

Fatal pulmonary embolism following ultrasound-guided foam sclerotherapy combined with multiple microphlebectomies

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Abstract

Ambulatory ultrasound-guided foam sclerotherapy (UGFS) for refluxing saphenous veins is considered a safe therapy. Venous thromboembolic complications after UGFS as well as after all other ambulatory ablative venous interventions are rarely reported. This paper reports a fatal pulmonary embolism (PE) following UGFS in combination with an extended phlebectomy, and questions what measures should be taken to minimize the risk for thromboembolic complications after these procedures. In the reported case (unsuspected), extensive non-occluding atherosclerosis as well as obesity in combination with use of an oral contraceptive might have contributed to the development of the PE while the use of a β -blocker might have increased its fatal course considerably. Routine measurement of the ankle-brachial pressure index reduces the risk for undetected atherosclerosis. It appears that 'in the real world' of ambulatory phlebological treatments thromboembolic complications are more common (2.4–4.7%) and appear accompanied by post-procedural mortality. It is concluded therefore that pharmacological thromboprophylaxis appears warranted in selected cases, perhaps even routine application could be considered. Attention is drawn to the highly thrombogenic but not uncommon combination of overweight and use of oral contraceptive. Apart from applying some form of pharmacological thromboprophylaxis, technical adaptations that might prevent or reduce spill over of foam into the deep venous system should be considered. Firstly, next to adherence to the generally accepted maximum of 10 mL of foam per session, it seems prudent to maximize the injected volume of foam per site. Secondly, it seems best to inject the foam in an elevated leg without groin compression. The concentration of the sclerosant does not appear decisive in this respect, although higher concentrations appear more effective and therefore might be injected in lower volumes without compromising efficacy.

Keywords

Foam sclerotherapy, ultrasound-guided sclerotherapy, pulmonary embolism, complications, venous thromboembolism prophylaxis

Introduction

Recently we experienced a case of fatal pulmonary embolism (PE) following ambulatory ultrasound-guided foam sclerotherapy (UGFS) of the anterior accessory saphenous vein (AASV) combined with multiple microphlebectomies under local anesthesia. Confronted with this serious adverse event we have reviewed the literature. In this paper, we report and discuss this case, review the epidemiology and risk factors of venous thromboembolic complications after UGFS of saphenous reflux, and present possible actions to prevent these complications.

Case

A 52-year-old woman developed varicose veins on the anterior and medial side of the left thigh and the medial

side of her lower left leg. Since 3 months she complained of a swollen left ankle and aching cramps in the left calf. Sitting with a raised leg reduced her complaints. Past medical history revealed migraine for which she was using propranolol medication for several years, three uneventful pregnancies and deliveries, and the use of an oral contra-conceptive (Microgynon-30) because of menometrorrhagia.

Physical examination showed bulging varicose veins antero-medially in the left thigh and medially in the

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lower leg with an average diameter of 5 mm, and a distinct edema at ankle level. No skin abnormalities were seen. A color-coded duplex scan of the left leg showed no signs of occlusion or reflux in the deep veins including the gastrocnemial veins. The great and small saphenous veins were free from occlusions and reflux. Reflux by way of an incompetent sapheno-femoral junction was seen in a centrally wide (diameter 7.8 mm) and markedly tortuous anterior accessory saphenous vein (AASV) of about 8 cm length arranged in 3 hairpin loops of about 2.5 cm each.

Based on these findings the phlebologist suggested treatment by foam sclerotherapy of the AASV and microphlebectomy of its tributaries. Three weeks later she was operated upon under local tumescent anesthesia. After ultrasound-guided introduction of a Venflon needle in the smaller peripheral ending of the AASV, approximately 12 cm below the inguinal crease, the operation table was placed in Trendelenburg position and 5 mL of foam, produced according to Tessari from 1 mL polidocanol (POL) 3% and 4 mL air, was injected and followed by ultrasound up to the sapheno-femoral junction. After this, the left leg was raised passively about 50° and she was requested to move her left foot for 2 min. Thereafter, 220 mL tumescent phlebectomy solution (1 L 0.9% saline to which was added 100 mL 1% lidocaine with 1:200,000 epinephrine and 10 mL 8.4% sodium bicarbonate) was applied around the tributaries of the AASV that were subsequently removed through 14 micro-incisions using hooks and fine tipped clamps. Finally, a compression bandage from the foot up to the groin was applied after which she was walked back to the recovery room. There she remained, sitting in a long-chair, for about 30 min, after which she returned home with detailed instructions about regular exercise of her calf muscles.

