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Original Article

The effect of percutaneous drainage using tiny incisions on the inflammatory factors in chronic venous insufficiency combined with lipodermatosclerosis of the lower extremities

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Abstract: Objective: To explore the efficacy of percutaneous drainage with tiny incisions in chronic venous insufficiency (CVI) combined with lipodystrophy syndrome (LDS) of the lower extremities and its effect on the inflammatory factors. Methods: Sixty patients with CVI and LDS hospitalized for surgical treatment in Jiading District Central Hospital were recruited as the study cohort and randomly divided into a control group and an experimental group. The control group (n = 30) underwent varicose vein stripping in the lower extremities, while the experimental group (n = 30) was additionally treated with percutaneous drainage with tiny incisions for LDS. The efficacy of the two treatments, the mRNA expressions of collagen type I alpha 1 chain 1 (COL1A1), the lower limb circumferences, the subcutaneous thicknesses, the transcutaneous partial pressure of oxygen ($TcPO_2$), the venous clinical severity scores (VCSS), the serum i TGF-β1, TNF-α, IL-2R, and IL-1β levels, the soluble intercellular adhesion molecule-1 (sICAM-1) levels, the soluble vascular cell adhesion molecule-1 (sVCAM-1) levels, and the quality of life scores (CIVIQ) were compared. Results: The total effective rate in the experimental group was 93.33% (28/30), which was higher than the rate of 73.33% (22/30) in the control group ($P < 0.05$). The experimental group exhibited shorter ankle circumferences and calf circumferences, smaller subcutaneous thicknesses, lower VCSS scores, lower sICAM-1, sVCAM-1, TGF-β1, TNF-α, IL-1β, IL-2R, and COL1A1 levels, and higher ABI and $TcPO_2$ levels, and higher CIVIQ scores than the control group at 6 months after the treatment ($P < 0.05$). Conclusion: Percutaneous drainage with tiny incisions has a high efficacy for CVI with LDS, and it can relieve the condition, inhibit the expression of adhesion molecules as well as the inflammatory response, improve the microcirculation of the lower extremities, reduce COL1A1 expression, and improve the quality of life.

Keywords: Chronic venous insufficiency in the lower extremities, lipodystrophy syndrome, efficacy, inflammatory response, COL1A1

Introduction

Chronic venous insufficiency (CVI) of the lower extremities is a peripheral vascular disease with clinical syndromes such as deep venous thrombosis of the lower extremities, skin pigmentation, primary valve incompetence, and venous edema. It is often caused by an impairment of the peripheral venous blood returning to the heart [1, 2]. CVI is often associated with lipodystrophy syndrome (LDS) due to the release of inflammatory mediators and leukocyte activation in response to venous hypertension, which predisposes to non-bacterial inflammatory reactions in the fat and skin [3]. LDS is mainly manifested as subcutaneous nodules, red plaques, or atrophic plaques in the lower extremities, and vascular stenosis occurs in patients with LDS due to a thickening of the vessel wall and abnormal fibrosis [4, 5]. The treatment option of CVI with LDS focuses on anti-inflammatory therapy and the improvement of local blood circulation through injections and oral steroids, wearing compression

stockings, and surgery, among which surgery can reduce the venous pressure of the lower extremities and inhibit the progression of LDS [6].

Drainage using tiny incisions is a new surgical technique that helps reduce the pain level and eliminate the subcutaneous redness and swelling by making small incisions at multiple points along the lesion to drain the liquefied and necrotic tissues [7, 8]. In a previous study, drainage with tiny incisions combined with conventional surgery was effective in the treatment of CVI with LDS, but the underlying mechanism was not analyzed in terms of the inflammatory factors and adhesion molecules [9]. This study enrolled 60 patients with CVI with LDS and analyzed the efficacy of drainage with tiny incisions, the expression of adhesion molecules and the changes in the microcirculation of the lower limbs, the inflammatory response, and the expression of collagen type I alpha 1 chain 1 (COL1A1).

