MULTICENTER ASSESSMENT OF VENOUS REFLUX BY DUPLEX ULTRASOUND

A DOUBLE BLIND, RANDOMIZED STUDY COMPARING PURE CHROMATED GLYCERIN WITH CHROMATIC GLYCERIN WITH 1% LIDOCAINE AND EPINEPHRINE FOR SCLEROTHERAPY OF TELANGECTASIAS AND RETICULAR VEINS
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Multicenter Assessment of Venous Reflux by Duplex Ultrasound

Contributing Editor/Reviewer: G Mark Malouf, FRACS
Associate Editor: Diana Neuhardt, RVT, RPhS

A double blind, randomized study comparing pure chromated glycerin with chromatic glycerin with 1% lidocaine and epinephrine for sclerotherapy of telangiectasias and reticular veins

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Neurological complications of sclerotherapy for varicose veins

Contributing Editor/Reviewer: Kurosh Parsi, MBBS, MSc Med, FACD
Associate Editor: Pauline Raymond-Martimbeau, MD, FACP

Failure of microvenous valves in small superficial veins is a key to the skin changes of venous insufficiency

Contributing Editor/Reviewer: Marlin Schul, MD, MBA, RVT, FACP
Associate Editor: Jean-Jerome Geux, MD, FACP

Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial

Contributing Editor/Reviewer: Peter J. Pappas, MD
Associate Editor: Lowell S. Kabnick, MD, FACS, FACP, RPhS

Contents
mar-apr '12
<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephanie Dentoni, MD</td>
<td>Recruitment &amp; Retention Cmte (C), Leadership Development</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Mark Forrestal, MD, FACPPh</td>
<td>ACP</td>
<td>CoolTouch: Stockholder</td>
</tr>
<tr>
<td>Mitchel P. Goldman, MD, FACPPh</td>
<td>Merz: Grant/Research Support, Consultant,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Speakers’ Bureau, Bioniche: Consultant, STD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmaceuticals: Consultant, BTG: Grant/Research Support, Consultant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New Star Lasers: Stock and/or Shareholder</td>
<td></td>
</tr>
<tr>
<td>Jean-Jerome Guex, MD, FACPPh</td>
<td>ACP BOD, Communications Standing Committee (C), International Affairs (C), Leadership Development Standing Committee, UIP 2013 Task Force, AMA HOD Task Force</td>
<td>Innotech International- Investigator; Pierre Fabre: Consultant; Sigvaris: Investigator; Vascular Insights, LLC: Scientific Advisory Board; Servier-Eutherapie: Speaker</td>
</tr>
<tr>
<td>Lowell Kabnick, MD, FACS,</td>
<td>ACP BOD, Education Standing Committee (C), UIP 2013 Task Force, Exhibitor Advisory (C), Phlebology Forum, Program Development, Leadership Development</td>
<td>Angiodynamics: Consultant, Scientific Advisory, Stockholder: Merz: Speaker; Vascular Insights LLC: Scientific Advisory</td>
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<tr>
<td>FACPh</td>
<td>ACP</td>
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<tr>
<td>Neil Khilnani, MD, FACPh</td>
<td>ACP</td>
<td>Sapheon: Consultant</td>
</tr>
<tr>
<td>Ted King, MD, FAAFP, FACPh</td>
<td>ACPF BOD</td>
<td>Angiodynamics: Investigator; BTG: Investigator; Merz: Speaker, Consultant</td>
</tr>
<tr>
<td>Mark Meissner, MD</td>
<td>ACP</td>
<td>Nothing to Disclose</td>
</tr>
<tr>
<td>Eric Mowatt-Larssen, MD</td>
<td>CME Committee</td>
<td>BTG: Consultant</td>
</tr>
<tr>
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<tr>
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<td>MD, FACPPh</td>
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<td></td>
</tr>
</tbody>
</table>
Dear Readers,

This issue of Phlebology Forum features a number of very important articles on practical situations involving both the deep and superficial venous system, with which we all routinely deal in our practices, and which are well-reviewed by renowned experts in the field of Phlebology. The Editorial staff of Phlebology Forum welcomes all feedback and suggestions from readers. Please respond to: marmitage@acpmail.org

Nick Morrison,
Editor-in-Chief
Multicenter Assessment of Venous Reflux by Duplex Ultrasound

Fedor Lurie et al.
Journal of Vascular Surgery 2011

Contributing Editor/Reviewer: G Mark Malouf, FRACS

Associate Editor: Diana Neuhardt, RVT, RPhS
Without any current standardization of venous reflux testing protocols or a clear understanding of the expected variability between repeated reflux time measurements it is impossible to define meaningful change over time or as a result of intervention. The American Venous Forum initiated the INVEST study – INvestigating Venous disease Evaluation and Standardisation of Testing – aiming to establish a standardized protocol for duplex assessment of venous reflux. This paper is the report of the first phase of that project. This study aimed to assess the repeatability of duplex-based identification of venous reflux and to assess the relative effects on reproducibility of key parameters: patient position, time of day, reflux provoking mechanisms, training/coaching of technologists, the change in the definition of clinical reflux from 1 to 0.5 sec, and whether deep or superficial veins were being examined.

