVIIa if chest tubes in place and in the 12 hours after rFVIIa administration) (12 hours).

Table 4. Standard Coagulation Tests Before and After the First Dose of rFVIIa

	Responders (n = 28)	Nonresponders (n = 10)	*p* Value
Pre-FVIIa			
Hemoglobin (g/L)	88 (64-112)	78 (50-101)	0.13
Platelet (10^9/L)	116 (66-183)	80 (34-157)	0.006
INR	1.5 (0.8-2.2)	1.8 (1.1-2.8)	0.09
PTT (s)	35 (25-65)	49 (31-70)	0.09
Fibrinogen (g/L)	1.9 (1.1-2.9)	1.7 (1.2-2.2)	0.08
Post-FVIIa			
Hemoglobin (g/L)	95 (78-122)	93 (61-108)	0.3
Platelet (10^9/L)	126 (73-175)	84 (36-256)	0.002
INR	0.9 (0.7-1.7)	1.1 (0.9-2.1)	0.003
PTT (s)	34 (26-59)	54 (35-67)	<0.0001
Fibrinogen (g/L)	2.1 (1.6-3.2)	1.8 (1.0-2.4)	0.03

NOTE. Variables are presented as median (range).

Abbreviations: Pre FVIIa, within 30 minutes before rFVIIa administration; After FVIIa, within 30 minutes after rFVIIa administration; rFVIIa, recombinant factor VIIa; INR, international normalized ratio; PTT, activated partial thromboplastin time; fibrinogen, plasma fibrinogen concentration.