

The role of recombinant activated factor VII in cardiac surgery

A. Richardson, M. Herbertson, R. Gill

Shackleton Department of Anaesthesia, Southampton University Hospitals NHS Trust

ABSTRACT

Recombinant factor VIIa may reduce surgical blood loss and transfusion of blood products in cardiac surgery. However, the true risks of its use in this setting remains to be elucidated, especially when it is administered with other potent pro-haemostatic agents. We reviewed the recent literature on this topic and suggest that the off label use of recombinant factor VIIa is likely to continue. It is our institutional practice to use it in the operating room at a dose of 90mcg/Kg to ensure there is no obvious correctable surgical source of blood loss, and to be certain that bleeding has stopped before the chest is closed.

Keywords: *recombinant factor VII, cardiac surgery, bleeding, transfusion.*

INTRODUCTION

Bleeding is a common complication following cardiac surgery, leading to transfusion and/or surgical re-exploration. Both interventions are associated with significant cost, in terms of both risk to the patient and financial outlay to the healthcare system (1).

Perioperative allogeneic red cell and haemostatic component transfusion has been shown to be associated with increased length of intensive care unit and hospital stay (2), increased infection rates (3), increased rates of every postoperative morbid event (4), and decreased short- and long-term survival rates (5, 6).

Re-exploration is associated with significant increases in mortality, the need for intra-aortic balloon counter-pulsation, haemofiltration, prolonged ventilation and intensive care unit stay (7). Novel haemostatic agents may have role in reducing surgical blood loss and the associated transfusion of blood products.

Recombinant factor VIIa (rFVIIa) is licensed for the prevention and treatment of bleeding in patients with haemophilia with auto-antibodies to coagulation factors VIII or IX, FVII deficiency, and acquired haemophilia. The binding of VIIa to perivascular tissue factor (TF) initiates coagulation, although the process can only progress beyond the generation of small amounts of thrombin when the injury allows platelets and larger proteins to leave the vascular space and adhere to TF-bearing cells in the perivascular area. However, TF may also be expressed on activated neutrophils, monocytes and microparticles.

RECOMBINANT FACTOR VIIA

The exact role of this circulating TF remains

Corresponding author:

Ravi Gill, BM, FRCA
 Shackleton Department of Anaesthesia
 Southampton University Hospitals NHS Trust
 Tremona Road, Southampton SO16 6YD, UK
 e.mail: ravi.gill@suht.swest.nhs.uk

controversial, as under normal conditions it is thought to be inactive or encrypted (8). Thus, although the effects of VIIa are believed to be localized predominantly to the site of vessel injury, concerns remain about the potential for thrombotic complications arising from its use. The complex nature of haemostasis and the role rFVIIa plays have been previously described (9).

USE

The medical literature increasingly describes “off-label” rFVIIa use to treat severe bleeding after major surgery in patients without haemophilia. Whilst some studies have used it to prevent bleeding and transfusion (prophylaxis), the majority have used it as rescue therapy when conventional surgical exploration and blood product and anti-fibrinolytic agent administration has failed to arrest bleeding.

It has therefore rarely been studied in isolation from other pro-haemostatic agents. The majority of trials have reported on rFVIIa use in adults; some have examined the paediatric population. The range of surgical procedures in which it has been used has been comprehensive, with a significant rate of redo cardiac surgery in the adult setting (10).

DOSE

The optimal dosing regime for rFVIIa in the post-cardiac surgical setting remains unclear. The reported dose range for single bolus administration has been broad (11.1 – 180 mcg/kg), although many have used single doses of 90 mcg/kg or less. Some studies have limited treatment to a single bolus dose, whilst others have used repeated doses at varying intervals. Recommendations made by various expert panels have

suggested doses in the order of 40-100 mcg/kg in the setting of uncontrolled post-cardiac surgical haemorrhage, with second doses considered if no response is seen after 30 to 60 minutes (10).

EFFICACY

The consensus is that rFVIIa reduces bleeding after cardiac surgery, as evidenced by a reduction in chest tube drainage and red cell and component therapy transfusion rates. Some authors have found that these effects are more sustained with increasing rFVIIa doses. There is also evidence that rates of surgical re-exploration for bleeding are reduced (11, 12). However the majority of trials have been underpowered, whilst case reports and series are subject to positive reporting and publication bias.

ADVERSE EVENTS

Since cardiopulmonary bypass may up-regulate the expression of systemic tissue factor, the main focus of concern has been inappropriate thrombosis associated with rFVIIa use in the cardiac surgical setting. Interestingly, the incidence of adverse thrombotic events is almost zero in the paediatric population. This may have something to do with their naive vascular endothelium. Observational uncontrolled data from the US Food and Drug Administration adverse event reporting system reveals an alarming 1 in 50 thromboembolic complication rate (associated with a 0.5% mortality) when “off label” rFVIIa is used in a diverse range of patients (13). In cardiac surgery, mortality and complication rates of patients who have failed to respond to standard transfusion therapy and then received rFVIIa are within range of 19% to 40%. The lack of control pa-

tients in most of these case series makes it difficult to determine whether the reported adverse events are related to the administration of rFVIIa or the critical unstable condition of patients when they received rFVIIa (14-17). When rFVIIa has been used on a compassionate basis to reduce uncontrolled bleeding in 51 patients after cardiac surgery, propensity matching techniques to adjust for baseline risks demonstrated that the rates of serious adverse events were equivalent (18). In a group of patients with very high risk of stroke, a matched analysis of patients receiving rFVIIa after major ascending and aortic arch reconstructive surgery suggested stroke rates were equal (19). A recent multicentre randomized clinical trial of rFVIIa in patients actively bleeding after cardiac surgery showed a non-significant trend to an increase in the rates of thromboembolic complications. This trial demonstrated a 50 % reduction in reoperation rates for bleeding and as expected a marked dose-dependant decrease in transfusion rates in those patients randomized to rFVIIa (11).

