Recombinant Coagulation Factor VIIa in Major Liver Resection

A Randomized, Placebo-controlled, Double-blind Clinical Trial


Background: Prevention of bleeding episodes in noncirrhotic patients undergoing partial hepatectomy remains unsatisfactory in spite of improved surgical techniques. The authors conducted a randomized, placebo-controlled, double-blind trial to evaluate the hemostatic effect and safety of recombinant factor VIIa (rFVIIa) in major partial hepatectomy.

Methods: Two hundred four noncirrhotic patients were equally randomized to receive either 20 or 80 µg/kg rFVIIa or placebo. Partial hepatectomy was performed according to local practice at the participating centers. Patients were monitored for 7 days after surgery. Key efficacy parameters were perioperative erythrocyte requirements (using hematocrit as the transfusion trigger) and blood loss. Safety assessments included monitoring of coagulation-related parameters and Doppler examination of hepatic vessels and lower extremities.

Results: The proportion of patients who required perioperative red blood cell transfusion (the primary endpoint) was 57% (23 of 65) in the placebo group, 41% (26 of 63) in the 20-µg/kg group, and 25% (15 of 59) in the 80-µg/kg dose group (logistic regression model; P = 0.09). Mean erythrocyte requirements for patients receiving erythrocytes were 1,024 ml with placebo, 1,354 ml with 20 µg/kg rFVIIa, and 1,036 ml with 80 µg/kg rFVIIa (P = 0.78). Mean intraoperative blood loss was 1,422 ml with placebo, 1,372 ml with 20 µg/kg rFVIIa, and 1,073 ml with 80 µg/kg rFVIIa (P = 0.07). The reduction in hematocrit during surgery was smallest in the 80-µg/kg group, with a significant overall effect of treatment (P = 0.04).

Conclusions: Recombinant factor VIIa dosing did not result in a statistically significant reduction in either the number of patients transfused or the volume of blood products administered. No safety issues were identified.

Despite improvements in surgical techniques during the past two decades, hepatic resection is often associated with significant intraoperative blood loss, primarily occurring from branches of the hepatic veins damaged during parenchymal transection or as a result of mobilization of tumors. Recent estimates show that perioperative blood transfusion is required in approximately 25–40% of unselected patients undergoing partial heptectomy. In addition to the inherent difficulties in adequately replacing blood components especially in cases of severe bleeding, allogeneic blood transfusion constitutes a risk factor for intraoperative and postoperative morbidity, including viral disease transmission, transfusion reactions, and the increased risk of postoperative infectious complications. The existence of an adverse effect of blood transfusion on tumor recurrence is still controversial but may be a further argument for reducing the need for blood transfusions. The latter point is especially pertinent for major liver resection, which is mostly performed for malignant disease. Many surgical techniques for vascular control in hepatic resection have been advocated. Techniques such as partial and total vascular exclusion are routinely used but may induce ischemic liver injury and, in the latter case, hemodynamic complications. Therefore, there is a need for treatment modalities that may induce a primary hemostatic effect.

Recombinant activated coagulation factor VII (rFVIIa, NovoSeven®; NovoNordisk A/S, Copenhagen, Denmark) is currently registered for perioperative prophylaxis and treatment of bleeding episodes in hemophilia patients with inhibitors against coagulation factors VIII and IX and in the European Union for patients with acquired hemophilia, FVII deficiency, and Glanzmann thrombasthenia who are refractory to platelets. Pharmacologic doses of rFVIIa have been shown to enhance thrombin generation on locally activated platelets, thereby contributing to the formation of a stabilized and lysis-resistant fibrin plug at the site of vessel injury. Patients experiencing bleeding in any situation of potentially subopt-
nal thrombin generation, including intraoperative depression of the coagulation system, may thus potentially benefit from dosing with rFVIIa. A hemostatic effect of rFVIIa has recently been demonstrated in patients with normal coagulation systems in a double-blind, placebo-controlled trial in retropubic prostatectomy, where a single bolus of 40 μg/kg rFVIIa in the early operative phase significantly reduced blood loss, transfusion requirements, and operating time when compared with placebo.17

The current randomized, controlled, double-blind, multi-national trial was designed to evaluate the efficacy and safety of rFVIIa in noncirrhotic patients undergoing major liver resection.

