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Impact of exercise training on fatigue, severity of nocturnal leg cramps, and sleep quality in chronic venous insufficiency

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ABSTRACT

Objectives: The aim of this study was to investigate the effects of exercise training on fatigue, nocturnal leg cramps, and sleep quality in patients with chronic venous insufficiency (CVI).

Patients and methods: A total of 42 patients with CVI (5 males, 37 females; mean age: 47.3±10.5 years; range, 25 to 67 years) were included in the study. The patients were randomly allocated to the exercise (n=21) group or control (n=21) group. The exercise group received stretching and strengthening exercises for the lower extremities for six weeks. The control group did not receive any exercise training. The severity of pain and leg cramps was assessed using the Visual Analog Scale (VAS). The Fatigue Severity Scale (FSS) was used to determine the severity of fatigue, and the Pittsburgh Sleep Quality Index (PSQI) to determine the sleep quality. The assessments were performed at baseline and at the end of the study (Week 6).

Results: The outcome measures of the two groups were comparable at baseline ($p>0.05$). Following exercise training, reduced severity of pain and leg cramps, as well as fatigue and improved sleep quality were observed in the exercise group ($p<0.05$). Control group showed an increase in the severity of leg cramps and a reduction in sleep quality ($p<0.05$).

Conclusion: Exercise training reduces the severity of nocturnal leg cramps and leg fatigue and improves sleep quality. A regular exercise program can be a useful alternative treatment for the management of CVI symptoms.

Keywords: Exercise training, muscle cramps, muscle fatigue, sleep habits, varicose veins.

Chronic venous insufficiency (CVI) is a condition which affects the venous system of the lower limbs, characterized by various symptoms such as pain, night cramps, fatigue, a feeling of heaviness, edema, restlessness, itching and skin changes in the legs.[1] Venous diseases encompass a wide spectrum of clinical manifestations ranging from telangiectases that only cause aesthetic concerns to painful varicose veins and even severe ulcerations. Chronic venous insufficiency is a major health problem with a high prevalence in the community and results in poor quality of life, loss of productivity, and significant economic burden.[2,3]

The calf muscle pump is the main mechanism that ensures return of blood accumulating in the lower extremities back to the heart and is supported by the foot pump, the thigh pump and the respiratory pump mechanisms. The ankle joint, which is an essential component the calf muscle pump, enhances blood circulation with dorsal and plantar flexion movements.[4] Limited ankle mobility is among the factors that increases the severity of edema and venous reflux in CVI. Fibrotic tissue formation in the lower extremity restricts movement, particularly in the ankle joint. Due to this limitation, the calf muscle cannot

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be activated and the return of venous blood back to the heart becomes difficult.[4] Structured exercise programs are used as an alternative treatment option to reduce calf muscle dysfunction and abnormalities involved in the pathophysiology of CVI and for relief of its symptoms.[5]

Leg cramps are defined as painful involuntary muscle contractions that usually occur at night and cause discomfort. They can be caused by a number of neurological, myopathic and metabolic problems, while nocturnal leg cramps (NLCs) of unknown etiology can also be seen in CVI. No definite treatment is available for nighttime leg cramps which are known to reduce sleep quality.[6]

Positive effects of regular exercise on fatigue have been demonstrated in different health conditions and several populations. Regular exercise increases tolerance to lactic acid and reduces lactic acid production in the muscle. It also improves enzymatic activity and local blood circulation required for muscle contraction. Therefore, approaches that involve regular exercise are used for the management of various diseases.[7]

Chronic venous insufficiency may present with specific objective signs, including telangiectasia, varicose veins, pigmentation, atrophy, and skin ulceration.[8,9] However, these clinical signs are not present in a number of patients seeking medical advice for a variety of other symptoms, such as cramps, swelling, leg tiredness and uncomfortable sensations in the legs. Since most of the symptoms are often not disabling or severe, both patients and healthcare professionals frequently neglect this condition.[10]

In the literature, there is no study examining muscle cramps, leg tiredness, and sleep quality in patients with CVI. In the present study, therefore, we aimed to investigate the effects of exercise training on the severity of muscle cramps, sleep quality, and fatigue in patients with CVI.

