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Mesotherapy *versus* oral medical treatment of chronic venous insufficiency in a general practitioner setting - A randomized controlled trial

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Abstract

Mesotherapy involves the introduction of drugs through dermal microinjections for preventive, therapeutic, or rehabilitative purposes. This study evaluates the safety, tolerability, and effectiveness of mesotherapy in treating Chronic Venous Insufficiency (CVI) compared to traditional oral treatments. Sixty-one patients with CVI (CEAP stage C3-C4) were randomized into two groups. The primary outcome was the measurement of bilateral ankle circumferences. Secondary outcomes included the evaluation of bilateral circumferences and subcutaneous ultrasound thicknesses at the thigh, calf, and medial ankle, and Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) stage variation. The treatment group (30 patients) received mesotherapy with a complex homeopathic product every 15 days for 3 months, and the control group (31 patients) was treated with oral flavonoids for 3 months. With no recorded adverse effects, mesotherapy led to significant reductions in bilateral ankle circumferences (right p=0.0008, left p=0.0075), CEAP stage (p=0.0212), ankle ultrasound thicknesses (right p=0.0037, left p=0.0015) and calf thicknesses (right p=0.0131, left p=0.0137). Mesotherapy was found to be safe, well-tolerated, and more effective with respect to oral drugs in CVI patients; however, further randomized, controlled, and blind trials with wider sample sizes are mandatory to confirm our results.

Key words: mesotherapy, chronic venous insufficiency, edema, varicose veins.

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Introduction

Chronic Venous Insufficiency (CVI) is a pathological condition of an evolving nature characterized by morphological and functional abnormalities of the venous system,[1] resulting in a persistent and progressive reduction in the volume of fluid drainage from the periphery to the central level, leading to stagnation, dilation, and inflammation of the vein walls and surrounding tissues.[2]

From an epidemiological standpoint, it is a highly prevalent condition, with mild forms affecting up to 80%[3] of the global population. The female sex is more commonly affected, while men tend to have a higher percentage of complications, such as ulcers.[4] CVI is primarily found in industrialized countries and is associated with lifestyle factors, reduced physical activity, and widespread obesity.[5]

A particularly significant finding from the RELIEF study[6] is that 78% of symptomatic patients are not treated, and only 45.9% of the population affected by CVI received a correct diagnosis from general practitioners, highlighting the need for significant public health education regarding this condition, which is too often underestimated or unrecognized.

In this context, mesotherapy, or District Intradermal Therapy (DIT), offers potential support. This technique, still relatively unknown and underutilized today, could prove to be a valid therapeutic alternative for patients with CVI, especially considering that an international committee has approved the recommendations for applying mesotherapy in pain medicine and aesthetic medicine, with over 100% consensus.[7]

Mesotherapy involves the introduction of drugs or substances into the dermis through microinjections in the specific lesion site to be treated. This creates a sort of "micro dermal depot" from which the substance diffuses very slowly into the underlying tissues via the hemolymphatic circulation. The active ingredient interacts almost exclusively with the local tissue receptors, exerting its biological effect with minimal doses of the product, without the need to reach a threshold plasma concentration, as is required with oral administration.[8,9]

The side effects observed with mesotherapy are generally mild and consist of local reactions that resolve spontaneously in a short period. These include a small wheal at the injection site, along with erythema, induration, bruising, small hematomas, and mild pain. Potential adverse reactions reported in the literature include allergic reactions and skin infections, resulting from inadequate hygiene during intradermal injection. These events are readily pre-

ventable through a thorough patient history and the maintenance of a sterile treatment environment.[10-12]

Unfortunately, the literature lacks studies comparing the treatment of CVI via mesotherapy with other pharmacological administration routes. Therefore, this study aims to assess whether the mesotherapeutic administration of phlebotonic drugs is safe, well-tolerated, and advantageous compared to standard oral treatment for the management of complicated venous insufficiency, using reproducible parameters as outcome indicators.