Repeatability was defined as the closeness of agreement between test results under conditions as constant as possible – same technologist, equipment and all parameters the same on repeat testing. Reproducibility was defined as closeness of agreement between test results using the same techniques but in a different vascular lab by a different technologist using different equipment. A standardized training course explaining the study protocol and stressing the test techniques, measurement, interpretation and recording of results was used for coaching the vascular technologists - facilitated reproducibility.

B mode and pulse-wave Doppler +/- color Doppler were employed. Reflux time was measured in a longitudinal view with the probe angle at ≤ 60°. Calf compression was achieved using manual compression then one of two types of mechanical rapid inflation devices. Valsalva maneuver was not used.

74 patients were studied (17 controls, 57 with primary CVD) sub-grouped thus:

- Repeatability was examined in 34 patients
- Reproducibility was examined in 43 patients, 39 of whom had facilitated reproducibility
- Morning and afternoon studies were performed in 34 patients for comparison
- The use of two different reflux provoking mechanisms was performed in 36 patients
- Different patient positions were studied in 30 patients

RESULTS:

Repeatability was best achieved with a morning examination in the standing position. Repeatability of reflux time measurements in deep veins were significantly better than in superficial veins. Using 0.5 sec cut off point for reflux was just as repeatable as 1.0 sec at approx 92%

Reproducibility: The mean difference between reflux measurements comparing two technologists was 0.12 sec falling
to 0.03 sec with facilitated reproducibility (coaching the technologist). Approximately 84% agreement between technologists improved with facilitated reproducibility to over 94%.

**Morning vs Afternoon Studies:** Afternoon duplex ultrasound examinations produced significantly longer reflux times; the longer the reflux time, the larger the difference between morning and afternoon measurements.

**Reflux Provoking Maneuvers:** Manual vs automated calf compression showed no significant difference in mean values.

**Patient Position:** Reflux time was shorter when the patient was standing, longer when the patient was supine.

**Defining Pathological Reflux at 0.5 sec vs 1.0 sec:** Different patient positions and times of the day did significantly alter interpretations of reflux between these two cut-off points with 0.5 sec having better agreement with no significant difference for deep vs superficial veins, time of day, patient position or method of calf compression.

**DISCUSSION:**

The lack of standardization of vascular laboratory testing is noted as a hindrance to improvements in care for CVD patients. Two identically repeated studies agreed on 80-96% of occasions in this study, better in the morning, standing. A current internationally consensus-accepted minimal standard of 70% for agreement between repeated duplex scans is stated as a low benchmark, greatly improved by the standardized methods in the study. Written information should be provided in the vascular lab report detailing variables: time of day, position of the patient, calf compression technique. The criteria of 0.5 sec pathological reflux improves reliability of the measurements. These measures raise the minimum agreement of venous reflux testing between centres from 70% to above 94% and the authors maintain that this will lead to improved research and improved clinical management of patients with CVD.

**COMMENTARY:**

This article, written by many of the world’s most esteemed venous experts, aims to assess and improve the factors that influence the reliability of our duplex measurement of venous reflux. The authors have taken the common variables in duplex scanning protocols used by the majority of us and assessed their effect on repeatability and reproducibility. They conclude that if we standardized the protocols and the parameters regarding venous reflux, and intensely train/coach our technologists, we can raise the frequency of agreement between results to over 90% from a currently accepted 70%.

Dr Lurie has extracted maximum information from the statistical analysis of repeated measurements of venous reflux in 74 patients. I agree with his emphasis on the uniform protocol and the standardization of the common variables.
mentioned; perhaps any change in these parameters of the study should be included in the written report. This paper strongly suggests that our most consistent venous incompetent duplex scanning is performed in the morning, with the patient standing, with either manual or automatic calf compression and adopting 0.5 sec as a cutoff point for reflux. The other major point is the improvement in accuracy when the technologists are comprehensively coached so we would all be using the same criteria to be able to report reflux in a specific vein.

The paper, like many of our protocols, describes venous reflux as being “present” or “absent” according to the cutoff time arbitrarily used to define venous reflux. There is no requirement to attempt quantification of a little reflux or a large amount of reflux or state the exact duration. There is no mention in the paper that reports should contain comment regarding where the reflux leads, possibly into obvious varicosities or accessory veins or tributaries.

