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USE OF RECOMBINANT ACTIVATED FACTOR VIIa IN A SIX-MONTH-OLD CHILD DUE TO MASSIVE HEMORRHAGE DURING ELECTIVE SURGERY FOR CHOROID PLEXUS CARCINOMA: CASE REPORT

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SUMMARY – We present the use of recombinant activated factor VIIa (rFVIIa) in a 6-month-old infant that suffered massive bleeding and subsequent coagulation disturbances during elective surgery for choroid plexus carcinoma in the lateral ventricle. The administration of rFVIIa resulted in good hemostasis. No intra- or postoperative thromboembolic complications were observed.

Key words: *Choroid plexus carcinoma – surgery; Surgical procedures, operative – complications; Hemorrhage; Supratentorial neoplasms – surgery; Recombinant FVIIa; Child; Case reports*

Introduction

Choroid plexus carcinomas (CPC) are rare malignant intraventricular tumors, primarily of young age, derived from choroid plexus epithelium in the lateral ventricles, followed by the fourth and third ventricles[1-3]. Usually, they are large at presentation with a high tendency to dissemination (45%) along the cerebrospinal fluid (CSF), which leads to poor prognosis. It is also related to the level of mitotic activity of tumor cells, degree of brain invasion by neoplastic cells, necrosis, and if there is relapse after primary treatment. Survival depends on the degree of surgical resection and absence of disseminated disease[1-4]. The 5-year survival rate is 58% after complete resection *versus* 20% after partial resection[5].

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Episodes of massive diffuse bleeding during intracranial surgery potentially deteriorate patient prognosis and outcome. Resection of richly vascularized brain tumors may be accompanied by excessive blood loss and therefore by extensive transfusions of blood and blood products and infusion of other fluids, which may result in volume overload and brain swelling[6,7].

Coagulation disturbances during the operation are due to dilution of coagulation factors secondary to massive hemodilution, consumption coagulopathy, hypothermia and metabolic acidosis. They usually result in coagulation disorders followed by diffuse bleeding. Conventional treatment of massive bleeding includes administration of red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate or fibrinogen, and platelet concentrates. However, large volumes of intravenous fluids can lead to exacerbation of coagulopathy[7].

In case of injury, tissue factor is brought into contact with naturally occurring activated factor VIIa (FVIIa), normally present in minute quantities, to initiate the coagulation pathway by forming a complex with

factor X, and subsequently causes localized increase in the generation of thrombin. In the cell-based models, it was shown that recombinant activated factor VIIa, in pharmacological, supra-physiological doses, is able to bind to activated platelets at the site of injury in the absence of tissue factor and activate factors IX and X directly, leading to a thrombin burst with development of a stable fibrin-impregnated plug. Since the action of recombinant factor VIIa (rFVIIa) is limited to the site of injury and to the exposed tissue factor, the risk of systemic activation of coagulation system is almost unlikely[8-11].

Indication for the use of rFVIIa has been approved for hemophilic patients with acquired coagulation factor inhibitors; also, consensus recommendations for off-label use of rFVIIa therapy in adults have been published, including neurosurgical patients[8,12-14]. rFVIIa was used in non-hemophilic children[9,15]. No randomized controlled trials are currently available to determine how to best use rFVIIa in non-hemophilic children. Concerning non-hemophilic neurosurgical pediatric patients, administration of rFVIIa has been reported in children after cerebral injury, with only four reports (twelve cases in children) on brain tumor resection. However, there are no reports on the administration of rFVIIa in a child younger than 1 year with intractable hemorrhage during choroid plexus carcinoma resection[6,7,16-18].