Materials and Methods

A total of 61 patients were recruited from the General Medicine outpatient clinic in Fossalta di Piave (VE) during the period from April 8th, 2023, to January 29th, 2024. All patients were diagnosed with chronic venous insufficiency, confirmed by color Doppler ultrasound performed by public consultant specialists of the same geographical area. Only subjects with the clinical class C3 (edema) and C4 (skin pigmentation and lipodermatosclerosis), according to the Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification, were included in the study.[2]

The exclusion criteria considered for the study were: allergy to the injected substances or hypersensitivity to Viscum album, positive medical history of autoimmune diseases, presence of active tumors, current pregnancy or breastfeeding, previous treatments for chronic venous insufficiency (e.g., use of compression stockings, physiotherapy, or thermal therapies), patients undergoing treatment with anticoagulants, concomitant lymphedema, age below 18 years.

After agreeing to participate in the study, all patients underwent the collection of demographic data, physical examination for the assessment of clinical CEAP status, completion of the clinical evaluation form using the Venous Clinical Severity Score (VCSS), height measurement, weight measurement with a Bioelectrical Impedance Analysis (BIA) scale to obtain the Body Mass Index (BMI) value and determine the percentage of body fat and water, and circumference measurements at specific reference points on the lower limb: above the medial malleolus, posteriorly at the calf level, and at the thigh (Figure 1). Additionally, the thickness of edema in the subcutaneous tissues was measured via ultrasound evaluation at the same reference points (Figure 1), and the personal assessment form «The Short Form - 36» (SF-36) was completed.

After the initial evaluation (baseline), the patients were randomized into two arms through a computed system provided by the University of Ferrara through an author who was not involved in performing the trial and in data collection.

The "cases" underwent District Intradermal Therapy (DIT): the treatment protocol consisted of two sessions per month for 3 months, during which two milliliters of injectable vials of a complex multicomponent homeopathic product were administered, diluted with saline in a 1:1 ratio. The composition per vial is as follows: Conium D3 2.5 mg, Hydrastis D3 2.5 mg, Viscum album D2 2.5 mg, Phytolacca D4 2.0 mg, Scilla D1 2.0 mg, sodium chloride, water for injections.

The possibility of injecting this homeopathic product via mesotherapy is specified in the product's leaflet[13] and approved by the Italian Society of Mesotherapy.[7] Moreover, the Italian Good Practice Clinical guidelines[11] indicate DIT as applicable to CVI. The contraindications for the use of this active ingredient in DIT include: a positive medical history of autoimmune diseases, neoplastic or paraneoplastic syndromes, a positive medical history of allergic diathesis to the drug or hypersensitivity to Viscum album, pregnancy, breastfeeding, and patients undergoing treatment with anticoagulants. Drug interactions remain unknown.[10,12-19] All individuals presenting any of these conditions were excluded from the study. The mesotherapy technique specifically involves drug infiltration with a disposable syringe at a 30-degree angle to reach a depth of 2 mm (corresponding to the dermal layer, which ranges from 1.5 to 3 mm). Micro-injections are performed approximately 2 cm apart from each other.[8,10]

Before undergoing DIT, all patients signed informed consent.

The "controls" received oral phlebotonic treatment, primarily consisting of diosmin and hesperidin, at a dosage of 1 and 2 tablets daily, respectively, for a duration of three months.

At the end of the 3 months, the patients were re-evaluated using the same methods as during the post-recruitment visit.

The primary outcome of the trial was the measurement of bilateral ankle circumferences. The secondary outcomes of the study included the measurement of bilateral circumferences (in centimeters, cm) and the evaluation of the subcutaneous thicknesses, assessed via ultrasound at the thigh, calf, and medial ankle (cm), respectively, points F, D, and B used for elastic stockings measurements. Moreover, the eventual change in the CEAP stage, the safety of the treatment (evaluated by the number of adverse reactions related to both treatments during the three-month treatment cycle), the Venous Clinical Severity Score, and the eight items of the subjective evaluation from Short Form-36 were analyzed as secondary outcomes. Additional outcome indicators included sex, age, Body Mass Index (BMI, kg/m^2), fat percentage (%), and water percentage (%).

Statistical analysis

Categorical variables were expressed as absolute (N) or relative (%) values, while continuous variables were expressed as mean ± Standard Deviation (SD). Non-parametric data were statistically processed using the Wilcoxon test. A p-value <0.05 was considered statistically significant.

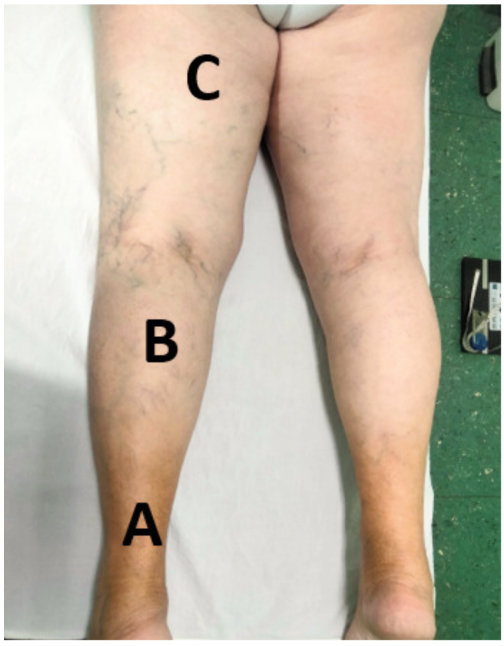

Figure 1. Reference points: **A**) above the medial malleolus; **B**) posteriorly below the knee; **C**) posteriorly on the thigh.

Results

Sixty-one patients, aged between 18 and 89 years, affected by CVI at CEAP stages C3-C4, were included and randomized into the two study groups (cases N=30 and controls N=31). The two groups were homogeneous in terms of age [58.73±5.34 years in the case group and 59.77±14.97 years in the control group (p=0.7896)] and sex (3 males and 27 females in the case group, 3 males and 28 in the control group). The two populations were homogeneous at baseline for all clinical and subjective well-being parameters evaluated, as shown in Table 1. At the end of the treatment, 59 patients were re-evaluated with the same baseline tests, as two subjects withdrew from the study (1 from the case group and 1 from the control group).

The primary outcome analysis showed significant reductions in the bilateral circumferences measured at the ankle level (A point in Figure 1) in the DIT group compared to the control arm (right p=0.0008, left p=0.0075). Among the secondary outcomes, in the "case" group, there were consistently significant reductions in ultrasound-assessed thicknesses at the medial malleolus (right p=0.0037, left p=0.0015) and at the calf (right p=0.0131, left p=0.0137). Additionally, in the DIT group, there was a subjective decrease in physical limitations due to CVI compared to the controls (p=0.0181), and a significant change in the clinical CEAP (p-value=0.0212). Furthermore, no major adverse events related to mesotherapy were recorded throughout the entire follow-up. Only mild side effects were observed in the DIT group: one patient reported mild pain during needle insertion, one patient experienced transient erythema, which resolved spontaneously within a few hours at most, and in 11 patients, an ecchymosis developed at the injection site, which resolved in approximately one week. In the control group, there was one participant who had a mild feeling of nausea and one who reported weakness. Additional details on the results from these measurements and the administration of study tests are shown in Table 2.

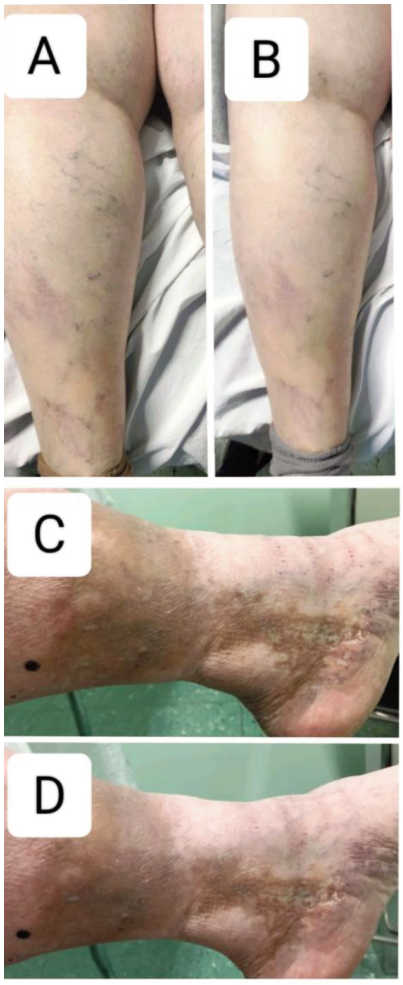

Figure 2. A) and C) represent lower limbs before mesotherapy, B) and D) represent them after mesotherapy.

Discussion

The results of the study highlighted that the mesotherapy treatment was both safe and well-tolerated. In fact, with systemic treatment, it is necessary to maintain high plasma doses to ensure constant drug action, thus requiring more frequent administrations compared to local injections.[9] It has been highlighted that intradermal administration of the same drug achieves a more constant and prolonged tissue kinetic curve.[10]

Furthermore, oral administration requires the drug to be systemically circulated, necessitating a much greater metabolic action than local infiltration, resulting in minimal passage into the general circulation. This is particularly relevant in patients with comorbidities, such as reduced hepatic biotransformation efficiency (chronic liver disease) or impaired renal excretory function (kidney failure), which can lead to alterations in the drug concentration reaching the site of action or an extended presence of the drug in the systemic circulation, increasing the risk of toxic effects.

Mesotherapy employs minimal drug doses sufficient to achieve the therapeutic effect swiftly, thereby reducing the risk of iatrogenic adverse events and preventing potential organ toxicity. This «drug-sparing» effect is particularly significant in patients undergoing polytherapy, who are already taking multiple pharmaceutical agents systemically, with the possibility of chemical-physical interactions both in the bloodstream and at the site of action,

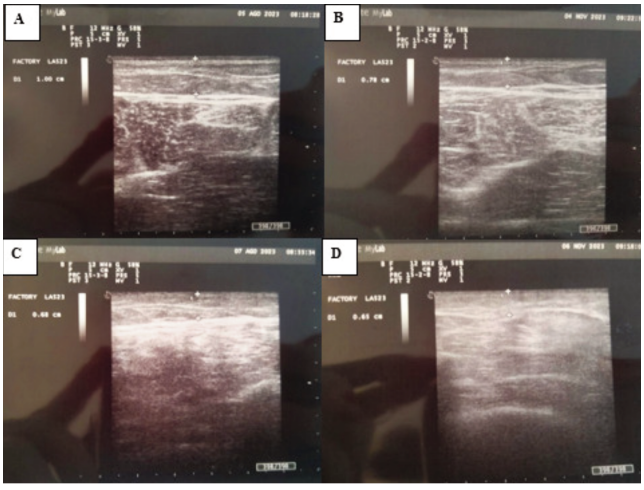

Figure 3. A) edema thickness before mesotherapy and B) post mesotherapy; C) edema thickness before oral treatment and D) post oral treatment.

Table 1. Evaluations of demographic, clinical parameters and questionnaires administered to patients in the two study groups at baseline.

	Age	p	Stage	p	BMI	p	Fat (%)	p	Water (%)	p	CircAdx (cm)	p
Baseline cases	58,73±5,34	0,7896	3,30±0,46	0,34	27,7±5,18	0,0713	34,2±6,78	0,2248	48,77±3,09	0,0507	27,46±2,49	0,9816
Baseline controls	59,77±14,97		3,41±0,50		30,60±6,63		36,70±9,24		46,63±5,02		27,45±2,57	
	CircBdx (cm)	**p**	**CircCdx (cm)**	**p**	**CircAsx (cm)**	**p**	**CircBsx (cm)**	**p**	**CircCsx (cm)**	**p**	**Thickness Adx (cm)**	**p**
Baseline cases	39±3,95	0,8504	57±6,38	0,9841	27,6±2,71	0,5543	38,96±4,08	0,8766	56,6±6,29	0,7311	1,03±0,30	0,5869
Baseline controls	39,19±4,02		57,03±6,18		27,19±2,62		39,12±4,03		57,16±6,39		0,98±0,40	
	Thickness Bdx (cm)	**p**	**Thickness Cdx (cm)**	**p**	**Thickness Asx (cm)**	**p**	**Thickness Bsx (cm)**	**p**	**Thickness Csx (cm)**	**p**	**VCSS**	**p**
Baseline cases	1,19±0,30	0,2599	1,48±0,34	0,2834	0,94±0,25	0,6606	1,10±0,27	0,5043	1,40±0,46	0,4018	11,1±3,16	0,6243
Baseline controls	1,10±0,29		1,36±0,54		0,97±0,35		1,05±0,28		1,29±0,51		11,51±3,33	
	Physical functioning	**p**	**Physical limitations**	**p**	**Emotional limitations**	**p**	**Energy/fatigue**	**p**				
Baseline cases	2,63±0,32	0,4095	1,45±0,27	0,726	1,61±0,30	0,1599	4,04±0,32	0,1977				
Baseline controls	2,7±0,27		1,42±0,22		1,72±0,30		4,15±0,34					
	Emotional wellbeing	**p**	**Social activities**	**p**	**Pain**	**p**	**Perception of general health**	**p**				
Baseline cases	4,46±0,24	0,305	2,83±0,33	0,9447	2,76±0,50	0,1721	2,88±0,35	0,6823				
Baseline controls	4,53±0,27		2,83±0,27		2,56±0,62		2,85±0,30					

Table 2. Re-evaluation at 3 months from the start of treatment, in both study groups, of the clinical, ultrasound parameters, and administered questionnaires.

	Stage	p	BMI	p	Fat (%)	p	Water (%)	p	CircAdx (cm)	p-value	CircBdx (cm)	p-value
Cases after 3 months	3,13±0,35	0,0212*	27,66±5,42	0,0559	32,49±7,16	0,0506	48,96±3,6	0,2922	24,75±2,23	0,0008*	37,44±4,4	0,1257
Controls after 3 months	3,40±0,49		30,71±6,7		36,91±9,88		47,69±5,53		26,93±2,53		39,13±4,08	
	CircCdx (cm)	**p**	**CircAsx (cm)**	**p**	**CircBsx (cm)**	**p**	**CircCsx (cm)**	**p**	**Thickness Adx (cm)**	**p-value**	**Thickness Bdx (cm)**	**p-value**
Cases after 3 months	55,52±6,72	0,4141	25,31±2,38	0,0075*	37,66±4,43	0,1839	55,31±6,42	0,2927	0,68±0,27	0,0037*	0,81±0,30	0,0131*
Controls after 3 months	56,90±6,40		26,97±2,43		39,13±4,15		57,06±6,50		0,91±0,32		1,01±0,31	
	Thickness Cdx (cm)	**p**	**Thickness Asx (cm)**	**p**	**Thickness Bsx (cm)**	**p**	**Thickness Csx (cm)**	**p**	**VCSS**	**p**		
Cases after 3 months	1,08±0,37	0,211	0,66±0,25	0,015*	0,80±0,29	0,0137*	1,08±0,37	0,1461	9,79±3,14	0,0790		
Controls after 3 months	1,21±0,47		0,90±0,31		1±0,31		1,25±0,53		11,27±3,29			
	Physical functioning	**p**	**Physical limitations**	**p**	**Emotional limitations**	**p**	**Energy/fatigue**	**p**				
Cases after 3 months	2,76±0,27	0,634	1,63±0,27	0,0181*	1,73±0,27	0,7618	4,05±0,31	0,3387				
Controls after 3 months	2,73±0,27		1,46±0,26		1,70±0,31		4,13±0,33					
	Emotional wellbeing	**p**	**Social activities**	**p**	**Pain**	**p**	**Perception of general health**	**p**				
Cases after 3 months	4,64±0,26	0,2714	2,84±0,38	0,9519	2,37±0,41	0,4107	2,98±0,41	0,3204				
Controls after 3 months	4,56±0,30		2,85±0,26		2,50±0,66		2,88±0,35					

which may compromise the bioavailability and efficacy of the treatments.[8]

Moreover, DIT can be combined with other techniques, leveraging multimodal therapeutic synergy by associating two approaches with different modes of action (pharmacological or non-pharmacological), allowing further dose-sparing and shorter recovery times.[8,11]

Additionally, mesotherapy proved to be effective, as the therapeutic response to this treatment was significantly better compared to the oral route.

It can be assumed that the reduction in circumferences, particularly at the distal level of the lower limbs, is associated with better tissue edema reabsorption in the mesotherapy group, as the ultrasound-measured subfascial thicknesses were significantly reduced in the same areas where a significant reduction in circumferences was observed. Therefore, it's not surprising that the reduction in edema, which is the most prominent manifestation of the chronic inflammation caused by the disease, led to a reduction in the CEAP clinical stage in 5 cases and 0 controls, along with a decrease in the Venous Clinical Severity Score (VCSS) values.[14-17]

The DIT performed involved initial local injections at the medial malleolus, which is the area most affected by increased hydrostatic pressure in CVI, followed by infiltrations in the leg and thigh. Therefore, the greater significance obtained in this region may be attributed to the larger amount of drug injected in that specific area (Figure 2). Furthermore, upon reassessing body weight at the third month of treatment, it was observed that weight did not always decrease, but instead remained stable or slightly increased in both the case group (DIT) and the control group (oral phlebotonics), as shown in Tables 1 and 2.

