Perioperative management of a patient with purpura fulminans syndrome due to protein C deficiency

[La démarche anesthésique périopératoire adoptée chez une patiente atteinte du syndrome de purpura fulminans causé par un déficit en protéine C]

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Purpose: Protein C is a vitamin K-dependent anticoagulant and homozygous protein C deficiency is a rare fatal thrombotic disease. This report describes the perioperative management of homozygous protein C deficiency in a patient who underwent a total of three surgical procedures under general anesthesia and the successful use of activated protein C concentrate.

Clinical features: A female baby, who developed disseminated intravascular coagulation and purpura fulminans shortly after birth, was diagnosed as purpura fulminans syndrome due to homozygous protein C deficiency. At one month of age, she suffered bilateral retinal detachment and glaucoma due to retinal hemorrhage. After marked improvement of her condition after administration of activated protein C concentrate, she underwent a left iridectomy and implantation of a Broviak catheter under general anesthesia. Her intraoperative course was uncomplicated but, on postoperative day four, she presented another episode of massive cutaneous necrosis and gangrene. Activated protein C concentrate was administered again, with good results. She underwent replacement of a Broviak catheter at four months of age, and right iridectomy for glaucoma at eight months. Both were uneventful.

Conclusion: The perioperative management of homozygous protein C deficiency and purpura fulminans requires appropriate measures for thromboembolic prophylaxis. Sufficient *iv* fluid administration is necessary. Attention should be paid to decrease the risk of tissue compression such as that associated with positioning, blood pressure cuff, and endotracheal intubation, which may cause necrosis over pressure points. Replacement therapy with activated protein C concentrate appears safe and effective. The anesthetic management is reviewed and discussed.

Objectif : La protéine C est un anticoagulant dont la synthèse dépend de la vitamine K. Un déficit homozygote en protéine C est une maladie thrombotique fatale rare. Le présent article décrit la démarche périopératoire adoptée chez une patiente qui présente un déficit homozygote en protéine C et qui doit subir trois interventions chirurgicales sous anesthésie générale. Nous faisons également état de l'utilisation réussie de concentré activé de protéine C.

Éléments cliniques : On a diagnostiqué un syndrome de purpura fulminans causé par un déficit homozygote en protéine C chez une nouveau-née qui présentait une coagulation intravasculaire disséminée et un purpura fulminans peu après la naissance. À un mois, elle a souffert d'un décollement de la rétine bilatéral et de glaucome causés par une hémorragie rétinienne. Son état s'est nettement amélioré après l'administration de concentré activé de protéine C et elle a subi une iridectomie gauche et l'implantation d'un cathéter Broviak sous anesthésie générale. L'opération s'est déroulée sans incident, mais le quatrième jour après, elle a présenté un autre épisode de nécrose cutanée massive et de gangrène. On a de nouveau administré un concentré activé de protéine C, ce qui a été bénéfique. Le cathéter Broviak a été remplacé à l'âge de quatre mois et une iridectomie droite pour glaucome a été réalisée à huit mois. Aucun incident n'est survenu.

Conclusion : Le traitement périopératoire d'un déficit homozygote en protéine C et d'un purpura fulminans nécessite une prophylaxie thromboembolique appropriée. L'administration *iv* suffisante de liquide est nécessaire. Il faut surtout veiller à diminuer le risque de compression tissulaire comme celle de la mise en position, celle du brassard du tensiomètre et de l'intubation endotrachéale pouvant causer une nécrose des zones soumises à la compression. Le remplissage vasculaire avec un concentré activé de protéine C se révèle sûr et efficace. La démarche anesthésique est revue et discutée.

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PROTEIN C is a vitamin-K dependent plasma glycoprotein which, when activated, exerts its anticoagulant effect by inactivating activated factor V and activated factor VII and promotes fibrinolysis by neutralizing a plasminogen activator inhibitor (Figure 1). In homozygous protein C deficiency, purpura fulminans syndrome may occur shortly after birth, resulting in life-threatening neonatal thrombosis. We report the perioperative management and successful use of activated protein C concentrate in a patient with congenital protein C deficiency.

Case report

The patient was a female baby, born at 37 weeks and one day of gestation, after a normal delivery (birth weight, 2430 g). Her Apgar score was 9 at one and 10 at five minutes respectively. At 15 hr of life, she presented ecchymosis and hemorrhagic bullae which culminated in gangrene on her buttock and inguinal region. She was transferred to our hospital. Laboratory values on admission are given in the Table.