Case Report

A 6-month-old girl, weight 6830 g, was presented to the neurosurgeon with a history of somnolence, eating problems, drowsiness and vomiting. She was highly hypotonic, slowly responsive and reactive. At neurological examination, the child was sleepy, with convergent strabismus bilaterally, initial paresis of the left abducens nerve, positive meningeal signs, tense large fontanel, and signs of raised intracranial pressure. Computer tomography (CT) scan showed a tumor in the rear horn of the right side ventricle with hydrocephalus. Magnetic resonance imaging (MRI) revealed a 4.5x4.5 cm large tumor in the right lateral ventricle that invaded the subependymal area, without spinal canal involvement. Four days later, the child was scheduled for elective operation. Hematologic parameters before the procedure were as follows: hemoglobin 10.4 g dL^{-1} (normal 12-16) and platelet count $317x10^9$ cells L^{-1} (140-340). On the ward, the child was premedicated with midazolam 2 mg orally and one peripheral intravenous line was inserted on the left hand. In the theater, she received phenobarbitone 50 mg, fentanyl 10 μg and vecuronium 1 mg intravenously (i.v.) for induction and she was intubated with orotracheal tube no. 4, without cuff. Another peripheral intravenous line in the left foot, arterial line in the left radial artery for invasive measurement of blood pressure and urine catheter no. 6 were inserted. Before the operation, a prophylactic dose of cefazolin 350 mg i.v. was administered. The patient's body temperature was maintained with heating pads and heating fluid. Body temperature was measured. The patient was ventilated with oxygen/air mixture (FiO_2 0.40) and anesthesia was maintained with sevoflurane, boluses of fentanyl 10 μg, according to vital signs. Osteoplastic trepanation was performed on the right parieto-occipital site, without local anesthetic infiltration. The tumor had risen from the choroid plexus of the right side ventricle; it was well perfused and adherent to the brain, infiltrating it in part. During the procedure, massive hemorrhage developed, blood loss was assessed to be about 800 mL. In total, 1020 mL packed RBCs, 200 mL FFP, 260 mL platelets and 10 mL of 20% albumins were administered. Also, 800 mL crystalloids and 180 mL colloids were infused. This resulted in the following laboratory parameters: hemoglobin 11.4 g dL^{-1}; platelet count $132x10^9$ cells L^{-1}; international normalized ratio (INR) 1.25; activated partial thromboplastin time (APTT) 45.5 s (normal 25.9-36.6); partial thromboplastin time (PTT) 22.4 s (14-21); fibrinogen concentration 1.95 g L^{-1} (1.8-3.5); antithrombin III (ATIII) 0.58 (0.8-1.2); and D-dimer concentration 517 μg L^{-1} (≤500). Since diffuse bleeding and oozing persisted (normothermia and pH >7.3 was maintained), 120 μg kg^{-1} of rFVIIa (rFVIIa; NovoSeven, Novo Nordisk Pharmaceutical, Inc., Princeton, NJ, USA) was administered. Ten minutes after rFVIIa administration, the bleeding stopped. Soon after rFVIIa administration, hemostatic parameters were as follows: hemoglobin 17.3 g dL^{-1}; platelet count $157x10^9$ cells L^{-1}; APTT 31.6 s; PTT 23.5 s; fibrinogen concentration 2.22 g L^{-1}; and ATIII 0.77. At the end of the operation, external ventricular drainage was inserted. After the procedure of 400-min duration,

the child was admitted to the Intensive Care Unit. On admission, she was hemodynamically stable. Short neurological investigation revealed both pupils equal and reactive, with no tension of the large fontanel. The child remained sedated and on ventilatory support. Anti-edematous therapy was introduced. Next morning (16 hours after rFVIIa application), hemostasis parameters were monitored (hemoglobin 16.9 g dL^{-1}; platelet count $161x10^9$ cells l^{-1}; INR 1; APTT 38.3 s; PTT 26.6 s; fibrinogen concentration 3.1 g l^{-1}; and ATIII 0.87). Follow up CT scan showed a 1-cm large hyperdense change in the upper posterior part of the right ventricle, which seemed as a possible residue of the tumor, with no shift of the brain structure or diffuse edema. After sedation was discontinued, the child was awakened, breathing spontaneously, was circulatory stable, with no signs of lateralization. She was extubated and moved to the ward. External ventricular drainage was removed. In due course, the patient needed internal ventricular drainage because of the development of hydrocephalus; also, additional dura seams were needed. Convergent strabismus and initial abducens nerve paresis persisted, otherwise she was lively, with good appetite and unaffected after the procedure. Approximately three weeks after the operation, the patient was discharged. Histopathology confirmed the diagnosis of CPC. Because of the possible tumor residue following incompletely resected CPC, the child was later treated with chemotherapy[1,2,4,5,19].

Discussion

The goal of treatment of CPC is gross total resection that is generally believed to be the major prognostic factor, followed by adjuvant treatment. Complete resection of CPC is rarely achieved (36%-57%) due to difficulties related to the large size of the tumor in infants with small blood volumes, extremely vascularized lesions with a tendency to hemorrhage, and propensity to invade the adjacent brain parenchyma[1,2,4]. Younger patients, especially infants, present an increased risk *versus* their older counterparts of massive bleeding resulting in hemodynamic instability and coagulation impairment[20]. Reasons for the development of hemorrhage in brain tumor surgery could be hypertension, coagulopathy, excessive CSF drainage, and intraoperative mechanical brain shifting. Also, characteristics of the tumor, vascularization of the tumor and size of the tumor bed may themselves contribute to hemorrhage. Systemic coagulopathy may be induced by tumor resection[6,7].

