Joint Theater Trauma System Clinical Practice Guideline

Use of Recombinant Factor VIIa (rFVIIa)

1) Background:

The most critically injured casualties may present hypothermic (T < 96 °F), acidemic (base deficit < -6) and coagulopathic (INR > 1.5). All three conditions contribute to worsening bleeding. Interventions aimed at reversing coagulopathy, starting as soon after arrival as possible, may improve casualty survival [1,2].

In a recent prospective, randomized human trauma study[3], rFVIIa was shown to be effective in decreasing transfusion requirements, to include those patients requiring massive transfusion (RBCs ≥ 10 units/24 hours), in humans with life-threatening hemorrhage, including patients with hypothermia (30-33 degrees C; pH > 7.1). However, rFVIIa is 90% inactivated in patients with profound acidosis (pH < 7.1), based on in-vitro data. Although this study was not powered to show safety, with 301 patients randomized, trends in favor of positive outcomes, adverse events, mortality, ventilator-free days, and ICU-free days were observed.

In a recently published retrospective review[4] of records for trauma admissions to Combat Support Hospitals in Iraq between Jan 04 and Oct 05, a total of 117 patients requiring a massive transfusion and receiving rFVIIa were identified. Complete records were available for review in 61 patients. Of those, 17 received rFVIIa early, or before 8 units of RBCs had been transfused, while 44 received the drug late, or after 8 units RBCs were given. At admission, temperature, Glasgow Coma Scale score, base deficit, hemoglobin, platelets, prothrombin time/International Normalized Ratio, and Injury Severity Score were similar in both groups, as were administered units of fresh frozen plasma, fresh whole blood, cryoprecipitate, and crystalloid. Although no statistically significant survival benefit was seen, this review demonstrated that early administration of rFVIIa decreased red blood cell use by 20% (5 units) in trauma patients requiring massive transfusion. It is well documented that increased exposure to blood products increases the risk of infection, multi-organ failure, and mortality. In addition, the FDA has acknowledged that decreased blood transfusion is an appropriate end-point when considering the evaluation of resuscitation interventions.

In an another article recently submitted for publication[5], a retrospective review of combat casualty patients with severe trauma (ISS > 15) and massive transfusion (RBCs ≥ 10 units/24 hours) admitted to one Combat Support Hospital in Baghdad, Iraq, was conducted. Admission vital signs and laboratory data, blood products, Injury Severity Score (ISS), 24-hour and 30-day mortality, and severe thrombotic events were compared between patients who received rFVIIa and those who did not receive rFVIIa. Of 124 patients who received massive transfusion, 49 patients received rFVIIa and 75 patients did not. ISS scores and vital signs did not differ between the two groups. A statistically significant decrease in

mortality was demonstrated in the group who received rFVIIa at 12 hours, 24 hours, and 30 days. When rFVIIa was given at a median of 2 hours from admission, an association with decreased mortality was seen. There was no statistical difference in the incidence of severe thrombotic events (DVT, PE, stroke) between the study groups. There is currently an ongoing Phase III trauma trial of rFVIIa which addresses the question of whether earlier administration of rFVIIa improves the outcome of severely injured patients.

2) FDA Position:

FDA Approved Use: Recombinant Factor VIIa is FDA-approved for use during critical bleeding or surgery in hemophiliac patients with inhibitors to Factor VIII or IX.

Unlabeled Use: Recombinant Factor VIIa is not FDA-approved to stop uncontrolled hemorrhage in severe trauma patients, but has been studied in randomized trials and is in widespread use in civilian trauma centers. It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

Potential adverse events[6]: In November 2005 (following publication of the data in Reference 3), the FDA issued new "Warnings and Adverse Reactions" to the labeling for Novoseven® Coagulation Factor VIIa (Recombinant). This new information is based on data from post-marketing studies and routine safety surveillance. The additional adverse events that were added are based on clinical studies of off-label uses (non-hemophilia patients) and on post-marketing safety surveillance. The following additional adverse events were reported in both labeled and unlabeled indications: high D-dimer levels and consumptive coagulopathy; thromboembolic events including myocardial infarction, myocardial ischemia, cerebral infarction and/or ischemia; thrombophlebitis, arterial thrombosis, deep vein thrombosis and related pulmonary embolism, and isolated cases of hypersensitivity.