As a standard procedure a nurse called her the next morning to verify her condition. She reported no complaints and no significant pain. The day thereafter she removed the compression bandage and wore an anti-embolic stocking. Later that day she acutely felt severe discomfort and managed to call her husband and general practitioner. The GP arrived first and found her unconscious with no cardiac output. Immediate basic life support was initiated. Paramedics arrived 8 min later and found a cardiac arrest with pulseless electrical activity (PEA). Under continuous CPR she was rushed into hospital where she was found deceased. Autopsy revealed an embolic occlusion of the left pulmonary artery. No deep venous thrombosis (by manual emptying of the femoral veins) or emboli in the remaining pulmonary arteries were found. Unexpectedly extensive non-occluding atherosclerosis of the entire aorta was found.

Discussion

In literature, we found only one case of fatal PE following ambulatory phlebological treatment.¹ This concerned a woman of 36 years without any indication of thrombophilia and without any personal risk factor for the development of thrombotic complications. Her right leg had been treated with 5 injections of 0.5 mL sodium tetradeceyl acetate 3% in three incompetent medial thigh and lower leg perforating veins and two small varicose veins in the lateral aspect of the calf. Immediately after treatment she returned home by car. Two days later she attended her general practitioner complaining of mild discomfort in her right calf. The patient was then apparently well and active until she suddenly collapsed and died 10 days after treatment. Autopsy showed bilateral embolic obstruction of the main lobar divisions of the pulmonary artery. Furthermore, there was evidence of venous thrombosis in the deep veins of the right calf.

We found another case of PE that probably would have been fatal had not the patient been still hospitalized.² A 54-year-old woman with varicose veins in her left leg caused by great saphenous vein (GSV) reflux had no risk factors for venous thromboembolism (VTE) other than obesity. She was treated under local anesthesia by high ligation of the GSV followed by 6 injections of 0.5 mL liquid POL 3%, 3 in the GSV at lower-thigh level and 3 in tributary varicose veins in the calf. Compression with cotton pads under an elastic bandage had been applied. The patient was encouraged to walk immediately after the operation. She stayed in the hospital that day and the night following. The following morning, after starting to walk, she complained of severe discomfort in the chest and suddenly collapsed. Her left leg showed marked swelling suggestive of iliofemoral deep venous thrombosis. Emergency pulmonary perfusion scintigraphy revealed multiple filling defects bilaterally. Aggressive anticoagulant and thrombolytic therapy was successfully instituted, and she was discharged on the 21st postoperative day, having been put on warfarin.

In the generally healthy population of patients who are treated for varicose veins in an ambulatory setting, serious adverse events are considered (very) rare phenomena and as such are discussed scarcely with these patients. The most frequently reported serious adverse events appear VTEs. However, the incidence of this complication appears rare, approximating 1%, as well as after endovenous thermal ablation^{3,4} as after foam sclerotherapy.^{5,6} Pharmacological thromboprophylaxis is not recommended in ambulatory surgery under local anesthesia with no limitation of postoperative mobility.⁷ Generally this rule also is applied to patients undergoing endovenous thermal ablation of saphenous veins ambulatory under local anesthesia,

thromboprophylaxis not being considered cost effective because of the perceived low risk.^{3,4} Both the Dutch and British clinical guidelines on the diagnosis and management of varicose veins do not address thromboprophylaxis at all.^{8,9} The American Guidelines recommend pharmacological thromboprophylaxis for open venous surgery if additional thromboembolic risk factors are present like known thrombophilia, history of DVT or thrombophlebitis, or obesity.¹⁰ In case of endovenous thermal ablations, patients with these risk factors are considered 'candidates for thrombosis prophylaxis' according to these guidelines. In the recently published *European Guidelines for Sclerotherapy in Chronic Venous Disorders*, pharmacological thromboprophylaxis is recommended 'in patients with high risk of thromboembolism such as those with a history of spontaneous DVT or known severe thrombophilia'.¹¹ In our clinic since 2008 thromboprophylaxis has been prescribed for these indications as well as for recent superficial venous thrombosis. Moreover, thromboprophylaxis has been applied in case of history of a first grade relative with VTE before the age of 45 years. No other indications than these were observed.

