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The use of recombinant factor VIIa (NovoSeven) for treatment of active or impending bleeding in brain injury: broadening the indications[☆]

Yakov Yusim MD^a, Azriel Perel MD^a, Haim Berkenstadt MD^a,
Moshe Attia MD^b, Nachshon Knoller MD^b, Avner Sidi MD^{a,c,*}

^aDepartment of Anesthesiology, Sheba Medical Center, Tel-Hashomer 52621, Israel

^bDepartment of Neurosurgery, Sheba Medical Center, Tel-Hashomer 52621, Israel

^cDepartment of Anesthesiology, University of Florida College of Medicine, Gainesville, FL 32610-0254, USA

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Comment by Gili Kenet MD

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Abstract We report three patients with severe traumatic brain injury, both open and closed, who were treated with recombinant activated factor VII. This treatment was given in a desperate, last-ditch effort to save the life of patient 1, as a preventive or early treatment of a developing hematoma in patient 2, and as treatment of a threatening hematoma in patient 3. One of the three patients survived. During the past few years we have broadened the indications for recombinant activated factor VII and started using it as a preventive measure rather than as a “last line of defense.” However, the potential complications of disseminated intravascular coagulation and thrombotic events, as well as the cost-effectiveness in view of the available evidence-based medicine, should be considered.

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1. Introduction

Hemorrhage is one of the serious problems encountered in the management of trauma patients. Control of coagulopathic bleeding during surgery is difficult—sometimes impossible—and recombinant factor VIIa (rFVIIa) has been suggested as a lifesaving treatment in such situations [1-3].^{1,2}

For the past 5 years, the indications for use of rFVIIa have been broadened from the approved indication of hemophilia patients with inhibitors to various off-label uses in massive bleeding in trauma, surgery, and other medical

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* Corresponding author. Editorial Office, Department of Anesthesiology, University of Florida College of Medicine, PO Box 100254, Gainesville, FL 32610-0254, USA. Tel.: +1 365 395 8012; fax: +1 365 395 8013.

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cases. Early use or preventive strategies (in the sense of preventing change of contusion to hemorrhagic lesion), rather than the last line of defense, have been suggested. For example, in patients with brain injury, in whom the combination of surgical difficulties for hemorrhage control and coagulopathic disorders is a major problem, use of rFVIIa may be appropriate [4-11].

Treatment with rFVIIa after the onset of intracerebral hemorrhage (ICH) can be effective in limiting the growth of hematoma, reducing mortality, and improving functional outcomes, despite a small increase in the frequency of thromboembolic events [10]. However, in a small patient sample of acute nontraumatic or spontaneous ICH, it was shown that rFVIIa increased mortality and, thus, raised concerns about safety [11]. In cases of ICH due to traumatic coagulopathy, among them patients with traumatic brain injury (TBI), rFVIIa therapy led to an immediate reduction in coagulopathic hemorrhage in most cases accompanied by significant improvement in laboratory measures. However, rFVIIa-treated patients had a higher mortality than did the coagulopathic controls [6].

By broadening the indications and using an early or preventive strategy, the potential complications of disseminated intravascular coagulation (DIC) and thrombotic events [12,13], such as myocardial infarction (MI), cerebrovascular thrombosis, and venous thrombosis, become a concern. In this article, we describe three patients with severe TBI who were treated with rFVIIa. This treatment was given either in a desperate effort or as a “preventive” treatment to a developing or threatening hematoma. We discuss broadening the indications for rFVIIa and also focus on potential complications.

2. Case reports

2.1. Case 1

A 12-year-old (35 kg) boy without previous medical history was admitted to the emergency department (ED) with severe head injury after being hit by the propeller of a radio-guided model helicopter. The patient had a Glasgow Coma Scale (GCS) score of 8. He had a large bleeding wound at the left parietotemporal region of the skull, with brain tissue extruding from the wound. His trachea was intubated and mechanically ventilated; 250 mL of universal donor packed red blood cells (PRBCs) and 500 mL of the colloid Haemacell (Behring, Malburg, Germany) were administered. A computed axial tomographic (CAT) scan of the brain (Fig. 1) showed multiple contusions and depressed skull fractures above the left hemisphere, with bone fragments penetrating brain tissue. Because of severe cerebral edema, only slitlike ventricles were present. The child was taken immediately to the operating suite (OR) for an emergent craniotomy. His body temperature on arrival to the OR was 35.5°C. Laboratory studies at the time gave the



