

## CASE REPORT

# Management of perioperative anticoagulation in a patient with protein 'C' deficiency and multiple comorbidities for spinal surgery

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## ABSTRACT

Patients with protein C deficiency (PCD) are at high risk of development of thromboembolic disorders. Interrupting the patients regular anticoagulants preoperatively and events during surgery and anesthesia significantly increase the thrombosis risk. But continuation of anticoagulants is associated with increased bleeding and the consequent need of transfusion. Here, we discuss the perioperative anticoagulation management of a 54-year-old woman with PCD who underwent lumbar microdiscectomy, and highlight other comorbid issues affecting anesthesia management.

**Key words:** Protein C deficiency; Anticoagulation; Spine surgery; General anesthesia

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## INTRODUCTION

Protein C deficiency usually manifests as various thromboembolic disorders, which could be life-threatening in its congenital form. But patients with heterozygous form of the disease manifest as venous thrombo-embolism and remain on lifelong warfarin therapy. Anesthesia management is complicated by increased risk of thrombosis. Here, we highlight the timing of stoppage and continuation of warfarin, as well as bridging therapy, in the setting of elective surgery.

## CASE REPORT

A 54-year-old female weighing 62 kg, presented with chronic low backache with bilateral radiculopathy. Past medical history revealed hypothyroidism following radio-iodine therapy 25 years ago, for which she was taking l-thyroxine 100 µg daily. She was a known asthmatic, with history of 4 times hospitalization for acute severe

asthma. Preoperatively, she was on formoterol and budesonide inhalational therapy. She was on prazosin 5 mg and losartan 50 mg daily for hypertension. Ten years ago, she had painful swelling of the left lower limb. On investigating, she was diagnosed with deep vein thrombosis and further investigation led to the diagnosis of protein C deficiency, and subsequently she was on oral warfarin (3 mg) therapy. Surgical history revealed two caesarean section under spinal anesthesia and L5-S1 laminectomy under general anesthesia.

Physical examination, including airway examination was within normal limits. Neurological examination showed bilateral straight leg raising test positive. Magnetic resonance imaging of the spine showed L4-5 posterolateral disc extrusion and bilateral L4 root compression. For this she was planned for L4-5 microdiscectomy. Coagulation study revealed international normalized ratio (INR) of 4.2 (target INR with warfarin: 2.0 to 3.0). Other coagulation and biochemical tests were normal.

Oral warfarin was stopped 5 days before surgery, but other medications were continued. Forty eighty hours later, repeat INR was 2.5, and we started on subcutaneous enoxaparin 40 mg twice daily. Another 48 hours later (day 4 of stopping warfarin), her INR was 1.3. We stopped enoxaparin 24 hours before her scheduled surgery. On the day of surgery, we omitted losartan, but she was instructed to take prazosin and l-thyroxine two hours before the surgery. On the day of the surgery, her INR was 0.98.

In the preoperative room, she was given intravenous (IV) midazolam 1 mg, pantoprazole 40 mg IV, hydrocortisone 100 mg IV, salbutamol and budesonide nebulization. Her pulse rate was 70/minute, blood pressure was 130/82 mmHg, oxygen saturation 99%. In the operating room (OR), standard monitors were attached. She was given fentanyl 120 µg, lidocaine 90 mg before anesthesia was induced with propofol 100 mg and sevoflurane 2%. Subsequently, tracheal intubation was facilitated by rocuronium 40 mg using a 7.5 mm ID cuffed flexometallic® tube. Then, she was positioned prone, with care being taken to pad the bony prominences and avoid compression of eyes and abdomen. She was ventilated using the circle system of anesthesia ventilator, ensuring adequate time for exhalation to avoid air trapping. Anesthesia was maintained with oxygen, nitrous oxide and sevoflurane 1-2%. Intraoperatively, we used intermittent pneumatic compression device in both lower limbs, warmed intravenous fluids, and forced air warmer to avoid hypothermia. Surgery lasted 45 minutes, with one episode of hypotension, which was treated with IV fluids, and ephedrine 6 mg. After achieving adequate hemostasis, she was turned supine. Before reversing, lidocaine 90 mg was repeated and neostigmine 3 mg and glycopyrrolate 0.5 mg was given to facilitate tracheal extubation.

Then, she was shifted to post-anesthesia care unit for continuous observation. Inj. paracetamol 1 gm was given IV for pain relief. In the evening, after consulting with surgeons for the adequacy of hemostasis, we restarted oral warfarin 3 mg. Following morning, we put her on enoxaparin 40 mg daily. Three days after starting warfarin, her INR came to be 2.1. Thereafter we continued enoxaparin for another two days, during which INR was 2.6. Subsequently, she was continued with only warfarin 3 mg. She recovered well and was discharged on 7th postoperative day with the advice to follow-up with the hematologist and continue all other medications.

