RECOMBINANT ACTIVATED FACTOR VII FOR OFF-LABEL USE

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DISCLOSURE

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EXECUTIVE SUMMARY

Introduction

Massive bleeds are associated with high mortality rate and are currently managed mainly through surgical interventions with simultaneous transfusion of blood and blood-derived products such as fresh frozen plasma, platelet concentrates and cryoprecipitates. However, in critical conditions the achievement of hemostasis and reversal of coagulopathy becomes more difficult, thus alternative approaches may be considered when hemorrhage in uncontrolled by conventional methods. Preliminary studies and case reports indicate that recombinant activated factor VIIa may be of use in treating patients with uncontrolled bleeding in 'off-label' indications.

Objective/Aim

The objective of this review was to determine the safety, effectiveness and cost effectiveness of recombinant activated factor VII for "off-label" use.

Results and conclusion

Based on available evidence, there is no clearly demonstrated benefit or harm from using rFVIIa in comparison to standard care in treatment of uncontrolled bleeding in patients without haemophilia. The cost effectiveness on the use of rFVIIa in the above cases is also inconclusive.

Recommendation

The use of recombinant activated factor VIIa outside its current license should be restricted to use in research or clinical trials in an effort to obtain conclusive evidence on the safety and effectiveness of recombinant activated factor VIIa for 'off-label' indications

Methods

Scientific electronic databases searched include Pubmed, Proquest, EBSCO Host, Medline, CINAHL, Science Direct, Cochrane database of systematic reviews, HTA databases, Horizon scanning databases and FDA website were searched. Only randomized control trials and systematic reviews were included in this review.

RECOMBINANT ACTIVATED FACTOR VII

1. INTRODUCTION

The process of hemostasis refers to the ability of the human body to maintain blood flow within the vasculature and to prompt a thrombotic response when blood escapes the vascular system. Maintaining hemostasis involves a complex interaction of the vessel wall, platelets, and the coagulation and fibrinolytic systems.[1]

The coagulation cascade which involves a sequence of enzymatic reactions is triggered upon tissue injury and bleeding. This results in the formation of blood clot at the site of tissue injury. Factor VII is one of the key initial components of the coagulation cascade. Clotting mechanism is initiated by the contact of factor VII with tissue factor expressed on damaged tissue, which converts factor VII to activated factor VIIa. This complex of activated factor VIIa and tissue factor generates coagulation factor Xa and subsequently thrombin. Thrombin is the enzyme which converts fibrinogen into fibrin; a major constituent of blood clot.[2]

When clotting is disrupted because of genetic conditions such as haemophilia or an acquired condition (surgery, trauma, or intracerebral hemorrhage), typical hemostasis does not occur. Acquired clotting disorders can be difficult to manage because they often arise from underlying problems and can be complicated by other illnesses. This may lead to uncontrolled or massive bleeding.

Massive bleeds are associated with high mortality rate and are currently managed mainly through surgical interventions with simultaneous transfusion of blood and blood-derived products such as fresh frozen plasma, platelet concentrates and cryoprecipitates. However, in critical conditions the achievement of hemostasis and reversal of coagulopathy becomes more difficult. Hence, alternative approaches may be considered when hemorrhage in uncontrolled by conventional methods. [3]

Recombinant activated factor VII is a medication originally approved for the treatment or prevention of bleeding, including surgical bleeding, in patients with haemophilia and inhibitory antibodies to Factor VIII or IX, acquired haemophilia and congenital Factor VII deficiency. However, in recent years, a number of studies and publications have suggested “off-label” indications for recombinant activated factor VIIa such as surgery, blunt or penetrating trauma, postpartum bleeding, intracranial hemorrhage, liver transplant, thrombocytopenia, and reversal of anticoagulant therapy.[4, 5]

This technology review was conducted following a request from a Consultant Hematologist who wants to develop guidelines for “off-label” use of recombinant activated factor VII.

2. OBJECTIVE/AIM

The objective of this review was to determine the safety, effectiveness and cost effectiveness of recombinant activated factor VII for "off-label" use.

