

THE EFFECTS OF MANUAL LYMPHATIC DRAINAGE ON LOCAL TISSUE WATER RATES AND QUALITY OF LIFE IN INDIVIDUALS DIAGNOSED WITH CHRONIC VENOUS DISEASE WITH AND WITHOUT VENOUS REFLUX: A PILOT STUDY

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ABSTRACT

Manual Lymphatic Drainage (MLD) is an alternative treatment approach that can be used in individuals diagnosed with Chronic Venous Disease (CVD). **Aim:** To examine the effects of MLD on local tissue water rates and quality of life in individuals diagnosed with CVD with and without venous reflux. **Methods:** Ten patients were included into the study. The individuals were divided into two groups as CVD with venous reflux (group 1) and CVD without venous reflux (group 2) according to the venous reflux greater than 0.5 seconds. The water percentages in the local tissue were measured with the MoistureMeterD Compact device. Quality of life (QoL) was assessed with the Venous Insufficiency Epidemiologic and Economic Study Quality-of-Life Questionnaire (VEINES-QOL/Sym). Symptom score increased from 28 (23-39) to 31 (28-42), and total QoL score improved from 49 (34-55) to 51 (46-60) significantly in Group 1. Symptom score increased from 35 (26-38) to 39 (28-43), and total QoL score improved from 50 (45-61) to 54 (52-65) significantly in Group 2 ($p<0.05$). There was no more significant improvement in QoL in any groups ($p>0.05$). When groups were compared, Group 2 had a significant improvement with MLD only in local tissue water percentage of 6 cm above the right medial malleolus ($p<0.05$). **Conclusion:** It was thought that MLD could provide a relief in the symptoms and an improvement in QoL, independent of the presence of venous reflux. It was concluded that there is a need for further studies that detect the change of local tissue water with MLD in more patients diagnosed with CVD.

Keywords: Venous insufficiency, Manual lymphatic drainage, Edema, Quality of life

VENÖZ REFLÜSÜ OLAN VE OLMAYAN, KRONİK VENÖZ HASTALIK TANILI BİREYLERDE MANUEL LENF DRENAJININ LOKAL DOKUDAKİ SU ORANLARI VE YAŞAM KALİTESİ ÜZERİNE ETKİLERİ: PİLOT ÇALIŞMA

ÖZ

Manuel Lenf Drenajı (MLD), Kronik Venöz Hastalık (KVH) tanılı bireylerde kullanılabilecek alternatif bir tedavi yaklaşımıdır. Venöz reflüsü olan ve olmayan, KVH tanılı bireylerde MLD'nin lokal dokudaki su oranları ve yaşam kalitesi üzerine etkilerinin incelenmesidir. Çalışmaya 10 hasta dahil edilmiştir. Venöz reflünün 0,5 sn üzerinde olmasına göre bireyler venöz reflüsü olan KVH (Grup 1) ve venöz reflüsü olmayan KVH (Grup 2) şeklinde iki gruba ayrılmıştır. Lokal dokudaki su yüzdeleri MoistureMeterD Compact cihazı ile ölçülmüştür. Yaşam kalitesi Venöz Yetmezliğin Epidemiyolojik ve Ekonomik Çalışması: Yaşam Kalitesi/Belirtiler Ölçeği ile değerlendirilmiştir. Grup 1'de semptom skoru 28 (23-39)'den 31 (28-42)'e ve toplam yaşam kalitesi skoru 49 (34-55)'den 51 (46-60)'e anlamlı olarak yükselmiştir. Grup 2'de semptom skoru 35 (26-38)'den 39 (28-43)'a ve toplam yaşam kalitesi skoru 50 (45-61)'den 54 (52-65)'e anlamlı olarak artmıştır. ($p<0.05$). Yaşam kalitesinde gruplar arasında iyileşme açısından daha anlamlı bir fark yoktur ($p>0.05$). Gruplar karşılaştırıldığında, Grup 2'de MLD ile sadece sağ medial malleolün 6 cm yukarısı için lokal doku su yüzdesinde anlamlı bir iyileşme saptanmıştır.

