



## Case Report

# Emergency rapid reversal of coumarin associated over-anticoagulation in a case of ruptured ovarian hemorrhagic cyst for surgery: A case report

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## ABSTRACT

Over-anticoagulation with coumarins is not uncommon in poorly followed-up patients whose international normalized ratio (INR) is not regularly monitored. Various treatment options available for emergency reversal of over-anticoagulation are either used alone or in tandem. A 36-year-old female with a history of aortic valve replacement came with complaints of severe generalized abdominal pain and hematuria. Hemoglobin was 5 mg/dL, and the INR value was >27.5. Ultrasonography had left a ruptured hemorrhagic ovarian cyst with hemoperitoneum. With a hematology consult, various products were used to reverse the over-anticoagulation. Two liters of hemoperitoneum drainage and left salpingo-oophorectomy were done laparoscopically. Post-surgical recovery was unremarkable, INR was stabilized, and 2 days later, the patient was shifted to the ward. As an anesthetist and critical care physician, it is important to stabilize, optimize, diagnose, and treat these conditions with the aid of various other specialties in a limited amount of time to prevent adverse events that can be fatal.

**Keywords:** Over-anticoagulation, Coumarins, Recombinant factor VIIa

## INTRODUCTION

Over-anticoagulation is not uncommon in patients who fail to follow up with their coagulation profile. The annual incidence of major bleeding in patients taking oral Vitamin K antagonists is approximately 2%/year.<sup>[1]</sup> Commonly used oral Vitamin K antagonists are warfarin and nicoumalone. They competitively inhibit the enzyme epoxide reductase. Patients taking these medications require regular monitoring of the international normalized ratio (INR) for dosage adjustments; otherwise can result in various events ranging from easy bruising to life-threatening intracranial bleeding. Treatment options available for emergency reversal of over-anticoagulation are injection of Vitamin K, fresh frozen plasma (FFP), recombinant factor VIIa, factor VIII inhibitory bypassing activity (FEIBA), and prothrombin complex concentrate (PCC). Depending on the severity of bleeding, these agents are used either alone or in tandem. Other factors to consider are the cost and availability of these agents, which can cause delays in management, resulting in significant adverse events.

## CASE REPORT

A 36-year-old female presented to the casualty with complaints of severe generalized abdominal pain with hematuria. History revealed that she had undergone aortic valve replacement in 2019

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and was on tablets nicoumalone 3 mg and tablets aspirin 75 mg with irregular monitoring of anticoagulation. On examination, the patient was fully conscious and oriented. Vitals showed tachycardia of 130 beats/min, blood pressure (BP) of 130/70 mmHg, examination of heart and lungs were unremarkable, and abdominal examination revealed gray-turner sign and suprapubic tenderness. A complete blood count revealed hemoglobin of 5 mg/dL, INR value was >27.5, and partial thromboplastin time ratio was 7.02. Ultrasonography of the abdomen and pelvis revealed a left ruptured hemorrhagic ovarian cyst with resultant hemoperitoneum. 2D echocardiography showed no paravalvular leak. The patient was shifted to the intensive care unit (ICU) and planned for laparoscopic left salpingo-oophorectomy with drainage of the hemoperitoneum. The central line and arterial line were placed, and arterial blood gas showed respiratory alkalosis. Oozing was noted from the lines, and hematuria continued. Meanwhile, 3 units of packed red blood cells (RBCs) and 8 units of FFP were transfused. Vitamin K 5mg IV was given. As per the hematologist, an injection of recombinant factor VIIa (novoseven) 2 mgs with PCC of 1500 units was given. The repeat INR value became 0.97. Three hours later, from the time of ICU admission, the patient was taken for surgery.

The patient was shifted to the operating room, all standard monitors were attached, and invasive BP monitoring was done. The patient was induced with IV fentanyl 100 mcg, IV propofol 50 mgs, muscle relaxant cisatracurium. Intubation was done by a senior anesthesiology consultant. Two liters of hemoperitoneum drainage and left salpingo-oophorectomy with cauterization of an active bleeding point from the epiploic vein were done laparoscopically. Intraoperatively, 1 unit of packed RBC was transfused, and urine output was adequately achieved. The patient was not extubated on the table in view of significant chances of transfusion-related acute lung injury (TRALI) and was later extubated in the ICU. Post-procedure hemoglobin was 9.2 mg/dL, and INR was 1.55. Injection of enoxaparin 60 mg subcutaneously was started 12 h post-surgery for protection of mechanical aortic valve. Post-surgical recovery was unremarkable, INR was stabilized, and 2 days later, the patient was shifted to the ward and later discharged with appropriate instructions.

