Recombinant activated factor VII for cerebral injury–induced coagulopathy in pediatric patients

Report of three cases and review of the literature

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Brain injury remains one of the leading causes of death and disability in children. Appropriate therapy involves aggressive management of intracranial pressure (ICP) and cerebral perfusion pressure, which often requires placement of an intraparenchymal ICP monitor or intraventricular catheter. These potentially life-saving interventions require normal coagulation function; however, several factors may lead to coagulopathy in the head-injured patient. Standard therapies, which often include multiple doses of fresh frozen plasma (FFP), have a number of drawbacks when used in the pediatric population. The use of FFP requires time to type and crossmatch, thaw, and administer. It imposes a significant volume load on a child in whom cerebral edema remains a problem. Success in using recombinant activated factor VII (rFVIIa) in the hemophiliac population suggests an alternative therapy.

Three patients suffered severe coagulopathy after cerebral injury. One patient received rFVIIa after repeated doses of FFP had failed to correct the coagulopathy; the other two patients received rFVIIa as the initial therapy. Treatment with rFVIIa consisted of a bolus of 90 μg/kg. Recombinant activated factor VII rapidly corrected the patients’ coagulopathies, which allowed placement of intraparenchymal fiberoptic lines and intraventricular catheters to monitor ICP. The patients suffered no complication from the placement of ICP monitoring devices, as demonstrated on computerized tomography scans obtained within 24 hours after placement.

Brain injury–induced coagulopathy may lead to significant secondary injury and delays the invasive monitoring necessary for the aggressive management of intracranial hypertension. Fresh frozen plasma takes time to administer, may require repeated doses of significant volume for the pediatric patient, and may ultimately fail. Preliminary data indicated that rFVIIa provides a rapid and successful correction of coagulopathy in the head-injured patient.

KEY WORDS • recombinant activated factor VII • coagulation disorder • pediatric cerebral injury • children

These interventions require normal coagulation function. Coagulopathy in the head-injured patient may result from several factors, including structural damage, hypoxia, and elevation of catecholamine and steroid levels. Coagulopathy may lead to a significant secondary injury by promoting secondary hemorrhage and by preventing the administration of monitor-directed therapy and surgery.

Correction of coagulopathy has traditionally involved the use of FFP and other blood products. Unfortunately, a number of drawbacks accompany this therapy, particularly when it is used in the pediatric population. Time is a factor, and the use of FFP and other blood products requires time to obtain a blood type and crossmatch it, to thaw the FFP, and to administer it. During this time, the patient not only suffers the risk of secondary injury, but the nature of the head injury continues to drive the coagulopathy. Thus, the patient potentially requires multiple doses of FFP to achieve a correction. This involves a significant volume load for a patient in whom cerebral edema remains a danger. Despite these multiple doses, control of coagulation may not be achieved in time to prevent deterioration. Stud-
ies performed in the hemophiliac population suggest another therapy to correct this coagulopathy effectively and rapidly.9,17,25,37

### Results of coagulation studies in patients treated with rFVIIa*

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<th>aPTT (secs)</th>
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<th>INR</th>
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<td>4.4†</td>
<td>53.8†</td>
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</table>

* Normal value ranges for these coagulations are the following: 11.7–14.1 seconds for PT, 0.8–1.2 for INR, and 22.5–36.7 seconds for aPTT.
† After these values were obtained 10 ml/kg FFP and 2 mg vitamin K (intravenous) were administered.
‡ After these values were obtained 15 ml/kg FFP was administered.

### Case Reports

We present a retrospective review of three patients who suffered severe coagulopathy after cerebral injury. The Institutional Review Board of the University of Missouri approved this retrospective review and waived the need for written informed consent. We reviewed blood-bank records and identified patients who had received rFVIIa. These patients were cross referenced with names on the admission log of our pediatric ICU to identify persons with closed head injuries in whom a probe had been placed for ICP monitoring. Computerized tomography scans obtained within 24 hours after placement of the monitors demonstrated no hemorrhage related to catheter insertion.

