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Activated Recombinant Factor VIIa should not be used in patients with refractory variceal bleeding – it is mostly ineffective, is expensive, and may rarely cause serious adverse events

Margaret S. Sozio, MD[*,#] and **Naga Chalasani, MD**[*]

[*]Indiana University School of Medicine, Indianapolis

[#]Richard L. Roudebush VA Medical Center, Indianapolis

Abstract

Activated Recombinant Factor VIIa Does Not Improve Mortality in Variceal Bleeding.
Bendtsen F, D'Amico G, Rusch E, de Franchis R, Anderson PK, Lebrec D, et al. Effect of recombinant Factor VIIa on outcome of acute variceal bleeding: An individual patient based meta-analysis of two controlled trials. J Hepatol 2014; 61: 252–259. (**Reproduced with Permission**)

Background & Aims—Two randomized controlled studies have evaluated the effect of recombinant Factor VIIa (rFVIIa) on variceal bleeding in cirrhosis without showing significant benefit. The aim of the present study was to perform a meta-analysis of the two trials on individual patient data with special focus on high risk patients.

Methods—The primary outcome measure was the effect of rFVIIa on a composite five day endpoint: failure to control bleeding, 5-day rebleeding or death. Analysis was based on intention to treat. High risk was defined as active bleeding on endoscopy while under vasoactive drug infusion and Child-Pugh score >8.

Results—497 patients were eligible for the meta-analysis; 308 (62%) had active variceal bleeding at endoscopy (oozing or spurting) and 283 of these had a Child-Pugh score >8. Analysis on the composite endpoint in all patients with bleeding from oesophageal varices did not show any beneficial treatment effect. However, failure rate for the primary composite end-point was significantly lower in treated patients with active bleeding at endoscopy (17%) compared to placebo (26%, $p = 0.049$). This difference was highly significant in patients with Child-Pugh score >8 and active bleeding at endoscopy (rFVIIa 16%, placebo 27%; $p = 0.023$). No significant treatment effect was found at 42 days. Five thromboembolic events occurred in rFVIIa treated patients compared to none in placebo treated patients.

Conclusions—The current meta-analysis shows a beneficial effect of rFVIIa on the primary composite endpoint of control of acute bleeding, prevention of rebleeding day 1–5 and 5-day mortality in patients with advanced cirrhosis and active bleeding from oesophageal varices at endoscopy. A major drawback of the treatment is a potential increased risk of arterial thrombo-

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embolic events. This treatment might be considered in patients with lack of control of bleeding after standard treatment.

Variceal bleeding in cirrhosis has a 15–20% mortality rate (1, 2). This has decreased from 40% thirty years ago through the use of endoscopic and pharmacologic interventions (2). However, even with these interventions, approximately 20% of patients fail to respond, or develop rebleeding within the first 5 days (3). Thus, there is an ongoing need to identify new, effective therapies in the management of variceal bleeding.

In cirrhosis, prothrombin time (PT) is prolonged, in part due to low factor VII levels. Activated recombinant factor VII (rFVIIa) was developed for use in hemophiliacs with inhibitors, but it has been used off-label in many different populations, including cirrhosis. It is thought to potentiate thrombin generation at the site of injury and has been shown to correct abnormal PT in cirrhotic patients with and without bleeding (4–6). This led to the hypothesis that its use could improve outcomes in acute bleeding episodes in cirrhosis.

In 2004, Bosch et al. published a randomized controlled trial examining the effects of rFVIIa on upper gastrointestinal bleeding (UGIB) in cirrhotic patients with Child-Pugh score of <13 (7). Patients at high risk for thrombotic events were excluded. 800 μcg/kg rFVIIa was given in divided doses over 30 hours, with the first dose prior to endoscopy, in addition to standard endoscopic and pharmacologic therapy. The primary composite endpoint included (1) failure to control acute bleeding, (2) rebleeding within the first 5 days, and (3) death within the first 5 days. Baveno II criteria were used to define rebleeding episodes (8).