3) Mechanism:

Recombinant Factor VIIa is activated in combination with tissue factor at sites of endothelial injury. High doses of rFVIIa result in the accelerated generation of thrombin. The resulting clots are stronger and more resistant to fibrinolysis than normal clots[7]. The potential effectiveness of rFVIIa degrades with time in the patient with poorly controlled hemorrhage due to fibrinogen, platelet and coagulation factor consumption and dilution. These patients may require clotting factors and platelet supplementation prior to administration of rFVIIa. In the forward surgical setting this supplementation is available by the early administration of fresh whole blood followed by rFVIIa.

4) Considerations for Use:

The extent of the risk of thrombotic adverse events after treatment with rFVIIa is not known, but is considered to be low. Coagulapathy is a major contributing factor to bleeding-related mortality, particularly when associated with metabolic acidosis and hypothermia. Additional factors contributing to coagulopathy in trauma patients are hemodilution and platelet dysfunction resulting from massive blood transfusion or fluid resuscitation. Patients who receive rFVIIa should be monitored for signs or symptoms of thrombosis.

Faced with the increase rate of massive transfusion inherent after military wounding, military clinicians have developed aggressive guidelines to pre-empt or reverse coagulopathy in patients requiring massive transfusions in the CSH. These guidelines fall under the term "Damage Control Resuscitation" and include the use of thawed plasma (1:1 ratio with PRBCs), apheresis platelets, pooled cryoprecipitate, fresh whole blood, and rFVIIa. Recombinant activated factor VII was originally developed for the treatment of patients with hemophilia who developed inhibitors to Factor VIII or Factor IX. However, rFVIIa is used in virtually all Level I trauma centers in the US, usually as part of a massive transfusion protocol. Although rFVIIa has been associated with pathologic thrombosis, in the only prospective, randomized study of injured patients receiving rFVIIa compiled to date, the clinical VTE rate was no different between patients who received rFVIIa and those that did not (2% vs. 3% in blunt trauma; 4% vs. 3% in penetrating trauma)[3]. At a recent DOD review, a group of Senior Civilian Surgeons reviewed data on 615 severely injured combat casualties from 2004-2006 compiled from the Joint Theater Trauma Registry. The DVT rate was 7.5%, with a PE incidence of 3.8% and there was no apparent difference in VTE between groups that received rFVIIa and those who did not. Among the most severely injured combat casualties who required a massive transfusion (defined as >10 units of PRBCs), the thrombotic rate in patients who did not receive rFVIIa was 13% vs. 18% for those who did (not significantly different). Conversely, rFVIIa significantly improved survival in a subgroup of severely injured and massively transfused casualties ($p < 0.05$)[5].

5) Guidelines for administration in the deployed surgical setting. rFVIIa should be considered for administration to trauma patients or patients in shock who have the following signs associated with hemorrhage:

a. Hypotensive from blood loss
b. Base deficit > 6
c. Difficult to control bleeding associated with hypothermia (T < 96° F)
d. Coagulopathic bleeding (clinically or an INR > 1.5)
e. Require damage control maneuvers
f. Require fresh whole blood
g. Anticipated or actual transfusion of > 4 units of PRBCs
h. Anticipated significant operative hemorrhage

6) Protocol for use:

a. Infuse rFVIIa at dose of 90-120 mcg/kg IV push.
b. If coagulopathic bleeding continues 20 minutes after infusion:
   (1) Administer 2 additional units fresh whole blood or 4 U FFP and/or 6 pack platelets
   (2) Redose rFVIIa 90-120 mcg/kg IV push and repeat ii) (1)

7) Administration Limits:

a. 3 doses within a 6 hour period
b. If bleeding persists after 3 doses there should be attention to conservation of resources. Consult senior surgeon at the MTF before administering more rFVIIa.

8) Storage

a) Refrigeration at 4^{o} C. (range 2-8^{o} C.).
b) Reconstitution is with sterile water for injection at room temperature.
c) The reconstituted solution may be used up to 24 hours after reconstitution.

9) Relative Contraindications[6]:

Known hypersensitivity to rFVIIa or any of its components. Known hypersensitivity to mouse, hamster, or bovine proteins.

10) Absolute Contraindications:

None.

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