We identified three patients with closed head injuries who had received rFVIIa. One of them was given rFVIIa after repeated doses of FFP failed to correct the coagulopathy, whereas the other two patients received rFVIIa as the initial therapy. Treatment with rFVIIa consisted of a bolus of 90 μg/kg. We basd this dose on mean doses reported in the literature for successful rFVIIa treatment of CNS hemorrhages.9,17,37

**Case 1**

This 20-month-old infant girl suffered nonaccidental trauma with brain injury. The infant presented to the pediatric ICU unresponsive; her pupils were fixed and dilated and she was experiencing respiratory failure. At presentation her Glasgow Coma Scale score was 3.15,39 She exhibited no brainstem reflexes or motor response to noxious stimuli. Her trachea was intubated and mechanical ventilation was started. The CT scan obtained at admission revealed diffuse bilateral obscuration of the gray–white matter junction, effacement of the third and fourth ventricles and the basilar cisterns, diffuse SAH, an 8-mm-thick subdural hematoma in the left hemisphere, and a left-to-right midline shift of 1 mm. Based on the clinical examination and CT findings, plans were made to place a fiberoptic ICP monitor (MicroSensor; Codman and Shurtleff, Inc., Raynham, MA) to confirm the severity of the patient’s ICP. Initial coagulation parameters revealed a PT of 22.7 seconds (normal range 11.7–14.1 seconds), an INR of 2.7 (normal range 0.8–1.2), and an aPTT of 65.4 seconds (normal range 22.5–36.7 seconds; Table 1). The fibrinogen level was 312 μg/dl (205–461 μg/dl). Two doses of FFP (20 ml/kg) were administered during a 15-minute and a 30-minute period, and repeated coagulation testing revealed a PT of 18.4 seconds, an INR of 2, and an aPTT of 58.3 seconds. After informed consent had been obtained from a parent, rFVIIa (90 μg/kg) was administered as an intravenous bolus. Within 15 minutes, repeated coagulation testing demonstrated a PT of 10.8 seconds, an INR of 0.8, and an aPTT of 33 seconds. A fiberoptic ICP monitor (Codman MicroSensor) placed at that time revealed an initial ICP of 40 mm Hg. The patient’s mean arterial pressure at the time ranged between 40 and 50 mm Hg. Therapy for her intracranial hypertension, which included mannitol and maintenance of CPP at 70 mm Hg by using dopamine, failed to control her ICP. A nuclear medicine cerebral blood flow study confirmed the diagnosis of brain death.

**Case 2**

This 11-year-old boy suffered a traumatic brain injury as a result of a motor vehicle accident. The patient’s initial Glasgow Coma Scale score was 7. His trachea was intubated and mechanical ventilation was initiated. The CT scan obtained at admission revealed diffuse SAH and cerebral edema. Other injuries included a fracture of the left femur and a liver laceration that were deemed stable. The admission neurological examination revealed nonspecific withdrawal of extremities to deep pain and no eye opening, with the pupils equal and reactive initially and no corneal or gag reflexes. The initial coagulation values were as follows: PT 20.2 seconds, INR 2.2, and aPTT 59.2 seconds (Table 1). After the parents gave informed consent, the patient received rFVIIa (90 μg/kg). Fifteen minutes later, repeated coagulation testing revealed a PT of 13.4 seconds, an INR of 1.1, and an aPTT of 33.2 seconds. An intraventricular catheter (Becker EDMS ventricular catheter; Medtronic PS Medical, Inc., Minneapolis, MN) was placed, revealing an ICP of 42 mm Hg. The patient received aggressive therapy for his ICP, which included mannitol, induced hypothermia, maintenance of CPP at 70 mm Hg by using dopamine, and, eventually, pentobarbital-induced coma.39 These therapeutic interventions succeeded in controlling his ICP. He was eventually extubated and transferred to a rehabilitation hospital, where he regained his preinjury state within 3 to 4 months.

**Case 3**

An otherwise healthy 5-week-old neonate displayed increased irritability and crying 5 days before admission. The parents took the patient to a chiropractor who performed manipulation of his spine and fontanel. The boy continued to display increased irritability. On the day before admission to our unit, the parents took him to his pediatrician. According to the parents, the pediatrician noted that their child appeared “a little bit yellow,” but otherwise seemed healthy. The parents declined further examinations. On the day of
admission, the boy had ceased nursing and become less responsive. The parents took him to the emergency department of another hospital, where he was found to be anemic (hemoglobin 6.4 g/dl, hematocrit 18.4%, white blood cells $23.7 \times 10^3/\mu l$, and platelets $782 \times 10^3/\mu l$). The CT scan obtained at that institution demonstrated an SAH in the right hemisphere, acute hydrocephalus, and a right intracerebellar hemorrhage (Fig. 1). At that time, the infant was described as opening his eyes spontaneously. He received an unknown quantity of midazolam for intubation and was transferred to our facility.

