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Phlebolymphology

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Phlebolymphology is an international scientific journal entirely devoted to venous and lymphatic diseases.

The aim of Phlebolymphology is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.

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Servier Affaires Médicales
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92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 38 98
Email: hurrem-pelin.yalirik@servier.com

Publication Director
Christophe CHARPENTIER
Suresnes, France

Publisher
Les Laboratoires Servier
50, rue Camot
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 60 00

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Dear Readers,

In this new issue of Phlebolymphology you will find the articles as below:

J. ULLOA, S. CIFUENTES, A. SOLANO, and V. FIGUEROA (Colombia) review several cardiovascular disease (CVD) management guidelines published by prestigious academic associations around the globe and summarize their recommendations about the use of micronized purified flavonoid fraction (MPFF) and the corresponding level of evidence, providing clinicians with a straightforward and practical source document to include MPFF in daily practice.

C. FRANCESCHI (France) introduces the basis of the CHIVA technique (Conservative and Hemodynamic Treatment of Venous Insufficiency), including the pathophysiological perspective, and makes a comparison with the ablation technique.

R. AKHMETZIANOV (Russia) presents a review of patient-oriented diagnostic tools currently used in patients with pelvic varicose veins and provides rationale for using disease-specific tools, as highlighted in the international consensus documents on the diagnosis and treatment of pelvic congestion syndrome.

Although compression is widely prescribed for patients post endovascular thermal ablation (EVTA), there is widespread disagreement on the optimal compression regimen and whether compression is even required postoperatively. M. TAN and A. DAVIES (UK) reexamine the literature surrounding this important clinical question, presenting current clinical opinion and practices and guideline recommendations, and discuss the evidence for and against the use of compression postoperatively.

N. MORRISON (USA) provides an overview of the evidence with cyanoacrylate closure in the treatment of varicose veins.

N. KHOREV and D. KUZNETSOVA (Russia) present the results of a study that aimed to evaluate the efficacy of MPFF in patients with primary chronic venous disease using venous photoplethysmography, which is an appropriate method for the quantitative instrumental assessment of total venous reflux.

Enjoy reading this issue!

Editorial Manager
Dr. H. Pelin Yaltirik
The place of micronized purified flavonoid fraction in the management of chronic venous disease from an international guidelines’ perspective

Jorge H. ULLOA, MD; Sebastian CIFUENTES, MD; Antonio SOLANO, MD; Valentin FIGUEROA, MD

1Vascular Surgeon, Chief of Vascular Surgery Department, Fundación Santa Fe de Bogotá University Hospital; Professor of Surgery, Universidad de los Andes School of Medicine, Bogotá, Colombia. 2Vascular Surgery Research Fellow, Vascular Surgery Department, Fundación Santa Fe de Bogotá University Hospital, Bogotá, Colombia.

Keywords:
CEAP classification; chronic venous disease; MPFF; phlebotonics; venous insufficiency.

Abstract
Chronic venous disease (CVD) is a highly prevalent disorder with a broad spectrum of symptoms determined by disease stage and whether there is deep or superficial venous system compromise. The treatment goal for CVD is to slow and prevent disease progression and provide symptomatic relief. Available options range from conservative mechanical strategies such as leg elevation, compression stockings, and daily exercise programs to complex surgical deep valvular implants. The adequate treatment option is selected according to the disease phase, and clinicians can add further options as the disease severity progresses. Additionally, pharmacological treatment plays an essential role in CVD management, especially micronized purified flavonoid fraction (MPFF), a vеноactive drug (VAD) with proven effectiveness and safety from early stages in C1 patients to complex C6 patients with severe ulcerations. Utilizing MPFF for CVD improves patients’ quality of life, symptoms severity, and ulceration healing. MPFF has been widely adopted by vascular practitioners and included in CVD management guidelines worldwide. Therefore, we reviewed several CVD management guidelines published by prestigious academic associations around the globe and summarized their recommendations about the use of MPFF and their level of evidence, providing clinicians with a straightforward and practical source document to include MPFF in daily practice.

Introduction
Chronic venous disease (CVD) is a highly prevalent disorder, with an overall worldwide reported prevalence of 83.6%.1 The burden of CVD is increasing, associated with rising obesity and sedentarism,2 with severe complications that affect quality of life (QOL) and represent a significant economic burden to health systems due to the loss of working days and elevated treatment costs. The spectrum of signs and symptoms associated with CVD has two major contributors, failure of either the deep or superficial venous system. The epidemiologic features of superficial venous disease (SVD) and deep venous disease (DVD) differ. Telangiectasias, a mild manifestation of SVD, might present in up to 80%
of the general population, whereas varicosities have heterogeneous prevalence estimations, ranging from 1% to 60% in men and women. This wide range might be due to the variability in the number of patients who consult for spider veins or varicosities. Many individuals suffer from venous disease but never look for treatment.

On the other hand, DVD presents more severe conditions, including deep venous thrombosis (DVT) with its potential pulmonary embolism (PE); and post-thrombotic syndrome (PTS) in a chronic setting. DVT has an annual incidence of 0.1%, with one-third of these patients developing fatal PE. Additionally, up to 80% of DVT cases can progress over time to PTS, a chronic debilitating disease with limited effective treatment options and devastating consequences in QOL, including ulceration in up to 3% of patients older than 65 years of age. Given the broad spectrum of CVD and extensive clinical features, effective and easily accessible treatment must be offered to these patients. Available treatment options are directed to prevent the progression of the disease and provide symptomatic relief and vary from simple conservative strategies such as lower-limb elevation and compression stockings to more advanced and specialized techniques to restore valvular function in PTS.

Although most of the current treatment options are directed to certain disease features (stage, deep vs superficial compromise), venoactive drug (VAD) therapy has demonstrated beneficial effects in all phases of CVD. Micronized purified flavonoid fraction (MPFF), an oral VAD composed of 90% diosmin and 10% active flavonoids, has shown efficacy in both early and advanced stages of CVD. The benefit can be attributable to the drug mechanism of action, which reduces inflammatory response triggered by venous hypertension, specifically by preventing leukocyte rolling and adherence, with a net effect of preventing and slowing disease progression.

Additionally, extensive studies have demonstrated that MPFF can provide at least 50% symptomatic relief, reducing swelling, cramping, pain, and heaviness. Due to its effectiveness and broad adoption by patients and clinicians, MPFF has been included as a recommended CVD treatment option in many international management guidelines for CVD. This study aims to review and compare the recommendations about MPFF utilization from several international management guidelines for CVD and provide clinicians with a comprehensive and updated summary of MPFF utilization.

Methods
This review included the CVD clinical practice guidelines from the following academic societies: the European Society for Vascular Surgery, published in 2022; the European Venous Forum, published in 2018 and 2020; Latin American guidelines published in 2016; and the Society for Vascular Surgery and the American Venous Forum published in 2014. The document’s selection process aimed to include representation from the most prestigious academic societies worldwide, with different perspectives about the use of MPFF in Western vascular surgery practice. All the recommendations mentioning MPFF, with the corresponding level of evidence, were included in the document. Finally, the primary outcomes and benefits of MPFF therapy in different settings of CVD management were outlined.

Results
A summarized description of each guideline’s recommendations about MPFF utilization is included below:


This document concludes that VADs in general have beneficial effects on objective measures of leg edema and symptoms and signs of CVD, such as pain, cramps, restless legs, sensation of swelling, paresthesia, and trophic disorders, on the basis of a large Cochrane review that included 53 trials. This guideline outlines that double-blind, placebo-controlled, randomized clinical trials (RCTs) specifically involving MPFF demonstrated improvement in leg symptoms, such as pain, heaviness, feeling of swelling, cramps, paresthesia, edema, functional discomfort, QOL, and ankle circumference. Accordingly, the European Society for Vascular Surgery establishes that given its low cost and relatively low incidence and low severity of associated adverse events, VAD should be considered for treatment of symptomatology and edema in CVD.

Additionally, the guideline addresses the beneficial effects of utilizing MPFF for the treatment of venous leg ulceration (VLU). There is a 32% higher chance of healing at 6 months in patients treated with MPFF as adjuvant to compression therapy than with compression alone.

Recommendations:
• For patients with symptomatic CVD who are not undergoing interventional treatment, are awaiting
intervention, or have persisting symptoms and/or edema after intervention, medical treatment with VADs should be considered to reduce venous symptoms and edema, on the basis of available evidence for each individual drug. Evidence was Class IIA (weight of evidence/opinion is in favor of usefulness/efficacy), level A (data derived from multiple RCTs or meta-analyses).

- For patients with active VLU, MPFF, hydroxyethylrutosides, pentoxifylline, or sulodexide should be considered as an adjunct to compression and local wound care to improve ulcer healing. Evidence was Class IIA (weight of evidence/opinion is in favor of usefulness/efficacy), level A (data derived from multiple RCTs or meta-analyses).

Guidelines from the European Venous Forum, the International Union of Angiology, the Cardiovascular Disease Educational and Research Trust (UK), and Union Internationale de Phlébologie: management of CVDs of the lower limb (2018-2020)\(^\text{20}\)

In this document, the authors evaluated the effect of VAD on individual symptoms and signs through the assessment of several meta-analyses and systematic reviews.\(^\text{20}\) Regarding the role of MPFF in signs and symptom improvement, this review concluded that pain, QOL, skin changes, functional discomfort, and feeling of swelling were reduced with the use of MPFF compared with placebo. These findings had a high level of evidence.\(^\text{21-26}\)

Additionally, the authors found beneficial effects of MPFF in leg redness, ankle circumference, and burning sensation, which were reduced; however, the level of evidence was moderate, thus more studies are needed to evaluate the real impact of MPFF on those symptoms.\(^\text{26-28}\)

Recommendations:
- Pain was reduced with the use of MPFF compared with placebo. Level of evidence was high (Grade A; Level A evidence derives from 2 or more scientifically sound RCTs or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population).
- Ankle circumference was reduced with the use of MPFF compared with placebo. Level of evidence was moderate (Grade B; Level B evidence is provided by 1 well-conducted RCT or more than 1 RCT with less consistent results, limited power, or other methodological problems, which are directly applicable to the target population, as well as by RCTs extrapolated to the target population from a different group of patients).
- Skin changes were improved with the use of MPFF compared with placebo. Level of evidence was high (Grade A; Level A evidence derives from 2 or more scientifically sound RCTs or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population).
- Leg redness was reduced with the use of MPFF compared with placebo. Level of evidence was moderate (Grade B; Level B evidence is provided by 1 well-conducted RCT or more than 1 RCT with less consistent results, limited power, or other methodological problems, which are directly applicable to the target population as well as by RCTs extrapolated to the target population from a different group of patients).
- Functional discomfort was significantly reduced with the use of MPFF compared with placebo. Level of evidence was high (Grade A; Level A evidence derives from 2 or more scientifically sound RCTs or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population).
- Burning sensation was reduced with the use of MPFF compared with placebo. Level of evidence was moderate to low (Grade B/C; Level B evidence is provided by 1 well-conducted RCT or more than 1 RCT with less consistent results, limited power, or other methodological problems, which are directly applicable to the target population, as well as by RCTs extrapolated to the target population from a different group of patients; Level C evidence results from poorly designed trials, observational studies, or from small case series).
- Feeling of swelling was reduced with the use of MPFF compared with placebo. Level of evidence was high (Grade A; Level A evidence derives from 2 or more scientifically sound RCTs or systematic reviews and

- QOL was improved with the use of MPFF compared with placebo. Level of evidence was high (Grade A; Level A evidence derives from 2 or more scientifically sound RCTs or systematic reviews and meta-analyses in which the results are clear-cut and are directly applicable to the target population).

**Clinical practice guidelines of the Latinoamerican Venous Forum - chronic venous insufficiency (2016)**

This document was published in 2016, and to date, no updated versions are available. In these guidelines, the authors highlight the benefits of MPFF on inflammatory process, edema, venous tone, lymphatic drainage, and venous pain. One of the most significant effects is the additional chance of healing for chronic ulcers as adjuvant therapy.

**Recommendations:**
- For venous ulcer treatment, we recommend MPFF as an adjuvant therapy based on the clearly superior benefits in comparison to risks. Evidence grade 1, level B (strong recommendation, moderate-quality evidence; derives from RCTs with important limitations [inconsistent results, methodologic flaws, indirect, or imprecise] or exceptionally strong evidence from observational studies).


This document was published in 2014, and to date, no updated versions are available; however, it provides a clear perspective about the use of MPFF. The guideline highlights the demonstrated effect of MPFF on ulcer healing by protecting the microcirculation from damage induced by venous ambulatory hypertension. MPFF as an adjunct to compression therapy and local wound care showed a greater healing rate (32% in 6 months) and shortened time to ulcer healing.

**Recommendations:**
- For long-standing or large venous leg ulcers, we recommend treatment with either pentoxifylline or MPFF used in combination with compression therapy.

Evidence was Grade 1, Level B (strong recommendation, moderate-quality evidence; derives from RCTs with important limitations [inconsistent results, methodologic flaws, indirect, or imprecise] or exceptionally strong evidence from observational studies).

**Discussion**

In comparison of the guidelines mentioned above, the main prescription criteria were edema and trophic disorders, as well as subjective symptoms including pain, heaviness, cramps, restless legs, and the sensation of swelling. Significant benefits of treatment were demonstrated for these items. When VADs were analyzed individually, MPFF subgroup analyses demonstrated significant treatment benefits for edema based on multiple studies and were effective for this range of symptoms. Since the American Venous Forum 2014 guidelines’ statement of recommendation for relief of symptoms associated with CVD in patients with CEAP classes C0s to C6s, MPFF has maintained a strong recommendation, on the basis of moderate evidence, as an adjuvant therapy for treatment of venous leg ulcers. Several reviews recommend combination of VADs and compression in addition to meta-analyses demonstrating efficacy of this combination to accelerate the healing of venous ulcers.

