REVIEW ARTICLE

Efficacy and Safety of Recombinant Activated Factor VII in Major Surgical Procedures

Systematic Review and Meta-analysis of Randomized Clinical Trials

Marco Ranucci, MD; Giuseppe Isgrò, MD; Giorgio Soro, MD; Daniela Conti, MD; Barbara De Toffol, MD

Objective: To investigate the efficacy and safety of recombinant activated factor VII (rFVIIa) treatment in patients undergoing major surgical procedures.

Data Sources: Relevant studies were searched in BioMedCentral, CENTRAL, PubMed, and PubMed Central.

Study Selection: Only randomized controlled trials on humans undergoing major surgery were included. Efficacy was determined as the rate of patients receiving allogeneic packed red blood cells; safety was assessed in terms of thromboembolic complications and mortality rate.

Data Extraction: We followed the Cochrane Collaboration method for data extraction and internal validity procedures, as well as the Quality of Reporting of Meta-analyses statement.

Data Synthesis: Seven randomized controlled trials met the inclusion criteria. Treatment with rFVIIa is associated with a reduced risk of receiving allogeneic packed red blood cells (odds ratio, 0.29; 95% confidence interval, 0.10-0.80). In a subgroup analysis, only patients receiving at least 50 μg/kg of rFVIIa had a significant benefit (odds ratio, 0.43; 95% confidence interval, 0.23-0.78). No differences in thromboembolic complications and mortality rates were observed.

Conclusions: Treatment with rFVIIa is effective in reducing the rate of patients undergoing transfusion with allogeneic packed red blood cells. However, the cost-benefit ratio is favorable only in patients who need a huge number of packed red blood cell units. No safety concerns arise from the present study.

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Author Affiliations: Department of Cardiovascular Anaesthesia, IRCCS Policlinico S. Donato, Milan, Italy.

RECOMBINANT ACTIVATED factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsværd, Denmark) is a pharmacologic agent currently registered for perioperative prophylaxis and treatment of bleeding episodes in hemophilic patients with inhibitors against coagulation factors VIII and IX (United States) and for patients with acquired hemophilia, coagulation factor VII deficiency, and Glanzmann thrombasthenia who are refractory to platelets (European Union). Its pharmacologic action induces thrombin generation in locally activated platelets and contributes to the formation of a stabilized fibrin clot at the site of vessel injury.[1,2]

See Invited Critique at end of article

In recent years, a consistent and growing number of studies and scientific publications have suggested many "off-label" indications for rFVIIa in bleeding disorders associated with surgical procedures in patients without any known congenital hemostasis or coagulation defects. The existent literature is mainly composed of case reports[3-17] and case series[18-35] apparently describing a positive experience. Some retrospective studies with historical controls[36-39] and randomized controlled trials (RCTs)[40-49] have been published, but at present, the results seem conflicting or biased by the underpower of many studies. Moreover, concerns about the safety of this drug, focused on its possible determinism for thromboembolic complications, have been raised by different case reports[50,51] and RCTs in nonsurgical patients.[52]

To address the efficacy and safety of rFVIIa in major surgical procedures, we conducted a systematic review and meta-analysis of data pooled from existing RCTs.

METHODS

END POINTS AND DEFINITIONS

This study has efficacy and safety end points. Efficacy was defined in terms of the proportion of patients requiring homologous packed red blood cell (PRBC) transfusions in rFVIIa-treated patients vs controls. Safety was defined as the thromboembolic complication rate and the mortality rate in rFVIIa-treated patients vs controls. We accepted the authors' definitions of throm-

Table 1. Description of Studies Included in the Systematic Review

Source	Journal	Setting	Transfusion Protocol	Main Outcome Measures
Friederich et al,[48] 2003	*Lancet*	Transabdominal retropubic prostatectomy	Yes (PRBCs if Hb <7.25 g/dL intraoperatively or <8.87 g/dL postoperatively)	Blood loss, volume of PRBCs transfused, number of patients transfused, adverse events, thromboembolic events, hospital stay, mortality
Lodge et al,[43] 2005	*Liver Transplantation*	Liver transplantation	Yes (PRBCs if HCT <25%, FFP if INR >1.5 or APTT >1.5 × control)	Volume of PRBCs transfused, number of patients transfused, adverse events, thromboembolic events, ICU and hospital stay, mortality
Lodge et al,[44] 2005	*Anesthesiology*	Liver resection in noncirrhotic patients	Yes (PRBCs if HCT <25%, PLTs if platelet count <30 000 × 10³/μL)	Blood loss, volume of PRBCs transfused, number of patients transfused, adverse events, thromboembolic events, mortality
Raobaikady et al,[47] 2005	*British Journal of Anaesthesia*	Reconstruction of traumatic pelvis fracture	Yes (PRBCs if Hb <8 g/dL, FFP if INR >1.5 or APTT >1.5 × control, PLTs if platelet count <100 000 × 10³/μL)	Blood loss, volume of PRBCs transfused, number of patients transfused, adverse events, ICU and hospital stay, mortality
Planinsic et al,[45] 2005	*Liver Transplantation*	Liver transplantation	Yes (PRBCs if HCT <25%, FFP if INR >1.5 or APTT >1.5 × control, PLTs if platelet count <30 000 × 10³/μL)	Volume of PRBCs transfused, adverse events, thromboembolic events, ICU stay, mortality
Diprose et al,[49] 2005	*British Journal of Anaesthesia*	Cardiac surgery (at high risk for bleeding)	Yes (PRBCs if Hb <8.5 g/dL, FFP on TEG variables, PLTs if platelet count <100 000 × 10³/μL or on TEG variables)	Blood loss, volume of PRBCs transfused, number of patients transfused, adverse events, ICU and hospital stay, mortality
Shao et al,[46] 2006	*American Journal of Surgery*	Liver resection in cirrhotic patients	No (PRBCs at discretion when intraoperative bleeding exceeded 500 mL)	Blood loss, volume of PRBCs transfused, number of patients transfused, adverse events