Materials and Methods

Patients

Noncirrhotic adults (≥ 18 yr of age) scheduled to undergo partial hepatectomy for liver cancer/metastasis, benign tumors, or both were recruited into the trial at 13 hospitals throughout France, Spain, Germany, and the United Kingdom (see appendix). A further requirement for inclusion was planned anatomical resection of three or more segments of the liver or planned nonanatomical resection of a volume equivalent to two or more segments of the liver parenchyma. Exclusion criteria included known hereditary bleeding disorders; the planned use of autologous blood transfusion, low-molecular-weight heparin before hepatectomy, tissue glue or hemodilution therapy during surgery, or hemostatic drugs for prophylactic purposes; renal insufficiency requiring dialysis; clinically documented portal vein or deep vein thrombosis or a history of the latter within the preceding 6 months; severe cardiovascular disease or previous myocardial/pulmonary infarction or stroke within the preceding 6 months; anticoagulation therapy not discontinued within 48 h before surgery; active bleeding; and the use of nonsteroidal antiinflammatory drugs within 7 days before surgery. The study protocol was approved by local ethics committees in the participating countries, and the trial was conducted according to standards of good clinical practice. All patients gave written informed consent.

Study Drug Administration

Patients were equally randomized in center blocks to receive an injection of either 20 or 80 μg/kg rFVIIa or placebo. Randomization was computer-generated and was performed after patient eligibility assessments on the day of surgery by means of a central interactive voice response system set up by Novo Nordisk A/S. The trial drug was administered as a slow intravenous injection within 5 min before the first skin cut to ensure sufficient amounts of rFVIIa in the liver circulation during surgical procedures and before any clamping procedures were performed. A second identical dose was given 5 h after the first skin cut if the surgery time was anticipated to exceed 6 h. This was done to achieve adequate plasma concentrations of rFVIIa during extended surgical procedures, given the expected half-life of rFVIIa of approximately 2.5 h.18

Blinding

To maintain blinding, an equal volume of trial drug per body weight was administered to all patients, irrespective of treatment group allocation. Furthermore, central laboratory analysis results for prothrombin time, which might reveal treatment allocation, were not transferred from the laboratory to the investigators or the sponsor before the trial was completed. Local laboratory results on prothrombin time or international normalized ratio were reviewed by an unblinded third party.

Hepatectomy and Transfusion Procedures

Partial hepatectomy was performed according to local standard practice at the participating centers in France, Spain, Germany, and the United Kingdom. Unless deviations were clinically indicated, the following transfusion guidelines were adhered to: erythrocytes were administered when the hematocrit was less than 25%; fresh frozen plasma was administered when the platelet count was less than 30,000/mm²; and cryoprecipitates or fibrinogen concentrate was administered when the fibrinogen concentration was less than 1.0 g/l. Prophylactic systemic administration of hemostatic drugs and low-molecular-weight heparin was not allowed before surgery, but treatment could be initiated if critical bleeding occurred during surgery. Topical administration of hemostatic drugs/agents was allowed in those cases where overt bleeding occurred even though transfusion guidelines were followed. During the postsurgical period, the hematocrit was to be kept above 28%. Blood samples were drawn at 15 and 60 min after the first skin cut and then at 1-hour intervals until completion of surgery for the determination of blood biochemistry, coagulation-related parameters, and plasma concentrations of rFVIIa. Treatment with low-molecular-weight heparin at maximum doses of 10,000 U every 24 h for at least 1 day was initiated at completion of surgery. Patients were monitored for 7 days after surgery or until discharge from the hospital, whichever came first.

