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CASE REPORT

Case Report

Perioperative Use of Protein C Concentrate for Protein C Deficiency in THA

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Abstract

Background Perioperative management of patients with heterozygous protein C deficiency is challenging because of the competing risks of bleeding and recurrent thrombosis.

Case Description We report the case of a 74-year-old man with protein C deficiency and heterozygous prothrombin G20210A gene mutation who had a successful left THA with perioperative administration of human zymogen protein C concentrate in addition to anticoagulation with enoxaparin.

Literature Review Several studies have reported the use of protein C concentrate in severe sepsis-associated purpura fulminans in patients with severe congenital protein C deficiency who have had thrombotic events. We reviewed studies and case reports pertinent to the treatment of patients with protein C deficiency, especially in the perioperative setting. We report the case of a patient undergoing THA in whom we used human zymogen protein C concentrate.

Purposes and Clinical Relevance THA, a particularly high-risk procedure, is associated with a 40% to 70% incidence of venographic deep venous thrombosis and a 2% to 3% incidence of symptomatic deep venous thrombosis. These risks are greater in people with thrombophilic defects such as protein C deficiency. The use of human zymogen protein C in our patient with heterozygous protein C deficiency during the perioperative period of a THA was associated with no evidence of excessive bleeding, hematoma, deep venous thrombosis, or pulmonary embolism.

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Each author certifies that his or her institution approved or waived approval for the reporting of this case, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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Introduction

The risks of deep venous thrombosis (DVT) and pulmonary embolism (PE) are influenced by environmental thrombotic risk factors, such as major surgery. THA is a particularly high-risk procedure and is associated with a 40% to 70% incidence of venographic DVT and a 2% to 3% incidence of symptomatic DVT without and with prophylaxis, respectively [8, 30, 31]. These risks are magnified in patients with underlying thrombophilic defects, such as protein C deficiency and the prothrombin gene mutation [24], particularly in patients with previous thrombotic events. For the purpose of our case report, protein C deficiency refers to the heterozygous type if "homozygous" is not stated directly.

Protein C deficiency, first described in 1981 [11], has been associated with an increased risk of venous [1, 15] and arterial [19] thromboembolic disease. This autosomal-dominant disorder [3] has an estimated prevalence in the

general population of 1.45 to 5 per 1000 [20, 27]. Homozygous protein C deficiency is much rarer and is associated with the life-threatening thrombotic disorder, neonatal purpura fulminans [14]. Protein C deficiency also can be acquired during disseminated intravascular coagulation, sepsis (especially meningococcal sepsis with purpura fulminans), liver failure, and vitamin K deficiency [14].

Protein C, an endogenous vitamin K-dependent antithrombotic plasma protein that circulates as a zymogen, is converted to an active form on the endothelial surface by a complex of thrombin and thrombomodulin. This interaction is coordinated and accelerated 20-fold by the endothelial protein C receptor protein [7]. Activated protein C (APC), in conjunction with its cofactor protein S, functions as an endogenous antithrombotic protein by proteolytic degradation of the essential procoagulant cofactor proteins, factors Va and VIIIa, thereby downregulating the coagulation cascade. APC also promotes fibrinolysis by inhibiting thrombin generation and competing with thrombin-activatable fibrinolysis inhibitor for activation by the thrombin-thrombomodulin complex [7, 11].

The prothrombin G20210A gene mutation, first discovered in 1996 [22], is a more commonly inherited thrombophilic mutation. It is present in 2% of Caucasians and associated with a twofold to threefold increased risk of DVT and PE [7]. This mutation results in thrombosis because of its positive effect on prothrombin mRNA translation and protein levels [7].

We describe the case of a 74-year-old man with a history of idiopathic PE, protein C deficiency, and heterozygous prothrombin 20210 gene mutation who had a successful THA with the use of perioperative human zymogen protein C concentrate.

Case Report

A 74-year-old man presented with bilateral degenerative joint disease of the hips. After 6 months of nonoperative therapy, the patient had worsening pain and gait and elected to proceed with THA. His preoperative medical history was notable for protein C deficiency (protein C activity level, 46%), which had been diagnosed 27 years previously during family studies conducted when his son sustained an idiopathic PE. The patient was asymptomatic until he was 65 years old, when DVT and bilateral PE developed. Subsequently, DNA analysis showed he was heterozygous for the prothrombin 20210 gene mutation. He had been prescribed indefinite warfarin therapy targeted to an international normalized ratio (INR) range of 2 to 3 and had not experienced any additional episodes of DVT or PE. Several family members also had been diagnosed with protein C deficiency and had symptomatic DVT and PE: father, brother, and two of three sons (protein C activity levels of 48%, 38%, 48%, and 50%, respectively).

