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PRACTICAL PEARL

Utilization of recombinant activated factor VII for intracranial hematoma evacuation in coagulopathic nonhemophilic neurosurgical patients with normal international normalized ratios

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Abstract
Background Recombinant activated Factor VII (rFVIIa) has recently gained popularity for rapid reversal of coagulopathy during operative neurosurgery. Patients undergoing chronic subdural hematoma (CSDH) or epidural hematoma (EDH) evacuation often have their coagulation status judged by preoperative international normalized ratio (INR). We present our experience in two patients with significant clinical coagulopathy who were successfully reversed with rFVIIa in the setting of normal INR.
Methods Patient one was a 79-year-old man with history of prostate cancer and three previous operative left CSDH evacuations, each complicated by coagulopathic bleeding, who presented with new-onset left EDH. Patient two was a 27-year-old woman with relapsed acute myelogenous leukemia with bilateral CSDH and mass effect on MRI. Neither patient had hemophilia, and preoperative INR was 1.2 in each case. Both patients underwent evacuation in the operating room, preceded by rFVIIa administration.
Results Patient one underwent removal of his previous craniotomy flap followed by EDH evacuation. In patient two, coagulopathic bleeding upon surgical approach necessitated an additional dose of rFVIIa. Burrhole evacuation was well-tolerated with visible brain re-expansion following irrigation. Each case occurred with minimal blood loss and relatively easy hemostasis, with postoperative CT and clinical course revealing adequate evacuation. Neither patient experienced thromboembolic complications or required re-operation.
Conclusion These two patients are the first to be examined for the use of rFVIIa for reversal of clinical coagulopathy in the setting of normal INR. Our experience suggests that normal INR should not be a deterrent for patients to receive rFVIIa in the setting of strong neurosurgical suspicion for underlying clinical coagulopathy.

Keywords Recombinant activated factor VII · International normalized ratio · Chronic subdural hematoma · Epidural hematoma · Nonhemophilic

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Introduction

Originally created for the treatment of hemophilic patients, recombinant activated Factor VII (rFVIIa) has recently gained popularity for rapid reversal of coagulopathy during operative neurosurgery in nonhemophilic patients [1–6]. Patients undergoing chronic subdural hematoma (CSDH) or epidural hematoma (EDH) evacuation often have their coagulation status judged by preoperative international normalized ratio (INR) values. We present our experience in two patients with significant clinical coagulopathy despite normal INR values who were successfully reversed with rFVIIa administration prior to emergent operative neurosurgery.

Clinical materials and methods

Patient histories

Patient one is a 79-year-old nonhemophilic man with history of prostate cancer, positive pulmonary and hepatic nodules on positron emission tomography (PET) scan, and

Greenfield filter placement due to previous thromboembolic disease. He initially underwent burrhole drainage of a left CSDH, with external subdural drain placement. One week later, he re-presented with a reaccumulation of his subdural fluid that necessitated redrainage in the operating room. Two weeks afterward, he again required re-evacuation of a left CSDH in the operating room. Each operative intervention was complicated by coagulopathic bleeding of unknown origin. Six days after his last surgery, he developed a left EDH that required operative evacuation (Fig. 1). He had no history of recent anticoagulant usage. Although his preoperative INR was within normal limits, because of his coagulopathic history in the setting of a known extracranial malignancy, he received a single 60 mcg/kg dose of rFVIIa preoperatively.

Patient two is a 27-year-old nonhemophilic woman with history of relapsed acute myelogenous leukemia that is refractory to chemotherapy and myeloablative double umbilical cord transplant. She has no history of thromboembolic disease. Two weeks prior to presentation, she underwent a lumbar puncture, after which she quickly developed headache with intermittent nausea, vomiting and gait difficulties. Upon presentation for a haploidentical natural killer cell bone marrow transplant, her headache had worsened and was accompanied by photophobia. Brain magnetic resonance (MR) imaging revealed bilateral SDH with mass effect, sulcal effacement and effacement of the suprasellar and basal cisterns. Laboratory findings revealed marked leukopenia (white blood cell count = 400 cells/microliter), thrombocytopenia (platelet count = 18,000 per microliter) and an INR of 1.4. She had no history of recent anticoagulant use. Attempted correction of her laboratory abnormalities prior to evacuation, involving intravenous administration of four units of a fresh frozen plasma (FFP) drip, 10 mg of vitamin K, two units of packed red blood cells, and 11 units of platelets reduced the INR from 1.4 to 1.2, with head CT confirming the persistence of the bilateral SDH (Fig. 2). However, due to her persistent leukopenia (700 cells/microliter) and thrombocytopenia (70,000 platelets/microliter) in the setting of her underlying AML, neurosurgical suspicion of an underlying coagulopathy was high, and she received a single 60 mcg/kg dose of rFVIIa preoperatively. Neither patient had any history of recent stroke, myocardial infarction, or EKG changes suggestive of myocardial ischemia.