Endpoints

The primary endpoint was whether patients required erythrocyte transfusion during surgery or the 48-h period after surgery (perioperative period). Efficacy was furthermore assessed by the amount of erythrocytes transfused, change in hematocrit, the proportion of patients who required perioperative transfusions of fresh...
frozen plasma, and total surgery time (from first skin cut to wound closure). Blood loss during surgery was as-
essed as the volume collected in suction containers and
sponges/dressings/swabs minus the irrigation volume,
and blood loss after surgery was evaluated using surgical
drain volume 0–24 h after surgery, as well as hematocrit
measured herein, as endpoints. Safety was assessed by
the occurrence of adverse events, focusing on thrombo-
embolic adverse events and bleeding complications, the
former evaluated by Doppler examination of the hepatic
vessels (before surgery, within 48 h after surgery, and
otherwise if indicated) and lower extremities (before
surgery and every 24 h until 3 days after surgery). Also,
changes in coagulation-related parameters (prothrombin
time, platelet count, and the concentrations of fibrino-
gen, D-dimer, prothrombin fragments 1 and 2, thrombin-
antithrombin complex, and antithrombin III) and blood
biochemistry (serum creatinine, calcium, potassium, so-
dium, bilirubin, serum albumin, alanine aminotransfer-
ase, aspartate aminotransferase, and alkaline phospha-
tase) were monitored.

Statistics
The trial size was planned to detect a 50% relative
reduction in the proportion of patients requiring periop-
erative erythrocyte transfusions from 40% in the placebo
group to 20% in the rFVIIa groups with 80% statistical
power at a significance level of 5%. This translated to a
sample size of 180 patients, 60 per treatment group. The
perioperative period was defined as spanning the intra-
operative period and the 48-h postsurgical period.

The comparison of the three treatment groups with
respect to the primary endpoint, i.e., the proportion of
the patients requiring perioperative erythrocyte transfu-
sions, was conducted with use of a logistic regression
model. Treatment group, country, baseline hematocrit,
whether clamping was performed (defined as portal
triad, inferior vena cava clamping, or both), type of
resection (according to the Brisbane 2000 terminolo-
gy19), and surgery type (hepatectomy vs. rehepatec-
tomy) were included as covariates in the model. Residual
diagnostics were used to check the statistical assump-
tions of the model.

Analysis of the treatment effect on the proportion of
patients requiring fresh frozen plasma during the peri-
operative period was conducted as for the primary end-
point. Amounts of erythrocytes transfused during the
perioperative period were compared between treat-
mant groups using a two-sided Jonckheere-Terpstra test.
This test was also applied for comparisons of treatment ef-
fects on requirements for systemic hemostatic drug as
well as for other secondary endpoints, with the one
exception of changes in hematocrit, which were ana-
lyzed using F tests. In all the above-mentioned analyses,
the type I error was set to 5%. All randomized patients
who were dosed were included in the safety analyses,
whereas efficacy data presented herein pertain to all
randomized patients who were dosed and underwent
liver resection.

Results
Between January 2001 and January 2002, 204 eligible
patients were included in the trial. Four patients were
withdrawn before dosing, the reasons being the investi-
gator’s decision not to perform a partial hepatectomy,
noncompliance with the protocol, failure to obtain a
drug dispensing form before surgery, and patient with-
drawal of consent. A flow diagram of patient allocation
is outlined in figure 1. Baseline characteristics and prog-
nostic factors were similar across treatment groups
(table 1). Six patients in the placebo group, five in the
20-μg/kg group, and two in the 80-μg/kg group received
a second dose 5 h after the initial injection as a result of
an extended surgery period.

Efficacy
Results are summarized in table 2. The proportion of
patients who required perioperative transfusion of ery-
throcytes (the primary endpoint) was 37% (23 of 63) in the
placebo group, 41% (26 of 63) in the 20-μg/kg group,
and 25% (15 of 59) in the 80-μg/kg group. The overall
effect of rFVIIa treatment was not statistically significant
(logistic regression model; \( P = 0.09 \)). Mean erythrocyte
requirements for patients receiving erythrocytes were
1,024 ml in the placebo group, 1,354 ml in the 20-μg/kg
rFVIIa group, and 1,036 ml in the 80-μg/kg rFVIIa group
(\( P = 0.78 \)).