Choroid plexus carcinoma is a very rare pathology in small children and CPC surgery is not a routine procedure in our hospital. Each patient is individually managed. However, Haliasos *et al*. report that using the protocol of preoperative embolization of CPC in children resulted in a high gross total resection rate and reduced perioperative blood loss[21,22].

When blood component replacement therapy is used, dilutional coagulopathy can occur; it is related to thrombocytopenia or dilution of coagulation factors. To correct hemostasis, large volumes of FFP and platelet concentrate are infused in addition to large quantities of crystalloids, colloids and RBCs, which may result in pulmonary and brain edema from overfilling, especially in children. With these treatments, the possibility of infectious disease transmission, anaphylactoid reaction, and alteration in serum calcium exists. The possible complications, such as multiple organ failure and acute respiratory distress syndrome, may result in increased mortality and morbidity[7,23].

Recombinant FVIIa was approved in Europe in 1996 for use in hemophilia A and B patients with inhibitors to FVIII and FIX. It has also been used to treat other coagulopathies and causes of intractable bleeding in non-hemophilic patients[8,12,24,25]. The advantages of rFVII include fast onset of action of 10 to 20 minutes and moderate duration of its effect (>6 hours)[8-11]. The half-life values for adults varied from 2.4 to 3.2 hours with bolus administration of rFVIIa, compared with 1.3 hours in children[26]. rFVIIa has a short half-life, shorter in children less than 15 years of age (1.3 h) as compared to adults (2.7 h). The clearance is faster in pediatric patients (67 mL/kg *per* hour) as compared to adults (33 mL/kg *per* hour)[27].

In children with hemophilia and adults with high-level bleeding (cirrhotic patients undergoing orthotopic liver transplantation) and patients with congenital FVII deficiency, plasma clearance is relatively higher (60-90 mL kg^{-1} h^{-1}) than in healthy volunteers and patients with no or low-level bleeding (adults with hemophilia, non-bleeding patients with cirrhosis) (30-40 mL kg^{-1} h^{-1})[28]. There is no risk of transfusion-transmissible infections, and no effect

from circulating inhibitors, but there is still the risk of adverse thrombotic events, such as acute myocardial infarction, pulmonary embolism, and disseminated intravascular coagulation[8,9,26]. In our case, bleeding stopped in about 10 minutes after 120 μg kg^{-1} rFVIIa administration and no thromboembolic complication appeared. In our patient, the tumor was well vascularized, it was adherent to and partly infiltrating the brain. Since surgical resection of the tumor was not radical, it was followed by chemotherapy[19].

In massive bleeding, defined as the loss of 1 blood volume in 24 hours, or in greater loss of blood volume, such as loss of 50% blood volume in less than 3 hours, administration of blood products would precede the administration of rFVIIa. Hypothermia, severe acidosis, low hematocrit values, and hypocalcemia should be corrected and open blood vessels surgically closed. Reduction of rFVIIa effectiveness in adults is associated with profound acidosis and low levels of platelets and fibrinogen. rFVIIa may be helpful to induce coagulation in the areas of diffuse bleeding and oozing. It is maximally effective when platelet count is more than 50,000x10^9 L^{-1}; fibrinogen concentration 0.5 to 1.0 g L^{-1}; pH ≥7.2; and hematocrit >24%. The recommended doses for surgical bleeding are between 80 and 120 μg kg^{-1} [8,29,30].

Herbertson and Kenet reviewed Internet data on rFVIIa use in 265 non-hemophilic children younger than 16 years. The median dose of rFVIIa administered was 78.4 μg/kg. Therapeutic areas included surgery, coagulopathy, spontaneous bleeding, trauma, and intracranial hemorrhage. Two patients experienced thromboembolic events following administration of rFVIIa and 39 patients died due to hemorrhage or complications related to their underlying condition, none of them related to rFVIIa administration. Bleeding stopped in 50%, markedly decreased in 23%, decreased in 21%, remained unchanged in 6%, and increased in 0.4% of cases[15].

Reiter *et al*. reviewed 46 cases in which the indications for use of rFVIIa in children were bleeding due to general surgery, hepatic failure, gastrointestinal bleeding, severe traumatic brain injury, bone marrow transplantation, cardiac, acetaminophen overdose, and multiorgan system failure. Reduction in the coagulation markers (PTT, APTT and INR) was observed without obvious adverse thrombotic events. They identified two types of patients that may benefit from this therapy: a child with profound acidosis and anemia due to bleeding, and a child with catastrophic brain injury and in whom withdrawal of life support is likely[9].

Recombinant FVIIa was also administered in children with severe bleeding due to open liver biopsy of hepatoblastoma, to prevent bleeding in orthotopic liver transplantation, in patients with large liver laceration after blunt abdominal trauma, and in children with severe coagulopathy and nonsurgical bleeding after liver graft reperfusion. No thrombotic complications were observed[31-34].

