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Comparison of Four Different Therapy Protocols on Extremity Volume in Breast Cancer Related Lymphedema

Meme Kanseri ile İlişkili Lenfödemde Ekstremite Hacmi Üzerine Dört Farklı Tedavi Protokolünün Karşılaştırılması

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ABSTRACT

Aim: *Since lymphedema is generally a chronic and persistive disorder, there is still need to determine the comparative benefits of different therapies for this condition. In this study, we aimed to retrospectively compare the efficacy of different therapy protocols on extremity volume in breast cancer patients with lymphedema (BCRL).*
Methods: *A total of 117 patients with BCRL were selected for the study. The patients were classified in 4 groups. The patients were treated with complex decongestive therapy (CDT) (n:25) in Group 1, with CDT + pneumatic compression therapy (PCT) (n:25) in Group 2, with CDT + PCT+ low- intensity laser therapy (LLT) (n:45) in Group 3, and with PCT+ LLT (n:22) in Group 4.*
Results: *Our analysis between groups suggested statistically significant reduction in the average volume of the upper limbs in all groups (Groups 1, 2, and 3) (p<0.001) except Group 4 (p:0.592). Besides, the results of post-hoc analysis between groups demonstrated a significant difference by means of delta limb volume (p<0.001). We noted that PCT+LLT group caused the statistical difference. The delta values in this group were significantly lower than the other groups.*
Conclusion: *The rationale behind conducting this study was to determine the most effective therapy protocol, and we observed that both CDT alone and CDT combined with PCT and LLT were effective in lymphedema treatment. However, since the PCT and LLT could reduce the volume significantly only in combination with CDT, we cannot conclude that they are effective treatments when applied solely.*

Keywords: *Complex decongestive therapy, Lymphedema, Low- intensity laser therapy*

ÖZ

Amaç: *Lenfödem kronik ve genelde kalıcı olan bir hastalık olduğundan, bu durum için farklı tedavilerin karşılaştırmalı yararlarını belirlemeye halen ihtiyaç duyulmaktadır.*
Bu çalışmada, farklı tedavi protokollerinin meme kanseri ile ilişkili lenfödem (MKİL) hastalarında ekstremite volümü üzerine olan etkilerini retrospektif olarak karşılaştırmayı amaçladık.
Yöntem: *Çalışmaya MKİL'si olan toplam 117 hasta dahil edildi. Hastalar 4 grupta sınıflandırıldı. Grup 1'deki hastalara (n: 25) kompleks dekonjestif tedavi (KDT), Grup 2'deki hastalara (n: 25) KDT + pnömotik kompresyon tedavisi (PCT), Grup 3'deki hastalara (n: 45) KDT + PCT+ düşük güçlü lazer tedavisi (LLT) ve Grup 4'deki hastalara (n: 22) PCT+ LLT tedavisi verildi.*
Bulgular: *Gruplar arasındaki analizimiz, grup 4 dışındaki hemen hemen tüm gruplarda (grup 1, 2, 3) (p<0,001) üst ekstremitelerin ortalama volümünde istatistiksel olarak anlamlı azalmayı gösterdi (p:0,592). Ayrıca, gruplar arasındaki post-hoc analiz sonuçları, delta ekstremite volümü (p<0,001) ile anlamlı bir farklılığı ortaya koymuştur. PCT + LLT grubunun istatistiksel farka neden olduğunu belirledik. Bu grupta delta değerleri diğer gruplara göre anlamlı olarak düşüktü.*
Sonuç: *En etkili tedavi protokolünü belirlemeyi amaçladığımız bu çalışmada; KDT tek başına ve KDT ile birlikte PCT ve LLT'nin lenfödem tedavisinde etkili olduğunu gözlemledik. Bununla birlikte, PCT ve LLT, KDT ile kombinasyon halinde kullanıldıklarında önemli miktarda volüm azalması ile sonuçlandığından tek başına kullanıldıklarında etkili tedaviler oldukları sonucuna varılamaz.*

Anahtar kelimeler: *Kompleks dekonjestif tedavi, lenfödem, düşük güçlü lazer tedavisi*

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INTRODUCTION

Long-term survival rates of breast cancer have been dramatically rising by virtue of effective and successful treatment modalities[1]. However, a significant increase in survival rates brings about many problems related to breast cancer or treatment itself; and unfortunately, these tend to persist during a lifetime period of these patients[2]. Secondary lymphedema (LE) is one of the complications associated with breast cancer treatment, and it occurs when fluid accumulates in the interstitial space and causes enlargement. It is usually described by the patients as a feeling of heaviness in the limb[3]. Because of some variations in diagnostic methods and heterogenous populations of studies, the prevalence rates of this disorder fluctuates between 0 and 56%[4].

For majority of patients, LE is not considered to be a life-threatening condition; though, it can be the cause of many physical, psychological or social problems[5]. Eventually, these problems cause functional impairments and significant deterioration in quality of life[6]. Neglected treatment of LE results in progression of the disease; therefore, patients are to contend with more difficulties in the treatment. Women with mild LE face three times higher risk of developing LE compared to those with no lymphedema[7]. An integrated multidisciplinary approach is essential for an effective treatment since LE is a chronic condition underlying many symptoms in patients.