Fig. 1 CT scan of brain, case 1. Multiple contusions and depressed skull fractures above the left hemisphere. Note the bone fragments inside penetrating brain tissue and the brain tissue extruding from the calvarium.

following values: hemoglobin (Hb), 8.4 g/dL; platelets, 412 000 cells/ μ L; international normalized ratio (INR), 1.24; partial thromboplastin time (PTT), 34 seconds; fibrinogen, 112 mg/dL; and D-dimer, 1469 ng/mL.

About 40 minutes into the operative procedure, blood loss was estimated to be more than 1500 mL; there was no change in body temperature, and the patient's hematologic studies showed the following values: Hb, 5.3 g/dL; platelets, 209 000 cells/ μ L; INR, 2.1; PTT, 73.4 seconds; fibrinogen, 52 mg/dL; and D-Dimer, 789 ng/mL. By this time, the child had received 500 mL of PRBCs, 300 mL of fresh-frozen plasma (FFP), 4 units of platelets, and 500 mL of Haemacell. Blood products were continuously administered to compensate for the massive hemorrhage, and after an additional transfusion of three units of FFP, 4 units of PRBC, 6 units of platelets, and 10 units of cryoprecipitate, his Hb level increased only to 9.7 g/dL. The patient's brain tissue was “oozing” out and blood loss remained profuse; surgical control of the bleeding was unattainable. In this critical situation, and after consultation with our hematology colleagues, we decided to give the child 1.2 mg (34 μ g/kg) of rFVIIa immediately after blood component transfusion. Two hours after the infusion of the rFVIIa, the child was hemodynamically stable, with the following laboratory study values: Hb, 9.2 g/dL; platelets, 186 000 cells/ μ L; INR, 0.9; PTT, 32 seconds; and fibrinogen,

356 mg/dL. The bleeding had stopped and the operative intervention was completed. During the intervention, after rFVIIa administration, the child received no additional units of PRBCs or FFP and only 4 units of platelets. Postoperatively, the child was transferred to the pediatric intensive care unit where he died 5 days later because of secondary complications of the severe head trauma.

2.2. Case 2

A 78-year-old man (70 kg; 164 cm) with a history of chronic obstructive pulmonary disease, ischemic heart disease, and chronic atrial fibrillation (he had a pacemaker and was being treated with Coumadin) fell at his home and was then admitted to the ED. He was endotracheally intubated and mechanically ventilated, as his GCS score was 7. CAT scan of the brain showed a right-sided, subacute-on-chronic subdural hematoma (SDH) with signs of cerebral herniation. The patient was taken to the OR for emergent evacuation of the SDH. Preoperative laboratory data were as follows: Hb, 12.6 g/dL; platelets, 187 000 cells/ μ L; INR, 6.8; PTT, 63 seconds; fibrinogen, 418 mg/dL; and D-Dimer, 55 ng/mL.

Because of the emergent nature of the process, as the patient was rushed into the OR leaving no time to order, thaw, and infuse FFP, it was decided to infuse the patient with 2.4 mg (34 μ g/kg) of rFVIIa rather than FFP or vitamin K. Fifteen minutes after infusion of the product, repeat preoperative laboratory data were Hb, 12.3 g/dL; platelets, 189 000 cells/ μ L; INR, 1.0; and PTT, 36 seconds. During the operative intervention, the patient showed no signs of bleeding and did not require any blood transfusion. The patient was discharged from hospital several days later in good condition.

2.3. Case 3

A 43-year-old man (80 kg; 175 cm) without previous medical history was admitted to the ED after severe TBI caused by a road accident while riding his bicycle. The emergency medical service endotracheally intubated the patient at the scene, as he had a GCS score of 7. He was transported to ED. CAT scan of the brain showed a right temporal bone fracture, bilateral cerebral contusions, and a small right SDH that, on repeat CAT scan several hours later, had enlarged. Laboratory data available were Hb, 12.3 g/dL; platelets, 181 000 cells/ μ L; INR, 1.1; and PTT, 22 seconds.

