Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study

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Objectives **We evaluated the efficacy and safety of recombinant activated factor VII (rFVIIa) in children aged < 18 years old with grade II or grade III Dengue hemorrhagic fever (DHF) who required blood component therapy for controlling bleeding episodes.**

Study design **Patients were randomized to the rFVIIa group or placebo group in a ratio of 2 : 1. rFVIIa or placebo (100 μg/kg body weight) was given by intravenous bolus injection. When bleeding was not effectively controlled, a second dose of rFVIIa or placebo (100 μg/kg) was given 30 min after the first dose.**

Results **Nine and 16 patients received placebo and rFVIIa, respectively. The demographics, bleeding manifestations and grade of DHF were similar for the rFVIIa and placebo groups. Apart from petechiae and ecchymosis, one to four additional bleeding sites were found in each patient, including hematemesis ($n = 15$), epistaxis ($n = 14$), gum bleeding ($n = 12$), melena ($n = 7$), hypermenorrhea ($n = 4$), hematochezia ($n = 2$) and hematuria ($n = 2$). The mean total dose of rFVIIa (138.4 ± 50.9 μg/kg) and placebo (145.4 ± 53.7 μg/kg) were comparable. The efficacy of bleeding control at 2 h after the first dose was completely ceased (rFVIIa 75.0% versus placebo 44.4%), decreased (rFVIIa 18.7% versus placebo 11.2%), and unchanged or worsened (rFVIIa 6.3% versus placebo 44.4%). Some patients with active bleeding received platelet concentrates 3–12 h after the first dose of rFVIIa or placebo. The subsequent efficacy of bleeding control at 6, 12 and 24 h was comparable between the two groups. The cumulative use of red blood cells (rFVIIa 31.3% versus placebo 33.3%) and plasma (rFVIIa 25% versus placebo 22%) during the 24-h period was not significantly different between the two groups. In contrast, platelet concentrate requirement in the rFVIIa group (6.3%) was lower than the placebo (33.3%). No clinical evidence of thromboembolic complications or mortality as a result of bleeding was observed.**

Conclusion **rFVIIa appears to be a useful adjunctive treatment to blood component transfusion for controlling active bleeding in children with DHF especially when platelet concentrate is not readily available. *Blood Coagul Fibrinolysis* 16:549–555 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Recombinant activated factor VII (rFVIIa) has been effectively used in patients with congenital or acquired hemophilia and inhibitors to factor VIII or factor IX [1–4], congenital factor VII deficiency [5,6] and Glanzmann's thrombasthenia [7]. Published data show that rFVIIa might also provide effective hemostasis in severe uncontrolled bleeding in patients without preexisting coagulopathy undergoing various major surgeries [8–13] or in patients receiving warfarin for thromboprophylaxis [14,15].

Dengue infection is the most common mosquito-borne viral disease of public health significance [16] caused by any of the four dengue serotypes (dengue 1–4). Clinical manifestations range from influenza-like symptoms known as dengue fever to a more severe and sometimes fatal disease, characterized by hemorrhage and shock so-called Dengue hemorrhagic fever (DHF). Bleeding diathesis is caused by vasculopathy, thrombocytopenia and mild coagulopathy, resulting in petechiae, epistaxis,

A complete list of the persons and institutions participating in the study appears in the Appendix.

hematemesis and melena. Shock is the result of massive plasma leakage due to increased vascular permeability. There are three stages of DHF [16], namely febrile, toxic and convalescent. The febrile stage lasts 2–7 days followed by an abrupt fall to normal or subnormal levels of temperature; the toxic stage lasts 24–48 h; and, finally, rapid clinical recovery without sequelae in the convalescent stage. The toxic stage is the most critical period requiring intensive supportive care. Optimal fluid therapy to maintain the function of vital organs during the critical period is essential. Hypovolemic shock not properly treated will lead to multiorgan failure. Moreover, ineffective control of the bleeding will result in total shock. The mortality rate can be as high as 15% in inappropriately treated patients [17]. Therefore, adequate fluid replacement and effective control of bleeding are essential for a favorable outcome.

The aim of this study was to evaluate the efficacy and safety of rFVIIa in controlling bleeding episodes in children with DHF grade II or grade III who required blood component therapy.