Setting an arbitrary lower limit of 0.5 sec helped standardize reproducibility of the presence of venous reflux. Further questions arise from this. The patients we see with gross C2 disease and most cases of C3 to C6 disease will demonstrate obvious duplex-detected venous reflux that will easily surpass the criteria for the 0.5 sec cut point. However in the western world we are witnessing increasing numbers of C0, C1 and early C2 patients undergoing venous incompetence duplex scans for a variety of reasons. With this group I have serious concern regarding possible over-diagnosis and over-treatment of venous reflux at >0.5 sec with little else to support the finding of pathology. Many of these patients are offered expensive and unnecessary treatment simply because a duplex scan reported “venous reflux” present, especially when remuneration for venous treatment is based on “duplex-proven reflux” and little else. This cutoff of 0.5 sec certainly may facilitate agreement with repeat studies but I have noted a recent outbreak of rampant over-diagnosis of venous reflux in duplex scan reporting. Should we lower the bar of pathological venous reflux without stressing to treating physicians the duplex findings MUST be taken in context with the clinical features and not be used in isolation to encourage patients to undergo possibly unnecessary treatment.

I commend this paper to you. I strongly agree that uniform protocols and good technologist training regarding the interpretation for venous reflux will allow us to monitor CVD better over time between practitioners.

Yes such standardization will facilitate progress in research and in clinical management of patients with CVD, but I suggest that clinical factors also be taken into account to achieve this.
A double blind, randomized study comparing pure chromated glycerin with chromatic glycerin with 1% lidocaine and epinephrine for sclerotherapy of telangectasias and reticular veins

P.Kern, A.A Ramelet, R Wutschert, L.Mazzolai
Dermatologic Surgery 2011; 37:1590-1594

Contributing Editor/Reviewer: Robert Weiss, MD, FACPh

Contributing Editor/Reviewer: Stefano Ricci, MD

Associate Editor: Mitchel Goldman, MD, FACPh
REVIEW AND COMMENTARY BY STEFANO RICCI, MD

Chromated glycerin (CG) (72% glycerin/0.8 chromium alum) is an effective sclerosing agent for telangectasias and reticular veins treatment. Its injection being painful, lidocaine-epinephrine may be added (1/3 + 2/3 of CG = CGX) but no true evidence exists that this solution is less painful and as efficacious as CG alone.

A prospective randomised double blind trial comparing pain scores and rate of vessel disappearance of GC versus GCX was developed on the basis of 110 patients in a private office of vascular medicine in Switzerland. All the patients presented cosmetic dilatation of lateral thigh reticular or telangectatic veins never treated before.

Injections were performed by 2 ml syringes and 30G needles with 10 mL as maximum amount, through 60-80 injections of very small volumes. Reticular veins were injected first. After treatment patients were asked to score their pain by a visual 100-point scale and to wear thigh-length stockings (23-32 mm Hg) for one- three weeks during the day. During the control visit at 5 weeks after treatment patient satisfaction was scored by a visual 100-points analogue scale. A photographic image of the treated area, in the same conditions of the one taken before treatment, was used to be compared by two blinded experts.

Fifty-two patients in CGX group and 50 in CG group were available. CGX was significantly less painful than CG with a pain score of 23.8+/−17 versus 41.5+/−8.8. There was no difference between the two groups in all the other comparative scores of satisfaction, veins clearance, side effects.

It is not clear how lidocaine induces an immediate pain reduction as usually it needs some time to induce anesthesia; possibly some lidocaine may diffuse during initial reticular veins injection. Although diluted by 1/3, CGX shows similar efficacy compared to pure CG. This may be explained by vasospasm allowing a longer contact of the agent with the vein wall.

Adding lidocaine-epinephrine to CG (ratio 1:2) almost halves the pain score without any reduction of its efficacy.

COMMENTARY

Scientific papers about scleroterapy of telangectasias are rare because the subject is apparently “cheap”. Even rarer are scientific papers about chromic glycerin, an old faithful agent (3) not sufficiently appreciated. But the interest is great for both subjects and the audience very large. That’s why this paper deserves attention. The authors have a vast experience of sclerotherapy with CG,
demonstrated by several papers published on the subject. Here they analyze the problem related to the pain upon injection and pain reduction by lidocaine; they show evidence of its efficacy even if the explanation of the mechanism of pain reduction is not given.

This mixture, popularised by Goldman in several recent writings is in reality indicated by Davy and Ouvry in a paper of 1984 where CG was considered already the treatment of choice for telangectasias, either diluted with xylocaine (1/3 or 2/3=CGX) or pure.

