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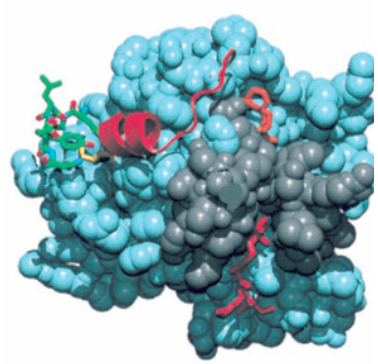
Recombinant Factor VIIa (NovoSeven) for Traumatic Coagulopathy

Introduction



Recombinant Factor VIIa (FVIIa) is currently licensed for use in haemophiliacs with antibodies to Factor VIII. At present, its use in trauma and haemorrhage is on a 'compassionate' basis. The first published account of the use of Factor VIIa in trauma was published by Gili Kenet in 1999. She described the successful use of FVIIa in a soldier with traumatic coagulopathy following a high velocity gunshot wound to the inferior vena cava, near its bifurcation.

Structure

Factor VIIa is a trypsin-like serine protease.

Recombinant Factor VIIa is produced by Novo Nordisk AG, Copenhagen, Denmark and marketed as Novoseven.

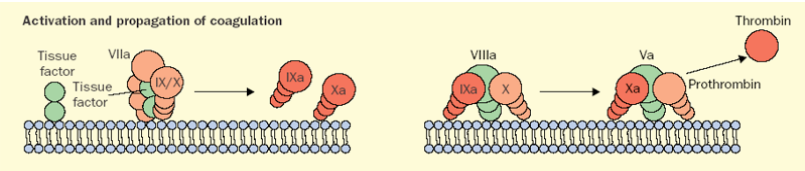
Function

Factor VIIa is an initiator of thrombin generation. Factor VIIa acts primarily via two pathways to activate Factor Xa. One pathway is at the site of tissue injury complexed with Tissue Factor, and the other is on the surface of platelets, independent of tissue factor.

1. Factor VIIa (FVIIa) forms an active complex with Tissue Factor (TF). Tissue Factor is present in the subendothelial layer of the vascular wall, and hence is not normally free to complex with circulating Factor VIIa. Following injury, the subendothelium is exposed and Tissue Factor is free to bind FVIIa. This TF:VIIa complex activates Factors IX & X.

2. Factor VIIa can also activate factors IX & X on the platelet membrane, in the absence of Tissue Factor. Although this is a lower affinity reaction for generation of Factor Xa, Factor IXa subsequently activates Factor Xa and amplifies this pathway dramatically. This reaction is often referred to as the 'Thombin Burst' and is thought to be responsible for the major of fibrin generated in response to a local injury.

Factor Xa, complexed with Factor V forms a complex called Prothrombinase. Prothrombinase cleaves Prothrombin to form Thrombin, which then generates Fibrin from Fibrinogen.



Tissue Factor - VIIa to Thrombin Pathway

Theoretically, both of these mechanisms localise the action of Factor VIIa to the site of injury, and hence avoid the complications of thromboses occurring in other vascular beds and leading to Acute Respiratory Distress Syndrome, Acute Renal Failure and Multiple Organ Dysfunction Syndrome.

Clinical Studies

Most reports of Factor VIIa use in trauma are anecdotal in nature and comprise small cas series. To date there has been one prospective, randomized, double-blind controlled trial Factor VIIa in trauma, conducted by Novo NorDisk.

Prospective, Randomized Trials

Novo Nordisk conducted a Phase II multicentre, multinational prospective randomised placebo-controlled trial of Factor VIIa in traumatic shock in 2001-2003. The final results have not yet been published, but results were presented in part at the 6th World Congre on Shock, Inflammation & Sepsis in Munich on 5th February 2004, and at the American Association for the Surgery of Trauma annual meeting in Maui, on the 1st October 2004.

Study Design

- Trauma patients who received 6 units of red blood cells within the first 12 hours of admission were randomised into the study, and the drug given after the 8th unit of blood had been administered.
- Major traumatic brain injury was excluded from the study.
- Blunt and penetrating injuries were randomized separately.
- Study dosing was 200micrograms/kg initially followed by 100micrograms/kg at 1 an 3 hours after the first dose.
- The primary endpoint for the study was transfusion requirement. Secondary endpoir were mortality and organ failure.