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Geliş tarihi/Received: 08.01.2022

Kabul tarihi/Accepted: 28.02.2022

DOI: 10.52881/gsbdergi.1055086

($p < 0.05$). MLD'nin venöz reflü varlığından bağımsız olarak semptomlarda rahatlama ve yaşam kalitesinde iyileşme sağlayabileceği düşünülmüştür. KVH tanısı alan daha çok sayıda hastada MLD ile lokal doku suyunun değişimini tespit eden ileriki çalışmalara ihtiyaç olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Venöz yetmezlik, Manuel lenfatik drenaj, Ödem, Yaşam kalitesi

INTRODUCTION

Chronic Venous Disease (CVD) is a morphological or functional disorder of the venous system with long-term symptoms (1) that contain pain, cramps, heaviness, burning, tingling; and/or signs that include telangiectasias, varicose veins, edema, skin changes, or venous ulcers in the extremities (2). Chronic Venous Insufficiency (CVI), defined as more advanced conditions of venous disease involving pain, edema, skin changes, and ulcerations, is characterized by venous hypertension (3). The quality of life (QoL) of these patients is affected by the symptoms (4).

In CVI, blood filtration increases due to the effect of inflammation, endothelial permeability, and increased intravascular hydrostatic pressure (5). The lymphatic system tries to compensate for this situation. Mixed edema with venous and lymphatic components develops in approximately 20-30% of patients due to the load on the lymphatic system as a result of excessive fluid increase (6).

Method to assess the changes in local tissue water can be used to demonstrate localization and differences in edema. The measurement evaluation of tissue water ratios can be more sensitive and used to show post-treatment changes (7).

Prevention of stasis by increasing venous return is the main goal in the treatment of CVD and is decisive in the prevention of venous complications (8). Many disease-related symptoms negatively affect the QoL

in patients with CVI (4). Rehabilitation of individuals diagnosed with CVI aims to prevent the progression of venous disease and complications of the disease, reduce symptoms, and increase QoL (9). Various treatment approaches increase the QoL in these patients (9,10). A conservative treatment for CVI, Manual Lymphatic Drainage (MLD) is a low-pressure skin stretching massage (11), as an adjunct to other treatments such as compression stockings and surgery (12,13).

MLD may avoid stasis and complications by increasing peripheral venous blood flow in superficial and deep veins in healthy and CVD-affected extremities (14-16), reduce tissue edema and inflammation by increasing venous flow and lymphatic resorption (17). In a study, measuring the water ratios in the tissue before and immediately after a session of MLD implementation, a slight change was shown in the measurements of tissue water ratio (7). In addition, MLD, which is effectively used in the treatment of lymphedema, can be an alternative to strategies such as exercise that can be used in the treatment of CVI patients (15).

It has been shown that MLD improves the QoL by decreasing the severity of the disease and the volumes of the feet and legs (12). Improvements in QoL, symptoms, and disease severity were observed after the treatment with MLD. Studies examining the effects of MLD were limited in the literature (12-14). To the best of our knowledge, there has been no study examining the effects of

video MLD-based telerehabilitation in CVD patients.

This study aimed to examine the effects of MLD on local tissue water rates and quality of life in individuals diagnosed with CVD with and without venous reflux.

MATERIALS AND METHOD

Patients with CVD who applied to Gazi University Cardiovascular Surgery Department and were referred to the Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation for physiotherapy recommendations were informed about the study and invited to participate. Ten voluntary participants were included in the study after signing informed consent. This study was approved by Gazi University Non-Interventional Clinical Research (March 9, 2020, No.24074710-604.01.01).

CVD was diagnosed by the physician as a result of Color Doppler Ultrasonography. In addition, the presence of reflux and the duration of reflux were measured. The patients were divided into two groups: Group 1 (CVD with venous reflux) and Group 2 (CVD without venous reflux) according to the presence of venous reflux. The cut-off value for venous reflux was defined as greater than 0.5 seconds of reflux in the vena safena magna and parva, and perforating veins (18).

Inclusion criteria:

- To be older than the age of 18,
- To have a diagnosis of CVD, and
- To get a score between C1-3 according to the “Clinical, Etiology, Anatomy, Pathophysiology” (CEAP) classification. CEAP (C0: No visible and palpable signs of venous disease, C1: Telangiectasias

or reticular veins, C2: Varicose veins, C3: Edema, C4: Skin changes, C5: Healed ulcer, C6: Active ulcer) is a frequently used classification in patients with CVD (19).

Exclusion criteria:

- To have a diagnosis of acute venous disease (deep vein thrombosis) and
- To have any infection, diagnosis of cardiac, rheumatologic, hematologic diseases, and/or malignancy that may lead to non-implementation of MLD.

The same treatments and evaluations were applied to both groups.

Treatment Methods

Patient Education: Each group was informed about the advice that they could apply in daily life that could help them cope with the disease, and suggestions were made. Suggestions include choosing appropriate shoes and clothing, avoiding hot weather, keeping the skin moist and avoiding sitting and/or standing for long periods of time, etc. (9). In addition, the patients were advised that they could perform pumping exercises. These pumping exercises consist of ankle dorsi flexion and plantar flexion, hip/knee flexion, and extension which were reported by Gardner and Fox (20) to increase venous return.

Simple MLD: This is a simplified version of MLD that the patient can apply by herself/himself (21). The purpose of this application is to stimulate the lymphatic system. While teaching simple MLD to the patients, there are some stages such as giving information about MLD, explaining by applying it on the patient by the physiotherapist, and controlling the self-implementation of the patient. In addition,

the video of the simple MLD performed by the same physiotherapist on herself was sent to the patients as a part of telerehabilitation applications. The patients could achieve physiotherapist during and after video session of MLD. The questions that the patient wanted to ask about MLD were answered once a week, and repeated controls were performed to determine how she/he applied it. Evaluation and patient education could be applied in a single session by taking the necessary precautions as a result of the coronavirus disease (Covid-19) pandemic. The patients were asked to perform the simple MLD implementation for 6 weeks, 5 days a week. It was recorded how many times she/he could perform this implementation until the second evaluation.

Evaluation Methods

Demographic and Clinical Information: Demographic and clinical information of the patients (age, height, body weight, disease duration, treatments, and venoactive drug use) were recorded. Body Mass Index (BMI) was calculated according to the formula of weight (kg)/height (m²) (22).

Measurements of Local Tissue Water: The measurements of local tissue water were performed with the MoistureMeterD Compact device (MMDc, Delfin Technologies, Kuopio, Finland) by calculating the tissue dielectric constant. This device can measure the water content of the tissue at a depth of 2.5 mm. The MoistureMeterD Compact device can measure 6 cm above the medial malleolus and on the dorsum of the foot between the 1st and 2nd toes (23). Gentle pressure was applied to these designated points, and the measurement was finished when the audible signal arrived. Three measurements were

made for each reference point, and the average of the measurements was determined.

Evaluation of Quality of Life: Health-related QoL was evaluated with the “Venous Insufficiency Epidemiologic and Economic Study Quality-of-Life Questionnaire (VEINES-QOL/Sym)”. This scale consists of 26 items and is based on the self-report of the patient. VEINES-QOL/Sym evaluated the effect of CVI on the patient's symptoms and QoL. The first 10 items are about the symptoms including fullness, pain, swelling, night cramps, warmth/burning sensation, restless legs, itching, tingling/pins, and throbbing in the lower extremities. The patient chooses the frequency of these symptoms with 5 different frequencies as “always, several times a week, once a week, every few weeks, and never”. Other items consist of limitations in daily activities (8 items), the most intense time of the day for leg problems (1 item), changes in the last 1 year (1 item), leg pain (1 item), social limitation (1 item), and psychological effects (5 items). The question about “At what time of the day are your leg problems most intense” provides descriptive information and is not included in the scoring. As a result of the evaluation, 2 different scores are obtained in the general QoL and symptom categories in the form of VEINES-QOL/Sym, in which higher scores indicate better results (24,25). The Turkish validity and reliability of this scale was published by Çırak et al. (26).

Statistical Analysis

The data were analyzed with the IBM SPSS Statistics 21.0 program. Continuous variables median (minimum-maximum) and categorical variables were expressed as numbers (n) and percentages (%). “Mann Whitney U” and “Chi-square” tests were

used to compare the demographic and clinical characteristics of the two groups. Since there was a significant difference in BMI between the groups when the Group 1 and 2 were compared, the "ANCOVA" test was used to compare the differences

between the two groups. The pre-and post-treatment changes within the group were analyzed with the "Wilcoxon" test. In all analyses, $p < 0.05$ was considered statistically significant.

RESULTS

Ten patients, 9 female, and 1 male were included into the study. The demographic characteristics of the patients and other descriptive characteristics associated with the disease are shown in Table 1. When the

demographic characteristics of the two groups were compared, a significant difference was found between the groups in terms of BMI ($p < 0.05$).

Table 1. Demographic and clinical information of patients

		Group 1 (n:5) Median (Min-Max)	Group 2 (n:5) Median (Min-Max)	P
Age (years)		41 (30-44)	31 (27-41)	0.115 ^a
Body Mass Index (kg/m ²)		29.24 (27.48-31.96)	23.24 (22.68-26.54)	0.009 * ^a
Disease Duration (years)		3 (2-17)	10 (2-15)	0.750 ^a
Total Number of Manual Lymphatic Drainage Implementation		20 (14-24)	15 (14-24)	0.421 ^a
		n (%)	n (%)	p
Gender	Female	5 (%100)	4 (%80)	1.000 ^b
	Male	0 (%0)	1 (%20)	
Family history of venous disease	No	0 (%0)	1 (%20)	1.000 ^b
	Yes	5 (%100)	4 (%80)	
Treatments	No	4 (%80)	2 (%40)	0.264 ^b
	Compression	1 (%20)	1 (%20)	
	Endovenous Laser Ablation		2 (%40)	
Venoactive Drug Use	No	4 (%80)	4 (%80)	1.000 ^b
	Yes	1 (%20)	1 (%20)	

Group 1: Chronic venous disease with venous reflux, Group 2: Chronic venous disease without venous reflux, Min: Minimum, Max: maximum, n: numbers, a: was used "Mann-Whitney U" test, b: was used "Chi-square" test,

The changes in the local tissue water and QoL parameters of the CVD with/without venous reflux before and after simple MLD are shown in Table 2. Although there was a decrease in local tissue water (%) with

simple MLD in Group 2, this decrease was not statistically significant ($p > 0.05$). There was no decrease in local tissue water (%) with simple MLD ($p > 0.05$) in Group 1.

Table 2. Changes in the local tissue water percentages and quality of life parameters before and after simple MLD in the Group 1 and 2

	Group 1			Group 2			
	Before Simple MLD Median (Min- Max)	After Simple MLD Median (Min- Max)	P	Before Simple MLD Median (Min- Max)	After Simple MLD Median (Min- Max)	P	
Local Tissue Water Percentages	Right Foot (on the Dorsum of the Foot Between The 1st and 2nd toes)	39.17 (30.50-40.20)	38.00 (33.03-41.63)	0.686	29.97 (26.07-37.93)	30.00 (23.20-34.83)	0.225
	Left Foot (on the Dorsum of the Foot Between the 1st and 2nd Toes)	38.50 (29.60-44.80)	38.33 (33.10-45.20)	0.345	33.27 (27.00-39.23)	34.10 (22.60-36.97)	0.345
	6 cm Above the Right Malleolus	37.97 (32.87-42.70)	38.07 (31.73-39.90)	0.345	38.13 (33.53-44.83)	33.43 (32.83-41.10)	0.225
	6 cm Above the Left Malleolus	38.50 (34.93-45.03)	38.23 (34.17-41.73)	0.080	37.53 (35.30-44.47)	34.10 (31.97-41.47)	0.138
	Venous Symptoms Change Over a Year	28 (23-39)	31 (28-42)	0.043*	35 (26-38)	39 (28-43)	0.042*
Parameters of Venous Insufficiency Epidemiologic and Economic Study Quality-of-Life Questionnaire	Limitations in Activities of Daily Living	14 (13-16)	16 (12-19)	0.221	16 (15-20)	17 (16-20)	0.102
	Social Impact of Venous Disease	4 (3-5)	5 (4-5)	0.180	5 (4-5)	5 (4-5)	1.000
	Intensity of Pain Felt	3 (2-4)	3 (3-5)	0.102	4 (3-5)	4 (3-6)	0.083
	Psychological Effect of Venous Disease	26 (13-28)	26 (20-28)	0.655	22 (21-28)	25 (21-30)	0.102
Total Score of Quality of Life	49 (34-55)	51 (46-60)	0.039*	50 (45-61)	54 (52-65)	0.042*	

Group 1: Chronic venous disease with venous reflux, Group 2: Chronic venous disease without venous reflux, MLD: Manual Lymphatic Drainage, Min: Minimum, Max:maximum

Although improvement was observed in all sub-parameters of VEINES-QOL except social limitation with simple MLD implementation, there was a statistically significant improvement only in symptom and total QoL scores ($p < 0.05$) in Group 2. When the patients were asked “At what time of the day are your leg problems most

intense”, all patients answered as “at the end of the day” in Group 2.

Although improvement was observed in all sub-parameters of VEINES-QOL with simple MLD, only the increases in symptom and QoL scores were statistically significant ($p < 0.05$) in Group 1. When the patients were asked “At what time of day

are your leg problems most intense”, 3 patients (60%) answered as "at the end of the day", 1 patient (20%) "overnight", and 1 patient (20%) "any time of the day" in Group 1. When both groups were compared, there was a significant

improvement in local tissue water percentage only for 6 cm above the right medial malleolus with MLD in Group 2 ($p < 0.05$) and no significant difference between the total QoL and parameters of QoL ($p > 0.05$) (Table 3).

Table 3. Comparison of difference values of local tissue water percentages and quality of life parameters of both groups

		Group 1 Adjusted Mean (95% CI)	Group 2 Adjusted Mean (95% CI)	p
Local Tissue Water Percentages	ΔRight Foot (on The dorsum of The Foot Between The 1st and 2nd toes)	-1.08 (-6.42 – 4.25)	-0.36 (-5.69 – 4.97)	0.863
	ΔLeft Foot (on The Dorsum of the Foot Between The 1st and 2nd Toes)	0.61 (-5.05 – 6.26)	-1.27 (-6.93 – 4.38)	0.676
Parameters of Venous Insufficiency	Δ6 cm Above The Right Malleolus	3.94 (-1.62 – 9.50)	-7.47 (-13.03 – -1.91)	0.031*
	Δ6 cm Above The Left Malleolus	2.38 (-3.72 – 8.47)	-7.08 (-13.17 – -0.99)	0.081
Epidemiologic and Economic Study	ΔVenous Symptoms	2.59 (-2.74 – -7.93)	6.21 (0.87 – 11.54)	0.403
	ΔChange over a Year	1.42 (-0.58 – 3.42)	0.58 (-1.42 – 2.58)	0.602
Quality-of-Life Questionnaire	ΔLimitations in Activities of Daily Living	-0.70 (-2.44 – 2.30)	1.87 (-0.50 – 4.24)	0.319
	ΔSocial Impact of Venous Disease	0.32 (-0.80 – 1.44)	0.28 (-0.84 – 1.40)	0.970
Life	ΔIntensity of Pain Felt	0.27 (-0.88 – 1.43)	1.13 (-0.03 – 2.28)	0.363
	ΔPsychological Effect of Venous Disease	-0.85 (-4.82 – 3.12)	3.45 (-0.52 – 7.42)	0.198
	Δ Total Score of Quality of Life	1.20 (-4.63 – 7.03)	7.40 (1.57 – 13.23)	0.205

Group 1: Chronic venous disease patients with venous reflux, Group 2: Chronic venous disease patients without venous reflux, ANCOVA: values were adjusted BMI

DISCUSSION

In this study, it was revealed that simple MLD, applied as telerehabilitation, had different effects on local tissue water ratio and the QoL (symptoms associated with venous disease and general) in the stages where venous diseases were mild or slightly more severe in the chronic period. Due to the Covid-19 pandemic conditions, the number of cases had to be limited. Although results did not reach a statistically significant level, improvements in QoL were achieved in this pilot study. This is the first known study in the literature examining the effects of simple MLD on local tissue water in CVD patients with/without venous reflux.

Water percentages in the local tissue showed a more significant decrease in the CVD without venous reflux group than in the CVD with venous reflux group with simple MLD. It was thought simple MLD was insufficient for fluid absorption from local tissue in CVD patients with venous reflux. It was determined that both venous symptoms and QoL improved with simple MLD implementation in both groups, but more improvement in QoL in the CVD with venous reflux, which is the more advanced stage of venous disease.

When the acute effect of MLD is examined in patients with lymphedema in one or both legs, it has been shown that there is a slight

decrease of 1.5%, and the calculation of local tissue water (%) is sensitive in the acute effect of MLD (7). Since MLD is an implementation performed by a physiotherapist in a clinical setting, simple MLD has an important place in the follow-up of the CVI-related lymphedema, which is a life-long disease, and in maintaining the effects of the treatment (27). In this study, the long-term outcome of simple MLD in CVD patients was examined, and it was observed that although it did not reflect statistics in most reference point in the CVD without venous reflux group, it provided a greater reduction in local tissue water (%) than in the CVD with venous reflux group. Venous edema in CVD with venous reflux may accompany by lymphatic edema more often than in the CVD without venous reflux group, and edema may be more permanent in CVD with venous reflux.