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Fig. 1. Flow diagram of patient allocation. rFVIIa = recombinant factor VIIa.

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Table 1. Baseline Characteristics and Prognostic Factors (Efficacy Population)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 µg/kg rFVIIa</th>
<th>80 µg/kg rFVIIa</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>63</td>
<td>63</td>
<td>59</td>
<td></td>
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<tr>
<td>Demographics</td>
<td></td>
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<tr>
<td>Age, yr</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Baseline hematocrit, %</td>
<td></td>
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<tr>
<td>Prothrombin time, s</td>
<td></td>
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<tr>
<td>FVII:C, U/ml</td>
<td></td>
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<tr>
<td>Tumor weight, g</td>
<td></td>
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<tr>
<td>Type of surgery</td>
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<tr>
<td>Rehepatectomy</td>
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<tr>
<td>Extended heptectomy*</td>
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<tr>
<td>Additional surgery</td>
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<tr>
<td>Tumor weight, g</td>
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<td></td>
<td></td>
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<tr>
<td>Clamping performed†</td>
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<tr>
<td>TVE performed</td>
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<tr>
<td>Complications increasing bleeding risk‡</td>
<td></td>
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</tbody>
</table>

Plasma factor VII clotting activity (FVII:C) normal range: 0.54–1.23 U/ml.
Continuous variables are expressed as mean ± SD.
* According to the Brisbane 2000 terminology.† Defined as portal trial, inferior vena cava clamping, or both.‡ As defined by the investigators.

The mean volume of blood loss during surgery was 1,422 ml in the placebo group, 1,372 ml in the 20-µg/kg group, and 1,073 ml in the 80-µg/kg group (P = 0.07). The reduction in hematocrit from before surgery to last observation during surgery was smallest in the 80-µg/kg group, with a statistically significant overall effect of treatment (P = 0.04), even though the amount of erythrocytes transfused during surgery was not greater in the 80-µg/kg group. However, the reduction in hematocrit during surgery was larger in the 80-µg/kg group than in the placebo group. No significant difference between treatment groups was found with respect to requirement for fresh frozen plasma or systemic hemostatic drug, operating time, total volume collected in surgical drains in the 24-h postsurgical period, or for the percentage of hematocrit measured herein (table 2).

Data on plasma FVII clotting activity are depicted in figure 2. As expected, measured maximum plasma concentration and area under the concentration curve to increase approximately proportionally with dose. Prothrombin time was significantly shortened with rFVIIa dosing, the effect being prolonged at the 80-µg/kg dose level when compared with the effect of 20 µg/kg (fig. 3).

Safety

Of the 200 dosed patients, 158 patients had 487 adverse events (table 3). The most frequently reported adverse events included nausea, constipation, fever, hypotension, and insomnia, and there were no apparent differences between dose groups in the types or frequencies of adverse events reported. All nonthromboembolic serious adverse events were considered by the investigators as unlikely to be related to trial drug treatment. Three thromboembolic events were observed in each of the three treatment groups. The total of nine events was comprised of the following.

