Warfarin induced Coagulopathy in a Patient of Protein S deficiency

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Abstract:

Deficiency of protein S is associated with increased thromboembolic risk in the venous & arterial system.Long term use of warfarin or even low molecular weight heparin maybe recommended for patients with thrombotic disease having persistent risk factors, eg.hereditory protein S deficiency. But increased incidence of major/minor haemorrhagic episodes with this therapy is a challenge for treating physician. We report a case of bilateral lower limb DVT in a protein S deficient patient who developed warfarin induced coagulopathy.

Introduction :

Protein S (PS) is 1 of the vitamin K-dependent natural anticoagulants and serves as a cofactor for activated protein C (APC) for inactivating factors Va and VIIIa. PS deficiency has been found in 1.5% to 7% of different groups of patients with thrombophilia.[1] Deficiency of PS, therefore, is associated with increased thromboembolic risk in the venous and arterial systems.[2,3]

The increasing number of patients receiving chronic vit K antagonists (VKA) therapy along with the expected risks of hemorrhagic complications have underscored the need for well defined stratagies for emergent reversal of warfarin associated coagulopathy.[4,5]

We here report a case of warfarin induced coagulopathy in protein S deficiency (rare genetic condition) having bilateral lower limb DVT.

Case report

A 29 year old male, construction work supervisor, was admitted with sudden onset severe pain and swelling in left calf 8 days prior to hospitalization. There was no history of fever, rash or trauma to limb. He denied history of air travel or hypertension. He was non smoker, non alcoholic. His past history revealed that he was diagnosed to have deep venous thrombosis involving the right lower limb 5 months back & was receiving warfarin 5 mg once a daily. He was compliant with treatment but was not monitoring his prothrombin time and INR. His last INR 7 weeks back was 2.3. On general examination pulse was 70/min regular, blood pressure was 130/80 mm. of Hg in right arm. No significant abnormal findings could be noticed on general examination except diffuse tense swelling involving left lower limb upto knee joint but more on calf. Swelling was tender. There was echymotic patch over left calf but no blister, bullae or gangrene. There were no signs of compartment syndrome. Right lower limb showed blackish discoloration over ankles. There was no other evidence of subcutaneous bleeding. No abnormality was detected on systemic examination. His lower limb vascular Doppler study revealed deep venous thrombosis involving left popliteal vein and arterial thrombosis involving anterior tibial artery. There was haematoma of around 29cm x 11cm x 4.2 cm. **(See Fig1)** Right lower limb Doppler showed recanilisation of deep venous system. His prothrombin time was 1min 20 sec. and INR was 6; grossly prolonged. Considering possibility of warfarin induced haematoma warfarin was stopped. He was given intravenous injection of vitamin k (5mg) to reverse the effects of warfarin. He was put on broad spectrum antibiotics and opiod analgesic. Since the calf swelling was increasing in size with impending risk of compartment syndrome, he underwent haematoma removal & also received fresh frozen plasma (FFP) 2 units. His pain and swelling decreased. Subsequently he

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was investigated for hypercoagulable state after 2 weeks of stopping warfarin, which showed normal homocysteine, protein C, anti thrombin III levels. Lupus anticoagulant and anticardiolipin antibody were negative but Protein S activity was severely decreased i.e.10 (normal 70-143%). His repeat INR came down to 1.5. Review Doppler showed decrease in hematoma volume to 10 ml. Warfarin 2.5 mg od. was restarted and was discharged from hospital with advice of strict monitoring of INR every 2 weeks.

Discussion

Protein S deficiency (PS) deficiency may be acquired or hereditary. PS levels can be influenced by several factors, including warfarin therapy, disseminated intravascular coagulation, primary thrombocytopenia, severe liver disease, diabetes mellitus, nephrotic syndrome, oral contraceptives, hormone replacement therapy, L-asparginase therapy for leukemia, pregnancy and postpartum stage and gender[6] Hereditary PS deficiency is an autosomal dominant genetic disease, in which active PS gene (PROS1 gene) defects are the underlying causes.[2,7]

Long-term use of warfarin or even low molecular-weight heparin may be recommended for patients with thrombotic disease secondary to persistent risk factors (*e.g,* hereditary PS deficiency)[8,9] . Warfarin therapy is challenging because of substantial individual variation in dosage requirement that make over coagulation common.[10,11] In addition warfarin has a narrow therapeutic window, treatment frequently results in bleeding; some times major or life threatening[12].The risk of haemorrhage increases with the intensity of warfarin anticoagulation. The variable most consistently associated with bleeding risk is elevation of international normalized ratio(INR)& standardized prothrombin time [13,14] .For the most indications warfarin is administered in doses that produce target INR of 2.0-3.0.An exception is patients with mechanical valves where target INR of 2.5-3.5 is recommended & increasing bleeding is seen with INR values >4.5[15,16,17]The reported incidence of bleeding complications in patients taking warfarin varies. The incidence of major haemorrhage has been reported at 1.0–3.0% per year. Minor haemorrhage complications are said to occur at a rate of 4.8–9.5% per year [18].

In the present case the bleeding was not life threatening but there was impending evidence of compartment syndrome and patient underwent surgical intervention for removal of hematoma. For reversal of warfarin induced coagulopathy recommendation are given by ACCP **(See Table)**

In the present case inspite of INR being 6, patient received FFP (It is recommended at INR 9 as per ACCP) because of impending compartment syndrome.

Warfarin necrosis of skin is an another important but rare side effect which occurs between 3rd & 10th day of therapy with warfarin[19]. Reported prevalence of this side effect is .01-0.1% & more seen with Protein C deficiency as compared to PS deficiency[20] Engesser et al,[3] did not observe warfarin necrosis of skin in any of the 30 cases with protein S deficiency in his case series. It is usually common in female .Common sites are breasts, thighs & buttocks. Presenting lesions are sharply demarcated, erythematous, indurated & purpuric. They may progressed to form large, irregular,haemorrhegic bullae with eventual necrosis & slow healing eschar formation.It is treated with Vit K.[19] In this case no hemorrhagic skin necrosis was observed.

Take Home message :

PS deficiency is a rare genetic condition associated with increased thromboembolic risk in venous & arterial system. Judicious use of warfarin in treating & preventing especially in DVT & pulmonary embolism should be the first cautious steps to keep warfarin toxicity at a distance. INR is by best method for monitoring warfarin toxicity. The management should be initiated promptly. Stoppage of warfarin with regular check up of INR is the cornerstone of treatment. Warfarin can be restarted after normalization of INR but with strict monitoring of INR.

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Table showing 1998 and 2001 ACCP Recommendations for Reversing Excessive Warfarin-Associated AC

Recommendation No.	INR	Bleeding	Recommendation/Action
1	< 5	No	Reduce dose or omit next few doses
2	> 5 but < 9	No	If no risk factors for bleeding, omit next few doses; if risk factors for bleeding, administer 1.0–2.5 mg oral vitamin K
3	> 9	No	3.0–5.0 mg oral vitamin K
4	> 20	Yes (serious)	10 mg IV vitamin K and FFP or PCC
5	Any	Yes (life-threatening)	10 mg IV vitamin K and PCC

Table adapted from Hirsh et al13 and Ansell et al.[12]

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Fig 1: Showing large Hematoma Left poplitial vein