

UK DEFENCE MEDICAL SERVICES GUIDANCE FOR THE USE OF RECOMBINANT FACTOR VIIA (RFVIIA) IN THE DEPLOYED MILITARY SETTING

TJ Hodgetts¹, E Kirkman², PF Mahoney³, R Russell¹, R Thomas³, M Midwinter¹

¹Royal Centre for Defence Medicine, Birmingham, ²Defence Science and Technology Laboratories, Porton Down, ³Derriford Hospital, Plymouth

Abstract

Use of recombinant Factor VIIa (rFVIIa) for trauma is currently an 'off label' use.

There are reports of rFVIIa contributing to the successful outcome of military trauma patients. This paper sets out the current position of the UK Defence Medical Services with regard to using rFVIIa in military trauma.

Key words: Military Medicine, Trauma, Haemorrhage, Guidelines.

Introduction

Factor VIIa occurs naturally in the body and combines with exposed Tissue Factor in the wall of injured blood vessels and possibly on platelets to activate the clotting cascade. Factor VIIa is also involved in the activation of clotting factors on the surface of platelets.[1] Recombinant Factor VIIa (rFVIIa) is a manufactured version of Factor VIIa for intravenous administration.[2] rFVIIa is licensed for treatment of bleeding episodes in patients with haemophilia A or B and patients with deficiencies of certain clotting factors (inhibitors of factors VIII and IX; congenital factor VII deficiency).[3,4] It is also approved for prevention of bleeding in surgical interventions or invasive procedures in these patients.[5]

Use of rFVIIa in trauma is currently an 'off label' use. The aim of this article is to set out current UK guidance on use of rFVIIa in trauma in the deployed military setting.

Haemorrhage management

Uncontrolled bleeding remains a significant cause of death in both civilian[6,7] and military[8] trauma patient groups. The initial management of bleeding is a combination of simple measures to control external bleeding (pressure, elevation) progressing to the use of tourniquets and/or topical haemostatic agents depending on the site of injury.

Advances in UK military training and equipment since early 2005 have enhanced the capability to aggressively treat catastrophic external haemorrhage.[9] Resuscitation for non-compressible internal haemorrhage includes the use of blood and blood products (fresh thawed plasma, cryoprecipitate and platelets) and early appropriate surgery. In parallel, intensive care measures to prevent or treat hypothermia and acidosis that will aggravate coagulopathy are essential in the critically injured.

The use of rFVIIa as an adjunct to standard methods to

control traumatic haemorrhage is no longer unusual in civilian practice in the UK or internationally.[10]

In a telephone study of 40 UK intensive care units conducted by the Royal Centre for Defence Medicine in September 2006, 80% of ICUs stated they would use rFVIIa as an adjunct to control life-threatening traumatic haemorrhage.[11] European guidelines published in Aug 06 endorse rFVIIa for use in blunt trauma as an adjunct to control massive bleeding when conventional measures have failed.[12]

rFVIIa should only be considered after:

- Surgical control and/or embolisation (note: embolisation not available in a deployed setting).
- Use of blood products.
- Correction of factors that inhibit coagulation (hypothermia, severe acidosis, low haematocrit, hypocalcaemia).

rFVIIa is not a substitute for these phases of resuscitation.

Table 1: European Guidelines: Key Constraints

Animal evidence for rFVIIa in trauma

The potential for rFVIIa as an adjunct to traumatic haemorrhage has generated substantial objective large animal research published in open sources (see reference 10 for primary sources). None of the published animal studies to date have demonstrated any evidence of thrombotic complications and several have reported significantly reduced volumes of haemorrhage after use of rFVIIa. Most animal studies did not demonstrate an impact on survival, although two studies did show that the use of rFVIIa was associated with a significant increase in survival. The first study showed that a very high dose of rFVIIa increased survival when assessed approximately 1 hour after injury [13]. Most recently, Sapsford et al have demonstrated that a single dose of rFVIIa (180 mcg/kg) in conjunction with a hypotensive resuscitation strategy does improve survival time over a period of 6 hours in an arterial model of incompressible haemorrhage [14]. This could potentially buy time on the battlefield.

Human evidence for rFVIIa in trauma

rFVIIa is in regular use in the international civilian community as an adjunct to traumatic haemorrhage management and many

Corresponding Author: Colonel TJ Hodgetts, QHP L/RAMC, Honorary Professor of Emergency Medicine, Academic Department of Military Emergency Medicine, Institute of Research & Development, Birmingham Research Park, Vincent Drive, Birmingham, B15 2SQ
Telephone: 0121 415 8844 Fax: 0121 415 8869
Email: Prof.ADMEM@rcdm.bham.ac.uk

institutions have implemented guidelines for its use in these circumstances.[15] Kenet et al described the first use in a trauma patient (an Israeli soldier) in 1999.[16] There are multiple additional anecdotal reports and some limited case series.[17,18]