3. TECHNICAL FEATURES

Recombinant factor VIIa (rFVIIa) concentrate (NovoSeven) is a genetically engineered product expressed in baby hamster kidney cells, which have been transfected with the human factor VII gene. The human gene for factor VII was isolated from chromosome 13 isolated from human hepatic cells. Recombinant factor VII is secreted into a culture medium (containing fetal calf serum) in its single chain form and then proteolytically converted by autocatalysis to the active two chain factor VIIa form during a series of ion exchange chromatographic steps. Triton-X 100 treatment is utilized to inactivate lipid-enveloped viruses. The resulting rFVIIa consists of 406 amino acid residues (MW = 50 kD) and is structurally identical to human plasma-derived factor VIIa, except for minor differences in the sialic acid and fucose contents and the presence of one glutamic acid residue (out of nine) which is only partially g-carboxylated. The proteolytic and enzymatic properties of rFVIIa, which activate factor X to Xa and factor IX to IXa when complexed to tissue factor, are similar to plasma-derived factor VIIa. As a recombinant protein, rFVIIa supply is theoretically unlimited (in contrast to plasma derived products, which depend on the adequacy of the blood supply), is virtually free of blood-borne viruses, and does not produce anamnestic antibody responses in hemophiliacs. Its high specific activity (50 U/mg) allows for small infusion volumes. Clinical studies indicate that rFVIIa has low thrombogenicity in comparison with prothrombin complex concentrates. [4,6]

In Malaysia, the licensed indication for rFVIIa is for treatment of bleeding episodes and prevention of excessive bleeding in connection with surgery in patients with inherited or acquired haemophilia with inhibitors to coagulation factors VIII or IX. The dosage recommended is 4.5 KIU (90 mcg)/kg body weight administered as IV bolus over 2-5 minutes, followed by 3-6 KIU (60-120 mcg)/kg body weight depending on type and severity of bleeding.[7]

Recombinant activated factor VIIa functions primarily through two mechanisms. The first pathway is tissue factor (TF) dependent and involves the formation, following a vessel injury, of a TF–activated factor VII complex, which in turn activates factor X leading to the conversion of prothrombin to thrombin. The initial limited amount of thrombin formed subsequently activates factor VIII, factor V and platelets so that the tenase complex (activated factor VIII/activated factor IX) and the prothrombinase complex (activated factor X/ activated factor V) assembled on the activated platelet surface lead to a full thrombin generation. This 'thrombin burst' is essential for the formation of a stable fibrin clot that is resistant to premature fibrinolysis, and thus provides reliable and maintained hemostasis. The hemostatic process, however, is not systemic but confined to the surface of the thrombin-activated platelets and the TF bearing cells at the site of vascular injury. The local activation of hemostasis constitutes

the rationale for the use of rFVIIa in DIC-associated severe bleeding. The second pathway involves a TF-independent mechanism. In fact, recent data suggest that rFVIIa can directly activate factor X on phospholipid vesicles and on the surface of activated platelets and monocytes. This mechanism, which is the most important mode of action of rFVIIa at pharmacologic doses, optimizes thrombin generation independently of the presence of TF.[5,8]

4. METHODOLOGY

4.1. Searching

Electronic databases which include Pubmed, Proquest, EBSCO Host, Medline, CINAHL, Science Direct, Cochrane Database of Systematic Reviews, HTA Databases, Horizon Scanning databases and FDA website were searched. There was no limitation in the search. The following keywords were used either singly or in combinations: rFVIIa, recombinant activated factor VII, Novoseven, effectiveness, safe*, cost*, off-label.

4.2. Selection

Only randomized control trials and systematic reviews on the use of rFVIIa for treatment of bleeding in non-hemophilia patients were included in this review.

5. RESULTS AND DISCUSSION

5.1. SAFETY

There are disadvantages of rFVIIa due to the content of trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum, 1.2 ng/mg), bovine IgG (maximum, 30 ng/mg), and protein from baby hamster kidney cells and culture media (maximum, 19 ng/mg). Recipients of rFVIIa may develop antibody responses to these bovine and murine proteins, and the use of rFVIIa is contraindicated in individuals with known hypersensitivity to mouse, hamster, or bovine proteins. Pharmacokinetic studies found the circulating plasma half-life of rFVIIa to be very short (approximately 2.3 h; range, 1.7 to 2.7 h), necessitating frequent and repetitive dosing at short intervals.[6]

Systematic review by Cochrane group examining the therapeutic role of rFVIIa in a range of different clinical scenarios showed trend towards increased thromboembolic adverse events with rFVIIa treatment but these events were not statistically significant (95% CI 0.93 – 1.58). [9 Level I]

