

HUMAN RECOMBINANT FACTOR VII FOR EMERGENCY REVERSAL OF COAGULOPATHY IN NEUROSURGICAL PATIENTS: A RETROSPECTIVE COMPARATIVE STUDY

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OBJECTIVE: Severe coagulopathy in a neurosurgical patient with intracranial hemorrhage is a common and serious problem. Current therapy with vitamin K and fresh-frozen plasma (FFP) may be too slow in certain situations. There are reports of rapid reversal of coagulopathy using human recombinant factor VII. We present a retrospective controlled study of our experience with factor VII.

METHODS: We used factor VII as a second-line therapy after initial attempts at reversal with FFP had failed. Factor VII was given to 29 patients in the neurosurgical intensive care unit; 24 patients treated before the introduction of factor VII were control subjects. The groups were matched by age, sex, cause of coagulopathy, and presence of intracranial hemorrhage.

RESULTS: After initial FFP administration, the international normalized ratio (INR) changed from a mean of 2.57 to 1.67 in the factor VII group and from 2.17 to 1.85 in control subjects. In all patients, INR tended to rebound. Before administration of factor VII, the mean INR was 2.206. After 1.4 mg of factor VII, mean INR decreased to 1.12 ($P < 0.05$). Measured from admission, INR in the factor VII group normalized within 6.78 ± 2.68 hours, and in control subjects, within 47.44 ± 9.88 hours ($P < 0.0005$). Six factor VII patients and six control subjects died. The number of patients with good functional outcome (Glasgow Outcome Scale score of 5) was greater among patients treated with factor VII compared with those who received only vitamin K and FFP (nine versus two, $P = 0.04$). None of the deaths were the result of a thrombotic complication. There were no thrombotic complications in the factor VII group.

CONCLUSION: Factor VII is safe and highly effective when emergency reversal of coagulopathy is desired and may improve the functional outcome. We speculate that the use of factor VII as first choice may result in decreased use of FFP and thus increase patient safety.

KEY WORDS: Coagulopathy, Recombinant activated factor VII, Treatment

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Neurosurgeons often must treat patients with coagulopathy, which may be the result of diverse causes, such as liver disease or pharmacological anticoagulation with warfarin. The patients may be experiencing intracranial hemorrhage (ICH) or have another neurological compromise that must be treated surgically. Coagulation must be rapidly restored in these patients to save their life and function and to make surgical intervention possible. This is usually achieved by the administration of phytonadione (vitamin K) and infusion of fresh-frozen plasma

(FFP). Both treatments are suboptimal. Vitamin K acts slowly and may not be effective in liver failure; FFP infusion takes time, requires administration of a large volume of what is essentially a colloid solution, and carries the risk of disease transmission. The use of recombinant activated factor VII (rFVIIa) to correct a coagulopathy before neurosurgical intervention was reported in 1998 in a hemophiliac patient with an epidural hematoma requiring craniotomy for evacuation (5). In early 2001, we decided to introduce factor VII in our practice in selected cases. At that time, we were

not aware of any publications about the use of rFVIIa in nonhemophiliac neurosurgical patients. We present a retrospective study of our experience with rFVIIa compared with the standard agent (FFP) for reversal of coagulopathy in patients requiring emergency neurosurgical intervention at our institution.

PATIENTS AND METHODS

Twenty-nine patients on the neurosurgical service at our institution received rFVIIa (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) from July 2001 to November 2002 for emergency correction of coagulopathy, usually before neurosurgical intervention. Most patients received 1.2 mg (1 vial). Some very large patients or those with extreme international normalized ratio (INR) values received 2 vials (2.4 mg). The mean dose was 1.4 mg rFVIIa. Twenty-four patients who were treated before the introduction of rFVIIa or who did not receive rFVIIa because of attending surgeon choice served as control subjects. All the patients received phytonadione and FFP initially. Some of the patients who failed initial coagulopathy reversal with FFP were then given rFVIIa. The control subjects were those who continued with FFP only until the neurosurgical procedure or until normalization of INR.