On arrival at our pediatric ICU the patient was comatose and displayed no eye opening in response to noxious stimuli. He exhibited extensor posturing with his left upper extremity. The diameter of his right pupil was 3 mm and that of his left was 1 mm; both were nonreactive to light. His corneal reflexes were preserved, and he demonstrated a gag reflex. His anterior fontanel was bulging and tense. He had obvious ecchymosis along his right axillary region. Laboratory studies of coagulation revealed a PT greater than 90 seconds, an INR of 30.5, and an aPTT greater than 150 seconds (Table 1). His parents were not available for informed consent. Based on the CT scan, which demonstrated acute hydrocephalus, and his physical examination, which was consistent with a significantly elevated ICP, the decision was made to give the patient 360 $\mu g$ of rFVIIa (90 $\mu g/kg$) to allow for emergency placement of a ventricular catheter. A repeated test of coagulation performed 15 minutes after administration of rFVIIa revealed a PT of 14.6 seconds, an INR of 1.2, and an aPTT of 53.5 seconds. Placement of the ventricular catheter (Becker EDMS ventricular catheter) occurred without complication and revealed xanthochromic cerebrospinal fluid and an opening pressure greater than 30 cm H$_2$O. After placement of the ventricular catheter, the patient’s pupils became equal and reactive. Within 2 hours he became responsive to noxious stimuli.

As indicated in Table 1, the patient’s coagulopathy subsequently worsened. Repeated coagulation studies performed approximately 7 hours after administration of rFVIIa demonstrated a PT of 29.8 seconds, an INR of 4.4, and an aPTT of 53.8 seconds. The patient had begun a regimen of vitamin K (2 mg intravenously each day) on admission because his medical history revealed that he had been delivered at home with no administration of vitamin K, leading to hemorrhagic disease in the newborn. He received a total of 40 ml/kg of FFP during a 4-hour period, contributing to improvements in coagulation to a PT of 23 seconds, with an INR of 2.8, and an aPTT of 43.7 seconds. The patient had a protracted 2-week course of therapy, but his trachea was eventually extubated and he resumed breast feeding without difficulty. An MR image and an MR angiogram of his head and blood vessels demonstrated no evidence of vascular abnormalities. He was discharged home with close developmental follow up scheduled.

Discussion

Rationale for rFVIIa

In vivo studies of healthy chimpanzees have revealed that high concentrations of rFVIIa (~ 50 $\mu g/kg$) result in accelerated activation of factors IX and X. This effect can be blocked by anti–TF antibody, which demonstrates that rFVIIa acts as an in vivo hemostatic agent through its interaction with endogenous TF. Current evidence demonstrates that the in vivo coagulation system is initiated by the binding of factor VII to TF exposed by injured cells. Tissue factor has been localized by immunostaining on a number of cell surfaces, including those in the nervous system. Binding of TF to factor VII results in the latter’s conversion to FVIIa through cleavage of a peptide bond. The FVIIa–TF complex activates factors IX and X, and activated fac-