Abbreviations: APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; Hb, hemoglobin; HCT, hematocrit; ICU, intensive care unit; INR, international normalized ratio; PLTs, platelets; PRBCs, packed red blood cells; TEG, thromboelastography.

SI conversion factors: To convert Hb to grams per liter, multiply by 10; HCT to proportion of 1.0, multiply by 0.01; platelet count to $\times 10^9$/L, multiply by 1.

boembolic events in each selected study. This meant considering as thromboembolic events the occurrence of myocardial infarction, stroke, peripheral arterial or venous thromboembolism, mesenteric infarction, and pulmonary embolism. Subgroup analyses based on rFVIIa dose were planned.

SEARCH STRATEGY

Pertinent studies were independently searched by 2 trained investigators (M.R. and G.I.) in BioMedCentral, CENTRAL, PubMed, and PubMed Central (updated September 15, 2006). The following key words were used: *rFVIIa, recombinant activated factor VII, NovoSeven,* and *surgery*. To conduct the research, we followed the strategy suggested by Biondi-Zoccai and coworkers.[53] Further searches, performed either manually or with computer assistance, involved the recent (since 2002) proceedings and abstracts from congresses of the following scientific associations: American Society of Anesthesia, European Society of Anaesthesiology, European Society of Intensive Care Medicine, Society of Cardiovascular Anesthesiologists, European Association of Cardiothoracic Anaesthesiologists, International Society on Thrombosis and Hemostasis, and American College of Chest Physicians. In addition, the references of retrieved articles and pertinent reviews were scanned, and international experts were contacted and interviewed. No ongoing trials were included. No language selection was applied.

STUDY SELECTION

A first selection of the references obtained by the previously described search was performed by 2 independent investigators (M.R. and G.S.) on the basis of the title and the abstract, with divergences resolved by consensus. If considered pertinent, the studies were retrieved as complete articles.

The following inclusion criteria were applied for selecting potentially relevant studies: (1) random allocation to treatment, (2) absence of known congenital hemostasis and coagulation defects, (3) comparison of rFVIIa vs placebo, and (4) study performed in patients undergoing major surgical procedures (procedures requiring open surgical access). The exclusion criteria were (1) duplicate publications (in this case only the article reporting the larger patient population was considered), (2) pediatric patients (<12 years), (3) nonhuman experiments, and (4) no outcome data. The selected studies were independently decided by 2 investigators (M.R. and G.S.), with divergences resolved by consensus (**Table 1**).

DATA ABSTRACTION AND STUDY CHARACTERISTICS

The baseline, procedural, and main outcome data in the selected studies were independently abstracted by 2 investigators (M.R. and B.D.T.), with divergences resolved by consensus (**Table 2**). Some studies included 2 rFVIIa treatment groups with different drug doses, and they are considered separately. In cases of missing data or when further information was required, at least 2 separate attempts at contacting the original authors were made.

INTERNAL VALIDITY

The internal validity of the selected trials was appraised by 2 independent researchers (M.R. and B.D.T.) according to the Cochrane Collaboration methods by assessing the risk of se-

Table 2. Number of Patients and Interventions in the 7 Selected Studies

Source	Patients, No.			rFVIIa Dose, µg/kg	Administration Protocol	Study Protocol
	Overall	Treated	Placebo Controlled			
Friederich et al,[48] 2003	**36**	8 16	12	20 40	Single bolus during the operation.	Randomized, double-blind, parallel-group, placebo-controlled
Lodge et al,[43] 2005	**179**	62 56	61	60 120	First bolus dose within 10 min after skin incision. Bolus doses repeated every 2 h until 30 min before the expected reperfusion of the transplanted liver. Final bolus dose at completion of wound suture.	Multicenter, randomized, double-blind, parallel-group, placebo-controlled
Lodge et al,[44] 2005	**185**	63 59	63	20 80	First bolus dose within 5 min before the skin incision. Bolus dose repeated after 5 h if the expected surgery time exceeded 6 h.	Multicenter, randomized, double-blind, parallel-group, placebo-controlled
Raobaikady et al,[47] 2005	**48**	24	24	90	Bolus dose at skin incision. Second bolus after 2 h if the hemoglobin concentration was <8.0 g/dL.	Randomized, double-blind, placebo-controlled
Planinsic et al,[45] 2005	**83**	18 24 22	19	20 40 80	Single bolus within 10 min after the skin incision.	Multicenter, randomized, double-blind, parallel-group, placebo-controlled
Diprose et al,[49] 2005	**20**	10	10	90	Single bolus after completion of cardiopulmonary bypass.	Randomized, double-blind, placebo-controlled
Shao et al,[46] 2006	**221**	71 74	76	50 100	First bolus dose within 10 min after skin incision. Bolus doses repeated every 2 h until the end of surgery. Maximum of 4 doses allowed.	Multicenter, randomized, double-blind, parallel-group, placebo-controlled

