The importance of antiphospholipid syndrome testing in venous thromboembolism after varicose vein surgery

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ABSTRACT

Anticoagulation treatment after a venous thromboembolism event is usually managed on a case-by-case basis. The risk of thrombosis must be weighed against the risk of bleeding. Identifying patients who could benefit from anticoagulation therapy requires the thromboembolism event to be assessed with respect to its presentation and the severity of the triggering factors. A case report is employed to explain the important aspects of practical approaches to venous thromboembolism events after vein surgery. The Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) study has prompted new considerations for anticoagulation management. Patients with antiphospholipid syndrome need to be identified early to lower the risk of thromboembolism also during anticoagulation treatment. (J Vasc Surg: Venous and Lym Dis 2020;8:1097-101.)

Keywords: Antiphospholipid syndrome; Venous thromboembolism; Varicose veins; Anticoagulants; Vein surgery

After a venous thromboembolism (VTE) event, patients are frequently referred to a vascular physician to clarify the type of oral anticoagulants they should take and how long they should take them. If no triggering event can be identified, thrombophilic diathesis is often suspected alongside a paraneoplastic cause. At first glance, a provoked case of VTE does not appear to play any special role in therapy management; but on closer examination, it could create difficulties in assessing the severity of the triggering risk factor. Only in isolated cases can a diagnosis of thrombophilia have therapy-relevant consequences.[1] The current body of data from the Trial on Rivaroxaban in AntiPhospholipid Syndrome (TRAPS) has brought to light new aspects in treating VTE. The problem can be explained by way of a case report.

CASE REPORT

A 44-year-old man (body mass index, 32.0 kg/m^2) presented in the emergency department with exertional dyspnea and a dry cough that had been present for 3 days. No pre-existing conditions were known. He had not been taking any medication. The patient stated that 3 weeks before, he had undergone varicose vein surgery (high ligation, subtotal stripping, phlebectomy) on the great saphenous vein (GSV) of his left leg. In the period between the diagnosis of the varicose veins ($C_4E_pA_{S2,3}P_r$) and the scheduled date of the operation, the patient experienced blunt trauma to the soft tissue, which led to extensive varicophlebitis in his left GSV. This was treated on an outpatient basis with a factor Xa inhibitor for 3 months until his operation. The varicose vein surgery was performed on an outpatient basis, and there were no complications. After the operation, the patient received thromboembolism prophylaxis with low-molecular-weight heparin (LMWH) for 1 week and compression therapy for 4 days. There was no postoperative immobility. A clinical follow-up was conducted 1 week after the operation, and no abnormalities were found.

The patient's circulation was stable in the emergency department (blood pressure, 123/84 mm Hg; heart rate, 62 beats/min). The patient exhibited elevated levels of D-dimer (3.26 mg/L) and a lower partial pressure of oxygen (6.6 kPa) so that computed tomography with a contrast agent was performed on his pulmonary arteries. This detected a central pulmonary embolism in the right pulmonary artery and peripheral pulmonary embolisms in the segmental arteries on both sides. Echocardiography ruled out a right ventricular load. In consultation with the patient, we decided against prescribing thrombolytic therapy as his circulation was stable. He underwent observation on the intermediate care ward. Duplex ultrasound showed phlebothrombosis adherent to the vein wall in the left common femoral vein and the branching point of the left femoral vein. Computed tomography also revealed thrombosis of the left iliac vein. The patient received anticoagulation therapy with apixaban. He did not recall any thrombotic event in his history or in that of his family. The vein surgery was considered a risk factor for provoked VTE, but it was ultimately identified as a weak risk factor. In addition, laboratory tests detected a suspected case of thrombophilia as well as a slightly increased partial thromboplastin time in several controls (activated partial thromboplastin time, 45 seconds; normal range, 25-35 seconds). Based on current knowledge, antiphospholipid syndrome (APS) with a triple-positive laboratory constellation (lupus anticoagulant, cardiolipin antibodies, and antibodies against β_2-glycoprotein) had to be ruled out because this constellation would have required a special anticoagulation regimen. APS was

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Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2020.03.008

subsequently identified with a triple-positive laboratory constellation (lupus anticoagulant ratio of 1.55 at a normal level of ≤1.2; anticardiolipin antibody of immunoglobulin [Ig] G, 76 GPL-U/mL [IgG phospholipid units] at a normal level of <12 GPL-U/mL; and anti-β2-glycoprotein 1 antibodies, 86 U/mL at a normal level of <20 U/mL) after neutralizing the direct-acting oral anticoagulant (DOAC) with a dilute Russell viper venom time. APS was confirmed in a control test after 12 weeks. The findings of TRAPS identified that with this laboratory constellation, therapeutic anticoagulation needs to shift toward vitamin K antagonists (VKAs). The patient consented to the publication of this case report.

DISCUSSION

The case raises five questions that required answers with respect to the blood thinning regimen.

Question 1. Is it a case of provoked VTE?

