

Letter to the Editor

Use of Low-Dose Recombinant Activated Factor VII in the Off-Label Setting: A Comment to “The Judicious Use of Recombinant Factor VIIa”

Peter Kubisz, MD, DSc¹ Jan Stasko, MD, PhD¹ Pavol Holly, MD, PhD¹

¹ National Center of Haemostasis and Thrombosis, Department of Haematology and Transfusion Medicine, Jessenius Faculty of Medicine of the Comenius University in Bratislava, Martin University Hospital, Slovak Republic

Address for correspondence Peter Kubisz, MD, DSc, National Center of Haemostasis and Thrombosis, Department of Haematology and Transfusion Medicine, Jessenius Faculty of Medicine of the Comenius University in Bratislava, Martin University Hospital, Kollarova 2, 036 59 Martin, Slovak Republic (e-mail: kubisz@jfm.uniba.sk).

Semin Thromb Hemost 2017;43:355–356.

We read with a great interest the review by Goodnough and Levy on the off-label use of recombinant factor VIIa (rFVIIa), which was published under the title “The Judicious Use of Recombinant Factor VIIa,” in an earlier issue of this journal.¹ The article clearly summarized the randomized trials with off-label rFVIIa performed in the past 20 years. The association of off-label rFVIIa with uncertain efficacy and mortality benefit and a significant risk of thromboembolic, especially arterial, events were emphasized. The authors stated that rFVIIa should be used with restraint in the setting of life-threatening hemorrhage and the risks of thromboembolic events should be evaluated carefully and individually. Although we do agree that thromboembolic events represent a serious complication of off-label rFVIIa, especially in a high-risk population (elderly, cardiovascular comorbidity, cardio-surgery, and intracranial bleeding), we would like to point out an issue that was not separately discussed in the review and could, at least in our opinion, improve the safety of rFVIIa while maintaining its efficacy.

The off-label studies and patient registries have reported the administration of rFVIIa mainly in doses originally intended for the hemophilia population, for example, single dose approximately 90 µg/kg or above. However, as shown in FVII deficiency, rFVIIa could, at least in certain conditions, be hemostatically effective in substantially lower doses. The experience with lower dosing in off-label setting remains limited, although some of the randomized trials performed included arms with single doses as low as 5 µg/kg.² Interestingly, most of those trials failed to show the superiority of arms with rFVIIa ≥ 80 µg/kg in terms of clinical outcome (efficacy, mortality, demands on transfusion therapy). The retrospective analysis by Schmid et al, that evaluated the intentional off-label use of low-dose (56–71 µg/kg) rFVIIa in the setting of life-

threatening hemorrhage (blood loss ≥ 1,000 mL/h) in a single institution and included 73 cases (49 related to surgery or trauma), found the comparable clinical outcome as reported for the “standard” (~90 µg/kg) rFVIIa doses. The rate of thromboembolic events in the study was surprisingly low – only two (2.7%) patients were affected.³

We were inspired by the above-mentioned study and performed a retrospective analysis (9-year period; unpublished data) of off-label rFVIIa use at our institution—a university hospital with specialized units for hepatobiliary surgery and renal transplantation. The analysis was intentionally restricted to the treatment of life-threatening bleeding related to surgery, since rFVIIa was given particularly often in those patient subgroups. Forty-six consecutively treated surgical patients (mean: 59.0 years; range: 31–83 years; 27 men; 30 [65.2%] with underlying malignancy; 21 [45.6%] with hepatic or pancreatic resection; 6 [13.1%] with renal transplantation; 4 [8.7%] with the resection of retroperitoneal tumor; 3 [6.5%] with vascular surgery; 3 [6.5%] with lung resection; 9 [19.6%] with other major surgical procedures) with 47 bleeding episodes were included. Twenty-one patients with 21 hemorrhages were treated with low-dose rFVIIa (mean: 26.4 µg/kg; range: 11.5–64.5 µg/kg), whereas 46 patients with 46 hemorrhages were given rFVIIa at a dose above 80 µg/kg (mean: 92.7 µg/kg; range: 82.5–109.0 µg/kg). The actual dose of rFVIIa was individually determined by the consultant hematologist according to the availability of the drug and the patient's condition. The low-dose group showed a comparable patients' survival (90.4 vs. 80.7%, 48 hours after the first rFVIIa administration) and blood product consumption (4.2 vs. 6.0 transfusion units [TU] of red packed cells, 3.7 vs. 4.5 TU of fresh frozen plasma, and 0.2 vs. 0.1 TU of platelet concentrates, during a 48-hour period after the first rFVIIa administration) to the group with standard dose rFVIIa. No

published online
August 11, 2016

Issue Theme Laboratory Assessment of Hemostatic and Anticoagulant Therapy; Guest Editors: Robert C. Gosselin, CLS, and Dorothy M. Adcock, MD.

Copyright © 2017 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0036-1584573>. ISSN 0094-6176.

significant differences in age, gender, factors influencing rFVIIa efficacy (time to rFVIIa administration, body temperature, pH, coagulopathy, prior transfusion therapy), repeated rFVIIa administration, and the use of other hemostatic agents (antifibrinolytics, hemostyptics, vasoconstrictors) or procedures were seen between the groups. The numbers of hepatic and pancreatic resection as well as renal transplantation were proportional in both groups. Only two thrombotic events possibly related to rFVIIa were observed, one in each group – deep vein thrombosis of the lower extremity in the low-dose group and myocardial infarction in the other group. It is important to emphasize, however, that the patient from the low-dose group had a high prothrombotic risk separate from the rFVIIa administration (high-risk orthopedic surgery, age older than 80 years, prolonged immobilization, and severe cardiovascular comorbidity).

Thus, in our experience, a low-dose rFVIIa dose appeared to be a reasonably effective and safe modality for the off-label treatment of life-threatening hemorrhage related to surgery. Our experience also stresses the importance of careful evaluation for prothrombotic risk factors before the rFVIIa administration, as we also pointed out in our previous work.⁴ Of

course, the results of our study are limited by several factors, most prominently by the small number of evaluated patients, retrospective design, and compassionate use of rFVIIa, and should be interpreted with caution. However, we do believe that the use of lower rFVIIa doses could represent a risk-reducing approach in the off-label setting, at least in case of surgery-related bleeding.

References

- 1 Goodnough LT, Levy JH. The judicious use of recombinant factor VIIa. *Semin Thromb Hemost* 2016;42(2):125–132
- 2 Simpson E, Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev* 2012;3:CD005011
- 3 Schmid P, Mordasini A, Luginbühl M, et al. Low-dose recombinant factor VIIa for massive bleeding: a single centre observational cohort study with 73 patients. *Swiss Med Wkly* 2011;141:w13213
- 4 Kubisz P, Stasko J. Recombinant activated factor VII in patients at high risk of bleeding. *Hematology* 2004;9(5–6):317–332