Recombinant Activated Factor VII Increases Stroke in Cardiac Surgery: A Meta-analysis

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Objectives: **Recombinant activated factor VII (rFVIIa) is used in various surgical procedures to reduce the incidence of major blood loss and the need for re-exploration. Few clinical trials have investigated rFVIIa in cardiac surgery. The authors performed a meta-analysis focusing on the rate of stroke and surgical re-exploration.**

Design: **Meta-analysis.**

Setting: **Hospitals.**

Participants: **A total of 470 patients.**

Interventions: **None.**

Measurements and Main Results: **Four investigators independently searched PubMed and conference proceedings including backward snowballing (ie, scanning of reference of retrieved articles and pertinent reviews) and contacted international experts. A total of 470 patients (254 receiving rFVIIa and 216 controls) from 6 clinical trials (2 randomized, 3 propensity matched, and 1 case matched) were included in the analysis. The use of rFVIIa was associated with an increased rate of stroke (12/254 [4.7%] in the rFVIIa group *v* 2/216 [0.9%] in the control arm, odds ratio [OR] = 3.69 [1.1-12.38], $p = 0.03$) with a nonsignificant reduction in rate of surgical re-exploration (13% *v* 42% [OR = 0.27 (0.04-1.9), $p = 0.19$]). The authors observed a trend toward an increase of overall perioperative thromboembolic events (19/254 [7.5%] in the rFVIIa group *v* 10/216 [5.6%] in the control arm [OR = 1.84 (0.82-4.09), $p = 0.14$]). No difference in the rate of death was observed.**

Conclusions: **The administration of rFVIIa in cardiac surgery patients could result in a significant increase of stroke with a trend toward a reduction of the need for surgical re-exploration. The authors do not recommend routine use in cardiac surgery patients. rFVIIa may be considered with caution in patients with refractory life-threatening bleeding.**

KEY WORDS: bleeding, cardiac surgery, FVIIa, recombinant factor VII, stroke, surgical revision, anesthesia

COAGULATION FACTORS like recombinant activated factor VII (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) recently gained special interest because they interact in their natural physiologic environment of coagulation cascade once being activated. As soon as the first reports on rFVIIa were published on the successful resuscitation and survival of combat victims, rFVIIa increasingly was used off-label in refractory bleeding associated with trauma[1] and cardiac surgery.[2-8]

Because rFVIIa exerts its pharmacologic action by inducing thrombin generation on locally activated platelets and contributes to the formation of a stabilized fibrin clot at the site of vessel injury,[9] safety concerns have been raised on the potential danger of severe thromboembolic events.[10,11] Recently, safety and efficacy data published by Gill et al[2] in a randomized controlled trial showed a reduced rate of patients undergoing surgical revision and a reduction in overall mediastinal drainage blood loss as well as transfusion requirements with a trend toward a higher incidence of critical severe adverse events.

A meta-analysis published in 2009 by Zangrillo et al[12] at the authors' institution reported a nonsignificant reduction in surgical re-exploration in patients receiving rFVIIa and a nonsignificant increase in the rate of perioperative stroke in these patients. At the time of the publication of the work of Zangrillo et al, safety concerns already had been raised, but the literature was inconclusive and did not focus on adverse effects in the area of cerebrovascular events like stroke.

These references out of various clinical settings in conjunction with the previous results of Zangrillo et al[12] led the authors to the decision to scrupulously review and scan scientific articles on this topic. A rising number of references and notices in literature currently being published showed the necessity to conduct a systematic review of data pooled from existing trials limited to the cardiac surgery setting. Considering the hypothesis that the potential beneficial hemostatic effects could be counterbalanced by adverse effects, the authors performed a meta-analysis and comprehensive review of the current literature to determine the potential impact of rFVIIa on surgical re-exploration and the risk of adverse arterial vascular effects, namely stroke complications.

METHODS

Search Strategy

Four trained investigators independently searched for clinical trials in PubMed (updated December 1, 2010). The search strategy was established by Biondi-Zoccai et al[13] and is available in Appendix 1. In addition to the special search strategy mentioned earlier, conference proceedings (2008-2010) from the European Society of Anaesthesia, International Anesthesia Research Society, American Society of Anesthesiologists, European Society of Intensive Care Medicine, Society of Cardiovascular Anesthesiologists, European Association of Cardiothoracic Anaesthesiologists, International Society of Thrombosis and Haemostasis, and American College of Chest Physicians congresses were scanned in order to detect further abstracts or recent scientific articles of relevance. In addition, the authors systematically applied backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) and contacted international experts for further studies. No language restriction was enforced, and non–English-language articles were translated before further analysis.