In fact CGX may be less painful simply because it is diluted. CG pain is due to the contact of the agent with the extra vascular tissues as an injection inside the vein without any extravasations is not painful. When used in very small vessels CG frequently has some sort of contact with the perivenous space (around the needle, in the transdermic trajectory, in case of too small calibre of the vein receiving the injection, when injecting extra-luminally) only then generating pain, defined as a burning sensation. This lasts about 30 seconds and is reduced by finger massage. Dilution with 1/3 of the volume with lidocaine/epinephrine is suggested by the authors with good results; however it corresponds to a very high dosage of this anesthetic mixture. If we consider the use of 10 ml of sclerosing solution we can calculate that about 3.5 ml of anesthetic solution is employed. Using this same amount, the whole area concerned in the treatment could be anesthetised by tumescence. Why employ so much volume of agents? The adrenaline effect would be the same even in a lesser amount, the lidocaine effect could be the same in a lower concentration. In fact in the experience of Robert Muller (and in my father’s experience too since the seventies), a 1/5 ratio of lidocaine/epinephrine was employed, this being enough for reducing the pain.

This study demonstrates also that diluted CG has the same efficacy of full CG. This could signify that full CG is quite strong for the purpose it is used and that a more dilute solution might be appropriate. This consideration would deserve a specific trial to understand what the limit of dilution that maintains efficacy is. CG mixed with 0.25 polidocanol in a 50% ratio, in my personal experience, has an even more satisfying effect with lower side effects, although the action of the second agent may alter the judgement. This solution has the advantage of being less viscous than CG or CGX, employing the polidocanol for both endothelial lesion and vasospasm effects.

Finally, we don’t know exactly what the effect of the CG on the vein wall is. The agent being a polyalcohol, it acts as a chemical irritant sclerosant. It is considered a weak sclerosant but with the advantage of rarely causing hyper pigmentation and matting. Its action is effectively slow, however very sure and constant; for this reason treatment sessions should not be repeated in the same area before 30-60 days, to give time for action. The endothelium of treated veins is not submitted to complete destruction and consequently does not thrombose, but the vein wall shrinks slowly probably due to some connective perivenous reaction. This explains also the rare thromboses,
matting, pigmentations and necrosis. This shrinking effect is proven by the fact that the venous network does not disappear but becomes less visible while the blood volume reduces progressively. When re-treating the same area fewer injections will be necessary to treat the same surface as the network reduces progressively. In this perspective, judging the results by photos may be questionable as the definition power of the pictures may not detect a less visible, but still present reticulum.

COMMENTARY BY ROBERT WEISS, MD

A well performed clinical study which validates what we have suspected all along which is that CG is an excellent sclerosing agent for telangiectasias with minimal incidence of pigmentation. The new information discovered from this study is that dilution with lidocaine with epinephrine not only does not diminish the effect, it actually enhances the reduction in pain and is most likely associated with reduced side effects. This is a win-win situation for patients and physicians as patients can be treated with greater efficacy plus less side effects. While CG is not available for physicians in the US, we can use glycerin off label without the chromate salt. Our experience (shared with Dr. MP Goldman) is that even plain glycerin diluted from 72% with lidocaine in a ratio of 2 parts 72% glycerin and 1 part lidocaine greatly reduces pain and achieves equivalent efficacy. The mystery yet to be solved is how lidocaine can have such an immediate effect, although the authors of this excellent study speculate that injection of reticular veins first results in enough time to induce anesthesia of associated telangiectasia before they are injected. As a result of this study we more clearly understand the safety and efficacy of CG with the ability to reduce pain with CGX. A significant contribution to phlebology in 2011.
Randomized Comparison of Low Molecular Weight Heparin and Coumarin Derivatives on the Survival of Patients With Cancer and Venous Thromboembolism

Lee AYY, Rickles FR, Julian JA, Gent M, Baker RI, Bowden C, Kakkar AK, Prins M, Levine MN
Journal of Clinical Oncology 2005; 23:2123-2129

Contributing Editor/Reviewer: P.L. Antignani, MD

Associate Editor: Stephanie Dentoni, MD
ABSTRACT:

Experimental studies and indirect clinical evidence suggest that low molecular weight heparins may have antineoplastic effects. We investigated the influence of a low molecular weight heparin dalteparin on the survival of patients with active cancer and acute venous thromboembolism. Survival data were examined in a posthoc analysis in patients with solid tumors and venous thromboembolism who were randomly assigned to dalteparin or a coumarin derivative for 6 months in a multicenter, open-label, randomized, controlled trial. All-cause mortality at 12 months was compared between treatment groups in patients with and without metastatic malignancy. The effect of dalteparin on survival was compared between the two patient subgroups. During the 12-month follow-up period, 356 of 602 patients with solid tumors and acute venous thromboembolism died. Among patients without metastatic disease, the probability of death at 12 months was 20% in the dalteparin group, as compared with 36% in the oral anticoagulant group. In patients with metastatic cancer, no difference in mortality between the treatment groups was observed (72% and 69%, respectively). The observed effects of dalteparin on survival were statistically significantly different between patients with and without metastatic disease. The use of dalteparin relative to coumarin derivatives was associated with improved survival in patients with solid tumors who did not have metastatic disease at the time of an acute venous thromboembolic event. Additional studies are warranted to investigate these findings.

