



Acute Reversal of Warfarin Therapy in Patient with Protein C and S Deficiency Presenting for Emergency Surgery

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The term "hypercoagulable state" is generally used to denote any conditions in which the normal balance between clotting and anti-clotting mechanisms becomes altered in such a way that the patient is predisposed to thrombus formation. There are a number of conditions that can lead to hypercoagulable state and protein C and protein S deficiency are one of the important causes. About one out of every 300 people has one normal gene and one faulty gene for protein C deficiency and protein S deficiency occurs in about 1 in 20,000 people¹. We present a diagnosed case of protein C and protein S deficiency with deranged coagulation parameters posted for amputation fingers in emergency.

Case report: A 19 year young male presented with swelling and blackening of right upper limb and abdominal pain since 10 days. He was a known case of protein C and protein S deficiency with history of deep vein thrombosis one year back for which he was on warfarin therapy. He had blackish discolouration and swelling of right middle, index and ring finger upto metacarpophalangeal joints and a 6x6cm necrotic patch over dorsum of right hand. All modalities of sensation were lost but the mobility of the fingers were preserved. He also had dull aching pain in abdomen which was not localized and not associated with vomiting but accompanied by intermittent bloody diarrhoea.

On examination, his pulse was 87 per minute, regular in left radial artery, with absent ulnar and radial pulsation on right side. His respiratory rate was 30per minute. Chest movement was equal and trachea was central. There was no adventitious sounds on auscultation and no hepatosplenomegaly on abdominal palpation. He had past history of right testicular artery thrombosis for which orchidectomy done under general anaesthesia one year back. He was on Tablet Warfarin 5mg once daily (OD).



His Investigations revealed Haemoglobin of 9gm%, total leukocyte count of 9000 with neutrophil 62%, lymphocyte 32%, eosinophils 6%, platelet count of 1,00,000/cc, haematocrit of 36% and ESR was 20. His Liver and Kidney function tests were normal. Serum sodium was 132meq and potassium 4.3meq. His 12lead ECG and chest x-ray chest were normal. Coagulation parameters showed a prothrombin time of 79 sec with control of 17 sec and INR 6.34, activated prothrombin time was 91.6 sec with control 32 sec. Antithrombin III, Sucrose lysis test, Acid Hamtest, Antiphospholipid antibodies, Factor V mutant tests all were negative. Protein C level was 70%(ELISA)(Normal 70-140%) and protein S level 55%(ELISA) (Normal 70-140%). Antinuclear antibody and anti ds-DNA antibody were negative. Doppler study of right forearm revealed right ulnar artery thrombosis. Right radial artery showed low velocity biphasic blood flow with non-visualization of right palmar arch. CT angiography showed narrowing of celiac trunk distal to its origin.

Plan of Anaesthesia: As INR of the patient was raised significantly considering the risk of perioperative bleeding, optimization of patients' condition by acute reversal of warfarin therapy was decided. Considering the cost and non-availability of Prothrombin complex (PCC) and easy availability of fresh frozen plasma(FFP), we used FFP and Vitamin K (2 mg i.v) in our case for reversal of warfarin therapy. FFP was started with intermittent monitoring of INR.

Table-1: Amount of FFP Transfused and Corresponding INR

Time	Prothrombin Time	INR	FFP
7 PM	79	6.34	
9 PM	73	5.8	After 1 FFP
11 PM	56	4.2	
01 AM	53	3.9	After 2 FFP
03 AM	36	2.5	
05 AM	28	1.8	After 3 FFP

General anaesthesia was planned. He was premedicated with injection (inj) glycopyrrolate (0.004mg/kg), inj ranitidine (2mg/kg), inj ondansetron (4mg) and inj fentanyl (2mcgm/kg). Vitals were monitored with pulse oxymeter, electrocardiogram, and manual blood pressure monitoring. He was induced with inj propofol (2mg/kg) air way secured with laryngeal mask airway (LMA no 3) and maintained with oxygen- nitrous oxide (40-60%) and sevoflurane 1.5% on spontaneous ventilation. Amputation of index, middle and ring fingers are done and tourniquet was avoided. Surgery duration was 45 minutes with blood loss of 50 ml. Postoperative recovery was uneventful. Prothrombin time and INR repeated in immediate post operative period and was found to be 2. There was no significant bleeding seen in post operative period and during the next check dressing after eight hours the wound was dry. Repeat INR at that time was 2.1 and warfarin (5 mg OD) reinstated after 12 hours of surgery with consultation of the surgeons. His coagulation profile the next day showed a PT=33 sec, INR=2.2, and plate count of 1,10,000/ cc. Warfarin was continued and repeat PT and INR done daily for next two days with INR value of 2.5 on both the occasions.