**Conclusion**

The role of VAD in the treatment of CVD has been studied in several meta-analyses and systematic reviews. Specifically, MPFF has been shown to significantly improve the signs and symptoms of CVD like pain, edema, and skin changes. In addition, improvement in QOL has been observed, as well as benefits in leg ulcer healing when MPFF is combined with compression therapy. After reviewing the current evidence, we suggest that MPFF is an effective treatment option for treating the main signs and symptoms of CVD and for the healing of ulcers when combined with compression.

**Corresponding author**

Jorge Hernando ULLOA, MD, FACS, Vascular Surgery Department, Fundación Santa Fe de Bogotá, Carrera 9 No. 116-20, Office 910. 110111, Bogotá, Colombia.

Email: cirugiavascular@yahoo.com
REFERENCES


REFERENCES


Abstract

CHIVA is the French acronym for Conservatrice et Hémodynamique de l’Insuffisance Veineuse en Ambulatoire, i.e., Conservative and Hemodynamic Treatment of Venous Insufficiency in outpatients. Ablation is not conservative, and CHIVA is based on a different hemodynamic approach. It is counterintuitive because it is difficult to imagine that the varicose veins could disappear without ablation either by extraction or by endovenous destruction. This treatment raises scientific questions that require us to revisit our understanding of classical venous pathophysiology in light of what echo-Doppler has contributed to our progressing knowledge of hemodynamics. CHIVA strategy requires more demanding diagnostic procedures than the ablative methods—in particular, a hemodynamic mapping that considers more elaborate hemodynamic data. Results from both methods allow us to evaluate the relevance of their respective pathophysiological basis. Studies have shown that results with CHIVA are often superior, sometimes equivalent, but never inferior to ablation. Such findings support conservative approaches, justified scientifically for hemodynamic reasons and ethically because of the preservation of the venous bypass capital. The effort made to improve knowledge of hemodynamics, making CHIVA possible, is rewarded by a much more in-depth understanding of venous disease, not only superficial disease, but also deep venous insufficiency and venous malformations.

Introduction

Comparing CHIVA (French acronym for Conservatrice et Hémodynamique de l’Insuffisance Veineuse en Ambulatoire or Conservative and Hemodynamic Treatment of Venous Insufficiency) proposed in 1988\(^2\) with ablation introduced in 1905\(^3\) cannot be reduced to a comparison of two techniques because they are two treatments based on radically different pathophysiological concepts. This explains the differences in instrumental evaluation and interpretation of data (especially ultrasound), which results in different diagnosis, strategy, tactics, and assessment of results. Due to their different concepts, the same signs, such as flow direction, have the same name of reflux—antegrade and retrograde flow—but differ in pathophysiological meaning. Furthermore, the hemodynamic model that explains CHIVA introduces new definitions such as venovenous shunts (open vicarious shunts, closed shunts, open deviated shunts, and mixed shunts) and
dynamic fractionation of gravitational hydrostatic pressure (DFGHSP). This new language is of course shocking to those who have been trained in the classical ablative approach. Their discomfort with it is amplified by the perhaps forgotten, though necessary, knowledge of fluid mechanics required to understand venous hemodynamics and to perform appropriate hemodynamic ultrasound examination.

With regard to CHIVA, flow pathology is not dependent on direction. It depends on its origin, destination, and the transmural pressure (TMP) exerted against the veins and capillary walls. TMP is pressure resulting from the opposition of the outer pressure (tissue + atmospheric pressure) and inner pressure (gravitational hydrostatic + residual pressure provided by the microcirculation + valvo-muscular pump pressure). TMP control is the cardinal function of the venous system, ie, tissue drainage, heart preload, and thermoregulation. The venous system consists not only of veins, but also of the venular side of the microcirculation, the cardiac, thoraco-abdominal, and valvo-muscular pumps. Types of venous dysfunction depend on the damage in this system, which can be valve incompetence, occlusions, or low microcirculation resistance responsible for corresponding hemodynamic pathologies such as DFGHSP impairment, shunts, and resistance to flow, which increase TMP.

Another cause of misunderstanding is the difference in instrumental assessment, especially echo-Doppler. The CHIVA strategy requires much more accurate topographic and hemodynamic mapping than ablation, owing to the greater complexity of the pathophysiological concepts involved.

Treatment is also assessed differently. Occlusion of the great saphenous vein (GSV) is considered an ablative success but a CHIVA failure. Persistent flow is a failure for ablation and a success for CHIVA, even if it remains retrograde if it is no longer overloaded.

The CHIVA hemodynamic model is a fresh approach for diagnosis and treatment of venous malformations and deep venous insufficiency, especially in post thrombotic syndrome.

In this regard, CHIVA methods arose out of concern to preserve the GSV because it was too often unusable for vital bypass procedures because of previous ablation for treatment of benign varicose veins. This raises ethical questions, and discussion on informed consent should stress this issue and offer conservative solutions besides ablation.

CHIVA is at least as painless and unrestrictive as noninvasive ablative procedures because it is open, mini-surgery under local anesthesia, and immediate resumption of walking post procedure is advised.

It is lower cost than most such procedures because it requires minor surgical equipment.

Like any scientific model, the CHIVA cure has been subjected to experimental proof and compared with ablative methods, of which stripping is the gold standard. Controlled trials have shown CHIVA to be strongly or slightly better vs all other methods, but its results are never inferior in terms of complications and long-term recurrences. Surprisingly, the advantage of GSV preservation is not mentioned in the trials despite its relevant value in terms of health with regard to vitally important arterial treatments in the aging population.

Unfortunately, more widespread use of CHIVA is thwarted by the steep learning curve associated with performing this technique: though previously reported to be better than compression and at least equivalent to stripping of varicose veins in preventing ulcer recurrence, in acknowledgment of the complexity of the approach, it has been noted that “a high level of training and experience is needed to attain the results presented” in that publication. Hindrances to more widespread use of CHIVA thus include the lack of teachers for training in this technique, and the popularity of easier, ready-to-go ablative techniques offered by the sponsors of so many congresses which would not otherwise exist.

Indeed, the CHIVA-based hemodynamic model is not yet taught in most universities and not included at most congresses.

This article, though too short for an exhaustive explanation, will suffice to introduce the basis of the CHIVA cure. For more information, an extensive PDF book published in 2021 can be downloaded free of charge.
Pathophysiology

Cause of varicose veins
In 2017, Jacobs et al.20 looked closely at the pathophysiology of varicose veins, which available evidence suggests is complex and influenced by a number of factors, with the inciting factor not known conclusively. For example, they asked the key question of whether venous hypertension and valvular incompetence lead to alterations in the venular wall or whether it’s such changes that lead to venous hypertension and valvular incompetence, something not known with certainty.

If vein wall changes precede venous hypertension and valvular incompetence of refluxing veins, ablation could be justified.

On the contrary, CHIVA considers that venous hypertension and valvular incompetence precede and influence the development of vein wall changes. This is proved by the caliber of reduction21 and remodeling after shunt disconnection and DFGHSP restoration. In his article published in 2019, Delfrate22 describes results from a study in 22 patients needing hydrostatic column fracturation 1 year after saphenous femoral disconnection:

In 21 of the 22 they found that the histoarchitecture of the 3 general layers of the GSV was maintained, including the following: (i) the endothelial layer, which remained intact; (ii) the medium layer consisting of 3 different smooth muscle layers showing only mild hypertrophy and hyperplasia; and (iii) the adventitial layer, consisting of nerves and vessels with multiple endothelial cells surrounded by smooth muscle cells.

Cause of varicose recurrence
Bradbury23 describes varicose recurrence as the development of new varicose veins, often in a second saphenous system, after the original operation. They state possible causes as: i) “inadequate assessment at the time of the initial treatment,” though they note that this should be less common since full duplex ultrasound mapping is carried out in most before intervention; and ii) “reflux developing at a site that was previously demonstrated to be competent; in other words, true disease progression.”

So, performance of the most extensive ablation possible is justified if true that post-ablation recurrence is not a result of the ablation itself but due to incompetent veins left behind or to true disease progression such as when reflux develops at a site that was previously demonstrated to be competent. However, studies do not support this. Even though varicose recurrence after CHIVA can also be due to untreated incompetent veins and recanalization of ligations rather than new “natural evolution of the disease,” only ablation produces neo varicose veins. This is clinically obvious in cases of post-ablation “anarchical” new varices and those with “no apparent source” or “uncertain cause” on echo-Doppler. For example, Perrin et al.24 in their study of cases of varicose recurrence after surgery report no apparent source of reflux in 10%, and uncertain or unknown cause in 35%. Such neo varicose veins are not seen after CHIVA.

Carandina et al.25 compared stripping and CHIVA in patients with superficial venous incompetence that resulted in chronic venous disease.

With regard to long-term results, they found that after 10 years, the main between-group difference was that the stripping group had 22% neo varicose veins with no detectable reflux point, a recurrence they believed was due to the absence of an all-important drainage by the saphenous system, something they believed key following varicose vein surgery to avoid neoangiogenesis. In support of this, they point out that even for CHIVA (a conservative surgery), if incorrectly performed and GSV thrombosis and occlusion arise after surgery, impeding drainage, the number of recurrences is higher than in draining GSV systems, and they suggest that this could also be relevant in the case of modern endovascular techniques in which the GSV is removed. They also point out that there is no published long-term evidence to consider with regard to the GSV after endovenous laser ablation, radiofrequency ablation and foam sclerotherapy.

Practically, it can be considered that a number of post-ablation recurrences are due to preexisting thin collateral veins that are dilated and forced by the draining flow (residual pressure [RP]) to bypass the ablated paths that impede tissue drainage.

Cause of venous ulcer
The cause of venous ulcer could be sole or multifactorial depending on the pathophysiological explanation.

The perforator underneath the ulcer is usually considered the cause. According to this assumption, these perforators are ablated (via ligation, sclerosis, subfascial endoscopic...
perforator surgery (SEPS, or Linton operation) and then discarded due to bad results. Yet, most of them are draining (substantial diastolic inward Doppler flow) despite a little systolic outflow and not considered pathologic in the absence of a deep obstacle downstream. Indeed, the CHIVA model considers the TMP excess to be the cause of the venous ulcer. Ulcer-centered perforators rarely indicate deep venous hypertension but usually drive inward the flow of superficial closed shunts submitted to DFGHSP impairment. So, restoring the DFGHSP and disconnecting the closed shunt at its escape point, CHIVA achieves healing. In this case, ablating the reentry would impair the drainage of the ulcer and, simultaneously, ulcer healing. The reason ablation is used so frequently seems to be because of the systolic reflux elicited by the vessel incompetence of large perforators below the knee, although not pathogenic when it precedes a very substantial diastolic inflow.

This is confirmed by the ulcer healing without any ablation of the ulcer-centered perforator. So, excess TMP is corrected by increasing the extravenous pressure with compression and/or reducing the intravenous pressure (via CHIVA). In 2002, CHIVA disconnection was reported to have less recurrence than compression,17 and in 2021, endovenous ablation showed similar results.26 Currently, there are no long-term results comparing CHIVA and ablation.

Vein ablation versus conservation

Ablation suppresses the reflux, but at the same time, it also suppresses flow drainage by the microcirculation. This obstacle to flow drainage can lead to skin conditions, such as telangiectasia, matting, and bypassing varicose veins. As a matter of fact, resistance to the draining flow increases the residual pressure, which opens micro shunts, forces and dilates capillaries, venules, and collaterals. Therefore, CHIVA preserves the veins, even if refluxing, so as not to impede drainage. This explains Perrin et al’s finding, as mentioned above, in cases of recurrence after surgery that there was no apparent source of reflux in 10%, and uncertain or unknown cause in 35%,24 and Carandina et al’s findings for a “detectable reflux point” in 0% (0/70 patients) treated via CHIVA in their study vs 22% (12/54 patients) treated with stripping.13

In addition, CHIVA-preserved GSV shows a reduction in caliber21 and normal histoarchitecture.22

Reflux ablation

Reflux ablation is mandatory for ablative methods according to the concept that any retrograde flow is pathogenic and the vein it flows through is pathological as well. For CHIVA, direction defines neither pathology nor pathogenicity of any flow. The content of the flow (volume, pressure, source, reentry) is more important than its direction. CHIVA consists of gravitational hydrostatic pressure (GHSP) fractioning, disconnection of the escape points (source) of the closed shunts and the open deviated shunts, and drainage preservation at reentry points. It leaves behind a “physiologic” flow, though refluxing, because it is no longer overloaded and complies with the “hierarchy of drainage.” This has been called a “shunt 0,” or a “no shunt.” In fact, a shunt is a conduit that steals part or all of the flow from another vessel. A venous reflux is a vein that drains all or part of the flow from another vein, flow it would not normally carry. The N3, N2, N1 venous network anatomy described in 199927 was translated from the French R3, R2, R1 network that was previously described via echo-Doppler in 1988, not only anatomically, but also functionally; there is a drainage hierarchy from the suprafascial tributaries (N3) into N2 (GSV and short saphenous vein [SSV] through duplicated fascia) and then into the deep subfascial network N1 or directly from N3 into N1. A closed shunt is N2 or N3 overloaded by an N1 through an N1>N2 or N1>N3 escape point that drains into N1 through an N3>N1 or N2>N1 reentry point. The N1>N2 or N1>N3 flow is a “true” reflux because contrary to the physiological hierarchical direction through an N1>N2 or N2>N3 escape point (perforator, saphenofemoral junction [SFJ], or saphenopopliteal junction [SPl]), it is elicited by calf valvo-muscular pump diastole (squeezing relaxation or Paranà maneuver diastole) and thoraco-abdominal pump systole (positive Valsalva) that drives it backward into N1 upstream of the valvo-muscular pumps. For CHIVA, finding and disconnecting the escape points is crucial (eg, perforator, SFJ, SPI, or pelvic leak points that are perineal, inguinal,28 clitoral,29 obturator, superior or inferior gluteal), whereas GSV endovenous ablation is performed below the descending tributaries of the GSV, so finding the SFJ escape point is not involved. Different types of closed shunts are created (eg, Shunt types I, III, IV, V, VI) according to these escape points and the succession of overloaded N2, N3 tracks. It is triggered by the calf valvo-muscular pump diastole (squeezing relaxation or Paranà maneuver diastole) and the thoraco-abdominal pump systole (positive Valsalva).

