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A Randomized Controlled Trial Comparing Platelet-Rich Plasma, Low-Level Laser Therapy, and Complex Decongestive Physiotherapy in Patients with Lower Limb Lymphedema

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Abstract

Background: Platelet-rich plasma (PRP) is an autologous concentrated preparation of platelets characterized by lymphangiogenetic and tissue-repairing effects. Although PRP has been safely used in many different fields, there is no clinical study regarding the use of PRP in lymphedema treatment in humans. We assessed the clinical outcomes of PRP in patients with lower extremity lymphedema (LEL) in a randomized controlled trial.
Methods and Results: Patients with secondary LEL were randomly allocated to one of three groups consisting of treatment with PRP with complex decongestive physiotherapy (PRP+CDP group), low-level laser therapy with CDP (LLLT+CDP group), and only CDP (CDP group). Assessment of Lymphedema Quality of-Life Questionnaire (LYMQOL) for health-related quality of life, lower-extremity-circumference (LEC) for edema, tissue dielectric constant (TDC) for extremity volume, 6-minute walking test (6MWT) for functional capacity, and numeric rating scale (NRS) scoring for extremity fullness were evaluated both before and after treatment. Forty-five patients (68.8% female) with mean age 40.84 ± 15.81 years were included in the study. Significant differences in LYMQOL, LEC, NRS, and TDC values both before and after treatment were found in all groups; however, there were no statistically significant difference in values between the three groups. In the PRP+CDP group, LYMQOL values had a larger effect size than the other two groups. Significant differences in 6MWT values both before and after treatment were found in PRP+CDP and LLLT+CDP groups; however, there was no statistically significant difference in the CDP group.
Conclusion: This is the first clinical study to evaluate the usage of PRP in patients with secondary LEL. PRP might be an additional treatment option of lymphedema management; however, more clinical trials in humans are needed to yield more evidence in the usage of PRP in patients with lymphedema.

Keywords: secondary lymphedema, platelet-rich plasma, low-level laser therapy, complex decongestive physiotherapy, QoL

Introduction

Lower extremity lymphedema (LEL), either primary or secondary form, presents as chronic unilateral or bilateral swelling of the lower limbs, which may be accompanied with pain, tissue fibrosis, and associated skin changes (e.g., skin thickening and hyperpigmentation).[1] Primary lymphedema occurs in ~ 1 in 100,000 people, and it is the result of genetic abnormality in the network of the lymphatic system.[2] Secondary lymphedema is more common, and it is mainly the consequence of cancer treatment, trauma, inflammation, and parasitic infections.[3]

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Functional deficits might occur in an extremity as a result of an increased feeling of fullness, pain, and development of skin and subcutaneous tissue infections as well as increased body weight. Musculoskeletal problems such as hip, back, and knee joint pain are secondary complications. The combination of mentioned factors significantly affects patient psyche and self-perception, thus it reduces the patient's quality of life.[4]

The current standard care for lymphedema is complex decongestive physiotherapy (CDP).[2] It has two stages:

The first stage is performed by a certified physiotherapist, which includes manual lymphatic drainage (MLD), compression therapy, exercise, and skin care.[2,5,6] MLD is performed to redirect lymphatic flow toward the nearest lymph nodes. Compression therapy is performed to increase pressure by bandaging or compression garments.

The second stage consists of self-administered lymphatic massage, usage of compression garments, and continuation of the exercises.[6]

Although the CDP is available for decreasing symptoms and physical findings of lymphedema, new therapies and efforts are being performed to stimulate new lymphatic vessels by lymphangiogenesis. Since the 1990s, low-level laser therapy (LLLT) has been suggested as a complement to lymphedema treatment.[7,8] Therapeutic light in the red to near-infrared spectral range is believed to stimulate lypmhangiogenesis, motility of the lymphatic system, and action of macrophages and the immune system, and to reduce lymphostatic fibrosis.[9]

We believe that one of the main targets of future lymphedema therapies might be the formation of undamaged lymphatic vessels and/or lymph nodes.