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FIG. 1. Case 3. Axial CT scans demonstrating hemorrhage of the right cerebellum, SAH, intraventricular hemorrhage, and acute hydrocephalus. A: Right cerebellar hemorrhage and SAH, with an increase in the size of the temporal horns. B: Ventriculomegaly of the lateral and third ventricles, with intraventricular hemorrhage.
tor X converts prothrombin to thrombin. The FVIIa–TF activation of factor X is initiated by a feedback loop in which thrombin separates factor VIII from von Willebrand factor to activate platelets. Activated factors VIII and IX then bind to platelets and activate more factor X. Tissue-factor pathway inhibitor binds to and inactivates the activated factor X. This complex, in turn, binds to and inactivates the FVIIa–TF complex. In patients suffering from hemophilia, antibodies against coagulation factors develop: factor VIII in cases of hemophilia A and factor IX in cases of hemophilia B. Much effort has been focused on finding an agent that bypasses inhibitors without triggering significant thromboembolic complications. A review of the clinical experiences with rFVIIa in the treatment of patients with hemophilia by using inhibitors established the efficacy of rFVIIa in the majority of patients. The response was considered to be “excellent or effective” in 17 (81%) of 21 patients with major surgical bleeding episodes, 49 (86%) of 57 patients with minor surgical bleeding episodes, and 24 (88%) of 27 patients with CNS bleeding episodes. Subsequent clinical experience has demonstrated the potential efficacy of rFVIIa in the treatment of bleeding disorders stemming from a variety of causes in patients without hemophilia, including those with hepatic insufficiency or failure, dilution coagulopathy from large-volume transfusions, and other conditions such as dicumarol anticoagulant therapy. Recombinant activated factor VII proved effective in a number of studies, including those conducted in patients with CNS hemorrhages, without systemic activation of the coagulation cascade.

Safety of rFVIIa

By 1999 the tolerability database for rFVIIa listed more than 8000 doses that had been given, with 16 serious and 217 minor adverse events reported. Of the 217 minor events reported in 1957 treatments, only 71 (3.6%) were considered possibly or probably related to treatment. These events included hypertension, skin reactions, fever, headache, epistaxis, decreased plasma fibrinogen, and prolonged PT. Only 16 (0.8%) of the reported serious adverse events that occurred in 11 patients were considered “possibly but not necessarily related to treatment.” These included two cases of DIC in patients with predisposing conditions for DIC, such as extensive myonecrosis and infection, angina, and tachycardia in two patients. One was a 54-year-old woman with systemic lupus erythematosus, chronic liver failure, lung disease, diabetes mellitus, and heart disease, whereas the other was a 76-year-old man with a factor XI deficiency. Both recovered and the association of these complications with rFVIIa could be coincidental. The one adverse event involving a patient suffering from head trauma consisted of ataxia, which occurred in a patient with serious intracranial bleeding who was treated with phenytoin. The remaining events consisted of acute renal failure in a patient with renal disease, anaphylactic shock in a patient with thrombocytopenia due to treatment for multiple myeloma and a history of allergic reactions, and two cases of abnormal liver function in patients suffering from DIC and anaphylactic shock. Lusher, et al., suggested that “analysis of each patient’s course suggested that the complications were most probably related to underlying or previously existing conditions and not to rFVIIa.”

Dosage of rFVIIa

The bolus dosage of 90 μg/kg was chosen based on literature detailing in vitro experiments and studies conducted in patients with hemophilia. Based on the in vitro effects on aPTT and studies in dogs, an initial dose of 70 μg/kg was administered to a patient with hemophilia who was undergoing synovectomy. After observing unsatisfactory hemostasis and repeated hemorrhage during surgery, a higher dose of 90 to 100 μg/kg was then recommended. Doses in the range of 90 to 120 μg/kg have become standard. Furthermore, the results of the study by Bernstein, et al., in patients with cirrhosis demonstrated that the degree and length of correction of their coagulopathies depended on the dose of rFVIIa. These authors studied doses of 5, 20, and 80 μg/kg. The mean PT in patients receiving each dose was corrected within 10 minutes, with the values associated with each dose decreasing to within their institution’s normal range, except for the 5 μg/kg dose. These authors obtained subsequent PT results at 30 minutes and at 2, 4, 6, and 12 hours postdosing. The mean values for patients fell within the therapeutic range for up to 2 hours for the 5 μg/kg dose, up to 6 hours for the 20 μg/kg dose, and up to 12 hours for the 80 μg/kg dose. The range of values for PT in patients receiving the 80 μg/kg dose decreased to entirely within the therapeutic range up to 6 hours postdosing.

Coagulation Disorders in Cerebral Injury

Coagulopathy is a common complication of cerebral damage, and findings in clinical series suggest that the degree of coagulopathy correlates with the severity of the cerebral injury. Although frequently seen as a consequence of trauma, coagulopathy may result from nontraumatic lesions of the brain. The three patients described in this paper suffered significant cerebral injuries, the first two from trauma and the last from a nontraumatic cause that was possibly exacerbated by chiropractic manipulation. Coagulopathy increases the risk of secondary injury by contributing to the development of recurrent and secondary hemorrhages and by preventing the placement of monitoring devices to direct treatment of increased ICP. Its presence further limits, if not prohibits, potentially life-saving surgical interventions.