Materials and methods

Clinical data

Sixty patients with CVI with LDS, including 25 males and 35 females, 29-72 years old, and admitted to Jiading District Central Hospital from January 2016 to June 2018, were recruited as the study cohort. Inclusion criteria: patients who met the diagnostic criteria established in the Chinese Expert Consensus on the Diagnosis and Treatment of Chronic Lower Extremity Venous Disease [10], patients with clusters of flattened subcutaneous nodules involving the skin, subcutaneous tissue, or even the fascia, patients with nodules that may be associated with scarring and contractures, patients meeting CEAP classifications C4-C6, and patients who met the surgical indications. Exclusion criteria: patients with allergic diseases such as necrotizing vasculitis, patients with severe arterial ischemic diseases such as thromboembolic vasculitis, occlusive arteriosclerosis, and arterial occlusion to the lower extremities, patients suffering from a mental illness, allergy, disorders of the cardiovascular, renal, hepatic, or hematopoietic systems, patients with coagulation dysfunctions, deep venous thrombosis of the lower limbs, gait dysfunctions, patients who were pregnant or lactating, and patients with cellulitis. This study was approved by the Affiliated Jiading Center Hospital of Shanghai University of Medicine & Health Science. All the patients or their families signed the informed consent.

Methods

(1) Control group. The patients in the control group underwent varicose vein stripping in their lower extremities. With the patient in a standing position, a 3 cm incision was made at the groin or popliteal fossa. A high ligation was first performed on the large and small saphenous veins, followed by the stripping of the primary venous trunk with a venous stripper and a closure of the superficial varicose veins using a laser. The flow of blood in the lower extremities was limited by twisting the superficial veins. 0.3 cm cuts were made to perform the stripping. The incision of the main trunk was sutured, and bandages were placed on the legs for 3 days. After the surgery, anticoagulation and the promotion of blood flow were routinely performed for 3 days.

(2) Experimental group. In addition to the varicose vein stripping, drainage with tiny incisions was additionally performed in the experimental group. With tourniquet usage in the lower extremities, a denser, longitudinal, multiple-point incision (0.3 cm) was made on the skin showing LDS. Vascular forceps were used to perform a blunt dissection of the subcutaneous tissue while the liquefied fat tissue and subcutaneous necrotic tissues were squeezed out, followed by suturing the incision of the primary venous trunk, without suturing the 0.3 cm incision. A bandage was placed on the incision for 3 days. After the surgery, anticoagulation and the promotion of blood flow were routinely performed for 3 days.

Outcome measurement

(1) Efficacy of the treatment. After the treatment, any disappearance of the clinical symptoms, such as lumps, pain, calf soreness and swelling, and a venous clinical severity score (VCSS) ≥90% were regarded as markedly effective; improvements in the clinical symptoms with a VCSS≥30% and < 90% were regarded as effective; no improvement or a worsening of the clinical symptoms and a VCSS < 30% were regarded as ineffective. Total effective = markedly effective + effective.

(2) Lower limb circumference and ABI. Ankle circumference, calf circumference, thigh circumference, knee circumference, and the ankle-brachial index (ABI) were measured before and at 6 months after the treatment.

(3) Subcutaneous tissue thickness, transcutaneous partial pressure of oxygen ($TcPO_2$) and the VCSS scores. The subcutaneous tissue thickness was measured before and at 6 months after the treatment using color Doppler ultrasonography (model Siemens-S2000); $TcPO_2$ was measured using laser Doppler (model Peri Flux5000) and a $TcPO_2$ monitoring system (purchased from PerimedAB, Sweden); the VCSS scale includes edema, pain, pigmentation, induration, inflammatory reaction, ulcers and LDS on a 0-3 Likert scale. A higher score indicates a more severe condition [11].

(4) Serum indicators. 5 mL of venous blood was drawn from the lower extremities before and at 6 months after the treatment. The blood was centrifuged for 10 min (3500 r/m, r = 10 cm) to obtain the supernatant. The serum soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), TGF-β1, TNF-α, IL-1β, and IL-2R levels were determined using double antibody sandwich enzyme-linked immunosorbent assays (China Wuhan Eliot Biotechnology Co.).

(5) Quality of life. The 20-item Quality of Life scale (CIVIQ) was used to assess the patients' quality of life before and at 6 months after the treatment in terms of 4 aspects: psychosocial, social activity, pain and physical fitness on a 0-5 Likert scale, covering 100 points. A higher score indicates a higher quality of life [12].

(6) COL1A1 expression. Intraoperatively, biopsies were performed with 0.2 × 0.2 cm of tissue at deep fascia from 2 cm next to the edge, the center, the edge of the scleroderma, respectively, to measure the COL1A1 expression. The COL1A1 expression was measured using a biopsy of 1 cm of tissue adjacent to the original edge at 6 months after treatment.