In view of the progressive, life-threatening nature of a potential increase of the intracerebral bleed and to prevent transformation of the contusion to a hemorrhagic lesion, the patient was given 6 mg (75 μ g/kg) rFVIIa intravenously. No operative intervention was recommended at this point.

Approximately 24 hours later, the patient showed signs of intracranial hypertension, including a dilated right pupil, increased arterial blood pressure, and bradycardia. An intracranial monitoring device was inserted, showing intra-

cranial pressure (ICP) to be 35 mmHg. While treatment of the elevated ICP was initiated, repeat CAT scan was performed, showing a large cerebral infarction in the region of the left posterior cerebral artery; this finding was confirmed by transcranial Doppler ultrasound. Because conventional, nonsurgical treatment was ineffective, the patient underwent decompressive hemicraniectomy. After 5 days of intensive treatment, the patient remained comatose. He was transported to the neurologic unit for further treatment and rehabilitation. On admission to the neurologic unit, his GCS was 3. A week later, he developed severe gastric bleeding. He died two weeks after the accident.

3. Discussion

Hemorrhagic shock from uncontrolled bleeding is one of the serious problems encountered in the management of trauma patients, and it accounts for approximately 40% of mortality in both military and civilian trauma victims [14,15]. Several reports regarding the use of rFVIIa in trauma and surgery have been published over the past 5 years [1-3].^{1,2} In a series of 9 trauma patients [1], traditional hemostatic measures failed to control life-threatening hemorrhage and, although surgeons predicted inevitable fatal outcomes, 6 (67%) of the patients survived after administration of rFVIIa. Another group of 9 patients who experienced uncontrollable hemorrhage during or shortly after surgery, despite appropriate and conventional therapy, received rFVIIa; 7 (78%) of the 9 patients recovered [2]. A recent double-blinded, randomized, multicenter study of 301 patients who had blunt and penetrating trauma suggests that the use of rFVIIa is very promising in this group of injuries.¹ This multicenter study (31 centers) included 301 trauma patients who were randomized to receive either rFVIIa or placebo. About half of the patients (52%) had blunt injuries. The hemostatic agent was given in three doses: the first (200 μ g/kg) was administered at study entry, and two additional doses (100 μ g/kg each) were given within the next few hours. Among those who survived for at least 48 hours, rFVIIa significantly reduced the need for PRBC transfusions in the group with blunt trauma. The agent also lowered the number of patients who required massive transfusions (>20 units of PRBC), and the difference was significant in the group with blunt trauma (14% vs 33%). A secondary, composite end point was the percentage of patients who died or developed adult

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respiratory distress syndrome or multiorgan failure within 30 days. Among patients with blunt trauma, rFVIIa administration produced a striking decrease in this secondary endpoint (29%, compared with 43% of the placebo cohort). Adverse events occurred with similar frequency among the rFVIIa recipients and the placebo cohort. However, the adverse event rates were higher in the patients with blunt trauma than in those with penetrating injuries.

Brain injury with active or threatening hemorrhage is a special problem, as bleeding may be related to central nervous system damage—secondary to trauma to the brain or elevated ICP—rather than DIC. The problem in head trauma is not one of DIC, but a local (closed compartment) problem, causing increased ICP. Hematoma volume is a critical determinant of mortality and functional outcome after ICH [16,17]. Hematoma growth occurs in 38% of patients with ICH scanned by CT within three hours of onset [18]. Patients with head trauma who are initially talking and then deteriorate into coma, even with an admission CAT scan of the brain read as normal, are found to develop new pathology (including hemorrhage) within the first few days of injury in 33% of cases [19]. More than 60% of these cases develop brain contusion/hematoma or epidural hematoma [20].

