Case Report

Management Considerations for a Heterozygous Protein C Deficient Patient Undergoing Open Heart Surgery with Cardiopulmonary Bypass

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ABSTRACT

The protein C system is an important antithrombotic pathway that regulates the coagulation system by inactivating procoagulant factors Va and VIIIa and enhancing clot lysis by inhibiting the activity of plasminogen activator inhibitor. Protein C deficiency, therefore, is a hypercoaguable state characterized by increased risk of thromboembolic events such as stroke, pulmonary embolism, and venous thrombosis. Extra caution would be warranted in patients with protein C deficiency who undergo cardiopulmonary bypass and are naturally predisposed to hypercoaguability. To our knowledge, however, the management considerations of a patient with protein C deficiency undergoing cardiopulmonary bypass have not been published. This case report presents a pediatric patient with heterozygous protein C deficiency and a prior history of venous thrombosis after open heart surgery who underwent repeat open heart surgery with cardiopulmonary bypass. Initiation of anticoagulation therapy upon admission to reduce procoagulant levels, the use of plasma replacement therapy to increase protein C levels prior to cardiopulmonary bypass, and the careful reinstatement of anticoagulation therapy once postoperative bleeding is controlled, are preliminary suggestions to decrease the risk of thrombotic events in this unusual patient population.

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INTRODUCTION

The protein C system has recently been established as an important regulatory mechanism of the coagulation cascade (1-4). Protein C, like Antithrombin III (AT III) is a naturally occurring anticoagulant that preserves blood fluidity and limits clot formation to the sites of vascular injury. Comparisons of PC and AT III are shown in Table 1.

The protein C system is activated upon the production of thrombin. Thrombin generation not only promotes clot formation by cleaving fibrinogen into fibrin, but also activates the protein C system, which subsequently suppresses further thrombin generation and enhances fibrinolytic potential (Figure 1).

The physiological significance of the protein C system becomes manifest in the observations of patients who are deficient in protein C. These protein C deficient patients exhibit a high potential for hypercoagualation and thromboembolic complications (5). Protein C levels have been shown to decrease beyond the typical dilution effect during cardiopulmonary bypass (CPB) despite heparinization, suggesting that the protein C system is activated and consumed during CPB (6-8). In the clinical setting of protein C deficiency, fatal massive cerebral venous thrombosis has been reported following open heart surgery with CPB (9). This indicates that consumption of protein C in an already deficient patient may produce catastrophic thromboembolic events.

The management considerations of patients with protein C deficiency undergoing CPB, to our knowledge, has never been published. This report presents a case of a pediatric patient with heterozygous protein C deficiency (with a prior history of venous thrombosis after open heart surgery) undergoing CPB for a revision of a pulmonary conduit.

CASE HISTORY

A 10 year old, 27 kg male with Tetralogy of Fallot (TOF) was admitted to Duke Children's Hospital with severe pulmonary insufficiency. Prior medical history included a Blalock-Taussig shunt at 4 months of age with no apparent postoperative complications. At $2^1/_2$ years of age, an elective cardiac catheterization was complicated by a lack of pulses, coolness, and cyanosis of the right lower leg and foot. The initial clinical impression was that of an arterial vasospasm, but, for the possibility of thrombus, the patient was started on heparin. Heparin was discontinued 14 hours later when pulses, though weak, improved. A complete correction of TOF was performed at 3 years of age and complicated on the 12th post-operative day by the development of a large right atrial thrombus necessitating emergent surgery and removal of the thrombus through the right atrium. This unusual complication prompted an evaluation of the child's coagulation system. A protein C deficiency, measured at 32% (normal 70-140%), was identified and confirmed one month later measuring 44%. Familial studies showed the father's protein C level to be normal (119%) indicating a heterozygous protein C deficiency in the child.

