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Article

Efficacy of High-Dose Diosmin Therapy in Chronic Venous Disease Treated with Endovenous Ablation: A Quality-of-Life Analysis

Antonia Rinaldi [1,†], Rita Zeno [1,†], Antonio Peluso [1], Luca del Guercio [1], Maurizio Sodo [2], Davide Turchino [1,*], Ruggero Iandoli [3], Davide Costa [4,5], Raffaele Serra [4,5,*] and Umberto Marcello Bracale [1]

1 Vascular Surgery Unit, Department of Public Health, University Federico II of Naples, 80138 Naples, Italy; antoniarinaldi94@gmail.com (A.R.); ritazeno95@gmail.com (R.Z.); antoniopeluso8784@gmail.com (A.P.); luca.delguercio@unina.it (L.d.G.); umbertomarcello.bracale@unina.it (U.M.B.)
2 General Surgery Unit, Department of Public Health, University Federico II of Naples, 80138 Naples, Italy; sodo@unina.it
3 General Surgery Unit, Sant'Ottone Frangipane Hospital, 83100 Avellino, Italy; iandoliruggero@libero.it
4 Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, 88100 Catanzaro, Italy; davide.costa@unicz.it
5 Interuniversity Center of Phlebolymphology (CIFL), International Research and Educational Program in Clinical and Experimental Biotechnology: University Magna Graecia of Catanzaro, 88100 Catanzaro, Italy
* Correspondence: dott.turchino@gmail.com (D.T.); rserra@unicz.it (R.S.)
† These authors contributed equally to this work.

Abstract: Background. Vasoactive drugs are considered an important therapeutic tool in managing phlebolymphologic disease. The current study was performed to evaluate the results of a high-dose diosmin-based combination (Venoplant 2g) in symptomatic patients with chronic venous disease (CVD), treated with endovascular venous surgery, regarding the efficacy of this treatment and the clinical signs and patients' compliance. Methods: We identified, between April 2022 and March 2023, 50 patients with symptomatic CVD who underwent endovenous ablation and additionally were administered high-dose micronized diosmin. Parameters analyzed in the pre- and post-operative period were the venous clinical severity score (VCSS), the calf circumference, and a VEINES-QOL/Sym questionnaire. Treatment efficacy was assessed in post-operative follow-ups at 1 month and 2 months. Results: Quality-of-life analysis showed a significant improvement between t1 and t2 in both tests administered (VEINES-QOL/Sym: 55.2 ± 2.9, 39.2 ± 12.3, *p*: 0.001) (VCSS: 6.6 ± 1, 5.1 ± 0.7, *p*: 0.001). At the secondary endpoint, the results maintained the same improvement trend. Calf circumference was significantly reduced between t1 and t3 (41.7 ± 5.1, 38.3 ± 3.4, *p*: 0.001). Conclusion: High-dose diosmin, combined with sweet clover 320 mg, Centella asiatica 40 mg, and Vitamin C 200 mg, in patients treated with endovenous ablation, can be significantly effective in terms of clinical results in treating superficial venous disease. A patient's calf circumference was also found to have decreased considerably during follow-up. No adverse effects have been recorded to date.

Keywords: venoactive drugs; chronic venous disease; quality-of-life; venous symptoms; endovenous ablation; mechanochemical ablation

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1. Introduction

Chronic venous disease (CVD) represents a mainstream disease. Overall, CVD is more prevalent in the oldest population >70 years (incidence rate of 80%), while it is less so in the youngest one (only 10% for adults younger than 30 years) [1]. The higher prevalence in elderly patients is also associated with more complex comorbidities. The geographic distribution mostly affects Europe (21%), North America (23%), South America (22%), Asia (17%), and Africa (5.5%). Moreover, a difference in sex distribution was recorded with a greater prevalence in women (OR = 2.6, IC 95%: 2.16–2.36, $p < 0.001$), but this gap is more

evident in the early stages of clinical–etiology–anatomy–pathophysiology (CEAP) (C1/C2), while it decreases until stage C4, where it is possible to notice a higher prevalence in the male population [2].

Additional risk factors involved in etiopathogenesis could be represented by hereditary factors, body mass index (BMI) > 30, sedentary lifestyle, and professional employment carried out mainly in orthostatic, pregnancy, and hormonal therapy [1,2].

The main causes of CVD are related to a dysregulation of microcirculation, like the activation of the immunity system in the degradation of the extracellular matrix, but also for hemodynamic changes in the venous system because of an increasing pressure linked to the incompetence of the vein wall and valves [3].

In every stage of CVD, a varied cohort of clinical evidence could occur, like leg pain, swelling, and itching, but also a burning sensation, heaviness, and restless legs syndrome. These clinical events can be annoying, with a consequent reduction in the quality of life (QoL), which significantly influences the overall evaluation of patients affected by CVD [4,5].

Several different strategies of therapeutic management can be offered to CVD patients. However, the treatment choice should consider patient comorbidities, such as cardiovascular disease with a first line of noninvasive treatments such as lifestyle changes, use of vasoactive drugs as well as compression therapies (bandages and elastic stockings), and even open or endovascular surgical procedures if necessary [6–8].

For decades, open surgical therapy has been the standard of care in the treatment of CVD, including great saphenous vein (GSV) stripping, the crossectomy of the GSV, and phlebectomy according to Muller technique, among the main therapies. According to the recent literature, the approach to CVD is changing, preferring minimally invasive techniques aimed at reducing post-operative recovery and hospitalization. The minimally invasive endovascular technique has become the first choice to treat CVD, especially endovenous thermal ablation (EVTA) [1].

Among the latest literature evidence, mechanochemical ablation (MOCA) is a safe alternative to the other mini-invasive surgery of the incontinent great saphenous vein with satisfying results in the short term, thanks to the absence of thermal cauterization of tissues without performing local tumescent anesthesia [9].

The goal is to discover a drug treatment in order to reduce symptoms in the early stages but also prevent or improve more serious CVD complications such as leg ulcers [10–16].

2. Materials and Methods

2.1. (Pharmaceutical) Food Supplement Features

Venoplant sachets 2 gr (Aesculapius Pharmaceutics Srl, Brescia, Italy), a newly formulated diosmin dosage, was developed to overcome the poor oral bioavailability of diosmin. Each sachet is divided into two half doses to facilitate administration, each of which contains: micronized diosmin 1000 mg, sweet clover 320 mg, Centella asiatica 40 mg, and Vitamin C 200 mg. Diosmin was micronized to obtain particles with a reduced size in order to significantly increase the absorption, as confirmed in a study with the labeled product, which reports that the average gastrointestinal absorption was significantly higher in the case of micronized 14C-diosmin than that of non-micronized 14C-diosmin in seventy patients (57.9 vs. 32.7 percent during 0–168 h after dose; $p = 0.0004$) [17].

Recent studies show that diosmin, a vasoactive drug (VAD), presents good results on lymphatic and vascular system symptoms with a consequent better quality of life (QoL). Diosmin is a natural flavonoid, and it can perform a vascular protective role due to its anti-inflammatory and antioxidant properties through the inhibition of several chemical inflammation mediators like cytokines, metalloproteases, histamine, etc., but also according to its phlebotonic characteristics, it is a valid therapeutic tool in case of CVD patients [18].

For many years, coumarin was shown to be very effective in reducing edema characterized by a high presence of protein [19,20]. Its mechanism of action, as demonstrated in studies carried out for more than a decade, is linked with the activation of immune-

competent system cells, as macrophages produce proteolytic enzymes that contribute to the breakdown of protein macromolecules trapped in the perivascular interstitium, making them smaller in size. Also, coumarin shows properties in increasing the number of macrophages and their rate of proteolytic features with a significant reduction in high-protein edema fluid [21,22]. Also, the total triterpene fraction of Centella asiatica (TTFCA) improves venous wall adaptations in chronic venous hypertension, protecting the venous endothelium. Clinical research has demonstrated the efficacy of TTFCA in the oral treatment of microangiopathy secondary to venous hypertension and diabetic microangiopathy. In order to enhance the effects of the active ingredients mentioned above, Vitamin C has been associated with the formulation in sachets at a dosage of 200 mg, which is recognized as having a protective action against oxidative stress and promoting the formation of collagen for the physiological function of blood vessels. Venoplant tablets, a nutraceutical product similar to Venoplant 2g sachets formulated as a gastro-protected tablet formulation and lower dosages, have shown good results in a series of studies conducted in patients with various venous diseases. More specifically, in one study of 700 patients with CVD, evidence of improvement or alleviation of core symptoms (nocturnal cramps, edema, and a sense of weightiness/heaviness) was reported, as well as a reduction in the progression of clinical manifestations as they progressed from more severe to less severe stages [23]. Other supporting evidence is the results of a study conducted on 182 patients who underwent hemorrhoidectomy via stapler, which showed that Venoplant 2g sachets effectively reduced the bleeding resulting from stapled anopexy with a lower incidence of internal hemorrhoids thrombosis and less post-operative pain [24].

2.2. Study Design

Our study objective was to evaluate the efficacy and safety of Venoplant 2g sachets during the clinical practice of CVD patients' management integrated with lifestyle counseling.

From April 2022 to March 2023, a prospective investigation was carried out on patients with CVD treated surgically with MOCA.

The study was approved by the Interuniversity Center of Phlebolymphology (CIFL) and the International Research and Educational Program in Clinical and Experimental Biotechnology (with approval number ER.ALL.2018.64A). All patients were informed about the aim of the study and about the eventual risks and complications related to the therapeutic protocol. Then, they signed an informed consent document for the treatment.

Statistical data analyses were performed on 1 April 2023 using RStudio (PBC). Continuous variables and outcomes were analyzed using Kruskal–Wallis's rank sum test and categorical variables with a sample test for the equality of proportions with continuity correction.

Our overview included a collection of key preoperative data (age, sex, BMI, CEAP classification, and the great saphenous vein diameter) as summarized in Table 1, and all intra-operative details and post-operative data with an emphasis on any complications arising within 30 days of surgery.

Table 1. Population data.

	N = 43
Clinical and anatomical characteristics	
Females	28/43 (65.1%)
Age (years)	52.6 ± 10.3
BMI (body mass index)	25.2 ± 2.1
CEAP 2	7/43 (16.2%)
CEAP 3	26/43 (60.4%)
CEAP 4	10/43 (23.2%)
Diameter of GSV (mm)	6.3 ± 0.6

BMI = body mass index; GSV = great saphenous vein.

Data were gathered by analyzing paper and electronic clinical records collected during hospital stays and the normal post-surgical patient follow-up. The follow-up was estab-

lished as per protocol with an objective examination (including the measurement of calf circumference), a ranking of the venous clinical severity score (VCSS), and an assessment of quality of life (CVQ-20 Sym) according to patient satisfaction.

VCSS was developed from elements of the CEAP classification as a descriptive instrument to objective symptoms and includes pain or rather discomfort (aching, heaviness, fatigue, soreness, and burning), varicose veins (″3 mm in diameter to qualify in the standing position), venous edema (presumes venous origin), skin pigmentation (does not include focal pigmentation over varicose veins or pigmentation due to other chronic diseases), inflammation (erythema, cellulitis, venous eczema, and dermatitis), induration (chronic edema with fibrosis, hypodermitis, includes white atrophy and lipodermatosclerosis), an active ulcer number, an active ulcer duration, active ulcer size and use of compression therapy, with ranking from none, mild, moderate to severe.

The VEINES-QOL/Sym is a patient-based questionnaire for self-completion, and it was developed in English with a translation into French, French Canadian, and Italian. It includes nine venous symptoms (heavy and aching legs, cramps during the night, swelling, burning and tingling sensation, restless legs, throbbing, and itching) with a ranking of five points about the frequency (never, less than once a week, about a once a week, several times a week, and every day), and leg pain with a score of six levels of intensity (none, very mild, mild, moderate, severe, and very severe).

A total of three visits were scheduled:

(1) A screening and baseline assessment visit (visit 1; day -14 to day 0);
(2) An intermediate follow-up visit (visit 2; week 4 ± 4 days after treatment) when subject assessment and symptom evaluation were carried out and where adverse effects, if present, were recorded and graded;
(3) A final visit (visit 3; week 8 ± 4 days after treatment): when final examination and symptom assessment were performed with a classification of adverse effects if they occurred.

All patients were treated with MOCA with a Flebogrif device (Balton, Warsaw, Poland), an endovascular device for the mini-invasive surgical treatment of GSV, characterized by a catheter with distal cutting hooks providing endothelial damage with a concomitant injection of a scleromousse composed via a polidodecan (POL) with a concentration from 1.5% to 2.5%.

The whole cohort was treated with Venoplant 2g sachets from the day after surgery to the last study visit (day $1 \pm$ week 8 after treatment), in combination with continuous compression stockings class 1 that were worn until 1 month after MOCA (day 1 ± 4 weeks after treatment).

2.3. Patients

The inclusion characteristics of enrollment in this study were age between 18 and 70 years and a CEAP classification stage from C2 to C4. The exclusion criteria regarded patients with other cardiovascular disease or diabetes, with lower extremity edema of a non-phlebolymphatic primary origin, lower extremity arterial disease and/or with metabolic, neurological, or orthopedic disorders including trauma and previous amputation, arthritis and neuropathy or other clinical events such as recent venous surgery, or deep or superficial venous thrombosis of the lower extremities during the previous 6 months and patients with BMI > 30. Also, this study considered as exclusion criteria a previously known hypersensitivity to diosmin, pregnancy, breastfeeding and fertile women not under adequate contraceptive therapy, a history of alcohol or drug dependence, and patients with a diet full of spicy foods. Patients were also excluded if they participated in a clinical trial in the previous 6 months or had any other clinically significant medical conditions to preclude inclusion in the study.

Preoperative planning was performed based on the objective examination and a Duplex scan that showed a great saphenous vein (GSV) diameter average of 6.3 ± 0.6 mm

and a percentage of belonging to class 3 of the CEAP classification 60.4% (CEAP 2 16.2%; CEAP 4 23.2%).

The expected primary endpoints were a reduction in calf circumference measured in cm for each affected leg and quality of life (QoL) as assessed using the Global Index Score (GIS) calculated using the CIVQ-20 questionnaire.

The secondary endpoint evaluated the improvement regarding the clinical conditions, such as reduction in pain and the patient's compliance with the therapy. The interpretation of the final global answers to the questionnaires applied has been the trend index to reach this study's goal at the last follow-up visit (t3).

3. Results

A total of 50 patients were enrolled, 7 of whom were excluded from statistical analysis due to discontinuing Venoplant 2g sachets therapy of their own free will (4 patients due to high cost and 3 due to low compliance).

Our patient pool included 43 patients aged between 39 and 70 years, 28 of whom were female. The highest BMI value was 30, and the lowest was 23.2, with a medium value of 25 ± 2.1. In our observed population, a pool of patients presented some comorbidities: three of them (6.9%) (all females) had hypothyroidism, three (6.9%) (two females and one male) had hypertension, and three (two females and one male) (6.9%) had dyslipidemia.

Out of the 43 patients, 7 were classified as CEAP 2, 26 as CEAP 3, and 10 as CEAP 4. The diameter of the great saphenous vein preoperatively ranged between 5 mm and 7.7 mm (medium value 6.3 ± 0.6) and was also considered for minimally invasive surgical treatment (Table 1).

A clinical examination was performed at the intermediate follow-up visit, and quality-of-life questionnaires were administered to determine the satisfaction grade after treatment. At the primary endpoint, a quality-of-life analysis immediately showed a statistically significant rate of improvement between t1 and t2 in both administered tests. (The VEINES-QOL/Sym: 55.2 ± 2.9, 39.2 ± 12.3, *p*: 0.001) (VCSS: 6.6 ± 1, 5.1 ± 0.7, *p*: 0.001) (Table 2).

Table 2. Clinical outcomes.

	T1	T2	T3	*p*-Value (<0.05)
Clinical outcomes (N = 43)				
Calf (cm)	41.7 ± 5.1	39.7 ± 4.1	38.3 ± 3.4	<0.001
	41.7 ± 5.1	39.7 ± 4.1	-	0.082
	41.7 ± 5.1	-	38.3 ± 3.4	0.001
	-	39.7 ± 4.1	38.3 ± 3.4	0.328
VEINES-QOL/Sym	55.2 ± 2.9	39.2 ± 12.3	35.9 ± 10.8	<0.001
	55.2 ± 2.9	39.2 ± 12.3	-	<0.001
	55.2 ± 2.9	-	35.9 ± 10.8	<0.001
	-	39.2 ± 12.3	35.9 ± 10.8	0.263
VCSS	6.6 ± 1	5.1 ± 0.7	4.3 ± 0.7	<0.001
	6.6 ± 1	5.1 ± 0.7	-	<0.001
	6.6 ± 1	-	4.3 ± 0.7	<0.001
	-	5.1 ± 0.7	4.3 ± 0.7	<0.001

VCSS = venous clinical severity score.

At the secondary endpoint, the results of the VEINES-QOL/Sym and VCSS maintained the same improvement trend. (The VEINES-QOL/Sym: 39.2 ± 12.3, 35.9 ± 10.8, *p*: 0.263) (VCSS: 5.1 ± 0.7, 4.3 ± 0.7 *p*: 0.001) (Table 2).

Moreover, patients presented a non-significant reduction in calf circumference between the first and the second examinations (t1 and t2), and for this reason, a longer follow-up period was scheduled for the third examination (t3). At the end of the longer follow-up, calf circumference showed a significant reduction (between t1 and t3: 41.7 ± 5.1, 38.3 ± 3.4, *p*: 0.001).

4. Discussion

The term CVD is often used to indicate the clinical signs of functional venous disease, such as the development of varicose veins. According to the International Guidelines, medical therapy is considered the first-line strategy in case of symptomatic CVD with pain and edema regardless of the CEAP stage [1].

The most important aim of medical therapy is to improve microcirculation, which includes endothelium damage in CVD with a clinical manifestation. The VAD plays a double role, primarily in regulating the adrenergic signs on the endothelium of veins and then modulation of inflammatory cells like leukocytes, with a better capillary permeability [11]. For this reason, medical therapy is an alley of the continuous compression stockings class 1 therapy in all the CEAP stages of CVD, even patients after surgery, because in this case, they can reduce the post-operative symptoms.

Several clinical therapies are available to treat varicose and insufficient veins, but studies on supplemental drug therapies are insufficient. Standard (over-the-counter) nutritional or pharmaceutical supplements are available for the supportive management of CVD as it progresses and can be used to mitigate signs and symptoms of CVD as an adjunctive treatment.

VADs are heterogeneous groups of substances, some of synthetic origin and some of natural origin. The micronized purified flavonoid fraction of diosmin (MPFF) has shown a more global efficacy on pain, fatigue, heaviness, paresthesia, and edema. The MPFF is the only molecule recommended in the guidelines with an evidence grade of 1B [1].

In particular, diosmin is characterized by a natural inhibitory effect on inflammation and phlebotonic properties, which is a very important effect on CVD due to its specific inflammatory etiopathogenesis linked with a dysregulation immunological system. In the wall of pathological veins, there is an overexpression of some inflammatory biomarkers such as the vascular–endothelial growth factor (VEGF), protein gene product 9.5 (PGP9.5), fibronectin (FN), interleukin 6 (IL-6), interleukin 8 (IL-8), the monocyte chemotactic protein (MCP), and matrix metalloproteinase-9 (MMP-9). This over-expression is directly related to the CEAP stage progression, especially in the case of MMP-9, which is an important predictor of CVD severity. This molecular dysregulation ends in a significant alteration of the extracellular matrix (ECM) with a consequent reduction in vein elasticity and ability to pump blood, which causes a dysfunction of valve cusps. The inflammatory environment could participate in the disorganization of the vein collagen fibers with structural deterioration and laxity. These changes were proven via histological stages that showed a thickness reduction in some areas, while other parts showed fibrosis as a typical chronic inflammatory disease.

The degeneration of the wall also seems to be linked to the local hypoxia mechanism. Such a mechanism is determined via a reduced oxygen tension within the vein vessel wall, which leads to the activation of leukocytes and other inflammatory cells, causing the apoptosis of the smooth muscle cells [25].

In addition to this inflammatory origin of CVD, the hemodynamic factors contribute to the dilation of the whole vein vessel in the lower extremities with consequent incompetence of the valve system [3]. For this reason, a high dose of diosmin could play an important role in the hemodynamic correction of CVD due to its phlebotonic properties.

Supported by the literature evidence, we decided to perform this study in order to evaluate the efficacy of Venoplant 2g sachets (Aesculapius Pharmaceutics Srl), which contains a high level of micronized diosmin 1000 mg, sweet clover 320 mg, Centella asiatica 40 mg, and Vitamin C 200 mg, particularly in the case of CVD patients treated surgically.

Minimal-invasive surgical venous treatments are progressively employed due to their reduction in costs and hospitalization time compared to open surgery or thermal ablation techniques. In an attempt to enhance post-CVD treatment, our study aimed to evaluate the supplemental protective effects of a high-dose diosmin-containing combination (Venoplant 2g sachets) in CVD in patients treated with MOCA.

MOCA is a non-thermal endovenous technique characterized by two actions on the venous wall: the first is represented by mechanical damage of the intima, and the second is by the penetration of a sclerosant solution in the vessel, producing an obliteration of the vein.