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Table 1. Description of the 6 Studies Included in the Systematic Review on rFVIIa Versus Control With the Number of Patients and Interventions

First Author	Journal	Year	rFVIIa (μg/kg) First Dose (Mean ± Standard Deviation)	No. of Patients Receiving a Further Dose	Cardiac Surgery Procedures	Study Design	No. of Patients in the rFVIIa Group	No. of Patients in the Control Group
Diprose	Br J Anaesth	2005	90 (0)	No	Complex noncoronary cardiac surgery	Randomized	10	10
Karkouti	Transfusion	2005	7 pts: 62 (13) 44 pts: 37 (9)	14	Varied procedures	Propensity-matched	51	51
Tritapepe	Crit Care Med	2007	70 (0)	4	Aortic dissection	Propensity-matched	23	23
Von Heymann	Crit Care Med	2005	60 (median)	10	Varied procedures	Case-matched	26	24
Gelsomino	Eur J Cardiothorac Surg	2008	18 (9-16) (median; interquartile)	Nonspecified	Varied procedures	Propensity-matched	40	40
Gill	Circulation	2009	35 pts: 40 69 pts: 80	No	Varied procedures	Randomized	104	68
Total							254	216

Abbreviation: pts, patients.

Study Selection

A total of 208 references obtained from database and literature searches first were examined independently at the title/abstract level by 4 investigators. Included studies had to compare the use of rFVIIa versus placebo or standard treatment; the authors only included scientific publications relating to adult cardiac surgical patients. Exclusion criteria were nonhuman experimental or animal studies, duplicate publications (in this case only the article reporting the longest follow-up was included), missing outcome data, and no case matching. In case of missing outcome data in studies, original authors were contacted and asked for additional information. Four investigators selected studies for the final analysis by independently assessing compliance to the selection criteria (Table 1).

Data Abstraction and Study Characteristics

Baseline, procedural, and outcome data were abstracted independently by 4 investigators, with divergences resolved by consensus and are listed in Table 1. Specifically, the authors extracted study design, population, clinical setting, rFVIIa dosage, and treatment duration. At least 2 separate attempts at contacting original authors were made in case of missing data.

The primary endpoint of this analysis was to determine the safety of rFVIIa in terms of stroke (as per author definition) and the efficacy of rFVIIa in terms of the reduction of surgical revision for bleeding. Secondary endpoints included death, the transfusion of blood products, and the incidence of overall venous and arterial vascular complications (ie, myocardial infarction, stroke, and deep venous thrombosis as per author definition).

Data Analysis and Synthesis

Binary outcomes from individual studies were analyzed and pooled in order to compute individual odds ratios (ORs) with pertinent 95% confidence intervals according to the fixed-effect Peto method in case of homogenous data (inconsistency $<50\%$); and the random-effect DerSimonian-Laird method in case of statistical heterogeneity (inconsistency $<50\%$).[13,14] Statistical heterogeneity (ie, the variability in effect estimates from study to study) and inconsistency (a more robust estimate of the variability in effect estimates from study to study, which is largely independent of the number of included studies) were measured using the Cochran Q test (which is largely comparable to the chi-square test, and, when yielding p values <0.10, suggests significant statistical heterogeneity) and I^2, respectively.[15] According to Higgins et al,[16] I^2 values around 25%, 50%, and 75% were considered as representing low, moderate, and severe statistical inconsistency, respectively. Specifically, OR <1 suggests that the first comparator is associated with a reduced incidence of the event, whereas OR >1 suggests that the 2nd comparator is associated with an increased incidence of the event. Unadjusted p values are reported throughout. The risk of small-study bias (including publication bias) was assessed by a visual inspection of funnel plots (ie, the graphic display of effect estimates and study precision, which enables appraisal of the potential asymmetry in meta-analysis datasets, often caused by the selective lack of publication of small negative studies, ie, publication bias).[16]

Statistical significance was set at the 2-tailed 0.05 level for hypothesis testing and at 0.10 for heterogeneity testing. Computations were performed with SPSS 11.0 (SPSS, Chicago, IL) and RevMan 4.2 (a freeware available from The Cochrane Collaboration).[14] This study was performed in accordance with The Cochrane Collaboration and the Quality of Reporting of Meta-Analyses guidelines.

RESULTS

Database searches, snowballing, and contacts with experts yielded a total of 208 citations. From these 208 citations, 187 nonpertinent titles or abstracts had to be excluded, and 21 studies were retrieved in complete form. A total of 15 studies were further excluded because they turned out to be review articles,[17,18] they were noncase matched[19] or had nonrandomized experimental design,[20-27] they studied a pediatric population,[28,29] they did not report outcome data,[30] or duplicate publication.[31] Six eligible clinical trials were identified (all of them recently published between 2005 and 2009), which were included in the final analysis[2-7] (Table 1).

Study Characteristics

The 6 included clinical trials were comprised of 470 patients (254 receiving rFVIIa and 216 controls) (Table 1). One trial was conducted in the setting of noncoronary artery surgery,[4] 1 in aortic dissections,[7] and the other 4 studies were involved in various cardiac surgery procedures.[2,3,5,6] All authors studied the hemostatic properties of rFVIIa and reported on vascular complications and/or surgical re-exploration. rFVIIa dosage varied across studies (Table 1), between 18 and 70 μg/kg being given in repeatable dosage and 90 μg/kg used as a single dose.

One study used rFVIIa prophylactically,[4] whereas the other 5 used rFVIIa in patients with refractory bleeding (definitions of refractory bleeding varied among authors). Five studies reported a