Review

Pro/Con Debate: Does recombinant factor VIIa have a role to play in the treatment of patients with acute nontraumatic hemorrhage?

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Abstract

Perhaps it is not surprising that in the critical care environment, where lives are frequently on the line, off-label use of certain drugs is relatively common. In general, there are two camps of opinion on this type of utilization. One camp would suggest that potentially life saving products cannot ethically be withheld from patients who may benefit. The other camp would counter that it is inappropriate to administer products if the risk/benefit ratio has not been clearly defined in clinical trials. Off-label use of factor VII is debated in this issue of *Critical Care* for a patient with uncontrolled nontraumatic hemorrhage. Perhaps this product promotes additional discussion given that its ability to control bleeding can be dramatic, yet its costs and potential for complications high.

The scenario

A 49-year-old male has been managed in the intensive care unit for 5 days after a large left diaphragmatic hernia repair and is currently being weaned from mechanical ventilation. He suddenly has significant hematemesis and becomes hemodynamically unstable, with alteration to his coagulation. You start to resuscitate him with fluid, blood and plasma, in order to reverse the hemorrhagic shock and correct the coagulopathy. An endoscopy reveals diffuse gastric erosions but fails to stop the bleeding. He continues to be unstable and surgical intervention is not an option. You are aware that factor VIIa (FVIIa) has been used in acute traumatic hemorrhage to stop bleeding. You wonder whether it has a role to play in this type of patient.

Pro: Potential benefit of recombinant FVIIa in the setting of coagulopathy associated with acute hemorrhagic gastritis

Paola Pieri and Deborah M Stein

FVIIa (NovoSeven™) was developed by Novo Nordisk for use in patients with congenital and acquired hemophilia and inhibitors of factor VIII or IX. Since it was licensed in Europe in the 1990s and in the USA in 1999 it has been utilized off-label in an increasing number of nonhemophiliac patients with severe bleeding, such as the patient described in the scenario above. At present the precise role of FVIIa in treating life-threatening hemorrhage has not been determined. However, numerous studies have demonstrated benefit from off-label use.

Several case series have been published that describe successful use of FVIIa in severely injured patients [1-4]. Additionally, in a recently published prospective randomized placebo-controlled double blind trial [5], a reduction in transfusion requirement was observed in trauma patients, as was a decrease in overall morbidity and mortality when early deaths were excluded from the analysis. There are numerous other reports of successful use of FVIIa in the noninjured patient with acute hemorrhage, such as that secondary to esophageal varices, hemorrhagic pancreatitis, and hemorrhage occurring during cardiac surgery and liver transplantation. Case reports of FVIIa use to treat patients with resistant coagulopathies that developed in the intensive care unit setting [1,6,7] have demonstrated efficacy in restoring hemostasis, with subsequent survival largely dependent on the underlying disease process. Prospective randomized trials [8,9] have demonstrated successful use of FVIIa in other patient populations, including those with acute intracerebral hemorrhage and those undergoing elective radical prostatectomy.

With FVIIa use, the potential complications of pathological and inappropriate thrombus formation is present but thought to be low. A recently published US Food and Drug Administration MedWatch database [10] described 151 complications associated with off-label use of FVIIa, the majority occurring in trauma patients. However, MedWatch is a database for voluntary reporting of observed complications, and therefore the incidence of complications cannot be calculated from it. Randomized studies [4,8] have found the frequency of adverse events associated with administration of FVIIa to be similar to those with placebo.

The patient presented above is a relatively healthy male, with no assumed underlying significant medical conditions, who undergoes an elective surgical procedure and subsequently develops stress gastritis and life-threatening upper gastrointestinal bleeding. Despite adequate and aggressive resuscitation and medical management, he continues to hemorrhage. Administration of FVIIa is certainly warranted in this patient. Life-threatening hemorrhage and coagulopathy in critical care patients carries significant morbidity and mortality, with increased incidence of respiratory failure and renal failure as well as multiple organ dysfunction. FVIIa has efficacy in restoring hemostasis. Additionally, early administration – before the development of acidosis, hypothermia, and subsequent additional coagulopathy – is likely to be more efficacious. The risk for adverse events after FVIIa administration is low, and in this case, although the patient is *in extremis*, the potentially life-saving benefit of correcting the patient's coagulopathy and ceasing his hemorrhage clearly takes precedent. Furthermore, the only other option for arresting hemorrhage in this patient in whom coagulopathy cannot be reversed is a total gastrectomy, which is a procedure with unacceptably high morbidity, both in the short and long term. Therefore, off-label use of FVIIa in this setting is not only warranted but also potentially beneficial and life saving.