In reviewing the relevant literature obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was found to increase the risk for VTE in primary care setting by a factor 2.¹² When introducing our protocol for thromboprophylaxis back in 2008, we considered this odds ratio too low to warrant thromboprophylaxis. Use of a second generation oral contraceptive increases the risk by a factor 3.6.¹³ On top of that it has appeared that overweight ($\text{BMI} > 25 \text{ kg/m}^2$) and use of oral contraceptives together show synergy for this effect, resulting in a 10-fold increased odds ratio.¹⁴ This is about two times the risk patients run with heterozygous factor V Leiden mutation, the most common genetic risk factor for VTE.¹⁵ Of this evidence we were not aware at that time, otherwise we would have listed this combination of oral contraceptive use and overweight as an indication for thromboprophylaxis.

In our case, an unexpected extensive atherosclerosis appeared present at aortic level at autopsy. It has been recognized that idiopathic VTE might be the first symptom of atherosclerotic disease.¹⁶ Possibly arterial obstructions in leg arteries were present, resulting in reduced venous leg flow. Stasis and hypercoagulability now are accepted as the most important factors of the Virchow triad to promote VTE.¹⁶ Obesity also promotes venous stasis.¹⁷ Furthermore, morbid obesity appears accompanied by a marked increase of blood coagulability, and is associated with a four- to six-fold increased risk for PE.¹⁸ Considering the synergistic effect of venous stasis and hypercoagulability on the risk for VTE, morbid obesity as such appears an

indication for thromboprophylaxis in ambulatory venous treatment. Venous stasis in our case may have been amplified by her using a β -blocker (propranolol). Also this medication increases the risk for a fatal course of PE since it markedly reduces contractility of heart muscle, thereby promoting acute right ventricle failure after PE.¹⁹ In case of a normally functioning heart, over 50% of the pulmonary vasculature should be obstructed by clot before right ventricular failure ensues.²⁰ Of course, had atherosclerotic disease been perceived before treatment, operation as well as her prescription of the β -blocker by the general practitioner for migraine would have been withheld. In our clinic, it is custom to rule out lower extremity peripheral arterial disease by clinical examination. In practice, a normal color and temperature of the skin of the foot is considered to rule out significant arterial disease. However, clinical examination, including palpation of arterial pulses, has been found unreliable in this respect compared to routine measurement of systolic ankle pressure index.²¹ Considering the increased odds for VTE in patients with atherosclerosis, it appears warranted to exclude its presence by routine measurement of systolic ankle pressure index.

In the presented case, an unhappy chain of events has lead to the fatal outcome, which can happen in the real world. After all, the risk for PE is not zero, and unknown as well as unrecognized conditions might cooperate in aggravating the consequences of a PE. Recently, a study has been published that according to its authors revealed the incidence of thromboembolic complications 'in the real world' of ambulatory varicose vein treatment with endovenous techniques.²² They found a prevalence of DVT within 30 days of treatment of 4.4% after radiofrequency ablation (RFA), 3.4% after 'multiple therapies – same day' (combination of techniques in one session), 3.1% after endovenous laser ablation (EVLA), 2.6% after 'multiple therapies – deferred' (mean deferral duration was 73 days), 2.4% after surgery, and 0.8% after sclerotherapy. For PE, this prevalence was 0.3% after RFA, surgery, and EVLA alike; and 0.2% for 'multiple therapies – same day', 'multiple therapies – deferred', and sclerotherapy alike. Prevalence of death within 30 days of the procedure appeared 0.05% after RF, 0.04% after EVLA and after 'multiple therapies – same day', 0.02% after 'multiple therapies – deferred', and zero after surgery and after sclerotherapy. The frequency of death associated with DVT or PE varied from 0.5% to 3.4%, and was highest for subjects experiencing a PE in the EVLA and 'multiple therapies' cohorts (range, 2.7–4.1%). The numbers of patients in both the surgery and the sclerotherapy group were about half or less the numbers of patients compared to the other groups. Furthermore, sclerotherapy, including foam