In preparation for surgery, the patient's warfarin was discontinued 5 days previously, and the next day, he was started on enoxaparin sodium (Lovenox®; Sanofi-Aventis US LLC, Bridgewater, NJ; 1 mg/kg twice daily until 24 hours before the procedure). To minimize the time without anticoagulation, the patient was admitted to the hospital the afternoon before surgery and started on intravenous unfractionated heparin adjusted to an activated partial thromboplastin time ratio of 1.5 to 2.5 times control. The night before surgery and before administration of protein C concentrate, the patient's protein C activity level was 46% (normal, 72%–142%) and his INR was 1.0 with a prothrombin time of 10.7 seconds. After discontinuation of his unfractionated heparin infusion, he was given 120 IU zymogen protein C concentrate (human) (Ceprotin®; Baxter International, Inc, Deerfield, IL) per kg intravenously preoperatively. During the first 24 hours on the day of surgery, the patient received 60 IU protein C per kg every 6 hours. His morning protein C activity level immediately before surgery was 163%, and his preoperative hematocrit was 44.2% (normal, 41%–53%).

He underwent an uncemented left THA via a two-incision approach by the operating surgeon. Throughout the procedure, there was more direct bone bleeding than normal, and a deep drain was placed before incision closure. Estimated blood loss was 1800 mL, and 2500 mL of intravenous fluids and two units of autologous packed erythrocytes were administered. The postoperative hematocrit was 40.2%.

On Postoperative Day 1, the patient received 60 IU protein C concentrate per kg every 8 hours for 24 hours; with time, his protein C activity level increased to 235% (target, 80%–100%). However, there was no increased bleeding from the surgical sites or a wound hematoma, and his hematocrit was 37.1%. On Postoperative Day 2, while receiving 60 IU protein C concentrate per kg every 12 hours, his protein C activity level decreased to 158%, still slightly above the top normal value. Warfarin (7 mg by mouth daily) was started on the evening after the surgery. Enoxaparin (30-mg subcutaneous injections every 12 hours) was started 12 hours after surgery and continued until a DVT was detected on Postoperative Day 3 (Fig. 1).

The patient had left lower extremity pain develop around the posterolateral aspect of his knee on Postoperative Day 3. A lower extremity duplex screening revealed a nonocclusive deep vein thrombus in one of the paired left peroneal veins. Whether this thrombus was old or new was not known because preoperative venous duplex screening had not been performed. There was no evidence of direct extension of the thrombus into the left popliteal vein or the

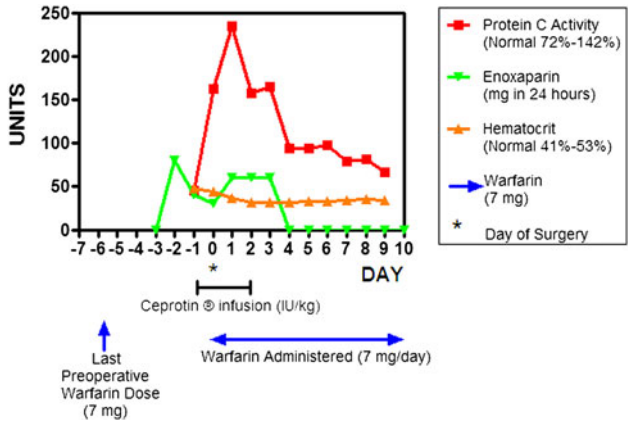

Fig. 1 A graph shows the trend of Ceprotin® doses and the patient's protein C activity levels, anticoagulant doses, and hematocrit during the perioperative period. Supraphysiologic levels of protein C were observed between the day of surgery and Postoperative Day 3.

left superficial femoral vein. Incidentally, however, a retrovalvular thrombus was noted in the left proximal profunda femoris vein. Based on the patient's risk factors and venous duplex findings, intravenous unfractionated heparin was initiated to intensify his anticoagulant regimen. We chose unfractionated heparin over therapeutic low-molecular-weight heparin because of unfractionated heparin's shorter half-life and greater degree of protamine reversibility, distinct advantages for this postoperative patient.

Postoperatively, daily laboratory studies were obtained to evaluate protein C activity levels and coagulation parameters. The patient's hematocrit decreased (lowest value, 31.8%) until Postoperative Day 4, after which it gradually increased; at discharge, it was 34.7%. Physical therapy was begun on Postoperative Day 1, and the patient was allowed to weightbear as tolerated on his left lower extremity. By Postoperative Day 9, the patient had a therapeutic INR (2.0), so unfractionated heparin was discontinued. His protein C activity at that point was 67%. Because he could walk with assistive devices, he was discharged on warfarin (7 mg daily by mouth) and was directed to continue with outpatient physical therapy. He had an uneventful recovery with no wound hematoma or infection.

At the 1-year followup, the patient reported no pain; he had a mild limp each time he began walking, but the limp disappeared within a few strides and he had resumed his active lifestyle (eg, playing competitive tennis). His hip ROM was pain-free. The hip radiographs showed class III heterotopic bone [4] and a well-positioned, well-aligned, and apparently ingrown uncemented THA. The patient was informed data concerning the case would be submitted for publication, and he consented.