Platelet-rich plasma (PRP) has been safely used and documented in many different fields, including orthopedics, sports injuries, dental/periodontal, cosmetic, plastic, cardiovascular, general, and maxillofacial surgery. The relevance of platelets for lymphangiogenesis and tissue repair has been described recently.[10] It was shown that platelets take the lead in the separation between lymphatic and blood vessels during the embryonic development.[11] The current evidence obtained from *in vitro* and animal studies pointed out that PRP may potentially be used to regenerate injured lymphatic vessels to treat or prevent lymphedema. There is no clinical study regarding usage of PRP in lymphedema treatment in humans; however, based on animal studies, PRP might be a new therapeutic alternative in lymphedema treatment.[12]

The aim of this study is to evaluate the effectiveness of PRP treatment in lymphedema and to compare the PRP with LLT and CDP treatments. To our knowledge, this is the first clinical trial assessing the effectiveness of PRP by comparing it with different treatment methods in patients with lower limb lymphedema.

Methods

Study design and setting

The study used a prospective randomized design. Approval of the study was obtained from the ethical committee (The Research Ethics Committee of Bakırköy Dr. Sadi Konuk Research and Training Hospital, Protocol No.: 2016-199, Decision No: 2016/08/02, Date: June 29, 2016), and the study was conducted in accordance with the Declaration of Helsinki. Patients attending the Istanbul University Faculty of Health Science Division of Physiotherapy and Rehabilitation, Istanbul, Turkey between July 2016 and May 2018 were included in this study. All participants were informed about the study and signed an informed consent form.

The eligibility criteria were patients aged 18–65 years (mean age 40.84 ± 15.81) with unilateral mild-moderate degreed secondary (due to trauma and/or inflammation) LEL. Patients who had primary lymphedema, active infection, severe cardiac disease, malignity, hypertension, musculoskeletal problems affecting lower extremity, and incapacity to comprehend implications were excluded from the study.

Forty-five patients with LEL were enrolled in the study. Computer-generated randomization was performed, and patients were divided into three groups:

1. PRP+CDP group; patients in whom LEL treatment was performed with PRP and CDP,
2. LLLT+CDP group; treatment was performed with LLLT and CDP,
3. CDP group; only CDP was used.

A-participant-flow diagram is presented in Figure 1.

Patients were diagnosed by a cardiovascular surgeon who was blinded to assignment of groups after the diagnosis was made (i.e., he did not decide to allocate patients among groups). Data collectors, the statistician and outcome assessors were blinded to patient allocation.

Assessments

Clinical classification of LEL swelling has been defined by the International Society of Lymphology (stage 0–III) using the following parameters:

- *Stage 0*: Latent or subclinical condition where swelling is not evident despite impaired lymph transport. It may exist months or years before overt edema occurs (stages I–III).
- *Stage I*: Early accumulation of fluid that is relatively high in protein content (e.g., in comparison with ''venous'' edema) that subsides with limb elevation. Pitting may occur.
- *Stage II*: Pitting may or may not occur as tissue fibrosis develops. Limb elevation alone rarely reduces tissue swelling.
- *Stage III*: Lymphostatic elephantiasis where pitting is absent. Trophic skin changes, such as acanthosis, fat deposits, and warty overgrowths, often develop.[6]

Health-related quality of life (Assessment of Lymphedema Quality of-Life Questionnaire [LYMQOL]), lower-extremity-circumference (LEC) (for extremity edema), tissue dielectric constant (TDC) (for extremity volume), 6-minute walking test (6MWT) (for functional capacity), and numeric rating scale (NRS) (for extremity fullness) were evaluated in all patients at before and after the treatment, and during follow-up period.

Health-related quality of life

LYMQOL was used for evaluating lymphedema-related symptoms.[13] LYMQOL is an effective tool for screening for lymphedema in patients with LEL. This questionnaire includes 28 items involving four domains (symptoms, body

