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Recombinant factor VIIa therapy in a patient on long term anticoagulant treatment with a bleeding and acute subdural hematoma

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ABSTRACT

In this paper we report on the successful correction of a coagulopathy with activated recombinant factor seven (rFVIIa) therapy which enabled surgical removal of a life threatening subdural hematoma. The severe coagulopathy developed due to long term warfarin therapy, which followed heart valvular reconstruction and replacement. The coagulopathy failed to improve following fresh frozen plasma and vitamin K therapy. Activated recombinant factor VII therapy became the treatment of choice, which enabled the life saving surgical removal of the subdural hematoma.

Key words: activated recombinant factor seven, subdural hematoma, anticoagulant therapy, neurosurgery.

Introduction

Recombinant activated coagulation factor VII (rFVIIa) has been developed as a suitable way for the treatment of spontaneous and surgical bleeding in patients with congenital and acquired hemophilia with antibodies (inhibitors) against factor VIII (FVIII) and factor IX (FIX) (1). In addition, it is a useful hemostatic agent proven effective in numerous other diagnostic and therapeutic procedures like biopsies in liver disease, thrombocytopenia with bleeding, total hip replacement, etc. (3, 9, 10). rFVIIa induces hemostasis at the site of injury independent of the presence of FVIII and by forming complexes with exposed tissue factor (TF) (1). It bypasses activation of factor VIII and directly activates factor X into Xa

and IX into IXa. The natural factor seven (FVII) is a vitamin K dependent protease primarily synthesized by the liver (4). Therefore, rFVIIa treatment could be effective and clinically protective in hemorrhages and coagulopathies caused by liver dysfunction (4). The long-term anticoagulant, warfarin, decreases circulating levels of vitamin K-dependent coagulation factors and increases the risk of hemorrhagic complications. Intracranial bleeding is one of the most ominous complications of anticoagulant therapy, calling for immediate intervention.

In this paper, rFVIIa therapy is described which led to a rapid correction of coagulation system abnormalities and enabled urgently required, life saving surgery.

Case report

A 35-yr-old woman was admitted to hospital with nausea, vomiting,

headache and drowsiness. She was hardly communicative with a GCS 12 and mild left sided weakness. Her pupils were reactive and isocoric. Head CT scan revealed a large hemispherical subdural hematoma with basal tentorial spread. Urgent surgical removal of the hematoma was indicated.

The patient was on long term, prophylactic, oral anticoagulant therapy with warfarin (6 mg daily) because of valvular heart surgery done 4 years ago. That operation had included the implantation of a tricuspid valve, commissurotomy of the mitral valve, and reconstruction of the aortic valve. The primary cause of the structural disintegration and functional valvular failure had been rheumatic fever in childhood. On admission, the acute coagulopathy was life threatening. The prothrombin time (PV) was 3% (normal value 70-130 %) and partial thromboplastin time (PTT) was 106 seconds (normal value 26-36

seconds), thrombin time (TT) was 14 seconds (normal value 14-21 seconds) and fibrinolysis 195, thrombocyte count was $153 \times 10^9/L$. The indicated, urgent, pending surgical procedure posed a high risk for excessive bleeding. Fresh frozen plasma (FFP) 1200ml (20ml/kg) and vitamin K 20 mg were administered. Correction of the coagulation parameters was slow. Three hours later, following FFP and vitamin K administration, the PV still remained too low (34%). In order to facilitate surgery, with a clinically acceptable PTT, we administered 1,2 mg of rFVIIa intravenously and repeated the same dose two hours later in the operating theatre (rFVIIa - NovoSeven produced by Novo Nordisk A/S, Bagsvaerd, Denmark). The coagulation parameters improved quickly reaching a PV 124% and PTT 33 seconds within this short period of time. During the operation no excessive bleeding occurred. The postoperative recovery was smooth and functional status normalized. Control CT scans ruled out any postoperative bleeding and appropriate intracranial structural relations were recorded. At the same time, the induced high PV might have been a risk factor for a thrombotic complication on the artificial heart valve surfaces. In order to continue with

anticoagulant prophylaxis, the patient was treated with a continuous heparin infusion and gated to an acceptable PTT (70-80%). No thrombotic complications occurred in the postoperative period.

Discussion

Warfarin, a widely prescribed oral anticoagulant, is used for the prevention of primary and secondary venous and arterial thromboembolic complications (6). In the case of our patient, prolonged warfarin therapy was prescribed to prevent thrombi formation, chronic atrial fibrillation and to maintain the mechanical prosthetic heart valves. The most common complication of warfarin use is adverse bleeding. Such therapy caused the acute bleeding and subdural hematoma, which the patient presented with on admission. Since fresh frozen plasma and vitamin K therapy failed to achieve safe hemostasis, rFVIIa was used to treat the bleeding. This procedure turned out to be very effective. The coagulation parameters improved and normalized promptly. The rapid correction made the urgent surgical procedure possible. The administered dose of rFVIIa was given according to the manufacturer's recommendation taking into account the patient's body weight. The

recommended doses for patients with hemophilia and alloantibody inhibitors are between 90 mcg/kg to 120mcg/kg (8). Lower doses 15 mcg/kg to 20mcg/kg are shown to procure an adequate hemostasis in patients with other disorders of coagulation (7). Our patient promptly reacted to two repeated doses of 20 mcg/kg. rFVIIa was developed as a new approach to hemophilia treatment. It has been used in various non-hemophilia patients with a few adverse events (2, 3, 9). Several case reports and small series have reported rFVIIa as effective and safe therapy in patients with trauma and abdominal surgery, other surgical indications as well as for some diagnostic procedures (3, 9, 10). Our report indicates that correction of warfarin induced coagulopathy in neurosurgery may be an additional indication for rFVIIa therapy.

Conclusion

In this paper we reported effective rFVIIa therapy in warfarin induced coagulopathy in neurosurgical patient. The fast improvement of hemostasis and the control of bleeding enabled the life saving neurosurgical operation, when effects of vitamin K and fresh frozen plasma were of limited value.

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