Treatment with rFVIIa in escalating doses (40, 80, 160 $\mu\text{g}/\text{kg}$) within 4 hours of the onset of ICH can be effective in limiting the growth of hematoma (to 16%, 14%, and 11%, respectively, vs 29% in the placebo group), reducing mortality and improving functional outcomes at 90 days (to 49%-55% vs 69%) despite a small increase in the frequency of adverse thromboembolic events [10]. Serious thromboembolic events (MI or cerebral infarction) occurred in 7% of rFVIIa-treated patients vs 2% of the placebo group. However, in a small sample (48 subjects) of acute nontraumatic or spontaneous ICH, use of rFVIIa over a wide dosage range resulted in no major safety issues that were of concern to the investigators, although mortality was still a significant 11% [11]. Half of the serious adverse events that occurred and overall caused 11% mortality were considered possibly related to rFVIIa treatment (including rash, vomiting, fever, electrocardiographic changes, and deep vein thrombosis). No myocardial ischemia, consumption coagulopathy, or dose-related increase in cerebral edema occurred [11]. In 81 patients with ICH resulting from traumatic coagulopathy of multiple etiologies, among them 20 patients with TBI, rFVIIa therapy led to an immediate reduction in coagulopathic hemorrhage in most cases and was accompanied by significant improvement in laboratory measures. However, rFVIIa patients had a higher mortality than coagulopathic control patients matched by specific anatomic injuries, admission lactate value, and predicted probability of survival [6].

The indications for treatment with rFVIIa in head trauma are not the same as those for reversal of Coumadin overdose in the case of intracerebral bleeding (case 2). In this case, the purpose of treatment was to reverse the anticoagulant effect,

and the dose was different—less than half of what would have been used to treat ICH [7,8]. In addition, FFP or vitamin K can and should be given for long-term control because the half-life of rFVIIa (2.5 hrs) limits its use and effect. There are only a few reports on the effectiveness of rFVIIa use as additional therapy in central nervous system bleeding emergencies and reversal of INR during Coumadin thromboprophylaxis and due to Coumadin overdose [7-9]. The experimental and clinical data support the recent suggestion that rFVIIa might substitute for FFP or prothrombin complex concentrate. These data suggest and support a prospective study.

The term “preventive” as it appears in this article does not mean “to prevent bleeding”—as we treat hemophilia patients before risky activities. We use the term here to describe prevention of change of contusion to hemorrhagic lesion, and not in the context of direct treatment of bleeding. Another term that may be used in this context is “early use.”

Because the results from controlled trials are lacking, the suggestions of multidisciplinary task forces [21,22] should be considered as guidelines rather than conclusive. These do, however, provide physicians with valuable guidance for using rFVIIa in off-label clinical situations. The recommended indication for rFVIIa is for any patient with massive, uncontrolled hemorrhage who has failed to respond to appropriate surgical measures and blood component therapy [22]. However, in case of an expanding hematoma, the question of broadening the traditional indication to cover a potentially life-threatening complication is a valid one. Unfortunately, there are minimal data in the peer-reviewed literature regarding use of rFVIIa treatment for head trauma [6,23] or other neurosurgical injuries [4].

Individual case reports have shown that rFVIIa may immediately correct coagulopathy associated with severe life-threatening bleeding [3].² Such was the situation described in case 1. In this case, the basic problem was diffuse bleeding from brain tissue. In such a situation, surgical control of bleeding was impossible, and the lack of coagulation control made the patient’s condition life-threatening. We used rFVIIa as a last resort to attempt to save the child’s life. Indeed, our experience has been to use rFVIIa as a “last-ditch” effort for life saving, rather than as the “first line of defense” [1-3].^{1,2} For the past few years, however, we have broadened our indications for the use of rFVIIa, giving it as “preventive,” rather than the “last line of defense,” therapy; this was the situation described in case 2.

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Our case reports do not show hypothermia in any of our patients. However, hypothermia can contribute to coagulopathy and to ineffective FVIIa activity. Recent data indicate an inability of rFVIIa, even at high doses (180 or 720 $\mu\text{g}/\text{kg}$ rFVIIa), to reduce blood loss or to increase survival time or percent survival in hypothermic, coagulopathic pigs with liver injuries [24]. Two previous studies used a similar hypothermic, coagulopathic pig model with severe liver injury [25,26]. In both, there were significant rFVIIa-associated reductions in blood loss but no effects on percent survival or survival time. Such data suggest that with a liver injury involving damage of large blood vessels, hypothermia, or noncorrection of other clotting factors, rFVIIa may be ineffective. In the multidisciplinary task force guidelines and recommendations for the use of rFVIIa in uncontrolled bleeding [22], it is clearly stated that its administration should be considered after blood component therapy had achieved certain levels (fibrinogen level, >50 mg/dL; platelet count, >50000), acidosis treated (pH > 7.1), and body temperature restored to physiologic values as much as possible. Although rFVIIa retains its activity in the presence of hypothermia, and the latter does not limit its use [22], we should be aware that the laboratory tests are conducted at 37°C and may not demonstrate the true measure of coagulopathy in a hypothermic patient.