Boffard et al have published the only RCT in relation to the use of rFVIIa in trauma, which found that rFVIIa significantly reduced the need for red blood cell transfusion and massive blood transfusions in blunt trauma patients and that there was a trend toward reduction in penetrating trauma.[19] However, this is not the only RCT for rFVIIa controlling haemorrhage in humans: Freiderich et al reported success in radical prostate surgery, showing a decrease in blood loss and transfusion requirements.[20]

A five year retrospective cohort study at a Canadian Level 1 trauma centre has concluded that rFVIIa may improve early survival of massively bleeding trauma patients, although surgical control of haemorrhage remains the principal therapeutic aim.[21]

The joint Australian and New Zealand Haemostasis Registry has 695 cases where rFVIIa has been used, 108 for trauma from 19 hospitals (87% blunt, 10% penetrating, 83% ISS>16) [22]. This represents a large series of rFVIIa use in trauma outside a randomized controlled trial. rFVIIa was found to be effective in controlling haemorrhage in 59% of cases. Analysis of the dataset has shown rFVIIa to be less effective in severe acidosis (pH<7.05) and/or hypothermia (T<35° C) with the best predictors of success in a multivariate analysis being pH, temperature and ISS.

US military experience of rFVIIa has been extensive and includes multiple military personnel injured by Improvised Explosive Device (IED) attacks [23]. The injury mechanism of IED attack is a combination of blunt, blast, burn and penetrating injury.

rFVIIa use in UK military operational casualties to date has been limited, with less than 20 recorded uses on the Joint Theatre Trauma Registry. One of these is the subject of a published report [24]. A detailed analysis of usage will be published independently.

Dosage

Based on the trial by Boffard et al, the European guidelines are for an initial dose of 200mcg/kg followed by two doses of 100mcg /kg at 1 and 3 hours after the first dose.

This is higher than the doses recommended on the product data sheet for use in Haemophilia A or B patients with inhibitors (for bleeding episodes use 90mcg/kg every 2 hours until haemostasis is achieved; for surgical intervention use 90mcg/kg before the intervention and repeated at 2 hourly intervals for the duration of surgery) and higher than the those for congenital Factor VII deficiency (15-30mcg/kg every 4-6 hours until haemostasis achieved).

The dose in use at the US 10th Combat Support Hospital in Baghdad in 2006 was ~100mcg/kg initially, repeated at 1 hour if clinically indicated.

Complications

rFVIIa is a potent pro-coagulant with the potential for thromboembolic adverse events in susceptible patients.

An analysis of safety of 400,000 standard doses of rFVIIa in haemophiliacs showed <1% incidence of serious adverse effects and <0.05% serious thrombotic events (not dose-related).[25]

In a study of 285 patients who received rFVIIa for traumatic haemorrhage at R. Adams Cowley Shock Trauma Center in Baltimore (2001-2006) looking specifically into complications of rFVIIa, 9.4% of patients had developed thromboembolic complications of which 3.1% were thought to be highly

probably related to rFVIIa.[26] This is highly consistent with other large scale rFVIIa studies.[27]

The Australian and New Zealand registry data recorded no adverse events which were “definitely” or “probably” causally related to rFVIIa use, but 3 cases where it was “possibly” implicated. Thromboembolic complications occurred in 3% patients, which is similar to that reported in other trauma series without rFVIIa use.

It is recognised that there may be morbidity from use of rFVIIa. However, as this drug is only advocated for life-threatening haemorrhage that cannot be controlled by conventional means, the ethical balance is in favour of administering the drug in these circumstances.

Current recommendations

Current UK military recommendations are summarized in Table 2:

- rFVIIa is currently authorised for consultant use only in life-threatening haemorrhage where conventional resuscitation and/or surgical techniques have failed. Life-threatening haemorrhage is defined as:
 - Loss of entire blood volume within 24 hours
 - Loss of 50% of blood volume within 3 hours
 - Blood loss at a rate of 150 ml min⁻¹
 - Blood loss at a rate of 1.5 ml kg⁻¹ min⁻¹ for 20 minutes or more
- In practical terms, rFVIIa should be considered if there is evidence of continued bleeding after 6-8 units of packed red blood cells and correction of coagulopathy with fresh frozen plasma.
- rFVIIa 100mcg/kg IV bolus (with a 2nd bolus after ~20mins if required) may be advocated as an adjunct in controlling haemorrhage following blunt trauma.
- Consultant clinician discretion must determine if there is a blunt component to blast injury that may respond to rFVIIa when conventional measures have failed.
- European guidelines recommend informing the patient or next of kin before using rFVIIa in an ‘off label’ manner: this is impractical in the context of managing severe military trauma casualties overseas.
- Contraindications to rFVIIa use as an adjunct to traumatic haemorrhage are:
 - Patient is expected to be unsalvageable despite rFVIIa
 - Known or suspected ischaemic heart disease
 - History of thrombo-embolic event in the preceding 6 months

Table 2: Current recommendations for UK military use

The dose of 100mcg/kg utilised by US military is recommended when criteria are met for rFVIIa as an adjunct to massive traumatic haemorrhage.