sclerotherapy, in the USA predominantly is reserved for treatment of patients with uncomplicated minor veins or thread veins, and the authors were not able to distinguish between the use of foam sclerotherapy for minor veins and great saphenous veins. These facts probably explain the better results with surgery and sclerotherapy. The authors stipulate that the rates observed in their study are especially noteworthy, since generally only *clinically significant* adverse events are coded in administrative claims databases. So, they remark, actual rates might be still higher (sic). These rates are about three to four times formerly reported rates, and for that might be discarded by the phlebological community. However, we should realize that reports on thromboembolic complications after ambulatory surgery might underestimate their prevalence as a result from publication bias, relatively high percentage of patients being lost to follow up, relatively small sample sizes, and relatively high incidence of asymptomatic or minimally symptomatic (and therefore undetected) VTEs. So, we regard this large, community-based study to mirror the state of affairs in this respect better than previous reports, and consider some form of pharmacological thromboprophylaxis warranted. Frequently routine scanning of treated legs has been proposed as a mean to detect and treat thrombotic complications after these interventions. However, this appears not justified for several reasons. Firstly, even with an unrealistic high sensitivity and specificity of 98% resp. 95% and a post-treatment VTE of 2.3%, screening 1000 patients will not only detect all 23 DVTs but another 49 patients will return with a false-positive scan giving a positive predictive value of 0.32.²³ This signifies that for each real DVT another 2 patients without DVT will be treated for DVT and suffer all the anxiety and possible bleeding complications accompanying this diagnosis and treatment. In the 'real world' this positive predictive value is considerably lower, so many more patients will be harmed.²³ Secondly, a patient scheduled for a scan after say one week, might develop and even die from a PE before that date. Thirdly, the attendant expense to the public health system of routine scanning will be considerable.²³

There are no randomized placebo-controlled trials concerned with the efficacy of pharmacological thromboprophylaxis in ambulatory endovenous surgery to guide us. The only indication that it might be effective in patients with increased risk comes from a publication of Hamel-Desnos et al.²⁴ In an earlier retrospective study they had found 5 cases of DVT in 56 patients (9%) with thrombophilia treated with sclerotherapy. In a prospective study, 105 patients with established thrombophilia scheduled for sclerotherapy (mostly UGSF of saphenous veins and tributaries) were randomized to single shot prophylaxis with nadroparine

(4000 IU) immediately before treatment or to fixed low dose (1 mg) of warfarin starting 10 days before first treatment session and continued until 4 weeks after the last treatment session. Seventy patients had been screened for thrombophilia because of a personal history of VTE, 14 of them a PE. In total 199 treatment sessions were performed, 160 with foamed and 36 with liquid POL. In both groups, not one case of VTE was reported. These results appear indicative for the effectiveness of thromboprophylaxis for these indications. However, randomized (placebo) controlled trials are needed.

Apart from pharmacological thromboprophylaxis the technique of deliverance of the foam, the concentration of the sclerosant, and appliance of measures to prevent spill over of foam into the deep venous system might influence the risk for VTE after UGSF. Unintentional damage of deep venous endothelium by foam injected into a superficial axial vein might be provoked by vessel wall approximation due to vasospasm, turbulent flow due to fast delivery, and the use of the foam format especially at high volumes.^{25,26} Although endothelial damage is the least important factor of the Virchow triad,¹⁶ and detergent sclerosing agents are rapidly deactivated when mixed with blood,^{27,28} it seems prudent to minimize spill of foam into the deep venous system.²⁷ Amongst others this might be effected by keeping the injected volume of foam per session low. Rather arbitrarily the preferred maximum has been set to 10 mL.^{11,26} However, this designation lacks preciseness. The volume of the venous segment, and possibly the fact that this will be reduced by reactive venous wall spasm, should be taken into account.²⁹ Some authors advise to limit the volume per injection to 0.5–3 mL, others to 3–5 mL.^{30,31}