Methods

The study was performed in accordance with the revised Declaration of Helsinki guidelines for biomedical research involving human subjects [18] and was approved by the respective institutional ethics committees. Patients were recruited from those who had been admitted or referred to the following hospitals: Ramathibodi Hospital (Bangkok, Thailand), Buddhachinaraj Hospital (Phitsanuloke, Thailand), Supprasithprasong Hospital (Ubonrajchathani, Thailand), University of Santo Tomas (Manila, Philippines) and Research Institute for Tropical Medicine (Muntinlupa City, Philippines). Their parents or legal guardians gave the informed consents to enroll in the study.

Diagnostic criteria for DHF

The clinical diagnosis [16] of DHF is based on four major characteristic manifestations: high continuous fever lasting for 2–7 days; hemorrhagic tendency such as a positive tourniquet test, petechiae or epistaxis; thrombocytopenia (platelet count $\leq 100\,000/\mu l$); and evidence of plasma leakage due to increased vascular permeability manifested by hemoconcentration (an increase in hematocrit (Hct) > 20%) or pleural effusion. The severity of DHF is categorized into four grades [16]: grade I, without overt bleeding but positive for the tourniquet test; grade II, with clinical bleeding diathesis such as epistaxis and ecchymosis; grade III, circulatory failure manifested by a rapid, weak pulse and narrowing pulse pressure (< 20 mmHg) or hypotension, with the presence of cold clammy skin and restlessness; and grade IV, profound shock in which pulse and blood pressure are not detected. The diagnoses of dengue infection, confirmed by serological assays, were either dengue-specific IgM and IgG determined by enzyme-linked immunosorbent assay or hemagglutination inhibition tests of sera from the acute and convalescent phases. A secondary dengue infection was diagnosed when the ratio of IgM to IgG was < 1.8 and when the hemagglutination inhibition titer was 1 : 2560 or more. Virus isolation was performed by culture or polymerase chain reaction using serum from the acute phase.

Patients

Twenty-eight children (< 18 years old) with DHF experiencing active bleeding and requiring blood component therapy were included in a randomized, double-blind placebo-controlled study between July 2001 and December 2002. All of the patients were in the toxic stage of DHF. Patients were randomized to either the rFVIIa group or placebo group at a ratio of 2 : 1. The first dose of rFVIIa (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) or placebo at 100 μg/kg body weight was given by intravenous injection. An identical looking placebo (freeze-dried sodium chloride) was reconstituted to the same concentration as rFVIIa (0.6 mg/ml). When the bleeding was not effectively controlled, a second dose (100 μg/kg) was given 30 min after the first dose.

Blood components were transfused any time after the first dose of trial medication depending on the clinical status assessed by the investigators. As general guidelines: red blood cells (RBC) were indicated for volume replacement in patients with massive bleeding; fresh frozen plasma (FFP) for massive bleeding due to coagulopathy, or circulatory failure that did not respond to intravenous crystalloid replacement; and platelet concentrates for massive bleeding.

The patients received supportive treatment, airway management, fluid and electrolyte therapy, and appropriate antibiotics according to their clinical manifestations and laboratory findings. In addition, in patients with epistaxis, anterior nasal packing with gel foam was applied. In patients with hematemesis, a small nasogastric tube was gently inserted for assessing and draining the bloody contents from the stomach. Cold gastric lavage was contraindicated.

The vital signs, clinical manifestations and amounts of bleeding were closely monitored and recorded.

Efficacy assessment

Patients were closely monitored for evidence of bleeding at 15, 30 and 45 min, and 1, 2, 6, 12 and 24 h after the first dose of rFVIIa or placebo. The evidence of bleeding included any visible bleeding such as epistaxis, hematemesis, melena or hematochezia. After adequate volume replacement, internal bleeding was suspected in the following conditions [19]: refractory shock with a hematocrit of less than 40%; systolic and diastolic blood

pressures were elevated or normalized but the pulse rate was still rapid at > 130/min in children and > 150/min in infants; patients with a drop in hematocrit of more than 10% within 10 h of fluid replacement.

The efficacy of bleeding control was assessed as effective, partially effective or ineffective by the investigators according to the following definitions: effective if a bleeding episode completely stopped; partially effective if a bleeding episode decreased; and ineffective if a bleeding episode worsened, remained unchanged, recurred or occurred at a new site.