Abbreviation: rFVIIa, recombinant activated factor VII.
SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

lection, performance, attrition, and detection biases, expressed as low (A), moderate (B), or severe (C) risk of bias or incomplete reporting leading to the inability to assess the underlying risk of bias (D). In addition, allocation concealment was distinguished as adequate (A), unclear (B), inadequate (C), or not used (D) (**Table 3**). Divergences between the reviewers were resolved by consensus.

DATA ANALYSIS, BIAS, AND HETEROGENEITY ASSESSMENT

The 3 binary outcomes were analyzed according to the Mantel-Haenszel model to compute an odds ratio (OR) with a pertinent 95% confidence interval (CI) for each selected study. Pooled summary effects were calculated by means of fixed- or random-effects models according to the heterogeneity and inconsistency detected using the Cochran *Q* test and I^2, respectively.[54,55] Publication bias was assessed by visual inspection of funnel plots and by computing the Egger test.[56] In the case of a significant ($P<.05$) Egger test for publication bias, adequate corrections were applied according to the trim and fill method.[57]

The number of null or negative studies needed to void the findings from the meta-analysis was computed according to the Klein formula.[58] Statistical significance was set at the 2-tailed $P<.05$ level (α) for hypothesis testing and at $P<.10$ (β) for heterogeneity testing. I^2 values of approximately 25%, 50%, and 75% were considered to represent low, moderate, and severe statistical inconsistency, respectively.[56] Unadjusted *P* values are reported throughout the text, tables, and figures. Computations were performed using a software program (Comprehensive Meta Analysis Version 2.2; Biostat, Engelwood, New Jersey). This study was performed in compliance with the Quality of Reporting of Meta-analyses guidelines.[59]

RESULTS

Database searches and other sources yielded a total of 288 studies (**Figure 1**). On the basis of title and abstract, 172 studies were excluded (nonhuman studies, human studies on patients with congenital hemostasis and coagulation defects, and biochemical studies without outcome measurements). Another 49 studies were classified as case reports and case series and were excluded. The remaining 67 articles were retrieved in complete form and were assessed according to the selection criteria. Of these articles, 53 were review articles, and, after cross-checking the references for possible missing articles, they were excluded from the meta-analysis. Careful revision of the remaining 14 articles led to the exclusion of 7 studies: 1 study[40] was a preliminary report of a subsequently completed RCT, 2 studies[21,42] focused on minor surgical procedures in patients with acquired coagulopathy, and 4 studies[37-39,42] were uncontrolled clinical trials. The final group of selected studies comprised 7 RCTs[43-49] dealing with major surgical procedures in patients without congenital hemostasis and coagulation defects.

STUDY CHARACTERISTICS

The 7 selected RCTs randomized 772 patients: 265 were placebo controlled and 507 underwent rFVIIa treatment at different doses (Table 2). To investigate the role of the dose, the analysis was repeated for the subgroups of patients receiving a low dose (<50 µg/kg) or a high

Table 3. Description of the 7 Full Studies Included in the Systematic Review

Source	Multicenter Study	Means of Randomized Allocation	Allocation Concealment[a]	Risk of Selection Bias	Risk of Performance Bias[b]	Risk of Attrition Bias[b]	Risk of Detection Bias[b]
Friederich et al,[48] 2003	No	Computer-generated random numbers	A	A	B	A	A
Lodge et al,[43] 2005	Yes	Not reported	D	C	D	C	A
Lodge et al,[44] 2005	Yes	Computer-generated random numbers	A	A	A	B	A
Raobaikady et al,[47] 2005	No	Computer-generated random numbers	A	B	B	A	A
Planinsic et al,[45] 2005	Yes	Not reported	D	C	D	B	B
Diprose et al,[49] 2005	No	Computer-generated random numbers	A	B	A	B	A
Shao et al,[46] 2006	Yes	Not reported	D	C	D	B	C

[a] Allocation concealment is expressed as adequate (A), unclear (B), inadequate (C), or not used (D).
[b] Risk of bias is expressed as low risk (A), moderate risk (B), severe risk (C), or incomplete reporting leading to the inability to assess the underlying risk of bias (D).

dose (≥50 μg/kg). Four studies were performed in hepatic surgery (transplantation or resection in cirrhotic and noncirrhotic patients), 1 in cardiac surgery (patients at high risk for bleeding), 1 in abdominal prostatic surgery, and 1 in orthopedic trauma surgery of the pelvis. The timing and total dose of rFVIIa varied across the studies. Three studies report a single bolus administration, and 4 applied a repeated bolus protocol. The reported dose range is 20 μg/kg (single bolus) to 360 μg/kg (6 repeated boluses of 60 μg/kg).