## DISCUSSION

Protein C is a vitamin K-dependent anticoagulant protein synthesized in liver. It is one of the major proteins involved in the antithrombotic pathway. It circulates in plasma as an inactive precursor until it is activated by thrombin. The binding of thrombin to thrombomodulin (protein located on vascular endothelium) rapidly converts protein C to activated protein C; which along with protein S as a cofactor, cleaves and inactivates factors Va and VIIIa. Thus, in the absence of protein C, coagulation process continues unopposed.<sup>1</sup>

Protein C deficiency (PCD) could be due to congenital or acquired causes. Patients with heterozygous PCD have a decreased protein C activity of 50% of the normal, and are at risk of venous thromboembolism (VTE). Patients with homozygous PCD present shortly after birth with life-threatening neonatal thrombosis, hemorrhagic necrosis and purpura fulminans.<sup>2</sup> Acquired causes of PCD include liver disease, disseminated intravascular coagulation, nephrotic syndrome, systemic lupus erythematosis, multiple myeloma.<sup>3</sup> PCD is present in approximately 2-5% patients presenting with VTE.<sup>4</sup>

Our patient was diagnosed with PCD, as a case of heterozygous defect, with less than normal protein C activity and antigen level (Normal: 70-130%).

The perioperative management of such patients is challenging, because the risk of thromboembolic event during interruption of warfarin needs to be balanced when antithrombotic therapy is administered in close proximity to surgery.<sup>5</sup> Continuation of warfarin in the perioperative period confers an increased risk of bleeding.<sup>6</sup> So, in these patients we need to address two issues: Is interruption of warfarin needed? If therapy interrupted, is bridging anticoagulation needed in preoperative period? Patients with high risk for perioperative arterial or VTE include: mechanical heart valve, atrial fibrillation, recent (within 3 months) VTE, severe thrombophilia (deficiency of protein C, S or antithrombin III, antiphospholipid antibodies). These patients need preoperative bridging anticoagulant therapy. Hence we opted for bridging therapy in our patient. The readers are requested to refer the American College of Chest Physicians recommendations for detailed guidelines, timing of therapy in the perioperative setting.<sup>7</sup>

Thrombosis may be triggered by endothelial damage, immobility and blood stasis; all are

of common occurrence during anesthesia and surgery. Hence, we used intermittent pneumatic compression device from intraoperative period itself till the start of enoxaparin. Adequate expansion of intravascular volume is needed to prevent dehydration and stasis. Although there are few case reports describing the anesthetic management of congenital form of PCD, there is no description of specific anesthetic technique for spine surgery in the literature.<sup>8</sup> Bleeding is a potential complication of microdiscectomy, and can be catastrophic if the blood clot compresses the spinal canal. So, adequate hemostasis must be achieved before starting anticoagulant.

Restarting anticoagulant postoperatively has to be done on a case-to-case basis, considering the risk of bleeding and VTE. In our case, intraoperative blood loss was minimal and adequate hemostasis was also achieved before closure. When warfarin is started after surgery, approximately 48 hours is required to attain a partial anticoagulant effect, with an international normalized ratio (INR)  $\geq 1.5$ .<sup>9</sup> Hence, it is reasonable, therefore, to resume warfarin on the evening of the surgery or the next day, without any potential risk of bleeding. Douketis JD et al, in one study of 650 patients, who resumed warfarin postoperatively, with the usual preoperative dose, the mean duration to achieve therapeutic INR was 5.1 days.<sup>10</sup> Starting a higher dose of initial warfarin therapy in order to achieve earlier anticoagulation effect might not be effective or is associated with potential bleeding. So, we started regular 3 mg warfarin on the evening itself and achieved therapeutic INR three days later. After achieving the therapeutic INR, enoxaparin has to be continued for 48 hours more to maintain the INR. Though the recommendations are to start therapeutic dose of enoxaparin, we preferred to use low dose, fearing catastrophic neurologic sequelae in case an epidural clot forms.

The anesthetic management in our case was further

complicated by other multiple comorbidities like asthma, hypertension and hypothyroidism. Endotracheal anesthesia as well as lighter plane of anesthesia are potential triggers for intraoperative bronchospasm. Hence, an anesthetic technique which is known to be safe and associated with least morbidity in the context of hyper-reactive airway should be adopted. Giving iv lidocaine before induction, not only depresses the airway reflexes further but also attenuates the pressor response to intubation, thus providing hemodynamic stability.<sup>11</sup> Patients treated with angiotensin receptor antagonists and its continuation is associated with exaggerated hypotension during anesthesia induction, mainly due to decreased sympathetic nervous system vasoconstrictive responses.<sup>12</sup> So, we discontinued losartan on the day of the surgery. Similarly, possible perioperative adverse responses in hypothyroid patients are plenty. Ensuring a clinical euthyroid status before elective surgery will go a long way in avoiding complications and depressant effects of anesthetics.<sup>13</sup>

To conclude, perioperative management of patients with PCD, is complex, more so when it is associated with multiple comorbidities; with each having their impact on anesthesia management. A thorough understanding of the pathophysiology of the disease, pharmacology of anticoagulants, potential drug interaction of warfarin should be kept in mind for successful management. The risk of development of catastrophic thrombosis and postoperative bleeding, needs to be balanced when timing the anticoagulants and their dosage. Though guidelines are there to help in the management, therapy should be individualized according to the need of the patient, surgery and other comorbid illness.

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**Author contribution:** All the authors contributed in management of the case and preparation of the manuscript

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