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Original Article

Efficacy of subcutaneous lidocaine injection in venous insufficiency: a prospective, randomized, controlled study, and new treatment protocol

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Abstract. [Purpose] The purpose of this study was to evaluate the efficacy of subcutaneous injection with lidocaine in patients with chronic venous insufficiency in the early stage. [Subjects and Methods] Patients (n=50) randomized to the treatment group received subcutaneous injections from a mixture of physiological saline sterile solution and lidocaine once a week to both legs below the knee for 5 sessions. Patients in the treatment group were also given ankle pumping exercises and compression stockings throughout the treatment. Patients randomized to the control group (n=50) received only ankle pumping exercises and compression stockings. Patients were evaluated using the visual analog scale (VAS) for pain and Chronic Venous Disease Quality of life Questionnaire (CIVIQ-20) for quality-of-life at months 1, 3, 6, at the end of month 12, and at the end of the injection treatment for 5 sessions. [Results] CIVIQ-20 and VAS results were significantly lower in the treatment group, than in the control group at months 1, 3 and 6. However, CIVIQ-20 and VAS results were not significantly different, compared with the pre-operative period at month 12. [Conclusion] We observed that 5-week subcutaneous lidocaine injection treatment was effective in patients who do not respond to oral medical treatment or in whom surgery is not considered.
Key words: Chronic venous insufficiency, Lidocaine, Local injection

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INTRODUCTION

The term chronic venous insufficiency (CVI) is used to define morphological and functional abnormalities in the peripheral venous system[1)]. In developed countries, the incidence of CVI is approximately 60%[2)].

The pathophysiology of CVI is not clearly understood. Researchers reported that fluid leaking out the veins does not join the lymphatic system, accumulates between tissues and, in time, causes edema, swelling, and inflammation between tissues[3, 4)]. Clinical findings of CVI highly differ. In particular, it has been characterized as swelling in extremities, changes in the skin, and ulcerations; various venous symptoms, mainly pain, may be frequently observed[5)].

Its treatment includes improving venous circulation, thus decreasing pathological changes, and inflammation in tissues[3)]. Various methods are used in the management of CVI, including medical treatment, compression stockings, exercise, changes in lifestyle, and weight loss. However, in some of the advanced cases, these methods are inadequate and patients are advised to undergo surgery[6)].

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The most common medication used to treat CVI is calcium dobesilate (Doxium; OM Pharma/ViforPharma, Meyrin, Switzerland), functioning as a synthetic vasoactive agent. Calcium dobesilate has been found to be effective in many diseases, particularly those with microcirculation pathologies and is recommended in many international guidelines[7].

Sclerotherapy is also a method used in CVI which involves injecting a sclerozan intraluminally to induce fibrosis resulting in obliteration of a vein[8].

In advanced CVI cases, ambulatory phlebectomy is performed under local anesthesia and comprises the removal of venous structures with abnormal pathological properties[6]. Apart from this, methods such as radiofrequency and endovenous laser application have also been performed in recent years[9].

Lidocaine is a peripheral sodium channel blocker and produces a selective and partial blockade on Aδ and C nerve fibers[10]. In addition, in vitro and in animal studies have demonstrated that lidocaine has modulator-inhibitor effects on inflammation, particularly tumor necrosis factor and prostaglandin E secretion[11–13]. These effects suggest that lidocaine can be used in pathological situations in which inflammation is prominent.

The purpose of this study was to evaluate the efficacy of subcutaneous injections of lidocaine in patients with early stage CVI, and prominent edema and pain, who are not considered for surgery.

SUBJECTS AND METHODS

Detailed physical examination and tests were performed in patients presenting to our Physical Medicine and Rehabilitation and Vascular Surgery Outpatient Clinics with leg pain. Patients were excluded from the study if their medical history and tests revealed a history of cancer, lumbar disc hernia, lumbar spinal stenosis, or diabetic neuropathy. Patients were also excluded if they had diseases causing symptoms including magnesium and vitamin D deficiency, pain, or cramps and numbness in legs. Patients with hypertension, hyperthyroidism, congestive heart failure, or primary and secondary lymph edema were also excluded. Arterial and venous Doppler ultrasound evaluation of lower extremities were performed in all patients. The clinical classification part of the "the clinical, etiological, anatomical and pathophysiological (CEAP) classification system" was used for CVI[14] (Table 1).

Overall, 140 women patients with stage 1 and stage 2 CVI according to Clinical classification with no indication for surgery and who did not respond to oral medical treatment (calcium dobesilate) for one month were enrolled in the study between February 2015 and July 2015. A total of 120 participants met the inclusion criteria and were randomly assigned to one of two groups using a computer-based protocol. Sixty mg lidocaine (20 mg/ml) was injected into 100 ml isotonic saline solution. Then, each time 0.2 ml of this solution was administered subcutaneously to each injection site of the limb with 1 cm intervals and administered for 5 sessions, once a week to both legs below the knee in patients in the treatment group (n=60). Patients also underwent ankle pumping exercises which were done by patients 20 times at one time in a day and were given above knee compression stockings throughout the treatment. Patients in the control group (n=60) only underwent ankle pumping exercises and received compression stockings. Following the completion of 5 sessions of injections, patients' pain and quality-of-life were evaluated at month 1, 3, 6, and 12. All patients continued exercises and compression stocking during the follow-up. Both groups received 600 mg oral gabapentin every 8 hours, three times daily, for neuropathic pain. Twenty patients did not continue treatment or were lost to follow-up, and 100 patients were prospectively evaluated at the 12-month follow-up examination (Fig. 1).

The visual analog scale (VAS) was used to evaluate pain and the chronic venous disease quality of life questionnaire (CIVIQ-20) to evaluate quality-of-life impairment from CVI. All of the participants provided written informed consent before this study. The study was approved by the Local Ethics Committee (ID Number: 2015/2–149).

The sample size estimation was calculated using GPower software. The minimum sample size was calculated using the 0.55 effect size, a false-positive rate of 5% (α=0.05), and a power of at least 80% (β=0.2). Using these parameters and adjusting for comparisons, we required a minimum sample size of 100 patients (50 per arm). A total of 60 patients per group were required, taking into consideration the estimated 20% dropout rate, thus giving a total of 120 patients enrolled in the study (Fig. 1).

Mean, standard deviation, median, minimum, maximum, frequency, and ratio were used in the definitive statistics of the study. Distributions of variables were measured using the Kolmogorov-Smirnov test. Mann-Whitney U test and independent samples t-test were used in the analysis of quantitative data. The Wilcoxon test was used in the analysis of repeated measurements. χ^2 test was used in the analysis of qualitative data. SPSS 22.0 program was used in the analyses.

RESULTS

Patients' ages were not significantly different between the treatment and and control groups ($p>0.05$). The ratio of class II CVI was significantly higher in the treatment than the control group ($p<0.05$) (Table 2).

Preoperative VAS values were not significantly different between the treatment and control groups ($p>0.05$). Month 1, 3, and 6 VAS values were significantly lower in the treatment group, compared with the control group ($p<0.05$). Year 1 VAS values were not significantly different between the treatment and control groups ($p>0.05$) (Table 3).

VAS values significantly decreased at month 1, 3, and 6, compared with the preoperative period ($p<0.05$). VAS values were

Table 1. CEAP classification

Stage	Definition
Stage 0	No finding observed with regard to venous disease
Stage 1	Telangiectasia or reticular veins
Stage 2	Varicose veins separate from reticular veins (3 mm or more in diameter)
Stage 3	Edema
Stage 4a	Pigmentation or edema
Stage 4b	Lipodermatosclerosis or atrophy (blanche)
Stage 5	Healed venous ulcers
Stage 6	Active venous ulcer

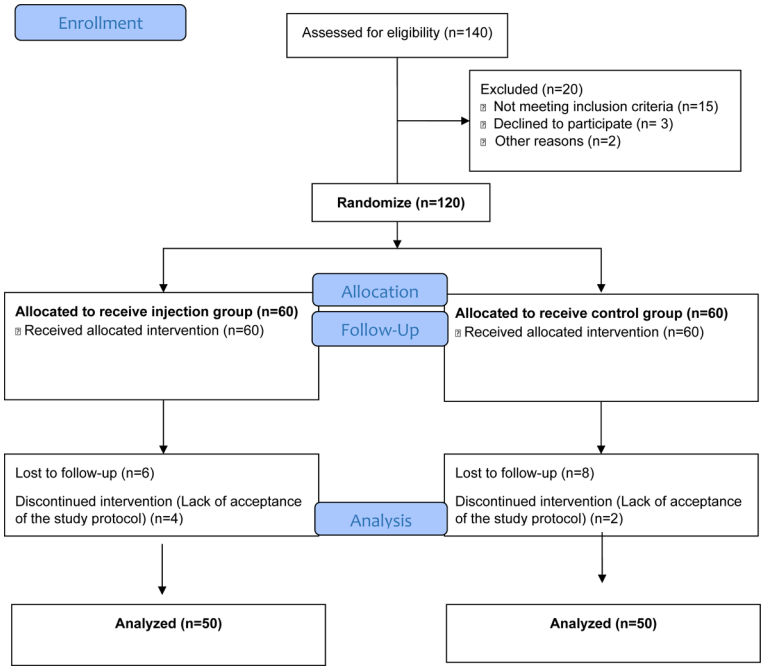

Fig. 1. Flow diagram of the study.

Table 2. Age and clinical stage comparison between the treatment and control group

		Case Group			Control Group			p
		Mean ± SD		Med (Min–Max)	Mean ± SD		Med (Min–Max)	
Age		56.4 ± 10.2		56 38–81	57.2 ± 9.1		58 38–72	0.412
CVI	Class I	28	56.0%		50	100%		0.000
	Class II	22	44.0%		0	0.0%		

χ^2 test, Student test.

not significantly different in the treatment group at month 12, compared with the pre-operative period (p>0.05) (Table 3).

VAS values were not significantly different in the treatment group at month 1, 3, 6, and 12, compared with the pre-operative period (p>0.05) (Table 3, Fig. 2).

CIVIC-20 scores were not significantly different in the case, compared with thecontrol group (p>0.05). CIVIC-20 scores in the case group were significantly lower than those in the control group at months 1, 3, and 6 (p<0.05). CIVIC-20 score was not significantly different in the treatment group, compared with the control group at month 12 (p>0.05) (Table 4).

CIVIC-20 scores in the case group significantly decreased at months 1, 3, and 6, compared with the pre-operative period (p<0.05). CIVIC-20 scores were not significantly different at month 12, compared with the pre-operative period in the treat-

Table 3. VAS scores pre- and post-treatment

	Case Group			Control Group			p
	Mean ± SD	Med (Min–Max)		Mean ± SD	Med (Min–Max)		
VAS							
Preop	7.4 ± 0.5	7	7–8	7.4 ± 0.6	7	7–9	0.700
1. Month	2.9 ± 0.4*	3	2–4	6.0 ± 0.0	6	6–6	0.000
3. Month	2.9 ± 0.4*	3	2–4	6.0 ± 0.0	6	6–6	0.000
6. Month	2.9 ± 0.4*	3	2–4	6.0 ± 0.0	6	6–6	0.000
1. Year	6.0 ± 1.0	6	5–8	6.0 ± 0.0	6	6–6	0.200

Mann-Whitney U test, Wilcoxon test, *Difference with preop p<0.05.

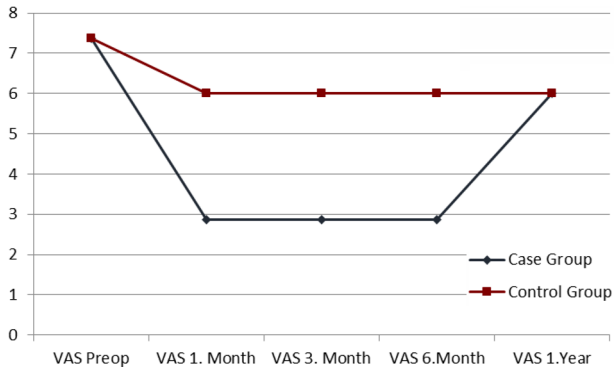

Fig. 2. VAS scores of groups pre- and post-treatment.

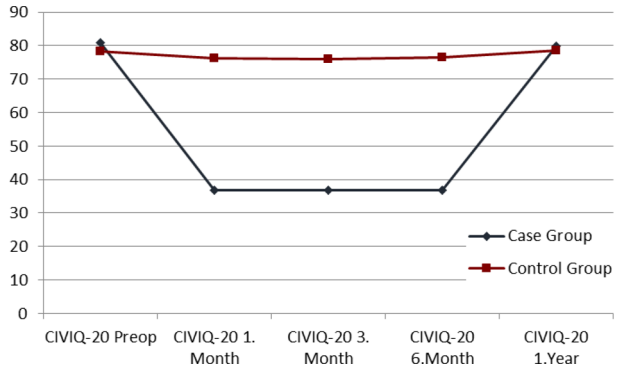

Fig. 3. CIVIC-20 scores pre- and post-treatment.

Table 4. Comparison of CIVIC-20 scores of groups pre- and post-treatment

	Case Group			Control Group			p
	Mean ± SD	Med (Min–Max)		Mean ± SD	Med (Min–Max)		
CIVIQ-20							
Preop	80.8 ± 8.3	76	76–95	78.2 ± 0.0	77	77–77	0.052
1. Month	36.9 ± 4.6*	38	19–38	76.1 ± 1.0	76	76–83	0.000
3. Month	36.9 ± 4.6*	38	19–38	76.0 ± 0.3	76	76–78	0.000
6. Month	36.9 ± 4.6*	38	19–38	76.4 ± 2.4	76	76–93	0.000
1. Year	79.9 ± 7.4	76	72–95	78.7 ± 1.0	78	78–82	0.101

Mann-whitney u test, Wilcoxon test, *Difference with preop p<0.05.

ment group (p>0.05) (Table 4). CIVIC-20 scores were not significantly different at months 1, 3, 6, and 12, compared with the pre-operative period in the treatment group (p>0.05) (Table 4, Fig. 3).

DISCUSSION

To our knowledge, this study is the first to use lidocaine for the treatment of CVI symptoms. Symptoms associated with CVI can be difficult to evaluate because they may present as very subjective symptoms, including discomfort and sensation of heaviness in legs, or more obvious symptoms, including cramp, pain, edema, and skin changes. CVI diagnosis, treatment, and impact on the workforce may be associated with serious financial burden and quality-of-life impairment. Therefore, early diagnosis and treatment initiation can have a substantial impact on the treatment and socio-economic aspects of the disease. Even though it is a very common disease, due to the lack of epidemiological data, the prevalence of CVI cannot be inferred. Previous studies have recorded specific characteristics in advanced cases, including patients who presented to the hospital and were diagnosed with varicose veins and leg ulcers[15, 16]. In our study, we only evaluated patients in the early stage of the disease (CEAP classification stage 1 and 2) to ensure a homogenous patient distribution.

It is generally accepted that pain associated with CVI is from a leukoendothelial inflammatory reaction caused by venous

stasis, and that the resulting inflammation is a basic stimulation originating from nociceptors in veins and venous walls[17]. This chronic inflammation stimulates Aδ and C fibers peripherally, and triggers central activation of different mediators, such as cyclooxygenase enzymes. Because of these changes, neurotransmitters, including glutamate, increase, and N-methyl-D-aspartate receptor activation increases. N-methyl-D-aspartate receptor disinhibition may lead to central sensitization in patients[18].

In addition, ischemia associated with venous microangiopathy and increased endoneural pressure may cause nerve entrapment, which may explain neuropathic pain in patients with CVI[19, 20]. CVI-related sensitization should be considered in these patients to develop effective treatment methods. In our study, both groups received 600 mg oral gabapentin every 8 hours, three times daily, for neuropathic pain.

Recently, studies evaluating genetic factors in the pathogenesis of CVI have been being conducted. In particular, they suggest that the risk for disease occurrence in individuals with familial CVI is higher than in individuals without familial CVI[21]. Another important cause in the CVI pathogenesis is P-selectin activation in platelets. P-selectin is a cell adhesion molecule found in the endothelial cells and alfa granules of platelets. When P-selectin is expressed, it binds to its ligand and stimulates leukocytes to form thrombus and fibrin. Data also indicate that P-selectin elevation is associated with stroke, acute myocardial infarction, coronary artery disease, and peripheral artery disease[22].

