ARTICLE:


ABSTRACT:

A beneficial effect of recombinant activated factor VII (rFVIIa) in Child-Pugh class B and C patients with cirrhosis who have variceal bleeding has been suggested. This randomized controlled trial assessed the efficacy and safety of rFVIIa in patients with advanced cirrhosis and active variceal bleeding. At 31 hospitals in an emergency setting, 256 patients (Child-Pugh >8; Child-Pugh B 26%, C 74%) were randomized equally to: placebo; 600 mcg/kg rFVIIa (200 + 4 X100 mcg/kg); or 300 mcg/kg rFVIIa (200 + 100 mcg/kg). Dosing was intravenous at 0, 2, 8, 14, and 20 hours after endoscopy, in addition to standard vasoactive, prophylactic antibiotic, and endoscopic treatment. The primary composite endpoint consisted of failure to control 24-hour bleeding, or failure to prevent rebleeding or death at day 5. Secondary endpoints included adverse events and 42-day mortality. Baseline characteristics were comparable between groups. Administration of rFVIIa had no significant effect on the composite endpoint compared with placebo (P = 0.37). There was no significant difference in 5-day mortality between groups; however, 42-day mortality was significantly lower with 600 mcg/kg rFVIIa compared with placebo (odds ratio 0.31, 95% confidence interval = 0.13-0.74), and bleeding-related deaths were reduced from 12% (placebo) to 2% (600 mcg/kg). A marked heterogeneity in the failure rate in all treatment groups was observed across participating centers. Adverse events, including overall thromboembolic events, were comparable between groups. Conclusion: Treatment with rFVIIa had no significant effect on the primary composite endpoint compared with placebo. Therefore, decision on the use of this hemostatic agent in acute variceal bleeding should be carefully considered, because results of this study do not support the routine use of rFVIIa in this setting. Adverse events were comparable across groups. (HEPATOLOGY 2008;47:1604-1614.)

DISCUSSION:

Recombinant activated factor VII (rFVIIa) does not appear to have a significant effect on the primary endpoints of rebleeding or short term (5 day) death. The improvement in the secondary endpoint of long term survival in the high dose group is not explained by this study and does not make intuitive sense based on the lack of benefit in all the measured short term outcomes. Overall, we cannot recommend rFVIIa at this time for treatment of acute variceal bleeding. While a subset of patients may benefit, this group is not clearly identified by this study. While there were statistically equivalent adverse events seen across groups in this study, the thrombotic complications demonstrated in studies of
rFVIIa for other indications must still be taken into consideration. The results of this study do not clearly show a significant benefit to overcome the cost and potential side effects of routine use of rFVIIa for this indication.

ANALYSIS:

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ARTICLE:

- **Country:** International (31 hospitals and 12 Countries in Europe and Asia)
- **Funding Sources:** Supported by Novo Nordisk A/S.

PURPOSE:

- **Research Question(s):** What is the efficacy and safety of rFVIIa in patients with advanced cirrhosis and active variceal bleeding.
- **Hypothesis:** rFVIIa treatment in addition to standard therapy might improve the control of variceal bleeding in high-risk patients with cirrhosis and reduce patient mortality. (Standard therapy defined as appropriate antibiotics, vasoactive medications including Terlipressin, Somatostain, and Octreotide, and endoscopic therapy with band ligation or sclerotherapy)

DESIGN:

- **Study Design:** prospective double-blinded, randomized controlled trial
- **Outcome Measure:** Primary endpoint was treatment failure defined as: failure to control acute bleeding in 24 hours, or clinically significant rebleeding, or death within 5 days. Clinically significant rebleed was defined as both new hematemesis/melena and transfusion of >2U blood in any 24 hour period.

Secondary endpoint was 42 day mortality and side effects of rFVIIa

- **Independent / research Variable:** rFVIIa 300mcgs/kg or 600mcgs/kg

SETTING / SUBJECTS:

- **Research Setting:** Inpatient setting in patients who presented to the ED. The study was conducted at 31 hospitals in 12 countries in Europe and Asia
- **Subjects:**
  - **Study population:** Adults with acute UGIB and advanced cirrhosis
  - **Inclusion criteria:** age 18-79, acute UGIB, advanced cirrhosis with a Child-Pugh score >8 (Class B 81% 1-year survival, Class C 45% 1 year survival), treatment with vasoactive therapy 0.5 hours prior to endoscopic therapy showing active bleeding, endoscopy performed within 6 hours of admittance to ED, and first dose of rFVIIa within 1 hour of endoscopic therapy.
Exclusion criteria: unfit for resuscitation, band ligation within 2 weeks or sclerotherapy within 1 week. Unstable angina, PVD, previous MI, PE, stroke, portal vein DVT within 6 months, hepatocellular carcinoma, pregnancy, thrombogenic disorder

Number: 265 Patients - 89 placebo, 88 allocated to 600mcg/kg rFVIIa group, 88 allocated to 300mcg/kg rFVIIa group.