Disseminated intravascular coagulation (DIC) was diagnosed and treated with human anti-thrombin III, gabexate mesilate, fresh-frozen plasma (FFP) and platelet concentrates. Although the infant's condition improved at first, a new purpuric lesion developed on the right arm at seven days of age. Further tests revealed that the protein C activity of the infant was 3% (normal range 80–130%) with a protein C antigen activity <5% (normal range 80–130%). The protein C activities of both of parents were 44% with protein C antigen activities of 41%. The diagnosis of purpura fulminans syndrome due to homozygous protein C deficiency was

made on the patient's ninth day of life. In addition to treatment with FFP and warfarin potassium, administration of activated protein C concentrate, affinity-purified from human plasma, (Teijin Co .Ltd., Osaka, Japan and the Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) was initiated on the 11th day of life after informed consent was obtained from the parents. An infusion of 600 U·kg⁻¹·day⁻¹ of activated protein C concentrate for six days followed a bolus injection of 100 U·kg⁻¹. After initiation of activated protein C concentrate therapy, the cutaneous manifestations of purpura fulminans stopped. However, bilateral retinal detachment and glaucoma due to retinal hemorrhage was diagnosed. At 43 days of age, she presented new ecchymosis on her precordia and left thigh and new petechial hemorrhage on her face. At the same time, left intraocular pressure was increased. Therefore left iridectomy for glaucoma and implantation of an indwelling Broviak catheter through the right jugular vein were planned under general anesthesia, after a bolus injection of 100 U·kg⁻¹ of activated protein C concentrate and an infusion of 600 U·kg⁻¹·day⁻¹ for three days and of 900 U·kg⁻¹·day⁻¹ for three days. The treatment with warfarin potassium was continued until the day before the operation.

The infant was not premedicated. Thiamylal and vecuronium bromide were used for a rapid sequence induction of anesthesia. Endotracheal intubation was achieved easily with a 3.0-mm tube. We selected a small endotracheal tube to decrease the risk of tracheal compression, and there was an air leak at a pressure of 10 cmH₂O. Gauze was put into laryngopharynx to create a seal around the endotracheal tube. Anesthesia was maintained with nitrous oxide, oxygen and 1%–2% sevoflu-

FIGURE 1 The site of action of protein C.

FIGURE 2 Administration of exogenous activated protein C increased activated protein C plasma concentration and was accompanied by an increase in platelet count and a decrease in D-dimer concentration. See text for details.

rane. The intraoperative course was uneventful. At the end of the procedure, residual neuromuscular block was reversed with neostigmine and atropine, and the trachea was extubated. The treatment with warfarin potassium was reintroduced on the second postoperative day. Yet, another purpuric lesion developed on the right foot on the fourth postoperative day. She was treated with FFP and activated protein C concentrate. On the first day of treatment, an infusion of $800 \text{ U}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ of activated protein C concentrate followed a bolus injection of $100 \text{ U}\cdot\text{kg}^{-1}$. From day two to day six, $900 \text{ U}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ of activated protein C concentrate were infused continuously. After the treatment, she experienced an immediate improvement in clinical symptoms with disappearance of skin erythema and the plasma concentration of activated protein C was increased from $1.6 \text{ ng}\cdot\text{mL}^{-1}$ to $118.2 \text{ ng}\cdot\text{mL}^{-1}$ (Figure 2).

She was treated with warfarin potassium and FFP postoperatively, and her condition remained stable. At four months, she weighed 5.4 kg and underwent

replacement of an indwelling Broviak catheter via the left jugular vein. No premedication was administered. After rapid induction of anesthesia with thiamylal and vecuronium bromide, the trachea was intubated with a 3.5-mm tube, with an air leak at a pressure of $10 \text{ cmH}_2\text{O}$. Anesthesia was maintained with 50%–100% oxygen and 1%–2.5% sevoflurane. The intraoperative and postoperative courses were uneventful.

At eight months, she weighed 6.9 kg and underwent right iridectomy for glaucoma. Her general condition was stable. Again, no premedication was given, and thiamylal and vecuronium bromide were used for rapid induction of anesthesia. The trachea was intubated with a 3.5-mm tube, with an air leak at a pressure of $7 \text{ cmH}_2\text{O}$. Anesthesia was maintained with 50%–100% oxygen and 2%–3.5% sevoflurane. The intraoperative and postoperative courses were uneventful.

No postoperative complications and no adverse effects related to the use of activated protein C concentrate were noted.