Operative hematoma evacuation and postoperative course

The evacuation for each patient was performed in the operating room. Patient one underwent bone flap removal, revealing a substantial left-sided epidural blood clot that was carefully evacuated. The dural sutures were then cut and opened along the previous incision line for visualization underneath the dura. Careful inspection revealed no SDH, and following subdural irrigation and dural closure, the original bone flap was reapproximated in place. The operation ended with an estimated blood loss (EBL) of

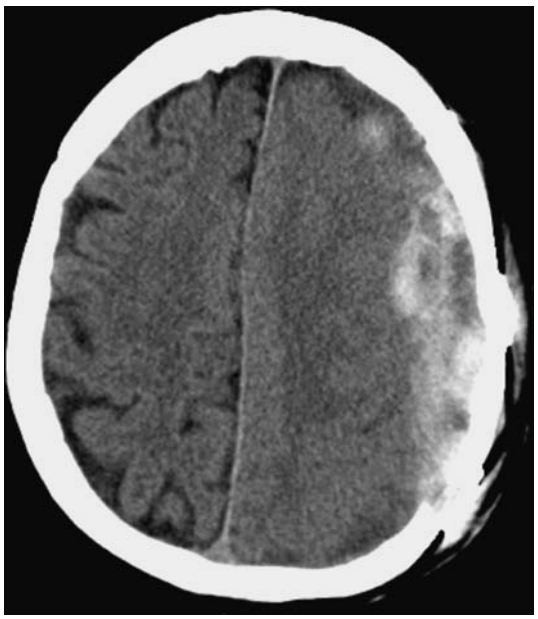

Fig. 1 Axial preoperative CT in patient 1 demonstrating a large left-sided hematoma. Although initially read as a chronic subdural hematoma, the lesion at operation was found to be an epidural hematoma

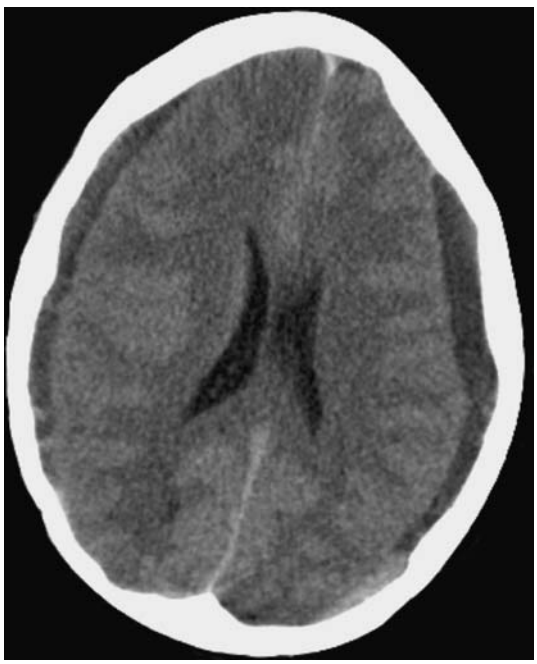

Fig. 2 Axial preoperative CT in patient 2 demonstrating the right- and left-sided subdural hematomas prior to bilateral burrhole drainage

100 ml, and a significantly easier time achieving hemostasis than in the patient's three previous CSDH evacuations.

In patient two, a horseshoe trauma flap was marked out on the patient's scalp bilaterally and four burrholes were created, one in the frontal region and one postoperatively in each hemisphere. During this process a significant amount of coagulopathic bleeding occurred, necessitating the administration of a second 60 mcg/kg dose of rFVIIa. The dura was then coagulated and the anterior frontal burrholes were opened bilaterally, resulting in the release of moderately high-pressure chronic subdural fluid. Due to the marked effusion of epidural blood, the posterior burrholes were never used for dural opening in order to prevent the epidural blood from migrating inside the dura. As the operation progressed, the surgical bleeding gradually became more viscous, and hemostasis became easier to obtain. Good flow was documented between the left and right burrholes, and the subdural cavities were irrigated, after which the brain visibly re-expanded. The operation ended with an EBL of 200 ml. The patient was extubated in the operating room, and was neurologically alert and intact prior to transfer to the ICU. Neither patient required intracranial re-operation or suffered any thromboembolic complications postoperatively.