Statistical analysis

Using SPSS 23.0 statistical analysis software, the measurement data conforming to a normal distribution ($\bar{x} \pm s$) were examined using independent samples *t* tests. The count data (%) were tested using χ^2 tests. $P < 0.05$ was considered a statistically significant difference.

Results

General information

No significant differences were found in terms of sex, age, disease duration, lesion site, CEAP classification, LDS score, or proportion of LDS with ulcers between the two groups, ($P > 0.05$), indicating that the two groups were comparable (**Table 1**).

Efficacy of treatment

The total effective rate of the experimental group was higher than of the total effective rate in the control group ($P < 0.05$), indicating that percutaneous drainage with tiny incisions can enhance the treatment efficacy and promote symptomatic relief in patients with CVI with LDS (**Table 2**).

Circumference of the lower extremities

There were no significant differences in the thigh and knee circumferences between the two groups ($P > 0.05$). At 6 months after the treatment, the experimental group exhibited shorter ankle circumferences and calf circumferences than the control group (all $P < 0.001$), indicating that drainage with tiny incisions can reduce the ankle circumferences and calf circumferences in patients with CVI with LDS (**Figure 1**).

Subcutaneous thicknesses, VCSS scores, and ABI

There were no significant differences in the subcutaneous thicknesses, the VCSS scores, or the ABI between the two groups ($P > 0.05$). At 6 months after the treatment, the subcutaneous thicknesses, the VCSS scores, and the ABI in the experimental group were higher than they were in the control group (all $P < 0.001$), indicating that drainage with small incisions can alleviate the symptoms of CVI with LDS, reduce the subcutaneous thickness, and improve the ABI (**Figure 2**).

$TcPO_2$, sICAM-1, and sVCAM-1

There were no significant differences in the $TcPO_2$, sICAM-1, or sVCAM-1 levels between the

Table 1. Comparison of baseline data between the two groups n/($\bar{x}$ ± S)

Grouping	M/F	Age (years)	Duration of illness (months)	Location of lesions	CEAP Classification	LDS score	LDS with ulcers
				Left lower extremity/ right lower extremity	C4/C5/C6	1 point/2 points/3 points	
Control group (n = 30)	13/17	58.61 ± 6.20	6.94 ± 2.19	16/14	21/5/4	2/21/7	10
Experimental group (n = 30)	12/18	57.12 ± 5.98	7.22 ± 2.64	18/12	20/7/3	5/20/5	8
χ^2/t	0.069	0.947	0.447	0.272	0.503	1.688	0.318
P	0.793	0.347	0.657	0.602	0.778	0.430	0.573

Table 2. Comparison of the efficacy [n (%)]

Grouping	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n = 30)	10 (33.33)	12 (40.00)	8 (26.67)	22 (73.33)
Experimental group (n = 30)	15 (50.00)	13 (43.33)	2 (6.67)	28 (93.33)#
χ^2				4.320
P				0.038

Note: Compared with the control group, #*P* < 0.05.

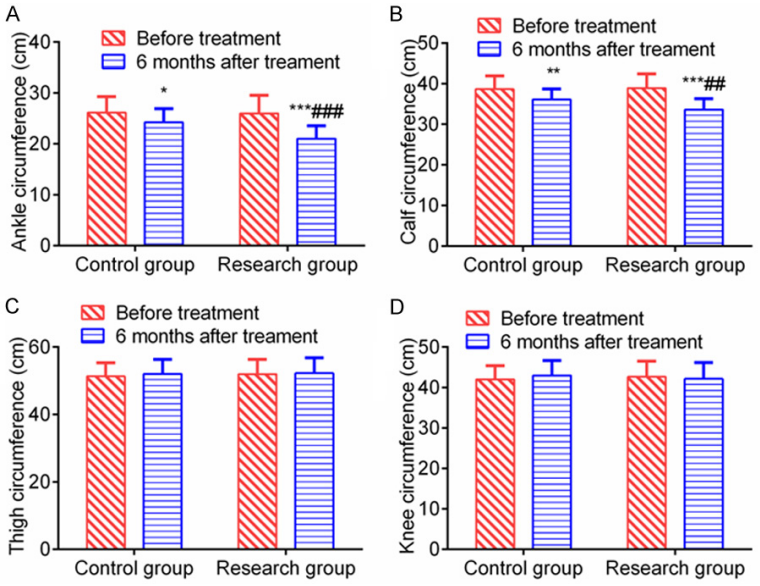

Figure 1. Comparison of lower limb circumferences before and after the treatment in the two groups. Note: A: Ankle circumference; B: Calf circumference; C: Thigh circumference; D: Knee circumference. Compared to that before treatment, **P* < 0.05, ***P* < 0.01, ****P* < 0.001; compared to the control group, ##*P* < 0.01, ###*P* < 0.001.