In the factor VII group of 29 patients, 6 had evacuation of an ICH, 2 had evacuation of a subdural hematoma (SDH), 5 had a spine procedure (primarily emergency decompression), 4 had aneurysm coiling, 2 had aneurysm clipping, 3 had a ventriculostomy or ventriculoperitoneal shunt, and 3 had other procedures (abscess evacuation, resection of tumor, bypass for symptomatic bilateral vertebral occlusion). Four patients had no surgery.

In the control group of 24 patients, 2 had evacuation of an ICH, 4 had evacuation of an SDH, 3 had a spine procedure, 1 each had aneurysm coiling or clipping, 4 had a ventriculostomy or a shunt, 1 had evacuation of an epidural abscess, and 8 had no surgery.

In addition to an abnormal INR, all of the patients had one of the following: worsening neurological examination, lack of improvement with medical therapy that in the opinion of the attending neurosurgeon required emergency surgery, or an ICH that was deemed likely to expand and cause death or further deficits. The decision to change to factor VII was clinical and empirical. In the factor VII group, among those who did not have a hematoma, the main diagnoses were as follows: 7 with subarachnoid hemorrhage without a focal hematoma, and 5 patients with an acute spinal problem (4 of those had cervical myelopathy that required immediate decompression, and 1 had a cerebral abscess).

For patients with subarachnoid hemorrhage, coagulation had to be corrected emergently to prevent rebleeding and allow urgent ventriculostomy and rapid diagnosis and treatment. In the spinal cases, the attending neurosurgeon decided that additional delay associated with more doses of FFP would jeopardize the patients' chances of recovery.

Coagulation parameters (prothrombin time, INR, and partial thromboplastin time) were recorded for each patient at admission, before treatment with FFP or rFVIIa, and after treatment. The baseline characteristics and results between the two groups were compared and analyzed by use of the *t* test to compare continuous variables (e.g., age, INR) and χ^2 test for those that were dichotomous. The paired *t* test was used for comparison within the same group (i.e., INR before and after factor VII). Comparison of Glasgow Outcome Scale (GOS) score outcomes was performed with a logistic regression test. Demographics recorded include age, sex, and initial diagnosis. Mortality and thrombotic complications, including deep venous thrombosis, were also recorded.

RESULTS

Baseline Variables

The two groups were closely matched. Mean age in the rFVIIa group was 60 years, and in control subjects, 57 years; 55% of the rFVIIa group were men (58% of control subjects).

Anticoagulation with warfarin was the cause of coagulopathy in 14 (48%) of 29 patients who received rFVIIa; warfarin was implicated in 9 (38%) of 24 patients in the control group. ICH was the admission diagnosis in 20 (69%) of 29 patients in the rFVIIa group, whereas 17 (71%) of 24 patients in the control group were admitted with the same diagnosis.

On admission, the mean INR for the patients in the rFVIIa was 2.33, whereas the mean INR in the control group was 2.15 ($P > 0.5$) (Fig. 1). Overall, there were no significant differences in the baseline variables between the two groups ($P > 0.5$).

Treatment Effects

In the rFVIIa group, the INR decreased from a mean value of 2.57 to a mean value of 1.67, with a standard error of ± 0.18 after a mean of 11.45 units of FFP was given; however, this INR value tended to rapidly rise again to a mean of 2.20 before the decision was made to administer rFVIIa. After rFVIIa was given (mean dose of 1.4 mg), a prompt and sustained decrease in the mean INR to a value of 1.12 ($P < 0.05$) was seen in these patients (Fig. 2).