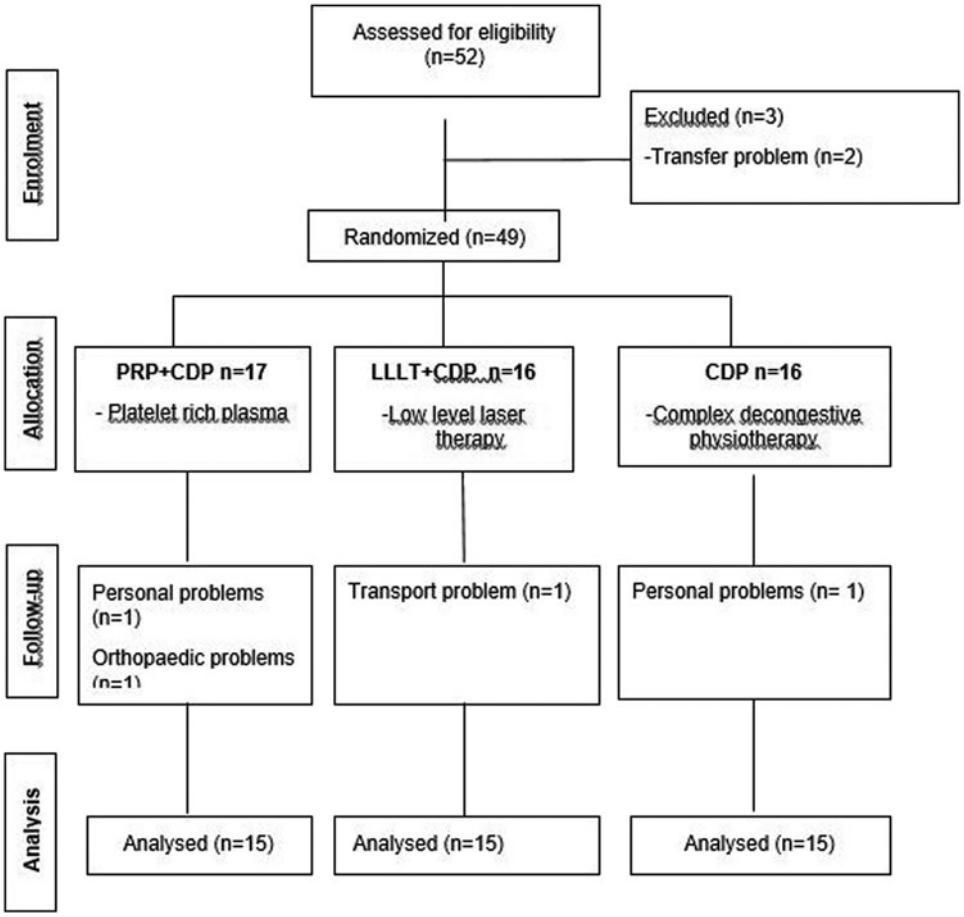

FIG. 1. Consort diagram of the study for lower extremity lymphedema. CDP group, only complex decongestive physiotherapy (CDP) was performed for treatment; LLLT+CDP group, treatment was performed with low-level laser therapy (LLLT) and CDP; PRP+CDP group, patients in whom treatment of lower extremity was performed with platelet-rich plasma (PRP) and CDP.

image/appearance, function, and mood). Each item in each domain was scored as ''Not at all = 1,'' ''A little = 2,'' ''Quite a bit = 3,''and ''A lot = 4.'' A total score for each domain was calculated by adding all scores together and dividing by the total number of questions answered. If fewer than 50% of the items were answered, the whole domain was scored as 0. All items of LYMQOL were scored 0–10, and the points of each item were summed as total score.

We used the original version of LYMQOL, and presented a detailed explanation to the subjects, and if any conflict and/or unsatisfactory feedback was revealed due to cultural, educational, and/or cognitive issues, the subject was excluded from the study.

Lower-extremity-circumference

LEC was calculated from circumference measurements taken at 10-cm intervals from the tip of the second toe to the thigh by using Frustum Formula.[14] The affected and unaffected lower limbs of the patients were measured with a standard 1'', retractable, fiberglass tape. Measurements were taken both before and after the 12-week intervention by the same physiotherapist.[15]

Numeric rating scale

Patients' subjective feedback on leg fullness associated with lymphedema was recorded by the method of NRS scoring of the affected lower extremity.[16] NRS scoring ranged from 0 to 10 (0 = absent, 10 = worst).

Six-minute walking test

Functional capacity was assessed by using the 6-minute walking test performed using American Thoracic Society Guidelines, including assessment of dyspnea at the end of the test.[17]

Tissue dielectric constant

TDC was measured with Moisture Meter-D (Delfin Technologies Ltd., Kuopio, Finland). It consists of a cylindrical probe connected to a control unit that displays the TDC when the probe is placed in contact with the skin. The device generates a high-frequency electromagnetic wave of 300 MHz and sends it into the coaxial probe and the skin.[18] This wave contains information of the water content of the measured tissue. Dielectric constant is a physical quantity without any unit. The instrument automatically converts the measured dielectric constant value into percentage of tissue

water of the measurement site and displays this water percentage value. The measured value is proportional to the tissue water content. A higher percentage value indicates higher water content.[19] All measurements were carried out with the subject supine on a padded examination table. All measurements were taken at 10-cm intervals from the ankle to the thigh similar to limb volume measurements.

Interventions

The patients were admitted to the program for 12 weeks. All groups received skin care, lymphatic drainage, and therapeutic exercises. The exercise protocol included 1 set with 10 repetitions. Active therapeutic exercises (toe flexion, ankle flexion-extension, knee flexion, hip adduction, hip flexion, and core stabilization) were done 10 times and repeated each session. Each therapy session lasted 50–60 minutes. All participants were informed about the factors that could increase lymphedema.

The first arm of the study was conducted as the PRP+CDP group:

PRP is an autologous plasma enriched with a platelet concentration,[20] which is prepared by centrifuging anticoagulated, autologous venous blood.[21] Centrifugation leads to separate whole venous blood into three layers as plasma (top layer in anticoagulated tubes), leukocyte layer (middle part), and bottom red blood cell layer.[21] In this study, PRP is used due to their therapeutic potential[22,23] to release high amounts of essential growth factors and cytokines to provide regeneration and repair in tissues.

Although there is still no general consensus on which procedure is the best for PRP preparation,[23] we used the method by Filardo et al.[24] Briefly, 150-mL venous blood was donated from each patient in the PRP+CDP group. Blood samples were placed in a centrifuge with an anticoagulant tube containing acid citrate dextrose. Two centrifugations were performed to produce 20 mL of PRP. The unit of PRP was divided into 5 small units of 4 mL each. Injections were performed with subdermal application on the leg where dermal and/or subdermal fibrosis was diagnosed and continued every 2 weeks with a total sum of eight administrations.

The second arm was the LLLT+CDP group. In each treatment session, eight grids on the leg were irradiated by using a laser device with a special head in noncontact mode at the distance of 1 cm from skin surface.[25] To deliver the laser energy, a Ga-As diode laser system was used (Laser BTL-4000, BTL Industries Ltd., Brno, Czech Republic). Treatment was applied in the supine position with leg abduction and external rotation.[26] The LLLT was administered every day for the first 4 weeks and then 2 days a week for 8 weeks.

The third arm was the CDP group. This group consists of patients who were treated with only CDP, which consisted of MLD, compression therapy, skin care, and therapeutic exercise.[27] We performed the treatment in two stages: stage I (intense phase) referred to as the phase of reducing the remission. In this phase, skin care and compression bandages are renewed after daily MLD application.[28] The patient is told how to bandage on his own. Stage I is expected to last 4 weeks. The duration of stage I may vary according to the patient. Patients receive stage II (protection phase) treatment when the measured zone approaches the normal values. In this stage, a specially produced compression console is required.[29] Stage II treatment aimed at protecting and further improving the results obtained in the stage I framework. In stage II, MLD can be administered two or three times per week depending on the needs of the patient. At this level, the patient is followed by a home program.[30] Patients were treated every day in stage I and 2 days/week in stage II according to MLD phases totally for 12 weeks.

Patients in the groups (PRP+CDP and LLLT+CDP) were also treated with CDP. Either PRP or LLLT was performed just before MLD and all the procedures were the same for CDP treatment in all three groups.

Statistical analysis

Statistical analysis was performed by using the SPSS software package (version 21.0; SPSS, Inc. Chicago, IL) for Windows. The level of statistical significance was set at 0.05. All the estimated p values were two-tailed. The normality of the data distribution was assessed by the Shapiro–Wilk test. The Kruskal–Wallis analysis of variance (*post hoc* Tukey's HSD test) was used to evaluate differences in the changes between the groups in all parameters. The nonparametric matched pair Wilcoxon test was used to compare the within-group results both before and after treatment. The Freidman test was used for the differences of volume changes in the repeated measurements.

Power analysis was calculated by using the Raosoft sample size and minimal clinically important difference of the LYMQOL, one of the primary measurement tools, based on a margin of error of 5%, a confidence level of 95%.

Results

A total of 52 patients with lymphedema were included in this study (Fig. 1). All patients had secondary LEL due to trauma and/or inflammation. Three patients in each group left the study for different reasons (two personal, three allergy, one orthopedic problem, and one transport problem). A total of 49 patients with LEL were included in this study. Four patients dropped out from the study because of different reasons (two personal, one orthopedic problem, and one transport problem). A total of 45 patients completed the study. There were no statistically significant baseline differences in demographic or clinical parameters between the groups (Table 1).

There was no statistically significant difference in outcome measures between the three groups at the start of the study. The majority of patients in all groups were stage II due to clinical classification of LEL swelling (Table 1).

Table 2 shows a comparison between the groups for LYMQOL, LEC, NRS, and 6MWT values both before and after treatment.

Significant differences in LYMQOL values both before and after treatment were found in all groups ($p=0.022$, $p=0.023$, $p=0.012$, respectively); however, there was no statistically significant difference in LYMQOL score between the three groups ($p=0.446$). In the PRP+CDP group, LYMQOL values had a ''very large'' effect size (2.05); however, it was ''moderate'' in the LLLT+CDP group (0.57) and ''large'' in the CDP group (0.90).

Significant differences in LEC values both before and after treatment were found in all groups ($p=0.000$, $p=0.000$, $p=0.000$, respectively); however, there was no statistically significant difference in LEC values between the three groups

Table 1. Demographic and Clinical Features of the Patients Who Underwent Therapies for Lower Extremity Lymphedema

	PRP+CDP group (n = 15)	*LLLT+CDP group (n = 15)*	*CDP group (n = 15)*	p
Age (year) (mean ± SD)	42.53 ± 15.91	38.20 ± 16.39	41.92 ± 15.92	0.732
BMI (kg/m^2) (mean ± SD)	30.20 ± 9.90	26.84 ± 6.52	27.49 ± 7.03	0.564
Time since diagnosis (months) (mean ± SD)	44.47 ± 62.31	143.40 ± 176.37	126.07 ± 137.81	0.110
Gender, *n* (%)				
Female	12 (80)	8 (53.3)	11 (73.3)	0.260
Male	3 (20)	7 (46.7)	4 (26.7)	
Dominant side, *n* (%)				
Right	14 (93.3)	14 (93.3)	14 (93.3)	1
Left	1 (6.7)	1 (6.7)	1 (6.7)	
Effected side, *n* (%)				
Right	9 (60)	8 (53.3)	8 (53.3)	0.701
Left	6 (40)	7 (46.7)	7 (46.7)	
Localization of lymphedema, *n* (%)				
Foot	1 (6.7)	1 (6.7)	3 (20)	
Lower leg	7 (46.7)	6 (40)	4 (26.7)	
Upper leg	1 (6.7)	1 (6.7)	1 (6.7)	
Whole leg	6 (40)	7 (46.7)	7 (46.7)	0.428
Disease stage				
I				0.359
II	14 (93.3)	13 (86.7)	15 (100)	
III	1 (6.7)	2 (13.3)		

BMI, body mass index; CDP group, only complex decongestive physiotherapy (CDP) was performed for treatment; LLLT+CDP group, treatment was performed with low-level laser therapy (LLLT) and CDP; PRP+CDP group, patients in whom treatment of lower extremity was performed with platelet-rich plasma (PRP) and CDP; SD, standard deviation.

($p = 0.678$). The effect size was ''small'' in all three groups (0.25, 0.31, and 0.32, respectively).

Significant differences in NRS scores both before and after treatment were found in all groups ($p = 0.000$, $p = 0.000$, and $p = 0.000$, respectively); however, there was no statistically significant difference in NRS scores between the three groups ($p = 0.257$). The effect size was ''very large'' in all three groups (3.24, 2.82, and 2.44, respectively).

Significant differences in 6MWT values both before and after treatment were found in PRP+CDP and LLLT+CDP groups ($p = 0.000$, $p = 0.001$, respectively); however, there was no statistically significant difference in CDP ($p = 0.109$).

Comparison between the groups for TDC both before and after treatment is shown in Table 3. The changes after treatment in all scores of limb volumes with TDC were statistically significant for all groups (for level-10 cm: $p = 0.26$, $p = 0.043$, $p = 0.037$; respectively). However, there was no statistically significant difference in limb volumes with TDC between the three groups except for level-40-cm extremity volumes ($p = 0.786$). In addition to this, although effect sizes were large to very large and significantly improved the results of almost all scores of limb volumes in the PRP+CDP group, scores of limb volumes with 40, 60, and 70 cm had an effect size as large to very large in the LLLT+CDP group, and scores of limb volumes with 40, 50, 60, and 70 cm had an effect size as large in the CDP group.