Open deviated shunts are generated with N3 overloaded by N2 through an escape point “true” reflux N2>N3 because it’s contrary to the physiological hierarchical
direction N3>N2. It is triggered by the squeezing relaxation or Paranà maneuver diastole like for a closed shunt, but not by the Valsalva maneuver, which is crucial for differentiating closed shunts from open deviated shunts.

Shunt 0 shows only N2 or N3 Paranà diastolic reflux and no N2>N3, N1>N2, or N1>N3 escape point.

Notice that both closed shunts and open deviated shunts work only when the valvo-muscular pump is activated, ie, essentially, when walking.

An open vicarious shunt is any vein—deep or superficial—that bypasses an obstacle. It is overloaded by a flow that is upstream of a block in another vein through an escape point and reinjected downstream through a reentry point. It is triggered by the systole of calf squeezing relaxation or Paranà maneuver, but not by the Valsalva maneuver. In some cases, these flows are retrograde (for example at the SFJ in spontaneous Palma), and their ablation aggravates the venous insufficiency!

A mixed shunt is made of the combination of a closed shunt and an open vicarious shunt that share the same escape point activated by both systole and diastole of the Paranà or squeezing relaxation maneuvers. Then, they flow through the same track, which splits into 2 tracks. One is activated only by systole and drains the open vicarious shunt into a specific reentry point. The other one is activated only by diastole and drains the closed shunt into its specific reentry point. So, they have the same escape point but different reentry points. A mixed shunt is fed most of the time by a systolic-diastolic reflux of the SFJ due to a constitutional stenosis of the femoral vein at the Hunter hole and by the SFJ in case of iliac vein occlusion.

By preserving the open vicarious shunt and disconnecting only the closed shunt part of the mixed shunt, one avoids impeding the drainage flow and leaves behind a drainage flow called shunt 0 in the specific track of the previous closed shunt.

Reservoir effect and siphon effect
Varicose veins, especially clusters, are sometimes implicated in reflux and worsening due to their alleged aspirative function, related to a so-called “reservoir effect” and/or “siphon effect” of varicose veins, though clusters do not fulfill the physical conditions for exerting a “reservoir effect” or “siphon effect.” In fact, varicose vein reflux is activated only by the diastolic valvo-muscular pump aspiration, regardless of the presence of clusters or dilated incompetent veins. This eliminates the reservoir effect of the clusters. Moreover, the classic physiologic “reservoir effect” is defined by the capability of the venous bed to amortize the pressure variations owing to its compliance. In physics, the siphon effect is an open circuit, with a pipe with one end immersed in a tank, emerging higher than the surface of the liquid, and then bending downward so that the other open end outside the tank is lower than the surface of the liquid. An incompetent GSV cannot be a siphon because it is not open but closed and connected to the deep veins through the escape and reentry points and has no emerging intermediate segment.

Varicogenesis according to upward or downward progression
Whatever the disputed model of varicogenesis direction, it doesn’t change the CHIVA approach. Varicogenesis could be an argument for intervening to prevent proximal varicose extension by ablating distal incompetent tributaries.

Diagnosis and mapping
As ablation-based concepts need to assess refluxing veins only, the resulting mappings are much simpler than those for CHIVA where the various types of shunts must be identified.

Treatments
What is the strategy for CHIVA or ablation?
CHIVA is usually performed as an outpatient procedure under local anesthesia with few incisions: 1 to 7, with an average of 3 incisions. CHIVA involves: (i) gravitational hydrostatic pressure fractionation; (ii) disconnection of closed shunts and open deviated shunts; (iii) no disconnection of open vicarious shunts; (iv) no vein ablation, particularly of GSV.

Ablation procedures vary according to technique, but involves vein ablation, particularly of the GSV.

What tactics are involved in CHIVA and ablation?
For CHIVA: under local anesthesia, GSV crossotomy (SFJ flush division; no absorbable ligation; no arch, tributaries division, or ligation) or triple saphenous flush ligation (TSFL) of the SFJ are performed. Shunts are disconnected at the flush escape points, with no stump.
For ablation: methods vary from use of general anesthesia for stripping to no anesthesia for foam sclerotherapy; it involves GSV crossectomy; open air or endovenous ablation.

Results

CHIVA results can depend on the physician’s level of expertise in performing the method: it has been described as being better than stripping if carried out by experts, but less so if carried out by non-experts.32

Note, there is no randomized controlled trial showing ablation to be better than CHIVA. However, out of 120 studies and trials about CHIVA, 5 randomized controlled trials13-17 are favorable for CHIVA.

A recent publication in the Cochrane Database System Review11 describes little or no difference in varicose vein recurrence when comparing CHIVA with either stripping or radiofrequency ablation and also no difference in recurrence or side effects when compared with endovenous laser therapy. However, it mentions a possible slight reduction in nerve injury and hematoma in the lower limb with CHIVA vs stripping, as well as the possibility of more bruising vs radiofrequency ablation. It should be noted that all these findings were based on low-certainty evidence, with limitations named as the small number of trials, the high risk of bias because surgery effects could not be hidden, and imprecision of results because of the small number of events.

Guo et al12 reported on a study including 39 eligible RCTs (a total of 6917 limbs), determining that CHIVA had the best long-term efficacy (the highest successful treatment rate, with a surface under the cumulative ranking [SUCRA] value of 0.37) and was most likely to achieve the lowest long-term recurrence rate (with a SUCRA value of 0.61).

Reliability of the main results was analyzed, with most direct comparisons based on moderate- or high-level evidence. Thus, CHIVA appears to have superior clinical benefits with regard to long-term efficacy in varicose vein treatment, though further trials to provide more supporting evidence are needed.

New trials comparing CHIVA and ablation should be carried out to ascertain superiority. Nevertheless, GSV ablation versus a better or at least equally conservative method presents an ethical issue when GSV remains the arterial bypass gold standard versus prosthetics.

Conclusion

CHIVA intervention results, short- and long-term, appear to be better or are at least equivalent to ablation. Furthermore, GSV sparing with CHIVA is a crucial difference between these two approaches in terms of the potential need for vital arterial bypass surgery. The approach taken by CHIVA requires a revisiting of classical pathophysiology, in particular hemodynamics, and therefore an intellectual effort for those trained in the dogmas of ablation. Moreover, this new hemodynamic knowledge offers a new diagnosis and a new therapeutic management of venous disease.
The new patient-oriented tools for clinical assessment of pelvic varicose disease

Rustem VILEVICH
AKHMETZIANOV, MD, PhD

Doctor of Medical Sciences, Cardiovascular Surgeon of the Department of Vascular Surgery, Inter-regional Clinical Diagnostic Center of the Ministry of Health of Russia, Assistant of the Department of Cardiovascular and Endovascular Surgery, Kazan State Medical University of the Ministry of Health of Russia, Kazan, Russia

Keywords:
chronic pelvic pain; chronic pelvic venous disorder; disease severity scale; micronized purified flavonoid fraction; pelvic congestion syndrome; Pelvic Varicose Veins Questionnaire, PVVQ, and the Pelvic Venous Clinical Severity Score, PVCSS) that were recently developed taking into account the clinical course of PCS and validated in accordance with international standards. This article also provides rationale for their use in monitoring of patients’ quality of life (QOL) and severity of disease manifestations and also as unified tools for objective clinical assessment. In addition, this article discusses issues of rational pharmacotherapy for PCS in the context of historical and modern research on this disease and in line with an evidence-based approach. Venoactive drugs (VADs) are described as the only group of agents with proven efficacy and safety in PCS. With the largest accumulated evidence base, micronized purified flavonoid fraction’s (MPFF) advantages in the conservative treatment of PCS are demonstrated. Treatment with MPFF is associated with QOL improvement and a decrease in the severity of disease and each of its symptoms.

Abstract
This article presents a review of patient-oriented diagnostic tools currently used in patients with pelvic varicose veins (pelvic congestion syndrome, PCS), and provides rationale for using disease-specific tools, as highlighted in the international consensus documents on the diagnosis and treatment of PCS. The authors present two original diagnostic tools (the Pelvic Varicose Veins Questionnaire, PVVQ, and the Pelvic Venous Clinical Severity Score, PVCSS) that were recently developed taking into account the clinical course of PCS and validated in accordance with international standards. This article also provides rationale for their use in monitoring of patients’ quality of life (QOL) and severity of disease manifestations and also as unified tools for objective clinical assessment. In addition, this article discusses issues of rational pharmacotherapy for PCS in the context of historical and modern research on this disease and in line with an evidence-based approach. Venoactive drugs (VADs) are described as the only group of agents with proven efficacy and safety in PCS. With the largest accumulated evidence base, micronized purified flavonoid fraction’s (MPFF) advantages in the conservative treatment of PCS are demonstrated. Treatment with MPFF is associated with QOL improvement and a decrease in the severity of disease and each of its symptoms.

Introduction
Chronic venous disease (CVD) is an urgent health care issue and a very common pathological condition with a prevalence of up to 83.6%.1 Pelvic congestion syndrome (PCS) as an independent nosological entity and one of the essential components of CVD is an important problem in modern medicine due to its high prevalence (6%-15% of women of reproductive age), variability in clinical forms, and progressive course of the disease.2-6 The clinical and social significance of PCS is related to a substantial reduction in the quality of life (QOL) of patients, their self-esteem, productive activities, and social relationships, as well as impaired reproductive, marital, and family functions and the lack of a persistent clinical effect after courses of treatment.2-11
Despite significant advances in the diagnosis and treatment of CVD, PCS remains one of the least studied disorders, with a number of aspects that need to be further addressed. These aspects include the terminology used for this disease, generally accepted and convenient classification, and a consensus on clinical and visual criteria.\(^{9,12-15}\) An important issue is the lack of adequate validated patient-oriented tools for the clinical assessment of PCS, namely the specific QOL questionnaires and clinical scales to grade the disease severity. These inadequacies in making the diagnosis of PCS preclude an objective and complete assessment of the effect of any treatment and the comparative analysis of the results of various treatments both in a single institution and in multicenter trials.\(^{16-18}\) The need for patient-oriented tools is highlighted in the consensus documents of the International Union of Phlebology and the Multidisciplinary Research Consensus Panel, as the tools commonly used in PCS assessment are not appropriate for the stated objectives.\(^{9,14}\)

The purpose of this work is to review the current state of patient-oriented assessment and pharmacotherapy in PCS, as well as to present new validated tools for the assessment of QOL and severity of PCS in women.

**Overview of the current state of patient-oriented diagnostic tools**

To date, several QOL questionnaires and standardized rating scales have been developed, tested, and used for the clinical assessment of various diseases. QOL is an integral parameter of the physical, psychological, emotional, and social functioning of an individual, which is based on subjective perception.\(^{19,20}\) This is a complex and multifaceted concept that includes a person’s physical health, mental state, level of personal independence, social relationships, and possibility of self-actualization in social settings.\(^{21}\)

Currently, QOL is actively studied and is becoming an indispensable element of the clinical examination of patients, which is used in almost all areas of medicine. It reflects the influence of the pathological process and its treatment on the well-being of the patient and is also an essential integrative indicator to support treatment rationale and secondary prevention of the disease.\(^{22}\) The main tools for assessing QOL are specific questionnaires used as reference instruments to evaluate a particular treatment in the context of a particular disease.

The methodology of QOL and disease severity assessment includes administration of general, specialized, or disease-specific questionnaires that take into account morphological, functional, and psychosomatic factors, as well as special subject-oriented clinical scales, which are focused on the influence of a specific pathological process and the treatment effect on health and severity of disease manifestations.\(^{11}\)

General or nonspecific questionnaires are designed to assess QOL regardless of the nosology, severity of the disease, and methods of treatment. The best-known general questionnaires are the Medical Outcomes Study, 36-item short form (MOS SF-36), Euro-Qol, the Quality of Well-Being Index, the Sickness Impact Profile, the Nottingham Health Profile, and the Quality of Life Index. Their advantage is the versatility and multidimensional assessment of QOL components, as well as the possibility of their use in a healthy population.\(^{19}\)

Specialized questionnaires provide an assessment not of the health state as a whole, but of its individual aspects. A significant drawback of both general and specialized questionnaires is the lack of consideration of peculiarities of a disease and its treatment and low sensitivity to the QOL changes in a particular disease.\(^{23}\)

Specialized questionnaires are focused on the effect of a particular pathological process and treatment on the health state and QOL of an individual. They are most sensitive in assessing particular diseases and contain components specific to those. To date, specialized questionnaires have been developed for almost every disease, and several hundred multicenter randomized studies have been conducted to assess QOL along with other parameters.\(^{19}\) At the same time, no questionnaire specific to PCS could be found in the available literature.