Table 2. Trial Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 µg/kg rFVIIa</th>
<th>80 µg/kg rFVIIa</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients who underwent surgery</td>
<td>63</td>
<td>63</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Perioperative* requirements (no. of patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Erythrocytes (primary endpoint)</td>
<td></td>
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<tr>
<td>Fresh frozen plasma</td>
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<tr>
<td>Platelet concentrate</td>
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<tr>
<td>Systemic hemostatic drug</td>
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<tr>
<td>Amount of red blood cells transfused, ml†</td>
<td>1,024 ± 1,001</td>
<td>1,354 ± 989</td>
<td>1,036 ± 904</td>
<td>0.78</td>
</tr>
<tr>
<td>Blood loss parameters</td>
<td></td>
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<tr>
<td>Blood loss during surgery, ml</td>
<td>1,422 ± 1,271</td>
<td>1,372 ± 1,301</td>
<td>1,073 ± 997</td>
<td>0.07</td>
</tr>
<tr>
<td>Change in hematocrit during surgery, %</td>
<td>−6.7 ± 5.7</td>
<td>−6.4 ± 6.7</td>
<td>−3.7 ± 5.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Drain volume 0–24 h after surgery, ml</td>
<td>409 ± 322</td>
<td>451 ± 698</td>
<td>346 ± 209</td>
<td>0.59</td>
</tr>
<tr>
<td>Hematocrit of surgical drain volume, %</td>
<td>3.3 ± 4.7</td>
<td>5.1 ± 7.1</td>
<td>2.8 ± 4.8</td>
<td>0.32</td>
</tr>
<tr>
<td>Operating time, h</td>
<td></td>
<td></td>
<td></td>
<td>0.21</td>
</tr>
</tbody>
</table>

Continuous variables are presented as mean ± SD.
* The perioperative period was defined as the intraoperative period and the 48-h postsurgery period combined.† For patients receiving erythrocyte transfusions. rFVIIa = recombinant factor VIIa.
Four events of deep venous thrombosis. All four events (two in the placebo group diagnosed at day 1 after dosing and two in the 80-μg/kg group diagnosed at days 2 and 3 after dosing, respectively) were without clinical symptoms and were thus only recognized through the protocol-specified routine Doppler examinations.

Two events of pulmonary embolism. A 62-yr-old patient of the 20-μg/kg group was diagnosed with a right basal segment arterial pulmonary embolism at day 2 after dosing. Doppler examination before the events showed no signs of deep vein thrombosis. A 58-yr-old patient of the 80-μg/kg group was diagnosed with a left apical pulmonary embolism at day 7 after dosing. Two days after the event, a Doppler ultrasound examination indicated a partial thrombosis of the left internal jugular vein corresponding to the site of central venous catheter placement. Doppler ultrasonography before the event and 4 days after the event did not indicate deep venous thrombosis in the lower extremities. Both patients recovered completely from the events.

An event of partial portal vein thrombosis experienced by a patient in the placebo group. Five days after extended hepatic resection and administration of trial drug, a 67-yr-old woman of the placebo group experienced fever, abdominal pain, and clouding of consciousness with signs of hepatic failure. A computed tomography scan indicated a partial portal venous thrombus at the stump of the ligated right portal vein. The thrombus was protruding into the main portal vein without impairment of the flow. Doppler ultrasonography confirmed good portal venous flow. The patient died of hepatic failure, most probably as a consequence of the extended hepatic resection performed 2 weeks previously.

Two events of myocardial infarction experienced by patients in the 20-μg/kg group. A 79-yr-old man experienced posterior myocardial infarction 1 day after administration of the trial drug. Subsequent angiography showed moderate left ventricle-apical hypokinesia and severe left main stem and triple vessel disease. The patient underwent coronary surgery and recovered completely. A 74-yr-old man experienced worsening of liver, renal, and respiratory function 4 days after receiving the trial drug and undergoing hepatic resection and extensive abdominal surgery. The patient subsequently had a hypotensive episode but recovered quickly after colloid therapy. An electrocardiogram showed a possible myocardial infarction, but this was unconfirmed because creatinine kinase concentrations were already increased. Renal, hepatic, and respiratory functions deteriorated over the course of the day, and chest radiographs suggested pulmonary edema. The condition of the patient continued to worsen, and he died from multiorgan failure 7 days later.

Seven adverse events recorded during the trial period had a fatal outcome, with death occurring on average 28 days after trial drug dosing (range, 9–92 days). Three deaths occurred in the placebo group, and four deaths occurred in the 20-μg/kg treatment group (causes of death were hepatic failure, pneumonia, pulmonary edema, and multiorgan failure). All seven deaths were evaluated by the investigators as unlikely to be related to the trial drug.