Unprovoked VTE events have more than twice the risk of recurring as transiently provoked VTE events.[2] Even if thrombophilia is detected, the risk of recurrence is low after a provoked VTE event with a hard risk factor.[3] Anticoagulation for 3 months is recommended if it is a case of provoked VTE with a transient risk factor. In the case of unprovoked VTE or provoked VTE with a weak risk factor, thromboembolism prophylaxis may need to be administered for an extended period.[4] In addition to distinguishing between a provoked and unprovoked VTE event, the severity of the triggering factor is a major factor in managing anticoagulation.[5]

Answer. Initially, we assumed that this must have been a case of provoked thrombosis after varicose vein surgery.

Question 2. How significant a role do varicose phlebitis and varicose surgery play in triggering an episode of VTE?

For patients with varicose veins, the risk of leg vein thrombosis is about 5.3 times higher (n = 212,984 case-control study); in the case of a pulmonary embolism, no difference in risk was identified between the study groups.[6] Galanaud et al[7] investigated the spontaneous development of superficial venous thrombosis (SVT) in a subgroup analysis of the OPTimisation de l'Interrogatoire pour la Maladie thromboEmbolique Veineuse (OPTIMEV) multicenter study (n = 8256). During 3 years, they compared isolated SVT (iSVT) in the lower leg with isolated proximal deep venous thrombosis (pDVT) without a dispositional risk factor. The recurrence rates did not differ significantly (pDVT, 6.5%; iSVT, 5.4%). The incidence of recurrence after discontinuation of anticoagulation therapy was somewhat lower after iSVT than after pDVT; however, half of all iSVT recurrences were DVTs. On average, recurrence developed 465 days for iSVT and 223 days for pDVT after completion of anticoagulation therapy. In patients with iSVT, the Prospective Observational Superficial Thrombosis (POST) study identified a pulmonary embolism rate of 0.5% and a DVT rate of 2.8% within 3 months.[8]

Table I shows the VTE risk in relation to the varicose vein treatment method. Even though VTE events occur less

Table I. Venous thromboembolism (VTE) risk in relation to the treatment measure compared with the incidence of deep venous thrombosis (*DVT*) in the general population of 100/100,000 (0.1%)[9]

Study	Enrollment	No.	Methods	Observation period, weeks	DVT, % after observation period	PE, % after observation period
van Rij et al[10]	1996-2002	397 patients	OS	52	5.30	No signs of PE
Noppeney et al[11]	2001-2009	89,616 patients	OS OS, EVLA, RFA	>4 >4	0.10 (unspecified) 0.099 (unspecified)	0.02 (unspecified) 0.017 (unspecified)
Sutton et al[12]	2006-2007	35,374 patients	OS, FS, EVLA + RFA	52	OS 0.37 FS 0.14 EVLA + RFA 0.40	OS 0.17 FS 0.05 EVLA + RFA 0.07
Barker et al[13]	2003-2013	261,169 procedures	OS, FS, EVLA, RFA	52	OS 1.53 FS 0.47 EVLA 0.58 RFA 0.47	
O'Donnell et al[14]	2008-2012	131,887 patients	OS, FS, EVLA, RFA	104	OS 2.40 FS 0.82 EVLA 3.05 RFA 4.41	OS 0.29 FS 0.15 EVLA 0.25 RFA 0.31
Nemoto et al[15]	2011-2013	43,203 patients	EVLA	12	0.076[a]	0.0067

EVLA, Endovenous laser ablation; *FS*, foam sclerotherapy; *OS*, open surgery; *PE*, pulmonary embolism; *RFA*, radiofrequency ablation.
[a]Endovenous heat-induced thrombosis class 4 and other DVT.

often than wound complications, they are of enormous significance because of the potentially serious consequences. Therefore, VTE continues to be regarded as a major complication after varicose vein intervention (foam sclerotherapy, endovascular therapy, open surgery).[16] The German guidelines recommend medication-based thrombosis prophylaxis for varicose vein procedures only when there are additional risk factors for VTE. In contrast to the American College of Chest Physicians guidelines, the German recommendations do not yet include the use of risk scores (eg, Caprini Score) in assessing perioperative VTE risk in clinical routines.[17]

Answer. In the case report, there was no obvious connection between the traumatically induced SVT and the DVT. Evidence of a localized DVT at the junction to the GSV and in the iliac vein indicated a thromboembolic complication after vein surgery. Vein stripping has to be considered a weak risk factor for a VTE event (short surgery time, <3 days inpatient care, no immobility >3 days). In the end, provoked VTE with weak risk factors was identified and a thrombophilia diagnosis was indicated.

Question 3. When is thrombophilia testing done and which parameters are of significance in the acute phase of VTE?

