

Received: 2002.08.22
Accepted: 2002.11.08
Published: 2002.12.27

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Recombinant Coagulation Factor VIIa for rapid preoperative correction of Warfarin-related coagulopathy in patients with acute subdural hematoma

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Summary

Background:

Intracranial hemorrhage, either spontaneous or traumatic is a well-known and potentially lethal complication of Warfarin treatment. Patients with Warfarin-related intracranial hemorrhage need urgent reversal of anticoagulation that must be especially rapid if surgical intervention is indicated. The traditional treatment with fresh frozen plasma (FFP) and vitamin K often fails to achieve the desired correction of coagulopathy in urgent neurosurgical settings.

Case report:

In the present case Recombinant Coagulation Factor VIIa (rFVIIa) was used for preoperative reversal of Warfarin-related coagulopathy. The patient was a fifty two years old man, mechanic valve recipient with Warfarin-induced coagulopathy: International Normalization Ratio (INR) of 6.39, who suffered from acute subdural hematoma and needed urgent neurosurgical intervention. He received a single dose of rFVIIa 120 µg/kg and immediately underwent craniotomy and evacuation of the hematoma. Appropriate hemostasis was achieved during surgery and coagulation test taken two hours after rFVIIa injection revealed INR of 1.25. The INR remained normalized for additional 14 hours. To the best of our knowledge, this is the first report on the use of rFVIIa in the preoperative management of Warfarin-induced intracranial hemorrhage.

Conclusion:

Recombinant Coagulation Factor VIIa provides rapid correction of coagulation to a level that allows safe neurosurgical intervention without significant delay. This agent is safe and effective; and should be considered for reversal of Warfarin-induced coagulopathy in cases of intracranial hemorrhage, especially when urgent surgical intervention is required.

key words:

anticoagulation • craniotomy • intracranial hemorrhage • recombinant coagulation factor VIIa

Full-text PDF:

http://www.MedSciMonit.com/pub/vol_8/no_12/3042.pdf

Word count:

1145

Tables:

–

Figures:

–

References:

12

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BACKGROUND

The optimal management of Warfarin-induced intracranial hemorrhage has not been determined in any randomized trial. The prevailing opinion holds that hemorrhages in accessible locations, when causing severe neurological symptomatology, should be treated surgically after correction of the coagulopathy. Preoperative reversal of anticoagulation in patients with Warfarin-induced intracranial hemorrhage, however, is a complex and challenging problem. The optimal agent used for this purpose should: 1. act immediately, allowing to perform life-saving neurosurgical procedures at appropriate INR and in due time; 2. have predictable effects when administered in standard doses according to preoperative INR; 3. have long standing therapeutic effect, thus preventing recurrent bleeding; 4. avoid unnecessary volume expansion which can cause elevation of the intracranial pressure or pulmonary edema; 5. not induce thromboembolic complications; and 6; exclude the risk of transferring viral infections.

Pharmacological agents currently used for correction of drug-induced coagulopathy include FFP, vitamin K, prothrombin complex concentrate and factor IX complex. These agents, however, do not fulfill all of the above criteria for different reasons.

In the presented case the authors used Recombinant Coagulation Factor VIIa for rapid preoperative reversal of Warfarin-related coagulopathy.

CASE REPORT

A 52 years old man, mechanic valve recipient, treated with Warfarin during several years, was admitted to our emergency room with the history of sudden loss of consciousness. On examination the patient was comatose with a dilated pupil and decerebrate rigidity on the left side. There was no history of recent trauma. A brain CT scan revealed left temporal acute subdural hematoma. Routine laboratory studies were remarkable only for INR of 6.39.

The patient received 120 µg/kg of Recombinant Coagulation Factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvard, Denmark) and was immediately brought to the operating room, where he underwent left fronto-temporal craniotomy with evacuation of acute subdural hematoma. There was no excessive bleeding during surgery and we were able to achieve appropriate hemostasis. Coagulation tests taken during surgery, one hour after injection of Novoseven revealed an INR of 1.25. The INR was relatively normalized (1.08–1.15–1.43) for additional 14 hours. Postoperatively the patient remained in deep coma and died four days later.

DISCUSSION

The incidence of non-traumatic intracranial hemorrhage in patients receiving Warfarin prophylaxis is estimated to be 1.6% with a mortality rate of 76% [1]. Rapid

reversal of anticoagulation is required to prevent the expansion of hematoma or to provide an adequate intraoperative hemostasis if surgical evacuation is undertaken.