Bleeding complications, as defined by the investigators, occurred with similar frequencies across treatment groups (P = 0.73). Furthermore, no clinically significant adverse changes in the investigated coagulation-related parameters were observed, and there were no indications of systemic activation of the coagulation cascade. A statistically significantly greater increase from baseline to 1 h after dosing (P < 0.01) and to 24 h after dosing (P =
0.04) was observed for D-dimer when comparing rFVIIa groups to placebo, which is consistent with the expected mode of action of rFVIIa. No significant differences between dose groups were observed for platelets, fibrinogen, prothrombin fragments 1 and 2, thrombin–antithrombin complex, or antithrombin III, although it should be noted that data for prothrombin fragments 1 and 2 and thrombin–antithrombin complex were inconclusive because of methodologic problems related to drawing of blood at some of the trial centers.

Discussion

This was a placebo-controlled, double-blind study of the effect of a single presurgical bolus injection of either 20 or 80 μg/kg rFVIIa administered to noncirrhotic patients undergoing major liver resection. No statistically significant overall effect of rFVIIa treatment across treatment groups was observed with respect to the proportion of patients requiring perioperative erythrocyte transfusions (primary endpoint) or other endpoints on transfusion and blood loss. The trial was dimensioned to detect a 50% relative reduction with respect to the primary endpoint, and the number of patients included would thus be expected to be insufficient to statistically verify any smaller relative reduction on the primary endpoint. A larger trial, powered for a smaller but still clinically relevant effect on transfusion requirements, would be needed to better evaluate any hemostatic effect of rFVIIa in this patient population. Prothrombin time was significantly shortened with rFVIIa dosing. However, the clinical relevance of this in vitro effect of rFVIIa remains to be determined.

The administration of a procoagulant such as rFVIIa to patients with otherwise normal coagulation systems might raise concerns that patients would be exposed to a higher risk of thromboembolic events. In this trial, the prevalence of thromboembolic events in these immobilized, anesthetized, noncoagulopathic patients undergoing major liver surgery did not differ between placebo-treated and rFVIIa-treated patients. Although there was a tendency for the thromboembolic events to be more severe in the rFVIIa-treated patients, the number of events is too small to draw any conclusions. The 1% overall incidence of pulmonary embolism observed in the current study corresponds to the incidence previously observed in cancer surgery.20 Moreover, no indications of systemic activation of the coagulation cascade were observed. The absence of systemic activation of the coagulation system with rFVIIa may be explained by its mode of action, confining propagation of coagulation to the site of injury of the vessel wall.15,16 Given the localized effect of rFVIIa, an increased incidence of thromboembolic complications or intravascular coagulation after dosing with rFVIIa would not be expected and has indeed not been observed previously.17,21 The low trial-related mortality rate of 3.5% (0.0% in the 80-μg/kg dose group) is in line with previous observations, where operative mortality of less than 10% has been reported in many series6,22 and is to be expected in this noncirrhotic patient population. No statistically significant effect of rFVIIa on mortality was observed. However, the trial was not powered to investigate mortality.

It should be noted that routine monitoring of laboratory coagulation parameters during surgery could potentially reveal dose group allocation. The effect of such bias on trial results, however, is judged to be small because of the requirement of adherence to protocol-defined transfusion guidelines.

In conclusion, dosing with 20 or 80 μg/kg rFVIIa did not raise safety concerns in this patient population without preexisting coagulopathy undergoing major liver resection. No statistically significant effect of rFVIIa across treatment groups was observed for transfusion requirements or blood loss. Further trials are needed to establish the hemostatic potential of rFVIIa in this clinical setting.

The authors thank the patients and the hospital staff participating in the trial, as well as Allan Blemmings, M.Sc. (Statistician), and Karsten Soendergaard, M.Sc. (Clinical Researcher), both at Novo Nordisk A/S, Copenhagen, Denmark.

References

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