CASE MANAGEMENT

At 10 years of age, the patient was admitted with severe pulmonary insufficiency and a residual ventricular septal defect (VSD). The planned surgical intervention was VSD closure and pulmonary valve replacement. Because the patient had protein C deficiency, he was electively anticoagulated preoperatively to reduce the risk of thrombosis. On the evening of admission, the patient was placed on a continuous heparin drip (11 - 21 U/kg/hr) to maintain the activated partial thromboplastin time (aPTT) at approximately 1.5 to 2.0 times the baseline value.

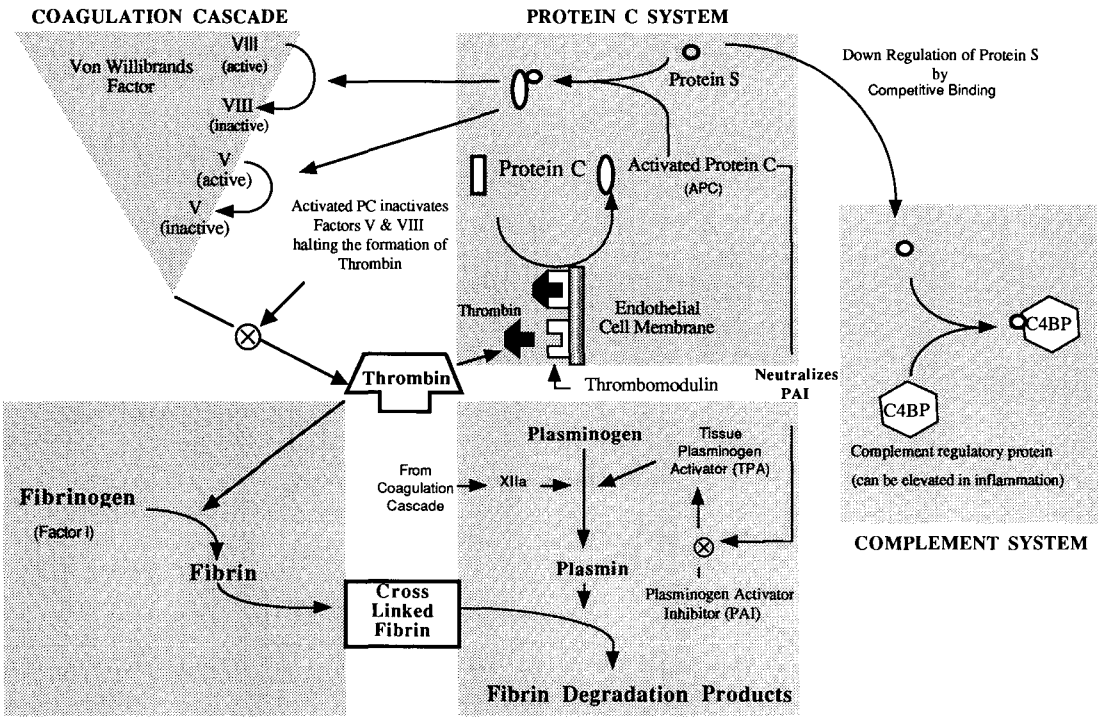
Immediately prior to initiation of CPB, the patient was fully anticoagulated with 400 U/kg porcine mucosal heparin and one unit of fresh frozen plasma (FFP) was administered to help normalize protein C levels. When the activated clotting time (ACT) was greater than 400 seconds, CPB was initiated, and the patient was cooled to 28° Celsius. The aorta was cross clamped