QUANTITATIVE RESULTS: rFVIIa EFFICACY

The analysis of the primary outcome variable for assessing rFVIIa efficacy (number of patients receiving homologous PRBCs) was conducted in 5 of 7 trials, with 8 dose-related subgroups and a total of 468 patients (298 treated and 170 placebo controlled). The study by Shao et al[46] was excluded from this analysis owing to lack of a transfusion protocol and, therefore, a possible bias in the efficacy end point determination, and the study by Planinsic et al[45] was excluded owing to absence of the number of patients transfused within the outcome variables. Patients receiving rFVIIa treatment (regardless of dose) had a reduced risk of homologous PRBC transfusion (166/298 [55.7%] vs 115/170 [67.6%] in the control arm; fixed-effects OR, 0.52; 95% CI, 0.31-0.86; $P = .01$ for effect) (**Figure 2**).

A subgroup analysis was applied by separating the group where the rFVIIa dose was always 50 μg/kg or higher (high dose) from the group receiving less than 50 μg/kg (low dose) (Figure 2). The high-dose group included the RCTs by Diprose and coworkers,[49] Raobaikady et al,[47] Lodge et al,[43] and the 80 μg/kg subgroup of the second RCTs from Lodge and coworkers,[44] for a total of 369 patients (211 treated and 158 placebo controlled). The low-dose group included 162 patients (87 treated [63 from the low-dose (20 μg/kg) subgroup of Lodge et al[44] and 24 from the RCT by Friederich et al[48] (subgroups taking 20 and 40 μg/kg)] and 75 placebo controlled).

Patients receiving high-dose rFVIIa treatment had a reduced risk of homologous PRBC transfusion (137/211 [64.9%] vs 108/158 [68.4%] in the control arm; fixed-effects OR, 0.43; 95% CI, 0.23-0.78; $P = .006$ for effect). Patients receiving low-dose rFVIIa treatment had no significantly different risk of homologous PRBC transfusion (29/87 [33.3%] vs 30/75 [40.0%] in the control arm; fixed-effects OR, 0.89; 95% CI, 0.46-1.71; $P = .71$ for effect).

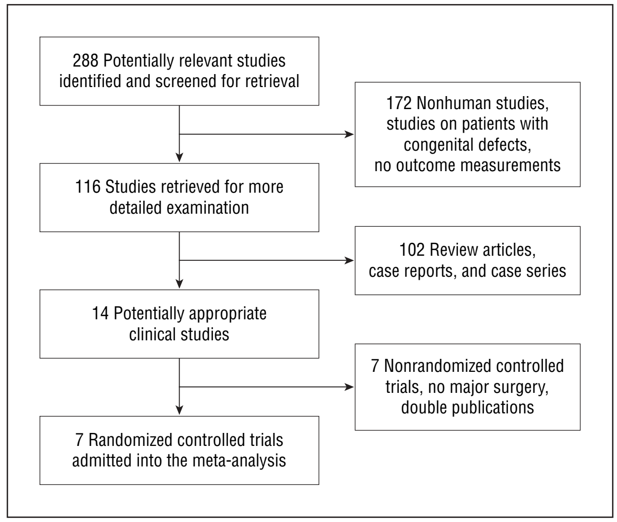

Figure 1. Study characteristics and selection.

QUANTITATIVE RESULTS: SAFETY

All the selected studies were used for the safety meta-analysis. The safety issue was addressed by computing the ORs (95% CIs) for thromboembolic events and mortality. There were 36 thromboembolic complications in 507 patients (7.1%) in the rFVIIa-treated group vs 14 in 265 patients (5.3%) in the placebo-controlled group (OR, 1.32; 95% CI, 0.69-2.52; $P = .40$ for effect, in a fixed-effects model) (**Figure 3**). Mortality was 2.8% (14 of 507) in the rFVIIa-treated group and 2.3% (6 of 265) in the placebo-controlled group, indicating no effect of rFVIIa treatment on the mortality rate (OR, 0.99; 95% CI, 0.37-2.68; $P = .99$ for effect, in a fixed-effects model) (**Figure 4**).

ADDITIONAL ANALYSES

Additional analyses addressed the existence of heterogeneity, the inconsistency of data, and publication bias and provided possible corrective tools.