PATIENTS AND METHODS

The design of this study was based on a pre-test versus post-test comparison of the method. A total of 50 patients who were diagnosed with CVI by a cardiovascular surgeon were screened. Eight patients not meeting the inclusion criteria were excluded from the study. Finally, a total of 42 patients (5 males, 37 females; mean age: 47.3±10.5 years; range, 25 to 67 years) were included. The patients were selected using simple random sampling by tossing a coin and allocated to either exercise group (n=21) or control group (n=21). Inclusion criteria were age over 18 years and a diagnosis of Class II, III or IV CVI according to the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification system.[11] Those with a history of ulceration, psychosomatic or neurological disorders and prior lower extremity surgery within the past three months were excluded from the study. There were no dropouts from the study during the study period. The exercise group received stretching and strengthening exercises for six weeks. Control group did not receive any exercise. All patients were informed about the nature and scope of the study and a written informed consent was obtained. The study protocol was approved by the Ethics Committee of Hasan Kalyoncu University, Institute of Health Sciences (No. 2017/03). The study was conducted in accordance with the principles of Declaration of Helsinki.

Study assessments

The severity of pain and muscle cramps was measured using the Visual Analog Scale (VAS). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Fatigue Severity Scale (FSS) was used to measure fatigue. All assessments were performed at baseline and at the end of the study (Week 6).

VAS-severity of pain and nocturnal cramps

The severity of pain and nighttime cramps was determined using the Turkish version of the VAS with demonstrated reliability and validity.[12] The VAS is a self-administered scale consisting of a 10-cm line with numerical statements. Patients rate the intensity of pain by marking their pain level on the line. The scores range from 0 (no pain) to 10 (unbearable pain). For the study, all patients were asked to mark the severity of their pain and muscle cramps on the VAS and assigned a score from 0 (no pain or no muscle cramps) to 10 (unbearable pain or muscle cramps).[12] The VAS scores for pain and muscle cramps were recorded and included in the statistical analysis.

FSS

The validated Turkish version of the FSS was used for the assessment of fatigue in the study population.[13] The FSS is a questionnaire consisting of nine items that are related to how fatigue interferes with certain activities. All items are scored on a seven-point scale where 1 point indicates “strongly disagree” and 7 points indicate “strongly agree”. The arithmetic mean of the responses to nine questions was calculated to derive the total score for each subject. A higher total FSS score indicates greater fatigue severity, whereas a lower FSS score indicates lower impact of fatigue.[13]

PSQI

Sleep quality was assessed using the validated Turkish version of the PSQI.[14] The scale consists of a total of 24 questions. Nineteen questions are self-rated by the individual and the latter five questions are rated by the bed partner. The self-rated questions comprise seven subdomains: sleep latency, sleep quality, sleep duration, habitual sleep efficiency, use of sleeping medication, sleep disturbances and daytime dysfunction.[14]

Each question is assigned a score between 0 and 3 points on a Likert scale where 0 point indicates no difficulty and 3 points indicate severe difficulty. The subdomain scores are summed to produce a global PSQI score. Possible maximum score is 21. A global score of ≤5 indicates good sleep quality.[14]

Exercise training

The components of the six-week exercise program used in the study included the following:

- Warm-up: ankle dorsiflexion and plantar flexion without bending the knees, and calf muscle stretching in long sitting position.
- Ankle dorsiflexion and plantar flexion against resistance band in long sitting position
- Standing on toes at upright position.
- Standing on toes with the toes pointed inwards at upright position.
- Standing on toes with the toes pointed outwards at upright position.
- Leaning the body toward the wall by bending the elbows at upright standing position (heel contact maintained) (wall push-up)
- Squat with the hands extended forward while standing upright.
- Cooling down: ankle dorsiflexion and plantar flexion with the knees straight out, calf muscle stretching in long sitting position.

Repetition and set numbers of the exercise program included 2 sets and 10 repetitions in the morning and evening three times a week for the first three weeks. In the last three weeks of the program, the same exercise program was performed five days a week without changing the repetition and set numbers.[15] Each session was completed in 30 to 40 min.

Statistical analysis

The study power and sample size calculation were performed using the G*Power version 3.1.9.7 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). Using the two-tailed hypothesis, α=0.05, a sample size of ≥17 per group were required. The study was completed with 21 patients in each group, assuming a dropout rate of 20% (d=0.8). At the end of the study, the effect size was found to be 1.78 compared to the control group, using the VAS-cramp (standard deviation [SD]). The study was designed to achieve 80% power, which was 99% after completion of the study.

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed in mean ± SD for the quantitative variables and in number and frequency for non-numerical variables. Whether the data followed a normal distribution was checked using the Kolmogorov-Smirnov test. Differences in pre-test and post-test values in the exercise and control groups were compared with the Student's t-test for normally distributed data. The paired samples t-test was used to analyze the data of pre-test and post-test values between group comparisons.[16] A p value of <0.05 was considered statistically significant.

RESULTS

All patients in the exercise group were female, and the control group consisted of 16 females and five males. Demographic and physical characteristics of the patients were similar between the groups (p>0.05)

Table 1. Demographic and physical characteristics of study population

	Exercise group (n=21)		Control group (n=21)			
	Mean±SD	Min-Max	Mean±SD	Min-Max	t	*p*
Age (year)	45.8±9.2	26-63	48.9±11.7	25-67	-0.935	0.355
Height (cm)	162.6±5.1	154-170	163.7±6.4	151-175	-0.608	0.547
Weight (kg)	70.7±10.7	(53-92	75.8±15.1	55-113	-1.252	0.218
BMI (kg/m^2)	26.8±4.1	20.7-37.4	28.2±4.4	19.8-37.7	-1.088	0.283

SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index.

Table 2. Inter-group and intra-group comparisons in terms of the severity of pain and nocturnal cramps, fatigue and sleep quality

	Exercise group (n=21)				Control group (n=21)				Between groups	
	Pre-test	Post-test			Pre-test	Post-test			Pre-test	Post-test
	Mean±SD	Mean±SD	t	*p*	Mean±SD	Mean±SD	t	*p*	*p*	*p*
VAS (pain)	5.95±1.6	3.8±1.6	9.312	0.001*	5.9±1.8	6.4±1.9	-1.672	0.110	0.857	0.001*
VAS (cramps)	5.1±2.1	3.1±1.6	5.898	0.001*	5.8±1.9	6.4±2.0	-2.434	0.024*	0.231	0.001*
FSS (score)	4.6±1.3	4.4±1.5	2.123	0.046*	5.2±1.0	5.4±0.7	-1.088	0.291	0.195	0.044*
Total PSQI (score)	8.6±2.5	6.3±2.2	4.951	0.001*	7.3±2.3	8.3±2.1	-3.008	0.007*	0.092	0.001*
PSQI subdomains (score)										
Sleep latency	1.9±0.7	1.4±0.6	4.264	0.000*	1.5±0.7	2.2±0.6	-0.439	0.666	0.087	0.471
Sleep quality	1.9±0.8	1.3±0.7	4.382	0.000*	1.9±0.8	1.5±0.7	-2.961	0.008*	1.000	0.000*
Sleep duration	1.0±0.4	0.9±0.5	1.000	0.329	1.0±0.6	1.2±0.6	-2.500	0.021*	0.770	0.054
Sleep efficiency	0.8±0.4	0.7±0.6	1.000	0.329	0.6±0.5	0.7±0.6	-1.000	0.329	0.182	1.000
Sleeping medication	0.3±0.7	0.3±0.6	1.000	0.329	0.2±0.4	0.3±0.5	-0.810	0.428	0.584	0.788
Sleep disturbances	1.6±0.6	1.1±0.5	3.990	0.001*	1.4±0.5	1.6±0.5	-1.706	0.104	0.165	0.005*
Daytime dysfunction	1.1±0.8	0.7±0.7	2.359	0.029*	0.8±0.6	0.9±0.5	-1.000	0.329	0.131	0.452