In pediatric cardiothoracic surgery, rFVIIa was successfully used postoperatively in patients on extracorporeal membrane oxygenation and also prophylactically in infants undergoing cardiopulmonary bypass surgery for congenital heart disease. There were no thrombotic complications associated with its prophylactic use, but it could lead to major thrombotic complications in patients bleeding from multiple sites or having pre-existing clots in the extracorporeal membrane oxygenation circuit[35-44].

The use of rFVIIa in premature babies with ruptured umbilical artery and for the treatment of massive liver fracture during surgery for resection of a large sacrococcygeal teratoma has also been reported[45,46].

In two patients undergoing scoliosis correction, rFVIIa was used to treat bleeding as a consequence of dilutional coagulopathy. Tobias succeeded to control bleeding due to dilutional coagulopathy using a 90 μg kg^{-1} dose of rFVIIa in two children undergoing posterior spinal fusion when FFP failed to correct coagulopathy[47-50].

Regarding neurosurgical procedures, Park *et al*. report a series of nine patients with coagulopathy requiring urgent neurosurgical intervention; they received a moderated dose of rFVIIa before undergoing surgery. Coagulopathy was due to medications, liver dysfunction, and posttraumatic hemorrhage. Surgery was performed without procedural complications[26]. rFVIIa 90 μg kg^{-1} was also used in 12 patients suffering life-threatening acute head injuries and no systemic coagulopathy, either to prevent the expected development of brain contusion or to assist in bleeding control during surgery. Two patients died, one from severe vertebrobasilar vasospasm 2 days after rFVII

administration, likely to be related to traumatic subarachnoid hemorrhage[51]. rFVIIa limited the progression of hematoma and improved the outcome of patients with spontaneous intracerebral hemorrhage[52]. In patients with coagulopathy requiring urgent neurosurgical intervention, rFVIIa was infused in a dose of 40 to 90 μg kg^{-1} before the procedure. Coagulation parameters obtained as early as 20 minutes after the infusion of the medication showed normalization of the values[26].

Four children, less than 12 kg weight, received rFVIIa 100 μg/kg because of head injury, after the operation of craniosynostosis, during reconstruction of skull due to Pfeiffer syndrome, and during surgery for brain tumor of the third ventricle. No thrombotic complications were observed[16]. rFVIIa 90 μg/kg was also administered in three children with head injury and coagulopathy prior to the intracranial pressure electrode insertion[17].

After the application of 100 to 120 μg kg^{-1} dose of rFVIIa during tumor resection in two children with massive blood loss (27.5 liters and 5 liters), Hartmann *et al*. report improvement in coagulation within 10 to 15 minutes. On postoperative day 1, in one child vasospasm occurred that led to mass cerebral infarction of both ventricles and death, possibly related to a high dose of rFVIIa (240 μg kg^{-1} within 30 min)[6]. The administration of rFVIIa at a dose of 90 μg kg^{-1} successfully controlled hemorrhage in a 10-year-old girl operated on for a brain tumor. Although hemorrhage was massive, coagulation parameters were only slightly disturbed, as also reported by Hartmann *et al*.[6]. In our patient as well, coagulation parameters did not differ much from the baseline values soon after rFVIIa administration and 16 hours later.

Conclusion

The use of rFVIIa in non-hemophilic children is still off-label. In case of massive diffuse bleeding during intracranial surgery, large volume of fluid and blood component replacement can result in brain and pulmonary edema, thus worsening prognosis. The administration of coagulation concentrates, such as rFVIIa, could be therapy of choice in such cases.

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Sažetak

PRIMJENA REKOMBINIRANOG AKTIVIRANOG FAKTORA VIIa U ŠESTOMJESEČNOG DJETETA ZBOG OPSEŽNOG KRVARENJA TIJEKOM ELEKTIVNE OPERACIJE KARCINOMA KOROIDNOG SPLETA: PRIKAZ SLUČAJA

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U radu prikazujemo primjenu rekombiniranog aktiviranog faktora VIIa (rFVIIa) u šestomjesečnog djeteta koje je pretrpjelo opsežno krvarenje s posljedičnim poremećajem zgrušavanja tijekom elektivne operacije karcinoma koroidnog spleta lateralne moždane komore. Primjena rFVIIa rezultirala je dobrom kontrolom zgrušavanja. Tijekom operacije i u poslijeoperacijskom tijeku nisu primijećene tromboembolijske komplikacije.

Ključne riječi: *Koroidni pleksus – kirurgija; Kirurški postupci, operativni – komplikacije; Supratentorijalni tumori; Krvarenje; rekombinantni FVIIa; Dijete; Prikazi slučaja*