The role of the recombinant Factor VIIa during cardiac surgery in the post-aprotinin era

By Mojca Remskar Konia, MD., PhD and Hong Liu, MD
University of California Davis Health System, Sacramento, CA

Bleeding is relatively common during the post-bypass period and after cardiac surgery, especially in patients with re-do surgery, prolonged bypass time, and recent anti-platelet agent use. It is a cause of a significant morbidity and mortality, prolonged ICU and hospital stay and increased cost. An antifibrinolytic agent used to decrease peri-operative bleeding in cardiac surgery, aprotinin, has recently been withdrawal from the market, because of the potential risks of renal failure and postoperative mortality.

Increasing number of reports on the use of the recombinant activated factor VII (rVIIa) in non-cardiac surgery has made it an interesting option in the treatment of refractory postoperative bleeding in cardiac surgery. It has been studied in a limited number of small randomized studies and cohort studies with a control group and a number of retrospective database reviews, case reports or series. Large double-blind, placebo-controlled, randomized studies are missing. Currently the use of rVIIa is FDA approved for patients with hemophilia A and B with inhibitors to coagulation factors VIII and IX. In Europe it is also approved for factor VII deficiency and Glanzmann’s thrombasthenia in patients who are refractory to platelet transfusions. Its use in trauma, hepatic, orthopedic, urologic, obstetric and cardiac surgeries is off-label.

The half-life of rVIIa is 1.7 to 3.1 hours and is not affected by liver disease. It appears to be shorter in children and bleeding patients. Studies suggest that the action of rVIIa is dependent on sufficient levels of coagulation factors (>30%), specifically fibrinogen (>50-75 mcg/dl), Factor V and Factor X (> 5-10%) and sufficient platelet count (50x10^9/ml). If pH is below 7.2, the proportion of patients responding to rVIIa decreases. Hypothermia decreases its effect at core body temperature below 33 °C.

The mechanism of action of rVIIa is not completely understood. Based on our knowledge of endogenous factor VII, we know that vessel injury exposes tissue factor (TF) expressed on subendothelial cells. Factor VII and TF interact and form a complex that catalyzes the conversion of factor X into its active form Xa, leading to thrombin formation and platelet activation. A high plasma concentration of rVIIa needed to induce hemostasis in the refractory bleeding suggests that TF-dependent activation of the coagulation is not the sole mechanism of action. It has also been shown that rVIIa can directly activate Factor X independently of TF.

In cardiac surgery rVIIa has been used recently for either prophylactically, as a treatment in patients with identifiable or probable coagulation defects or as a rescue therapy in hemorrhage refractory to other treatments. Although there may be some beneficial effect on blood loss, prophylactic use of rVIIa in cardiac surgery is currently not recommended. Routine use of rVIIa in patients with identifiable and probable coagulation defects is also not recommended because the potential benefits do not appear to outweigh its potential side effects as compared to the standard hemostatic management in cardiac surgery. The administration varied from a single dose to multiple doses and from as low as 11-25 mcg/kg to as high as a cumulative dose of >400 mcg/kg. Current recommendations, however, consider the use of rVIIa in refractory hemorrhage in cardiac surgery appropriate in cases in which significant clotting factor replacement therapy has occurred. The suggested dose is 41-90 mcg/kg. The dose may have to be repeated in 2 to 4 hours if bleeding persists.

A concern in cardiac patients receiving rVIIa is the risk of a thromboembolic event. This is especially a concern because cardiopulmonary bypass may up-regulate local and systemic “blood-borne” TF. These patients also express aberrant TF in atherosclerotic lesions. Suggested TF-dependent mechanism may lead to unwanted systemic thrombosis. Reported event rate in the cardiac population is 5.3%. In addition, there is a concern of possible effects of rVIIa on renal function. A propensity score-matched, case-control study involving 51 patients with massive blood loss after cardiac surgery showed that the incidence of acute renal dysfunction among patients receiving rVIIa was 2.4 times that in the control group.

In summary, even though most published studies reported reduction in blood loss either as witnessed by surgeon, decreased chest tube drainage or decreased need for further blood products, in the absence of large double-blinded, placebo-controlled, randomized studies, the exact role of rVIIa in cardiac surgery is hard to predict with certainty. Current data suggest a potential benefit in refractory bleeding, but further investigation is warranted in order to design guidelines on the use of rVIIa in cardiac surgery and to determine its safety and efficacy profile.

References:


