Efficacy of micronized purified flavonoid fraction on postoperative symptoms after endovenous thermal ablation. A pilot randomized controlled study

Christos Karathanos, Konstantinos Batzalexis, Petroula Nana, Georgios Psaras, Konstantinos Spanos, Nikolaos Roussas, Miltiadis Matsagkas, Athanasios D. Giannoukas

Department of Vascular Surgery, University Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

Abstract:

Objectives: Micronized purified flavonoid fraction (MPFF) is a venoactive agent with proven positive effects in the treatment of chronic venous disease. The aim of our study was to assess its clinical efficancy in the postoperative symptoms after endovenous thermal ablation (EVTA) associated with phlebectomies.

Methods: Patients undergoing endovenous thermal ablation [Laser (EVLA) or Radiofrequency (RFA)] of the greater saphenous vein associated with phlebectomies were randomized in those receiving MPFF agent 500mg Bid 7 days before and 30 days after the procedure (MPFF group) and in those who did not receive MPFF (Control group). Clinical classification (CEAP), 10-cm Visual Analog Scale (VAS) for pain, Venous Clinical Severity Score (VCSS) and Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) were recorded. Assesment visits were performed 7 days prior to ablation and 7 and 30 days post-ablation. Primary outcome was postoperative pain using the VAS scale and CIVIQ pain score. Secondary outcomes were improvement of VCSS and CIVIQ scores.

Results: 21 patients were randomized to the MPFF group and 21 in the control group. Patients' demographics, CEAP classification, type of ablation (EVLA or RFA), mean linear endovenous energy density, average vein diameter and length of ablated vein were comparable between the two groups. Mean preoperative VAS pain score and CIVIQ pain score were 5.7± 1.8 and 10.2± 3.7 in the MPFF and 5.7± 1.7 and 9.8± 3.8 in the control group while at 7-day post-operatively there was improvement in both groups (2.7± 1.1 VAS pain score and 6± 1.3 CIVIQ pain score in the MPFF vs. 3.5± 1.2 and 7.4± 2.2 in the control group, respectively), (p=.03). At 7–day postoperatively the MPFF group had better outcome compared to the control one in the CIVIQ pain score (from 10.2± 3.7 to 6± 1.3 vs. from 9.8± 3.8 to 7.4± 2.2) (p=.04). At 30-day post-operatively all patients showed a significant improvement in all domains compared to preoperative assessment (p=.02), but there were no differences between the two groups.

Conclusions: MPFF in patients undergoing endovenous thermal ablation may improve early postoperative pain. Larger studies are needed to confirm these findings.

Abbreviations: EVTA, endovenous thermal ablation; EVLA, enovenus laser ablation; RFA, radiofrequency ablation; CEAP, clinical-etiology-anatomy-pathophysiology; VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire.

INTRODUCTION

Chronic venous disease (CVD) is a common disorder reported to affect up to 60% of the general population.[1] The symptoms attributed to CVD varing to different degrees of severity including asympotomatic forms to disabiliting pain, heaviness and ulceration of the limbs affecting patients' quality of life (QoL).

Author for correspondence:

Christos Karathanos, MD, MSc, PhD

Department of Vascular Surgery, University Hospital of Larissa, Mezourlo, 41 110 Larissa, Greece
Tel/Fax: +30 2413501739,
E-mail: christoskarathanos@yahoo.gr
ISSN 1106-7237/ 2019 Hellenic Society of Vascular and Endovascular Surgery Published by Rotonda Publications

The treatment options of patiets with CVD includes conservative treatment, traditional stripping surgery with ligation of the saphenofemoral juction (SFJ), endothermal thermal ablation (EVTA), mechanochemical ablation (MOCA), injection of cyanoacrylate glue and ultrasound guided foam sclerotherary.[2] Venoactive drugs (VADs) are considered an important component of the conservative treatment of CVDs, either alone or in combination with compression therapy.[2,3] Micronized purified flavonoid fraction (MPFF) is a venoactive agent with proven positive effects in the treatment of CVD, improving leg symptoms, edema and quality of life.[4] A recent study reported that, administration of VADs such as MPFF, may improve postoperative pain and hematoma in patients undergoing stripping surgery of the great saphenous vein (GSV).[5]

Current guidelines recommend EVTA techniques in preference to surgery, for the treatment of patients with GSV reflux (level of evidence A, class I).[2] The aim of our study was to as-

sess the clinical efficancy of MPFF in the postoperative symptoms after EVTA associated with phlebectomies.