Systematic review by The Canadian Agency for Drugs and Technologies in Health reported the following results for different indications.[10 Level 1]

a) Trauma

There were no statistically significant differences in mortality in patients who were treated with rFVIIa relative to placebo for blunt and penetrating trauma 48 hours or 30 days after treatment or for traumatic brain injury 15 days after treatment. Differences in serious and thromboembolic adverse event rates between rFVIIa and placebo were not statistically significant for blunt and penetrating trauma. The proportion of individuals with traumatic brain injury who experienced thromboembolic adverse events ranged from 0% to 17%, depending on the dose, compared to 6% in the placebo group. The RR was not statistically significant for any dose.

b) Gastrointestinal Bleeding

There were no statistically significant differences in mortality five or 42 days after dosing for patients who were treated with 300 μg/kg or 800 μg/kg of rFVIIa compared to placebo. In patients who were treated with rFVIIa 600 μg/kg, the relative and absolute risks of mortality 42 days after dosing were reduced by 47% and 14% respectively, with the number needed to treat being seven. The RR of serious or thromboembolic adverse events was not significantly increased in patients who were treated with 300 μg/kg or 600μg/kg of rFVIIa. The proportion of patients who experienced serious adverse events was not reported for the 800 μg/kg dose, but the number of events was higher in individuals who were treated with placebo.

c) Surgery

One surgical (spinal surgery) trial was identified and included in the review. There were no statistically significant differences in mortality, serious adverse events, or thromboembolic adverse effects between patients who were treated with 30 μg/kg, 60 μg/kg, or 120 μg/kg and those treated with placebo.

d) Intracerebral Hemorrhage

The pooled estimates of the RR of mortality favoured rFVIIa over placebo for all dosages (20 μg/kg, 40 μg/kg, 80 μg/kg, 160 μg/kg) of rFVIIa, but were not statistically significant for any dose. The pooled RRs for mortality ranged from 0.96 (95% CI 0.68 to 1.35; P = 0.80) for the 20 μg/kg dose to 0.68 (95% CI 0.41 to 1.10; P = 0.12) for the 160 μg/kg dose. The pooled risk of thromboembolic or ischemic adverse events in patients who were treated with rFVIIa compared with patients on placebo was not statistically significantly different for any dose, with estimates ranging from 1.16 (95% CI 0.71 to 1.91; P = 0.56) for the 20 μg/kg dose to 2.54 (95% CI 0.39 to16.40; P = 0.33) for the 160 μg/kg dose.

A randomized control trial was conducted by Gill *et al*. to investigate the efficacy and safety of different doses of recombinant activated factor VII in patients bleeding after cardiac surgery. There was a numerical increase in critical serious adverse events (death, myocardial infarction, cerebral infarction, clinically symptomatic pulmonary embolus

and thrombotic events) in patients treated with rFVIIa compared with placebo but the difference was not statistically significant.[11 Level I]

5.2. EFFECTIVENESS

The Cochrane Group conducted a systematic review on the use of recombinant factor VIIa for prevention and treatment of bleeding in patients without haemophilia. The review included eleven trials examining the therapeutic role of rFVIIa in a range of different clinical scenarios including blunt and penetrating trauma, gastrointestinal haemorrhage, dengue hemorrhagic fever, intracranial hemorrhage and stem cell transplantation. The outcomes were mortality, control of bleeding, red cell transfusion requirements, numbers transfused and thromboembolic events. There was no significant difference in overall mortality (95% CI 0.77 – 1.03), control of bleeding (95% CI 0.88 – 1.03), red cell transfusion requirement and numbers transfused (95% CI 0.29 – 3.04) in rFVIIa treated group compared to placebo. **It was concluded that there is little evidence of benefit for off-label use of rFVIIa in patients without haemophilia.**[9 Level I]

The Canadian Agency for Drugs and Technologies in Health conducted a systematic review to determine the clinical efficacy of rFVIIa compared to that of other standard therapies for the treatment of uncontrolled bleeding due to blunt or penetrating trauma, surgery unrelated to trauma, gastrointestinal bleeding, or intracerebral hemorrhage (ICH) in individuals without hemophilia, inherited platelet disorders, or other coagulopathies. The results of the systematic review are as following.[10 Level I]

a) Trauma
   In blunt and penetrating trauma, there were no statistically significant differences in death or critical complications (multiple organ failure or acute respiratory distress syndrome [ARDS] at 30 days), between patients who received rFVIIa or placebo. The risk of ARDS alone in patients with blunt trauma was statistically significantly reduced compared to placebo (RR = 0.27, 95% CI 0.08 to 0.91). The absolute risk reduction for ARDS was 12%, and the number needed to treat was 8.

