

Joint Theater Trauma System Clinical Practice Guideline

DAMAGE CONTROL RESUSCITATION AT LEVEL IIb/III TREATMENT FACILITIES

Original Release/Approval	18 Dec 2004	Note: This CPG requires an annual review.	
Reviewed:	Oct 2008	Approved:	26 Nov 2008
Supersedes:	Damage Control Resuscitation at Level IIb and III, updated Apr 08; Use of rFVIIa, Oct 07		

1. Goal. Outline a method of trauma resuscitation in which Recombinant Factor VIIa (rFVIIa) plus packed red blood cells (pRBCs), thawed plasma and platelets in a 1:1:1 ratio are used to obtain systemic hemostasis and manage non-compressible hemorrhage.

2. Background.

- a. Utilizing the Tactical Combat Casualty Care (TCCC) guidelines, medics and corpsmen use tourniquets and hemostatic dressings to treat compressible hemorrhage. It is the non-compressible hemorrhage (i.e., truncal, axillary, neck, and groin) that remains the unsolved problem, as well as one of the leading cause of death on today's battlefield.
- b. Following Advanced Trauma Life Support guidelines, surgeons traditionally begin resuscitation with aggressive use of crystalloids, followed by the addition of pRBCs and finally plasma. Excessive crystalloid use in civilian trauma has demonstrated a greater incidence of abdominal compartment syndrome (16% vs. 8%), multiple organ failure (22% vs. 9%), and death (27% vs. 11%).
- c. New evidence, based largely on objective criteria, supports resuscitation in which rFVIIa plus pRBCs, thawed plasma and platelets (1:1:1 ratio) are used first and crystalloid infusion is limited.
 - 1) rFVIIa has recently shown improved hemostasis in combat casualties, decreasing blood loss by 23% (see Appendix A for more information on the use of rFVIIa).
 - a) Usual Dose: 100 mcg/kg intravenously; May be repeated in 20 minutes
 - b) Contraindications: Active cardiac disease
 - c) Storage: Refrigerate (2°C – 8°C/36°F – 46°F) prior to reconstitution and use. The FDA recently approved a room temperature stable product. This will be distributed throughout the CENTCOM AOR as the current supplies are exhausted.
 - 2) Increased use of plasma and platelets has recently been shown to improve mortality rates in combat casualties.
 - 3) Thawed plasma for emergency use should be type A or AB. No more than two units of un-typed plasma should be administered under these conditions. All subsequent transfusions should be type-specific.

3. Emergency Department (ED) Resuscitation. rFVIIa plus pRBC, plasma and platelets (1:1:1 ratio) are indicated for any one of the following findings:

- a. Uncontrolled truncal, axillary, neck, or groin bleeding

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

- b. Uncontrolled bleeding secondary to large soft tissue injuries
- c. A proximal amputation or mangled extremity
- d. Chest tube output > 1000 cc upon insertion , or > 200 cc/hr for four consecutive hours
- e. Physical exam findings:
 - 1) Declining mental status secondary to injury and shock
 - 2) Severe head injury
 - 3) Clinically coagulopathic
- f. Vital signs measurements:
 - 1) Hypothermia secondary to bleeding ($T < 96^{\circ}\text{F}$)
 - 2) Hypotension secondary to bleeding ($\text{SBP} < 90$ or weak/absent radial pulse)
- g. Laboratory results:
 - 1) $\text{INR} \geq 1.5$
 - 2) Base deficit ≥ 6
 - 3) $\text{Hgb} \leq 12$

4. OR Resuscitation.

- a. The goal of OR resuscitation is to normalize both casualty temperature and laboratory parameters.
 - 1) The operating room must be kept as warm as possible; ideally 108°F or greater.
 - 2) Consider a second dose of rFVIIa for $\text{INR} > 1.0$.
 - 3) Administer THAM (non-bicarbonate buffer) to maintain $\text{pH} > 7.2$.
 - 4) Administer Ca^{++} after every four units of pRBCs and/or to keep ionized $\text{Ca}^{++} > 1.0$ (via i-STAT®).