Laboratory investigation

Complete blood counts and biochemistry tests were performed by each participating center. The activated partial thromboplastin time, thrombin time, prothrombin time, prothrombin time-International Normalized Ratio, factor VII clotting activity and D-dimer were measured by a central laboratory.

Statistical analysis

Descriptive statistical analyses were performed with the PC Statistical Analysis System version 6.12 (SAS Institute Inc., Cary, North Carolina, USA). The chi-square or Fisher's exact test was used for discrete data, where appropriate. The Mann–Whitney U test or Wilcoxon Signed Ranks test was used for continuous data. $P < 0.05$ was considered statistically significant.

Results

Eighteen patients received rFVIIa while 10 patients received placebo. The mean ages of patients with rFVIIa and placebo groups were 9.1 ± 4.1 and 10.5 ± 3.4 years, respectively. One patient in each group who had only petechiae and did not require any blood component was excluded from the efficacy analysis but was included in the safety analysis. Another patient from the rFVIIa group was also excluded because dengue infection was not confirmed. Hence, efficacy analysis included 16 rFVIIa-treated and nine placebo-treated patients.

The demographics, bleeding manifestations, grade of DHF and the total doses of trial medication were comparable between the two groups, except that the rFVIIa group had a greater proportion of females (Table 1). Apart from petechiae and ecchymosis, one to four additional bleeding sites were found in each patient, including hematemesis ($n = 15$), epistaxis ($n = 14$), gum bleeding ($n = 12$), melena ($n = 7$), hypermenorrhea ($n = 4$), hematochezia ($n = 2$) and hematuria ($n = 2$). The patients in both groups whose bleeding was not effectively controlled at 30 min after the first dose of rFVIIa or placebo received a second dose. Two patients in the rFVIIa group received the second dose at 2 h 50 min and 3 h 10 min. The mean total doses of rFVIIa and placebo were comparable at 138.4 ± 50.9 and 145.4 ± 53.7 μg/kg, respectively. The mean duration of hospital stay in the placebo group (6.3 ± 1.4 days) was slightly longer than those in the rFVIIa group (5.8 ± 1.3 days) but there was no statistical difference.

Table 1 Descriptive data of recombinant activated factor VII (rFVIIa)-treated patients and placebo-treated patients

	Number of patients	
	rFVIIa ($n = 16$)	Placebo ($n = 9$)
Sex (male/female)	5/11	6/3
Grade of Dengue hemorrhagic fever		
Grade II	7	5
Grade III	9	4
Bleeding manifestation[a]		
Hematemesis	10	5
Epistaxis	9	5
Gum bleeding	6	6
Melena	6	1
Hypermenorrhea	3[b]	1
Hematochezia	2	0
Hematuria	1	1
Number of bleeding sites[a]		
One	3	3
Two	4	2
Three	7	2
Four	2	2
Requiring a second dose of trial medication	8	5

[a]Petechiae and ecchymosis were not included. [b]One patient received intravenous conjugated estrogen 25 mg with complete cessation of hypermenorrhea before rFVIIa administration. The estrogen was continued at 6-h intervals for 24 h.