MATERIALS AND METHODS

Patiets and Study Design

We conducted a single center, prospective, pilot randomized controlled study on patients undergoing EVTA at a tertiary center. Consecutive patients over 18 years of age with GSV incompetence confirmed by duplex ultrasound (DUS), clinical etiologic anatomic pathophysiologic classification (CEAP) clinical score C2 or more and anatomic criteria suitable for EVTA were eligible. Patients with deep vein incompetence, malignancy, recent surgery or trauma, pregnancy, lactation, deep vein thrombosis and/or pulmonary embolism within 6 months, systematic use of non steroid anti-inflammatory or other analgesics drugs, use of any venoactive drugs 30 days prior randomization or known allergy to the drug were excluded.

All patients underwent DUS of the superficial and deep veins of the lower limbs. Reflux was defined as retrograde flow during more than 0.5 s after calf compression.

Medical history, demographic characteristics, clinical examination defining the clinical class C of the CEAP classification, 10-cm Visual Analog Scale (VAS) for pain, Venous Clinical Severity Score (VCSS) and Chronic Venous Insufficiency Quality-of-Life Questionnaire (CIVIQ) were recorded.

After giving written informed consent, patients were randomly assigned in those receiving MPFF agent 500mg Bid 7 days before and 30 days after the procedure (MPFF group) and in those who did not receive MPFF (Control group). The randomization sequences were generated by a computerized random-number and distributed to each participant by the data coordinator in identical, sealed envelopes. Only patients that provided their consent to participate to the study, fulfilled our inclusion criteria and completed the follow up were included.

Procedures

We used the same procedural characteristics in both groups. EVTA was performed under local tumescent anaesthesia with a 1470-nm diode radial laser (EVLA) (Biolitec, East Longmeadow, Massachusetts) or radiofrequency (RFA) (ClosureFast™ Procedure, Medtronic, Mineapolis). The refluxing GSV was entered under DUS guidance and the tip of the fibre was positioned 1-2 cm from the SFJ. A perivenous tumescent anaesthesia was administered under DUS guidance in a fix solution consisting of 1000ml cold nature saline 0.9% with 50ml Xylocaine and 10ml sodium bicarbonate before EVTA. Laser was performed in the continuous mode at 10 W of power with a linear endovenous energy density of 80 J/cm. RFA was performed with a ClosureFAST device with a 7-cm heating element. Segmental energy delivery at 120°C was delivered in 20-second cycles. Two cycles were applied to the proximal vein, followed by one cycle to the remaining venous segments. Tributaries were removed by concomitant phlebectomies. At the end of all treatments, a compression bandage was applied. After 48 h, the bandage was replaced by a medical elastic compression stocking (ankle pressure 23-32mmHg) for 1 week during the day.

Outcome assessment and follow up protocol

Assesment visits were performed 7 days prior to ablation and 7 and 30 days post-ablation. Postprocedural DUS was performed to assess the status of vein occlusion and thrombosis. Any adverse events were also recorded. Patients were asked to complete a questionnaire at each visit that focused on pain assessment using a validated visual analog scale ranging from 0 (no pain) to 10 (most severe pain) (VAS score) and a validated CIVIQ score. All aspects (clinical, physical, social and psychological) of the CIVIQ score were recorded and analyzed. Primary outcome was postoperative pain using the VAS scale and CIVIQ pain score. Secondary outcomes were improvement of VCSS and CIVIQ scores.

STATISTICAL ANALYSIS

The relationships of categorical variables and the main outcomes observed (pain cores, CIVIQ, VCSS) were examined with the use of the x^2 statistic, whereas the relationships between main outcomes and continuous measurements were assessed with the independent samples t test or the Mann-Whitney test, where appropriate. For the change in the CIVIQ measures, the paired samples t test was applied for each of the dimensions measured.