The control group (FFP only) received a mean of 11.54 units of FFP. After the initial dose of FFP, there was a reduction in the mean INR from a value of 2.17 to a value of 1.85, with a standard error of ± 0.22 . The initial mean INR values noted here for both

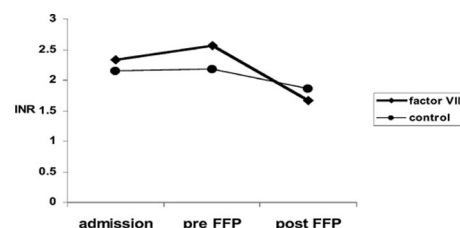


FIGURE 1. Graph showing that INR on admission and before and after the initial dose of FFP is similar in both groups.

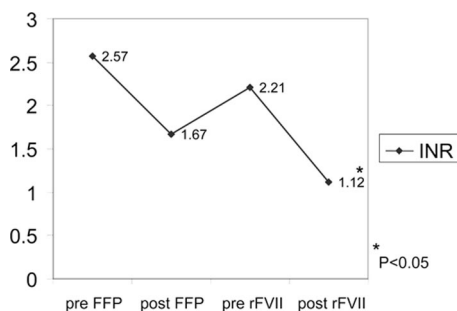


FIGURE 2. Graph showing INR in the rFVIIa group. FFP failed to normalized INR initially, and a tendency to revert to higher levels was seen. After a single dose of rFVIIa, the mean INR values decreased significantly, into the normal range.

groups are different from admission values because another blood sample was drawn from all patients just before the administration of the first dose of FFP.

The INR in the rFVIIa group normalized within 6.78 ± 2.68 hours of admission and typically immediately after the first dose of factor VII. Three patients in the control group never achieved normal INR during their admission. In the other 21 patients in the control group, the time before normal coagulation parameters were achieved was 47.44 ± 9.88 hours (Fig. 3). The difference was highly significant ($P < 0.0005$).

Clinical Outcomes

In the factor VII group, 6 patients had a GOS score of 1 (died), none had GOS scores of 2, 3 had GOS scores of 3, 11 GOS scores of 4, and 9 GOS scores of 5. The average GOS score was 3.56 ± 0.27 .

In the control group, 6 patients had GOS scores of 1, 0 GOS scores of 2, 7 GOS scores of 3, 9 GOS scores of 4, and 2 GOS scores of 5. The average for the control group was 3.04 ± 0.27 . Outcomes tended to be better in the factor VII group ($P < 0.07$ by logistic regression). The only parameter that was significantly better in the factor VII group was the number of those with GOS scores of 5 (9 versus 2 patients, $P = 0.04$, Pearson χ^2 test).

None of the deaths were a result of a thromboembolic complication. One patient in the control group developed deep vein thrombosis; there were no thrombotic complications in the FVII group.

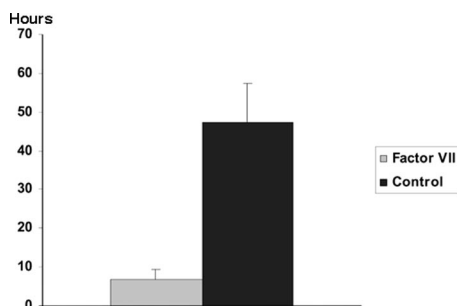


FIGURE 3. Bar graph showing that the mean time from admission to normal INR in the rFVIIa group was 6.78 ± 2.68 hours, and in the control (FFP only) group, it was 47.44 ± 9.88 hours. The difference was highly significant ($P < 0.0005$).

DISCUSSION

We present the largest experience so far with rFVIIa in neurosurgical patients. The most striking finding was the rapid reversal of coagulopathy when FFP had been inadequate. This treatment also seems to be very safe. We observed no thrombosis or thromboembolic complications in all 29 patients who received rFVIIa. We were able to compare these patients with a similar group of patients who did not receive rFVIIa. Overall reversal of coagulopathy took much longer in the control group. Factor VII seems to work rapidly and safely when FFP alone fails. The mortality was the same in both groups, but the functional outcome was somewhat better in the factor VII group. The number of patients with GOS scores of 5 (the best score) was significantly greater in the factor VII group: 9 patients, versus only 2 in control subjects.