two groups before the treatment (*P* > 0.05). At 6 months after the treatment, the experimental group showed lower levels of ICAM-1 and sVCAM-1 and higher levels of $TcPO_2$ compared to the control group (all *P* < 0.001), showing that drainage with small incisions can modulate the $TcPO_2$, sICAM-1, and sVCAM-1 levels in patients with CVI with LDS (**Figure 3**).

TGF-β1 and inflammatory factors

The two groups showed no differences in their TGF-β1, TNF-α, IL-1β, and IL-2R levels before the treatment (*P* > 0.05). At 6 months after the treatment, the TGF-β1, TNF-α, IL-1β, and IL-2R levels in the experimental group were lower than they were in the control group (all *P* < 0.001), indicating that drainage with small incisions can regulate TGF-β1 and reduce the inflammatory response in patients with CVI with LDS (**Figure 4**).

Quality of life and COL1A1 expressions

At 6 months after treatment, the experimental group exhibited higher CIVIQ scores and lower COL1A1 expressions than the control group (all *P* < 0.001), suggesting that drainage with small incisions can improve the quality of life and down-regulate COL1A1 expression in patients with CVI with LDS (**Figure 5**).

Discussion

The etiology of CVI with LDS has not been fully elucidated, but it is believed to be caused by multiple factors, including lymphovascular insufficiency, trauma, the inflammatory response, and vascular circulation disorders of the lower extremities [13, 14]. Therefore, a randomized, controlled study was conducted to analyze the effect and mechanism of drainage with small incisions for CVI with LDS in terms of the inflammatory factors, adhesion factors, and COL1A1 expressions in the lesions, so as to guide the clinical treatment.

Compared with the control group, the experimental group had a higher treatment efficiency, ABI and CIVIQ scores, shorter ankle circumferences and calf circumferences, smaller subcutaneous thickness, and lower VCSS scores at 6 months after the treatment, indicating that the drainage with small incisions can definitely improve the condition of CVI with LDS and improve the patients' quality of life. The reason

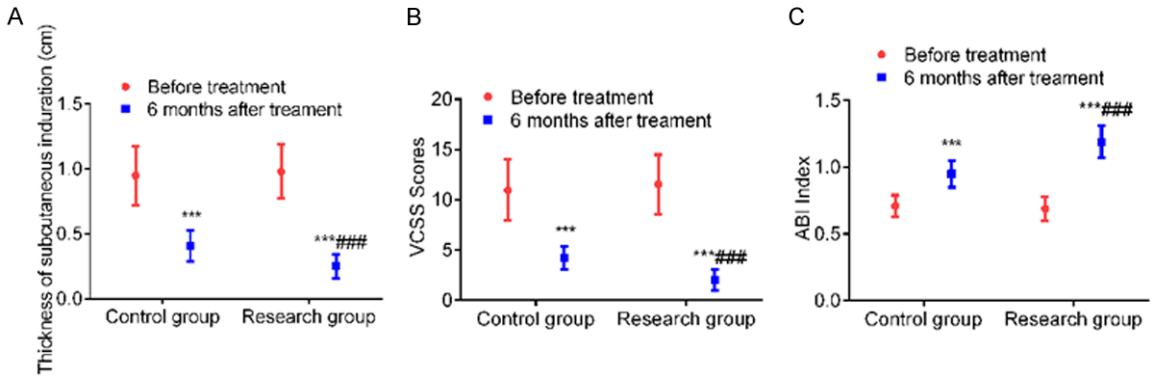

Figure 2. Comparison of subcutaneous thicknesses, VCSS scores, and ABI between the two groups. Note: A: Subcutaneous thickness; B: VCSS score; C: ABI index. Compared with before the treatment, $^{***}P < 0.001$; compared with the control group, $^{\#\#\#}P < 0.001$.

