Tertiary/Quaternary Level Essential Medicine List

Review

MEDICATION: Recombinant Factor VIIa

INDICATION:

1. Adjunct in the management of coagulopathy following trauma with massive bleeding or the need to enter the massive transfusion protocol.
2. Management of Intracranial Haemorrhage within 4 hours of onset.
3. Intractable bleeding after cardiac surgery.

Clinical background

Recombinant Factor VIIa (rFVIIa) is used in the clinical setting in public hospitals for management of intractable bleeding. According to Charlotte Maxeke Massive transfusion protocol, rFVIIa is used specifically to reverse coagulopathy associated with massive transfusion. Blood Bank will issue the required rFVIIa for administration immediately after completion of the 6th, and 12th Unit of transfused blood.

rFVIIa could **only** be used in the following cases:

- In the presence of active bleeding after the protocol for massive bleeding has been used
- Where possible, its use should be backed up using thromboelastography (TEG)
- Increased 'r' time on TEG despite fresh frozen plasma
- If all surgical bleeding has been controlled.
- After transfusion of > 6 units of blood
- If the platelet count is > 50000/mm3
- If the pH is > 7.2
- If the temperature is > 34° C
- If calcium level are normal.
- Fibrinogen > 50mg/dl

Although no protocols exist, rFVIIa is used in intractable bleeding post cardiac surgery as well as acute intracranial haemorrhage (ICH).

SEARCH STRATEGY:

We searched electronic databases including MEDLINE/PubMed, HighWire, Critical Care Medicine, Cochrane and Scholar for randomized controlled trials and systematic reviews on recombinant factor VIIa in trauma, intracranial haemorrhage and cardiac surgery. The search strategy was based on combinations of medical subject headings and keywords. Search was also performed by checking the bibliographies in the original reports and review articles. We extracted case series, observational studies, systematic reviews of RCT, systematic reviews of observational and randomised controlled studies and Systematic reviews of RCTs. Only

Systematic reviews of RCT and RCT were appraised. Only randomized control trial (Boffard et al) and its sub analysis study (Bizoli et al) were appraised studies conducted in South Africa.

PICO strategy

Indication	Patients	Intervention	Comparator	Outcome
Trauma	Trauma patients with	rFVIIa +	Standard	Mortality

	intractable bleeding Severe trauma patients	standard treatment	treatment + placebo	Morbidity: Multiple end organ failure (MOF) & Respiratory distress syndrome (RDS)
Intracranial Haemorrhage	Patients with acute **traumatic** and **spontaneous** intracranial haemorrhage (within 4 hours of onset	rFVIIa + standard treatment	rFVIIa + standard treatment	Reduction in hematoma size Disability using modified Ranking Score or Extended Glasgow Outcome Scale Mortality Thrombotic adverse events
Intractable bleeding in cardiac surgery	Patients undergoing cardiac surgery with intractable bleeding	rFVIIa + standard treatment	rFVIIa + standard treatment	Mortality Thrombotic adverse events

Quality of studies

Almost all studies were funded by the manufacturer, Novo Nordisk, including the SA trial. Some systematic review included observational and RCTs. This would affect test of homogeneity

RESULTS:

The rFVIIa did not have any effect on mortality in all the 3 indications. It did however reduce respiratory distress syndrome

EFFICACY:

1. **Trauma:**
   a. **South African Based Randomised Controlled studies: Boffard et al, Rizoli et al [2,3]**

   rFVIIa reduced the risk of multiple organ failure, respiratory distress syndrome. There was no difference in mortality between treatment and placebo group. A sub-analysis of the Boffard study looking at severe trauma patients confirmed similar results including no difference in ventilator and ICU free days. Patients receiving rFVIIa required 3 **units less** blood compared to controls.

   b. **Systematic reviews of RCTs: Lin et al, Yank et al [1,4]**

   There was no difference in mortality between the treatment and placebo group. The treatment reduced the risk of acute respiratory distress syndrome (ARDS) but not multiple end-organ damage (MOF).

2. **Intracranial Haemorrhage: Systematic Reviews Al-Shashi, Yuan et al, Yank et al [5,6,4]**

rFVIIa did not significantly reduce death or dependence on the modified Rankin Scale (grades 4 to 6) within 90 days of ICH (RR 0.91)

3. **Cardiac Surgery: Yank et al [4]**

rFVIIa did not significantly reduce death

SAFETY CONCERNS:

The recombinant rFVIIa is associated with increased risks of thromboembolic events

