FACTOR VIIA (RECOMBINANT) (NOVOSEVEN®) IN TRAUMA

SUMMARY

Factor VIIa (recombinant) (NovoSeven®) is indicated for the treatment of severe coagulopathic bleeding due to traumatic injury when all conventional means of hemorrhage control have been exhausted. Due to its extreme cost, a careful assessment of the potential risks and benefits must be made. The optimal time to administration and dose in the trauma population have not been definitively established.

RECOMMENDATIONS

- **Level 1**
  - None
- **Level 2**
  - In vitro data supports correction of pH to as close to physiologic levels (pH 7.35 - 7.45) as possible for optimal effect of Factor VIIa (recombinant) infusion.
  - Consider recombinant Factor VIIa (recombinant) in patients with blunt and penetrating trauma when bleeding is refractory to all conventional treatment modalities, including surgical intervention.
- **Level 3**
  - Early recognition of refractory coagulopathy and subsequent administration of recombinant Factor VIIa (recombinant) may decrease mortality rates and reduce transfusion requirements
  - Avoid Factor VIIa (recombinant) in patients:
    - With pre-existing risk factors for thromboembolic complications
      - History of thromboembolic event
      - Crush injury
      - Advanced atherosclerotic disease
    - Brain injury
    - Deemed to have non-survivable injuries
  - Administer Factor VIIa (recombinant) as follows:
    - Assure adequate platelet count prior to administration
    - Administer 90 mcg/kg (rounded DOWN to the nearest 1000mcg) IV over 2-5 minutes
      - Available vial sizes: 1mg, 2mg, 5mg

INTRODUCTION

Uncontrollable hemorrhage is a leading cause of death from trauma. It is often due to a combination of surgical and coagulopathic bleeding. Coagulopathy in trauma is multi-factorial, involving hemodilution, hypothermia, consumption of clotting factors and metabolic derangements (1). Attempts at reversal with conventional treatment modalities, such as transfusion of blood products and preservation of core

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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temperature, can be unsuccessful. Factor VIIa (recombinant) has been used to control life-threatening traumatic bleeding that remains uncorrected by other means.

MECHANISM OF ACTION, DOSING and CONTRAINDICATIONS

Recombinant Factor VIIa (rFVIIa) is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX (2). It promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. It forms a complex with tissue factor (TF) at the site of injury, thereby activating coagulation Factors IX and X. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, leading to the formation of a hemostatic plug by converting fibrinogen to fibrin, inducing local hemostasis. The half-life of rFVIIa is approximately 2 hours. It is intended for intravenous bolus administration only. The recommended dose for patients with hemophilia is 90 mcg/kg administered every two hours until adequate hemostasis is achieved. Once hemostasis has been achieved in severe hemorrhage cases, the interval for maintenance doses is 3 to 6 hours. While generally tolerated in clinical studies, a significant adverse effect is the potential for thromboembolism, which has been associated with disseminated intravascular coagulation (DIC), crush injury, advanced atherosclerotic disease, and/or septicemia. Coagulation parameters do not necessarily correlate with or predict the effectiveness of rFVIIa therapy. The interaction between rFVIIa and coagulation factor concentrates has not been adequately evaluated in clinical studies and the concomitant use of activated prothrombin complex concentrates (e.g., Factor VIII) should be avoided.

Two major conditions often present in the setting of severe coagulopathy and trauma are acidosis and hypothermia, both of which have a profound impact on coagulation and clot stability. In an in-vitro study, rFVIIa's activity on platelets and phospholipid vesicles was not reduced at 33ºC compared to 37ºC. A decrease in pH from 7.4 to 7.0, however, significantly reduced rFVIIa activity by > 90% (3).

In a study by Viuff and Holcomb supported by Novo Nordisk (manufacturer of rFVIIa) and the US Army Institute of Surgical Research, the ability of rFVIIa to form clot in whole blood specimens were measured by thromboelastogram (TEG). TEG data was gathered on samples made acidic to pH 7.0, cooled to 32 C or diluted 20, 40 and 60% with albumin, hespan and hydroxyethyl starch, respectively. The clot formation rate (CFR) before and after addition of rFVIIa was compared to the CFR of an unadulterated whole blood control. There were significant declines in CFR for all samples prior to addition of rFVIIa. After its addition, rates of CFR were either significantly greater or showed no significant difference from the whole blood control under conditions of acidosis, hypothermia and dilutions of less than 40%.

Given that rFVIIa functions by triggering an enhanced coagulation response still dependent on multiple agents of the clotting cascade, correction of acidosis, hypothermia and coagulopathy to the greatest extent possible will likely optimize the efficacy of rFVIIa.

FACTOR VIIa and TRAUMA

Numerous anecdotal reports of rFVIIa's efficacy for control of traumatic hemorrhage have been published over the past decade (1,5-8), but data from randomized controlled trials was lacking until the 2005 publication of the NovoSeven Study Group. In two parallel, randomized, placebo-controlled double-blind studies, rFVIIa was found to significantly reduce the need for blood transfusion in patients with hemorrhagic shock from blunt trauma. In blunt trauma patients given rFVIIa, the need for massive transfusion, defined as transfusion of greater than 20 units of packed red blood cells (pRBC) was 14% versus 33% for patients who received placebo (p=0.03). Similar trends were noted in penetrating trauma, but did not reach significance. It was also noted that there were trend towards a reduction in mortality and critical complications, but this did not achieve statistical significance (8).

In a follow-up study, Rizoli et al. performed a post-hoc analysis of these two studies and demonstrated a reduction in pRBC transfusion by 2.6 units for the entire population studied (p=0.02) and a reduction of 3.5 units for those patients who survived greater than 48 hours. Rizoli also demonstrated a significant reduction in both multisystem organ failure and acute respiratory distress syndrome in those patients who

received rFVII (3% versus 20%, p=0.004). Thromboembolic events were evenly distributed among both study groups (9,10).

COST

NovoSeven(®) is supplied in 1mg, 2mg, and 5mg vials at an AWP cost of $1.10/mcg.
**1mg vial = 1000mcg x $1.10/mcg = $1100
**2mg vial = 2000mcg x $1.10/mcg = $2200
**5 mg vial = 5000mcg x $1.10/mcg = $5500

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