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.

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...
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].

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Competition Interest

Defence 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
11. RCDM telephone survey, Sep 06.