As might be expected, however, the potential complications of rFVIIa treatment, especially ischemic events, must be weighed in any risk-benefit calculation. A cerebrovascular event may have caused the deterioration in case 3, although this deterioration could have been the result of inevitable cerebral herniation due to the trauma. There is also no proof in this case that the infarction was caused by rFVIIa because, frequently, infarctions are complicating traumatic brain injuries due to increased pressure or local intravascular coagulation. Moreover, the half-life of rFVIIa is 2.5 hours and the infarction should appear close to its administration if it were the cause. By 24 hours, when the clinical deterioration occurs, it is unlikely that even traces of rFVIIa were present.

Similar to other drugs, rFVIIa has adverse effects. Most are rare, but serious adverse effects have been reported, including DIC and thrombotic events such as MI, cerebrovascular thrombosis, and venous thrombosis [4,5,12,13]. The routine use of other procoagulant agents, such as ϵ -aminocaproic acid in trauma, was stopped for similar reasons [27]. A suggestion has been made to minimize and prevent adverse effects of rFVIIa by routine venous Doppler monitoring or even prophylactic inferior vena cava filter placement.

We feel that addressing the cost issue is beyond the scope of this case presentation. Given the high cost of the drug (about US \$7000 per dose), the cost issue should definitely not be ignored, especially if there are other alternatives (ie, clotting factors or platelet administration) and the time to do it. However, cost should never be a primary indication or contraindication, and we tried in this

article to address the issue of broadening the indications for absolute primary, and not relative secondary indications, in cases of active or threat of bleeding in brain injury.

Thus, the physician who wishes to use rFVIIa needs to consider what is known about the drug, including its complication profile, and weigh this against the possible benefits. In addition, given the high cost of the drug, each health institution must determine who will be the "gatekeeper" for drug use: the hematologist, anesthesiologist, or trauma surgeon, and work to devise an algorithm for control of the agent.

4. Comment by Gili Kenet, MD

Recombinant factor VIIa was first approved in Europe in 1996 for the treatment of bleeding episodes and surgical interventions in patients with congenital hemophilia and inhibitors to FVIII or FIX, or acquired hemophilia. From this period until April 2003, more than 700 000 standard doses of rFVIIa have been administered for hemophilia therapy [28]. The European health authorities recently approved the use of rFVIIa for therapy of patients with FVII deficiency and Glanzmann thrombasthenia.

The classic coagulation cascade that was the paradigm for hematologists for many years consisted of the extrinsic pathway, which is activated by FVIIa and tissue factor (TF), and the intrinsic pathway, which is activated by FXII and high molecular weight kininogen. Both pathways joined in a common cascade leading to thrombin formation, which ultimately directs the production of a fibrin clot. The cell-based model of coagulation introduced the importance of the contribution of FVIIa to hemostasis. The mode of action of FVIIa suggests enhancement of hemostasis at the site of injury without activation of the systemic coagulation cascade. After vascular injury, FVIIa binds to exposed TF, and the TF/FVIIa complex, in association with FVa, generates small amounts of FXa and thrombin. Thrombin activates platelets recruited to the site of vascular injury [29,30]. These activated platelets then serve as a template for the binding of factors IXa, VIIIa, Xa, and Va, resulting in the formation of the prothrombinase (Va and Xa) complex on the surface of activated platelets. As a result, larger amounts of thrombin are then generated, also referred to as the "thrombin burst" [31]. As more thrombin is generated, positive feedback loops with factors V, VIII, and XI occur. Shortly after thrombin formation, the cross-linked fibrin clot is formed by thrombin activation of FXIII, protected from degradation via activation of the thrombin-activated fibrinolysis inhibitor. In pharmacologic concentrations (50 nmol/L or higher), rFVIIa can bind to the surface of activated platelets and directly activate FX in the absence of TF [31]. The platelet surface FXa can then, in complex with FVa, lead to a thrombin burst in the absence of FVIII or FIX. Tissue factor and phospholipids remain at the site of injury where inhibitors to the TF-rFVIIa complex (tissue

factor pathway inhibitor and antithrombin) are active [30], thereby minimizing systemic activation of the clotting system [32]. Higher doses of rFVIIa generate a more rapid thrombin burst, which has been shown to produce a more stable fibrin clot, less prone to fibrinolysis [33,34].