Outcome

301 trauma patients were enrolled.
277 were analysed. Withdrawals were primarily for protocol violations and data collection issues
143 blunt, 137 penetrating.

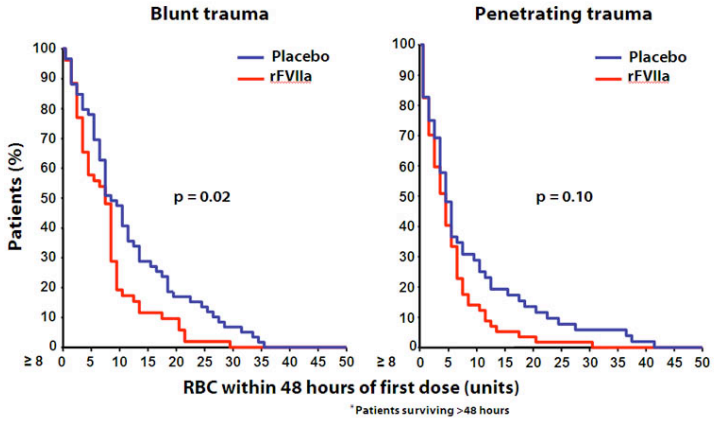
Overall, there was no significant difference in outcome measures between the Factor VIIa and Placebo groups.

Blood transfusions

After excluding early deaths (before 48 hours) from the analyses, there was a significant difference in blood transfusion requirements within in the blunt trauma group, and a trer towards decreased use in the penetrating trauma patients.

Blunt trauma patients receiving Factor VIIa were transfused a median of 2.6 units less blood than patients receiving placebo (90% CI: 0.7-4.6 units). There was also a significa reduction in FFP, platelet and cryoprecipitate transfusions in the blunt trauma group.

Penetrating trauma patients had an estimated reduction of blood transfusion requiremer of one unit (90% CI: 0-2.6 units) which did not reach significance.



Mortality

There was no significant difference in mortality in the two groups:

Blunt: FVIIa 25%, Placebo: 30% (p=0.58)
Penetrating: Factor VIIa: 24%, Placebo: 28% (p=0.69)

Multiple Organ failure & ARDS

There was a trend towards a reduced incidence of multiple organ failure & ARDS in the FVIIa group:

Blunt: FVIIa 10%, Placebo: 23% (p=0.07)
Penetrating: Factor VIIa: 7%, Placebo: 17% (p=0.11)

There was a similar trend to increased ICU- and Ventilator- free days (30-day)

ICU-Free Days (30-day):
Blunt: FVIIa 13, Placebo: 8 (p=0.18)
Penetrating: Factor VIIa: 24 Placebo: 20 (p=0.26)

Ventilator-free days:
Blunt: FVIIa 17, Placebo: 14 (p=0.44)
Penetrating: Factor VIIa: 26, Placebo: 22 (p=0.17)

Comments

One of the main criticisms of the study design has been the failure to identify a need for on-going blood transfusion at the time of drug dosing. That is, there was a possibility tha patients receiving their 8th unit of blood had their haemorrhage controlled at this point, were not coagulopathic and hence would not have required procoagulant therapy under normal clinical conditions.

Although blunt and penetrating groups were randomized separately, it is possible to analyse the two groups as one, as the study protocol was not different between the groups. Analysing the 277 patients as a whole cohort gives a signficant difference to the incidence of ARDS/MOF, but mortality remains unchanged.

ARDS / Multiple Organ Failure:
Factor VIIa: 8.6%, Placebo: 20.3% (p=0.006)

Cohort Studies

To date, the largest cohort study is from the Maryland Shock Trauma Institute. Dutton and coworkers present a case series of 81 patients in which Factor VIIa was given to trauma patients on a compassionate use basis. This is rather a mixed bag of patients. 2 patients received FVIIa for Factor VII deficiency, and 9 patients received FVIIa for reversa of Warfarin anticoagulation in the setting of 'life-threatening' haemorrhage.. Only 59 patients received Factor VIIa within the first 24 hours of admission.