   There was no statistically significant differences in the number of units of RBCs transfused, platelet requirements, fresh frozen plasma, intensive care unit-free days or ventilator-free days in patients with blunt or penetrating trauma in comparison to placebo.

b) Intracerebral Hemorrhage (ICH)
   The Extended Glasgow Outcome Scale (eGOS) describes overall social function and reflects how disability and handicap affect life. In the three studies, the risk of having an unfavourable outcome on the eGOS showed no statistically significant difference between any dose (20 μg/kg, 40 μg/kg, 80 μg/kg, 160 μg/kg) of rFVIIa relative to placebo. The RR ranged from 0.91 (95% CI 0.79 to 1.05; P = 0.18) in the 40 μg/kg group to 0.99 (95 % CI 0.67 to1.45; P = 0.95) in the 80 μg/kg group.

For the pooled analysis on absolute change in ICH volume from baseline to 24 hours post-dose, Hedge's ranged from 0.002 (95 % CI −0.55 to 0.55; P = 0.99) in the 20 μg/kg group to −0.38 (95 % CI −0.67 to −0.10; P = 0.008) in the 160 μg/kg group. The difference in the absolute change in ICH volume was also statistically significant in the rFVIIa 80 μg/kg group (Hedge's g = −0.25, 95% CI −0.39 to −0.10; P = 0.001).

c) Gastrointestinal bleeding
There were no statistically significant differences between any of the three rFVIIa dosages (300 μg/kg, 600 μg/kg, 800 μg/kg) and placebo for a composite end point of five-day mortality and two bleeding end points (failure to control acute bleeding in 24 hours and failure to prevent clinically significant rebleeding between 24 hours and 5 days). The number of RBC units required within 24 hours (Hedge's g= −0.39, 95% CI −0.70 to −0.09) and five days (Hedge's g = −0.37, 95% CI −0.69 to −0.05) was statistically significantly lower in patients who were treated with 300 μg/kg of rFVIIa, but not for other dosages.

d) Surgery
After adjusting for factors (duration of surgery, number of vertebral segments fused, and estimated blood volume), the volume and percentage of estimated blood volume lost, total transfusion volumes, mean number of allogenic blood products transfused, and number of RBC units transfused in spinal surgery were statistically significantly lower for all three dosages (30 μg/kg, 60 μg/kg, 120 μg/kg) of rFVIIa relative to placebo.

Gill *et al*. reported in their study involving 172 patients that patients receiving rFVIIa for bleeding post cardiac surgery, had significantly fewer reoperations and significantly less transfusion of allogeneic blood and blood products. However, these results must be interpreted cautiously because the trial is underpowered.[11 Level I]

5.3. COST / COST- EFFECTIVENESS

The cost per vial of rFVIIa (NovoSeven) 60 kiu (1.2mg) in Malaysia is approximately [redacted]. There is no local data available on cost-effectiveness of rFVIIa.

Primary economic analysis on use of rFVIIa in blunt trauma was done by the Canadian Agency for Drugs and Technologies in Health.[10 Level I] The results of the analysis are:

Cost:
Based on estimates, the average medical costs that were associated with rFVIIa over a year were [redacted] per patient and [redacted] per patient in the placebo group. Incremental costs were estimated to be [redacted] The largest differences in mean patient costs were in study drug costs ([redacted]), followed by hospital costs ([redacted]) and long-term care ([redacted]).

Probability sensitivity analysis

This analysis showed the probability that rFVIIa is cost-effective (compared with placebo) ranges from 0% at a willingness to pay of [redacted]/QALY to 64% at a willingness to pay of [redacted]/QALY. Assuming a willingness-to-pay threshold of [redacted]/QALY, the probability that rFVIIa is cost-effective is 49.2%.

6. CONCLUSION

Based on available evidence, there is no clearly demonstrated benefit or harm from using rFVIIa in comparison to standard care in treatment of uncontrolled bleeding in patients without haemophilia. The cost effectiveness on the use of rFVIIa in the above cases is also inconclusive.

7. RECOMMENDATION

The use of recombinant activated factor VIIa outside its current license should be restricted to use in research or clinical trials in an effort to obtain conclusive evidence on the safety and effectiveness of recombinant activated factor VIIa for 'off-label' indications.

8. REFERENCES

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