Author	Topic	Type of Study	Sample Size	Intervention	Results for Effic
Lin Y, et al. 2010 [1]		Prophylactic	14 trials on off-label use (n=1137)	Patients given rFVIIa prior to high risk surgery	Blood loss: -276 −411 to −141 M in blood loss tre Red blood trans 281 mL (95% CI −129 mL)
	Use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia: a systematic review and meta-analysis	Systemic review and meta-analysis. Sub analysis into therapeutic and prophylactic use	12 trials therapeutic use (n=2538)	Therapeutic trials: Patients received various doses of rFVIIa	Mortality: RR= 0.76 to 1.06) Controlled Bleed loss: -276 ml (95 to −141 Ml). red blood loss treatr Red blood trans mL (95% CI −108 Transfusion with : 0.81 (95% CI 0.
Boffard et al. [2]	Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo controlled, double-blind clinical trials	Parallel randomized, placebo-controlled, double-blind clinical trial	301:143 blunt trauma and 134 penetrating trauma	Randomized to rFVIIa (200, 100, and 40 microg/kg) or placebo in addition to standard treatment (probably the SA massive transfusion protocol)	**Blunt trauma:** RBC transfusion (p=0.02) Need for massiv transfusion (>20 RBCs) was reduc 33% of patients; In favour of rFVI Mortality: No di mortality **Penetrating trau** RBC transfusion p = 0.10) Massive transfu 19%; p = 0.08. I rFVIIa
Rizoli et al. [3]	Recombinant activated factor VII as an adjunctive therapy for bleeding control in	Sub-analysis of Boffard et al trial	N= (136) 60 rFVIIa-treated and 76 placebo subjects were retrospectively	Randomized to rFVIIa (200, 100, and 100 microg/kg) or placebo in addition	Morbidity: treat control ARDS (2% vs. 12 MOF: 13% vs. 3%

	severe trauma patients with coagulopathy: subgroup analysis from two randomized trials Indication: Severe Trauma		identified as being coagulopathy	to standard treatment	Mortality: 18% v p=0.48 Ventilator-free d 25 p= 0.08 ICU-free days 16 p=0.06
Yank V, et al. 2011 [4]	Systematic Review: Benefits and Harms of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications **Cardiac** **Trauma** **ICH**	Systematic Review	16 RCTs, 26 comparative observational studies, and 22 non-comparative observational studies met inclusion criteria	Various doses of rFVIIa with standard treatment, controls received standard treatment and placebo or no placebo in observational trials	**Adult cardiac su** mortality differe **Body trauma**: N differences in m reduced risk for respiratory distr syndrome (RD, − −0.02 to −0.08]) **ICH:** no differen mortality
Al-Shashi Salman [5]	Haemostatic drug therapies for acute spontaneous **intracerebral haemorrhage.**	Systematic Review	5 RCT 973 received rFVIIa	rFVIIa did not significantly reduce death or dependence on the modified Rankin Scale (grades 4 to 6) within 90 days of ICH (RR 0.91	Non-significant t thromboembolic rVIIa patients
Yuan et al. [6]	A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute **intracerebral**	Systematic review	5 RCT N=47 N=399 N=40 N=819 N=97	Dose of rFVIIa: 10,20,40,80,120 or 160 40,80,120 or 160 5,20,40 or 80 (20 or 80) microg/kg	Non-significant t mortality, modif Scale (mRS) scor extended Glasgo Outcome Scale (score in patients

	haemorrhage without hemophilia			vs placebo 40,80,120,160 or 200	with rFVIIa or pl

References:

1. Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Use of recombinant factor VIIa for the prevention and treatment of bleeding in patients without hemophilia: a systematic review and meta-analysis. *Canadian Medical Association Journal*. 2010; 183(1). Available from: http://www.cmaj.ca/content/183/1/E9.full [Accessed 17th May 2016].
2. 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; 59(1): 8-15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16096533 [Accessed 17th May 2016].
3. Risoli SB, Boffard KD, Riou B, Warren B, Iau P, Kluger Y, et al. Recombinant Activated Factor VII as an djunctive therapy for bleeding control in severe trauma patients with coagulopathy: subgroup analysis from two randomized trials. *Critical Care*. 2006; 10(6): R178. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17184516 [Accessed 17th May 2016].
4. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al. Systematic Review: Benefits and Harms of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications. *Ann Intern Med*. 2011; 154(8): 529-540. Available from: http://annals.org/article.aspx?articleid=746935 [Accessed 18th May 2016].
5. Al-Shashi Salman R. Haemostatic drug therapies for acute spontaneous intacerebral haemorrhage. *Cochrane Database Systematic Review*. 2009; 7(4): CD005951. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19821350 [Accessed 18th May 2016].
6. Yuan ZH, Jiang JK, Huang WD, Pan J, Zhu JY, Wang JZ. A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral haemorrhage without haemophilia. *J Clin Neurosci*. 2010; 17(6): 685-693. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20399668 [Accessed on 18th May 2016].