Table 1: Comparison of AT III and Protein C

	Protein C	AT III
Plasma Protein	zymogen	$alpha_2$-globulin
Molecular Weight	62,000 Daltons	65,000 Daltons
Synthesis Site	liver	liver
Normal Plasma Levels concentration activity	 2.7-5 µg/ml 70-140%	 22-39 mg/dl 80-120%
Half Life	≈ 8 hours	2.8 ± 0.3 days
Physiological Action	serine protease inactivator of factors Va and VIIIa, also inhibits plasminogen activator inhibitor	inhibition of thrombin, cofactor of heparin efficacy, inhibition of serine proteases
Deficiency prevalence (general pop.) long term therapy short term therapy	 0.1%-0.5% vitamin-K antagonist FFP or protein C concentrates	 0.2%-0.4% vitamin-K antagonist FFP or AT III concentrates
ACT's response to heparin in deficiency	unaffected	greatly reduced

and antegrade cold blood cardioplegia (4:1) was administered. The repair included a primary closure of the small residual VSD, insertion of a 23 mm St. Jude[a] pulmonary valve, and enlargement of the right ventricular outflow tract with a Gore-Tex[b] patch. After adequate rewarming, the patient was weaned from CPB in normal sinus rhythm and on 5 μg/kg/min of dopamine. The total cross clamp time was 45 minutes and time on CPB was 83 minutes. Heparin was carefully reversed, the chest was closed and the patient was transferred to the acute care unit.

Figure 1: The Protein C System. Activation of the blood clotting cascade results in the formation of thrombin. Thrombin functions as a procoagulant by catalyzing the conversion of fibrin to fibrinogen. Thrombin also stimulates the protein C system by binding to thrombomodulin (an endothelial cell surface membrane protein). The Thrombo-thrombomodulin complex converts protein C to activated protein C. Activated protein C interacts with protein S to form a complex which rapidly inactivates factor V and factor VIII. Activated protein C also exerts a profibrinolytic effect by neutralizing plasminogen activator inhibitor. The protein C system can be inhibited by inflammatory mediators by the binding of protein S with the complement regulatory protein, C4BP.



Sixteen hours after CPB was terminated, bleeding was under control and heparin therapy was again started to keep the aPTT at approximately 1.5 to 2.0 times baseline value. Oral warfarin therapy was started 48 hours postoperatively. The prothrombin time (PT) was prolonged to approximately 1.5 times normal on postoperative day five, at which time heparin was discontinued. The patient was discharged on the seventh postoperative day on oral warfarin, with plans for six months of postoperative oral anticoagulation to decrease the odds of a thrombotic event in the distant postoperative period. No coagulation problems were identified during or after this admission.

DISCUSSION

Protein C is a vitamin K-dependent plasma glycoprotein synthesized by the liver. Protein C becomes activated upon contact with the thrombin-thrombomodulin complex formed on endothelial surfaces. Activated protein C is a key factor in the anticoagulant system which inhibits the coagulation cascade by inactivating Factors Va and VIIIa, and enhancing fibrinolysis. In individuals with protein C deficiency, down regulation of thrombin formation is impaired and fibrinolysis is reduced. The result is a hypercoaguable state which can result in venous thrombosis. Homozygous protein C deficiency is an inherited disorder which may result in massive fatal venous thrombosis in the neonatal period (10). A protein C level below 55% (normal 70-140%) is consistent with heterozygous protein C deficiency which has been associated with an increased risk of venous thrombosis, pulmonary embolism, and stroke (5,11,12). In the general population, the prevalence of heterozygous protein C deficiency is 0.1% to 0.5%. Approximately 50% of the heterozygotes belonging to families with a history of symptomatic thrombosis can be expected to have thrombotic complications (2).

The influence of CPB on the protein C system has been studied in normal patient populations, and has demonstrated a reduction of circulating protein C and protein S levels (6-8). This CPB effect is considered to reflect activation and consumption of the protein C system which leads to enhanced fibrinolytic activity (see Figure 1). This enhancement of the fibrinolytic pathway by activated protein C during CPB is thought to play a protective role in the maintenance of the microcirculation, as there is

a St. Jude Medical, Inc., St. Paul, MN 55117
b W.L. Gore & Associates, Inc., Flagstaff, AZ 86003-2200

evidence that thrombin activity and some fibrin formation continue during bypass despite heparinization (8,13). The reduced activation of plasminogen by tissue plasminogen activator occurs predominately at sites where fibrin is formed, which may result in the dissolution of microthrombi formed during CPB (14).