Discussion

Lymphedema is a chronic debilitating disease due to impaired lymphatic drainage and it is characterized by excessive accumulation of protein-rich fluid in interstitial space in soft tissues. The findings in skin and subcutaneous tissue in LEL are caused by the changes in the extracellular matrix, such as fibrosis, fat accumulation, an increased number of mast cells and adipocytes, and interstitial protein-rich fluid accumulation.[31,32] Fibrosis is a clinically serious pathological process of secondary lymphedema. One of the main mechanisms of fibrosis is elevated chymase and TGF-β1 expression by mast cells in the fibrotic tissues of secondary LEL.[31] Mast cells have been implicated in tissue remodeling and fibrosis in tissues by various mechanisms.[33–36]

Mast cells are significantly increased in the fibrotic skin of secondary LEL, and the increased expression of mast cell-derived chymase in the skin may play an important role in the development fibrosis in the lymphedematous skin.[37,38] One of the main targets of PRP and LLLT are mast cells, and PRP and LLLT lead to degranulation of the mast cells by which the fibrotic inflammation process is modulated.[37,39]

The current mainstay of lower leg lymphedema treatment is still nonoperative, conservative therapy with physiotherapeutic techniques. The purpose of this ''effort'' is to move accumulated interstitial fluid from periphery to central venous circulation. By this ''effort,'' the reason of the mentioned disease is not resolved, and it only temporarily relieves symptoms as well as physical findings. Further, patients are also advised to exercise, maintain a normal body mass index, and protect the diseased lower leg from trauma. Education and psychological support are also the main parts of the treatment.[32]

Up to date, when early diagnosed, this ''effort'' helps patients to diminish lymphedema progression, which may lead

Table 2. Comparison of Three Groups for LYMQOL, LEC, NRS, and 6MWT Scores Before and After Treatment

	PRP+CDP group (n = *15*), *mean ± SD*					*LLLT+CDP group* (n = *15*), *mean ± SD*					*CDP group* (n = *15*), *mean ± SD*					
	BT	*AT*	Δ	*Effect size*	p	*BT*	*AT*	Δ	*Effect size*	p	*BT*	*AT*	Δ	*Effect size*	p	Δp
LYMQOL	98.50 ± 20.12	65 ± 11.31	33.50 ± 9.19	2.05	**0.022**	105.33 ± 58.92	74.40 ± 48.09	30.83 ± 23.25	0.57	**0.023**	121.50 ± 77.02	59.25 ± 40.80	62.25 ± 58.00	0.90	**0.012**	0.446
LEC	8503.74 ± 3401.90	7688.51 ± 2912.80	815.23 ± 1385.92	0.25	**0.000**	9120.75 ± 4320.99	7905.84 ± 3215.21	1214.90 ± 1525.47	0.31	**0.000**	7977.29 ± 3947.85	6837.33 ± 3128.99	1139.96 ± 967.57	0.32	**0.000**	0.678
NRS	5.93 ± 1.58	1.80 ± 0.86	4.13 ± 1.68	3.24	**0.000**	7 ± 1.92	1.93 ± 1.66	5.06 ± 2.08	2.82	**0.000**	6.40 ± 1.84	2.27 ± 1.53	4.13 ± 1.45	2.44	**0.000**	0.257
6MWT	490.64 ± 59.72	531.27 ± 61.88	40.63 ± 2.16	−0.66	**0.000**	486.73 ± 55.14	516.55 ± 65.49	29.82 ± 10.35	−0.49	**0.001**	481.90 ± 58.43	502.30 ± 56.92	20.4 ± 1.41	−0.35	0.109	0.567

Effect size: small; 0.2, moderate; 0.5, large; 0.8, very large; 1.3.

The bold values are statistically significant ($p < .05$).

AT, after treatment; BT, before treatment; LEC, lower-extremity-circumference; LYMQOL, Lymphedema Quality of-life Questionnaire; 6MWT, 6-minute walking test; NRS, numeric rating scale; Δ, difference of BT-AT.