5. Massive Transfusion (MT):

- a. Most casualties that receive hemostatic resuscitation in the ED or the OR require a MT. Defined as greater than 10u pRBCs/24 hours MT patients present a unique challenge both in the ED and OR, as well as the ICU post-operatively. Anticipating the need for a MT requires experience and the coordination of extensive resources. Once a MT patient is identified, the Blood Bank must be notified immediately. Ideally, the blood bank provides pRBCs that are less than 14 days old.
- b. For all MT patients the policy of “Last in First Out” (LIFO) will be applied for all blood products provided to the surgical/ICU team. The CENTCOM Blood Bank staff, in conjunction with in-theater personnel and the USAF, has developed an extensive logistical process that helps ensure the Level III facilities in Baghdad, Balad and Bagram are adequately supported with the newest and freshest pRBCs.

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

6. ICU Resuscitation.

- a. Patients aggressively resuscitated in the ED and OR frequently arrive in the ICU warm (98 °F) and with a base deficit ~ (-) 3 and INR ~1.0. This clinical picture is not unusual despite receiving an average of 7.2 mg rFVIIa, four liters of crystalloid, 17 units pRBCs, 13 units plasma, 20 units cryoprecipitate, and 8 platelet packs. Occasionally, the casualty will require ongoing plasma resuscitation and a second rFVIIa dose, as well as a 50 cc/hr crystalloid infusion.

7. Conclusion

- a. The approach to a critically injured soldier, marine, sailor, or airmen requires a massive expenditure of resources and the coordination of a diverse group of health care providers. This is also potentially done in the face of multiple casualties and limited resources. It is incumbent upon the chief trauma surgeon at each facility to be fully versed on his or her resources and to employ them judiciously.
- b. Patients requiring massive transfusion should be resuscitated using a guideline of 1:1:1 ratio of plasma:platelets:pRBCs.

8. References.

- ¹ Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, Moore FA: Supra-normal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch. Surg.* 138:637-643, 2003.
- ² Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y; NovoSeven Trauma Study Group. 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 Jul;59(1):8-18.
- ³ Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, Scalea TM. Factor VIIa for correction of traumatic coagulopathy. *J Trauma.* 2004 Oct;57(4):709-19.
- ⁴ Hedner U. NovoSeven as a universal haemostatic agent. *Blood Coagul Fibrinolysis.* Apr 2000; 11 Suppl 1:S107-11.
- ⁵ Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. *J Trauma.* 2005 Jun;58(6):1298-303
- ⁶ Holcomb JB, Hoots K, Moore FA. Treatment of an acquired coagulopathy with recombinant activated factor VII in a damage-control patient. *Mil Med.* Apr 2005;170(4):287-90.
- ⁷ Holcomb JB, Wade, CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, Williams KL, Park MS. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg.* 2008 Sep; 248(3):447-58.
- ⁸ Kenet G, Walden R, Eldad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 354: 1879, 1999.
- ⁹ Lynn M, Jerokhimov I, Jewelewicz D, Popkin C, Johnson EW, Rashid QN, Brown M, Martinowitz U, Cohn SM. Early use of recombinant factor VIIa improves mean arterial pressure

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

and may potentially decrease mortality in experimental hemorrhagic shock: a pilot study. *J Trauma*. Apr 2002;52(4):703-7.

¹⁰ Martinowitz U, Holcomb JB, Pusateri AE et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma* 50: 721-729, 2001.

¹¹ Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. *Lancet*. 2004 Jun 12; 363(9425):1988-96.

¹² Novoseven Coagulation Factor VIIa (Recombinant) package insert. Novo Nordisk Pharmaceuticals Inc.

