THE HAZARD OF COMPARING APPLES AND ORANGES: THE PROPER INDICATION FOR THE USE OF RECOMBINANT ACTIVATED CLOTTING FACTOR VII IN CARDIAC SURGERY

To the Editor:

We read with interest the article by Uber and colleagues[1] regarding the use of recombinant activated clotting factor VII (rFVIIa) after complex cardiovascular surgery and would like to raise the following issues.

First, in our opinion it is inappropriate to compare the pharmacologic management of bleeding with surgical reexploration, especially when the origin of the bleeding is unknown. Postoperative bleeding is a common complication after cardiac surgery and a major cause of reexploration. Bleeding after cardiac surgery has 2 principle causes: multifactorial coagulopathy and surgical bleeding, each accounting for about 50% of cases.[2]

When bleeding arises from a coagulopathy and we can identify a defect of primary hemostasis (platelets), secondary hemostasis (clotting factors), or both, it is appropriate to replace the deficient circulating factors. In such cases, rFVIIa may play a role,[3] as may other blood products and clotting factors. Conversely, when the hemorrhage is the result of a surgical-problem, reintervention to correct the defect is the necessary course of action. Thus it is extremely important to distinguish between surgical bleeding and coagulopathy to choose the appropriate treatment. In identifying the cause of bleeding after cardiac surgery, rotational thromboelastometry plays an important, emerging role. Rotational thromboelastometry allows point-of-care testing of whole blood with respect to clot quality and intrinsic and extrinsic pathways, identifying both hypercoagulable and hypocoagulable states. Moreover, rotational thromboelastometry is able to guide the use of hemostatic agents, such as rFVIIa.[2]

In recent years, in our center we have treated 10 patients with rFVIIa, all according to a specific diagnostic and therapeutic algorithm (Figure 1). All patients presenting with postoperative bleeding undergo classic coagulation studies, platelet count, and rotational thromboelastometric profile to discriminate between surgical bleeding and coagulopathy. The rotational thromboelastometry tests adopted are INTEM and EXTEM, for the intrinsic and extrinsic pathways respectively, FIBTEM for the qualitative study of fibrinogen status, and HEPTEM to monitor heparin effects. Patients with important bleeding but essentially normal coagulation profiles are treated with surgical reexploration. Conversely, patients with coagulopathy are treated with fresh-frozen plasma, platelets, fibrinogen, and protamine as guided by rotational thromboelastometric results. Whenever refractory bleeding persists despite this treatment, rotational thromboelastometry is reperformed, and if a state of hypocoagulability persists (prolonged clotting time in the EXTEM test with a cutoff point greater than 180 seconds), a dose of rFVIIa (80–120 μg/kg) is administered.[4,5] Among our 10 patients, hemostasis was successfully achieved in 100% of cases, and there have been no cases of thromboembolism.

Indeed, rFVIIa can play a role in the management of bleeding after cardiac surgery; however, it carries significant attendant risks of thromboembolic complication.[2,4,5] In our opinion, it should be used with care,

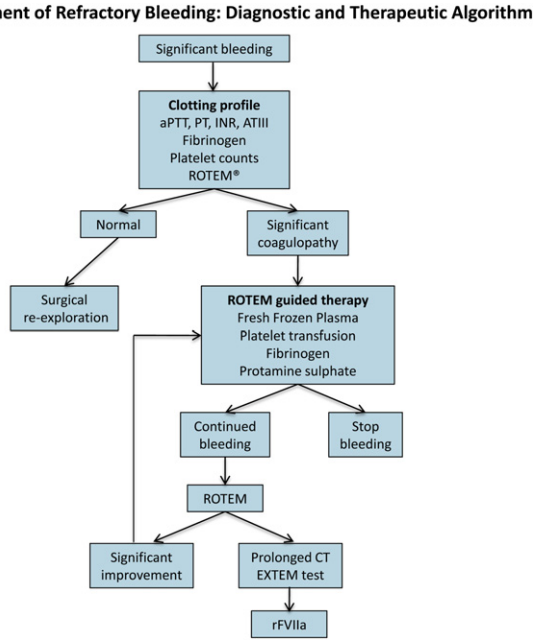

FIGURE 1. Management of refractory bleeding diagnostic and therapeutic algorithm. *aPTT,* Activated partial thromboplastin time; *PT,* prothrombin time; *INR,* international normalized ratio; *ATIII,* antithrombin III; *ROTEM,* rotational thromboelastometry; *CT,* clotting time; *EXTEM,* rotational thromboelastometric test for extrinsic pathway.

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and only for patients presenting with a coagulopathy as confirmed by rotational thromboelastometric analysis. Ideally, the lowest dose capable of correcting the coagulopathy should be given, avoiding a hypercoagulable state and thus thromboembolic events. Adopting this protocol avoids placing patients with a surgical cause of bleeding at an unjustified risk of thromboembolism and reserves rFVIIa for those who truly need it.

In conclusion, rFVIIa represents a treatment with its own specific indications, and we should not consider it as an alternative to reexploration in cardiac surgery. Indeed, the two are ''horses for courses.''

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Reply to the Editor:

We appreciate Tarzia and colleagues' letter regarding our article.[1] They take exception to comparing reexploration with pharmacologic management using recombinant activated factor VII (rFVIIa) in the intensive care unit because the source of bleeding is not known. They also elucidate a well–thought out algorithm for the management of postoperative bleeding.

Our initial experience with rFVIIa was in the operating room, where we found it to be highly effective at controlling intraoperative bleeding and to reduce the incidence of packing and delayed closure for hemostasis.[2] We developed criteria for correction of coagulopathy (including platelet count, prothrombin time, partial thromboplastin time, and fibrinogen levels), acid–base status, temperature, and ionized calcium levels before the administration of rFVIIa. We found that patients who continued to bleed despite correction of these variables responded quickly to rFVIIa.

All intensive care unit patients in our current study had undergone similar evaluations in the operating room and were considered not to have surgical bleeding. Unfortunately, the source of significant bleeding in the intensive care unit is always unknown, and this is the clinical conundrum our study attempted to address. In this study, we found 1 case of surgical bleeding out of the 12 patients who received rFVIIa. This is substantially lower than the 50% quoted by Tarzia and colleagues. This emphasizes the importance of having a well–thought out algorithm for the management of bleeding. Ours begins by defining significant bleeding as 3 mL/kg/h for 2 or more consecutive hours. Correction of the previously mentioned variables is accomplished as early as possible. Hemothorax and pericardial tamponade are considered indications for reoperation. Finally, the attending surgeon's index of suspicion for surgical bleeding is the final determinant of therapy. As we had previously observed in the operating room, bleeding intensive care unit patients with corrected coagulation factors, temperature, ionized calcium, and acidosis quickly responded to rFVIIa. This suggests that we are not capable of measuring a clinically significant coagulation deficiency. Perhaps rotational thromboelastometry will be able to shed light on these difficult patients. Rotational thromboelastometry was only recently approved by the Food and Drug Administration in 2010 (after our study period), and furthermore only 2 of the 4 reagents described by Tarzia and colleagues, INTEM and HEPTEM, have been approved.

We anxiously await new tools for the diagnosis and treatment of postoperative coagulopathic bleeding. It is important that they be incorporated into a well-designed and well–thought out algorithm for the treatment of postoperative bleeding.

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CANNULATION SITES AND TYPES FOR ANTEGRADE CEREBRAL PERFUSION DURING ARCH SURGERY

To the Editor:

We read with great interest the recent published paper by Shi and