Confirmation of dengue infection

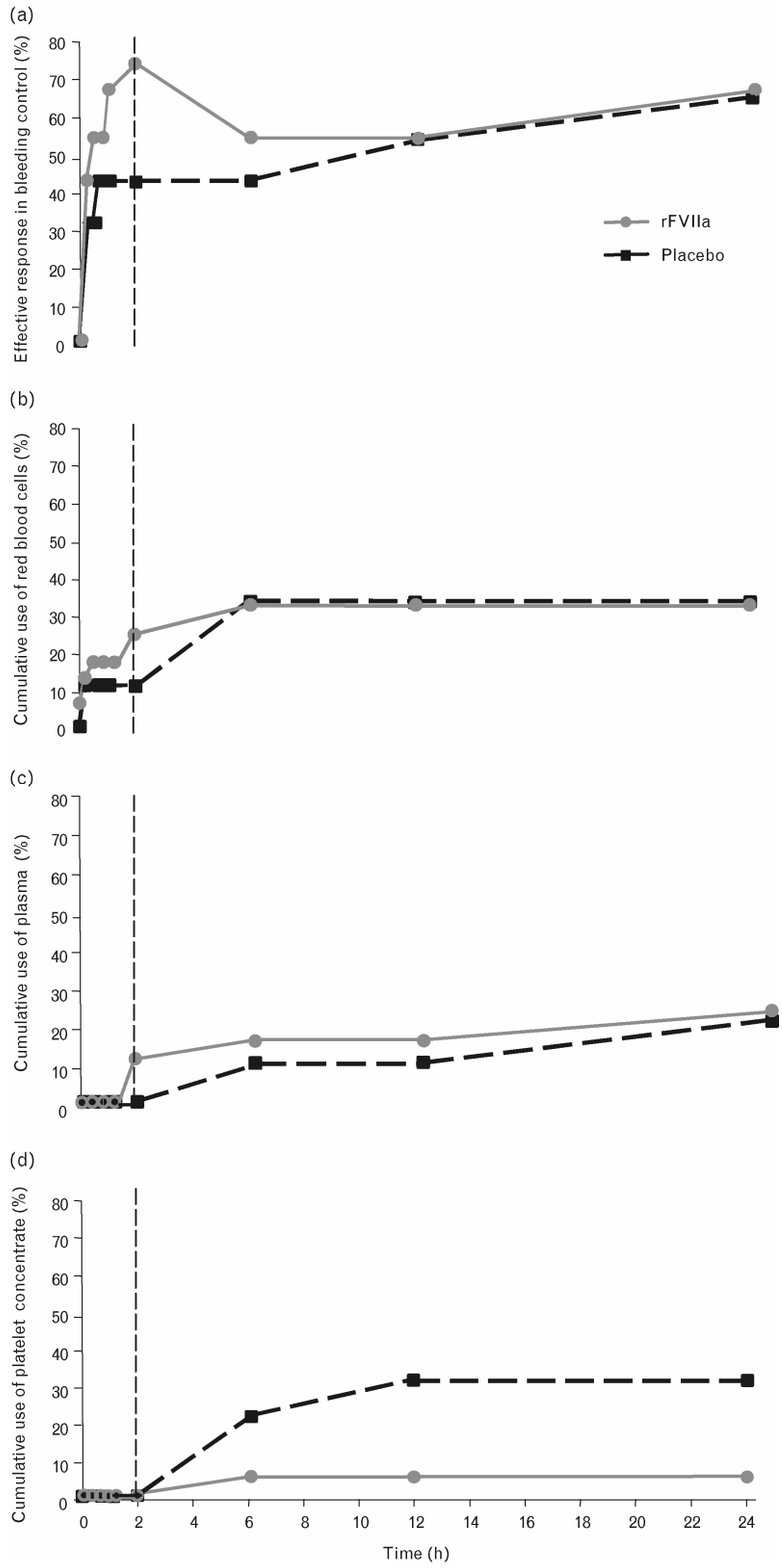
Nineteen patients had complete serology results, and primary and secondary dengue infections were confirmed in six and 13 patients, respectively. Five of these 19 patients also had positive results of virus isolation revealing dengue 2 ($n = 2$), dengue 3 ($n = 2$) and dengue 4 ($n = 1$). Blood samples had not been obtained during convalescent period in eight patients. However, all these patients had positive dengue-specific IgM and three had positive virus isolation revealing dengue 2 ($n = 2$) and dengue 3 ($n = 1$).

Efficacy assessment

The efficacy of rFVIIa and placebo are shown in Figure 1. The response to treatment at 2 h was considered effective in 12 of 16 (75.0%) patients in the rFVIIa group compared with four of nine (44.4%) in the placebo group, and partially effective in three of 16 (18.7%) in the rFVIIa group compared with one of nine (11.2%) in the placebo group. The treatment was judged ineffective in one of 16 (6.3%) and four of nine (44.4%) in the rFVIIa and placebo groups, respectively.