The role of rFVIIa as a potential general hemostatic agent and its mechanism of action support the drug's use in patients with impaired thrombin generation due to severe acquired coagulopathy. Recent reports and studies discuss a wide array of bleeding situations (eg, cardiac surgery, liver transplantation, and prostatectomies) successfully treated with off-label rFVIIa, all in individuals without any prior coagulopathy [35-37]. An important subgroup consists of trauma patients who have a combination of acute injury, severe consumptive coagulopathy, and multitransfusion syndrome often accompanied by acidosis, hypothermia, and increased fibrinolysis [38]. The recently published results of the international ICH trial have been encouraging, demonstrating a good safety profile along with reduction of hematoma size and improved neurologic outcome for patients treated within three hours of onset of spontaneous ICH [10,11]. A prospective trial evaluating the safety and efficacy of rFVIIa in TBI is currently under way and the rationale that led the authors toward off-label use of rFVIIa in the cases reported is quite obvious.

However, in the context of the cases discussed above, several considerations should be addressed:

1. Intravenous bolus administration of rFVIIa can rapidly lower the INR, and it appears to be safe for patients with warfarin-related ICH [7]. The early administration of rFVIIa in case 2 created a "hemostatic window" that clearly enabled early surgical SDH evacuation without long-term interference with the patient's anticoagulation, because of the short half-life of rFVIIa [39]. Prospective, controlled studies are needed to determine whether rFVIIa can prevent hematoma expansion and improve neurologic outcomes in patients with warfarin-related ICH or TBI.
2. Last-ditch rFVIIa therapy in patients resistant to conventional treatment may not rescue these patients or significantly alter outcomes [40]. Thus, despite the beneficial effect of rFVIIa on hemostatic control in case 1, the poor outcome might have been inevitable because of the severity of the injury.
3. Safety is certainly a major issue, as shown in case 3. Relatively few adverse events have occurred with the use of rFVIIa within the hemophilia setting, with only a few documented serious adverse events probably related to the product. Nevertheless, we should remember that very limited safety data exist for off-label rFVIIa use. The annual incidence of venous thromboembolism in the United States is 1.07 to 1.17 per 1000, similar to the incidence of cerebrovascular events [41]. The incidence of

thrombosis in the hemophilia population is more difficult to discern and is probably lower than what is reported for the general population [42]. Since the licensing of rFVIIa in 1996, 20 thrombotic events and 5 cases of DIC have been reported [28,43,44]. Most cases occurred in elderly patients with acquired hemophilia and prothrombotic, comorbid risk factors. Hence, precaution regarding rFVIIa use in patients with associated disease states where TF is aberrantly expressed, is advised [28]. Traumatic brain injury is certainly associated with exposure of TF at injury site, and its natural course may be complicated by cerebral thrombosis [45]. The patient in case 3, although young, was treated for TBI with enlargement of contusion despite no evidence for systemic coagulopathy. Whereas, judging from the ICH trial results, such an intervention (if indeed performed very early; no timing for rFVIIa administration postinjury is provided by the authors) may have been justified, it should be noted that the patient presented with substantial shortening of PTT values. Such shortening of PTT may stem from increased levels of plasma contact factors (eg, FVIII and von Willebrand factor). The latter may account for a hypercoagulable state because high levels of von Willebrand factor and FVIII in plasma confer a moderately high risk of arterial and venous thrombosis, respectively [46].

In summary, until TBI trial data are available, one may conclude that the compartmentalized mode of action of rFVIIa, along with its good safety profile and the ICH trial results, provide encouraging data to justify its off-label use in selected TBI patients, especially in the presence of any coagulopathy. Potential hypercoagulable laboratory markers and timing of treatment may affect the outcome and should be considered when assessing the individual risk-benefit profile.

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