DISCUSSION

There appears to be general agreement that rFVIIa has the potential to reduce bleeding, blood product administration and re-operation rates post-cardiac surgery. However, these are not outcomes in themselves, and the true risks of its use in this setting remain to be elucidated, especially when it is administered with other potent pro-haemostatic agents. The under-powering of trials performed to date mean that differentiation between adverse events arising specifically from rFVIIa use, and arising generally from the critical condition of those receiving is currently impossible. There has also been a lack of longer-term follow-up in studies

in this context. Thus, it remains to be seen whether rFVIIa use may reduce the mid- to late-term complications of red cell transfusion, such as pulmonary dysfunction and sepsis. There is currently no consensus on the appropriate “off-label” dose of rFVIIa. Since the thrombin-generation response to VIIa depends on the availability of other coagulation factors and platelets, it would seem that the ‘optimal’ rFVIIa dose will vary according to the degree of transfusion of other blood products. This will need to be accounted for when planning future studies. Given the uncontested efficacy of rFVIIa in preventing and reducing bleeding and transfusion, it’s “off label” use is likely to continue.

Clinicians must be aware of both the potential risk and benefits when using this potent thrombin-generating agent. It is our institutional practice to use it in the operating room at a dose of 90mcg/Kg to ensure there is no obvious correctable surgical source of blood loss, and to be certain that bleeding has stopped before the chest is closed.

Dr Herbertson and Dr Gill worked on advisory boards for Novo Nordisk; Dr Gill received speaker fees from Novo Nordisk.

REFERENCES

1. Freedman J, Luke K, Monga N, et al. A provincial program of blood conservation: The Ontario Transfusion Coordinators (ONTraC). *Transfus Apher Sci* 2005; 33: 343-349.
2. Hein OV, Birnbaum J, Wernecke KD, et al. Three-year survival after four major post-cardiac operative complications. *Crit Care Med*. 2006; 34: 2729-2737.
3. Murphy PJ, Connery C, Hicks GL Jr, Blumberg N. Homologous blood transfusion as a risk factor for postoperative infection after coronary artery bypass graft operations. *J Thorac Cardiovasc Surg* 1992; 104: 1092-1099.
4. Koch CG, Li L, Duncan A, et al. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated

- coronary artery bypass grafting. *Crit Care Med* 2006; 34: 1608-1616.
5. Koch CG, Li L, Duncan AI, et al. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg* 2006; 81: 1650-1657.
 6. Surgenor SD, Kramer RS, Olmstead EM, et al. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. *Anesth Analg* 2009; 108: 1741-1746.
 7. Choong CK, Gerrard C, Goldsmith KA, et al. Delayed re-exploration for bleeding after coronary artery bypass surgery results in adverse outcomes. *Eur J Cardiothorac Surg* 2007; 31: 834-838.
 8. Smith SA. The cell-based model of coagulation. *J Vet Emerg Crit Care* 2009; 19: 3-10.
 9. Monroe DM, Hoffman M. What does it take to make the perfect clot? *Arterioscler Thromb Vasc Biol.* 2006; 26: 41-48.
 10. Warren O, Mandal K, Hadjianastassiou V, et al. Recombinant activated factor VII in cardiac surgery: a systematic review. *Ann Thorac Surg* 2007; 83: 707-714.
 11. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII. A randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009; 120: 21-27.
 12. Zangrillo A, Mizzi A, Biondi-Zoccai G, et al. Recombinant activated factor VII in cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth* 2009; 23: 34-40.
 13. O'Connell KA, Wood JJ, Wise RP, et al. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006; 295: 293-298.
 14. McCall P, Story DA, Karapillai D. Audit of factor VIIa for bleeding resistant to conventional therapy following complex cardiac surgery. *Can J Anaesth* 2006; 53: 926-933.
 15. von Heymann C, Redlich U, Jain U, et al. Recombinant activated factor VII for refractory bleeding after cardiac surgery: a retrospective analysis of safety and efficacy. *Crit Care Med* 2005; 33: 2241-2246.
 16. Herbertson M. Recombinant activated factor VII in cardiac surgery. *Blood Coagul Fibrinolysis* 2004; 15: S31-S32.
 17. Isbister J, Phillips L, Dunkley S, et al. Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. *Intern Med J.* 2008; 38: 156-165.
 18. Karkouti K, Yau TM, Riazi S, et al. Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery. *Can J Anaesth* 2006; 53: 802-809.
 19. Tritapepe L, De Santis V, Vitale D, et al. Recombinant activated factor VII for refractory bleeding after acute aortic dissection surgery: a propensity score analysis. *Crit Care Med* 2007; 35: 1685-1690.