The authors found that PT was reduced in all patients following administration. However, they classified 20 of the 81 patients as 'non-responders' given their continued requireme for blood & blood product administration. However these non-responders had received significantly more blood & fluid administration prior to dosing with FVIIa, and were also more acidotic. at the time of dosing. The authors attempted to compare their results wit historical controls matched for degree of coagulopathy, injury type & severity. It is difficu to draw any conclusions from this process, but mortality was higher in the groups receiving FVIIa than in matched controls.

Other smaller case series have mirrored these findings.

Current Studies

Current studies of Factor VIIa include a study by the Western Trauma Association to collect information in trauma cases where Factor VIIa has been used. This study is being coordinated by Dr. Peggy Knudson at San Francisco General Hospital.

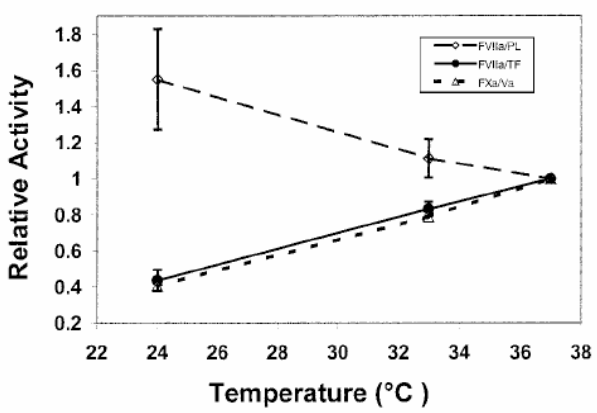
You can download the data entry form here: FactorVIIa DataSheet (pdf)

A Phase II/III trial of Factor VIIa in the USA is currently in the design phase and should start enrolling patients some time in 2005.

Pre-clinical studies

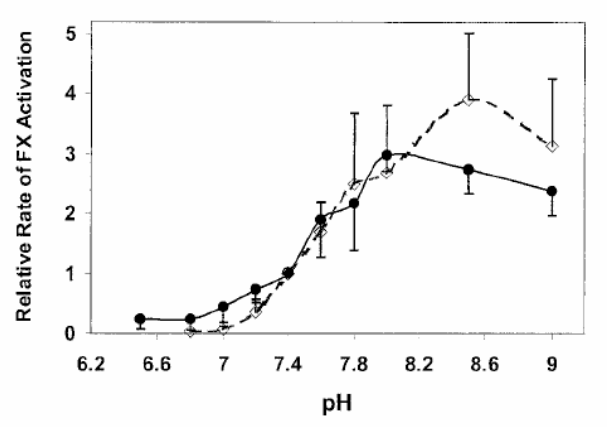
Meng and co-workers have studied the effect of temperature and acidosis on the activity Factor VIIa with in-vitro studies of human volunteer blood.

They found that TF:VIIa activity was reduced linearly with reduced temperature, retainin approximately 50% of its activity at temperatures of 28oC. However Factor VIIa activity o platelet surface membranes rose as temperature falls, probably due to increased stability the protein at lower temperatures. Thus hypothermia should have little effect on FVIIa activity.



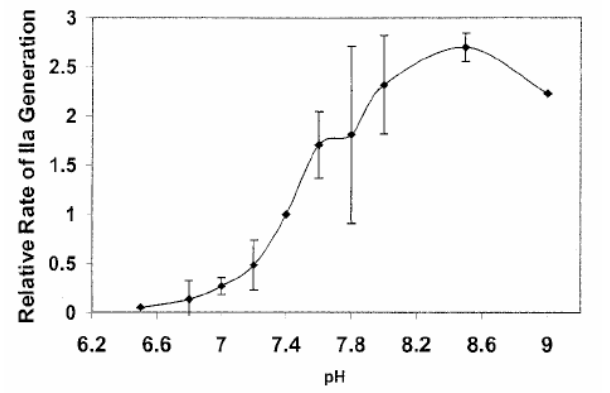
VIIa & TF:VIIa - Hypothermia

Factor VIIa activity falls dramatically over the pH range 7.4 to 6.8, such that TF:VIIa activity is reduced to 50% of normal at pH 7.0 and activity of VIIa on platelet surfaces reduces even faster.