Discussion: Proteins C and S deficiencies are frequently described as causes of the hypercoagulable states². Proteins C and S are two of the vitamin K-dependent proteins. Activated protein C (protein Ca) inactivates factors Va and VIIIa. Protein C is activated to protein Ca 20 000 times faster than by thrombin alone through the interaction of thrombomodulin and thrombin on the endothelial cell surface³. In addition, protein C proteolytically inactivates the inhibitor to tissue plasminogen activator, thus increasing the natural fibrinolytic activity of plasma. Protein S is a cofactor for protein C. The activity of protein Ca is increased several orders of magnitude by its non-enzymatic cofactor protein S.

Proteins C and S deficiencies may be seen in both congenital and acquired forms. They are inherited in an autosomal dominant manner. In the congenital conditions, those homozygous for protein C deficiency usually die in infancy, while heterozygous have antigenic protein C levels less than 60% of normal and present with recurrent venous thrombosis. Acquired deficiencies are usually associated with conditions that interfere with hepatic synthetic functions, as these factors are produced in the liver⁴.

This patient had been diagnosed of having protein C and S two years back when he first presented with deep vein thrombosis of right leg two years back. As regards to the onset of symptomatic disease at the age of 18 years and with no co-relating family history, heterozygous protein S deficiency in this case can be thought of the onset of episodes of thrombosis, especially venous thrombotic events, in patients with heterozygous deficiency is known to begin in the late teens and twenties. Even then, thrombotic events are often precipitated by another factor, such as trauma, surgery, or childbirth.

Instances of arterial thromboses have been reported, especially in young patients, but the majority of patients with protein C and/or S deficiency have venous thrombosis, noted in as many as 4% and 5% of young patients with venous thrombotic disorders². The only established treatment for patients with thrombotic events is heparin therapy followed by lifelong warfarin therapy. Although anticoagulation with heparin has been the treatment of choice for most patients with DVT, catheter directed thrombolysis for symptomatic iliofemoral deep vein thrombosis may be safe and effective in selected cases⁵.

The precise incidence of warfarin associated haemorrhage is unclear, but many studies have consistently reported the annual rate of fatal haemorrhage to approach 1%. The incidence of "major" and "minor" bleeding has varied considerably between studies⁵. A rare but serious complication resulting from treatment with warfarin is warfarin necrosis, which occurs more frequently shortly after commencing treatment in patients with a deficiency of protein C. Since warfarin initially decreases protein C levels faster than the coagulation factors, it can paradoxically increase the blood's tendency to coagulate when treatment is first begun (many patients when starting on warfarin are given heparin in parallel to combat this), leading to massive thrombosis with skin necrosis and gangrene of limbs. Its natural counterpart, purpura fulminans, occurs in children who are homozygous for certain protein C mutations⁶.



This patient gave the history of skin excoriation in right thigh on initiation of warfarin therapy for the first time one year back and was diagnosed as warfarin induced skin necrosis then. Other side effects with warfarin are osteoporosis and purple toe syndrome.

Reversal of Warfarin Therapy: If warfarin reversal is required, the method chosen should reflect the clinical seriousness of bleeding and balance against the thrombotic risk of a temporary suspension/reduction of anticoagulation. Factors that require consideration include the indication for warfarin treatment, the seriousness of bleeding (if any), and the speed and completeness of reversal required. In addition, the need for ongoing anticoagulation in any patients who require reversal (particularly for major haemorrhage) should be reviewed.

The anticoagulant effect of warfarin may be reversed by a variety of methods. Options include simple dose omission or administration of vitamin K. For serious bleeding, the replacement of coagulation factors is required. The administration of fresh frozen plasma (FFP) has been the most widely used method for coagulation factor replacement. As a result of concern that FFP may not be the most effective way to reverse warfarin rapidly, prothrombin complex concentrates (PCCs) have been increasingly recommended. More recently, it has been suggested that recombinant activated factor VII (rFVIIa) may be effective⁵.