The study showed no difference in the composite endpoint between rFVIIa and placebo (7). However, post-hoc analysis revealed a significant reduction in failures in patients with Child-Pugh class B or C and active bleeding from varices treated with rFVIIa (8% failure) compared to placebo (23% failure), p=0.03 (7). Of the primary endpoints, rFVIIa significantly improved control of acute bleeding, with trend towards significance on preventing rebleeding. Mortality (5- and 42-day) was not different between the two groups.

Given these findings, Bosch et al. published a second study in 2008 examining the effects of rFVIIa on active variceal bleeding in patients with Child-Pugh score >8 (9). Patients were randomized to three groups: placebo, 600 μcg/kg rFVIIa, or 300 μcg/kg. The 300 μcg/kg group would only be evaluated if the 600 μcg/kg showed statistically significant results. The primary composite endpoint was the same, though rebleeding was defined by modified Baveno II-IV criteria, which removed the requirement for hemodynamic changes (9, 10).

There was no difference between placebo and rFVIIa on the composite primary endpoint – failure rates were 23% and 20% respectively (9). Five-day mortality rate was similar between groups, while the 42 day mortality rate was significantly decreased (29% with placebo and 15% with rFVIIa, OR 0.31 (95% CI 0.13–0.74)) (9). Failure to meet its primary outcome was attributed to a lower than expected placebo failure rate. This was due, in part, to significant heterogeneity between study sites; when sites with < 10% overall failure rate were excluded, the placebo failure rate was higher than the treatment arm.

In an attempt to clarify the results of the two trials, Bendtsen et al. performed a meta-analysis on the two studies focusing on 497 high risk patients (Table 1) (11). The composite endpoint was the same, but as the definition of rebleeding differed, studies were analyzed using the original criteria and using the criteria in the 2008 study.

In the ITT analysis, there was no difference in the failure rate of the composite endpoint. However, in active variceal bleeding with Child-Pugh score > 8, the failure rate was lower with rFVIIa at 16% compared to placebo at 27%, p = 0.023 (11) . By applying the definition for rebleeding from the second trial to all patients in the ITT analysis, there was a significantly lower failure rate on the composite endpoint (rFVIIa 16% vs placebo 23%, p=0.041), while the patients with Child-Pugh score > 8 and active variceal bleeding showed an even greater difference (rFVIIa 16% vs placebo 28%, p=0.014). The dose of rFVIIa had no effect.

Of the three components of the composite endpoint, only rebleeding within the first 5 days was significantly different between groups (OR 0.28 (95% CI 0.18–0.45)) (11). RFVIIa had no effect on failure to control acute bleeding (9% rFVIIa vs 13% placebo, p=0.304), on 5 day mortality (rFVIIa 8% vs placebo 13%, p=0.160), or 42 day mortality (rFVIIa 22% vs placebo 28%, NS).

The meta-analysis included the only randomized controlled trials on the effect of rFVIIa on bleeding in cirrhosis. Review of the literature reveals a number of small retrospective studies as well as case series on this subject. In 2004, 8 patients with bleeding varices non-responsive to standard therapy were treated with rFVIIa and responded (12). 2 out of 8 experienced rebleeding at day 6 and 7, and 4 out of 8 died. Similarly, Vilstrup et al. reported on a case series of patients with liver disease and UGIB treated with rFVIIa after failing to respond to other measures (13). Bleeding in 5 out of 6 patients stopped or “markedly” decreased, while 2 out of 6 died. A retrospective cohort study out of Australia and New Zealand found that 66% of 30 patients with end stage liver disease and UGIB refractory to treatment responded to rFVIIa (14). There was no difference in mortality between responders and nonresponders (68% and 69% respectively, p=0.9063). In 2013, a retrospective study reported on 1459 critically ill patients in the ICU, of which 6% had cirrhosis, treated with rFVIIa (15). Patients treated with rFVIIa had higher mortality compared to controls (36% vs. 16%, p<0.0001), though they were found also to be sicker overall.

