Management of life-threatening bleeding with coagulopathy. A consensus document on the use of rFVIIa in patients without haemophilia

Background

Recombinant activated factor VII (rFVIIa) is approved for the prevention or treatment of bleeding in haemophiliac patients with coagulation factor inhibitors. There are case series, and limited controlled trials suggesting a role for rFVIIa in the management of life-threatening bleeding in non-haemophiliac patients who have failed to respond to conventional therapy.

Widely agreed guidelines for the management of uncontrollable haemorrhage, coagulopathy and the role of rFVIIa do not exist. A multidisciplinary Clinical Advisory Board (see Appendix 1) has established practical clinical guidelines for the appropriate use of rFVIIa. These guidelines address the use of rFVIIa in the management of uncontrollable haemorrhage and coagulopathy unresponsive to conventional management. These guidelines reflect the multidisciplinary experience and consensus of clinicians from the fields of Anaesthesia, Haematology, Intensive Care Medicine and Surgery (Appendix 1).

Where appropriate the use of these guidelines should incorporate and reflect local policies and procedures and the specific clinical context. It is also advised that a multidisciplinary group of clinicians should oversee the introduction of local guidelines and monitor the use of rFVIIa. All use of the drug should be audited, and the group encourages inclusion in the Haemostasis Registry (www.med.monash.edu/epidemiology/traumaepi/haemostasis.html)

Guidelines

The guidelines use a step-wise approach:

1. Identify patients with uncontrollable haemorrhage and coagulopathy. (trauma, medical or peri-operative)
2. Ensure adequate surgical and non-surgical haemostasis procedures are performed.
3. Ensure conventional measures to prevent and correct coagulopathy are performed.
4. Consider Damage Control Surgical management strategies.
5. Triage to ensure that only potentially salvageable patients are given rFVIIa.
6. Consider the administration of rFVIIa and if administered, clinically monitor the response.

1. Potential patients are recognised as those suffering uncontrollable haemorrhage and coagulopathy unresponsive to conventional measures. This will usually be in the setting of a massive transfusion represented by:

- replacement of the blood volume within a 24-h period; this corresponds to about 70 ml/kg of body weight or 5 litres in a 70-kg patient
- replacement of 50% of the total blood volume within 3 h
- need for at least four RBC units within 4 hours in the setting of continued major bleeding
- blood loss exceeding 150 ml/min
- need for platelet and plasma replacement

It is recognized that massive trauma, or preexisting coagulopathy may induce massive non-surgical bleeding at losses less than these.

2. Any surgical and non-surgical definitive haemostasis procedures to arrest active bleeding should be considered prior to consideration of rFVIIa administration.

This may include operative surgical exploration, orthopaedic fixation and embolisation by interventional radiology.

3. Appropriate conventional measures to prevent and correct coagulopathy should be performed prior to consideration of rFVIIa administration. Patients considered for treatment with rFVIIa will be in an acute care environment (e.g. resuscitation room, operating theatre, ICU, angiography room). Patients should receive full resuscitation including the following before consideration of rFVIIa therapy.

- Adequate venous access
- Adequate blood product and volume replacement
- Address measures to prevent and reverse hypothermia
- Address measures to prevent and reverse acidosis
- Blood tests for FBC, PT, APTT, fibrinogen or TEG if available
- The empiric, or guided by laboratory tests, use of FFP, platelets and cryoprecipitate.
- In the situation of rapid haemorrhage, after 6 units of RBCs and faced with continued blood loss, give 20ml/kg of FFP and 2 packs of platelets empirically.
- Repeat the above blood tests after each 4-6 units of RBCs cells, or every 30 mins.
- Repeat the FFP and platelet administration after each 4-6 units RBCs or as guided by tests:

    - Give 4 units of FFP if PT and APTT are over 1.5 x control
    - Give 2 units of cryoprecipitate empirically or if fibrinogen < 1.0 g/L
    - Give at least 2 adult packs of platelets if platelet count is < 100 x $10^{9/L}$
    - Monitor Ionised Calcium and consider calcium administration to keep in normal range.

When appropriate consider the following specific measures:
Reversal of warfarin (vitamin K, prothrombinex)
Reversal of heparin (protamine sulphate)
Antifibrinolytic agents. Commence if there is clinical ooze, unrelated to surgical bleeding or laboratory evidence of fibrinolysis. Use tranexamic acid 0.5-1G IV, or Aprotinin 2 MU followed by an infusion of 500,000U/hr.