In the rFVIIa group, three of 12 patients (25%) with effective response at 2 h experienced recurrent bleeding at 3–24 h after the first dose. The first patient who developed hematemesis and epistaxis at 2 h 50 min responded effectively to a second dose of rFVIIa given at the time of recurrent bleeding and 12 U platelet concentrate

Fig. 1



(a) Effective response in bleeding control, (b) cumulative use of red blood cells, (c) cumulative use of plasma, and (d) cumulative use of platelet concentrate during the 24 h after the first dose of trial medication. rFVIIa, recombinant activated factor VII.

were given at 4 h 50 min to sustain hemostasis. In the second patient, who developed hematochezia and hematemesis at 3 h 10 min, the bleeding decreased after a second dose of rFVIIa but deteriorated at 12 and 24 h. A total of 1280 ml RBC (58 ml/kg) was transfused during the 22-h period. Platelet concentrate was not available at the time. The third patient experienced gum bleeding at 3 h 40 min but spontaneously subsided at 12 h and completely ceased at 24 h. The bleeding in the remaining patients with partially effective ($n = 3$) and ineffective responses ($n = 1$) decreased or stopped at 24 h without platelet transfusion, one patient received 1 U cryoprecipitate (7 ml/kg) and another received 3 U FFP (34 ml/kg) due to hypotension and rapid pulse. At 24 h, the efficacy of rFVIIa was considered effective in 68.7% (11/16), partially effective in 25.0% (4/16), and ineffective response in 6.3% (1/16).

In the placebo group, one of four (25%) patients with initial effective response had recurrent epistaxis at 3 h 20 min. The bleeding spontaneously decreased at 12 h and completely ceased at 24 h. In another patient with hematuria, the bleeding continued for 24 h requiring 2 U FFP (17 ml/kg) because of narrowing pulse pressure (< 20 mmHg). In addition, three out of four patients with ineffective response required platelet concentrate transfusion 3–12 h after the first dose to stop their active bleeding while the remaining patient had his coffee ground content from the nasogastric tube spontaneously slowed down at 12 h and completely ceased at 24 h without receiving any blood component. Finally, at 24 h, the placebo-treated patients showed effective response, 66.7% (6/9) and partially effective response, 33.3% (3/9).

In comparison, 2 h before the platelet concentrate transfusion the rFVIIa-treated patients appeared to have a higher effective response (75.0%) compared with that of the placebo-treated patients (44.4%). However, the subsequent efficacy of bleeding control at 6, 12 and 24 h was comparable between the two groups.

Blood component requirement

Figure 1 shows the efficacy, cumulative use of RBC, plasma and platelet concentrates during the 24 h after the first dose of the trial medication. No platelet concentrates were available at 2 h after the first dose. From 1–2 h after the first dose, RBC was transfused to patients in both groups [rFVIIa four of 16 (25%) versus placebo one of nine (11.2%)] due to the anemic state from acute blood loss. FFP of 10 ml/kg was transfused to two rFVIIa-treated patients due to circulatory failure manifested by the narrowing pulse pressure < 20 mmHg and rapid pulses. Both of them were assessed as having partially effective responses at 2 h.

The cumulative uses of RBC [rFVIIa 5/16 (31.3%) versus placebo 3/9 (33.3%)] and plasma [rFVIIa 4/16 (25%) versus placebo 2/9 (22.2%)] during 24 h between the two groups were not statistically different. Three out of five rFVIIa-treated patients required two to five doses of RBC transfusion, while three placebo-treated patients required only one dose of RBC transfusion. The total amount of required RBC in the five rFVIIa-treated patients was higher (median, 15.5 ml/kg; interquartile range, 5.2–45.8 ml/kg) than that of three placebo-treated patients (median, 10.0 ml/kg; interquartile range, 5.4–10.0 ml/kg) but was not statistically significantly different. Also, the total amount of plasma in four rFVIIa-treated patients (median, 18.5 ml/kg; interquartile range, 9.8–31.2 ml/kg) was comparable with that of two placebo-treated patients (median, 17.2 ml/kg; interquartile range, 14.8–19.6 ml/kg).