Con: Recombinant FVIIa is not a cure for all bleeding

Sandro Scarpelini and Sandro Rizoli

We understand the clinical scenario and debate question as whether one should administer a drug outside its licensed indications (off-label) to treat a condition (upper gastrointestinal bleeding) without any evidence for the drug's efficacy and safety.

The first issue is the off-label use. After a single successful report of off-label use of recombinant FVIIa (rFVIIa) in 1999, many physicians began to experiment with this drug in numerous bleeding situations [11]. Retrospective case reports followed, almost invariably describing remarkable results and further stimulating unlicensed use of rFVIIa [11]. More recently, many of the expectations raised by retrospective reports are being revised as more balanced results from randomized controlled trials (RCTs) are published [8,9,11-15]. Particularly in gastrointestinal bleeding, RCTs have contradicted many initial expectations and demonstrated no clinical benefit of rFVIIa. In 2004 Romero-Castro and coworkers [15] reported that all 10 patients with cirrhosis and bleeding varices stopped bleeding after a single bolus of rFVIIa. However, a subsequent 245-patient European RCT conducted in this same population [13] demonstrated that rFVIIa had no effect. The same occurred in liver transplantation, in which a pilot six-patient study reported 100% efficacy in reducing bleeding but an 86-patient RCT concluded that rFVIIa had no impact on perioperative blood loss or need for blood transfusion [12]. One more caveat comes from a multicenter survey of off-label use of rFVIIa in American academic hospitals [16], which reported that only 52% of the patients stopped bleeding within 6 hours of rFVIIa administration and 9% suffered adverse events. The latter finding is worse than any case report or series and is curiously similar to the 7% complication rate reported in a 399-patient RCT on intracerebral hemorrhage [9]. In conclusion, off-label use might be inappropriate, wasteful, and cause adverse effects more often than is currently estimated.

The second issue is the lack of evidence. There are no reports of rFVIIa use in diffuse gastric erosions, with the arguable exception of a sketchy report [17]. In other gastrointestinal bleeds, there are two RCTs (discussed above and found no clinical benefit) and case reports/series in Crohn's disease, peptic ulcer, cancer/hematological diseases, anticoagulant use, pancreatitis, and cirrhosis [12,13]. The case reports/series are dismally small (two patients with Crohn's disease, one with peptic ulcer, one receiving anticoagulant, and two with pancreatitis); case reports are typically biased toward positive results, and the diseases reported are different from the case in question. In conclusion, there is no evidence suggesting rFVIIa might benefit this patient.

A third consideration is that the moral/ethical implications of administering a drug with unknown efficacy/safety, for unlicensed indications. These implications should not be neglected.

Finally, rFVIIa is an attractive proposition with potential to change current practice [18]. There is reasonable evidence to justify its off-label use in trauma, intracerebral hemorrhage, cardiovascular surgery, large perioperative hemorrhage, obstetrics, and anticoagulant-induced hemorrhage [5,8,11, 14]. However, there is also evidence disproving any benefit in liver transplant, gastrointestinal bleeding (cirrhosis), liver resection, and pelvic/acetabular surgery [11-13]. rFVIIa is not

a panacea for all bleeding, and inappropriate use should be as much a concern as not using it when it could be beneficial. Since most indications for rFVIIa remain largely untested, we should struggle to enroll patients into clinical trials that will eventually define which patients do benefit from rFVIIa, rather than promoting off-label use.

Pro's response: This patient cannot wait for the randomized controlled trial …

Paola Pieri and Deborah M Stein

Dr Rizoli presents accurate and important information concerning the off-label use of rFVIIa. The clinical situation presented, however, is more akin to the coagulopathy seen in trauma, in which rFVIIa has demonstrated efficacy without increased complications, than to a patient with a chronic disease. Although some RCTs have shown no benefit in patients with cirrhosis, varices, or transplants, this is not necessarily relevant in the patient who was previously healthy and developed life-threatening hemorrhage. Although rFVIIa is certainly not a 'panacea', the potentially life-saving benefit should outweigh concern that administration may fail, and should not preclude its use.

Con's response: Use of rFVIIa requires not only bleeding but also a reasonable expectation of benefit

Sandro Scarpelini and Sandro Rizoli

Many believe that rFVIIa cures all bleeding, which is an unsustainable conviction considering the current evidence. RCTs have questioned the near perfect efficacy described by many case reports, particularly in upper gastrointestinal bleeding. The reasons to avoid rFVIIa in this patient are as follows: it has not previously been used for a similar indication; RCTs have shown no benefit in upper gastrointestinal bleeding (cirrhotic); and use of rFVIIa as 'last resort' is futile [19].