COMMENTARY:

Venous thromboembolism (VTE) in cancer is also associated with a high rate of recurrence, bleeding, a requirement for long-term anticoagulation, and worsened quality of life. VTE and the hemostatic complications are the second most common cause of mortality in cancer patients, particularly in those with pancreatic, gastrointestinal or lung cancer and 10% of newly diagnosed myeloma patients treated with any type of chemotherapy develop deep venous thrombosis. Anticoagulant therapy is safe and efficacious for prophylaxis and treatment of VTE in patients with cancer. Available anticoagulants include warfarin, heparin, and low-molecular weight heparins (LMWHs). LMWHs represent the preferred therapeutic option for VTE prophylaxis and treatment. Moreover, their use may be associated with improved survival in cancer, as reported in the reviewed paper.

The impact of cancer cells and chemotherapy on the activation of the coagulation cascade is responsible for a pro-thrombotic state found in many cancer patients. Various mechanisms related to the activation of the coagulation or fibrinolytic systems in cancer may be involved in tumor development, progression and metastasis. Activation of coagulation can have both systemic and local consequences. The systemic consequences involve deep vein thrombosis or metastasis. Local consequences involve the deposition of fibrin and plasma proteins in the tumor interstitium. This fibrin deposition results in imposition of the initial tumor structure, regulation of inflammatory cell infiltration, induction of angiogenesis and formation of a mature stroma. In addition, accumulation of fibrin and other plasma proteins in the tumor microenvironment contributes significantly to

increased interstitial pressure that impedes the penetration of chemotherapeutic agents into the tumor. Tumor generated polymerized fibrin also results in the formation of a physical barrier protecting the tumor from natural killer cells and other exogenous anticancer agents.

Tissue factor (TF) is also abundantly expressed in newly forming vessels associated with physiological and pathological angiogenesis, and has been shown to induce cellular signaling and to promote angiogenesis and tumor metastasis. Initial studies have demonstrated potent anti-angiogenesis and anti-metastasis efficacy for various mechanisms that interfere with TF/VIIa. Administration of low molecular weight heparin (LMWH) has been shown to induce the localized release of tissue factor pathway inhibitor (TFPI), a key endogenous inhibitor of the TF/VIIa complex, from the endothelium and significantly inhibit angiogenesis.²

The effects of LMWHs on survival of cancer patients may be due to direct or indirect effects on tumor growth and/or angiogenesis. Retrospective analyses of clinical trials in which LMWH had been used to treat cancer patients with established thrombosis have suggested a survival advantage for the treated groups. The first prospective, randomized, double-blind study designed to determine the potential value of long-term LMWH therapy to improve survival in cancer patients suggested a striking survival advantage for LMWH heparin treatment in a subgroup of patients with good-prognosis.³ A second clinical trial in patients with small-cell lung carcinoma showed advantages in terms of progression-free and overall survival for patients who received LMWH for 18 weeks.⁴ Additional recent studies demonstrated survival advantage in patients without evidence of metastatic disease and in a subgroup of patients with a variety of tumor types. In the latter study, the benefits of LMWH therapy were seen for months and years after the period of active administration. In a post hoc subgroup analysis of patients with a better prognosis in one of the studies, survival was significantly better with dalteparin than with placebo: 2-year survival estimates of 78% and 55%, respectively, and 3-year estimates of 60% and 36%. In a prespecified analysis by life expectancy in another trial, the hazard ratios with nadroparin versus placebo were

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0.61 for patients expected to live for 6 months or longer and 0.82 for those expected to live for <6 months. In a retrospective analysis of data from the CLOT study, patients without metastases had a significantly lower 1-year mortality rate with dalteparin than with oral anticoagulation (20% and 34.7%, respectively), and this advantage persisted after adjustment for differences in baseline risk factors. In contrast, among patients with known metastatic disease, the estimates for 1-year mortality with dalteparin did not differ significantly from those with oral anticoagulation (72% and 69%, respectively). Again, these studies cannot evaluate a direct antitumor effect of anticoagulation, particularly LMWHs, although preclinical studies have suggested such an effect. A recent meta-analysis also showed that anticoagulants, particularly LMWH, significantly improved overall survival in cancer patients without VTE but also increased the risk of bleeding complications. Fatal bleeding events were extremely rare, however, and LMWHs appeared to have a more favorable bleeding profile than vitamin K antagonists (VKAs) did.