In contrast, the platelet concentrate requirement in the rFVIIa group (1/16, 6.3%) was lower than that of the placebo group (3/9, 33.3%) ($P = 0.1$). They all received

Table 2 Hematological-related parameters (median and interquartile range), comparing between recombinant activated factor VII (rFVIIa)-treated patients and placebo-treated patients

	Group	0 min	30 min	24 h
Activated partial thromboplastin time (s)	rFVIIa	56.2 (48.9–70.1) ($n = 13$)	47.8 (39.5–54.4) ($n = 11$)	53.8 (41.0–58.3) ($n = 14$)
	Placebo	50.1 (43.5–61.3) ($n = 8$)	46.3 (42.3–58.3) ($n = 8$)	43.3 (40.2–45.7) ($n = 8$)
Thrombin time (s)	rFVIIa	21.9 (17.5–28.8) ($n = 15$)	25.1 (20.3–27.5) ($n = 12$)	24.8 (16.1–28.2) ($n = 15$)
	Placebo	22.4 (16.8–33.3) ($n = 8$)	22.7 (16.8–33.0) ($n = 8$)	19.5 (18.6–28.3) ($n = 8$)
Prothrombin time (s)	rFVIIa	14.8 (12.9–16.6) ($n = 15$)	9.7 (7.90–10.7) ($n = 13$)	12.9 (11.6–13.8) ($n = 15$)
	Placebo	14.0 (12.9–15.0) ($n = 8$)	13.9 (12.6–15.3) ($n = 8$)	12.7 (12.1–14.4) ($n = 8$)
International Normalized Ratio	rFVIIa	1.2 (1.0–1.3) ($n = 15$)	0.7 (0.6–0.8) ($n = 13$)	1.0 (0.9–1.1) ($n = 15$)
	Placebo	1.1 (1.1–1.2) ($n = 8$)	1.1 (1.0–1.2) ($n = 8$)	1.0 (1.0–1.1) ($n = 8$)
D-dimer (μg/l)	rFVIIa	344.0 (329.0–487.0) ($n = 7$)	371.0 (344.0–588.0) ($n = 7$)	331.0 (304.0–604.0) ($n = 7$)
	Placebo	461.0 (139.0–868.5) ($n = 4$)	454.0 (143.0–851.5) ($n = 4$)	393.5 (168.5–696.0) ($n = 4$)
Factor VII clotting activity (%)	rFVIIa	83.0 (52.0–114.0) ($n = 15$)	1012.0 (300.0–2948.0) ($n = 5$)	129.0 (79.0–172.0) ($n = 15$)
	Placebo	70.5 (57.5–107.5) ($n = 8$)	82.0 (54.5–109.0) ($n = 8$)	106.0 (84.50–147.0) ($n = 8$)
Platelet ($\times 10^3/\mu l$)	rFVIIa	26.5 (20.0–43.9) ($n = 16$)	24.0 (20.0–46.0) ($n = 16$)	35.3 (21.0–60.5) ($n = 16$)
	Placebo	36.1 (20.2–40.0) ($n = 9$)	28.7 (20.0–42.0) ($n = 9$)	40.0 (25.0–60.0) ($n = 9$)
Hematocrit (%)	rFVIIa	38.5 (24.5–44.0) ($n = 9$)	38.0 (24.0–43.0) ($n = 15$)	36.0 (33.0–39.9) ($n = 16$)
	Placebo	42.0 (37.0–48.0) ($n = 9$)	43.2 (37.0–49.0) ($n = 9$)	37.0 (32.0–39.0) ($n = 9$)
Hemoglobin (g/L)	rFVIIa	129.5 (83.5–150.0) ($n = 16$)	125.5 (79.5–148.5) ($n = 16$)	124.5 (109.5–133.0) ($n = 16$)
	Placebo	143.0 (123.0–159.0) ($n = 9$)	143.0 (122.0–160.0) ($n = 9$)	126.0 (109.0–131.0) ($n = 9$)

one dose of 0.1–0.3 U/kg platelet concentrate transfusion.

Laboratory findings

The hematological-related parameters are presented in Table 2. At 0 min, median Hct was lower in the rFVIIa group than in the placebo group ($P = 0.047$). Seven rFVIIa-treated patients had Hct $< 36\%$ compared with only one in the placebo-treated patients. In the placebo group, the median Hct levels at 0 min, 30 min and 24 h after the first dose of trial medication were 42.0, 43.2 and 37.0%, respectively. In contrast, the median Hct levels in the rFVIIa group were unchanged. White blood cell counts and differential counts were not significantly different between the two groups.