Approved by CENTCOM JTTS Director, JTS Director
and Deputy Director and CENTCOM SG

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

APPENDIX A

1. Background. The most critically injured casualties often present hypothermic ($T < 96^{\circ}\text{F}$), acidemic (base deficit < 6), and coagulopathic ($\text{INR} > 1.5$). 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 study³, rFVIIa was shown to be effective in decreasing transfusion requirements, including those patients requiring massive transfusion (pRBCs ≥ 10 units/24 hours), in humans with life-threatening hemorrhage, including patients with hypothermia (30-33 degrees C; $\text{Ph} > 7.1$). However, rFVIIa is 90% inactivated in patients with profound acidosis ($\text{Ph} < 7.1$), 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 review⁴ 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 pRBCs had been transfused, while 44 received the drug late, or after 8 units pRBCs 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 the number of 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 another article recently submitted for publication,⁵ a retrospective review of combat casualty patients with severe trauma ($\text{ISS} > 15$) and massive transfusion (pRBCs ≥ 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.

Joint Theater Trauma System Clinical Practice Guideline

2. FDA Position.

- a. 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.
- b. 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 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.
- c. 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. Coagulopathy 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 Level IIb/III facilities. 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

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

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, 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 ($T < 96^{\circ} F$)
- d. Coagulopathic bleeding (clinically or an $INR > 1.5$)
- e. Require damage control maneuvers
- f. Require fresh whole blood (FWB)
- g. Anticipated or actual transfusion of > 4 units of pRBCs
- h. Anticipated significant operative hemorrhage
- i. Protocol for Use
- j. Infuse rFVIIa at dose of 90-120 mcg/kg IV push.
- k. 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

6. Administration Limits

- a. 3 doses within a 6 hour period
- b. If bleeding persists after 3 doses, attention should be directed toward conservation of resources. Consult senior surgeon at the MTF before administering additional rFVIIa.

7. Storage

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

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

- d. **The FDA has recently approved a non-heat sensitive rFVIIa. This product will be distributed throughout the AOR to replace expended stocks.**

8. Relative Contraindications.⁶ Known hypersensitivity to rFVIIa or any of its components. Known hypersensitivity to mouse, hamster, or bovine proteins.

9. Absolute Contraindications. Active cardiac disease.

10. References.

¹ Tieu BH, Holcomb JB and Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. *World J Surg.* May 2007; 31(5):1055-65.

² Borgman M, Spinella P, Perkins J, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. Accepted, *J Trauma.* 2007.

³ Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y; NovoSeven Trauma Study Group. 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.* Jul 2005; 59(1):8-18.

⁴ Perkins JG, Schreiber MA, Wade CE and Holcomb JB. Early versus late recombinant factor VIIa (rFVIIa) in combat trauma patients requiring massive transfusion (MT). *J Trauma* 2007;62:1095-1101.

⁵ Spinella PC. The effect of recombinant activated factor VII on mortality in combat-related casualties with severe trauma and massive transfusion. Oral Presentation at the 2007 AAST annual meeting. Submitted *J Trauma.*

⁶ NovoSeven Coagulation Factor VIIa (Recombinant) package insert. Novo Nordisk Pharmaceuticals Inc. (Updated with new warnings and adverse reactions, Nov 2005.)

⁷ Sondeen JL, Pusateri AE, Hedner U, Yantis LD and Holcomb JB. Recombinant Factor VIIa Increases the Pressure at which Rebleeding Occurs in Procine Uncontrolled Aortic Hemorrhage Model. *Shock.* Aug 2004; 22(2):163-8.

⁸ Aiyagari V, Menendez JA, Diringner MN. Treatment of severe coagulopathy after gunshot injury to the head using recombinant activated factor VII. *J Critical Care.* Jun 2005; 20(2):176-9.

⁹ DeLoughery TG. Management of bleeding emergencies: when to use recombinant activated factor VII. *Expert Opinion on Pharmacotherapy.* Jan 2006; 7(1):25-34.

¹⁰ Dutton RP, McCunn M, Hyder M, D'Angelo M, O'Connor J, Hess JR, Scalea TM. Factor VIIa for correction of traumatic coagulopathy. *J Trauma.* Oct 2004; 57(4):709-19.