In patients with a protein C deficiency, the effects of CPB on the coagulation/anticoagulation systems are not well understood. One can predict that there would be less enhancement of fibrinolytic activity during CPB than that of a patient with normal protein C levels. Furthermore, regulation of coagulation after CPB may be impaired and rapid neutralization of heparin could result in a hypercoaguable state. Protein C deficiency has been associated with massive cerebral thrombosis following CPB (9). Clearly, the management of hemostasis in this patient population must be carefully evaluated.

Current treatment of protein C deficient patients includes administration of a vitamin-K antagonist, FFP, or protein C concentrate. The use of a vitamin-K antagonist, such as warfarin, is the long term method of choice for prevention of thrombotic events in protein C deficient patients (15). While it is true that protein C is a vitamin-K dependent, the use of a vitamin-K antagonist is recommended to reduce procoagulant factors that help regulate hemostasis. Replacement therapy using FFP or protein C concentrates is another method of treatment for protein C deficient patients. Marlar et al. have reported that the concentration of protein C in FFP is 87 ± 15 U/dL and that, as a general rule, 2 units of protein C per kilogram of body weight will give a 1% rise in the plasma concentration of protein C (16). The concentration of protein C in protein C concentrates varies greatly among the different commercial products and even from lot to lot within the same commercial product. The half-life of protein C is approximately 8 hours (16); therefore, long term use of FFP or protein C concentrate may not be an alternative.

Aggressive new approaches to circumvent severe bleeding complications after reoperations involving CPB include perioperative use of aprotinin and epsilon-aminocaproic acid (EACA). Utilization of these agents in patients with hypercoaguable disorders must be carefully debated and consultation with a hematology service is recommended. Aprotinin is a serine protease and kallikrein inhibitor that inhibits fibrinolysis and preserves platelet function (17). Use of aprotinin during CPB has been shown to decrease postoperative bleeding (18). Boldt et al. recently studied normal children for the effect of aprotinin on the thrombomodulin/protein C system during CPB. They demonstrated that when compared with controls, aprotinin did not alter protein C or protein S concentrations (19). Though there are no data on the effects of aprotinin on the protein C deficient patient, it has been shown that aprotinin competitively inhibits activated protein C in a dose dependent manner (20). This aprotinin effect could further decrease activated protein C activity in an already deficient patient, heightening the hypercoaguable state during and after CPB. We suggest that aprotinin should not be administered without prior normalization of protein C levels with FFP or protein C concentrate. EACA is an antifibrinolylic agent that has been shown to decrease postoperative bleeding (21,22). There are no data on the effects of EACA on the protein C deficient patient. However, with replacement therapy and normalization of protein C levels, we believe EACA could be considered in this patient population.

CONCLUSION

Protein C deficient patients who are elective candidates for cardiac surgery and CPB should be anticoagulated with a heparin drip to prolong the aPTT to 1.5 to 2.0 times the baseline value upon admission to the hospital. In cases where an increased risk of bleeding is suspected, the perioperative use of agents such as aprotinin and EACA could be discussed with a hematology service. Immediately prior to CPB, a sufficient amount of FFP should be administered to raise protein C levels into normal ranges and the ACT should be elevated above 400 seconds and maintained at that level with heparin until the patient is weaned from CPB. This strategy of using FFP to increase levels of a deficient factor is utilized in patients with AT III deficiency undergoing CPB (23). Heparin should be carefully reversed. When postoperative bleeding is under control, heparin therapy can once again be started to keep the aPTT at 1.5 to 2.0 times the baseline value. Oral warfarin should be initiated and the PT prolonged to 1.5 times normal at which time the heparin should be discontinued. The duration of warfarin therapy should be discussed with a hematology service.

Further studies of the role of CPB and hypercoaguable states are needed to evaluate the effects of CPB on patients with a protein C deficiency so that a more definitive management strategy can be instituted in this unusual patient population.

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