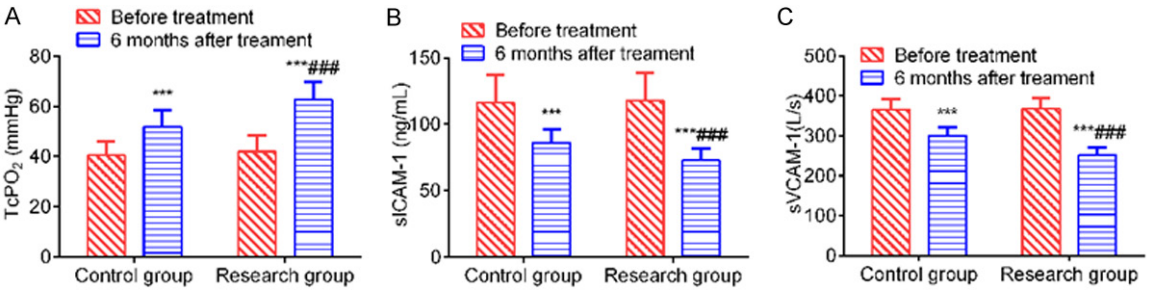

Figure 3. Comparison of two groups' $TcPO_2$, sICAM-1, and sVCAM-1 levels. Note: A: $TcPO_2$; B: sICAM-1; C: sVCAM-1. Compared with before the treatment, $^{***}P < 0.001$; compared with the control group, $^{\#\#\#}P < 0.001$.

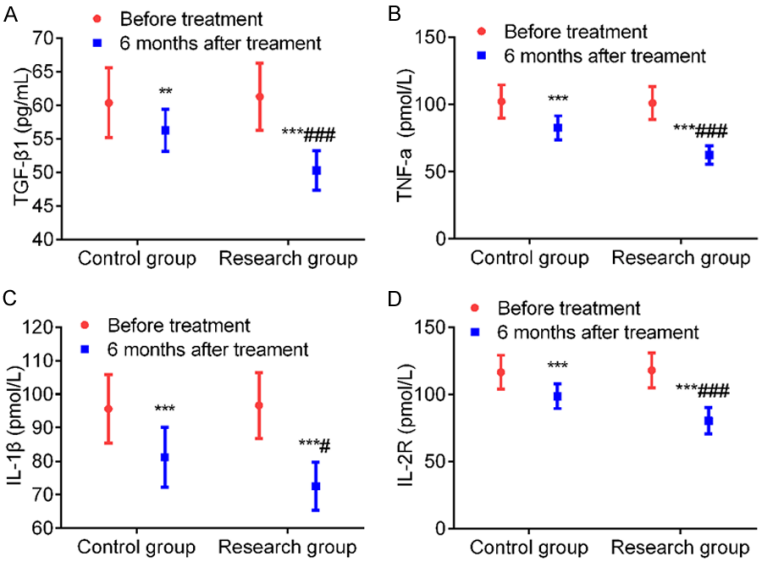

Figure 4. Comparison of the TGF-β1 and inflammatory factors between the two groups. Note: A: TGF-β1; B: TNF-α; C: IL-1β; D: IL-2R. Compared with before the treatment, $^{**}P < 0.01$, $^{***}P < 0.001$; $^{\#\#\#}P < 0.001$ compared with the control group.

may be that varicose vein stripping alone can eliminate venous hypertension, but the long-term accumulated necrotic tissue and fluid retention cannot be directly removed, which would be slowly absorbed, making it difficult to achieve satisfactory results. However, when longitudinal, small incisions are made at the lesion, followed by blunt dissection and draining, the procedure can completely remove local necrosis and liquefied fatty and necrotic tissues, and the skin induration, skin redness and swelling, and skin tenderness disappear [15, 16]. Microcirculation disorders in the lower extremities are particularly prominent in the occurrence and development of CVI with LDS. On the one hand, it can cause ischemia and hypoxia of the gastrocnemius muscle of the lower extremities, impair the function of the calf muscle pump, and indi-