There are two MOCA systems, the first one providing endothelial damage through cutting hooks on the catheter top, Flebogrif (Boston, Poland), and the second provided by a rotating wire, Clarivein (Merit Medical, South Jordan, UT, USA).

In our experience, we had encouraging results from the use of Flebogrif (Boston, Poland) in combination with POL, using a concentration from 1.5% to 2.5%, according to the VGS diameters, because POL is considered a useful sclerosing agent, especially due to its possibility to make a scleromousse, which can also treat veins with a large diameter. POL has shown tolerability and very low incidents of toxicity, a minimal risk, few complications, and an immune reaction [10].

According to this evidence, we wanted to identify a more functional medical treatment to reduce clinical symptoms after surgery with Flebogrif (Boston, Poland) and POL together with continuous compression stockings class 1 during the post-procedural follow-up.

Fifty patients were enrolled, but seven of these were excluded due to poor compliance with therapy and also for the post-operative visits scheduled. At t1, all patients received a questionnaire to determine the quality of life before the treatment in order to objectify the discomfort, and at the same time, the calf circumference was assessed.

Based on the evidence from the literature, we decided to adopt the VEINES-QOL/Sym questionnaire that proved acceptable, reliable, valid, and accurate to objectify the incidence of CVD in patients' daily lives. Due to its versatility and Italian translation, it could be easily administered to all patients during every follow-up visit [26].

In addition to the previous questionnaire, all groups of patients also answered the VCSS, a validated system of scoring CVD used to evaluate clinical changes in signs and symptoms before and after therapy [27]. In particular, in this study, both of these questionnaires were useful to determine the clinical improvements after mini-invasive venous surgery with Flebogrif (Boston, Poland) and VAD therapy at every visit step, from the first access to our vascular unit to the last control during follow-up.

From day 1 to 4 weeks later, patients took daily Venoplant 2g sachets and wore continuous compression stockings class 1. At intermediate follow-up visits, there was a clear improvement in patients' QoL, as evidenced by the positive results of the VEINES-QOL/Sym and VCSS questionnaire. Conversely, the decrease in calf circumference was not as good as expected at t2. This evidence could be related to the need for a longer period of continuous therapy, and after eight weeks (t3), a significant reduction in calf circumference was finally noted.

As a secondary endpoint, after our last follow-up visit (t3), we found an improvement in the global patient clinical status, evidenced by reduced pain and higher patient compliance with the therapy.

This evidence supports the recommendation to give Venoplant 2g sachets for a longer period to achieve a final aesthetic and functional result.

Also, our limited patient study has shown that diosmin's anti-inflammatory, antiradical, and antimutagenic properties can benefit cardiovascular disease symptoms and quality of life (QoL).

Carbone et al. reported a similar favorable result with Venoplant tablets, which were administered to a cohort of 700 patients. Specifically, improvements in principal symptoms, such as night cramps, edema, sense of weight/heaviness, and a reduction in the clinical progression of the venous disease [23] directly contributed to significant improvements in patients' QoL and a significant reduction in disease symptoms were recorded [28]. Due to the vasoactive effect of diosmin, our patient sample showed a significant reduction in calf circumference and ensuing symptoms such as edema and swelling, thereby confirming the anti-edemigenous action exerted by Venoplant 2g sachets, which had already been reported in the literature in other districts [23].

In light of the current study, high-dose diosmin in the soluble formulation, combined with simultaneous endovascular CVD treatment, can be a safe, effective, and manageable combination leading to improved cardiovascular disease symptoms and quality of life, as demonstrated in our patient sample.

Despite its novelty, the current study is not devoid of limitations because, first of all, it does not represent a randomized trial. In fact, there is no control group of patients treated with a placebo. However, this study represents the first to address the safety and efficacy of Venoplant 2g sachets for the treatment of CVD. Second, there is no evidence that these results are associated with a successful operation, rather than Venoplant 2g sachets. In order to give significant weight to this study's findings and to monitor the treatment's safety and durability of effects, a future strategy could be the enrollment of a broadened number of cases with an extended follow-up period. Also, it should include a control group to evaluate the effective role of Venoplant 2g sachets in CVD.

5. Conclusions

High-dose diosmin, combined in a new sachet formulation with sweet clover, Centella asiatica, and Vitamin C, in patients treated with mini-invasive endovenous ablation performed with MOCA using Flebogrif (Boston, Poland) can significantly reduce the clinical signs of superficial venous disease with a subsequent improvement in patient's quality of life. As expected, VEIN-QOL/Sym and VCSS scores were two valid instruments to investigate the benefits of our medical treatment after surgery. Calf circumference was also found to have decreased considerably during follow-up. No significant adverse effects have been recorded to date.

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References

1. De Maeseneer, M.G.; Kakkos, S.K.; Aherne, T.; Baekgaard, N.; Black, S.; Blomgren, L.; Giannoukas, A.; Gohel, M.; de Graaf, R.; Hamel-Desnos, C.; et al. Editor's Choice—European Society for Vascular Surgery (ESVS) 2022 Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* **2022**, *63*, 184–267. [CrossRef]
2. Serra, R.; Grande, R.; Butrico, L.; Fugetto, F.; De Franciscis, S. Epidemiology, diagnosis and treatment of chronic venous disease: A systematic review. *Chirurgia* **2016**, *24*, 34–45.
3. Jacobs, B.N.; Andraska, E.A.; Obi, A.T.; Wakefield, T.W. Pathophysiology of varicose veins. *J. Vasc. Surg.* **2017**, *5*, 460–467. [CrossRef] [PubMed]
4. Nicolaides, A.N.; Labropoulos, N. Burden and Suffering in Chronic Venous Disease. *Adv. Ther.* **2019**, *36* (Suppl. S1), 1–4. [CrossRef] [PubMed]
5. Davies, A.H. The Seriousness of Chronic Venous Disease: A Review of Real-World Evidence. *Adv. Ther.* **2019**, *36* (Suppl. S1), 5–12. [CrossRef] [PubMed]