Our study was limited by its retrospective design. We could not reliably time the administration of rFVIIa and subsequent surgery or compare the INR values of rFVIIa patients and control subjects at precisely the same time. These can be dependably performed only in a prospective study. The two groups seem to be closely matched by demographics, initial INR, and diagnosis, increasing the validity of the comparison. However, biases could still be present. A few of the control patients were treated at a time when rFVIIa had already been used by our service. The decision not to use it in a particular patient may have been affected by the perceived degree of urgency or severity of coagulopathy. This may have resulted in the selection of more urgent patients to the rFVIIa group. The long time to reversal in the control group may have reflected less effort at reversal and a more leisurely pace of treatment. Such a bias would not affect the basic conclusions regarding the safety and efficacy of rFVIIa. Actually, the total amount of FFP used was similar in the two groups, with a significantly different effect.

rFVIIa promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. It is a vitamin K-dependent glycoprotein, similar to the human plasma-derived factor VIIa (9). It is indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX (2). There is a theoretical basis for the use of rFVIIa: it seems to be the "bottleneck," the critical factor most depleted when patients are profoundly anticoagulated (8).

There have been several reports of successful application of rFVIIa to treat severe bleeding in nonhemophilic patients, including a perioperative use in neurosurgery (3, 4). It was given to stop intracerebral bleeding and to reverse the effects of warfarin in patients with critical INR values and was effective in patients with severe liver failure (1, 6, 10, 11). More recently, Park et al. (7) reported nine neurosurgical patients in whom rFVIIa was used to reverse coagulopathy. Rapid correction of coagulopathy was the rule in all these reports, with a decreased rate of additional bleeding after the procedure and a low risk of associated thromboembolism or other complications (7). The results of our study support the findings in these published reports, in a larger series of patients with matched retrospective control subjects.

Factor VII is expensive. The estimated wholesale price of rFVIIa is \$1.18/ μ g of drug (University of Illinois Pharmacy). Our patients received 1.4 mg on average, for the total cost of \$1652 per dose. It also has a short half-life, 2.3 hours. Therefore, it should be administered with vitamin K and may require repeat doses or the addition of FFP. For comparison, the cost of FFP in our institution was \$55 per bag. The real cost was probably higher, because FFP requires extra time, effort, and medical supervision to administer. There is also a factor that cannot be precisely quantified even in a prospective study: the risk of transmission of blood-borne diseases with FFP. A pooled blood product has a higher risk of pathogen transmission than does a unit of packed red blood cells.

Nevertheless, rFVIIa has important advantages. It is not a blood product, it is readily available in pharmacies, and it does not carry the risk of transmission of infection. Theoretically, the high cost of rFVIIa may be wholly or partially offset by savings on the number of units of FFP transfused. However, in our study, rFVIIa was used only as second-line therapy, after patients had received vitamin K and FFP. Therefore, it was not possible to assess whether the use of factor VII as a first line of therapy would have further benefits of decreasing FFP use or shortening the time to life-saving surgical intervention.

CONCLUSION

Our study suggests that rFVIIa is safe and effective in rapid reversal of coagulopathy in neurosurgical patients when used as a second-line therapy after initial administration of vitamin K and FFP. Although the mortality did not change, the number of patients with good functional outcome (GOS score of 5) was greater among patients treated with factor VII compared with those who received only vitamin K and FFP.

To make rFVIIa a first-line intervention in neurosurgical patients who require immediate reversal of coagulopathy, we recommend a prospective trial, designed to evaluate key issues of time to reversal, the need for repeat doses, the need for additional FFP, any time savings to get to surgery, and the relative cost by intent to treat with rFVIIa compared with FFP.