¹¹ Grounds RM, Seebach C, Knothe C, et al. Use of recombinant activated factor VII (Novoseven) in trauma and surgery: analysis of outcomes reported to an international registry. *J Intensive Care Medicine.* Jan-Feb 2006; 21(1):27-39.

¹² Haas T, Innerhofer P, Kuhbacher G and Fries D. Successful reversal of deleterious coagulopathy by recombinant factor VIIa. *Anesthesia & Analgesia.* June 2005; 100(1):54-8.

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

- ¹³ Harrison TD, Laskosky J, et al. "Low-dose" recombinant activated factor VII results in less blood and blood product use in traumatic hemorrhage. *Journal of Trauma-Injury Infection & Critical Care*. Jul 2005; 59(1):150-4.
- ¹⁴ Hedner U. NovoSeven as a universal haemostatic agent. *Blood Coagul Fibrinolysis*. Apr 2000; 11 Suppl 1:S107-11.
- ¹⁵ Holcomb JB. Use of recombinant activated factor VII to treat the acquired coagulopathy of trauma. *J Trauma*. Jun 2005; 58(6):1298-303.
- ¹⁶ Holcomb JB, Hoots K and Moore FA. Treatment of an acquired coagulopathy with recombinant activated factor VII in a damage-control patient. *Mil Med*. Apr 2005; 170(4):287-90.
- ¹⁷ Kenet G, Walden R, Eldad A and Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 354: 1879, 1999.
- ¹⁸ Martinowitz U, Holcomb JB, Pusateri AE, et al. Intravenous rFVIIa administered for hemorrhage control in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma* 50: 721-729, 2001.
- ¹⁹ Martinowitz U, Zaarur M, Yaron BL. et al. Treating traumatic bleeding in combat setting: possible role of recombinant activated factor VII. *Military Medicine*. Dec 2004;169(12 Suppl):16-8, 4.
- ²⁰ Mayer SA, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *NEJM*. 2005;352:777-785.
- ²¹ Selin S, Tejani A. *Issues in Emerging Health Technologies*. Mar 2006; (82):1-4.
- ²² Shamsi T, Tufail M, Aftab M and Ansari S. Role of recombinant activated factor VII in securing haemostatic failure in gun shot trauma. *J Pakistan Medical Association*. May 2006;56(5):238-41.
- ²³ Stein DM, Dutton RP. Uses of recombinant factor VIIa in trauma. *Current Opinion in Critical Care*. Dec 2004;10(6):520-8.
- ²⁴ Stein DM, Dutton RP, O'Connor J, Alexander M and Scalea TM. Determinants of futility of administration of recombinant factor VIIa in trauma. *J Trauma-Injury Infection & Critical Care*. Sep 2005; 59(3):609-15.
- ²⁵ White CE, Schrank AE, Baskin TW and Holcomb JB. Effects of recombinant activated factor VII in traumatic nonsurgical intracranial hemorrhage. *Current Surgery*. Sep-Oct 2006; 63(5):310-7.
- ²⁶ Wilson SJ, Bellamy MC and Giannoudis PV. The safety and efficacy of the administration of recombinant activated factor VII in major surgery and trauma patients. *Expert Opinion on Drug Safety*. May 2005; 4(3):557-70.
- ²⁷ Holcomb JB, McMullin NR, Pearse L, Caruso J, Wade CE, Oetjen-Gerdes L, Champion HR, Lawnick M, Farr W, Rodriguez S and Butler FK. Causes of Death in U.S. Special Operation Forces in the Global War on Terrorism: 2001-2004. *Ann Surg*. Jun 2007; 245(6):986-991.

Guideline Only/Not a Substitute for Clinical Judgment

November 2008

Joint Theater Trauma System Clinical Practice Guideline

²⁸ Holcomb JB, Jenkins D, and Rhee P, Johannigman J, et al. Damage Control Resuscitation: Directly Addressing the Early Coagulopathy of Trauma. J Trauma. Feb 2007; 62(2):307-10.

Guideline Only/Not a Substitute for Clinical Judgment

November 2008