Table 3. Comparison of Limb Volumes with TDC Before and After Treatment

	PRP+CDP group (n = *15*), *mean ± SD*					*LLLT+CDP group* (n = *15*), *mean ± SD*					*CDP group* (n = *15*), *mean ± SD*					
	BT	*AT*	Δ	*Effect size*	p	*BT*	*AT*	Δ	*Effect size*	p	*BT*	*AT*	Δ	*Effect size*	p	Δp
10 cm	52.13 ± 11.73	46.20 ± 8.95	5.93 ± 5.40	0.56	**0.026**	51.80 ± 12.89	47.20 ± 11.86	4.60 ± 6.74	0.37	**0.043**	68.07 ± 12.88	52.13 ± 11.42	5.53 ± 3.50	1.30	**0.037**	0.786
20 cm	62.47 ± 12.44	58.33 ± 11.65	4.13 ± 2.19	0.34	**0.046**	62.93 ± 13.36	59.07 ± 11.24	3.86 ± 3.68	0.31	**0.047**	69.60 ± 13.58	64.80 ± 11.89	3.26 ± 5.40	0.37	**0.049**	0.831
30 cm	79.33 ± 4.86	71.13 ± 1.84	8.20 ± 4.94	2.23	**0.023**	67.24 ± 13.86	62.33 ± 11.89	4.93 ± 6.16	0.63	**0.023**	69.93 ± 19	64.33 ± 12.86	5.26 ± 414	0.34	**0.033**	0.174
40 cm	80.13 ± 7.94	53.53 ± 5.75	28.46 ± 4.76	3.83	**0.001**	68.93 ± 20.62	54.13 ± 11.23	14.80 ± 16.78	0.89	**0.012**	72.60 ± 21.06	52.87 ± 12.05	17.06 ± 17.47	1.14	**0.011**	**0.027**
50 cm	71.47 ± 18.87	46.60 ± 1.99	31.80 ± 8.16	1.85	**0.001**	71.67 ± 21.13	61.47 ± 3.91	18.13 ± 18.63	0.67	**0.025**	73.27 ± 14.51	58.25 ± 13.46	18.66 ± 20.90	1.07	**0.023**	0.052
60 cm	56.93 ± 11.08	35.40 ± 2.26	24.86 ± 20.77	2.69	**0.005**	65.20 ± 22.15	46.73 ± 5.41	18.46 ± 24.57	1.14	**0.002**	63.47 ± 18.11	50.27 ± 6.77	13.20 ± 21.44	0.96	**0.001**	0.367
70 cm	51.60 ± 9.83	36.67 ± 3.61	21.53 ± 11.41	2.01	**0.023**	53.73 ± 13.80	38.33 ± 5.30	15.40 ± 16.22	1.47	**0.023**	62.67 ± 20.12	41.67 ± 10.81	21.00 ± 20.82	1.30	**0.001**	0.539
80 cm	56.27 ± 10.20	47.55 ± 10.88	3.93 ± 9.52	0.82	**0.036**	42.07 ± 6.94	38.13 ± 5.39	3.93 ± 7.39	0.63	**0.033**	46.47 ± 13.98	41.47 ± 12.73	5.00 ± 8.33	0.37	**0.023**	0.924

Effect size: small; 0.2, moderate; 0.5, large; 0.8, very large; 1.3.

The bold values are statistically significant ($p < .05$).

TDC, tissue dielectric constant.

to extremity disability, physical discomfort, cosmetic deformity, recurrent skin and extremity infections, psychological consequences and mental depression, and malignant transformation (lymphangiosarcoma). Although there is no accurate treatment of lymphedema, currently the optimum evidence-based treatment is still CDP. In many studies, the reduction in the amount of edema is the most important result in lymphedema treatment.[28] So CDP is presented as gold standard practice in the management of lymphedema.[29] In one randomized controlled trial of CDP in LEL, Do et al.[15] reported that CDP applied in LEL increased the quality of life by decreasing edema. Zasadzka et al.[29] reported that CDP with multi-layer compression bandaging reduced limb volume and circumference in patients with LEL and improved the health-related quality of life. Similarly, we found that three treatment methods decreased the amount of edema and increased health-related quality of life by evaluating LYMQOL values in the present study; however, LYMQOL values had a ''very large'' effect size in the PRP+CDP group, which might show the ''better'' clinical results of PRP applications.

Chronic lymphedema significantly deteriorates the quality of patient life.[21] This is a particularly distressing experience for the patients, who may already suffer from reduced mobility or other limitations. Walking impairment makes it difficult for them to leave home, which may result in weakened social and family connections, as well as decreased self-esteem. This, in turn, has a negative impact on their psychosocial functioning, and it may either lead to depression or worsen the existing problems. So, we think that assessment of functional capacity is essential in patients with LEL and functional capacity is the most important parameter for understanding effects of treatment in this study because of revealing the effect of one's daily life. In this study, we found that the functional capacity was decreased in the three groups of patients before treatment, which is known to be at least 550 m in healthy adult subjects. After the treatment, we achieved a significant increase in the LLLT and PRP groups, which may be due to the fact that both treatment modalities were applied to lymph nodes and provided permanent therapeutic effects. The fact that CDP treatment did not provide improvement in functional capacity suggested that this application might be related with providing symptomatic benefits.