RESULTS

Between September 2017 and March 2018 we randomly allocated 21 eligible patients to the MPFF group and 21 to the control group. Table 1 shows the main characteristics of the study population. There were no significant differences between the groups regarding demographics and clinical characteristics. The majority of the patients (86%) were C2 - C3 CEAP clinical class. Preoperative clinical scores including VAS, VCSS and CIVIQ were not different between the two groups (table 2).

	MPFF group	CONTROL group
No	21	21
Female	9	13
Age (mean), (min-max)	52 (33-70)	53 (33-80)
Limb Right	10	10
CEAP 2,3	18	18
CEAP 4,5,6	3	3

Table 1. Study population characteristics
Abbreviations: CEAP, clinical-etiology-anatomy-pathophysiology

Twenty patients underwent RFA and 22 EVLA. Limbs treated with EVLA received a mean linear endovenous energy density of 83 ± 5.6 J/cm. Mean maximum vein diameter measured 15cm below SFJ and mean length of treated segment were comparable between 2 groups (16 ± 3.4 vs 17± 4.2 and 32±3 vs 35± 5, respectively). The amount of tumescent anaesthesia used was 450ml ± 80 in MPFF group and 470ml ± 60 in the control group (p=.89).

	MPFF group	CONTROL group	P Value
VAS	5.7 ±2.1	1.3 ±1	.785
VCSS	5.8 ±2.6	5.8 ±2.8	.962
CIVIQ Global	37.5±11.3	40.8±15.4	.403
CIVIQ Pain	9.7±3.7	10.2±3.8	.655
CIVIQ Physical	7.2±3.3	7.9±3.8	.556
CIVIQ Social	5.1± 2.4	5.9±2.5	.322
CIVIQ Psychological	15.2±4.5	17.1±7.3	.325

Table 2. Preoperative characteristics of the patients
Abbreviations: VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire
Note.-Values expressed as means ±SD.

Primary outcomes

As illustrated in Fig 1 both groups improved the VAS pain score 7 days after the intervention in comparison to baseline (5.7± 1.8 vs 2.7± 1.1 in MPFFgroup and 5.7± 1.7 vs 3.5± 1.2 in control group) and kept improving it 30 days postoperatively (1.1± 0.4in MPFFgroup and 1.5± 0.6in control group) but without any statistical difference. At 7-day postoperatively the MPFF group had better outcome compared to the control one in the CIVIQ pain score (from 10.2± 3.7 to 6± 1.3 vs. from 9.8± 3.8 to 7.4± 2.2) (p=.04) (Fig 2). This statistical difference was not sustained at 30-day postoperatively as both groups showed a significant improvement in the CIVIQ pain score compared to preoperative assessment (4.8± 1.6 vs 5.2± 1.2) (p=.02) (table3).

	Preoperative	30-days Postoperative	P Value
VAS	5.7 ±3.2	2.7 ±2.2	.032
VCSS	5.8 ±2.6	5.8 ±2.8	.039
CIVIQ Global	39±13.5	24.5±4.8	.038
CIVIQ Pain	10±3.7	5±1.4	.022
CIVIQ Physical	7.5±3.5	4.8±1.2	.033
CIVIQ Social	5.5± 2.5	3.7±1.1	.042
CIVIQ Psychological	16.2±6	11.2±2.4	.045

Table 3. QOL scores changes of study population
Abbreviations: QOL, quality of live; VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire
Note.-Values expressed as means ±SD.

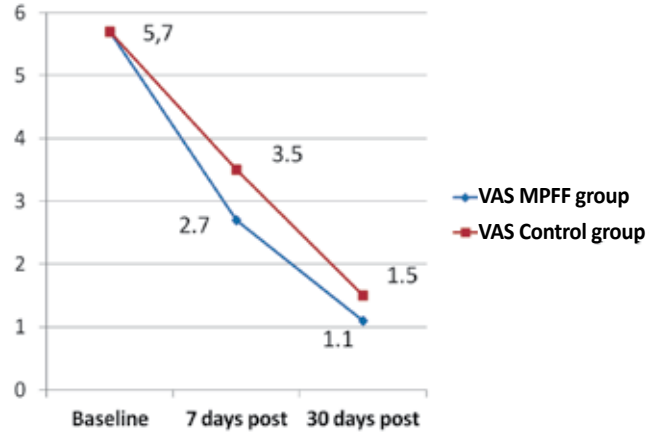

Figure 1. Changes in VAS score

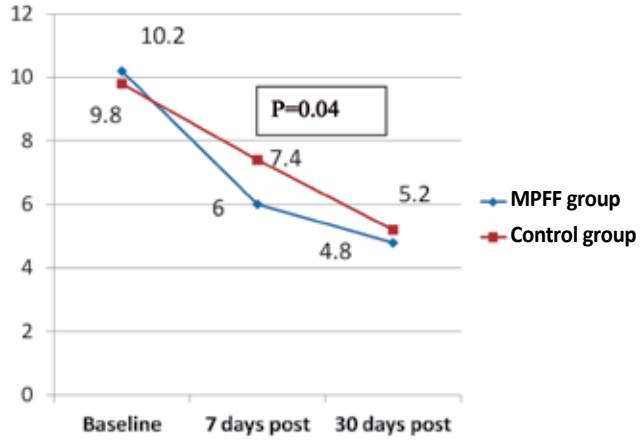

Figure 2. Changes in CIVIQ pain score

Secondary outcomes

There were no significant differences in VCSSs between treatment groups preoperatively (5.8± 2.8 in MPFF group vs 5.8± 2.6 in control group, p=.96). At 30-day postoperatively all patients showed a significant improvement in VCSS (2.0± 2.1 vs 2.1± 2.4, respectively), although non- significant between the two groups (p=.94).

CIVIQ scores between treatment groups at randomization were comparable (p=.403) (table2). As it demonstrates in table 3 there was a significant improvement in all patients in global and also in all domains of CIVIQ score 30 days after treatment but there were no significant differences between the two groups (table 4). GSV occlusion was achieved in all cases and no advesre events related to the procedure such as thrombosis were observed.

	MPFF group	CONTROL group	P Value
VCSS	2±2.1	2.1±2.4	.945
VAS	1.1± 0.8	1.5± 0.7	.104
CIVIQ Global	23.6±4	25.3 ± 5.4	.240
CIVIQ Pain	4.9±1.7	5.2± 1.2	.455
CIVIQ Physical	4.5± 0.9	5± 1.4	.167
CIVIQ Social	3.4± 0.9	4± 1.2	.089
CIVIQ Psychological	10.8± 2	11.7±2.8	.233

Table 4. QOL scores measurements at 30 days postoperative
Abbreviations: QOL, quality of live; VAS, visual analog scale; VCSS, venous clinical severity score; CIVIQ, chronic venous insufficiency quality-of-life questionnaire
Note.-Values expressed as means ±SD.

DISCUSSION

The current study focused on early postoperative recovery period differences between patients receiving MPFF after EVTA in a prospective, randomized manner. The trial demonstrates the early favourable clinical outcomes and QoL improvement following EVTA, with significant improvement in postoperative pain in patients receiving MPFF.

MPFF is an established VAD, and its marketed formulation (Daflon®) is a flavonoid based venoactive drug containing 90% of micronized diosmin and 10% of other active flavonoids (di-

osmetin, hesperidin, linarin and isorhoifolin).[4] Diosmin acts on microcirculation by reducing the capillary hyperpermeability and fibrinolysis, increases the frequency and the intensity of the venous contractions, improves venous tone and reduces venous stasis.[6] In a randomized, double-blind, placebo-controlled parallel-design trial using VAD, there was a significant improvement in QoL and also in limb edema and pain/ burning sensation in the aminaphthone and MPFF groups.[6] A recent meta-analysis by Kakkos et al,[4] reported that MPFF is high effective in improving leg symptoms, edema and quality of life in patients with CVD. The effect of MPFF in the postoperative period in patients undergoing convesional surgery has also been studied. Vervekova et al,[5] showed that patients receiving Daflon 500mg Bid 14 days prior to and 14 days after surgery had smaller hematoma, lower postoperative pain and a lower consumption of analgesics. A recent multicenter study by Bogachev et al,[7] reported that administration of MPFF agent in patients undergoing phlebosclerosing procedures for reticular veins and telangiectasias showed greater improvement in venous symptoms and QoL scores and also reduced the occurrence of post injection hyperpigmentation compared to sclerotherapy alone.

In the recent years EVTA have become very popular in the treatment of saphenous vein incompetence, as a minimally invasive procedure alternative to classical surgery (high ligation and stripping). The two most frequently used techniques are EVLA and RFA.[2] In our study clinical and procedural characteristics between MPFF and control group were comparable. In addition, all patients underwent a concomitant plebectomies. The amount of tumescent anaesthesia used was not different between the two groups. In order to avoid any potential bias of tumescent anaesthesia used assessment visits were performed at 7 and 30 days post ablation. Both groups improved VAS pain score, CIVIQ and VCSS at 7 and 30 days postoperatively without any statistical difference. A subgroup analysis of all aspects of CIVIQ score showed a significant improvement in the CIVIQ pain score at 7 days in the MPFF group compared to the control. The administration of MPFF in these patients seems to improve postoperative pain. This can result in lower consumption of analgesics, quicker recovery and faster return to normal activities.

Comparing EVLA with RFA, our study shows equal levels of postoperative pain. Others reported that, patients treated with RFA have less postoperative pain and bruising compared with EVLA.[8-11] However, in these trials the ClosureFast catheter was compared with lower wavelength lasers using a bare fibre. Arslan et al [12] compared 980 nm versus 1470 nm wavelength, and it was demonstrated that 1470 nm diode laser had a significant reduction in pain levels, ecchymosis, paraesthesia and induration. The 1470 nm wavelength radial-tip fiber system enables the procedure to be done at lower energy levels with lower side effect incidence. Another possible explanation for comparable postoperative pain between EVLA and RFA is the usage of MPFF agent.

Numerous studies have showed that, patients treated with EVTA reports less postoperative pain compared to patients treated with convesional surgery.[13-16] One such study compared the results of conventional surgery done under tumescent local anesthesia with EVLA, RFA and foam sclerotherapy[14]. The results showed that the postoperative average pain scores at 10 days was significantly lower in the groups treated with RFA and foam sclerotherapy comparing to surgery and EVLA, however the VCSS, QOL scores and efficiency at 3 years were not significantly different between all treatment modalities. Venermo et al[16] reported that, perioperative pain was significantly reduced and the duration of sick leave was shorter after EVLA (8 days) than after surgery (12 days).

In our study occlusion rates 30-day postoperative was 100% in both techniques. In numerous studies EVLA and RFA shows comparable occlusion rates.[8-11] Weiss et al,[17] published a retrospective comparison of three different EVTA systems. At 5-year follow-up, successful ablation rates of RFA, 810 nm, and 1,320nm wavelengths were 61.7%, 65.7%, and 84.7%, respectively. In our study we used the 1470 nm diode radial laser (EVLA) (Biolitec, East Longmeadow, Massachusetts) and the ClosureFast™ Procedure catheter (RFA), (Medtronic, Mineapolis). Up to now no comparative trials have been published comparing the use of these two ablation systems.

This study has some limitations. It is a pilot study with small number of patients. Most of the patients included to the study were categorized to C2,3 severity of venous disease according to CEAP classification. Therefore, the number of the patients with severe disease was relatively small to allow consistent comparisons with the group of patients with moderate disease. The small number of patients did not allowed us to make comparison between different EVTA techniques and the role of MPFF agent in the early postoperative period. The possibility of bias was minimized by the use of validated QOL scores patient-reported outcomes, and objective criteria and ultrasound protocols were used in the assessment of researcher-reported outcomes. Another potential limitation is that patients in the control group did not receive any medication similar to the MPFF group and there is a chance for reporting bias as we have conduct a pain severity and QoL scores study.

CONCLUSION

Patients with CVD treated with EVTA significantly improve both clinical and physical aspects during early postoperative period. The administration of MPFFagent may improve early postoperative pain. Larger studies are needed to confirm these findings.

REFERRENCES

1 Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. Phlebology. 2008;23(3):103-111

2 Wittens C, Davies AH, Baekgaard N, Broholm R, Cavezzi A, Chastanet S, et al. Editor's Choice - Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2015;49:678- 737

3 Nicolaides A, Kakkos S, Eklof B, Perrin M, Nelzen O, Neglen P, et al. Management of chronic venous disorders of the

lower limbs - guidelines according to scientific evidence. Int Angiol 2014;33:87-208

4 Kakkos SK, Nicolaides AN Efficacy of micronized purified flavonoid fraction (Daflon®) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials Int Angiol. 2018 Apr;37(2):143-154

5 Veverková L, Kalač J, Jedlička V, Wechsler J. Analysis of the various procedures used in great saphenous vein surgery in the Czech Republic and benefit of Daflon 500 mg to postoperative symptoms.Phlebolymphology. 2006;13:193-199

6 Belczak SQ, Sincos IR, Campos W, Beserra J, Nering G, Aun R. Veno-active drugs for chronic venous disease: A randomized, double-blind, placebo-controlled parallel design trial. Phlebology 2014;29(7) 454-460

7 Bogachev VY, Boldin BV, Turkin PV. Administration of Micronized Purified Flavonoid Fraction during sclerotherapy of reticular veins and telangiectasias: Results of the national, multicenter, observational program VEIN ACT PROLONGED-C1. Adv Ther (2018) 35:1001-1008

8 Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg. Aug 2011;98(8):1079-1087

9 Almeida JI, Kaufman J, Gockeritz O, et al. Radiofrequency endovenous ClosureFAST versus laser ablation for the treatment of great saphenous reflux: a multicenter, single-blinded, randomized study (RECOVERY study). J Vasc Interv Radiol. Jun 2009;20(6):752-759

10 Gale SS, Lee JN, Walsh ME, Wojnarowski DL, Comerota AJ. A randomized, controlled trial of endovenous thermal ablation using the 810-nm wavelength laser and the ClosurePLUS radiofrequency ablation methods for superficial venous insufficiency of the great saphenous vein. J Vasc Surg. Sep 2010;52(3):645-650

11 Goode SD, Chowdhury A, Crockett M, et al. Laser and radiofrequency ablation study (LARA study): a randomised study comparing radiofrequency ablation and endovenous laser ablation (810 nm). Eur J Vasc Endovasc Surg. 2010;40(2):246-252

12 Arslan Ü, Çalık E, Tort M, Yıldız Z, Tekin A, Limandal KH, Kaygın MA, Da Ö, Erkut B. More successful results with less energy in endovenous laser ablation treatment: Long-term comparison of bare-tip fiber980nm laser and radial-tip fiber1470nm laser application. Ann Vasc Surg 2017;45:166-172

13 Siribumrungwong B, Noorit P, Wilasrusmee C, Attia J, Thakkinstian A. A systematic review and meta-analysis of randomised controlled trials comparing endovenous ablation and surgical intervention in patients with varicose vein. Eur J Vasc Endovasc Sur 2012;44(2):214-223

14 Rasmussen L, Lawaetz M, Bjoern L, Blemings A, Eklof B. Randomized clinical trial comparing endovenous laser ablation and stripping of the great saphenous vein with clinical and duplex outcome after 5 years. J Vasc Surg 2013;58: 421-426

15 Subramonia S, Lees T. Randomized clinical trial of radiofrequency ablation or conventional high ligation and stripping for great saphenous varicose veins. Br J Surg. 2010;97(3):328-336

16 Venermo M, Saarinen J, Eskelinen E, Vähäaho S, Saarinen E, Railo M, Uurto I, Salenius J, Albäck A et al. Randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. BJS. 2016;103: 1438-1444

17 Weiss RA, Weiss MA, Eimpunth S, Wheeler S, Udompunturak S, Beasley KL. Comparative outcomes of different endovenous thermal ablation systems on great and small saphenous vein insufficiency: Long-term results. Lasers Surg Med. 2015;47:156-160

18 Erevnidou K, Launois R, Katsamouris A, Lionis C. Translation and validation of a quality of life questionnaire for chronic lower limb venous insufficiency into greek. Int Angiol.2004;23(4):394-39