Table-2: Option for Warfarin Reversal⁵

Type of Reversal	Approach
Rapid (complete; within 10–15 minutes)	PCC (immediate replacement of vitamin K dependent coagulation factors) plus IV vitamin K (switch on hepatic synthesis within a few hours)
Fast (partial)	FFP (immediate replacement of vitamin K dependent coagulation factors—but the correction of the coagulopathy is partial)
Prompt (within 4–6 hours)	IV vitamin K
Slow (within 24 hours)	Oral vitamin K
Ultraslow (over days)	Omit warfarin dose (no vitamin K)

Table-3: UK Guidelines for Warfarin Reversal⁵

Clinical situation	Action
Major bleeding	Stop Warfarin Vitamin K (5 mg IV or oral) PCC (50 U/kg) or FFP (15 ml/kg) Caution: FFP may not fully reverse the effect of warfarin—for example, factor IX does not rise >20% post FFP (not reflected in INR)
Non-major bleeding	
INR <6.0	Omit Warfarin



INR >6.0 to <8.0	Omit Warfarin
No minor bleeding	
INR >8.0	Omit Warfarin
INR >8.0 + other risk factors for bleeding	Omit warfarin + 0.5–2.5 mg vitamin K (IV or oral)

It is clear from comparing these guideline documents that there are pronounced differences in approach. Both mention a potential role for both FFP and PCCs in major haemorrhage. A variable dose of vitamin K is suggested in different clinical settings. Since the publication of these guidelines, there have been several new studies that have led to an increase in the evidence base for some of the clinical decisions in the area of Warfarin reversal. It may be time to review these guidelines.

There is a consensus that potentially life threatening bleeding requires rapid warfarin reversal. This is based on the view that the clinical priority in the face of severe haemorrhage is to stop the bleeding as quickly as possible, regardless of the reason for anticoagulation. According to guide lines “Whenever possible, surgery in a chronically anticoagulated patient should be undertaken on an elective basis to allow for planned anticoagulant reversal. However, in situations where an urgent or emergent surgery/procedure is required and warfarin reversal is indicated, proceed as follows”:

- Surgery/procedure to be done in <24 hours: Discontinue warfarin and administer intravenous vitamin K1or frozen plasma.
- In extreme circumstances: Other blood products such as recombinant factor VIIa or prothrombin complex concentrate could be considered upon specialist consultation. Monitor INR closely⁷.

In this case the patient presented with gangrene of hand with impending sepsis and an altered INR. As regards to the emergent nature of surgery and anticipating perioperative bleeding due to impaired coagulation profile(INR>6) we decided for normalization of INR prior to subjecting the patient to surgery.

The debate persists as to whether FFP or a PCC should be used. The use of PCCs is based on the evidence that the traditional approach using FFP is less effective in the correction of the coagulopathy as assessed by both the INR value and assay of the individual vitamin K dependent clotting factors^{8,9}. This is particularly in relation to the difficulty in achieving a haemostatic concentration of factor IX after FFP infusion⁸. In addition, several studies have shown that FFP is administered much more slowly than PCCs, and volume overload may lead to difficulties in giving an adequate dose of FFP^{10,11,12}. PCCs are also subjected to virus inactivation to reduce the risk of transfusion transmitted viruses, which is still a potential problem with FFP (unless methylene blue or solvent detergent treated FFP is used). The drawbacks with PCCs are in relation to cost, thrombogenicity, and the residual concern that pooled plasma products may transmit prions or unknown pathogens.

It is essential that intravenous (IV) vitamin K is given at the same time as a PCC or FFP to switch on endogenous synthesis of vitamin K dependent clotting factors⁸. It is now clear that oral

vitamin K has no therapeutic usefulness in clinical settings that require rapid warfarin reversal because it works too slowly¹³. According to UK guidelines for warfarin reversal FFP can be used for immediate replacement of vitamin K dependent coagulation factors but the correction of the coagulopathy is partial⁵. FFP and Vit K are the options for us due to unavailability of PCC.

Anaesthesia was induced with inj propofol 2mg/kg i.v and was maintained with oxygen-nitrous oxide (40-60%) with isoflurane on spontaneous ventilation with LMA. Though Warfarin effects are antagonized by lipid emulsions and they may interfere pharmacodynamically with warfarin activity by enhancing the production of clotting factors, facilitating platelet aggregation, or supplying vitamin K and facilitating warfarin binding to albumin¹⁴. This effect is pronounced in chronic infusion of lipid emulsion as in parenteral nutrition and long term propofol infusion, and is insignificant for single dose propofol during induction

Conclusion: Patient on chronic Coumadin therapy often have altered coagulation profile. Preoperative optimization of the coagulopathy by FFP and Vit K is of utmost importance to minimize the risk of perioperative bleeding.



Figure 1. Healed warfarin skin necrosis



Figure 2. Right hand with amputated fingers



Figure 3. CT scan showing Coeliac trunk narrowing

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