4. If mixed surgical and non surgical bleeding continues in spite of the above treatment, initiation of Damage Control Surgery should be considered, especially if the

pH < 7.2, and/or HCO_3 < 15 mmol/l
core body temp < 34°C
ongoing coagulopathy.

This usually includes abandonment of definitive surgical repair, rapid haemostasis, packing and closure. The patient is then transferred to ICU for warming, coagulopathy and inotropic management. A later definitive procedure is then undertaken.

Failure to manage non surgical bleeding despite surgical haemostasis, fibrin glue, embolisation

Treat the patient to maintain:

- **Hb > 70 g/l with RBC**
- **Fibrinogen > 1.0 g/L with 2 units cryoprecipitate**
- **Platelet count >100 x 10^9/L with 2 adult packs platelets**
- **INR < 1.5 with 20ml/kg FFP**
- **Calcium to normalise ionised Ca++**
- **Antifibrinolytics**

If bleeding is uncontrolled after

10 units RBCs
8 units FFP
2 units platelets
2 units cryoprecipitate

Repeat FBC / coag. screen every 30 minutes

Is the patient's

Temp less than 35°C

pH < 7.2

YES → **Consider Damage Control Surgery** → **ICU**

NO → **Further resuscitation appropriate?**

YES → **rFVIIa 100 µg/kg (rounded to whole ampoule)**

Consider $NaHCO_3$ if pH<7.2
Ensure Platelets >100
Fibrinogen >1.0g/L

Aggressive warming

If no response in 20 minutes **Consider 2nd dose of rFVIIa (100 µg/kg)**

Note:

- Use of rFVIIa in children and pregnancy requires special consideration of risk/benefits
- Early use may be considered in high-risk groups e.g. patients with cirrhosis and undergoing liver surgery
- Does not apply to cardiac surgery

NZ rFVIIa Guidelines ver4

5. If conventional therapy has failed to control the blood loss (usually 10 units of RBCs, 8 units of FFP, 2 adult packs of Platelets, and 2 units of cryoprecipitate will have been given)

and

bleeding with coagulopathy continues

and

all surgical and embolisation procedures have been attempted

and

consultation with appropriate clinicians in your institution to confirm optimal conventional therapy and the appropriate dosage of rVIIa

give

recombinant activated factor VII (rFVIIa, NovoSeven) 100 mcg/kg. The dose should be rounded up or down to the nearest 1.2mg vial size to avoid any wastage.

If the pH is less than 7.2, consider temporary correction with $NaHCO_3$ or THAM

When administrating rFVIIa, aim to have the

Platelet count above 100 x 10^9/l
Fibrinogen above 1.0 g/l

Laboratory monitoring for response to rFVIIa is currently unsatisfactory. The Prothrombin time is not useful in this respect. Where TEG is available this may be helpful. In most cases, the response to treatment will be assesses on the basis of the clinical response.

Clinical response is usually obvious within 20 minutes. If no response within 20 minutes, a second dose of 100 mcg/kg rFVIIa may be considered.

Use in children and pregnancy requires special consideration of the risks and benefits associated with rFVIIa.

Early use may be considered in high-risk groups e.g. patients with cirrhosis and undergoing liver surgery or patients bleeding post-cardiac surgery. Local agreements and protocols should be developed for these groups.

Having administered rFVIIa the patient should be monitored for subjective and objective signs of improvement and for adverse events.

In Australia and New Zealand rFVIIa (NovoSeven) is indicated for the control of bleeding and surgical prophylaxis in patients with inhibitors to coagulation factors VIII and IX. It is supplied and manufactured by Novo Nordisk. For further product information please contact Novo Nordisk Pharmaceuticals Pty Ltd.

APPENDIX 1

New Zealand Clinical Advisory Board Members

Dr Kerry Gunn (Chair)	Anaesthesia
Dr Paul Harper	Haematology
Dr Tony Joseph	Emergency Medicine
Dr Mark Smith	Haematology
Dr Cornelis Kruger	Cardiothoracic Anaesthesiology
Dr Tony Williams	Intensive Care
Dr Julia Phillips	Haematology