TABLE Laboratory findings on admission

	Patient's result	Normal range
Platelets	$58 \times 10^3 \mu\text{l}^{-1}$	$150 \times 10^3 - 350 \times 10^3 \mu\text{l}^{-1}$
Activated partial thromboplastin time	75.3 sec	30.0 - 40.0 sec
Fibrinogen	810 mg·dl ⁻¹	200 - 400 mg·dl ⁻¹
Antithrombin III	31%	80 - 120%
Fibrinogen degradation products	108 $\mu\text{g}\cdot\text{mL}^{-1}$	<10 $\mu\text{g}\cdot\text{mL}^{-1}$
α_2 - plasmin inhibitor	33%	80 - 120%

Discussion

This is one of the first reports of the perioperative management of a patient with purpura fulminans syndrome due to protein C deficiency with activated protein C concentrate.

Protein C is the central protein in a major antithrombotic regulatory system of hemostasis, the protein C pathway.¹⁻⁵ Protein C is a vitamin K-dependent glycoprotein circulating in plasma as an inactive zymogen. This zymogen is activated on the endothelium of the cell wall by a complex of thrombin and the endothelial thrombin receptor thrombomodulin. Activated protein C exerts its anticoagulant effects by inactivating activated factor V and activated factor VII, and it facilitates fibrinolysis by neutralizing a circulating inhibitor of tissue-type plasminogen activator. In the large vessels most of the thrombin is free and therefore catalyses clotting. In the microcirculation, most of the thrombin is bound to thrombomodulin, clotting activity is depressed, and protein C activation is enhanced. Therefore protein C activation probably occurs primarily in the microcirculation.⁶

Congenital protein C deficiency, which is inherited as an autosomal-dominant trait, predisposes to venous thrombotic disease.^{2,4} Patients with heterozygous protein C deficiency are at risk for superficial thrombophlebitis, deep venous thrombosis and pulmonary embolism, which may occur without apparent cause at a young age.^{7,8} Patients with homozygous protein C deficiency present shortly after birth with life-threatening neonatal thrombosis, hemorrhagic necrosis due to vascular thrombosis, retinal hemorrhage and purpura fulminans. The site of mutation in this patient was found recently.⁹

Purpura fulminans defines an acute, often lethal syndrome of DIC with rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis.^{10,11} Pathological specimens in purpura fulminans reveal microvascular thrombosis involving the dermis with perivascular hemorrhage. Clinically,

skin lesions are characterized by a progression from ecchymotic areas to circumscribed lesions of purplish-black skin containing hemorrhagic bullae, eventually culminating in gangrene.

A precautionous atraumatic anesthetic technique is indispensable. To decrease the risk of tissue compression, attention should be paid to intraoperative positioning and possible pressure points such as the blood pressure cuff. A water bed would have been useful but was not available in our institute. In addition, intravascular volume should be expanded adequately to avoid dehydration, which increase the risk of thromboembolism.

We have found only one report of the anesthetic management of purpura fulminans due to homozygous protein C deficiency.¹² In line with that report we selected a small endotracheal tube to decrease the risk of tracheal compression, submucosal thrombosis, and necrosis. A seal with gauze between the endotracheal tube and laryngopharyngeal mucosa minimized the risk of aspiration and provided adequate oxygenation and ventilation.

Previously reported treatments such as FFP, prothrombin-complex concentrates, or oral anticoagulants, have many disadvantages.¹⁰ Administration of FFP can lead to hyperproteinemia, fluid overload and hypertension, and carries an increased risk of infection. The use of prothrombin-complex concentrates is controversial.^{13,14} Vitamin K antagonist therapy carries the risk of breakthrough bleeding. Casella *et al.* reported the successful treatment by orthotopic hepatic transplantation,¹⁵ but the long-term benefits and complications are unknown. Recently the availability of monoclonal antibody purified protein C concentrates allows specific replacement of protein C, avoiding the above-mentioned problems.¹⁶⁻²⁰

We used activated protein C concentrate preoperatively and postoperatively in the first operation for treatment of thrombosis and thromboembolic prophylaxis with, apparently, good results. To our knowledge, this patient is the first case of purpura fulminans treated with activated protein C concentrate and the effective dosage of activated protein C concentrate has not been determined. In view of the disadvantages of previously reported therapies, we suggest that the perioperative use of activated protein C concentrate is a safe and effective treatment for infants with severe homozygous protein C deficiency.

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