Discussion

The emergence of recombinant activated factor VIIa (rFVIIa) as an agent for rapid reversal of coagulopathy has provided a powerful tool in the treatment of coagulopathic patients requiring emergent surgical intervention [1, 3, 6, 7]. Originally it was created to aid the surgical treatment of patients with hemophilia. However, a report of its successful use in a soldier with no pre-existing coagulopathy to stop hemorrhage from a gunshot wound prompted the subsequent exploration of rFVIIa use in nonhemophilic patients [8]. The scope and indications of rFVIIa usage subsequently have enlarged in all surgical disciplines [9–17].

Previous studies involving neurosurgical patients have demonstrated rapid reversal of hemorrhage in both adult and pediatric nonhemophilic patients with minimal thromboembolic sequelae [2, 4–6]. Recent prospective randomized double-blind placebo-controlled trials in patients with acute intracerebral hemorrhage have shown that early administration of rFVIIa reduces hematoma growth, reduces mortality, and improves functional outcomes at 90 days following administration at a wide range of dosages [18, 19]. The use of rFVIIa for reversal of coagulopathy in neurosurgical patients with a normal INR has not been previously examined. For this reason, we reported our experience with two patients requiring emergent operative neurosurgery.

Our findings confirm the conclusions of previous reports that the rFVIIa is efficient and useful in reversing coagulopathy in neurosurgical patients [1, 3, 5, 6]. Both of our patients required operative neurosurgery and had clinical evidence of coagulopathy despite INRs within the normal range. Neither patient had a history of hemophila or recent anticoagulant medication use, nor did either have any history of recent stroke, myocardial infarction, myocardial ischemia on EKG, or untreated thromboembolic disease (patient one had an indwelling Greenfield filter, and patient two had no history of thromboembolism), which would have been contraindications for rFVIIa administration. Noteworthy of mention is that both patients had known extracranial malignancies (prostate cancer in patient one, and acute myelogenous leukemia in patient two). Additionally, patient one demonstrated repeated evidence of coagulopathic bleeding during surgical intervention, and patient two had marked thrombocytopenia during the pre-operative course. In each instance, more traditional measures of hemostatic correction (fresh frozen plasma, vitamin K, platelet transfusions) proved insufficient for hemostasis, and the administration of rFVIIa preoepratively in each case contributed to the quick and sustainable control of coagulopathic bleeding during operative intervention, allowing for good postoperative outcomes without thromboembolic adverse events.

The administration of rFVIIa may be met with opposition from the hematology services due to the high cost of the intervention in the setting of normal INR values [20]. In our first instance, although the use of rFVIIa was denied for the patient's second and third SDH evacuations, the prospect of coagulopathic bleeding during the patient's EDH enabled him to receive approval for rFVIIa despite his normal INR. For the second patient, the pervading opinion among our hematology colleague was that there was no role for rFVIIa preoperatively due to the patient's normal INR. Despite eventually being given rFVIIa preoperatively, upon operative exploration, this patient clearly demonstrated coagulopathic bleeding necessitating an additional dose of rFVIIa. This illustrates the importance of clinical suspicion of coagulopathy in these patients, and the importance of not relying solely on INR to determine the appropriateness of rFVIIa administration. Our findings also concur with previous studies demonstrating that the earlier rFVIIa is administered, the more efficacious it is and the less of it needs to be administered [17–19]. Although rFVIIa is clearly not an intervention without potentially serious thromboembolic adverse events [21], our experience in these two patients demonstrates that rFVIIa can be safely administered in appropriately selected patients with normal INR without the occurence of thromboembolism.

However, given the thromboembolic risks (i.e., stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism) associated with rFVIIa, it is possible that smaller doses of rFVIIa than those used in this study (60 mcg/kg) may provide similar efficacy while reducing the risk of thromboembolism. Prospective studies involving larger patient size will be necessary to definitively address the efficacy, safety, and dosing parameters of the pre-surgical use of rFVIIa described in this manuscript.

Conclusion

This report of two patients is the first to examine the use of rFVIIa for reversal of clinical coagulopathy in neurosurgical patients with a normal INR. Our experience suggests that in the setting of a normal preoperative INR, rFVIIa can adequately and safely reverse clinical coagulopathy in nonhemophilic patients requiring emergent operative neurosurgery. Although administration of rFVIIa is not without risk of adverse thromboembolic complications, in the setting of strong neurosurgical suspicion of coagulopathy (thrombocytopenia, known extracranial malignancy, previous coagulopathic bleeding during surgery), a normal INR should not prevent patients in need of emergent operative neurosurgery from receiving rFVIIa preoperatively.

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