In general, thrombophilia testing at the time of acute DVT in the leg is not recommended. Thrombophilia testing is also not recommended after provoked thromboses with strong risk factors; however, it can be considered for patients with provoked thrombosis with a weak risk factor, a positive family history, and repeated thromboses.[18] The current European Society of Cardiology guidelines recommend thrombophilia testing after a pulmonary embolism if an idiopathic thromboembolic event has been identified in a younger patient (<50 years) and there is no related family history. The guidelines emphasize that there is no evidence of any clinical benefit for detecting a factor V Leiden gene mutation and prothrombin 20210A mutation but do recommend testing for the presence of APS.[19] Therapeutic anticoagulation with VKAs, non-VKAs (DOACs), or heparins (unfractionated heparin, LMWH) should be paused at the time of testing (VKAs for at least 2 weeks, DOACs for at least 2 days, unfractionated heparin and LMWH for at least 24 hours).

Answer. Based on the results of TRAPS, testing for APS should be performed when there is a weak risk factor so that the blood thinning regimen can be managed.

Question 4. Which characteristics make managing APS-related VTE so crucial?

APS is characterized by thromboses in the arteries, veins, or small blood vessels or is the result of complications during pregnancy. Its prevalence in the general population is 1% to 5%.[20] In addition to clinical symptoms, certain parameters must be measured to make a diagnosis according to the Sapporo criteria: lupus anticoagulant, anticardiolipin antibody of IgG and/or IgM, and anti-β2-glycoprotein 1 antibody of IgG and/or IgM.[21] The test results must be confirmed after at least 12 weeks.[20,22] In the case of thrombophilia testing, the anticardiolipin and anti-β_2-glycoprotein 1 antibodies results are not distorted under a blood thinning regimen or as a result of acute thrombosis. The lupus anticoagulants can be erroneously high when DOACs or VKAs are administered.[22,23] Control testing during a pause in treatment or through bridging with LMWH is recommended.[24] A neutralization (dilute Russell viper venom time) of the blood thinner is necessary when VKAs and DOACs are used as part of the anticoagulation treatment.

Table II shows which patients need to be tested for APS. The risk of thrombosis with APS increases in proportion to the number of positive measurement parameters. The annual risk of thrombosis for APS is 2% to 5%; the cumulative risk for high-risk patients is 12% after 1 year, 26% after 5 years, and 44% after 10 years.[20,26]

In choosing the treatment anticoagulant, the results of the three laboratory test variables for APS play a significant role.[24] TRAPS had to be discontinued prematurely because compared with warfarin, rivaroxaban significantly increased the number of arterial thromboses in APS patients with triple-positive testing

Table II. For which patients is antiphospholipid syndrome (APS) testing appropriate?[20,25]

Appropriateness high	Unprovoked thromboses and arterial thromboses in young patients (<50 years)
	Atypical locations of thrombosis
	One or more pregnancy-related complications (eg, unexplained death of the fetus *after* week 10 of pregnancy)
Appropriateness moderate	Provoked thrombosis in young patients
	Multiple spontaneous miscarriages *before* week 10 of pregnancy or other causes
	Asymptomatic patients with prolonged activated partial thromboplastin time
Appropriateness low	Venous or arterial thromboses in older patients

parameters (lupus anticoagulant, anticardiolipin antibody of IgG and/or IgM, and anti-β2-glycoprotein 1 antibody of IgG and/or IgM).[27] These were patients with high-risk APS. Dabigatran and apixaban also showed increased thrombosis recurrence rates in high-risk APS patients.[28] When all three testing parameters are positive, no DOACs may be administered. Testing should be meticulous and comprehensive, and these parameters must be verified in a confirmation test; the results of an incomplete test cannot be used to make treatment decisions.

Answer. Because we were dealing with a high-risk APS patient, the anticoagulant treatment with VKAs needed to continue. The test results could be confirmed after 12 weeks.

Question 5. Which coagulation value may indicate APS (pitfall)?

The presence of a prolonged activated partial thromboplastin time may indicate APS.[18] The activated partial thromboplastin time describes the intrinsic pathway of coagulation activation triggered by phospholipids. Antibodies (lupus anticoagulant) inhibit the phospholipid-protein components and thus prolong the time of the intrinsic coagulation activation. Unlike with VTE, the prolonged activated partial thromboplastin time would indicate hemophilia if bleeding should occur.

Answer. If patients have a weak VTE trigger or if a prolonged activated thromboplastin time has been determined, testing for APS should also be done in the acute stage. This may affect the length of treatment as well as the choice of anticoagulant.

CONCLUSIONS

The following key statements can be extracted from this case study and should be considered by vascular physicians in their everyday practice:

→ VTE can be provoked through vein stripping, foam sclerotherapy, or endovenous therapy.
→ However, vein stripping, foam sclerotherapy, and endovenous therapy are *weak risk factors* for VTE.
→ Thrombophilia testing should be considered for patients with provoked thrombosis with a *weak risk factor*, a positive family history, and experience with recurring thromboses.
→ Thrombophilia testing is generally not recommended during the acute phase except in the case of APS.
→ A prolonged partial thromboplastin time may also indicate APS.
→ DOAC is contraindicated in patients with a high risk of APS.

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Submitted Jan 15, 2020; accepted Mar 13, 2020.