Guex²⁹ supplied a detailed table with requested volumes according to venous diameter and length. Fegan²⁷ only injected 0.5 mL aliquots in 5 cm segments that were isolated by finger pressure during 30–60 s after the injection had been delivered. In over 13,000 patients treated by him or his registrars no symptomatic VTE was noted. When Fegan²⁷ started with sclerotherapy in 1953, it had been demonstrated already that spill over into deep veins is likely if more than 0.5–1.5 mL of solution is injected at a single site.³² Yamaki et al.³³ found in an ultrasound-controlled study, that spill over into the deep venous system was halved by halving the injected median volume of foam per injection site from 0.9 to 0.4 mL. The mean total volume of 3% POL to treat the great saphenous vein was only 1.5 mL, which explains their rather poor occlusion rate at 6 months of about 55%. Possibly multiple injections, spaced about 10 cm from escape points, with a somewhat higher foam volume might reduce spill over enough to reduce the thrombotic risk without affecting

efficacy. In contrast, in our personal series rather long segments (15–40 cm) were treated with single injections of foam from 3 to 10 mL, according to diameter and length as mentioned before.²⁹ So, although evidence is scarce, it seems logically more prudent to restrict injection volumes to about 2 mL at a distance of about 10 cm from a communicating vein between the superficial and deep system. Of course, all the time the advancement of the hyperechogenic cap at the front of the injected foam should be followed echoscopically, and injection halted immediately when this cap reaches a communication with the deep venous system within a few centimeters. In case of foam migration to the deep system, vigorous ankle flexion-extension will dissipate the foam fragments.³¹ Several experts in this field have advocated to compress the groin once the front of the foam is near to the sapheno-femoral junction. Although this reduces the leakage of foam, it does not abolish spill over in the deep system.³⁴ Furthermore, after release of compression foam appeared on echocardiography more frequent and more intense in the right heart than in patients treated without compression and in whom the leg had been elevated during the injection.³⁵ So, it seems UGFS of GSV (and AASV) is best performed with the leg elevated without manual pressure at the groin.³⁵

Finally, foam produced from POL 3% appears equally effective to foam produced from POL 1% according to one study,³⁶ and more effective according to another study,³⁷ without increase in side effects including VTE in both studies. The advantage of using POL 3% is that the injected volume might be reduced compared to POL 1% without losing efficacy.

Conclusions

1. VTE complicating ambulatory venous treatments (including foam sclerotherapy) most probably presents itself 'in the real-world' in a frequency of 2.4–4.7%. Even fatal complications, although very rare, are possible. The combination of stasis and hypercoagulability, much more than endothelial damage, is crucial for the occurrence of VTE.
2. Obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) appears an important risk factor for VTE, both because it is associated with hypercoagulability as well as with venous stasis.
3. The prothrombotic effect of overweight ($\text{BMI} > 25 \text{ kg/m}^2$) is synergistically enhanced in women by use of oral contraceptives resulting in a 10-fold increased odds ratio for VTE.
4. Even extensive atherosclerosis might go unnoticed by clinical examination alone.
5. Pharmacological thromboprophylaxis might be effective in patients with increased risk for VTE but more, preferentially randomized placebo-controlled, trials are needed.
6. Spill over of foam into the deep system appears correlated with the amount of foam injected per site.
7. Foam produced from POL 3% does not appear more thrombogenic than POL 1%.
8. When treating saphenous veins in connection with the sapheno-femoral junction, compression at the groin does not appear effective in preventing foam to reach deep veins and the right heart. Injecting foam in an elevated leg appeared much more effective in this respect.

Recommendations

1. In ambulatory venous treatments including UGFS pharmacological thromboprophylaxis appears warranted:
 - (a) In selected cases of known or suspected thrombophilia like personal history of VTE or SVT, demonstrated congenital or acquired thrombophilic serum factors, or history of VTE in a first grade member of the family at the age of 45 and younger.
 - (b) In case of obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$).
 - (c) In case of overweight ($\text{BMI} > 25 \text{ kg/m}^2$) combined with the use of oral contraceptive.
2. Routine measurement of ankle pressure-index should be considered in patients scheduled for ambulatory venous treatment to rule out clinically significant atherosclerosis.
3. It seems logical and prudent to individualize the injected volume of foam according to the length and diameter of the vein that has to be treated and restrict the injected volume of foam per injection site to avoid (or reduce) the spill over into deep veins.
4. It seems best to prevent foam from entering the deep system by injecting it in an elevated leg.

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Conflict of interest

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