There is no exact data at which INR can surgery for intracranial pathology be safely performed. According to Mathieson et al [1], an INR of 1.2–1.5 is sufficient for neurosurgical hemostasis, while Boulis et al [2], chose an INR of 1.3 to be the goal of preoperative Warfarin reversal. Kawamata et al [3] reported that 15 of their 17 patients with Warfarin-related ICH were operated upon with INR values of 1.13–1.81.

The standard treatment for correction of Warfarin coagulopathy have included FFP and vitamin K. The main disadvantage of this therapy is a slow rate of INR correction. Kawamata et al [3] mentioned that they were unable to obtain sufficient reversal of anticoagulation using vitamin K alone in any of their patients with Warfarin-related acute subdural hematoma and cerebral contusions. It has also been found that the rate of INR correction was about 0.18 Δ INR/hour for patients treated with FFP and vitamin K [2]. Treatment with FFP also has other disadvantages since successful rapid preoperative Warfarin reversal needs rapid infusion of relatively large volumes of FFP. First, this can precipitate pulmonary edema in a group of patients, most of whom are usually elderly with previous cardiac problems. Secondly, there might be further elevation of the intracranial pressure in patients with already compromised brain. Administration of FFP also carries a definitive risk, although very low, of the transfer of human viruses.

Alternative strategies for urgent Warfarin reversal have been proposed during the last decade. The prothrombin complex concentrate [4] and factor IX complex [2] were shown to reverse anticoagulation more rapidly than FFP in patients with Warfarin-related intracranial hemorrhage, although the reported time to INR correction (4.8 hours for prothrombin complex concentrate and about 3 hours for factor IX complex) seems to be slower than that required in urgent neurosurgical settings. In addition, these agents can also induce thromboembolic complications [5].

Recombinant FVIIa is derived from cultured baby hamster kidney cells [6] and is almost identical to human activated factor VII. It does not activate general coagulation but joins with tissue factor only at the site of vascular wall injury, creating a complex that promotes local hemostasis. The drug is an effective hemostatic agent and is FDA approved for treatment of bleeding in patients with hemophilia A and B inhibitors [7]. It has also been used in the conservative management of intracranial hemorrhages from different etiologies such as hemophilia [6], refractory thrombocytopenia [8] and neonatal factor VII deficiency [9]. The role of this agent in preoperative management of Warfarin-related intracranial hemorrhage however, has not been established.

Since factor VII has the shortest half-life (3–4 hours) of the vitamin K-dependent clotting factors [9] and is the most quickly reduced factor during Warfarin therapy [10], it seems reasonable to use it for reversal of Warfarin-induced coagulopathy. The ability of rFVIIa to reduce INR in healthy volunteers treated with oral anti-coagulant has been demonstrated in a randomized double-blind study [11]. Twelve patients with INR > 2.0 were given rFVIIa in doses ranging from 5 to 320 µg/kg. The lowest dose of 5 µg/kg normalized the INR for 12 hours, while with high doses above 120 µg/kg, the INR remained normal for 24 hours. Berntorp [12] reported the case of a patient with Warfarin-induced spontaneous bleeding from the nose and throat. A single dose of rFVIIa 80 µg/kg stopped the bleeding after 6 minutes and INR was normal within 30 minutes.

These preliminary data show that rFVIIa may be highly effective for rapid anticoagulation reversal in Warfarin-treated subjects. Other potential advantages of rFVIIa treatment are that it does not induce thromboembolic complications and, as a recombinant product, this agent has no risk of transfer of human viruses.

CONCLUSIONS

In the illustrative case the patient was obviously overtreated with Warfarin with INR of 6.39. He presented with acute subdural hematoma and needed urgent operation. On the other hand, the deterioration in the patient's condition was so rapid, and INR was so high that it was definitely unworthy to start the conventional treatment with FFP and vitamin K. The infusion of rFVIIa provided rapid normalization of INR which allowed us to operate relatively soon with adequate intraoperative hemostasis. Despite the fatal outcome, which is probably related to the poor preoperative neurological condition, this case demonstrates that rFVIIa is safe and effective for rapid correction of Warfarin-

induced coagulopathy when urgent neurosurgical treatment is indicated. Further investigations are required to establish the role of this drug in the preoperative or conservative management of Warfarin-induced intracranial hemorrhage.

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