SD: Standard deviation; VAS: Visual Analog Scale; FSS: Fatigue Severity Scale; PSQI: Pittsburgh Sleep Quality Index; t: Student's t test; * p<0.05.

(Table 1). There were no comorbidities in 14 (33.3%) patients. Of the remaining 28 patients, 12 (28.5%) had hypertension, eight (19%) had asthma, five (9.6%) had a history of cardiac disease, and three (71%) had leg trauma.

According to the profession of the patients, 22 (52.3%) were housewives, seven (16.6%) were teachers, eight (19.1%) were working in private sector, three (7.1%) were civil servants, and two (4.7%) were nurses. Female patients had about three deliveries.

At baseline, the groups were comparable with respect to the intensity of pain and muscle cramps and FSS, total and subdomain scores of PSQI ($p>0.05$); however, significant differences were observed in all parameters at the end of the study ($p<0.05$) (Table 2). The intensity of pain and muscle cramps as well as FSS and PSQI scores were greater in the control group than in the exercise group ($p<0.05$). There were significant differences in sleep quality and sleep disturbances subdomain scores ($p<0.05$), except for sleep latency, sleep duration, habitual sleep efficiency, use of sleeping medication, daytime dysfunction of PSQI subdomain scores ($p>0.05$) (Table 2).

Intra-group comparisons showed improvements in the severity of pain and muscle cramps and FSS and PSQI scores during the study period in the exercise group ($p<0.05$). Also, the sleep quality, sleep latency, sleep disturbances, and daytime dysfunction of PSQI subdomain scores improved ($p<0.05$), but other subdomain scores did not change ($p>0.05$).

In the control group, no improvement was observed in FSS scores and the intensity of pain ($p>0.05$); however, there were significant differences in leg cramps and total PSQI score, and also in sleep quality and sleep duration subdomain scores ($p<0.05$). No change was observed in other subdomain scores ($p>0.05$) (Table 2).

DISCUSSION

In this study, we investigated the impact of exercise training on the severity of pain and cramps, sleep quality, and fatigue in patients with CVI and found that exercise training reduced the severity of pain and cramps and improved sleep quality in this group of patients.

With advancing age (i.e., after 40 years of age), vein walls may weaken and venous valves may lose their tone.[8] In line with this observation, our patients were over the age of 40 years, with a mean age of 45.8±9.2 years for the exercise group and 48.9±11.7 years for control group. In addition, a female preponderance was observed, with 37 (88%) females and 5 (12%) males, which reflects the higher prevalence of varicose veins in females than in males.[8]

Obesity is an important risk factor for the development and progression of CVI. Body mass index has been shown to correlate with the clinical severity of CVI among females[17] Individuals with a greater number of venous segments affected by reflux were reported to have a higher BMI than those with a few affected segments or no reflux.[18] Lack of physical activity, venous flow restriction, sedentary lifestyle, limited ankle range of motion, and calf muscle dysfunction are among the factors that increase the clinical severity of CVI in obese patients.[19] Obese women were reported to have higher levels of estrogen compared to non-obese women.[9] Intravascular volume expands and venous return becomes more difficult due to the increased estrogen level and adipose tissue. In the present study, the patients in both groups were overweight, which may have contributed to the development of CVI.