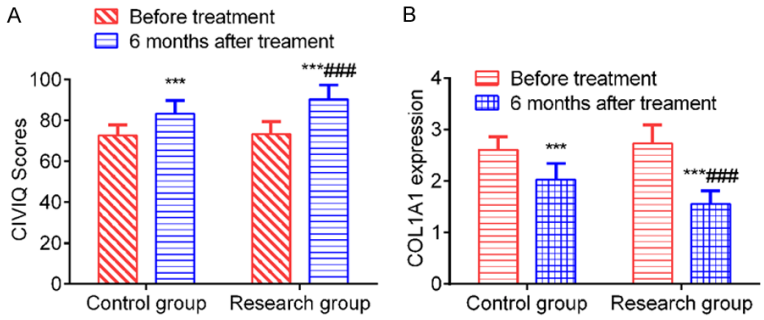

Figure 5. Comparison of the CIVIQ scores and the COL1A1 expressions in the two groups. Note: A: CIVIQ score; B: COL1A1 expressions. Compared with before the treatment, $^{***}P < 0.001$; compared to the control group, $^{###}P < 0.001$.

rectly cause a disturbance of the venous drainage of the lower extremities, and then induce varicose veins and edema. On the other hand, microcirculation disorders can increase the permeability of local capillaries, cause the accumulation of metabolites and fluid, and promote the pathological injuries, such as induration, skin pigmentation, *etc*. [17, 18]. The $TcPO_2$ assay can accurately and continuously reflect microcirculation, and in this study, the $TcPO_2$ in the experimental group was higher than it was in the control group at 6 months after the treatment, indicating that drainage with small incisions helps relieve microcirculation disorders, improve the skin's ability to acquire oxygen, and improve microcirculation.

The inflammatory response in tissues caused by leukocyte migration is closely related to the development of CVI with LDS. The migration and activation of leukocytes under hypoxia and venous hypertension can promote the release of chemokines such as TGF-β1, aggravate the damage of microvasculature and perivascular tissues, and accelerate tissue necrosis [19]. As a pro-fibrotic cytokine, TGF-β1 can induce gene transcription and protein synthesis of fibronectin, type I collagen and type III collagen, and fibroblasts, stimulate proliferation, and inhibit apoptosis, thus forming a highly cross-linked dense matrix [20]. A retrospective analysis of LDS has shown that the elevation of TGF-β1 promotes the occurrence of LDS [7]. Type I collagen secreted by fibroblasts plays an important role in the formation of lesions, and COL1A1 is an important component of type I collagen, so measurements of the COL1A1 expressions in tissues can be used to reflect the disease progression of LDS and guide the evaluation of the therapeutic effect [21]. In the present study, the TGF-β1 and COL1A1 expressions in the experimental group were lower than they were in the control group at 6 months after the treatment, indicating that drainage with small incisions in CVI with LDS helps inhibit disease progression and reduce TGF-β1 levels and COL1A1 expressions. Under normal physiological conditions, there is no leukocyte adhesion in the vasculature, but when fluid shear stress is reduced, leukocyte activity can be increased, leading to the inflammatory responses. In addition, venous valvular incompetence in superficial veins or the communicating veins that connect the deep and superficial veins can result in varicose veins, which can lead to hypertension and stasis in the venous system of the lower extremities and the elevation of inflammatory factors such as TNF-α and IL-1β [22, 23]. The body triggers inflammatory responses related to adhesion molecules and inflammatory factors, and adhesion molecules act in a ligand-receptor manner and are important in cell extension and movement and cell signaling and activation [24]. In this study, the sICAM-1, sVCAM-1, TGF-β1, TNF-α, IL-1β, and IL-2R levels in the experimental group were lower than the corresponding levels in the control group at 6 months after the treatment, indicating that drainage with small incisions can inhibit the expression of adhesion molecules in patients with CVI with LDS, reduce vasoconstriction and platelet adhesion and aggregation, as well as the inflammatory response.

In summary, drainage with small incisions for CVI with LDS is highly effective in reducing the condition, blocking the expression of adhesion molecules, inhibiting the inflammatory response, improving the microcirculation of the lower extremities, and improving the quality of life. However, this study has some limitations. Since CVI with LDS is a chronic disease, the treatment is difficult, and the treatment cycle is long, so it is impossible to rule out the poor results of some cases due to a too-short treatment cycle. Moreover, in this study, the patients

were not followed up for a long time, so it was not observed whether prolonging the treatment cycle was more conducive to patient rehabilitation. Therefore, it is necessary to appropriately increase the sample size, prolong the treatment cycle and follow-up times, so as to further explore the long-term efficacy of the therapy.

Disclosure of conflict of interest

None.

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