Factor VIIa - Acidosis

Decreasing the pH of the reactions decreased the rate of FXa formation by the FVIIa/TF complex (solid circles) and even more dramatically decreased the activity of FVIIa alone o phospholipid vesicles (open diamonds).



Factor Xa Activity - Acidosis

Decreasing the pH also decreases the rate of prothrombin activation by the FXa/FVa complex on phospholipid vesicles.

Animal Studies

There have been several animal studies performed to evaluate dose and efficacy of recombinant Factor VIIa in haemorrhagic shock & trauma. These may be summarized as follows:

- No efficacy in non-coagulopathic animals
- Reduction in blood loss and prothrombin time (PT)
- No difference in mortality (but increased time to death)
- Saturation of system at dose of 180micrograms/kg (porcine)

Summary of FVIIa Studies

Utility

Factor VIIa lowers the Prothrombin Time and reduces visible coagulopathic haemorrhage following trauma. Factor VIIa reduces blood transfusion requirements in blunt trauma patients (who have already received 8 units of blood) and there is a similar trend in

penetrating injury.

An outcome benefit in terms of mortality, morbidity, ICU stay and cost has not been demonstrated, although there was a trend to reduction in the incidence of Multiple Organ Failure & ARDS. Cohort studies have also not demonstrated improved survival from FVIIa administration. There are several possible reasons for this, including study methodology. is conceivable that the drug was given as salvage therapy too late, or with too severe a metabolic derangement, for potential benefit to be seen in this group of patients. Alternatively, FVIIa may have adverse effects that counterbalance its effects in reducing transfusion requirements.

Safety

There are two main safety concerns with FVIIa:

1. FVIIa will lead to a hypercoagulable state and increase the incidence of Deep Venous Thrombosis and Pulmonary Embolism.

This has not been borne out in studies in trauma, nor where FVIIa has been used for non-trauma conditions.

1. FVIIa will lead to microvascular coagulation and subsequent Acute Lung Injury (ALI), Acute Renal Failure and the Multiple Organ Dysfunction Syndrome (MODS). There are anecdotal reports of severe ARDS following the use of FVIIa. However the Phase II trial above showed an overall trend to reduced incidence of ARDS & MODS. Concerns still exist however and should be addressed by subsequent studies.

Dose

The dosing regimen in the Phase II trial was 200mcg/kg initially followed by repeat dosing of 100mcg/kg at 1 hour and 3 hours. The half-life of FVIIa is 2 hours, so repeat dosing may be required, especially in the patient with significant on-going haemorrhage.

Some investigators believe the initial dose to be too high, and subsequent studies will like be conducted with reduced dosing. The recommended dose of FVIIa in haemophiliacs in 90mcg/kg.

Recommendations

At this point there can be no firm recommendations for the use of Factor VIIa in severe traumatic haemorrhage. Factor VIIa is not yet licensed in any country for this condition, and its use proceeds on a 'compassionate' basis. Given the high cost associated with usir Factor VIIa, its use should be restricted to those situations where it is likely to be of maximum benefit. Additionally, evidence is emerging that the coagulant and metabolic milieu must be favourable, or made favourable, for the drug to work.

At this stage the following recommendations can be made:

- Where the use of Factor VIIa is being considered, hospitals should have a set of guidelines in place for the availability and use of Factor VIIa.
- The use of Factor VIIa should be closely monitored and ideally submitted to a nationa or international registry.
- Factor VIIa will not stop surgical haemorrhage.
- Factor VIIa should not be given instead of other blood product administration. Adequate FFP, Cryoprecipitate and Platelets need to be present for full effect.
- Factor VIIa should not be used too early, but neither should it be used only after 'super-massive' transfusions of 40-60 units. Therapy at between 8 and 20 red blood cell infusions is probably appropriate. (opinion only)
- The current recommended dose is 100micrograms/kg. This dose should be repeatec at 1-2 hourly intervals if required.

- The Prothrombin time is used to monitor drug effect
- When the pH is below 7.2, consideration should be given to:
  - not using FVIIa (futility)
  - increasing the dose of FVIIa
  - Treating the patient with bicarbonate or THAM to raise the pH (no evidence to support this)

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External Links

Novo Nordisk
www.novoseven.com

Western Trauma Association
www.westerntraumaassociation.org

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