Off-Label Use of Recombinant Human Factor VIIa

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Pharmacologic agents are routinely used to modulate the coagulation system, a strategy that is an important component of patient blood management [1]. Multiple procoagulant therapies are available for clinicians, including desmopressin acetate, tranexamic acid, aminocaproic acid, fibrinogen concentrates and prothrombin complex concentrates. In perioperative surgical management with use of procoagulants, reports have focused on cardiac surgical patients but continue to expand to other surgical patients. For example, tranexamic acid has long been approved and available for clinical use as a hemostatic agent but more recently a large scale clinical trial was able to demonstrate both efficacy and safety for its prophylactic use in trauma patients [2]. The role of antifibrinolytic therapy in trauma emerged from earlier studies in cardiac and other surgical patients [3]. One additional prohemostatic agent, recombinant human factor VIIa (rFVIIa), has undergone an ever-increasing off-label use within the first 10 years of its approval for treatment of hemophilia patients with inhibitors (Fig 1) [4]. Postapproval, inpatient use of rFVIIa from 2000 to 2008 increased 143-fold for off-label indications compared with a fourfold increase for use in patients with hemophilia.

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In this issue of The Annals of Thoracic Surgery, Alfirevic and colleagues [5] report a single institution, retrospective 5-year analysis of nearly 28,000 cardiac surgery patients with perioperative coagulopathy, of whom 164 (0.6%) received rFVIIa. They matched 144 of these to 359 control patients using propensity techniques for comorbidities and intraoperative red blood cell transfusions, and analyzed for mortality as a primary outcome, with thrombosis, renal, and neurologic complications as secondary outcomes. They report 40% of patients treated with rFVIIa died, compared with 18% of controls (odds ratio [OR] 2.82, 1.64 to 4.87, \( p < 0.001 \)). Renal morbidity was significantly greater at 31% in the rFVIIa cohort compared with 17% of controls (OR 2.07, 1.19 to 3.62, \( p < 0.002 \)). Neurologic and thrombotic complications were not different compared with controls, and no dose effect of rFVIIa was found. The authors conclude that caution is advised in the off-label administration of rFVIIa to cardiac surgical patients.

Retrospective, observational studies like this are often fraught with potential confounding issues from patients who receive “last ditch” therapies like rFVIIa. Patients are already destined to have adverse outcomes that, despite propensity matching, bleed for uncontrollable and under-recognized reasons that may include retrocardiac surgical tears that are exceedingly difficult to fix or other potential complications that may not be predictable. As in the case of other therapies, retrospective database analysis is helpful in identifying the critically ill, problematic patients who may have adverse events, and thus worse outcomes. All prohemostatic agents in these circumstances will potentially be associated with adverse effects because they are administered for patients having these complications. Placebo, controlled randomized study data are critical for interpreting risk versus benefit considerations in such “last ditch” therapies.

Of note is a 2012 Cochrane review [6] of 29 randomized controlled trials, 16 of which involve 1,361 participants with prophylactic use of rFVIIa in 729 subjects and 13 trials involve 2,929 participants that examined the therapeutic use of rFVIIa in 1,878 subjects. There was a trend in favor of rFVIIa for reducing mortality (relative risk [RR] 0.91; 95% confidence interval [CI] 0.78 to 1.06). However, there was also a trend against rFVIIa for increased thromboembolic adverse events (RR 1.14; 95% CI 0.89 to 1.47). The authors of this Cochrane review concluded that the use of rFVIIa as a hemostatic drug, either prophylactically or therapeutically, remains unproven and that its use should be restricted to clinical trials. This position has been echoed by the Canadian National Advisory Council (NAC) on blood and blood products; the NAC recommends that rFVIIa no longer be used off-label for prevention and treatment in patients without hemophilia [7].

However, current guidelines from the Society for Thoracic Surgery and Society of Cardiovascular Anesthesiologists recommend use of rFVIIa in open heart surgical patients with refractory microvascular bleeding [8]. This is in part based on an important rFVIIa study in cardiac surgery evaluating the safety and efficacy of recombinant activated factor VII in a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery that was a dose-escalation study in high-risk patients after cardiac surgery and were bleeding greater than 200 mL/hour [9]. The primary endpoints were critical serious adverse events, and secondary endpoints included rates of reoperation, amount of blood loss, and transfusion. Return to the operating room for

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reexploration was approximately 25% for placebo, compared with approximately 12% to 15% in the rFVIIa groups. There were more critical serious adverse events in the rFVIIa groups which did not reach statistical significance [9]. We and others have followed the off-label use of rFVIIa based on this report and other published experience [10,11].

As the authors suggest, additional data from placebo-controlled randomized trials is not available nor will likely in the foreseeable future, primarily because of feasibility issues (eg, difficulty in obtaining informed consent in a timely manner, ethical concern of administering a placebo to patients with refractory blood loss, and lacking standardized alternative therapies), but also because further clinical development of rFVIIa or its analogs will be for licensed indications. Therefore, it would be ill advised to use rFVIIa outside of approved indications without considering its risk–benefit profile in the specific setting of refractory hemorrhage in cardiac surgical patients. As has been noted, clinicians need to carefully scrutinize data from randomized trials for applicability and data from observational studies for selection bias (for or against the drug) [12]. Other considerations include that patients are increasingly receiving irreversible antiplatelet agents (eg, clopidogrel, prasugrel, and ticagrelor) which also increase the potential for refractory bleeding. As there is no specific antidote for the P2Y12 receptor inhibitors, we have shown that rFVIIa can significantly reduce the platelet defect associated with these agents [13,14]. Further prospective clinical studies are needed for these patients who are at high risk for refractory blood loss and may benefit from novel prohemostatic therapies, including rFVIIa and prothrombin complex concentrates.

In the meantime, it is important when to consider rFVIIa as a therapeutic off-label agent to treat refractory bleeding after major surgery or trauma in view of randomized clinical trial data showing it to be ineffective and possibly harmful in various other clinical settings. When presented with a patient who continues to bleed despite administration of all available therapies, clinicians have only two choices; they can keep administering the same interventions that have been unsuccessful, or they can administer a procoagulant agent such as rFVIIa or prothrombin complex concentrates [12]. We believe that in the setting of refractory blood loss, clinicians are justified in choosing procoagulant agents for several reasons. Patients with ongoing refractory bleeding will have dismal outcomes unless the blood loss is controlled in a timely manner, and are already subject to adverse outcomes that may not be adequately matched with propensity scoring [15]. Even if the safety data from randomized trials apply as previously reported, which indicate that rFVIIa increases the risk of thrombotic complications by several percent [16], this risk may be dwarfed by uncontrolled hemorrhage that is commonly fatal.

References

Fig 1. Estimated annual in-hospital cases of rFVIIa use for hemophilia and off-label indications. Cases signify the number of hospitalizations during which rFVIIa was used. The graph depicts all cases for each year. The width of each segment represents the number of cases for each category as indicated by differential shading. (CV = cardiovascular; hemophilia = hemophilia A and B; ICH = nontraumatic intracranial hemorrhage; trauma = body and brain trauma.)