It is believed that the PCS assessment can be performed using the QOL tools developed for CVD, such as the Chronic Venous Insufficiency Questionnaire (CIVIQ), the Venous Insufficiency Epidemiological and Economic Study (VEINES), the Aberdeen Varicose Vein Questionnaire (AVVQ), the Charing Cross Venous Ulceration Questionnaire (CCVUQ), and the Freiburg Questionnaire of Quality of Life in Venous Diseases. At the same time, none of them is universal and does not cover the entire continuum of CVD with consideration of the course of a particular disease.\(^{17,24}\)
A systematic review has demonstrated that in most studies in chronic pelvic pain (CPP), the investigators used the SF-36 questionnaire for the QOL assessment, and only in 22.2% of the studies did the QOL instruments meet more than half of the clinical validity criteria. The use of SF-36, despite its informativeness, is limited by complex and lengthy mathematical calculations to obtain results, such as reverse conversion of the values of some scales, calculation of the summary score for each scale using certain keys, and the use of cumbersome formulas to determine the value of general indicators.

The most popular tool for assessing QOL in patients with CVD is CIVIQ. This questionnaire, due to its specificity, is focused on assessing changes occurring in the lower extremities and is not able to reflect manifestations disturbing patients with PCS, which precludes its use in this disease. At the same time, the relevance and need for a tool for assessing QOL in this disease is beyond doubt.

Currently, the clinical assessment of PCS is mainly restricted to the measurement of pain via various modified tools, which, unfortunately, do not comprehensively reflect the entire multifaceted palette of clinical manifestations of this disease.

Most often, when evaluating changes in the clinical course of PCS, the visual analog scale (VAS) of pain is used as a quantitative tool for assessing symptoms. The intensity of pain as assessed by patients with PCS ranges from scores of 7.2 to 8.5. In addition, to rank the pain syndrome, the numerical rating scales, verbal rating scales, and the McGill Pain Questionnaire (MPQ) are used. In this case, the patient is given an evaluation sheet with a scale offering to evaluate pain sensations in numerical values from 0 (no pain) to the value defined as maximum intensity (up to 10 or 100). The results gathered from such scales strongly depend on the subjective psychosomatic characteristics of the patient, as well as on the degree of responsibility of the researcher explaining the rules for filling in these scales. A significant drawback of these scales is the emotional component of the respondent, which introduces significant biases in the indicators. The subjectiveness of VAS can significantly distort the objective picture of the disease, as the patient may deliberately underestimate or overestimate the values.

As for PCS, the use of the following severity scores has been proposed: the Venous Clinical Severity Score (VCSS), the Venous Segmental Disease Score (VSDS), and the Villalta-Prandoni scale. Unlike VAS, rating scales exclude the arbitrary selection of responses by the patient. The VCSS is the most commonly used tool for assessing CVD severity, and it involves 4 response options (each with scores from 0 to 3) with a defined characteristic of the pain symptom. Such a formulation of questions limits the influence of the investigator’s personality and excessive subjectivization by the patient. In addition to the pain symptom, the scale includes other clinical characteristics of CVD and consists of 10 items. The high reproducibility of responses, good validation results, its suitability for patients with all classes of CVD, and the ability to demonstrate minor changes in the patient’s condition make it an ideal tool for assessing CVD severity and determining the clinical efficacy of treatment. Despite its advantages, this clinical scale, due to its specificity, is focused on the assessment of changes occurring in the lower extremities and is not able to reflect the manifestations that disturb female patients with PCS.

VSDS takes into account an involvement of various segments of the venous bed of the lower extremities in the process of reflux or obstruction. The Villalta-Prandoni scale is focused on the dynamic assessment of the state of the lower extremities in post-thrombotic disease. The above factors exclude the use of these scales in female patients with PCS due to low informativeness of these methods. As for other potential tools for assessing PCS, the von Korff questionnaire, which was validated in a group of patients with chronic prostatitis, and the Endometriosis Health Profile-30 and Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaires, due to their specificity to the underlying disease, are not acceptable for PCS assessment.

Therefore, the main priorities in the clinical assessment of CVD will be to evaluate the status of the lower extremities.

**Pelvic Varicose Veins Questionnaire**

On the basis of the analysis of complaints and objective symptoms in patients with PCS, we developed an original QOL questionnaire for female patients with PCS. The prototype of the questionnaire was the well-known CIVIQ tool, which was adapted taking into account the manifestations of PCS. This tool was named by analogy with the prototype as Pelvic Varicose Veins Questionnaire (PVVQ).

PVVQ reflects 4 main dimensions of a person’s physical and mental health: pain, physical and social activity, and
psychological well-being, which are the most informative
criteria for self-assessment of QOL. Each dimension
includes 5 questions that maximally reveal the depth of
pathological changes occurring in PCS in terms of the
studied health factor.

The QOL assessment is carried out using a special form with
20 questions, each with a 5-score scale (1, normal; 2, mild;
3, moderate; 4, severe; and 5, very severe disturbances)
(Tables I-IV).

| Have you experienced the pain described below in the last 4 weeks? If so, what was the intensity? |
|---|---|---|---|---|---|
| Lower abdominal pain that’s getting worse in the 2nd phase of the menstrual cycle (from day 14 or 15) (not during menstrual bleeding) | No pain | Mild pain | Moderate pain | Severe pain | Very severe pain |
| 1 | 2 | 3 | 4 | 5 |
| Pain during and/or after sexual intercourse | 1 | 2 | 3 | 4 | 5 |
| Pain in the area of sacrum and coccyx during prolonged sitting | 1 | 2 | 3 | 4 | 5 |
| Pain in the lumbar and inguinal areas, worsening by the end of the working day and after physical exertion | 1 | 2 | 3 | 4 | 5 |
| Tenderness and hypersensitivity in the perineum and vulva | 1 | 2 | 3 | 4 | 5 |

Table I. The Pelvic Varicose Veins Questionnaire (PVQ): pain syndrome.

| How much have the below manifestations disturbed you or limited your daily physical activity during the last 4 weeks? |
|---|---|---|---|---|---|
| Heaviness and discomfort in the lower abdomen and/or perineum | Not disturbed | Slightly disturbed | Moderately disturbed | Severely disturbed | Extremely disturbed |
| 1 | 2 | 3 | 4 | 5 |
| Urination disorder (painful and frequent urination, urinary incontinence, feeling of incomplete emptying of the bladder) | 1 | 2 | 3 | 4 | 5 |
| Varicose veins of the external genitalia, perineum, posterior thigh, or gluteal areas | 1 | 2 | 3 | 4 | 5 |
| Violations of the menstrual cycle (irregular timing and duration of bleeding, heavy or poor bleeding) | 1 | 2 | 3 | 4 | 5 |
| Premenstrual syndrome and/or painful periods | 1 | 2 | 3 | 4 | 5 |

Table II. The Pelvic Varicose Veins Questionnaire (PVQ): physical dimension.

| To what extent did the manifestations of the disease limit your social activity when performing the actions listed below? |
|---|---|---|---|---|---|
| Professional duties | Not limited | Slightly limited | Moderately limited | Severely limited | Impossible to perform |
| 1 | 2 | 3 | 4 | 5 |
| Daily house activity (cooking, keeping the baby in your arms, washing and ironing the clothes, washing the floor and cleaning, gardening) | 1 | 2 | 3 | 4 | 5 |
| Shopping | 1 | 2 | 3 | 4 | 5 |
| Going to the theater, cinema, or visiting friends | 1 | 2 | 3 | 4 | 5 |
| Doing sports/fitness activities | 1 | 2 | 3 | 4 | 5 |

Table III. The Pelvic Varicose Veins Questionnaire (PVQ): social dimension.
The lower the summary score, the better the QOL from the patient’s perspective. The summary score for all 20 questions is interpreted as the following: 20, the highest (best) QOL; 21-40, mild impairment of QOL; 41-60, moderate impairment of QOL; 61-80, severe impairment of QOL; and 81-100, gross violation of QOL.

PVVQ was validated in line with international standards and the QOL research methodology with an assessment of the main psychometric properties (reliability, validity, and sensitivity). The validation study included 304 females with verified PCS and 93 controls without signs of CVD (397 females in total). The results of validation were very encouraging, which allows us to consider PVVQ an appropriate tool for assessing QOL.

The reliability of PVVQ was proven by evaluating 3 parameters: internal consistency (intra-item $\alpha=0.807$, inter-item $\alpha=0.919$, average Spearman rank correlation coefficient $r_s=0.598$), discriminant validity ($P<1\times10^{-20}$), and internal consistency ($P=0.346$). The analysis of construct validity versus an external tool such as SF-36 confirmed statistically significant correlations based on the convergent (-0.663 $\leq r_s \leq -0.709$) and divergent (-0.293 $\leq r_s \leq -0.399$) validity. The sensitivity assessment demonstrated a statistical significance of the results after the treatment ($P=7.75\times10^{-8}$).

Table IV. The Pelvic Varicose Veins Questionnaire (PVVQ): psychological dimension.

<table>
<thead>
<tr>
<th>Manifestations of the disease can also affect mental balance. To what extent do the following phrases correspond to how you felt during the past 4 weeks?</th>
<th>Never</th>
<th>Very rarely</th>
<th>Sometimes</th>
<th>Quite commonly</th>
<th>Almost always</th>
</tr>
</thead>
<tbody>
<tr>
<td>I’m screwed up, annoyed</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I quickly get tired</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I feel that I burden my relatives</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I am suffering from depression, tearfulness, insomnia</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I have a heightened sense of anxiety</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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**Table IV. The Pelvic Varicose Veins Questionnaire (PVVQ): psychological dimension.**

| I’m screwed up, annoyed | 1 | 2 | 3 | 4 | 5 |
| I quickly get tired | 1 | 2 | 3 | 4 | 5 |
| I feel that I burden my relatives | 1 | 2 | 3 | 4 | 5 |
| I am suffering from depression, tearfulness, insomnia | 1 | 2 | 3 | 4 | 5 |
| I have a heightened sense of anxiety | 1 | 2 | 3 | 4 | 5 |

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**Table IV. The Pelvic Varicose Veins Questionnaire (PVVQ): psychological dimension.**

| I’m screwed up, annoyed | 1 | 2 | 3 | 4 | 5 |
| I quickly get tired | 1 | 2 | 3 | 4 | 5 |
| I feel that I burden my relatives | 1 | 2 | 3 | 4 | 5 |
| I am suffering from depression, tearfulness, insomnia | 1 | 2 | 3 | 4 | 5 |
| I have a heightened sense of anxiety | 1 | 2 | 3 | 4 | 5 |

In PVCSS, each of the 10 manifestations of PCS is rated by the severity of objective and subjective signs from scores ranging from 0 to 3: 0, no symptoms; 1, episodic symptoms; 2, persistent symptoms without a decrease in QOL; and 3, severe symptoms with QOL reduction.

**PVSS** provides low variability in the patient’s responses regardless of the characteristics of the personalities of both investigator and patient. In addition, the survey and examination of the patient in accordance with the scale items reminds the doctor of all the necessary studies that must be performed for a thorough examination. After filling in the form, the investigator calculates the summary score rated from 0 (no PCS signs) to 30 (most advanced disease). The global index is interpreted as follows: 1-10, mild; 11-20, moderate; and 21-30, severe disease.

The PVCSS validation was consistent with the validation principles of PVVQ and proved its validity as a tool for assessing PCS severity. The construct validity was assessed against VAS elements as external criteria. Good internal consistency was confirmed, with moderate relationships ($\alpha=0.803$, $r_s=0.365$). The validation tests demonstrated a high discriminant validity ($P<1\times10^{-30}$) and internal consistency ($P=0.981$), a high and marked strength of relationships with VAS when assessing convergent validity ($0.663 \leq r_s \leq 0.813$), as well as weak and moderate relationships when assessing divergent validity ($0.081 \leq r_s \leq 0.349$). A high sensitivity was also confirmed ($P=3.65\times10^{-7}$).

Similarly, the clinical severity scale for female patients with PCS, the Pelvic Venous Clinical Severity Score (PVCSS), was developed based on the analysis of clinical manifestations. Its prototype was the well-known venous clinical severity score (VCSS).
Evaluation of the clinical efficacy of pharmacotherapy for PCS

The history of pharmacotherapy for PCS includes the combined use of agents from different classes. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the level of CPP but cannot constitute the background and long-term treatment.\textsuperscript{14,56} 

Several limited studies of hormonal and psychotropic drugs have been performed in small samples of patients and provided contradictory results. The findings from one of two known placebo-controlled studies of the use of hormones suggested there are some treatment benefits in terms of temporary CPP relief, although at a higher rate of adverse events.\textsuperscript{57} However, the second study did not confirm the efficacy of such treatment.\textsuperscript{58} A number of studies conducted without a placebo group also could not provide unequivocal evidence of the safety and benefits of using various hormonal drugs.\textsuperscript{59,59-61} The analgesic effect of sex hormones is achieved by the suppression of ovarian function with a decrease in estrogen production and inhibition of menstruation. Adverse effects of hormonal treatment include weight gain, emotional lability, flashes, and osteoporosis. Thus, the positive effect of hormonal drugs is very doubtful, given a significant number of complications, temporary effects, and suppression of fertile function.