The abnormal laboratory findings were similar at 0 min and 24 h including aspartate aminotransferase > 40 U/l in all patients, alanine aminotransferase > 40 U/l [rFVIIa, 13 of 17 (76.5%) versus placebo, 9 of 10 (90.0%)], total protein < 60 g/l [rFVIIa, 13 of 17 (76.5%) versus placebo, 7 of 10 (70.0%)] and albumin < 35 g/l [rFVIIa, one of 17 (5.9%) versus placebo, none of 10 (0%)].

Adverse events

No clinical evidence of thromboembolic complications was observed and no patient died as a result of bleeding or severe complication. The commonly found abnormal physical signs including pleural effusion [rFVIIa, 3/17 (17.6%) versus placebo, 4/10 (40%)] and decreased breath sound [rFVIIa, 1/17 (6.3%) versus placebo, 2/10 (20%)] were considered to be related to the clinical course of DHF, and not the trial medication.

Discussion

Bleeding in DHF is mainly caused by thrombocytopenia, which is most prominent during the toxic stage. The mechanisms of thrombocytopenia include decreased platelet production and increased platelet destruction. Furthermore, mild prolonged prothrombin time and partial thromboplastin time, and reduced fibrinogen levels have been demonstrated in patients with DHF [20,21]. Variable degrees of decreased levels of several coagulation factors and anticoagulants, including factors II, V, VII, VIII, IX and X, antithrombin and α_2-antiplasmin, have also been observed. Moreover, fibrin degradation product or D-dimer is slightly elevated [21,22]. Based on 167 Vietnamese children with Dengue shock syndrome, Willis *et al*. found that low levels of anticoagulant proteins C and S, and antithrombin III were associated with increased severity of shock, presumably due to plasma leakage [23]. In addition, tissue factor, thrombomodulin and plasminogen activator inhibitor-1 levels were elevated reflecting endothelial, platelet and/or monocyte activation and possibly a secondary response to direct activation of fibrinolysis by the dengue virus. The coagulation abnormality is well compensated in the majority of patients without circulatory collapse [24]. In the minority of patients with uncontrolled massive bleeding or prolonged shock, the coagulation abnormality may be difficult to manage and may lead to disseminated intravascular coagulation or may enhance ongoing disseminated intravascular coagulation. Intensive supportive care is the most important aspect in the management of patients with DHF. Prompt treatment with adequate fluid replacement during the critical period and effective control of bleeding episodes are essential for a favorable outcome. Platelet and FFP transfusions are usually required for the control of severe bleeding. However, platelet concentrate is not always readily available, as demonstrated by this study in which platelet concentrate was not available in the first 2 h.

The proposed mechanism of action of rFVIIa is enhancing thrombin generation locally at the site of vascular injury, resulting in the formation of a firm fibrin clot [25]. The localized hemostatic effect of rFVIIa was substantiated by the results from our study in which no laboratory or clinical evidence of systemic activation of coagulation was seen.

In our study, rFVIIa as an adjunctive treatment improved the efficacy of bleeding control, especially in the gastrointestinal tract, compared with conventional treatment with ranitidine or omeprazole alone. Although the extent of bleeding manifestation was comparable between the two groups, the median Hct level at baseline (0 min) (38.5%) in the rFVIIa group was significantly lower than the placebo (42.0%) ($P = 0.047$), suggesting that patients in the rFVIIa group were more severe than the placebo. This may explain the high RBC requirement in the rFVIIa group compared with the placebo.

The limitation of the present study is the small number of patients. Moreover, there were two protocol violations; two patients in the rFVIIa group receiving the second dose at approximately 3 h due to the recurrent bleeding. However, platelet concentrate was also transfused at 4 h 50 min after the first dose in one of these patients, who was the only patient in the rFVIIa group receiving platelet concentrate. The response at 6 h in this patient might be the combined effect of rFVIIa and platelet concentrate.

In conclusion, based on our preliminary study, rFVIIa appears to be useful as an adjunctive treatment to blood component replacement in controlling active bleeding episodes in children with grade II or grade III DHF when platelet concentrates are not available. Nevertheless, we could not show the effect of rFVIIa on the reduction of RBC transfusion requirement, possibly due to the small number of patients and non-optimized dose regimen of rFVIIa. Concerning safety, patients with DHF grade II or grade III have mild consumptive coagulopathy, and

rFVIIa does not appear to aggravate their clinical condition to full-blown DIC. Further studies to establish the optimal dose regiment of rFVIIa are warranted.

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