Lidocaine is a commonly administered drug in local and general anesthesia. In particular, it is frequently used to prevent ventricular arrhythmia of the heart and has various effects in many different areas. Lidocaine, along with a substantial number of other local anesthetics, modulate inflammatory response and platelet aggregation[23, 24]. It has also been demonstrated that local anesthetic agents can decrease reperfusion damage in heart, lung, brain, and pulmonary damage associated with endotoxins and hypoxia in vivo[25]. Furthermore, local anesthetics have been shown to inhibit signal properties of macrophages or granulocytes in vitro, inhibiting early responses of the inflammatory response[26]. In a study conducted by Huang et al., the researchers showed that lidocaine inhibited adenosine diphosphate-dependent P-selectin expression in blood dose-dependently. It also has been suggested that lidocaine reduces inositol triphosphate calcium outflow from the platelet membrane[27]. Because calcium is a strong stimulant of platelet granule secretion, the reduction of calcium release may be linked to the inhibition of P-selectin expression and platelet granule secretion[28]. In a study by Piegeler et al., it was shown that ropivacaine and lidocaine inhibit tumor necrosis factor binding of to the endothelium of pulmonary endothelial cells, reducing endothelial hyperpermeability, and neutrophil adhesion via phosphatidylinositol 3-kinase[29]. Because design of our study was prospective in nature and rules of our Ethics Committee, it was not possible to measure the level of P-selectin in the blood of our patients. Although we evaluated our patients clinically and functionally, we recommend that P-selectin and other biochemical markers be tested to assess the efficacy of CVI treatment. In addition, although pain and swelling decreased in our study—they were venous signs in the group injected with lidocaine—the well-being of our patients, in terms of symptoms, was maintained in the first six months after the treatment. Quality-of-life improvements were also observed. We believe that the decrease in pain and swelling was associated with the lidocaine injections and decreased inflammation in the tertiary tissues. Specifically, we believe that reduction in inflammation decreased edema, which indirectly decreased the secretion of inflammatory neurotransmitters, slowing down the effect of inflammation-ischemia-central sensitization in patients with CVI.

Previous study have shown that compression stockings and exercise programs were associated with a significant reduction in the symptoms in some patients[30]. We made sure to include patients who did not respond to medical treatment, including compression stockings and exercise. Therefore, we believe that favorable response to the treatment is associated with the injections that were administered.

Among patients with CVI, edema accumulates around the muscle and bone as much as it accumulates in subcutaneous adipose tissues and the skin[31]. Since subcutaneous lidocaine injection can resolve edema in the subcutaneous adipose tissue and intradermal edema, measurement of the leg circumference could have been used to assess the success of treatment. We will consider this parameter in future studies. However, since a reduction in leg edema can be detected in long-term use (>3 weeks) of calcium dobesilate, and calcium dobesilate was administered in the study conducted by Rabe et.al and in our study, it may not have been possible to differentiate whether the reduction in edema was associated with subcutaneous lidocaine or calcium dobesilate[32].

In this study, we used compression stockings, oral therapy (calcium dobesilate), and an exercise program, all of which are optimal methods for the treatment of this condition, and considered a conservative treatment protocol. We preferred calcium dobesilate, especially because it is well tolerated, and has a low side-effect profile[32]. Various agents and different methods have been used to treat patients with CVI. In a study carried out by Aguilar-Ferrándiz et al. of women with CVI, the kinesiotaping method was evaluated, and demonstrated favorable results for pain, walking, and quality of life[17]. Several studies have evaluated the efficacy of mesotherapy in the treatment of patients with CVI. Maggiori et al. performed an intradermal administration of an agent with naturopathic component (Lymdiaral) and found that it was beneficial in reducing fibrosclerotic edema in patients with CVI[33]. Our study is the only study investigating the efficacy of subcutaneous lidocaine on pain and quality of life in patients with CVI. There is no publication concerning the injection treatment administered in order to reduce edema other than Lymdiaral® despite the fact that it is a study conducted with multiple agents used particularly for sclerotherapy as mesotherapy.

As a limitation of the study, since we recorded the measurements of femur and leg circumferences of patients to determine

their edema, it was not possible to subjectively detect swelling in the legs of patients. We could not have detected the reduction in edema in femur and legs objectively as well. However, as we stated in the discussion, the fact that patients received calcium dobesilate could affect the measurement results of leg edema since both calcium dobesilate and lidocaine reduce edema in the leg. However, clinically and with feedbacks we received from patients, we detected that swelling in legs reduced as well. Moreover, it was not possible to evaluate the favorable response to lidocaine with the biochemical markers in our study. The message our study gives could have been stronger with this evaluation. Even though staging with ultrasonography was performed in the beginning of the study, we did not perform ultrasonography for control. Due to wide biochemical effects of lidocaine, well-being with regard to disease stage could have been achieved. In future studies that we intend to conduct, we aim to increase the lidocaine dose and evaluate quality of life and pain for the purpose of control as well as to use measurement of leg circumference and ultrasonography.

As a conclusion, patients who were in stage 1–2 according to the CEAP classification and did not respond to conservative treatment benefited from subcutaneous injection treatment for 5 weeks. In the long-term follow-up, well-being was maintained until Month 6 in the injection group with regard to pain and quality of life. Therefore, we recommend injection treatment in certain intervals, according to the new treatment protocol we developed, in patients with early-stage CVI who do not respond to conservative treatment and in whom surgery is not considered.

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Conflicts of interest

None.

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