6. Ruggiero, M.; Grande, R.; Naso, A.; Butrico, L.; Rubino, P.; Placida, G.D.; Cannistrà, M.; Serra, R. Symptoms in patients with skin changes due to chronic venous insufficiency often lead to emergency care service: An Italian observational study. *Int. Wound J.* **2016**, *13*, 967–971. [CrossRef]
7. Nicolaides, A.; Kakkos, S.; Eklof, B.; Perrin, M.; Nelzen, O.; Neglen, P.; Partsch, H.; Rybak, Z. Management of chronic venous disorders of the lower limbs—Guidelines according to scientific evidence. *Int. Angiol. J. Int. Union Angiol.* **2014**, *33*, 87–208.
8. Mansilha, A. Early Stages of Chronic Venous Disease: Medical Treatment Alone or in Addition to Endovenous Treatments. *Adv. Ther.* **2020**, *37* (Suppl. S1), 13–18. [CrossRef]
9. Ayala-García, M.A.; Reyes, J.S.; Muñoz Montes, N.; Guaní-Guerra, E. Frequency of use of elastic compression stockings in patients with chronic venous disease of the lower extremities. *Phlebology* **2019**, *34*, 481–485. [CrossRef]
10. Ammollo, R.P.; Petrone, A.; Giribono, A.M.; Ferrante, L.; Del Guercio, L.; Bracale, U.M. Early Results of Mechanochemical Ablation with Flebogrif® in Great Saphenous Vein Insufficiency: Does Polidocanol Concentration Affect Outcome? *Transl. Med. UniSa* **2020**, *21*, 47–51.
11. Serra, R.; Grande, R.; Butrico, L.; Buffone, G.; Caliò, F.G.; Squillace, A.; Rizzo, B.A.; Massara, M.; Spinelli, F.; Ferrarese, A.G.; et al. Effects of a new nutraceutical substance on clinical and molecular parameters in patients with chronic venous ulceration. *Int. Wound J.* **2016**, *13*, 88–96. [CrossRef]
12. Mansilha, A.; Sousa, J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. *Int. J. Mol. Sci.* **2018**, *19*, 1669. [CrossRef]
13. Marinović Kulišić, S.; Lupi, D. Pharmacological treatment in patients with chronic venous disease. *Acta Dermatovenerol. Croat. ADC* **2012**, *20*, 197–200.
14. Perrin, M.; Ramelet, A.A. Pharmacological treatment of primary chronic venous disease: Rationale, results and unanswered questions. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* **2011**, *41*, 117–125. [CrossRef]
15. Andreozzi, G.M. Sulodexide in the treatment of chronic venous disease. *Am. J. Cardiovasc. Drugs Drugs Devices Other Interv.* **2012**, *12*, 73–81. [CrossRef]
16. Forte, R.; Cennamo, G.; Finelli, M.L.; Bonavolontà, P.; de Crecchio, G.; Greco, G.M. Combination of flavonoids with Centella asiatica and Melilotus for diabetic cystoid macular edema without macular thickening. *J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther.* **2011**, *27*, 109–113. [CrossRef]
17. Forte, R.; Cennamo, G.; Bonavolontà, P.; Pascotto, A.; de Crecchio, G.; Cennamo, G. Long-term follow-up of oral administration of flavonoids, Centella asiatica and Melilotus, for diabetic cystoid macular edema without macular thickening. *J. Ocul. Pharmacol. Ther. Off. J. Assoc. Ocul. Pharmacol. Ther.* **2013**, *29*, 733–737. [CrossRef]
18. Cova, D.; De Angelis, L.; Giavarini, F.; Palladini, G.; Perego, R. Pharmacokinetics and metabolism of oral diosmin in healthy volunteers. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **1992**, *30*, 29–33. [PubMed]
19. Kakkos, S.K.; Nicolaides, A.N. 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. J. Int. Union Angiol.* **2018**, *37*, 143–154. [CrossRef] [PubMed]
20. Bolton, T.; Casley-Smith, J.R. An in vitro demonstration of proteolysis by macrophages and its increase with coumarin. *Experientia* **1975**, *31*, 271–273. [CrossRef] [PubMed]
21. Casley-Smith, J.R.; Casley-Smith, J.R.; Gwyn Morgan, R.; Piller, N.B. Treatment of lymphedema of the arms and legs with 5, 6-benzo-[alpha]-pyrone. *N. Engl. J. Med.* **1993**, *329*, 1158–1163. [CrossRef] [PubMed]
22. Casley-Smith, J.R. Benzo-pyrones in the treatment of lymphoedema. *Int. Angiol. J. Int. Union Angiol.* **1999**, *18*, 31–41.
23. Carbone, F.; Del Guercio, L.; Viola, D.; Ficarelli, I.; Amabile, G. Insufficienza venosa cronica: Indagine pilota sugli effetti coadiuvanti del Venoplant contenente principi funzionali a riconosciuta azione vasoprotettiva. *Minerva Cardioangiol.* **2008**, *56*, 1–5.
24. Incandela, L.; Cesarone, M.R.; Cacchio, M.; De Sanctis, M.T.; Santavenere, C.; D'Auro, M.G.; Bucci, M.; Belcaro, G. Total triterpenic fraction of Centella asiatica in chronic venous insufficiency and in high-perfusion microangiopathy. *Angiology* **2001**, *52* (Suppl. S2), S9–S13. [CrossRef] [PubMed]
25. Serra, R.; Bracale, U.M.; Chilà, C.; Renne, M.; Mignogna, C.; Ielapi, N.; Ciranni, S.; Torcia, G.; Bevacqua, E.; Di Taranto, M.D.; et al. Clinical and Pathological Correlations in Chronic Venous Disease. *Annu. Vasc. Surg.* **2022**, *78*, 19–27. [CrossRef]
26. Kahn, S.R.; Lamping, D.L.; Ducruet, T.; Arsenault, L.; Miron, M.J.; Roussin, A.; Desmarais, S.; Joyal, F.; Kassis, J.; Solymoss, S.; et al. VEINES-QOL/Sym questionnaire was a reliable and valid disease-specific quality of life measure for deep venous thrombosis. VETO Study investigators. *J. Clin. Epidemiol.* **2006**, *59*, 1049–1056. [CrossRef]
27. Passman, M.A.; McLafferty, R.B.; Lentz, M.F.; Nagre, S.B.; Iafrati, M.D.; Bohannon, W.T.; Moore, C.M.; Heller, J.A.; Schneider, J.R.; Lohr, J.M.; et al. Validation of Venous Clinical Severity Score (VCSS) with other venous severity assessment tools from the American Venous Forum, National VenousScreening Program. *J. Vasc. Surg.* **2011**, *54*, 2S–9S. [CrossRef]
28. Tozzi, U.; Santillo, V.; Tartaro, G.P.; Sellitto, A.; Gravino, G.R.; Santagata, M. A Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Comparing the Efficacy of Anti-edema Drugs for Edema Control in Orthognathic Surgery Using Digitizer 3-D to Measure Facial Swelling. *J. Maxillofac. Oral Surg.* **2015**, *14*, 386–392. [CrossRef]