The colleagues incorrectly stated that the trauma RCT [5] demonstrated that rFVIIa decreases mortality in trauma.

rFVIIa is efficacious in many but not all circumstances. Apart from ongoing bleeding, even off-label use demands reasonable expectation of benefit. Ongoing bleeding and reasonable expectation of benefit are mandatory even for compassionate off-label use of rFVIIa.

Competing interests

SR is a member of the Niastase/NovoSeven International Scientific Advisory Board and has received consultancy fees from NovoNordisk A/S.

References

1. 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, **57:**709-719.
2. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M: **Recombinant activated factor VII for adjunctive hemorrhage control in trauma.** *J Trauma* 2001, **51:**431-439.
3. O'Connell NM, Perry DJ, Hodgson AJ, O'Shaughnessy DF, Laffan MA, Smith OP: **Recombinant FVIIa in the management of uncontrolled hemorrhage.** *Transfusion* 2003, **43:**1711-1716.
4. Geeraedts LM Jr, Kamphuisen PW, Kaasjager HA, Verwiel JM, van Vugt AB, Frolke JP: **The role of recombinant factor VIIa in the treatment of life-threatening haemorrhage in blunt trauma.** *Injury* 2005, **36:**495-500.
5. 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, **59:**8-18.
6. Holcomb JB, Nevilee HL, Fischer CF, Hoots K: **Use of recombinant FVIIa for intraperitoneal coagulopathic bleeding.** *Curr Surg* 2003, **60:**423-427.
7. Khan AZ, Parry JM, Crowley WF, McAllen K, Davis AT, Bonnell BW, Hoogeboom JE: **Recombinant factor VIIa for the treatment of severe postoperative and traumatic hemorrhage.** *Am J Surg* 2005, **189:**331-334.
8. Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, Buller HR, Levi M: **Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomized trial.** *Lancet* 2003, **361:**201-205.
9. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators: **Recombinant activated factor VII for acute intracerebral hemorrhage.** *N Engl J Med* 2005, **352:**777-788.
10. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM: **Thromboembolic adverse events after use of recombinant human coagulation factor VIIa.** *JAMA* 2006, **295:**293-298.
11. Enomoto TM, Thorborg P: **Emerging off-label uses for recombinant activated factor VII: grading the evidence.** *Crit Care Clin* 2005, **21:**611-632.
12. Planinsic RM, van der Meer J, Testa G: **Safety and efficacy of a single bolus administration of recombinant factor VIIa in liver transplantation due to chronic liver disease.** *Liver Transpl* 2005, **11:**895-900.
13. Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Abraldes JG, Fabricius S, Erhardtsen E, de Franchis R: **Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial.** *Gastroenterol*ogy 2004, **127:**1123-1130.
14. Diprose P, Herbertson MJ, O'Shaughnessy D, Gill RS: **Activated recombinant factor VII after cardiopulmonary bypass reduces allogeneic transfusion in complex non-coronary cardiac surgery: randomized double-blind placebo-controlled pilot study.** *Br J Anaesth* 2005, **95:**596-602.

15. Romero-Castro R, Jimenez-Saenz M, Pellicer-Bautista F, Gomez-Parra M, Arguilles AF, Gurrero A, Sendon-Peres A, Herrerias-Gutierrez JM: **Recombinant-activated factor VIIa as hemostatic therapy in eight cases of severe hemorrhage from esophageal varices.** *Clin Gastroenterol Hepatol* 2004, **2:**78-84.
16. MacLaren R, Weber LA, Brake H: **A multicenter assessment of recombinant factor VIIa off-label usage: clinical experiences and associated outcomes.** *Transfusion* 2005, **45:**1434-1442.
17. Vilstrup H, Markiewicz M, Biesma D, Brozovic VV, Laminoga N, Malik M, Milanov S, Patch D, Platikanov V: **Recombinant activated factor VIIa in an unselected series of cases with upper gastrointestinal bleeding.** *Thromb Res* 2005, Epub ahead of print.
18. Rizoli SB, Chughtai T: **The emerging role of recombinant activated Factor VII (rFVIIa) in the treatment of blunt traumatic haemorrhage.** *Exp Opin Biol Ther* 2006, **6:**73-81.
18. Clark AD, Gordon WC, Walker ID, Tait RC: **'Last-ditch' use of recombinant factor VIIa in patients with massive hemorrhage is ineffective.** *Vox Sang* 2004, **86:**120-124.