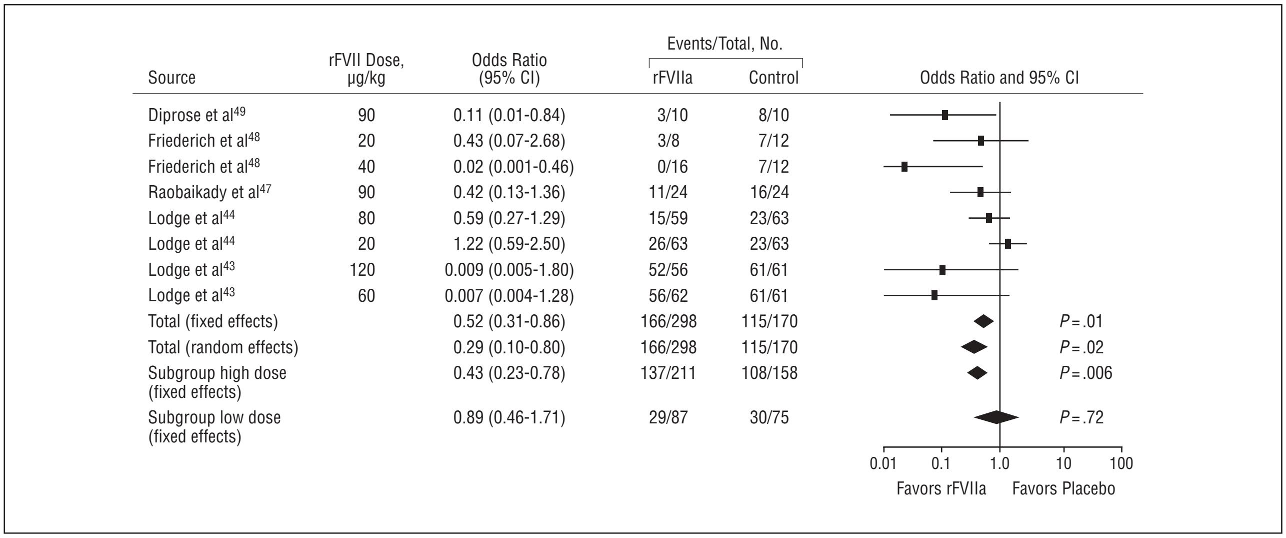

Figure 2. Plot of allogeneic packed red blood cell transfusion rates in the selected studies. CI indicates confidence interval; rFVIIa, recombinant activated factor VII.

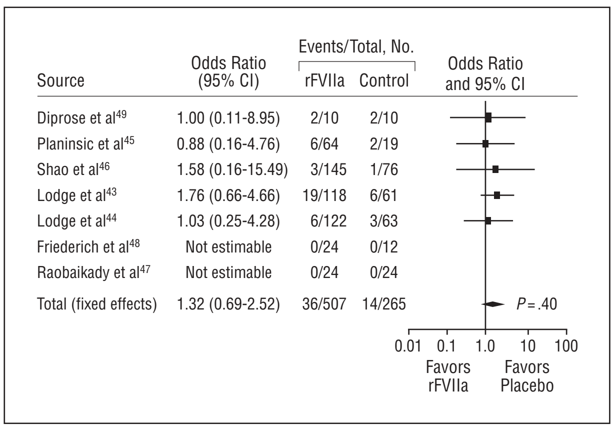

Figure 3. Plot of thromboembolic complication rates in the selected studies. CI indicates confidence interval; rFVIIa, recombinant activated factor VII.

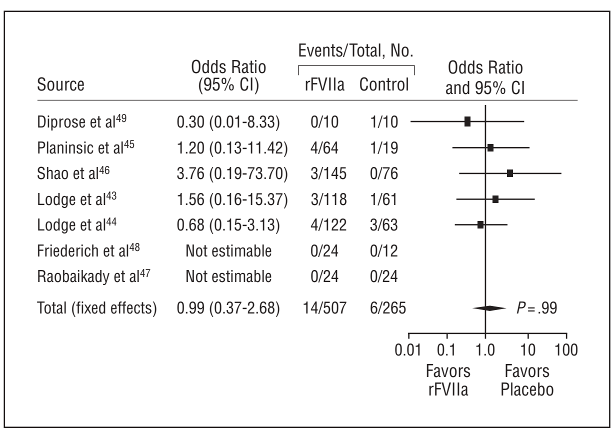

Figure 4. Plot of mortality rates in the selected studies. CI indicates confidence interval; rFVIIa, recombinant activated factor VII.

Efficacy of Treatment (Regardless of Dose)

Heterogeneity was assessed using the Cochran Q test ($Q = 10.2$; $P = .04$) and I^2 (60%, suggestive of moderate to severe inconsistency). According to current practice,[60] being in the presence of heterogeneity, random-effects variables have been computed: the random-effects OR was 0.29 (95% CI, 0.10-0.80; $P = .02$ for effect). Publication bias was assessed using funnel plot inspection and the Egger test: both at visual inspection by computing the Egger regression intercept test($\alpha = -2.8$; 95% CI, −4.4 to 1.1; $P = .01$ for bias), the efficacy analysis revealed a significant publication bias. The number of negative or null studies required to make not significant the results of the meta-analysis for the efficacy of rFVIIa treatment was established at 14. By applying the trim and fill technique, 2 studies were trimmed and a new model was estimated. After this correction, the OR (random effects) for homologous PRBC transfusions became 0.61 (95% CI, 0.38-0.98), with a still significant P value for effect.

