

# Recombinant activated factor VII in cardiac surgery

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Adult cardiac surgery has an incidence of 1–1.25 million procedures per year. Overall costs are in the range of US\$50 billion per year and are increasing. Included in these costs is an increasing burden from the use of blood and blood products. The central haemostatic problems associated with cardiac surgery are impaired platelet function associated with pre-operative medication and cardiopulmonary bypass, consumption of platelets, dilution of coagulation proteins and triggering of fibrinolysis. Anecdotal data suggest that recombinant activated factor VII (rFVIIa) has a possible role in cardiac surgery, but randomized, controlled trials are required to confirm this potential. We have undertaken a prospective, randomized, placebo-controlled trial in adult cardiac surgery with a high risk of serious haemorrhage. Drug (rFVIIa) or placebo is given after cardiopulmonary bypass and following the administration of protamine. The primary endpoints of the

study are use of blood and blood products. Secondary endpoints are blood loss, length of stay in the intensive care unit and in the hospital, and survival. This study will give us further information on the potential efficacy and safety of rFVIIa in cardiac surgery. *Blood Coagulation and Fibrinolysis* 15 (suppl 1):S31–S32 © 2004 Lippincott Williams & Wilkins.

Blood Coagulation and Fibrinolysis 2004, 15 (suppl 1):S31–S32

Keywords: cardiac surgery, cardiopulmonary bypass, bleeding, coagulopathy, recombinant activated factor VII

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## Introduction

Of the 12 million units of blood used in the USA per year, 15% are used in cardiovascular surgery. Worldwide figures are similar. In the United Kingdom, 35 000 adult patients have cardiac surgery requiring cardiopulmonary bypass each year, and the worldwide figures are above one million. The rising costs and the increasing difficulty in maintaining an adequate supply of blood, as well as the potential adverse effects of transfusion, have major implications for the future use of allogeneic blood in cardiac surgery. Furthermore, Engoren *et al.* have shown that blood transfusion during or after adult cardiac surgery is associated with increased long-term mortality [1]. Therefore, mechanical or pharmacological strategies that can reduce transfusion requirements would be of great benefit. The present article provides an overview of these strategies, focusing on the results from our group.

## Mechanical and pharmacological methods for reduction of blood transfusion in cardiac surgery

There has been very extensive work, worldwide, looking at strategies to reduce blood loss and transfusion need in cardiac surgery. Our work and findings characterize much of this research in relation to both mechanical and pharmacological strategies. We first investigated the mechanical areas of potential benefit. We carried out a randomized, controlled trial in 252 adult patients who underwent elective cardiac surgery [2]. Patients were randomized to one of three groups: intraoperative cell salvage, intraoperative cell

salvage with acute perioperative normovolaemic haemodilution, or no mechanical blood conservation (control group). There was a significant reduction in the number of patients transfused in each of the cell salvage groups when compared with controls. Furthermore, the number of units of allogeneic blood transfused per patient was lower in the cell salvage groups than in the control group. However, acute perioperative normovolaemic haemodilution did not confer an additional advantage over cell salvage alone. Intraoperative cell salvage has become a standard of care in all adult cardiac surgery in our centre.

Subsequently, we have added to our understanding of mechanical therapies by studying the potential additional benefits of pharmacological therapies. In a randomized, controlled trial of 180 adult patients having a range of cardiac surgery, patients were randomized to one of three groups: cell salvage alone (control), cell salvage and high-dose aprotinin, and cell salvage and tranexamic acid. We found that high-dose aprotinin significantly decreased transfusion requirement when compared with control [3].

## Recombinant activated factor VII in cardiac surgery

According to our database, which covers a period of more than 10 years, 5–10% of adult patients undergoing cardiac surgery have a major risk of coagulopathic haemorrhage due to the complexity of the surgery. In addition, 5–10% of patients undergoing coronary bypass or heart valve surgery also have a major risk of

coagulopathic bleeding because of the preoperative use of anti-platelet or anticoagulant therapy. Overall, 10–20% of patients are at high risk of coagulopathic bleeding, despite cell salvage, antifibrinolytic drugs and appropriate surgical skill and care. This is the subpopulation of adult patients having cardiac surgery that might benefit from recombinant activated factor VII (rFVIIa).

rFVIIa has been used as rescue therapy in major coagulopathic bleeding in cardiac surgery. Furthermore, it has also occasionally been used prospectively in complex cardiac surgery. However, the published data so far available are based on open-label use with a small number of cases.

#### Open-label use of rFVIIa in cardiac surgery

From 2002 to 2003, we used rFVIIa as rescue treatment in 17 adult patients undergoing high-risk cardiac surgery involving cardiopulmonary bypass surgery [4]. All patients received high-dose antifibrinolytic drugs. The dose of rFVIIa varied from 13 µg/kg to 90 µg/kg. There were no thrombotic complications. Patients had experienced major haemorrhage and had required significant transfusion of blood and blood products before rFVIIa was given. We observed significant reductions in blood loss after administration of rFVIIa and apparent clinical benefit in several settings of life-threatening haemorrhage (Table 1). Nevertheless, as these data were obtained from open-label use, no definitive conclusions can be drawn of benefit for survival, or reductions in blood loss or transfusion need.

#### Randomized controlled trial on rFVIIa use in cardiac surgery

We undertook a randomized, double-blind, placebo-controlled trial to investigate the role of rFVIIa in adult patients with high risk of coagulopathic bleeding undergoing non-coronary artery surgery requiring cardiopulmonary bypass. A dose of 90 µg/kg rFVIIa was given prospectively after cardiopulmonary bypass and after administration of protamine. Twenty patients were recruited for this pilot study. The primary endpoints

were the proportion of patients transfused allogeneic red cells or blood products and the number of units of blood and products transfused. The secondary endpoints were blood loss, length of stay in the intensive care unit and in the hospital, and survival. The study has now completed and the results are being analysed.

#### Conclusions

In high-risk cardiac surgery, rFVIIa has a potential benefit in reducing blood loss and transfusion requirement. However, these reductions require quantification. Furthermore, future studies that examine the question of blood loss and transfusion requirement reduction with rFVIIa should include an analysis of cost benefits. Future studies should also formally investigate the dose-dependent effects of rFVIIa in cardiac surgery, and investigate effects in both routine and high-risk cardiac surgery. The use of rFVIIa as rescue therapy in severe coagulopathic bleeding is also an important area for prospective randomized study as this has been the area of most open-label use in cardiac surgery until now. rFVIIa potentially has an important role in cardiac surgery and there is an urgent need for a range of randomized trials to define this possible role.

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**Table 1 Parameters of blood loss and transfusion before and after open-label use of recombinant activated factor VII (rFVIIa) in Southampton University Hospital, UK. Reprinted from Diprose et al. with permission [4].**

	Before rFVIIa	After rFVIIa
Blood loss (ml/h)	933 (182–1500)	34 (7–80)
Red blood cells(U)	4 (0–18)	1 (0–2)
Fresh frozen plasma(U)	2 (0–12)	0 (0–2)
Platelets (U)	3 (0–5)	0 (0–3)
Cryoprecipitate (U)	10 (0–20)	0 (0)
Prothrombin complex	1000 (0–2500)	0 (0)

Results presented as median (range).