## DISCUSSION

Oral Vitamin K antagonists are used to prevent arterial and venous thromboembolism. A commonly used class of drugs is coumarins, which include warfarin and nicoumalone. They are structurally similar to Vitamin K and competitively inhibit Vitamin K epoxide reductase, thereby preventing the regeneration of reduced Vitamin K. In our case report, the patient was using nicoumalone.

The advantages of nicoumalone over warfarin are nicoumalone, which has a rapid onset of action, which induces therapeutic prothrombin levels 36 h after the initial dose and prompt reversal. Assessment of the level of anticoagulation is done by prothrombin time/INR, which measures factors II, VII, and X.<sup>[2]</sup> The therapeutic range of INR for metallic heart valves is 2.5–3.5. Adverse effects of coumarins can range from minor bruises to major life-threatening bleeding due to their narrow therapeutic index, significant drug, dietary and disease interactions, and CYP2C9 mutations. According to a multicenter study, the three variables for increased risk of bleeding were as follows: Age >70 years, first 90 days of anticoagulation, and INR >4.5.<sup>[3]</sup>

There are various treatment options available to reverse the over-anticoagulation. The reversal agents and the factors reversed by them are given in Table 1.

### Withholding of coumarin dose

Coagulopathy starts to correct within 24–36 hours. With nicoumalone, the prothrombin time normalizes within 36–48 hours as the anticoagulant activity of nicoumalone is not seen in its metabolites.

### Vitamin K

It can be administered orally or intravenously. Replaces the factors depleted by Vitamin K antagonists but takes 24 h post-treatment. Intravenous Vitamin K acts much faster but has a chance of severe anaphylaxis reactions. Emergency reversal with major bleeding should receive 5 mg intravenous Vitamin K with PCC.

### FFP

It is a commonly used agent for the replacement of coagulation factors containing factors II, VII, and X and insufficient levels of factor IX. Hence, it provides sub-optimal INR correction, so PCC is preferred over FFP in emergencies. Other disadvantages of FFP are the need for ABO compatibility, time taken for thawing, and increased chances of TRALI. The dosage of FFP is 15 mL/kg.

### FEIBA

It is a form of activated PCC. It contains factor VII and small amounts of factor II, IX, and X. It is currently indicated in patients with hemophilia with inhibitors only for prevention and for acute bleeds.<sup>[4]</sup> Factor VIIa or novoseven is used similarly and not for the treatment of hemophilia without inhibitors. However, few studies have been conducted on FEIBA for warfarin over-anticoagulation reversal, providing positive results.

**Table 1:** Reversal agents and the factors reversed by them.

Reversal agents	Factors restored
Recombinant factor VIIa	VII
FFP	II, VII, X
3 factor PCC	II, IX, X
4 factor PCC	II, VII, IX, X
FEIBA	II, VII, IX, X

FFP: Fresh frozen plasma, PCC: Prothrombin complex concentrate, FEIBA: Factor VIII inhibitory bypassing activity

### Recombinant factor VIIa

It acts by activation of factor X to Xa thereby forming thrombi.<sup>[5]</sup> Dosage is 90–120 mcg/kg IV bolus given over 2–5 min. Maximum activity is seen in 5–10 min. Half-life is 2.5–3 h.

### PCC

Two types of PCC are available. The better one is the 4-factor PCC, which has all the four factors of Vitamin K but is not commonly available. 3 Factor PCC majorly has factors II, IX, and X, so it needs to be combined with other agents. PCC comes as a powder that is diluted and given as a short infusion. The dosage is 25 units/kg. Hence, for major life-threatening bleeds, 4-factor PCC is given as the sole agent, or 3-factor PCC can be used with Vitamin K and recombinant factor VIIa.<sup>[6]</sup>

Major intraoperative considerations include the immediate start of surgery once INR is optimized, as certain agents like recombinant factor VIIa have a short half-life. Cross-matching of adequate blood and blood products is required. Intubation is preferably done by the senior anesthesiologist to avoid any airway trauma. Reduced anesthesia and surgical time with adequate perfusion and overall maintenance of hemodynamics are crucial.

### CONCLUSION

Over-anticoagulation is not uncommon, but these patients presenting with hemorrhage requiring urgent major surgery are rare. Hence, swift diagnosis and reversal are of utmost priority. In this case, various treatment options were used in tandem to reverse the over-anticoagulation. As an anesthetist and critical care physician, it is important to stabilize, optimize, diagnose, and treat the condition with the aid of various other specialties in a limited amount of time to prevent adverse events that can be fatal.

### Ethical approval

Institutional Review Board approval is not required.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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