Discussion

We report a case of perioperative use of zymogen protein C concentrate (human) in a patient undergoing THA. Protein C concentrate has been used previously with promising results and apparent safety in patients with severe sepsis-associated purpura fulminans [23, 25, 26, 29] and in conjunction with conventional anticoagulation for patients with severe congenital protein C deficiency who have had thrombotic events [6, 13]. Protein C use also has been reported to prevent vascular thrombosis in a patient with familial protein C deficiency undergoing renal transplantation [28]. Ceprotin® has an excellent safety profile: no reported medication interactions, overdose, blood-borne infections, bleeding, or prothrombotic complications [6, 9, 14, 23, 25, 26]. Given our patient's personal and family history of idiopathic PE, the presence of two thrombophilic mutations, and the substantial thrombotic and bleeding risks posed by THA [21], we decided the off-label use of protein C concentrate represented the most efficacious approach. We believe the favorable results obtained establish it as an attractive treatment strategy for patients who are highly thrombophilic with protein C deficiency who require major surgery associated with substantial risks of bleeding and thrombosis.

There were several other possible approaches to our patient's perioperative treatment. For example, we could have used APC concentrate (Xigris®; Eli Lilly and Co, Indianapolis, IN), which has been used extensively to treat patients with severe sepsis [5, 17] and patients with congenital protein C deficiency [18]. Our patient did not have sepsis; therefore, the endothelial activation of zymogen protein C was expected to be normal, making the infusion and subsequent activation of zymogen protein C a more physiologic and safe process with respect to bleeding risks. Although APC concentrate has been used in conjunction with anticoagulation [16, 17], patients receiving high-risk pharmacologic prophylaxis (eg, enoxaparin 30 mg subcutaneously every 12 hours) or therapeutic anticoagulation have been excluded from randomized clinical trials of Xigris® because of concerns regarding excessive bleeding complications [2, 10].

Alternatively, we could have used fresh-frozen plasma as a protein C source and introduced therapeutic anticoagulation soon after surgery. This approach, however, is limited by the large volumes required to provide adequate protein C (protein C concentration in fresh-frozen plasma is only 0.85 units/mL), its attendant risk of fluid overload and allergic reactions, and the short plasma half-life of protein C. In fact, it is difficult to achieve substantial increases in protein C activity in plasma without aggressive plasma exchange [12].

Another possible approach would have been the introduction of therapeutic anticoagulation during the first 24 hours after THA. We did not use this approach because early introduction of therapeutic anticoagulation has been associated with a high incidence of bleeding complications after orthopaedic surgery [21]. Because postoperative bleeding invariably results in greater delays in reinstitution of anticoagulation, we believe this approach would have exposed our patient to greater risks of perioperative thrombotic and hemorrhagic complications.

Based on our experience with this patient, we found perioperative administration of protein C concentrate to be safe: there was no hypersensitivity reaction with Ceprotin® administration, and despite the supraphysiologic levels of protein C during the perioperative period, we observed no increased surgical site bleeding or wound hematoma. However, intraoperative blood loss was greater than normal: the average for a routine two-incision minimally invasive THA is 500 mL (range, 200–700 mL), whereas blood loss in our patient was 1800 mL. It is unclear whether this disparity was the result of the supraphysiologic levels of protein C or of another unknown factor. In a study of another protein C concentrate, increased bleeding during surgical procedures was not noted, although no intraoperative blood loss data were provided [6]. Additional study should help clarify whether supraphysiologic levels of protein C contribute to excessive surgical bleeding.

There are several cautionary points raised by our case report. We initiated therapy with protein C concentrate preoperatively after discontinuation of anticoagulation because of concern that the patient was at exceptional risk for venous thromboembolism. Despite aggressive perioperative treatment with protein C concentrate and prophylactic anticoagulation, a nonocclusive distal deep vein thrombus developed in our patient. Because there was no preoperative duplex study, we cannot definitively conclude this thrombus was new; however, the concomitant presence of related symptoms supports this conclusion. The development of this thrombus could be seen as an indication that our approach was unsuccessful, but we believe it underscores the highly thrombophilic nature of this patient and suspect he likely would have had more severe clinical consequences with a less aggressive treatment course. In addition, the protein C activity levels measured during our patient's clinical course indicated we might have been able to achieve the same results with lower doses of protein C concentrate. Because Ceprotin® is expensive ($1.15 per unit at our blood bank), it is important to use this product in a cost-effective manner. Although we used the manufacturer's recommended doses, our case shows lower doses may be sufficient for patients with heterozygous protein C deficiency because these patients still may have relevant protein C activity compared with patients homozygous for protein C deficiency. Also, monitoring protein C activity levels is essential, as emphasized by the manufacturer.

We report a case in which human protein C concentrate was used in an off-label fashion to safely perform a THA in a patient who was highly thrombophilic and with protein C deficiency and prothrombin 20210 gene mutation heterozygosity. We believe this strategy is a promising and alternative approach to treating highly thrombophilic individuals with protein C deficiency who require major surgery associated with substantial thrombotic and hemorrhagic risks. Because randomized trials are unlikely to be obtainable, given the rare occurrence of patients with this severe degree of thrombophilia, we urge the establishment of a registry to prospectively collect data regarding the outcome of highly thrombophilic individuals undergoing major surgery for confirmation of our results and identification of the most cost- and clinical-effective approaches to surgery in such patients.

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