Our results also indicate that PRP+CDP, LLLT+CDP, or CDP methods were found to be effective in the treatment of secondary LEL. There are no statistically significant differences in the volume and circumferential measurement in these three methods; however, PRP+CDP and LLLT+CDP improved the functional capacity superiorly.

The current evidence obtained from *in vitro* and animal studies pointed out that PRP may potentially be used to regenerate injured lymphatic vessels to treat or prevent lymphedema.[22,40] Therefore, we have reviewed existing literature on the clinical uses of PRP in lymphedema and inquired whether there is enough evidence to support the use of PRP in clinical practice as a treatment option.[12] There is no clinical trial regarding the use of PRP in lymphedema treatment but only two animal studies matched to our research yielded positive and promising results in terms of the potential role of PRP in future for lymphedema therapies.[12] In the light of these findings, it is clear that this is an important issue that should be studied in greater depth to clarify the efficacy of PRP in the management of lymphedema in humans.

In a murine tail model, Ackermann et al. evaluated the effect of PRP and adipose stem cells (ASC) on lymphangiogenesis.[40] The study results indicate increased epithelization and faster wound healing with PRP and the authors offered PRP and ASC as a promising approach for prevention/treatment of lymphedema.[40] One of the important points of the study, they suggested, was the use of PRP alone or in combination with other treatment methods.[40] So we decided to use PRP applications in combination with CRP therapy.

Low-level lasers have been used for treating several acute and chronic conditions. However, their application for managing post–breast cancer surgery is still recent, often based on empirical evidence. Treating upper-limb lymphedema with low-level laser presented positive results, with a reduction in the circumference or volume of the affected limb. However, more studies of high methodological quality are needed to better understand the mechanism of action of low-level lasers on the lymphatic system and its effects on lymphedema treatment.[8,9]

A recent systematic review evaluates the effect of LLLT for breast cancer-related lymphedema for short-term follow-up. The review indicated strong evidence for limb circumference/volume reduction over sham treatment, moderate evidence for short-term pain relief over sham laser treatment, and limited evidence for limb swelling over no treatment.[26] Mahram and Rajabi[25] reported that LLLT in a patient with LEL had reduced edema, but it did not result in a reduction in extremity volume. In our study, we found a significant decrease in both edema and extremity volume with LLLT. In this case study, we can say that the inability to decrease the extremity volume may be related to the dosage or duration of use of the LLLT device.

The LEL is associated with diseased lymphatic network—lymphatic vessels, nodes, and surrounding tissue-range from congenital disorders (primary LEL), trauma, and cancer and cancer's therapies (secondary LEL). We excluded patients with primary LEL, since the genetic defect in primary lymphoedema is carried in all cells and any new lymphatics that develop will also be affected, which means that the damaged lymphatic network would be re-established due to PRP-derived angiogenesis. We also excluded patients with cancer since the application of PRP might disseminate cancer cells through to lower extremity.

One of the limitations of the study might be in the diagnosis of secondary LEL since we did not use lymphoscintigraphy in all patients for the diagnosis and/or for the staging of the disease. This is the result of our experience in lymphedema and we believe that the diagnosis of secondary LEL is mainly diagnosed clinically on the basis of physical findings and the patient's history; however, it may be found to be subjective and may not be helpful in staging the disease.[41] Recent studies show that Doppler ultrasound is one of the effective methods in the diagnosis and staging of LEL in experienced hands.[41,42] So our experienced radiologist performed Doppler ultrasound in every patient and we compared the results with lymphoscintigraphies; no difference was seen.

One of the other limitations might be the patients' awareness to the treatment. It would be better to use a different design such as sham laser or injection of saline instead of PRP; however, as patients were not blinded to their own treatment, they were blinded to the treatment allocation and treatment performed in the other groups.

In conclusion, this study was the first clinical study in which the PRP method was applied in patients with LEL. PRP might be an additional treatment option of lymphedema management and it is obvious that more clinical trials in humans are needed to yield more evidence in the usage of PRP in patients with lymphedema.

Authors' Contributions

A.A.: Conceived, designed, data collection, and editing of article; E.T.: Data collection, editing of article, statistical analysis, and editing of article; N.A.: Data collection and editing of article; T.K.: Data collection and editing of article.

Author Disclosure Statement

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