The available studies of psychotropic drugs with a placebo group have not demonstrated a decrease in the VAS pain score.\textsuperscript{62,63} Other studies that have proven their benefit in this category of patients are limited by a number of

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Sign & Scoring system & 0 & 1 & 2 & 3 \\
\hline
1. Abdominal pain (not during menstruation) & 0 – No & 1 – Rare, not requiring analgesics & 2 – Every day with a moderate restriction of activity, episodical intake of analgesics & 3 – Every day with a significant restriction of activity, constant use of analgesics \\
\hline
2. Abdominal heaviness & 0 – No & 1 – Rare & 2 – Every day, in the second half of the day or after physical exertion & 3 – Every day, permanent \\
\hline
3. Abdominal discomfort & 0 – No & 1 – Rare & 2 – Every day, in the second half of the day or after physical exertion & 3 – Every day, permanent \\
\hline
4. Pain in the sacrum and coccyx & 0 – No & 1 – Rare & 2 – Occurs with prolonged sitting & 3 – Occurs quickly in the sitting position \\
\hline
5. Dysuria (painful and frequent urination, urinary incontinence, feeling of incomplete emptying of the bladder) & 0 – No & 1 – Rare & 2 – At the end of the working day or after physical exertion & 3 – Occurs with light physical exertion \\
\hline
6. Atypical varicosity & 0 – No & 1 – On the external genitalia & 2 – Plus in the perineum, lower abdomen and above pubis & 3 – Plus in the groin, on the posterior thigh, buttocks \\
\hline
7. Dyspareunia (pain during and/or after sexual intercourse) & 0 – No & 1 – Rare & 2 – Constant during sexual intercourse & 3 – Constant during and persisting after sexual intercourse \\
\hline
8. Menstrual disorders & 0 – No & 1 – Rare & 2 – Excessive or irregular bleeding, with moderate premenstrual syndrome & 3 – Disabling and prolonged abundant or irregular bleeding, preceded by premenstrual syndrome \\
\hline
9. Tenderness in the external genitalia area and perineum & 0 – No & 1 – Rare & 2 – Not every day & 3 – Every day \\
\hline
10. Edema in the external genitalia area and perineum & 0 – No & 1 – Rare & 2 – At the end of the working day or after severe physical exertion & 3 – Occurs with light physical exertion \\
\hline
\end{tabular}
\caption{The Pelvic Venous Clinical Severity Score (PVCSS).}
\end{table}
significant factors, such as small sample sizes, the absence of a placebo group, and reported data on the rate and severity of adverse events.\textsuperscript{64-66} In one study, all patients received additional physiotherapy and psychotherapy.\textsuperscript{67} Thus, the lack of a convincing evidence base does not allow for unconditional advisement of widespread use of psychotropic drugs in patients with PCS.

Unfortunately, almost all reviews on the pharmacological treatment of PCS include the selective vasoconstrictor ergotamine and suggest its positive effects. However, the results of 2 studies cannot substantiate a basis for its administration in patients with PCS. One of these studies reported a decrease in the diameter of pelvic veins (by 35%) and in the level of CPP for a maximum follow-up period of 4 days, and the second confirmed venous constriction within 20 minutes of its administration.\textsuperscript{68,69} The drug can provoke episodes of arrhythmias and angina pectoris, convulsions, confusion, etc. The above factors support the need to “forget” about this drug in the treatment of PCS.

Meta-analyses and systematic reviews indicate some short-term efficacy of drugs suppressing ovarian function in the reduction of CPP. However, due to inhibition of fertility and several adverse effects, along with their limited efficacy, these agents are not appropriate for the long-term treatment of CPP.\textsuperscript{70-73}

The only pharmacological agents recommended by consensus documents are vеноactive drugs (VADs).\textsuperscript{14,43} The largest evidence base in this group has been obtained for the micronized purified flavonoid fraction (MPFF). In the well-known placebo-controlled studies performed by one research team, MPFF use was accompanied by a significant decrease in the intensity of CPP and had no adverse effects. The use of certain vitamins, which may provoke episodes of arrhythmias and angina pectoris, convulsions, confusion, etc. The above factors support the need to “forget” about this drug in the treatment of PCS.

During the study, one adverse event group (dyspeptic phenomena) was registered in a patient from the MPFF group, which resolved spontaneously by the third day of taking the drug.

Therefore, the largest evidence base accumulated for VADs indicate that these agents and, particularly, MPFF are safe and effective treatments for PCS due to their ability to improve QOL and reduce the disease severity, as well as each of its symptoms.

**Discussion**

The modern armamentarium of doctors includes both instrumental and clinical methods for the objective assessment of treatment efficacy. The ultimate goal for any treatment effect on the pathological process in the human body is the improvement in the patient’s clinical state in terms of elimination of symptoms and signs and the absence of complaints. Evaluation of treatment results
based only on the laboratory or instrumental tests is always risky, as it is incomplete and does not take into account the patient’s personality. Better results from instrumental diagnostic methods are not a sufficient target. Such positive instrumental changes do not always correspond with an improvement in the patient’s state. Despite improvements with instrumental diagnostic tools, patients aren’t prone to consider treatment results satisfactory when they do not see improvement in their state. For comprehensive assessment of the quality of treatment, as well as practical evaluation of its success or failure, the investigator needs a unified tool for objectifying the patient’s clinical state, which is based on the quantitative criteria developed by standardizing the characteristics and symptoms of the disease at certain time points.19,20

The proposed tools for clinical evaluation, PVVQ and PVCSS, have been used in our clinic for a long time, creating a positive experience, and they have proven their feasibility in the evaluation of conservative and surgical methods of treatment.7,79-83

Having these tools available to an investigator enables them to evaluate efficacy of the health care provided and to receive an objective assessment of its quality by the patient, the main object of its application. Statistical and graphical analysis of the status of patients with PCS provides individual monitoring of QOL and disease severity, as described by clinically significant changes in parameters after use of various treatment methods in various groups of patients in order to select the most optimal one.

Our study demonstrates the wide possibilities of using these tools for assessment, as well as the efficacy and safety of MPFF in the treatment of patients with PCS in routine clinical practice.

The pathophysiological component of the symptomatic manifestations of PCS is a disturbance in venous hemodynamics due to blood stasis in the lower pelvis. In patients with PCS, treatment with MPFF is associated with a decrease in venous reflux, correction of hemorheology and venous tone, restoration of physiological pelvic circulation, elimination of microcirculatory disorders, relief of inflammatory reactions, improvement in lymphatic drainage function, and reduction in blood congestion in the veins of the lower pelvis with subsequent symptom relief.7,79,84-87

Therefore, from the position of evidence-based medicine, MPFF plays a very important role in the treatment of female patients with PCS, contributing to its advantages over other VADs. MPFF therapy leads to pain relief, increase in physical and social activity, and correction of the psychological state of a woman, her marital and family functions and working capacity.7,79

Despite the evidence of progress in medical treatment of PCS, there are still many issues that need to be addressed. The latest studies on the use of hormonal and psychotropic agents in PCS were carried out about 20 years ago. Since that time, many new agents and a variety of laboratory and instrumental tools have become available. Therefore, an integrated interdisciplinary approach is needed for the scientific developments in this area, with the involvement of gynecologists-endocrinologists and psychoneurologists. New large-scale studies of MPFF efficacy are warranted to address questions about the optimal dosing regimen of the drug and the possibility of its use in pregnant women. The listing of PCS as a separate nosological entity in MPFF instructions for use is advised.

**Conclusion**

The new patient-oriented tools of clinical assessment in PCS, namely PVVQ and PVCSS, are disease-specific, simple, accessible, and convenient clinical diagnostic methods that make it possible to carry out quantitative assessment, statistical processing, analysis, and interpretation of the data obtained. They are characterized by high reliability, validity, and sensitivity to changes.

The practical use of these tools in the evaluation of the pharmacological treatment of PCS has proven the clinical efficacy of MPFF in terms of the reduction in disease severity and an improvement in the QOL of patients.

**Corresponding author**

Rustem VILEVICH AKHMETZIANOV, 12A, Karbysheva str., Kazan 420101
Russia

Email: arustemv@mail.ru
REFERENCES


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Is compression necessary after endovenous thermal ablation of varicose veins? Clarifying a (com)pressing matter

Chronic venous disease (CVD) represents a significant impact on patients’ lives with negative financial, social, and health-related quality of life consequences. The gold standard for treatment of varicose veins and CVD is now considered to be endovenous thermal ablation (EVTA). Although compression is widely prescribed for patients post EVTA, there is widespread disagreement on the optimal compression regimen and if compression is even required postoperatively. This review reexamines the literature surrounding this important clinical question, presenting current clinical opinion and practices and guideline recommendations, and discusses the evidence for and against the use of compression postoperatively. It further considers the differences between the benefits of compression observed in endovenous laser ablation and radiofrequency ablation. Overall, the data still indicate the lack of knowledge regarding the efficacy of post-EVTA compression. Although using compression for a longer duration post EVTA appears to have some impact on early postoperative pain, these conclusions are potentially confounded by a multitude of variables including analgesia regimen, adherence to compression therapies, and energy modality. The literature suggests that extending compression beyond 7 days is unlikely to confer any additional benefits, but due to these confounding variables, further clarification is required to determine if compression type and duration should be personalized to target specific groups of patients, or if any compression post EVTA is required at all.

Introduction

The term chronic venous disease (CVD) covers a spectrum of clinical presentations, which increase in severity from telangiectasia to varicose veins, edema, skin changes, and eventually, venous ulceration. These presentations significantly impact patients’ lives, with negative health-related quality of life (HRQOL) changes related to chronic pain, decreased mobility, social isolation, and other psychosocial issues. CVD is a common condition, with varicose veins affecting up to 40% of the population and venous ulcers prevalence being up to 4% in patients above the age of 65.

Keywords: bandages; compression; endovenous laser ablation; endovenous thermal ablation; radiofrequency ablation; stockings.
Historically, the management of varicose veins involved surgical ligation and stripping of saphenous veins. However, since the beginning of the 21st century, there has been a rapid evolution of endovenous thermal ablation (EVTA) technologies, with endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) shown to be as clinically effective as these surgical techniques. Endovenous interventions for this disease have been found to be cost-effective in multiple trials and even more so when performed in an outpatient setting. These techniques are now considered “gold-standard” and are endorsed by national and international guidance.

What is perhaps less clear is the prescription of compression after EVTA (Figure 1). Although compression after EVTA is widely thought to be beneficial and is regularly provided in clinical practice and randomized controlled trials (RCTs), there exists significant debate over its impact on clinical and patient-reported outcomes. Even if compression is assumed to be beneficial after EVTA treatment, there is still widespread disagreement regarding the type (bandages versus stockings), level, and duration of the compression regimen.

Figure 1. Compression stockings used after endovenous thermal ablation.
Photo provided courtesy of Alun H. Davies.

Clarifying this matter is of utmost importance for a few reasons. Firstly, compression is often poorly tolerated by patients—a survey reported that only 29.1% of patients consider compression therapy to be “comfortable.” Extended durations of compression may also contribute to skin irritation, leading to negative impacts on patients’ HRQOL, contrary to treatment intentions. Secondly, in view of this discomfort and potential adverse effects, adherence to compression therapy is a known challenge, with adherence rates estimated to be as low as 30% in trials. Finally, from a financial point of view, regular use of compression post EVTA may represent an unnecessary cost should this not provide any benefits to patients. This is an area of potential cost savings for patients and the health care service, estimated at up to £182 per patient per annum.

Current practices

In 2016, a survey was sent out to consultant members of the Vascular Society of Great Britain and Ireland, with questions on their prescribing patterns of compression following treatment of varicose veins. Although all respondents prescribed compression after EVTA, the duration ranged from 2 days to 6 weeks and 4 different combinations of stockings, bandages, and paddings were used in these prescriptions. Only 28% of vascular units used the same method, and 10% used the same duration of compression.

This discordance in practice was noted in the literature as well. Systematic reviews from the same year observed compression strategies used in randomized clinical trials that included endovenous ablation as a trial arm, showing compression to be prescribed for anywhere between 2 days to 6 weeks. Most trials used stockings and bandages in combination or bandages alone for an initial duration of compression, after which most patients were switched to isolated stockings for the remainder of the prescription. This inconsistency in compression regimens can also be seen in the studies identified in this review (summarized in Table I).

What do the current guidelines say?

As mentioned above, international guidelines are quite unanimous regarding their recommendations for supporting the use of EVTA options in the treatment of varicose veins and CVD, with such technologies now the gold-standard treatment for varicose veins. These guidelines, however, are less unified when it comes to recommending compression after EVTA (examples from the United States [US], the United Kingdom, and Europe are summarized in Table II).