This supports the interpretation that the observed results might be due to an improvement in the venous circulation and that the decrease in measurements is reasonably attributed to the reduction of edema rather than fat mass. In fact, extracellular fluid is elevated in CVI due to fluid stagnation in the lower limbs, and mesotherapy aims to reduce it through local injections of the homeopathic product. This substance has a positive effect on the lymphatic system as it improves the system's ability to remove excess filtrate from the capillaries in the interstitial space and accelerates the drainage of toxins, causing inflammation. This mechanism may contribute to the reduction of edema.[18,19] Supporting this, ultrasound imaging demonstrated a reduction in subcutaneous layer thickness, which contains extracellular water (Figure 3).

Furthermore, post-treatment Bioimpedance Analysis (BIA) revealed an increase in Total Body Water (TBW): as Fat Mass (FM) decreased, Fat-Free Mass (FFM) increased, leading to a corresponding rise in TBW, as FFM contains a higher proportion of water than adipose tissue.[20] Since BIA can be influenced by external factors and the patient's health status, prior to the measurement, patients were provided with specific instructions on how to prepare for the examination.

However, the subjective experience of the patient and their perception of the disease itself must not be overlooked. Thus, this study included the SF-36 questionnaire, which documented an improvement in the patient's perceived general health after the treatment for CVI, with a statistically significant difference only in physical limitations due to pain. Recent studies[21,22] suggest that the effectiveness of mesotherapy is not only due to the local pharmacological action but also to the technique used (intradermal injection): the needle stimulates a reflex analgesic action, while the osmotic action and the increased pressure in the tissues, due to the deposited solution, lead to the activation of A-delta and C afferent fibers, resulting in the activation of the «gate control» mechanism, which modulates pain[11]. Thus, while mesotherapy is already considered a valid and relevant technique, as denoted by experts' consensus,[6,8,10,11,23] and recommended in various fields such as pain management, rehabilitation, dermatology, aesthetics, and immune prophylaxis, there remain open questions regarding the standardization of methodology, treatment protocols, drug dosages, estimation of actual therapy success rates, and potential combination with other treatments. In current literature, no other studies have evaluated the efficacy of DIT in CVI by comparing it with a control group treated solely with oral therapy, both from a clinical perspective and by assessing more objective parameters (although not entirely objective) such as ultrasound evaluation of subcutaneous tissue thickness, lower limb circumferences, and Bioimpedance Analysis (BIA), which represents one of the study's main limitations. Another limitation of this study is the small sample size, but the data collected might provide a solid foundation for further research on this topic.

Conclusions

The main shortcoming of our study is the competitor of mesotherapy, which is represented by the less powerful available therapy for CVI, *i.e.* the medical treatment. Surgery, compression, sclerotherapy are certainly the most effective treatments for CVI,[24-26] and the most recommended in Guidelines.[27] There is no discussion about such a statement, and the authors do not want to push mesotherapy as a more powerful therapy. However, in the general practitioner setting, there are frequently patients who refuse surgery or even sclerotherapy and/or have scarce compliance to compression, albeit proposed by specialists. In these cases, the family doctor prescribes phlebotonic drugs, and our findings now support to prefer the intradermal route of administration because safe and more effective.

Moreover, a second limitation of this trial might be considered the use of a homeopathic drug in the treatment arm. The lack of injectable phlebotonic drugs on the market led the researchers to use an injectable product without any specific validated medical indications, but with scientific articles supporting possible therapeutical effects in CVI.[27-29]

The encouraging results of this study could, therefore, allow for the calculation of the sample size necessary for conducting further randomized, controlled, placebo-blind clinical trials, opening a new frontier in the treatment of a widespread condition like CVI. This technique of drug administration could potentially be aimed to become a complementary or adjuvant treatment for CVI, especially for patients refusing invasive treatments and\or compression in case of edema and lipodermatosclerosis.

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