These studies, though small case series and retrospective, agree with the findings of the meta-analysis. RFVIIa appears to have an effect on bleeding in the short term, but mortality, even in those that respond, remains high. Thus, based on the available data, rFVIIa as a therapeutic strategy for bleeding varices has limited potential utility. Anecdotally, our own clinical experience seems to support these conclusions, as the use of rFVIIa has declined markedly over the past few years.

It was suggested that rFVIIa could be useful as a temporizing measure to bridge to more definitive therapy, such as TIPS, in those who do not respond to standard therapy (11). The results of this study provide minimal support for that use, as neither control of acute

bleeding (to allow for stabilization until TIPS), nor 5-day mortality were improved. Additionally, the cost of rFVIIa should be considered. At our institution a 90 μcg dose in a 75 kg patient would cost approximately US $7,500. *Given that the number needed to treat to prevent one rebleeding episode is 14,[11] we estimate that it costs ~ US $350,000 to prevent one rebleeding episode at our institution, and that too with no improvement in mortality*.

The risk of arterial thromboembolic events is also significant. There were 5 arterial thromboembolic events leading to 3 deaths in patients treated with rFVIIa and none in the placebo group. Review of other studies/case reports in similar populations revealed only one report of a thromboembolic event, which may have been due to the dose of rFVIIa (14). Studies have shown that the risk of thromboembolism with rFVIIa is dose dependent (16). The risk may also be due to the tenuous balance between procoagulant and anticoagulant factors seen in cirrhosis. Recent papers have emphasized that regardless of PT time, patients with cirrhosis may either be hypo- or hypercoagulable (17).

In summary, any limited benefit of rFVIIa in individuals with acute variceal bleeding is largely limited to a highly selected group of patients with advanced liver disease with active bleeding who failed endoscopic therapy with no clear cut survival benefit. It is awfully expensive and is associated with arterial thromboembolic events. Based on this, we believe it is very hard to justify the use rFVIIa in patients with acute variceal bleeding, however desperate the patient's condition may be.

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Table 1
Summary of the 2 trials and meta-analysis

Note that values for 24-hr control of bleeding and 5 day rebleeding represent the results from the population of active variceal bleeders with Child's Pugh class B or C. All values are listed in the order of placebo vs. rFVIIa.

	Bosch et. al. 2004 (n=121 placebo, N=121 rFVIIa)	Bosch et. al. 2008 (n=86 placebo, n=85 rFVIIa 600 µcg/kg)	Bendtsen et. al. 2014 (n=205 placebo, n=287 rfVIIa)
Population	Child Pugh < 13 upper GI bleed w/in 24 hours	Child Pugh >8 Active variceal bleeding	ALL patients in the two studies (including those dosed with 300 µcg/kg in the 2008 study)
Failure on primary endpoint (placebo vs rFVIIa)	16% vs 14%, p= 0.72	(see below)	23% vs 16%, p=0.04
Failure on primary endpoint Child's Pugh B/C and variceal bleeding	23% vs 8%, p=0.03	23% vs 20%, p=0.37	28% vs 16%, p=0.01
24-hr failure to control bleeding	11% vs 0%, p=0.01	9% vs 9%, p=1.00	13% vs 9% p=0.30
5 day rebleeding	13% vs 5%, p=0.13	9% vs 4%, p= 0.26	10% vs 3%, p=0.006
5 day/ 42 day mortality	3% vs 6%, p=0.38 9% vs 14%, p=0.31	13% vs 12%, p=0.22 29% vs 15%, p=0.004	13% vs 8%, p=0.16 28% vs 22%, NS
Adverse events	2 cerebrovascular accidents in rFVIIa group	3 Myocardial infarctions (including one in 300 µcg/kg dosed group)	See other studies