In the context of the authors’ national guidelines, the National Institute for Health and Care Excellence (NICE) recommends the use of compression (bandages or hosiery) for no more than 7 days after intervention. However, recognizing the uncertainty of evidence surrounding compression compared with no compression after treatment, the NICE Guideline Development Group advocated further research into this postintervention treatment, with specific questions regarding its clinical- and cost-effectiveness. This guideline,
### Table I. Different compression regimens used in the studies included in this review.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Treatment</th>
<th>Comparison arm 1</th>
<th>Comparison arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker et al(^17) 2013</td>
<td>RCT</td>
<td>EVLA</td>
<td>Continuous stockings for 7 days</td>
<td>48 hours stockings only</td>
</tr>
<tr>
<td>Elderman et al(^18) 2014</td>
<td>RCT</td>
<td>EVLA</td>
<td>24 hours of bandages, then continuous stockings for 2 weeks</td>
<td>24 hours bandages only</td>
</tr>
<tr>
<td>Ye et al(^19) 2016</td>
<td>RCT</td>
<td>EVLA</td>
<td>12 hours elastic bandages, then continuous stockings for 2 weeks</td>
<td>12 hours elastic bandages only</td>
</tr>
<tr>
<td>Krasznai et al(^20) 2016</td>
<td>RCT</td>
<td>RFA</td>
<td>Continuous stockings for 72 hours</td>
<td>4 hours stockings only</td>
</tr>
<tr>
<td>Pihlaja et al(^21) 2020</td>
<td>RCT</td>
<td>RFA</td>
<td>Continuous stockings for 48 hours, then daytime only for 5 days (7 days total)</td>
<td>No compression</td>
</tr>
<tr>
<td>Onwudike et al(^22) 2020</td>
<td>RCT</td>
<td>RFA</td>
<td>Continuous stockings for 2 weeks, then daytime only for 2 weeks (4 weeks total)</td>
<td>No compression</td>
</tr>
<tr>
<td>Zolotukhin et al(^23) 2017</td>
<td>RCT</td>
<td>RFA</td>
<td>Continuous full leg compression sleeves for 7 days, then at least 8 hours a day until 30 days after procedure (30 days total)</td>
<td>Continuous full leg compression stockings for 7 days, then at least 8 hours a day until 30 days after procedure (30 days total)</td>
</tr>
<tr>
<td>Ayo et al(^24) 2017</td>
<td>RCT</td>
<td>RFA (91%) + EVLA (9%)</td>
<td>Continuous stockings for 1 week</td>
<td>No compression</td>
</tr>
<tr>
<td>Bootun et al(^25) 2021</td>
<td>RCT</td>
<td>RFA (97%) + EVLA (3%)</td>
<td>24 hours of bandages, then continuous stockings for 7 days</td>
<td>24 hours bandages only</td>
</tr>
</tbody>
</table>

### Table II. Current guidelines and recommendations for post-endovenous-thermal-ablation (EVTA) compression.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation regarding provision of compression after treatment</th>
<th>Class/Grade</th>
<th>Evidence level</th>
<th>Recommendation regarding duration of compression after treatment</th>
<th>Class/Grade</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE(^9)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>If offering compression bandaging or hosiery for use after interventional treatment, do not use for more than 7 days.</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AVF/SVS/ACP/SVM/IUP(^26)</td>
<td>When possible, we suggest compression (elastic stockings or wraps) should be used after surgical or thermal procedures to eliminate varicose veins.</td>
<td>2</td>
<td>C</td>
<td>In the absence of convincing evidence, we recommend best clinical judgment to determine the duration of compression therapy after treatment.</td>
<td>Best practice</td>
<td>Best practice</td>
</tr>
<tr>
<td>ESVS(^8)</td>
<td>For patients with superficial venous incompetence undergoing ultrasound-guided foam sclerotherapy or endovenous thermal ablation of a saphenous trunk, postprocedural compression treatment should be considered.</td>
<td>IIa</td>
<td>A</td>
<td>For patients with superficial venous incompetence undergoing intervention, the duration of postintervention compression, used to minimize postoperative local complications, should be decided on an individual basis.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

EVLA, endovenous laser ablation; RCT, randomized controlled trial; RFA, radiofrequency ablation.

However, was formulated in 2013 and the new evidence published since then might change recommendations in its future iterations.

More recent guidelines from societies from the US and the European Society for Vascular Surgery (ESVS) do provide recommendations regarding providing compression after EVTA. These recommendations, however, are of weak to moderate strength. The recommendation from the US societies, for example, suggests provision of compression after EVTA, but this recommendation is graded as 2C (“weak recommendation, low-quality or very-low-quality evidence”). That from the ESVS recommends that clinicians “consider” providing postprocedural compression. This recommendation, however, has been downgraded to class IIa in the latest edition of the guidelines, suggesting conflicting evidence but in favor of usefulness or efficacy. These two guidelines also were not able to provide firm durations for compression use, suggesting that it be left to “clinical judgment” or “decided on an individual basis.”

This marked variation in practice highlights a lack of evidence for an optimal compression strategy post EVTA. With no clear agreement between vascular units from both a clinical and academic perspective, and indeed from national and international guidelines, and the disparity not improving over time, it would be prudent to reexamine the evidence specific to compression regimens post EVTA to determine if this practice confers any benefits to patients, and if perhaps the benefit differs depending on the energy source of the interventional modality.

### Evidence post EVLA

In the current literature, 3 RCTs have considered the impact of different compression regimens on clinical and patient-reported outcomes after EVLA. Whereas 2 other RCTs included EVLA as a treatment option, most patients in these RCTs underwent RFA, and the outcomes from these trials will be considered in the next section.

The evidence surrounding compression post EVLA largely showed isolated improvements in postoperative pain, with little impact on other clinical and patient-reported outcomes. In one RCT, 111 patients (clinical, etiologic, anatomic, pathophysiologic classification [CEAP] C2-4) underwent EVLA treatment followed by a compression regimen of either 24-hours bandaging only, or 24-hours bandaging followed by 2 weeks of compression stockings. When measuring time taken to return to daily activity or work, there were no significant differences between the groups. This was also reflected in another RCT that randomized 400 varicose veins (CEAP C2) patients, with the two groups either using stockings for 12 hours or using stockings for 2 weeks. This RCT showed no difference in the average time taken to return to work as well.

In these 2 RCTs, patients also did not report any significant differences in HRQOL improvements associated with the different compression regimens, as measured using the Aberdeen Varicose Vein Questionnaire (AVVQ) or the RAND 36-Item Health Survey. In the remaining RCT, 93 patients were randomized into wearing stockings for 48 hours or continuously for 7 days. In contrast to the findings from the other 2 trials, patients who wore the stockings for 7 days showed better Short Form-36 physical functioning and vitality scores than those who only wore them for 48 hours. This HRQOL benefit, however, was short-lived, with no significant difference found at 6-week follow-up.

When considering pain, all 3 studies showed statistically significant improvement in pain scores in patients who were randomized to a longer duration of compression-stocking use. However, this positive impact on pain only lasted up to 7 days postoperatively, with no longer-term differences when patients were followed-up at 2 weeks and 6 weeks. As a surrogate measure for postoperative pain, 1 study also measured analgesia use. This study showed that while the extended compression group reported lower pain at 1-week follow-up, this group also used significantly greater quantities of paracetamol over the course of the 6-week study, although nonsteroidal anti-inflammatory drug use was similar.

### Evidence post RFA

Considering compression regimens post RFA, 6 RCTs have been identified in the literature. These RCTs again consider a range of clinical and patient-reported outcomes, observing how different compression regimens affect these results. Five of the RCTs considered the impact of different durations of compression, whereas the remaining trial compared different types of compression, comparing leg sleeves with stockings.

Once again, the RCTs examining compression post RFA showed no significant impact on most clinical or patient-reported outcomes. Three studies observed the impact that compression regimens had on HRQOL. The largest of the 3 randomized 204 patients (CEAP C2-5), comparing
Interestingly, unlike the patients who were treated with EVLA, of the 5 RCTs that compared compression duration to 24 hours to improve short-term postoperative pain relief, 3 failed to show any significant difference in pain relief at all time points measured.20,22,24 Unlike the benefit of pain improvement at 1 week shown in the EVLA studies, no significant differences in time taken to return to work or usual activities were shown in 3 RCTs.20,21,25 Finally, whereas clinical severity scores were shown to be improved post RFA intervention in 3 RCTs, these improvements were not statistically different or related to changes in compression regimens.22,24,25

A study randomizing 100 patients (C2-6) into 2 arms comparing no compression with wearing compression stockings for 4 weeks showed no significant difference in pain scores at 12- to 14-week follow-up.22 Whereas this study’s finding would be consistent with the diminishing impact of pain relief seen after 1 week in the EVLA cohort, 2 other RCTs observed pain outcomes at 1 week24 and 10- days follow-up,21 both showing no improvements in pain relief with longer durations of compression. Only 1 RCT showed an association between longer compression and better pain improvement at 2 to 5 days postoperatively, but once again showed no lasting benefit with no significant difference in median pain scores over 1 to 10 days after EVTA intervention. This study, however, showed that there was no difference in analgesia use between groups, suggesting that there was a potential benefit to pain relief with a longer duration of compression post EVTA.25

Discussion

In recent years, 2 systematic reviews have considered these questions surrounding post EVTA compression, examining the results from the trials discussed above.22,28 Both reviews recognized that the evidence supports extending compression past the initial 48 hours to improve short-term pain relief for up to 10 days postoperatively. Considering this result, the first review supported the use of compression postoperatively, suggesting that the effect it had on pain relief justified the practice.22 However, in view of the lack of improvements in HRQOL and complication rates, the authors of the more recent review felt that the discomfort and difficulty of applying compression therapies outweighed the slight benefits to pain relief that they identified in their meta-analysis.28 Unfortunately, most studies included in that review failed to report on compliance; it would be hasty to draw such conclusions based on anecdotal experience, and it would behoove future studies to include this as an outcome measure.

One major source of heterogeneity in such trials revolves around the postoperative analgesia regimen used. Of the 9 RCTs discussed in this review, only 4 reported specifically on the use of analgesia post EVTA.18,19,21,25 One noted that no analgesia was prescribed but failed to determine if there was any over-the-counter simple analgesia used by patients in either comparison arm.19 Another noted that whereas the group that underwent a longer duration of compression showed improved pain relief, this was potentially confounded by the higher use of paracetamol seen in that patient population (although NSAID use was similar).18 Two other studies documented similar analgesia use between treatment arms, but despite this, one study showed improved pain relief with longer compression duration,23 while the other showed no difference between groups.21 This raises a potential cost-benefit question regarding compression therapies—if an appropriate analgesia regimen is recommended for patients post EVTA, this might represent a more cost-effective method of improving short-term postoperative pain.

Additionally, in clinical practice, EVTA is often not performed in isolation and may be combined with other techniques, such as foam sclerotherapy, phlebectomies, or multiple stab avulsions. A previous systematic review looking at postsclerotherapy compression qualitatively identified potential benefits of longer duration and higher grades of compression on postoperative complications (including pain) and wound healing (including those from concomitant...
phlebectomies). This benefit, however, was once again limited to short-term follow-up. In the 2 RCTs that included patients that underwent concomitant phlebectomies with RFA treatment of the truncal veins, one showed no difference in pain relief with varying compression type, whereas the other showed improvement in pain scores with a longer duration of compression stockings. Combining multiple treatment modalities is essential in clinical practice due to the various clinical presentations and patterns of refluxing veins that clinicians encounter. Personalizing compression regimens may be essential to maximize the benefits it confers while minimizing the discomfort it might impose.

Finally, this review has provided an opportunity for a closer look at the evidence, with the benefit of subdividing the published trials according to the 2 different modalities of energy used. Studies have shown that pain levels are significantly lower in patients whose varicose veins are treated with RFA than in those ablated using lasers. This may explain why the analgesic benefits of compression post EVLA were more pronounced than that of the RFA trials. It must be noted that improvements in EVLA devices have shown reduced postprocedural pain, and this observation may not hold true in trials with these newer devices.

Conclusions

Despite a significant number of trials over the last decade, compression regimens post EVTA remain heterogeneous. The extent of their benefits remains muddled by this heterogeneity, with current studies suggesting a benefit to short-term pain relief. This benefit, however, may potentially be negated should an appropriate postoperative analgesic regimen be employed. Current trials also suggest a greater benefit for compression post EVLA than post RFA; this may also be less significant with development of newer devices. It is unlikely that offering compression post EVTA for more than 7 days would be effective at providing any benefits to patients, but further clarification is required to determine if compression type and duration should be personalized to target specific groups of patients, or if any compression is required at all.

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Cyanoacrylate closure in the treatment of varicose veins – what is the evidence?

Nick MORRISON, MD, FACS, DBVLM
Center for Vein Restoration, Phoenix, Arizona, USA

Abstract

Introduction
Cyanoacrylate ablation for incompetent saphenous veins is a recent addition to the armamentarium of venous surgeons. It does not require the instillation of tumescent anesthesia during the procedure, thus reducing patient discomfort, and neither are compression hose necessary after treatment.

Early cyanoacrylate ablation trials
VenaSeal™ (Medtronic, Minnesota, USA) was the first reported use of a formulation of cyanoacrylate used in the ablation of incompetent saphenous veins. Clinical series and randomized controlled clinical trials demonstrated the safety and efficacy of this ablation method. The VeClose trial compared VenaSeal™ to the radiofrequency ablation (RFA) method and showed clear noninferiority of safety and efficacy compared with RFA.

Subsequent VenaSeal™ trials
The WAVES trial demonstrated efficacy of VenaSeal™ in large great saphenous veins without the use of compression hose. And in a 60-month extension study of patients from the VeClose trial, long-term occlusion success and freedom from adverse events has been confirmed.

Other cyanoacrylate-formulation studies
Among alternative cyanoacrylate formulations first reported was N-butyl cyanoacrylate adhesive (NBCA), used successfully in saphenous vein ablations in Turkey. Several trial reports have been published comparing NBCA with thermal ablation techniques, showing equal or better efficacy and safety for NBCA ablation.

Conclusion
The safety and efficacy of differing formulations of cyanoacrylate for ablation of incompetent saphenous veins have been demonstrated through many clinical trials internationally.
Introduction

The incidence of chronic venous disease (CVD) in the population overall is 18.2% and increases with advancing age. The progression of CVD as evidenced by advancing clinical classification significantly impacts a patient’s quality of life (QOL).

There has been a dramatic evolution over the past 3 decades in the management of CVD in general and saphenous insufficiency in particular with minimally invasive endovenous techniques replacing conventional surgical therapy.

The safety and efficacy of endovenous therapies, including radiofrequency ablation (RFA), ultrasound-guided foam sclerotherapy, and endovenous laser ablation (EVLA), have been reported in numerous clinical trials.

In the recently published clinical guidelines from the European Society of Vascular Surgery, for patients requiring intervention for superficial truncal venous incompetence, endovenous thermal ablation is recommended at a class I level A; endovenous ultrasound-guided foam sclerotherapy of smaller superficial truncal vein incompetence at a IIb Level B.

Some concern has been raised in the literature about neurosensory adverse events in association with ultrasound-guided foam sclerotherapy. Initially, a report was published in the Journal of Vascular Surgery in 2006 by Forlee and colleagues regarding a patient who developed a stroke following foam sclerotherapy attributed to gas bubbles passing through a previously undiagnosed right-to-left intracardiac shunt (18-mm patent foramen ovale). An immediate carotid duplex scan demonstrated moving echogenic particles consistent with gas bubbles, although magnetic resonance imaging (MRI) of the brain was normal. The patient recovered most of his neurological deficits, but the report was cause for great concern in the international phlebologic community. Because of this and a number of other reports of neurosensory adverse events, there remains some concern about the intravenous injection of foam in the treatment of what is almost exclusively a nonlethal condition and has stimulated investigations into alternative ablation methods.