Demographics: Mean age 54 years, approximately 70% male
Baseline characteristics similar across groups (age, etiology of cirrhosis, severity of liver disease, pharmacologic therapy used, endoscopic therapy) shown in Table 1.

Attrition: 1 withdrawn from the 600mcg group due to uncontrolled bleeding. 4 withdrawn from 300mcg group; 2 for violation of exclusion criteria, 1 adverse event, and 1 withdrew consent. 0 withdrawal of patients in the placebo group

METHODS:

- Interventions: rFVIIa
- Study Groups: placebo, group 2 received rFVIIa 600mcgs/kg, and group 3 received 300mcg/kg. All groups received their respective doses at 0 hour of confirmed bleeding by endoscopy with subsequent doses given at 2, 8, 14, and 20 hours
- Instruments: Randomization was computer generated and stratified among centers with equal allocation among groups.
- Data Collection: Data was collected by the investigators and analyzed by the sponsor with input from the trial advisory board. Investigators had full access to unblended data.

DATA ANALYSIS:

- Level of Data: Interval
- Statistics Used: mixed logistical regression model
- What, if any, variables were controlled for? A multivariable post-hoc analysis was performed using a logistic regression with treatment and significant prognostic factors as fixed effects. Nonsignificant factors were removed where P>0.05. The dependent variables were 24 hour bleeding rates, treatment failure at day 5 or mortality at day 42.

RESULTS:

- Brief answers to research questions: There was no significant effect with treatment with the 600mcg/kg rFVIIa group vs. placebo at the primary composite endpoint of control of acute bleeding, prevention of rebleeding, and reducing 5-day mortality in patients with advanced cirrhosis and active variceal hemorrhage. There was a trend toward lower failure rate in the rFVIIa 300mcg/kg group at, but this was not statistically significant.
Treatment with rFVIIa 600mcg/kg significantly reduced the secondary endpoint (42 day mortality), which was related to the decreased bleeding related deaths. Deaths due to bleeding were reduced from 12% in placebo to 2% in this group.

Overall incidence of adverse events and thromboembolic events were similar among groups. Venous thromboembolic events were slightly more common in the placebo group; arterial thromboembolic events were only observed in the rFVIIa groups. There was 3 MI’s in the rFVIIa groups (2 of which were fatal), none in the placebo group.

- **Additional findings:** There was a marked heterogeneity in failure rate across participating centers. 16 of the 31 centers unexpectedly had a <10% failure rate across all groups, whereas the remaining centers had a failure rate of 36%. A multivariable analysis of prognostic factors for failure on the primary endpoint and 42 day mortality showed that patients with a Child-Pugh score >11, presentation with melena, and requirement for >1 vasoactive drug treatment were significantly associated with worse outcome. There was marked variability in these characteristics across centers, which might explain some of the heterogeneity in overall failure rates across centers.

- **Limitations:** sample size, controlling for important prognostic factors that may affect outcome in each study setting

**IMPLICATIONS FOR PRACTICE:**

- **Applicable to this clinical practice:** This is an entity that is seen in our hospital and in most emergency settings. While the study population differed in nationality and ethnicity from ours, the pathophysiology is likely applicable and these results can likely be applied to most populations with similar disease as the study group.

- **Feasible:** Cost-benefit analysis has not been studied. rFVIIa is expensive but is available at our institution.

- **Clinically Relevant:** This may have clinical implications for patients presenting to the ED with severe liver cirrhosis and active UGIB.

**LEVEL OF EVIDENCE / DECISION FOR USE:**

- **Level of Evidence:**
  - Ia Evidence obtained from meta-analysis of randomized controlled trials
  - Ixb Evidence obtained from at least one RCT
  - IIa Evidence obtained from at least one well-designed controlled study without randomization
IIb  Evidence obtained from at least one other type of well-designed quasi-experimental study
III   Well-designed non-experimental studies
IV    Expert committee reports, opinions of experts