The results of the reviewed paper represent a confirmation of the efficacy of LMWH treatment in improved survival in patients with solid tumors without metastatic disease but further studies need to establish what kind of tumors could have an effective benefit from LMWH treatment in absence of VTE.

Neurological complications of sclerotherapy for varicose veins

Sarvananthan, T., et al.,

Contributing Editor/Reviewer: Kurosh Parsi, MBBS, MSc Med, FACD
Associate Editor: Pauline Raymond-Martimbeau, MD, FACPh
Sarvananthan et al. have performed an excellent systematic review of the world literature on foam sclerotherapy and its reported neurological complications. This included 15 case reports, 5 prospective randomized studies and 23 other publications. Altogether, these publications contained clinical information on 10,819 patients who underwent sclerotherapy with liquid or foam sclerosants. The electronic search covered a 64-year period with the earliest case report dating back to 1947. Sodium tetradecyl sulphate (STS) was used in 5990 cases, polidocanol (POL) in 3999, chromated glycerine in 52 cases and sodium morrhuate in one case.

This review contains 9 transient ischaemic attacks (TIA) and 12 cases of stroke, in keeping with a recent review by the author who presented data on 13 published cases of stroke. The overall frequency of neurological complications of sclerotherapy was estimated at 0.9%. This included minor events such as speech, visual and motor disturbances (not including migraine) as well as ischaemic complications such as TIA and stroke. The figure of 0.9% is consistent with previous studies which reported the incidence to be up to 2% despite the inclusion of migraine. All cases of stroke were reported in case reports or case series and none appeared in any of the cohort or randomized prospective trials. The authors acknowledge that the true incidence of neurological complications following sclerotherapy remains unknown and is subject to reporting bias.

The review contains a discussion of possible pathogenic mechanisms. The most common risk factor is identified as a right-to-left cardiac shunt (RLS) and in particular a patent foramen ovale (PFO). This has been studied extensively by Morrison and Raymond-Martimbeau. Given the 27% average prevalence of PFO in the general population and the frequency of neurological complications of sclerotherapy estimated at 0.9%, the authors acknowledge that additional risk factors play a major role in the pathogenesis of this complication and that screening for a RLS is not mandatory. No conclusion is drawn with respect to aetiology.

As previously reported by this author, a pattern emerges with the reported cases of stroke following foam sclerotherapy. In half the published cases, symptoms developed within minutes of the procedure and in all these cases bubbles were imaged either in the brain circulation or in the brain supplying arteries. Given the rapid onset of the event, paradoxical gas embolism (PGE) is the most plausible cause in these cases. Room air was used as the foaming gas in all the reported cases of stroke supporting the use of a more physiological gas such as CO2. In the remaining cases, stroke happened a few days (1-5 days) after the treatment rendering paradoxical clot embolism (PCE) the most reasonable cause. In the review by the author, 6 patients had a delayed onset of stroke after sclerotherapy. One patient had a concurrent deep vein thrombosis (DVT), one had a DVT and a pulmonary embolism and one had clinical superficial thrombophlebitis. In the remaining 3 cases, no thrombotic complication was reported. This may be due to dislodgement of thrombus from the saphenofemoral (SFJ) or saphenopopliteal junctions (SPI) or less likely via large perforators. Currently there are no established sonographic criteria to differentiate between superficial venous thrombosis (SVT) as against venous sclerosis/fibrosis and

non-compressibility rather than echogenicity is used is to identify both. In the case of a loose thrombus dislodging from the SFJ, ultrasound screening may miss SVT as the non-compressibility of the great saphenous vein may be considered an expected outcome of the treatment. Clearly, the phlebological community needs to work on establishing clear sonographic criteria that would differentiate venous thrombosis from venous sclerosis/fibrosis.

The aetiology of the ischaemic neurological complications of sclerotherapy is undoubtedly multifactorial. However, a classification into PGE (immediate events) and PCE (delayed events), although simplistic, may be a useful tool to assist with the immediate management (e.g. the immediate management of gas embolism and the use of hyperbaric chambers) and appropriate and timely investigations.