RFA and EVLA require the use of tumescent anesthesia (TA) and post-procedural compression stockings, both of which often produce discomfort during and after the procedure.

To address the discomfort associated with TA, newer, nonthermal nontumescent therapies (NTNT) for the treatment of saphenous insufficiency have been introduced. One relatively recent NTNT technique is the use of cyanoacrylate (CA) adhesive to produce occlusion and eventual fibrosis of the saphenous trunk. The first CA developed for this purpose was VenaSeal™ (Medtronic, Minnesota, USA), which has been most commonly used in clinical trials originating in the USA, western Europe, and much of Asia (see attached video demonstration of procedure using VenaSeal™).

The first-in-human trial reported by Almeida demonstrated occlusion of the GSV in 92% of the patient cohort at 1 year, along with significant reduction (improvement) in the Venous Clinical Severity Score (VCSS). Soon thereafter, in a single-arm, multicenter, cohort study, the European Sapheon™ Closure System Observational Prospective study (eSCOPEstudy), Proebstle et al published an occlusion rate at 12 months of 92.1%. Subsequently, the randomized controlled VeClose trial was published in which the VenaSeal™ adhesive was compared with RFA in a noninferiority trial. This was a prospective randomized controlled trial into which 242 patients were enrolled, with the first 20 patients used as roll-in to assure investigators were familiar with the procedure. All investigators were experienced endovenous surgeons. Patients aged 21 to 70 years in Clinical, Etiologic, Anatomic, and Pathophysiologic (CEAP) class C2-C4b with symptomatic GSV incompetence and a reflux time of ≥0.5 seconds assessed in the standing position with duplex ultrasound were enrolled. Patients with significant reflux of the small saphenous vein or anterior accessory GSV, who had previous treatment for venous disease in the target limb, symptomatic peripheral arterial disease, history of deep venous thrombosis or pulmonary embolism, or aneurysm of the target GSV with >12-mm diameter were excluded from the trial.

Patients were randomized into 2 groups: those treated with RFA and those treated with CA (VenaSeal™). Treatment was confined to the GSV only without adjunctive treatment for 3 months following the index procedure. The primary end point of occlusion of the GSV at 3 months without any patent segment >5 cm was achieved in 99% of the CA group and 96% of the RFA group, thus demonstrating noninferiority of CA vs RFA. Nearly equal improvement in the secondary end points of VCSS score QOL instruments was reported; no deep venous thromboses (DVTs) were identified in either group; and there was no significant difference in side effects or complication, including phlebitis. At 1 year, nearly
identical occlusion rates were seen in the CA and RFA group (97.2% for CA vs 97% for RFA). At that time point, disease-specific and generic QOL improvement was also similar in the 2 groups and the inflammation seen early on in patients from both groups had subsided on its own or with the addition of a brief course of over-the-counter anti-inflammatory medication. In the subsequent 24-month and 36-month follow-up of the VeClose trial, the occlusion rates were identical in both the CA and RFA groups, and parallel improvements in the VCSS and QOL scores were found, demonstrating durable noninferiority of CA closure (CAC) compared with RFA. There were 5 adverse events in the CA group between 24 and 36 months, 2 of which were related to the procedure. During the same time period, there were 4 serious adverse events in the CA group, none of which were related to the procedure (liver cancer, breast cancer, cervical pain, and suicide attempt).

Long-term follow-up studies are required to establish the durability of the treatment in terms of efficacy and safety. The first to be published was a 5-year extension study of patients from the VeClose trial aimed to assess the long-term efficacy and safety of CA and RFA in patients with incompetent GSV. The study included a 36-to-60-month interval evaluation of eligible patients from the VeClose trial for occlusion rates, 60-month CEAP classification, VCSS and QOL scores, patient satisfaction with treatment, need for adjunctive treatment, and adverse events. At month 60, VCSS score improvement was maintained (Figure 1), and complete occlusion of the GSV was reported in 94.6% of patients who had undergone VenaSeal™ ablation (CAC method) and 100% of patients in the RFA group (P=0.292) (Table I). No C0 or C1 patients were enrolled at the outset of the study, but interestingly, by the end of the extension study, 29/47 patients having undergone CA ablation were then classified as C0 or C1 (Figure 2). Presumably, if the investigators had been more successful with patient

Figure 1. Mean Venous Clinical Severity Score (VCSS) during a 60-month follow-up period of eligible patients from the VeClose trial.

Signs/symptoms associated with venous reflux disease (assessed by investigator via VCSS score, with scores ranging from 0 [no venous disease] to 30 [severe venous disease]) improved over time and was maintained through 60 months. Reduction from baseline: VenaSeal™ CS, 75%; radiofrequency ablation, 72%.


Figure 2. Results from the VeClose trial showing secondary end point of changes in C clinical classification (Clinical, Etiologic, Anatomic, and Pathophysiologic [CEAP] classification system): C classification of subjects at eligibility and at 60 months with cyanoacrylate closure (VenaSeal™ CS) and radiofrequency ablation.

Changes in C clinical classification were observed in all subjects.

Abbreviations: RFA, radiofrequency ablation; VSCS, VenaSeal™ closure system.

recruitment, even more C0 and C1 patients would have been identified. QOL improvements were maintained over the long term, and the need for adjunctive treatment was minimal during this 36-to-60-month time interval (5 had sclerotherapy, no patient had phlebectomy). There were no adverse events from 36 to 60 months, including pulmonary embolisms (PEs), DVTs, and of note, no long-term inflammatory or hypersensitivity reactions. And finally, 100% of the patients in the study were either very or somewhat satisfied with their treatment. Table II shows overall conclusions of the study.

An important limitation of the 60-month extension study was that 89 of the original 242 patients agreed to the 60-month evaluation. Patients were enrolled in the VeClose trial with the understanding that the follow-up period would be 36 months. It proved difficult to find and convince subjects to participate in the 60-month follow-up in-person visit. However, patients in this study group were evenly divided between those who had RFA and those who had CAC.

Other VenaSeal™ trials

A 1-year GSV occlusion rate of 78.5% was reported by Chan and colleagues, with improvement of VCSS and generic and disease-specific QOL scores using VenaSeal™. Larger vein diameter (≥8 mm) was predictive of incomplete occlusion.

Hwang and colleagues expounded on the concept first reported by Gibson of the diminished need for adjunctive therapy for varicose veins following adhesive ablation of the GSV. In Gibson’s report, successful occlusion was achieved in all patients despite the absence of compression hose and adjunctive treatment. In the Hwang report, complete occlusion of all treated GSVs at 3 months was seen. Even more importantly, regression of varicose tributaries occurred in 71.7% and complete or >50% regression occurred in 90%.

In many CA trials, the use of compression hose post procedure has not been required. In the VeClose trial, because compression hose is standard procedure following RFA, and because this was a head-to-head comparison, compression hose were used in all patients, including those undergoing CA ablation. However, in the WAVES trial (Lake Washington Vascular VenaSeal™ Post-Market Evaluation) reported by Gibson and colleagues, compression hose were not used, even for patients with GSVs >10 mm in diameter, with no difference in occlusion rates.

In an early report from Lane and colleagues, there appeared to be a suggestion that treatment with CA in a patient on anticoagulation may not lead to successful vein ablation. That has not been the experience of this investigator, and to my knowledge no other similar reports have appeared in the literature.

In another retrospective review of 335 patients treated with VenaSeal™ compared with RFA, Yang and colleagues reported 100% successful ablation at 2 months.
To improve occlusion rates in patients with GSVs >8 mm in diameter, Chan et al. have applied an extra 0.09 mL of VenaSeal™ at the most proximal saphenous treatment site. Whereas occlusion rates significantly improved compared with the standard volume of adhesive, the occlusion rate was still not as high as in saphenous veins <8 mm in diameter. The study also determined that the extra drop of adhesive did not increase the rate of adhesive extrusion through the saphenofemoral junction.

Interim 1-year results reported by Tang et al. demonstrated a 12-month occlusion rate of 97.9%. At 3 months, revised VCSS and QOL scores were significantly improved in all patients, but between 3-month and 12-month follow-up there was no further improvement, nor were there any adverse events.

Park has published a case report of a patient with a 2.84-cm diameter GSV undergoing successful VenaSeal™ ablation by depositing additional adhesive in the dilated areas of the GSV.

Vicente-Jimenez and colleagues in two hospitals in Spain retrospectively studied 233 patients who had undergone surgical stripping (SS), RFA, or CA adhesive ablation for incompetent saphenous veins. The clinical outcomes were measured by quality-adjusted life years (QALYs), complications, and reintervention, with a cost-effectiveness analysis comparing the 3 ablation methods. Clinical outcomes were essentially the same for RFA and CA, but the complication rate for SS was roughly 4 times that of RFA or CA. Cost-effectiveness analysis revealed that whereas health care costs only favored SS, CA was the most cost effective when direct health care costs were added to the cost of workdays lost.

Cyanoacrylate (VenaSeal™) perforator ablation

The feasibility of treating incompetent perforator veins with CA was studied in 33 incompetent perforator veins by Toonder et al. Occlusion rate at 3 months was 76%. In a subsequent retrospective review of 367 patients, Gibson treated 56 incompetent perforator veins in combination with CA ablation of superficial truncal veins. An occlusion rate of 85% at 1 month was demonstrated. And in a more recent publication, Mordhorst et al. report 83 perforator veins were treated with VenaSeal™ with 86.5% occluded at 6 weeks.

In a retrospective review of CEAP 6 venous leg ulcer patients undergoing VenaSeal™ ablation (CAC) or ClosureFast™ thermal ablation of saphenous veins, Kiguchi and colleagues reported a less frequent need to treat perforator veins following VenaSeal™ ablation than after ClosureFast® thermal ablation. It is theorized by the authors that treatment of a longer saphenous vein segment made possible with VenaSeal™ without the risk of nerve injury attendant to thermal ablation techniques is the reason for less-frequent subsequent perforator treatment in venous leg ulcer patients.

International cyanoacrylate alternative formulation trials

More recently, a number of clinical trials from various countries have been published also documenting the safety and efficacy of other formulations of CA adhesives.

In a randomized controlled trial comparing N-butyl cyanoacrylate adhesive (NBCA; VariClose System, Biolas, FG Grup, Turkey) with RFA and EVLA published by Erasglu and Yasim, at 2 years, all 3 groups experienced similar occlusion rates (NBCA 92.6%, RFA 90.9%, and EVLA 91.5%, \( P=0.89 \)), with less periprocedural pain, faster return to work, and more improvement in VCSS scores for the group treated with NBCA.

In a prospective comparative study of CA ("Turkish Glue Kit") vs EVLA for GSV treatment involving 208 CA procedures, Calik et al reported the 12-month occlusion rate for the
CA patients was 96.6%. Similar improvements were seen in VCSS scores and values from the Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ version 2) between the CA group and the EVLA group. Procedural pain was less, and induration, ecchymosis, and rate of paresthesia were all significantly less in the CA group. And in a retrospective analysis from Daylan and colleagues of 246 patients who had undergone CA (VenaBlock, Ankara, Turkey), at 5 years, the occlusion rate was 91.1%. The VCSS and Aberdeen Varicose Vein Questionnaire (AVVQ) scores significantly improved.

A report from India by Premnath and colleagues describes 124 patients undergoing saphenous and perforator ablation (269 in the group) using “commonly available n-butyl [CA] glue (which is used as topical skin adhesive or for endovascular embolization of arteriovenous malformations and vascular tumors)” (Endocryl®, Samarth Pharma Pvt Ltd, India).

Complications associated with adhesive ablation

The viscosity of the different formulations of CA and their associated rates of complications has been the subject of discussion in medical conferences.

VenaSeal™ is very viscous and polymerizes in less than 2 minutes. Adhesive manufactured in Turkey and India (Variclose®, Endocryl®), on the other hand have essentially the same viscosity of water but is said to polymerize in a matter of seconds.

The importance of this difference is that embolization of adhesive can theoretically more readily be seen with adhesive of lower viscosity, thus increasing the risk of DVT. Premnath et al reported 96.5% occlusion rates at 1 year with all venous ulcerations healed but with 3/145 legs treated showing DVT, suggesting easier migration of the less viscous adhesive (Endocryl®, Samarth Pharmathan, India) than VenaSeal™. However, Cho et al reported a thrombus extension rate of 3.5% after VenaSeal™ ablation of GSVs.

In a systematic review of 17 studies regarding CA ablation for truncal superficial veins of 1981 patients, among which up to 2-year occlusion rates were 93.7% and inflammatory reactions were seen less frequently after NBCA ablation than after RFA or EVLA, VCSS and QOL scores improved after the adhesive ablations. No differentiation was made by the authors between CA adhesive of different formulations. Complications such as bruising, phlebitis, and pain were seen less frequently in the NBCA group than in thermal ablation groups.

Chan, et al41 have recently reported a review of several short and mid-term clinical trials using VenaSeal™ in the Asian population, with 1-year occlusion rates of 90% in patients with GSV diameters <6.6 mm, low rates of DVT, and rates of inflammatory reaction up to 25.4%. A diameter >6.6 mm was a risk factor for recanalization of the target vein.

In the Cho retrospective review of 191 patients having had VenaSeal™ ablation of saphenous veins, extrusion of adhesive through the saphenofemoral junction or saphenopopliteal junction was seen in 5.8%, all limited to <50% of the common femoral vein lumen. Anticoagulation was not deemed necessary, and no further complications were identified.

