The use of recombinant factor VIIa in a pediatric septic shock patient with disseminated intravascular coagulation

Utilização do fator recombinante VIIa em paciente pediátrico com choque séptico e coagulação intravascular disseminada

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ABSTRACT
This is a report on a pediatric patient with septic shock and disseminated intravascular coagulation, who developed life-threatening bleeding which was successfully treated with recombinant factor VIIa.

Keywords: Shock, septic; Disseminated intravascular coagulation; Intensive care unit; Factor VIIa; Child; Case reports

RESUMO
Relata-se o caso de uma paciente pediátrica que apresentou choque séptico e coagulação intravascular disseminada, desenvolveu sangramento grave e foi tratada com sucesso com fator recombinante VIIa.

Descritores: Choque séptico; Coagulação intravascular disseminada; Unidade de terapia intensiva; Fator VIIa; Criança; Relatos de casos

INTRODUCTION
Various etiologic factors may be responsible for coagulation disturbances in children, including: congenital deficiencies; hepatic insufficiency; disseminated intravascular coagulation (DIC) from sepsis, shock, or closed head injury; dilution of coagulation factors after cardiopulmonary bypass or large-volume transfusions; and medications. Treatment includes reversal or elimination of the inciting event and when clinically significant bleeding occurs, correction of coagulation function with the administration of blood products, including cryoprecipitate, fresh frozen plasma (FFP), and platelet concentrates⁴.

Recombinant activated factor VII (rFVIIa), which are Novoseven® and Novo Nordisk® (Bagsvaerd, Denmark), has been approved for treatment of patients with congenital hemophilia and inhibitors of factor VIII or IX, as well as for patients with acquired hemophilia. However, rFVIIa is also likely to provide hemostasis in other situations of profuse bleeding and impaired thrombin generation. It enhances thrombin generation at sites of vascular injury, by forming tissue factor VIIa complex and thereby activating factor X to Xa, as well as by providing Xa on the surface of already activated platelets⁵.

Despite its efficacy, there are some problems with the use of FFP, including the potential for the transmission of infectious diseases, volume overload, anaphylactoid reactions, and alterations in serum ionized calcium level⁶. In addition, the time required for thawing and administration may require 30 to 60 minutes, depending on the patient’s cardiorespiratory status and ability to tolerate rapid fluid administration. Concerns regarding FFP are further magnified by the report of Cote et al. about cardiac arrest and severe hypotensive episodes with the administration of FFP⁷. Such disturbances of cardiovascular function may be especially detrimental and poorly tolerated in the critically ill pediatric patient. In addition, in selected cases, despite the administration of significant volumes of FFP, coagulation disturbances may persist.

Most of the experience with rFVIIa comes from treatment of patients with hemophilia, who developed auto-antibodies against factor VIII and IX, making infusions of factor VIII ineffective during bleeding episodes⁸.

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We report here a seven-year-old girl with abdominal distension, fever and jaundice, with thoracoabdominal life-threatening bleeding after surgery.

CASE REPORT

A seven-year-old girl was brought to our pediatric intensive care unit (PICU) one month after a car accident, presenting multiple bruises on her overlying skin, left arm fracture and thoracoabdominal trauma (left hemothorax and spleen laceration). Two laparotomies were performed, one for a partial splenectomy and the second for surgical cleaning of the abdominal cavity.

On admission to the PICU, she presented fever, jaundice, abdominal distension and tachypnea, and went into shock, acute renal and respiratory failure due to abdominal sepsis. The patient was stabilized by the sixth day after admission, when she developed another acute abdominal distension, nausea and vomiting, and her overall condition deteriorated. She had a low platelet count and leukopenia. A computed tomography scan of the thorax and abdomen showed bilateral pleural effusion, periporal swelling and an important amount of intra-abdominal fluid. The girl was submitted to another laparotomy, and during the procedure started to bleed. So, she was given fresh frozen plasma, platelets and packed red blood cells. After fluid resuscitation and inotropic support was initiated, she returned to the PICU hemodynamically unstable, developing DIC with thoracoabdominal bleeding. The hemoglobin value was: 5.7 g/dl, platelet count: 12,000 mm$^3$, and lactate: 39 mmol/l. It was given rFVIIa, after appropriate hemostatic management without recovery. Eight hours later, the coagulation measurements improved and transfusion requirements declined considerably. No adverse effects associated with rFVIIa were observed.

DISCUSSION

In the operating room and intensive care unit, effective treatment of severe or uncontrolled bleeding is a challenge for physicians, since even aggressive conventional therapy may ultimately fail in some patients. Administration of rFVIIa may be the only remaining therapeutic option to stop a life-threatening coagulopathic bleeding. It was described here the clinical course of a pediatric patient exhibiting severe continuous bleeding, which could not be stopped by appropriate conventional hemostatic management, but was resolved after administration of rFVIIa.

Recombinant activated factor VII forms a complex with expressed tissue factor that markedly increases thrombin formation. This thrombin burst allows for the formation of fibrin, which forms a more stable clot. Besides, rFVIIa binds directly to the surface of activated platelets, in a tissue factor-independent manner, and induces a sufficient thrombin burst for cleavage of fibrinogen and hemostasis. Factor VIIa is so effective at inducing thrombus formation that the presence of platelets is not an absolute requirement for its hemostatic effect, as evidenced by multiple case reports of rFVIIa use in patients with severe thrombocytopenia or inherited platelet function defects.

The use in trauma patients suffering uncontrolled hemorrhage appears to be rationale. Martinowitz et al. described seven massively bleeding, multitransfused, coagulopathic trauma patients who were treated with rFVIIa after failure of conventional measures to achieve hemostasis. They concluded that in trauma patients rFVIIa may play a role as an adjunctive hemostatic measure.

Recombinant activated factor VII was given to children with acute bleeding resulting from liver failure and DIC. Two of them were diagnosed with dengue hemorrhagic fever and prolonged shock, and a boy had undergone left lobe hepatectomy due to hepatoblastoma, in which 60% of his liver was removed. All three patients exhibited active bleeding and rFVIIa combined with replacement of other blood components, showing some efficacy in controlling the acute bleeding.

Tobias et al. retrospectively, reviewed the records of pediatric patients who received rFVIIa in the intensive care unit or operating room for treatment of coagulopathy. Ten patients, in age ranges from three months to 19 years, received 22 doses of rFVIIa. Before the administration of rFVIIa, seven of the ten patients had received fresh frozen plasma and cryoprecipitate. After rVIIa administration, there were significant decreases in prothrombin time, international normalized ratio, and partial thromboplastin time. No adverse effects were noted. They concluded that rFVIIa can be used to effectively reverse coagulation disturbances in the pediatric patient, even when treatment with fresh frozen plasma has failed.

In a recent experimental report, Lynn et al. tested the hypothesis that administration of rFVIIa early after injury may decrease bleeding and improve survival after experimental hepatic trauma. Significantly shorter prothrombin time and higher mean arterial pressures were observed in the rFVIIa group. The authors concluded that intravenous administration of rFVIIa early after induction of hemorrhage shortens prothrombin time and improves mean arterial pressure.

Our patient with life-threatening bleeding illustrates many important features of the recent advances in the treatment of bleeding. The conventional treatment including administration of platelets and fresh frozen...
plasma was ineffective, and her bleeding was only controlled by using rFVIIa.

CONCLUSION
In patients with life-threatening bleeding, which is unresponsive to other treatment measures, rFVIIa may be life-saving.

REFERENCES