Sarvananthan et al briefly discuss the variability of treatment techniques in foam sclerotherapy. It is essential to remember that foam sclerotherapy is not a standardized procedure by any means. A number of maneuvers such as remaining supine following treatment for a period of time or leg elevation before or after the treatment have been recommended to prevent gas embolism but none have been shown to be effective. There are infinite technical variables which to list a few include the choice and concentration of the sclerostats, the foaming technique, the composition of foam (liquid + gas ratio), the foaming gas (room air vs. CO2 vs. various gas compositions), the total volume of foam, the treatment approach (distal to proximal vs. proximal to distal), the use of ancillary techniques such as internal compression with tumescent fluid and the mode of delivery via percutaneous puncture or various catheter techniques. When reviewing the literature, it is essential to remember that we are not comparing apples with apples by any means. Solid prospective studies are urgently required to compare various treatment approaches and technical variations. In the absence of reliable data, the venous community needs to assess the available evidence and recommend a set of best practice guidelines that may help standardize this popular procedure and reduce the rate of complications. The total volume of the injected foam, although dismissed by some as irrelevant, possibly plays an important role in the onset of local and distant complications and in the author’s opinion should be kept at a minimum. Especially diffusion of large volumes from a single entry point should be abandoned and replaced by multiple point injections that are also shown to reduce the incidence of deep vein occlusion.

In summary, stroke remains a serious but a very rare complication of foam sclerotherapy. Sclerotherapy is not a simple act of injecting a substance into a vein and practitioners interested in performing this procedure should undergo adequate training in broader aspects of phlebology, be familiar with venous anatomy, have a working knowledge of duplex ultrasound and appreciate the biological activity of sclerostats and foams at various concentrations and compositions.

Editor’s Note: It is important to emphasize that given the tens of thousands of foam sclerotherapy sessions conducted worldwide on a daily basis, reports of TIA and “stroke” (not all agree with this terminology - see Gillet, Phlebology 2010;25:261–266) remain extremely rare. Even if such complications are under-reported, the rare incidence should provide the perspective that it has been well established foam sclerotherapy is safe and effective when performed properly by experienced phlebologists.


Failure of microvenous valves in small superficial veins is a key to the skin changes of venous insufficiency


Contributing Editor/Reviewer: Marlin Schul, MD, MBA, RVT, FACPh

Associate Editor: Jean-Jerome Geux, MD, FACPh
Small cutaneous veins of the lateral thigh have revealed reflux with duplex ultrasonography. Patients with isolated patterns of small vein disease elicit an array of symptoms, many of which are relieved with chemical ablation. Vincent et al., in an attempt to garner a greater understanding of small cutaneous veins and their role in skin changes with venous leg ulcers (VLU), harvested fifteen limbs for the purposes of this research study. The group was comprised of eight duplex proven reflux negative limbs and seven limbs with C6 disease, and the protocol met the approval of the local ethics and standards committee. Amputation was indicated for non vein related conditions with the exception of two limbs with refractory ulcers.

In an attempt to study anatomic patterns and characteristics of small vein networks and tributaries, casts were created by cannulating the great saphenous vein at the medial malleolus, and infusing resin proximally. Vessels were ligated as resin reached the proximal end and infused until significant resistance was noted. The limbs were macerated to permit detailed casts as seen with prior neovascularization lesions shared by this group. Once the casts were complete transillumination microscopy and scanning electron microscopy were employed.

The results were striking. All but one of the duplex proven normal limbs demonstrated tributary reflux, half with reflux demonstrated thru 6th generation small vein networks. Valve structures were clearly delineated, the largest concentration noted in the 3rd generation vessels, yet competent valves could be demonstrated through the 6th generation. Valveless segments were observed predominately beyond 3rd generation vessels where resin was seen.

to reach segments with competent valves, planting the theory that once incompetence is reached at the 3rd level, unabated venous hypertension may be seen as blood is permitted to pool in small vein networks of the skin. The C6 limbs revealed valvular incompetence with far more extensive resin deposits within tributaries and small vein networks. These limbs were simply affected to a far greater degree when compared to those without gross axial reflux.

So many questions may be asked to the significance of findings in this study. Are there common denominators among the nonulcerative limbs? What for instance was the occupational history for the subjects? What role if any did body mass index play in the patients with VLJU and small vein networks? Are patients with grossly bulbous varices and no visible telangiectasia at less risk for ulceration over time? If all VLJU patients develop small vein networks as seen in this population, early intervention suggests the potential to prevent future morbidity. Observations in France have suggested that early intervention has changed the severity at time of presentation compared to the three decades prior.