Therapy for coagulopathy currently centers on FFP, which has a number of drawbacks when used in the pediatric patient. Fresh frozen plasma requires time to type and crossmatch, to thaw and administer. Management of coagulopathy may require multiple doses of FFP, which impose a significant volume load on a child in whom cerebral edema may develop. During this time, the patient cannot receive interventions such as placement of ICP monitors, ventriculostomies, and surgery.

Cost of rFVIIa

One criticism regarding rFVIIa is its cost. Recombinant activated factor VII is currently available in 1.2-, 2.4-, and 4.8-mg vials at a cost of approximately $800 per mg. The time to reconstitute and make rFVIIa available for use is approximately 15 minutes. In comparison, at our institution FFP and cryoprecipitate cost $161 and $266 per unit, respectively. Each coagulation panel used to assess PT, aPTT, and INR costs $133. For the patient in Case 1 who received
Cerebral injury–induced coagulopathy and rFVIIa

FFP before rFVIIa, the cost of two sets of coagulation panels and two doses of FFP added up to approximately $600 without any therapeutic reduction in coagulation values. Each additional dose of FFP and subsequent coagulation panel would have added approximately $200 to the cost of treatment, along with the time necessary to thaw and deliver the FFP to the patient and obtain new results. The patient in Case 3 demonstrated severe coagulopathy with acute hydrocephalus. Treatment with FFP required repeated doses. Five coagulation panels and three treatments of FFP cost $665 and $483, respectively, for a total cost of $1148, without adequate control of the coagulopathy. The 360 μg of rFVIIa that the patient received required the use of one 1.2-mg vial at a cost of $960. The cost of the single dose of rFVIIa that rapidly corrected his coagulopathy and allowed invasive monitoring critical to his treatment compared very favorably to the cost of the previous unsuccessful standard therapies used in that case.

Conclusions

Pediatric patients may experience clinically significant coagulopathy as a result of cerebral damage. Although it is most commonly reported in cases of trauma, coagulopathy may result from any lesion that damages cerebral tissue. In our series, the patients in Cases 1 and 2 suffered cerebral injury due to trauma, whereas the patient in Case 3 suffered a nontraumatic insult. All three children required invasive monitoring to direct the management of increased ICP. Two of the patients (Cases 2 and 3) required ventriculostomies for immediate relief of increased ICP.

Treatment of coagulopathy in patients with cerebral damage has traditionally involved the use of FFP and cryoprecipitate. Although these therapies are effective, both require time and potentially repeated doses before adequate correction is achieved. In the case of FFP, a repeated dose places a significant volume load on a pediatric patient. Results of clinical studies in patients with hemophilia have suggested that rFVIIa may provide a rapid and effective therapy without a significant risk of complications. We present three pediatric cases in which clinically significant coagulopathy prevented monitoring and treatment of increased ICP. In Case 1, two doses of FFP failed to mitigate the patient’s coagulopathy. Given the urgency and severity of the underlying conditions and coagulopathies in these patients, they were given rFVIIa. In all three cases, treatment with rFVIIa corrected the coagulopathy. The clinical experience in the hemophilic population has revealed rFVIIa to be a very safe therapy. None of our patients demonstrated a side effect related to treatment with rFVIIa.

With regard to cost, physicians must consider both the severity of the coagulopathy and the urgency of correction. Patients who require surgery or emergency placement of ICP monitors and intraventricular catheters may not be able to wait for multiple doses of FFP and cryoprecipitate. Repeated doses of FFP and cryoprecipitate and subsequent coagulation panels incur costs that can equal, if not surpass, that of a dose of rFVIIa. In Case 1 two doses of FFP failed to manage the patient’s coagulopathy. In Cases 2 and 3 the patients required emergency intervention. Recombinant activated factor VII provided immediate correction of coagulopathy in these two cases, allowing placement of intraventricular catheters to help manage increased ICP. Nevertheless, because rFVIIa only replaces factor VII, FFP and/or cryoprecipitate may still be required in addition to rFVIIa when deficiencies in multiple factors exist.

Disclaimer

None of the authors has any financial interest in rFVIIa.

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