In addition, higher symptom scores and more frequent complaints such as fullness and swelling in CVD patients with venous reflux supported the information that edema is more persistent and intense. It was thought that simple MLD might help water absorption from the tissue in the early stages of the venous disease, while it might be more beneficial in the QoL and control of symptoms in the CVD with venous reflux stage.

Symptoms in the lower extremity in CVI patients may not have a specific venous origin and may also be associated with inflammation in the tissue. Hypoxia and a decrease in venous flow occur by the adhesion of leukocytes to the endothelium. As a result, large amounts of inflammatory mediators released into the vessel wall, and interstitial space (responsible for changes in the skin) are known to initiate the process. Such inflammatory mediators are

hypothesized to be responsible for pain and restless legs due to their stimulation of nociceptive nerve endings in the skin and other tissues (17). MLD can reduce tissue edema and leukocyte-endothelial inflammatory reaction by increasing venous flow (28) and lymphatic reabsorption (29). It has been reported in the literature that there is relief in the pain sub-parameter of QoL and edema (14). In this study, pain and local tissue water ratio did not change significantly, but improvements in venous symptoms and VEINES-QOL total scores were observed. In future studies, a statistically significant difference can be achieved with larger patient groups.

It has been reported that when MLD was applied before surgery in venous disease patients, some improvements in CEAP classification, QoL, depression, anxiety, and symptoms were obtained (12-14). In this study, while there were statistically improvements in the symptoms parameter and general QoL with simple MLD, no statistically improvement was recorded in the psychological parameter of QoL. The CVD with venous reflux group was more advanced in the CEAP clinical class, but there was no more significant change in QoL in this group. It can be suggested that MLD is a more effective treatment modality than simple MLD in controlling CVD symptoms.

It has been reported that fast recovery can be achieved with MLD applied after the surgery in patients with a diagnosis of CVD (13). In another study, improvements in CVD-related symptoms, pain, and QoL, clinical severity (mostly associated with venous edema) were achieved with MLD, independent of vascular surgery, with outcomes of MLD persisting after 1 month follow-up. However, it revealed that MLD

had no effect on changes in lower extremity volume and the physical, social, or psychological components of QoL (14). Similarly, no statistically improvement was noted in the social and psychological components of QoL in this study. Although this situation provides a varying rate of improvement in patients, it was thought that MLD or simple MLD alone was insufficient in the wide-effective sub-parameters of QoL.

It is recommended that MLD can be used for edema, relief of symptoms and severity of the disease, and improvements in QoL. It emphasizes that these positive effects are more sustained and effective when applied with MLD compression therapy (12-14). In situations where compliance with compression therapy is difficult, MLD may be an option for symptom relief and improving QoL in patients with CVD (14). Owing to the fact that simple MLD application could be performed as telerehabilitation due to Covid-19 pandemic conditions, this study become the first telerehabilitation application for patients with CVD. It was thought that examining the results would contribute to the literature since telerehabilitation is frequently used for rehabilitation of the patients.

CONCLUSION

In conclusion, it was reported that by increasing local tissue fluid absorption with simple MLD, symptoms of CVD such as fullness, pain, swelling, and night cramps can be relieved, and QoL might be improved.

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Future studies should evaluate changes in local tissue water, symptom relief, and improvement in QoL with simple MLD with a larger number of patients in more advanced CVD patients with venous reflux.

Limitations

The simple MLD, which was requested to be applied to the patients 5 times a week, was applied less frequently by the patients. This prevents simple MLD from achieving effective results. Ensuring the promotion of simple MLD with more regular applications can increase its positive effects, decrease the local tissue water (%), the psychological and social limitation of the QoL, and the leg pain.

Researchers' Contribution Rate Statement

Idea: ESE, İK; Design: ESE, İK; Data Collection: ESE, AÖ, EC; Statistical analysis of the data: ESE; Literature review: ESE, İK; Article writing: ESE, İK; Critical review: ESE, İK, AÖ, EC.

Financial Support/Acknowledgements

Elif Sakızlı Erdal was a TUBITAK PhD scholar during her doctoral education. This study is part of a doctoral thesis. We would like to thank TUBITAK for its contributions.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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