The authors should be commended on their unique approach in this investigation. The imagery shared in the article is truly amazing. It is nice to see that something positive can bloom from what was likely a tragic situation leading to amputation. The study and detailed exploration of small vein networks revealed an anatomic susceptibility to skin changes. The discovery of boundary valves and valveless segments may represent how a thermoregulation system may be converted to adversely affect the microcirculation in the lower extremity. As hypothesized, unabated venous pressure will occur when boundary valves fail, leading to sustained venous hypertension at the surface of the skin. This research further confirms that reflux may exist in tributaries without axial disease, and that valvular incompetence is seen in small vein networks. We recognize there are scores of presentations for patients with venous pathology. The amputees with C0 or C1 disease were not likely suffering from symptoms of venous hypertension and were not seeking vein care. Given the sample size it is difficult to apply the findings to all lower extremities with and without venous pathology. Further study will be needed to determine which patients with visible small vein networks of the lower leg warrant early intervention in an effort to prevent progression to chronic venous insufficiency.

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Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial.

Enden T, et al, on behalf of the CaVenT Study Group

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Contributing Editor/Reviewer: Peter J. Pappas, MD

Associate Editor: Lowell S. Kabnick, MD, FACS, FACPh, RPhS
The CaVenT trial was an open-label, randomised, multi-center prospective trial designed to test the hypothesis that catheter directed thrombolysis (CDT) in conjunction with standard anticoagulation would reduce the development of the post-thrombotic syndrome (PTS) compared to standard anti-coagulation therapy alone at 24 months. Two hundred and nine patients were randomized to either CDT with anti-coagulation (n=101) or anti-coagulation alone (Control, n=108). All patients were required to use 30 to 40 mmHg compression stockings while on anti-coagulation therapy. Anti-coagulation was with a low molecular weight heparin, Daltaperin or Enoxaperin, followed by Warfarin with a target INR of 2-3. Only patients with first time venous thrombi and thrombi in the ilio-femoral system were enrolled in the study. Patients with clots up to 21 days old were eligible for enrollment. The primary end-points were the development of PTS as determined by the Villalta scoring system and ilio-femoral venous patency at 24 months.

At 24 months, the trialists reported that the development of PTS in the CDT and control groups were 41.1% and 55.6% respectfully, with an absolute risk reduction of 14.5%. Similarly, patency of the ilio-femoral segments in both groups was 66% and 45% with an absolute difference of 21%. Twenty bleeds with three categorized as major and 5 as clinically relevant were observed in the CDT group. No bleeds were observed in the anti-coagulation group. The three major bleeds consisted of a rectus sheath hematoma that required evacuation, a lower extremity compartment syndrome that required a fasciotomy and a puncture site hematoma. No deaths, pulmonary emboli or intra-cranial bleeds were observed.

Compliance with compression therapy use at 24 months in the CDT and control groups was 63.3% and 51.5% respectively. Similarly, maintainance of therapeutic INR levels in both groups was 65.45 and 50%. Adjunctive therapies such as angioplasty and stenting were utilized in 23 and 15 patients respectively. Average thrombolysis time was 2 to 4 days.

The data from the CaVenT trial raises several interesting points. The first observation is the high incidence of PTS in both the CDT and control arms compared to previously reported investigations. The authors point out that CaVenT is the only trial that strictly enrolled ilio-femoral venous thrombi alone and utilized the Villalta scoring system. Ilio-femoral thrombi have a higher incidence of PTS and the Villalta scoring system is a sensitive indicator of the development of PTS. However, it must be noted that only one patient developed severe PTS during the trial period. The absolute risk reduction of 14.5% strongly suggests that early alleviation of clot burden should reduce the incidence of PTS. To achieve this goal 7 patients must receive CDT to prevent the development of PTS in...
one patient. The authors correctly indicate that compliance with compression and anti-coagulation therapy was greater in the CDT group suggesting that the poorer results in the control group may be related to sub-therapeutic anti-coagulation and non-compliance with compression stocking use. Poor anti-coagulation is an independent risk factor for the development of PTS yet the authors stated that the compliance differences for anti-coagulation and compression therapy were not statistically significant. One has to wonder whether or not these differences would be significant with a larger sample size. Finally, the trialists did not utilize mechanical methods to reduce clot burden and relied solely on chemical thrombolysis. As a result, only 43 patients achieved complete lysis while 37 demonstrated partial lysis and 10 patients failed. Similarly, the use of adjunctive procedures such as angioplasty and stenting were used sparingly. Although the degree of clot lysis did not appear to affect the development of PTS one cannot help but speculate whether more aggressive clot removal and/or the use of adjunctive measures could have further decreased the incidence of PTS.

In conclusion, the authors have demonstrated a reduction in the incidence of PTS at 24 months and improved venous patency with CDT, anti-coagulation and compression therapy over traditional anti-coagulation and compression therapy alone. Compliance with post-procedure anti-coagulation and compression therapy may have affected the overall data set. Furthermore, the role of adjunctive procedures such as angioplasty and stenting and mechanical debulking devices still remains controversial.
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