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COMMENTS

This is an interesting, well-designed retrospective study on the use of recombinant factor VII (rFVIIa) for rapid reversal of coagulopathy in patients requiring urgent neurosurgical intervention. Patients treated with rFVIIa had a statistically significant improvement in clinical outcome, probably because faster coagulopathy reversal leads to earlier surgical intervention. A randomized prospective trial is now indicated to fully evaluate rFVIIa as a first-line treatment in coagulopathic patients who require surgery. Although the immediate treatment cost of rFVIIa is much higher than conventional fresh-frozen plasma (FFP) administration for reversing coagulopathy, the total cost of prolonged hospitalization and possible rehabilitation care for patients who experience delays in surgery would likely be even more exorbitant.

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This article by Roitberg et al. provides information of practical interest on the potential use of rFVIIa for the treatment of coagulopathic patients with an intracerebral hemorrhage. This subset of patients presents a difficult challenge; in particular, when one needs to urgently reverse the elevated international normalized ratio (INR) in the midst of treating a life-threatening hemorrhage. The challenge is not only seen in the preoperative and intraoperative periods, but also in the postoperative period. It is not unusual that the initially corrected INR elevates postoperatively, leading to the need for the additional administration of FFP and the potential rehemorrhage into the fresh post operative cavity. An additional issue with the administration of FFP includes fluid management, which can also compromise the condition of these often medically tenuous patients.

The main limitation of this study is the retrospective nature of the design. The authors clearly and properly acknowledge this issue in the discussion. Can the potential biases that are part of a retrospective trial design account for the observed results? This is always possible, although it seems unlikely. I hope that this group will pursue a prospective study on this important question in order to provide definitive and clear data on the matter.

Robert M. Friedlander
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Roitberg et al. have provided us with a retrospective study regarding the use of human rFVIIa (Novo VII) in coagulopathic neurosurgical patients. The authors used Novo VII as second line therapy in 29 patients after an initial attempt at reversal with vitamin K and FFP

failed, with 24 patients treated before the introduction of Novo VII serving as matched controls. Considering the inherent study design limitations, the authors found significantly shorter time to INR normalization without thrombotic complications in the treatment group, supporting Novo VII as safe and effective for the reversal of coagulopathy in patients necessitating emergent neurosurgical intervention.

Although this study grants us preliminary data on the efficacy of Novo VII, many questions remain. In an attempt to provide answers, Phase 2a trials are underway to address the safety, feasibility, and possible efficacy of giving Novo VII to patients with acute intracranial hemorrhage. In the meantime, Roitberg et al. further support the therapeutic potential of Novo VII to facilitate neurosurgery in coagulopathic patients. Their findings, as well as those from ongoing prospective trials, should engender a strong impetus within the neurosurgical community for a follow-up, fully powered, Phase III trial led by the National Institutes of Health to rigorously examine the drug's potential safety and efficacy in neurosurgical disease.

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The authors have shown that human rFVIIa can be successfully used to emergently reverse coagulopathy in patients requiring neurosurgical intervention. Most neurosurgeons who manage trauma patients have encountered situations in which a patient required urgent surgical intervention, but this intervention was delayed by several rounds of administration of FFP. Furthermore, the serial INR values that need to be drawn after each FFP administration further delayed treatment. Whereas the authors used recombinant factor VII as a second line treatment for those patient (all had received previous FFP), it may be even more useful if rFVIIa proves successful as a first line treatment. This would significantly reduce the time required to normalize the INR levels before emergent surgery. Furthermore, as the authors point out, there would be a significant reduction in the use of FFP and the potential transmission of blood borne infections. rFVIIa seems to be easily and rapidly administered, with no reported side effects in this series. If this data is borne out in additional prospective trials, it may significantly change the treatment of patients with a coagulopathy requiring emergent neurosurgical intervention.

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Cleveland Rams players bundle in straw for warmth during the 1945 National Football League championship game. (Photograph courtesy of the Sporting News Archives.)