Efficacy of Treatment (High-Dose Subgroup)

In this subgroup, the Cochran Q value was 3.6 ($I^2 = 18\%$; $P = .3$ for heterogeneity), not significant for heterogeneity or inconsistency of data. Therefore, no random-effects model was applied. Visual inspection of the funnel plot and the Egger regression intercept test ($\alpha = -2.14$; 95% CI, −3.5 to −0.7; $P = .02$ for bias) revealed a significant publication bias. The number of negative or null studies required to make not significant the results of the meta-analysis for the efficacy of high-dose rFVIIa treatment was established at 8. By applying the trim and fill technique, 2 studies were trimmed, and a new model was estimated. After this correction, the OR for homologous PRBC transfusions became 0.53 (95% CI, 0.30-0.94), with a still significant P value for effect.

Safety of Treatment

Thromboembolic event analysis had a Q value of 0.99 ($I^2 = 0\%$; $P = .99$ for heterogeneity), indicating no heterogeneity or inconsistency of data. Visual inspection of the funnel plot and the Egger intercept test ($\alpha = -0.37$; 95% CI, −1.07 to 0.34; $P = .24$ for bias) did not demonstrate a significant publication bias. Mortality analysis had a Q value of 1.7 ($I^2 = 0\%$; $P = .94$ for heterogeneity), indicating no heterogeneity or inconsistency of data. Visual inspection of the funnel plot and the Egger intercept test ($\alpha = 0.07$; 95% CI, −1.15 to 1.30; $P = .24$ for bias) did not demonstrate a significant publication bias.

OTHER OUTCOME MEASUREMENTS NOT INCLUDED IN THE META-ANALYSIS

Other outcome measurements were present in the 7 selected RCTs; however, they were not included in the meta-analysis owing to (1) nonhomogeneous ways of presenting the information for continuous variables (eg, mean[SD] of the mean or median and range); (2) nonhomogeneous method for outcome variable measurement (eg, operative bleeding or postoperative bleeding), and (3) outcome variable measured in no more than 2 studies (eg, perioperative hematocrit variation).

COMMENT

The main results of the present meta-analysis can be summarized as follows. First, there is a significant effect of rFVIIa treatment in terms of reduction in the number of patients being exposed to allogeneic PRBC transfusions, regardless of the dose applied. There is significant heterogeneity of the data and significant publication bias; however, after adjustment for both of these confounding effects, the treatment effect remained significant.

Second, in the subgroup of patients receiving at least 50 μg/kg of rFVIIa, there is a significant effect of the treatment in reducing the number of patients being exposed to allogeneic PRBC transfusions. In this subgroup, data are homogeneous and consistent; there is a residual reduced, albeit still significant, publication bias, but after correction, the treatment remained significantly associated with a decrease in allogeneic PRBC transfusion exposure. In the subgroup receiving a low dose of rFVIIa, there is apparently no effect on the transfusion rate. However, this subgroup has a low sample size and a wide CI for the effect; therefore, the issue of dose-related effects of rFVIIa deserves further studies correlating doses and effects.

Third, treatment with rFVIIa is not associated with increased rates of thromboembolic events or mortality; safety data are homogeneous, consistent, and not burdened by any publication bias. However, mortality rates were low in the studies included in this analysis, and the resulting wide CI does not allow a clear statement.

The main reasons for the heterogeneity of the efficacy data are the existence of different dose regimens and the coexistence of trials with an overall very high transfusion rate (eg, liver transplantation, 94%) and with a less pronounced transfusion rate (eg, retropubic prostatectomy, 30%). Moreover, these factors interplayed together, because low doses were more frequent in the studies where the transfusion rate was lower. Another heterogeneity factor in this study is the presence of different surgical procedures, which can raise the problem of pooling the data. For this reason, and the existence of a publication bias, the significant effect of rFVIIa treatment regardless of dose should be considered with considerable caution. Conversely, the information about the positive effect of high-dose rFVIIa treatment is more sound, not biased by heterogeneity, and convincing even after accounting for the moderately significant publication bias. In fact, the "high dose" (≥50 μg/kg) is closer to the therapeutic single dose suggested for the treatment of patients with hemophilia or factor XI deficiency.[61,62]

Other outcome measurements related to bleeding and transfusion needs are unavailable for the meta-analysis owing to the heterogeneous measurements in the selected RCTs. However, it is worthwhile to consider that 2 of 7 studies demonstrated a significant reduction in the volume of PRBCs transfused: 1 study[48] demonstrated a significant reduction in blood loss and the other[44] a significantly better preservation of the hematocrit value. No RCT demonstrated any difference in terms of intensive care unit or hospital stay.