Diffuse inflammation in the thigh is commonly seen after CA ablation of the GSV (Figure 3), and readily responds to anti-inflammatory and antipruritic medications. Park et al described it as a "phlebitis-like abnormal reaction (PLAR)" with quite liberal criteria and thus occurring in 25.4% in their series of 271 veins treated.

It has been the experience of this author that in the presence of an inflammatory reaction, compression hose routinely provides comfort to the patient and that an inflammatory reaction does not seem to affect occlusion of the saphenous vein as shown in a case report from Fiengo and colleagues.

The hypersensitivity reaction seen in some patients after CA adhesive ablation is an erythematous effect generally near the venous treatment, with symptoms ranging from mild pruritis and/or erythema requiring no treatment for resolution to rare recurrent severe inflammation and pruritis.

In an excellent discussion from a combined retrospective/prospective review of 286 patients from Gibson et al, in which 379 veins were treated with VenaSeal™, it was seen in 6.3% of patients and were subdivided into mild presentations (4.2%) requiring either no or over-the-counter medications; moderate (1.3%), requiring steroids; and severe (0.3%), if the reaction lasted over 30 days or required explantation. The authors suggest avoidance of CA in patients with known allergy to CA (such as used in application of prosthetic eyelashes and fingernails), in patients with multiple contact allergies.
and in patients with skin conditions like psoriasis or atopic dermatitis. Interestingly, previous treatment with CA was not predictive of development of hypersensitivity. Careful removal of the delivery catheter to avoid leaving adhesive in the subcutaneous tissue may be protective against hypersensitivity and can be achieved simply by withdrawing the delivery catheter into the access sheath prior to removal of the entire apparatus as suggested by Sermathamassawadi and colleagues. It should be remembered that CA is a permanent implant and will produce a foreign body reaction, albeit usually mild and localized. Clinically relevant granulomas are uncommon and generally related to extravasated adhesive on withdrawal of the delivery catheter.

Conclusion

CA adhesive is overall a safe and effective method of achieving improvement in signs and symptoms of venous disorders with robust long-term occlusion rates. Adherence to instructions for use and avoiding use in patients with known allergic reactions, hypersensitivity, or immune compromise is important.

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Pharmacological correction of total venous reflux in patients with varicose veins

Nikolai KHOREV, MD, PhD; Darya KUZNETSOVA, MD, PhD

1Department of Cardiology and Cardiovascular Surgery, Altai State Medical University, Barnaul, Russia
2Department of Pathological Anatomy, Department of Pathophysiology, Altai State Medical University, Barnaul, Russia

Abstract
The study was aimed at evaluating the efficacy of micronized purified flavonoid fraction (MPFF) in patients with primary chronic venous disease (CVD). It included 35 patients with varicose veins of the lower extremities (18 with bilateral and 7 with unilateral lesion). A total of 53 legs with varicose veins were evaluated in 3 groups based on the CEAP (Clinical, Etiology, Anatomic, Pathophysiology classification system) clinical class: group C2 consisted of 21 legs, and groups C3 and C4 consisted of 16 legs each. Patients received MPFF at a dose of 1000 mg daily for 1 month. The venous function of the lower extremities was evaluated using venous photoplethysmography before and after a course of pharmacotherapy. Venous refilling time (VRT) and half VRT \(\frac{1}{2}\)VRT were measured as parameters of total venous reflux. In the general sample of patients with C2-C4 classes, a significant increase in the venous photoplethysmography parameters was observed after the MPFF treatment course. Thus, VRT increased from [median (interquartile range)] 16 (12; 18) to 18 (13; 25) seconds, and \(\frac{1}{2}\)VRT increased from 6 (5; 7) to 7 (5; 9) seconds. In addition, a significant increase in VRT was observed in each group of patients with classes C2, C3, and C4. An inverse relationship was found between an increase in VRT after the treatment and both the CEAP clinical class and patient’s age. Therefore, the treatment with MPFF for 1 month is associated with a decrease in total venous reflux in patients with primary CVD. The effect of MPFF on total venous reflux was greater in younger patients and in patients with a lower clinical class of the disease.

Introduction
Venoactive drugs (VADs), including micronized purified flavonoid fraction (MPFF) represent an effective pathogenetic therapy for primary chronic venous disease (CVD), or varicose veins of the lower extremities. The MPFF treatment acts on almost all components of the CVD pathogenesis and is associated with a reduction in the inflammatory process and venous edema and an increase in the venous tone and venous wall resistance to hyperemia. The efficacy of pharmacotherapy for CVD is assessed by instrumental methods, among which...
Duplex ultrasound scanning (DUS) is considered the “gold standard” for evaluating venous function. However, this method does not provide a standardized quantitative characteristic of total venous reflux as the main pathogenetic manifestation of CVD. Among other noninvasive methods for examination of patients with primary CVD, venous photoplethysmography (PPG) is of particular interest. This easy-to-perform method makes it possible to identify and quantify venous reflux. According to the results of some studies, the parameters measured by venous PPG correlate with direct measurements of the venous pressure and phlebography data, as well as with data obtained by DUS. Some authors have successfully used venous PPG not only to identify and measure venous reflux in CVD, but also to monitor the efficacy of surgical or pharmacological treatment.

Previously, we have shown that venous PPG is an appropriate method for the quantitative instrumental assessment of total venous reflux.

The aim of this study was to evaluate the efficacy of MPFF in the treatment of CVD using venous PPG.

Materials and methods

The study included 35 patients (24 women and 11 men) with CVD (mean age 52 ± 12 years). Of them, 18 patients had signs of varicose disease on both legs (the CEAP [Clinical, Etiology, Anatomic, Pathophysiology classification] clinical class on the right and left legs could be different), and 7 patients had signs only on one leg. In total, varicose veins were present on 53 lower extremities. The diagnosis was made clinically and confirmed by DUS. The patients were allocated into 3 groups on the basis of the CEAP clinical class, and one patient could fall into 2 groups if classes for the right and left legs were different. Group C2 included 16 patients (21 legs), and groups C3 and C4 included 16 legs each.

All patients underwent venous PPG using a SmartDop 30EX Doppler analyzer with an additional photosensor (Hadeco Inc., Japan). Venous refilling time (VRT, sec) and half VRT (½VRT, sec) were evaluated. The measurements were carried out with the patient in a sitting position with legs lowered without support. The photosensor was fixed on intact skin 1 to 2 cm above the medial malleolus and somewhat posterior to it. The load on the muscle-venous pump of the lower leg consisted in performing 5 flexion-extensions in the ankle joint, followed by a period of rest, during which the PPG device built a plethysmogram and calculated VRT and ½VRT. After PPG results were obtained, MPFF was prescribed to all patients at a dose of 1000 mg daily. The mean (standard deviation [SD]) duration of MPFF treatment was 33.9 (± 10.4) days. After the treatment course, the follow-up venous PPG was performed.

Statistical analysis was carried out using nonparametric tests. Differences between the groups in the rates of CVD signs were assessed using the Mann-Whitney U test and Kruskal-Wallis test (one-way analysis of variance [ANOVA]). Differences between the values at baseline and after the treatment were assessed using the Wilcoxon signed rank test. The Spearman rank correlation coefficient was used to identify relationships between the variables. Data are presented as median and interquartile range (25%; 75%).

Results

The study revealed a significant correlation between the CVD clinical class and the parameters of total venous reflux. Using Kruskal-Wallis ANOVA, we confirmed the patterns of differences in venous PPG parameters (VRT and ½VRT) that we had previously discovered in patients with different CEAP clinical classes. Thus, the H-test was 27.37 for VRT (P < 0.0001) and 19.97 for ½VRT (P < 0.0001). The significant differences in VRT were observed between all groups, and significant differences in ½VRT were observed between all except between C3 and C4 groups (Figure 1). These findings justified using venous PPG to study the drug efficacy.

In the general sample of patients with classes C2 to C4, the treatment with MPFF for 1 month was associated with a significant increase in venous PPG parameters (Figure 2). Thus, VRT increased from 16 (12; 18) to 18 (13; 25) seconds (P < 0.0001) and ½VRT increased from 6 (5; 7) to 7 (5; 9) seconds (P = 0.0012). The changes in PPG parameters in each group are presented in Figure 3. Thus, in the C2 group, VRT significantly increased from 19 (18; 22) to 25 (20; 28) seconds (P = 0.0006) and ½VRT nonsignificantly increased from 7 (7; 9) to 9 (6; 11) seconds. In the C3 group, both VRT and ½VRT significantly increased from 14 (12; 17) to 17 (14; 22.5) seconds (P = 0.0026) and from 5 (4.5; 7) to 7 (6; 8) seconds (P = 0.0071), accordingly. In the C4 group, VRT significantly increased from 10 (7.5; 15) to 12 (7; 17) seconds (P = 0.024), while ½VRT remained unchanged (5 [4; 6] before and after the treatment). In summary, the treatment with MPFF at a daily dose of 1000 mg for 1 month was associated with a reduction in the venous reflux in patients with CVD of clinical classes C2 to C4.
An inverse relationship was identified between the CEAP clinical class and both the venous PPG parameters and increase in VRT after the treatment. In addition, a moderate positive relationship was revealed between an increase in VRT after the treatment with MPFF and both the treatment duration and increase in ½VRT after the treatment. There was also a moderate negative relationship between an increase in VRT and the patient’s age (Table I). Therefore, the higher the CEAP clinical class and the patient’s age, the lower the MPFF efficacy observed. Also, the longer the duration of treatment with MPFF, the greater its observed effect.

Figure 1. Venous refilling time (VRT) and half venous refilling time (½VRT) in patients with different CEAP clinical classes of CVD. *P<0.05 vs C2 class; #P<0.05 vs C4 class.

Figure 2. Changes in venous photoplethysmography parameters in the general sample of patients before and after the treatment with micronized purified flavonoid fraction (MPFF). *P<0.05 vs baseline.

VRT, venous refilling time; ½VRT, half venous refilling time.

Figure 3. Changes in venous photoplethysmography parameters in the different groups of patients before and after the treatment with micronized purified flavonoid fraction (MPFF). *P<0.05 vs baseline.

VRT, venous refilling time; ½VRT, half venous refilling time.
Discussion

The efficacy of MPFF in CVD has been demonstrated in a number of studies. Thus, MPFF treatment resulted in a significant reduction in the rates of typical adverse events after endovascular treatment of class C2 CVD and demonstrated its clinical efficacy as a strategy of vein-specific pharmacological protection during endovascular treatment of CVD. In patients with a combined varicose vein disease of the lower extremities and pelvis, the use of MPFF contributed to the reduction in pain in the lower extremities and chronic pelvic pain. In a number of studies, the treatment with MPFF in CVD was associated with a reduction in venous edema and in trophic disorders, and also with an acceleration in the healing of venous ulcers. Most studies have demonstrated the efficacy of MPFF clinically, on the basis of reduction in patient complaints and with the use of venous questionnaires and clinical scales. In some studies, changes in venous status in patients receiving MPFF were assessed by instrumental methods. Thus, the treatment with MPFF was associated with such positive changes in DUS as a reduction in the venous wall thickness, venous diameter, and duration of reflux. Ultrasonic elastography has also demonstrated MPFF efficacy in terms of an increase in the perivascular areas of elastographic homogeneity. However, no accurate instrumental evaluation of the hemodynamic efficacy of MPFF, in particular by the quantitative assessment of total venous reflux, has been published.

In this study, we used the venous PPG to evaluate MPFF efficacy in CVD. This instrumental method does not reveal the exact anatomical location of the reflux but most fully reflects the degree of functional impairment of venous function and correlates well with clinical outcomes. Venous PPG allows the quantitative characterization of venous reflux. The venous PPG parameters are global indicators of venous reflux and valvular insufficiency and directly correlate with the severity of functional disorders. Previously, we have already shown a close correlation between the CEAP clinical class of primary CVD and the parameters of venous PPG. In the present study, this pattern has been confirmed. At the advanced stages of CVD and, therefore, a greater clinical severity of the process, the parameters of venous PPG were lower, which suggested an increase in total venous reflux.

We found a significant increase in venous PPG parameters (VRT and \( \frac{1}{2} \)VRT) in patients with CVD after the treatment with MPFF at a dose of 1000 mg daily for 32.3 (± 9.3) days, which demonstrates a decrease in total venous reflux and an improvement in venous function.

An important fact is that a significant increase in VRT and \( \frac{1}{2} \)VRT was observed in patients of clinical classes C2, C3, and C4. At the same time, an inverse correlation was shown between the increase in VRT after MPFF treatment and the clinical class of CVD. Therefore, the lower the clinical class of CVD, the greater the efficacy of treatment with MPFF 1000 mg daily for 1 month in terms of the effect on total venous reflux. Perhaps, in patients with advanced classes of CVD, the longer treatment duration is required for positive changes in venous function and improvement in venous PPG parameters. This is evidenced by the direct correlation between the treatment duration and magnitude of the VRT increase. In other words, the longer the duration of treatment with MPFF, the more pronounced the observed changes in VRT as an integral parameter of venous reflux.

Besides venous reflux, an important role in the development of venous dysfunction in CVD is played by the calf muscle pump, which ensures optimal emptying of the venous system of the lower extremities. The muscle pump weakens with age, so its contribution to the venous function of the lower extremities decreases, and its role in the development of CVD increases. The present study has revealed a significant inverse relationship between an increase in VRT and patient’s age, despite the fact that there were no significant relationships between age and venous PPG parameters (VRT and \( \frac{1}{2} \)VRT) at baseline. Thus, in patients with CVD receiving MPFF, the positive changes in VRT decrease with age, which is probably explained by a larger contribution of the calf muscle pump failure to the development of CVD.
Conclusions

Finally, we conclude that treatment with MPFF is associated with a reduction in total venous reflux in patients with primary CVD. Furthermore, the effect of MPFF on total venous reflux is greater in younger patients and in patients with a lower clinical class of CVD.
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