There is a close relationship between pain and CVI severity. Several theories have been proposed to explain the pathophysiology of pain occurring in CVI including sensory innervation changes in vein walls, increased venous pressure on the neural membrane, and ischemia of the capillaries.[20] As an adaptation to the improvement of aerobic capacity with exercise training, increased tolerance to ischemic environment may occur due to decreased blood flow velocity and reduced oxygen demand.[21] Additionally, regular exercise may reduce the release of substance P, an excitatory neurotransmitter, which is increased in painful muscles and causes an increase in the pain threshold.[22,23]

Increased severity of pain and cramps in the control patients who did not exercise supports the aforementioned considerations. It was expected that the control group would not experience an increase in pain threshold and positive effects of exercises on the circulatory system would not occur.[23] Studies examining exercise in CVI have reported that implementation of exercises to strengthen calf and quadriceps muscles reduce pain intensity.[24] In one study, reduced pain severity was achieved using a combined exercise program including an isokinetic exercise device, Thera-band, balance, and stretching exercises.[25]

Nocturnal leg cramps are a common problem which affects sleep quality adversely. Patients with painful NLC episodes experience a variety of sleep disturbances including frequent awakening at night, insufficient sleep time and daytime sleepiness.[26] Muscle cramps are caused by factors such as abnormal motor nerve excitability, electrolyte imbalance, and use of diuretics and steroids. While there is no established method for the treatment of muscle cramps in the clinical setting, medical therapy and stretching exercises are prescribed to sufferers.[27] Reduced muscle and tendon length is considered a mechanical factor.[26] In particular, stretching exercises can cause an abrupt interruption of muscle cramps induced by increased muscle length and after nerve block by electrical stimulation distal to the block. Additionally, stretching of the muscle or contraction of the antagonist muscle provides fast relief from cramps.[28,29] This is consistent with the current study finding that the severity of NLCs was reduced with the use of stretching exercises in patients with CVI.

In the present study, exercise training decreased leg fatigue. Venous hypertension leads to pathophysiological changes in the gastrocnemius muscle by reducing the pump function of the calf muscle. Pathological changes in the gastrocnemius muscle include muscle cell denaturation and necrosis, elevation of lactic acid concentration, infiltration of inflammatory cells, involvement of muscle fibers and impairment of mitochondrial structure.[30] Abnormal cytosolic calcium ions result in muscle dysfunction, impaired muscle contraction mechanism, physiological elevation of calcium ions, slower relaxation, mitochondrial damage, disorganization of myofibrils, and muscle weakness. Moreover, alterations in the pH and enzymatic activity of the muscle occur in the presence of elevated lactic acid levels. These pathophysiological changes are responsible for leg fatigue in patients with CVI. Exercise delays accumulation of lactic acid in the blood and muscles and improves lactic acid tolerance by enabling earlier removal of lactic acid from the bloodstream.[31] Strengthening exercises improve muscle function by stimulating intramuscular mitochondrial activity and protein synthesis. We believe that physiological and mitochondrial adaptation to exercise in muscle fibers, myofibrillar hypertrophy, regulation contraction and relaxation mechanism could increase muscle pump function and prevent fatigue.[32]

The key strength of the present study is the ability to demonstrate a reduction in CVI symptoms. However, if we could objectively measure the improvement (e.g., strength and flexibility) in the musculoskeletal system achieved by our exercise program, it would provide us further quantitative data. In addition, muscle biopsies along with an analysis of biochemical parameters could help us to better characterize the effects of exercise on the musculoskeletal system and explain the improvement in CVI symptoms. Our exercise program focused on calf muscle strengthening and stretching. However, if we could add exercises for other large muscles of lower extremity, it may have been more effective for the relief of CVI symptoms. Nevertheless, we believe that our study is valuable, since it clearly demonstrates beneficial effects of a regular exercise program on CVI symptoms.

In conclusion, regular strengthening and stretching exercises can reduce CVI symptoms such as pain, leg tiredness, or NLCs and improve sleep quality. Inclusion of regular exercise programs in treatment plans may be helpful for the management of this condition.

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