Many case reports or case series presenting a positive experience with the use of rFVIIa in different surgical settings have been published. The most represented surgical scenario is adult and pediatric cardiac surgery.* In this setting, there are some retrospective trials with historical controls: Karkouti and coworkers[37] demonstrated a beneficial effect of rFVIIa in terms of blood loss and blood product use in patients with intractable bleeding after cardiac surgery; von Heymann and coworkers[39] reported similar results in the period immediately after treatment, but in a 24-hour period the only difference was reduced platelet concentrate use. The only RCT is that by Diprose et al,[49] where in a limited number of patients preemptive treatment with rFVIIa exerted a beneficial effect in terms of the nontransfused patient rate. Another well-represented surgical setting is liver resection and transplantation in cirrhotic and noncirrhotic patients: for liver transplantation, 1 case series[25] and 2 nonrandomized, uncontrolled studies[36,38] exist, the last 2 reporting a reduction in transfusion needs in rFVIIa-treated patients. Two large multicenter RCTs[43,45] have been published, with different results: in both the articles there is no impact of rFVIIa treatment in terms of blood loss or total amount of blood products transfused; conversely, 1 study[43] reports a significantly lower rate of patients needing allogeneic blood products, whereas the other does not address this end point. Liver resection accounts for the other 2 multicenter RCTs,[44,46] with neither demonstrating a beneficial effect of rFVIIa treatment. Finally, liver biopsy in cirrhotic patients has been addressed by a case series[21] and an uncontrolled, randomized, dose-ranging study.[42] Both the articles report a positive experience.

Many case reports dealing with gynecologic and obstetric surgery have been published,[3-5,10,13,17] all reporting successful experiences in patients with intractable, often life-threatening, perioperative bleeding. Three successful case reports[6,9,16] where intractable bleeding was stopped after rFVIIa treatment are reported in kidney transplantation. In orthopedic surgery, there is 1 case report[28] and 1 RCT, where treatment with rFVIIa failed to reduce blood loss or transfusion requirements[47] in patients operated on for traumatic pelvis fracture.

In abdominal surgery there is an important RCT[48] in patients undergoing retropubic prostatectomy: patients treated

*References 7, 15, 18, 19, 22, 23, 27, 32, 34, 35.

with rFVIIa had significant reductions in blood loss, the number of PRBC units transfused, and the transfusion rate. Other successful case reports and series where rFVIIa was used for treating severe perioperative bleeding have been described in vascular surgery,[12,14,29,33] general surgery,[20,24,30] neurosurgery,[8,26,31] and pediatric surgery.[23]

There is an important methodological difference between the RCTs and the case reports, case series, and even uncontrolled trials. All the RCTs have an experimental design based on prophylactic use of rFVIIa in surgical patients at high risk for bleeding and allogeneic transfusions; conversely, all the other studies report the results of rFVIIa as a "salvage" treatment in patients being already polytransfused due to severe bleeding after different surgical procedures. In this last setting, the results seem promising, but there is no RCT published yet, even as a large multicenter trial at different rFVII doses is currently ongoing in cardiac surgery.

From this meta-analysis, the prophylactic use of rFVIIa\]=is effective in reducing the rate of patients receiving allogeneic PRBCs; after adjustment for heterogeneity and publication bias, the best significant OR found in this analysis was 0.43 for patients receiving a dose of at least 50 µg/kg. This introduces the important issue of the financial impact of prophylactic treatment with rF-VIIa. For a single-dose regimen of 90 µg/kg, the cost of treatment may be considered in the range of €5000 (about US $7000) per patient (with significant country-to-country variations). Considering that no RCT could demonstrate any significant benefit in terms of intensive care unit or hospital stay, or any difference in mortality rates, this huge financial burden should be compared only, from a cost-benefit point of view, with the cost of blood products saved. If we accept a risk reduction of 50%, and consider a mean cost for 1 U of PRBCs of €250, (US $350) the cost-benefit ratio is favorable only if each transfused patient is expected to receive 40 PRBC units.

Safety issues have been repeatedly raised in the literature. The main concern is that use of a procoagulant drug, with strong thrombin-generation properties, may induce thromboembolic complications, especially in patients with a high risk profile for these kinds of complications. Of course, it is difficult to attribute a thromboembolic event to a drug with a reasonable level of certainty because many other factors could be considered responsible. However, there are case reports[50,51] in which the researchers attribute thromboembolic events to the use of rFVIIa in nonhemophilic patients. Some case series showed a high rate of thromboembolic events in patients treated with rFVIIa,[30,49,63] and in a recent RCT[52] where patients with intracerebral hemorrhage were randomized to receive rFVIIa or placebo, a significantly higher rate of thromboembolic complications was found in the rFVIIa group. However, 2 retrospective studies[37,39] did not demonstrate different rates of thromboembolic complications in patients undergoing cardiac surgery, and all 7 RCTs considered in this meta-analysis did not find any difference in thromboembolic complication rates. Review articles[64,65] and a recent expert recommendations article[66] confirm that the present knowledge does not enable the assertion that in surgical patients the use of rFVIIa is associated with an increased thromboembolic risk, even if in selected high-risk patients this possibility cannot be excluded. In particular, patients with procoagulant diseases (eg, cancer or infections) or with a history of thromboembolic events and patients receiving concomitant procoagulant drugs (eg, aprotinin or tranexamic acid) were not studied as a subgroup in the present analysis.

In conclusion, the huge amount of heterogeneous information about the off-label use of rFVIIa has raised increasing interest in the past 2 years. Review articles exploring the role of this drug in selected settings[67-72] or in the general population[64-66] provided a comprehensive analysis of the published articles and left the possibility open that rFVIIa may have a role in the surgical setting. Most of these articles conclude that the prophylactic use is still debated or not recommended[66] and that the therapeutic use is still based on uncontrolled trials and experiences.