Summary

UK DMS policy for haemorrhage management is under regular review and the use of haemostatic agents and injected rFVIIa will continue to be assessed as further evidence emerges from US, European and Israeli experience, both civilian and military. Published US military experience of aggressive use of fresh frozen plasma in tandem with packed cells has now been implemented as part of the UK DMS evolving strategy to manage massive transfusion needs within the emerging concept of damage control resuscitation [28].

Acknowledgements

We thank Professor Keith Porter, Selly Oak Hospital Birmingham for advice during the writing of this paper.

Competing Interest

Dstl Porton Down are involved in a collaborative study with Novo Nordisk and have received donations of rFVIIa for the study.

References

1. A detailed description of the structure and function of FVIIa can be found at <http://www.trauma.org/resus/FactorVIIa.html>
2. NovoSeven® Product Sheet, Version 10. Novo Nordisk, October 2006 2880 Bagsvaerd, Denmark.
3. Hedner U, Kisiel W. The use of human factor VIIa in the treatment of two hemophilia patients with high-titer inhibitors. *J Clin Invest* 1983; **71**: 1836-1844.
4. Shapiro AD, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb and Haemost* 1998; **80**: 773-778.
5. http://www.us.novoseven.com/patient/aboutN7_Overview.aspx
6. Sauer A, More FA, More EE. Epidemiology of trauma deaths: a reassessment. *J Trauma* 1995; **38**: 185-193.
7. Heckbert SR, Vedder NB, Hoffman W, Winn RK, Hudson LD, et al. Outcome after hemorrhagic shock in trauma patients. *J Trauma* 1998; **45**(3): 545-549.
8. Champion HR, Bellamy RF, Roberts CP, Leppaniemi A. A profile of combat injury. *J Trauma* 2003; **54**(5): S13-S19.
9. Hodgetts TJ, Mahoney PF, Russell MQ, Byers M. ABC to <C> ABC: redefining the military trauma paradigm. *Emerg Med Journal* 2006; **23**: 745-746.
10. Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. *J Trauma* 2005; **58**: 1298-1303.
11. RCDM telephone survey, Sep 06.
12. Vincent J-L, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding—a European perspective. *Critical Care* 2006;10. Available on-line <http://ccforum.com/content/10/4/R120>
13. Jeroukhimov I, Jewelewicz D, Zaias J, Hensley G, MacLeod J, Cohn SM et al. Early injection of high-dose recombinant factor VIIa decreases blood loss and prolongs time from injury to death in experimental liver injury. *Journal of Trauma-Injury Infection and Critical Care* 2002; **53**(6): 1053-7.
14. Sapsford W, Watts S, Cooper G, Kirkman E. Recombinant activated factor VII increases survival time in a model of incompressible arterial hemorrhage in the anesthetized pig. *J Trauma* in press (accepted 2007).
15. Shander A, Goodnough TL, Ratko T, Matuszewski KA, Cohn S, Diringner M et al. Consensus recommendations for the off-label use of recombinant human factor VIIa (NovoSeven) therapy. *P&T* 2005; **30**(11): 644-658.
16. Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; **354**(9193): 1879.
17. Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. *J Thromb Haemost* 2005 April; **3**(4): 640-8.
18. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *Journal of Trauma-Injury Infection and Critical Care* 2001; **51**(3): 431-8.
19. Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. *J Trauma* 2005 July; **59**(1):8-15.
20. Freiderich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T et al. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003; **361**(9353): 201-5.
21. Rizoli S, Nascimento B, Osman F, Netto F, Kiss A et al. Recombinant activated coagulation Factor VII and bleeding trauma patients. *J Trauma* 2006; **61**: 1419-1425.
22. The use of recombinant activated factor VII in trauma patients: experience from the Australian and New Zealand haemostasis registry. Cameron P, Phillips L, Balogh Z, Joseph A, Pearce A, Parr M, Jankelowitz G. *Injury*, 2007; **38**: 103001038
23. Perkins J, Schreiber M, Wade C, Holcomb J. Early Versus Late Recombinant Factor VIIa in Combat Trauma Patients Requiring Massive Transfusion. *J Trauma* 2007; **62**: 1095-1101.
24. Williams DJ, Thomas GOR, Pambakian S, Parker PJ. First military use of activated Factor VII in an APC-III pelvic fracture. *Injury-International Journal of the Care of the Injured* 2005; **36**(3): 395-9.
25. Roberts HR, Monroe DM, Hoffman M. Safety profile of recombinant factor VIIa. *Seminars in Hematology* 2004; **41**(1): 101-8.
26. Thomas R, Dutton R, Hemlock B, Stein D, Hyder M et al. Thromboembolic complications associated with rFVIIa administration. *J Trauma* (accepted Sept 2006).
27. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringner MN et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 352: 777-785, 2005.
28. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P et al. Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma. *J Trauma* 2007; **62**: 307-310.