We believe that this meta-analysis may offer quantitative information on the size effects of rFVIIa in the surgical setting: its results confirm that prophylactic use is significantly but marginally effective and probably burdened by a high cost-benefit ratio. Additional quantitative information confirms that presently there is no evidence of increased thromboembolic risk in surgical patients. There is evidence of different effects at different doses, which introduces the need for more dose-oriented trials. Large RCTs on rFVIIa as therapeutic rather than prophylactic treatment are required to finally define its role in the surgical environment. To approach this crucial point, a possible RCT should include patients at high risk for bleeding submitted to surgical procedures, randomizing them to receive placebo or rFVIIa ($\geq$60 µg/kg) once bleeding is evident (eg, after cardiopulmonary bypass in cardiac procedures) and before starting massive blood product transfusions. End points should not only be the rate of patients being transfused but even the number of units transfused. With the hypothesis of a transfusion rate of 60% in patients receiving placebo and a reduction to 30% in treated patients (OR, 0.5), the total number of patients to be enrolled is 80 (40 in each group).

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Correspondence: Marco Ranucci, MD, Department of Cardiovascular Anaesthesia, IRCCS Policlinico S. Donato, Via Morandi 30, 20097 San Donato Milanese, Milan, Italy (cardioanestesia@virgilio.it).
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INVITED CRITIQUE

In 1999, the US Food and Drug Administration approved the use of rFVIIa for the treatment of bleeding episodes in patients with the inherited coagulation disorder hemophilia A or B and inhibitors to factor VIII or IX. Increasingly, however, this product is being used by surgeons to treat patients with acquired coagulopathy, particularly during surgical procedures in which large blood loss is anticipated, such as cardiac, vascular, and liver transplantation surgery. As experience continues to accumulate and the literature documents its effectiveness, this drug is often administered prophylactically to limit transfusion requirements. However, as outlined in the meta-analysis by Ranucci et al, there is considerable variation across studies in the dose used and in the timing of administration. Because the effectiveness of rFVIIa in promoting clot formation may be affected by other factors, such as the platelet count, the fibrinogen level, and the pH at the time of administration, further research in this area is clearly in order. In addition, although most studies document a decrease in transfusion requirements in patients receiving rFVIIa, improvements in mortality rates are not well supported by the small and underpowered studies reviewed. The prohibitive cost of this drug must also be taken into consideration. Most important, there is the potential to do harm by administering a procoagulant in a patient who has other risk factors for thrombosis. In January 2006, O'Connell et al[1] released a summary of the adverse events associated with the use of rFVIIa as reported to the Food and Drug Administration. One hundred eighty-five thrombotic events were reported, with most occurring when the drug was administered for an unlabeled use. The total number of patients receiving rFVIIa during that period is unknown, so the number 185 hangs out there as a numerator without a denominator. Mayer et al[2] suggested that treatment with rFVIIa within 4 hours of the onset of intracerebral hemorrhage was effective in limiting the size of the hematoma, reduced the mortality rate, and improved functional outcomes at 3 months. However, serious thromboembolic events (including myocardial and cerebral infarction) occurred in 7% of patients treated with rFVIIa vs 2% of those treated with placebo.

Conspicuously absent from the review by Ranucci et al is any mention of patients with multiple trauma. Trauma surgeons using rFVIIa will attest to the dramatic control of coagulopathic bleeding that is possible when the drug is administered in a timely manner and not as a "last-ditch" attempt at rescue. A recent informal survey of trauma surgeons revealed that most use rFVIIa to some extent in their practice, primarily as part of a massive transfusion protocol. This drug may be particularly effective in limiting the need for transfusions in areas where blood products are limited, such as combat situations. True cost-effective analyses are lacking, but at our trauma center, we demonstrated that the cost of 1 dose is approximately equivalent to the cost of 1 whole blood transfusion (including red blood cells, clotting factors, and platelets). In the only randomized, multicenter trial available to date on injured patients, Boffard et al[3] reported a significant reduction in red blood cell transfusions in patients with blunt trauma and a trend toward a decrease in patients with penetrating trauma who had received rFVIIa compared with matched controls. Thrombotic events were low and similar in all groups (2%-4%). In the United States, a randomized controlled study investigating the use of rFVIIa in injured patients is currently under way, as is a registry-based study open to all centers using the drug. Until large-scale studies in trauma and in other areas of surgery are completed, surgeons who choose to use rFVIIa to control coagulopathic bleeding should administer a relatively high dose (80-90 μg/kg) of this drug after control of accessible surgical bleeding and before acidosis and hypothermia limit its effectiveness, being ever vigilant to the potential of inducing life-threatening thrombotic complications.

M. Margaret Knudson, MD

Correspondence: Dr Knudson, Department of Surgery, San Francisco General Hospital, Ward 3A, 1001 Potrero Ave, San Francisco, CA 94110 (pknudson@sfghsurg.ucsf.edu).

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