Although treatment of LE includes various modalities, complete decongestive therapy has been considered as a gold standard[8]. Complex Decongestive Therapy (CDT) achieves an effective volume reduction (%50-70) while preventing skin fibrosis or cellulitis, improving skin condition and functional status of the patient. Besides, it enhances quality of life by relieving symptoms[3]. Treatment includes skin care, manual lymphatic drainage (MLD) and compression therapy that are applied in two sessions.

While majority of patients with lymphedema benefit from CDT, it has some disadvantages such as the need for a physician/physiotherapist experienced in this field, the need for excellent patient compliance while the procedure is time consuming and expensive. Pneumatic compression pump and low-intensity laser therapies are also utilized supplementary to the CDT therapy and sometimes as an isolated treatment modality[9-11]. A pneumatic compression therapy (PCT) is used when treating lymphedema to restrict edema formation and to remove the fluid accumulated in the extremities as well as for the prevention of secondary tissue changes[9]. Low-intensity laser therapy (LLT), on the other hand, not only accelerates lymph flow by increasing the pumping rate and regeneration (lymph angiogenesis) of lymphatic vessels but also diminishes pain and softens fibrous tissue and surgical scars[10]. There is not much evidence about the efficacy of pneumatic compression therapy in BCRL and so far, very few studies have reported about the benefits of low-intensity laser therapy in the treatment of post-mastectomy lymphedema.

Based on a review of the literature, we did not encounter any studies comparing the effectiveness of the CDT, laser and pneumatic compression therapies as described in our study. For this reason, we aimed in our study at assessing the efficacy of these treatment methods in volume reduction and their superiorities to each other, if any.

MATERIAL and METHODS

Patients

The patients who were diagnosed with breast cancer and admitted to the Physical Medicine and Rehabilitation Department of our University Hospital were included in this retrospective study. All participants were diagnosed with BCRL and their mean age was calculated to be 57.38±9.75 years. The patients were referred to our outpatient clinic after medical evaluations in other primary, and secondary medical centers. Patients aged between 35-85 years and diagnosed with BCRL were included in the study. The exclusion criteria were acute inflammation, history of recurrent infections, significant congestive heart failure, and acute deep vein thrombosis.

The files of 130 patients included in the rehabilitation program were reviewed in the lymphedema outpatient clinic. Thirteen patients were excluded from the study because of missing or inconsistent data in their files, so 117 patients were eligible for analysis. Demographic data (age, gender, marital status, occupation, education, activity levels), and previous medical records (date and type of the operation, number of chemotherapy cures, radiotherapy sessions, use of tamoxifen or hormonal therapy) were recruited from medical files, and then analyzed.

Determination of lymphedema:
The extremity lymphedema was evaluated by the same physiotherapist before and after the treatment protocol using environmental and volumetric methods. Circumferential measurements of both extremities were performed at every 5 cm intervals starting from the level of carpometacarpal joint. We then used a computer program (extremity volumes professional version 5.0) to convert these values to milliliters of extremity volumes.

Treatment:
After a retrospective evaluation of existing data, all patients were assigned to four different groups regarding the treatment method they already had.

Group 1 (n:25) were administered CDT in 20 sessions of 1 hour for 4 weeks. This program consisted of patient training, MLD (self), short-stretch bandaged compression therapy for 23 h per day, exercise, and skin care. After four weeks of treatment, phase 2 started. This phase included use of compression garments in order to maintain the volume reduction and recommendation of daily exercise, regular MLD and skin care.

Group 2 (n:25) were administered CDT together with PCT therapy 5 days a week for 4 weeks. This therapy was applied in our clinic at 60 mmHg pressure for 30 minutes (with DrLife brand device). Prior to their treatment, patients had a self-massage therapy.

Group 3 (n:45) were administered CDT + PCT + LLT. The laser therapy was applied in our clinic at a 1.5 J/cm2 dose for 10 to 20 seconds per point in each region (axillary and antecubital region with EnrafNonius Endolaser 422 brand device).

Group 4 (n:22) were administered only PCT + LLT.

In addition, patients were advised to lose weight and were given detailed brochures on lymphedema prevention and exercise.

A written informed consent form was received from all participants and written permission from their doctor allowing their participation and the hospital ethics committee of our University had approved the study protocol (Ege University Clinical Researches Ethical Committee, 24th August, 2016, 16-7/2).

Statistical Method
The data were analyzed with SPSS version 20.0. The continuous variables were expressed as mean + standard deviation. Differences between treatment methods according to quantitative variables were assessed using the Kruskal-Wallis test and the differences between the treatment methods based on categorical variables using the Chi-Square test. Wilcoxon Signed Rank test was used to determine whether there was a difference between pre-, and post-treatment volumes of the patients. The post hoc Bonferroni test will be used to identify statistical differences. The level of significance was set at $p<0.05$ for all statistical analyses.

RESULTS

The demographic characteristics of the patients are shown in Table 1. There was no difference between the groups in terms of age, gender, education level, marital status, and activity level ($p>0.05$).

In the initial evaluation, there was also no difference between the groups from the time of operation until the onset of lymphedema, cures of chemotherapy or sessions of radiotherapy, number of patients having hormonotherapy, duration of lympedema and initial arm volume ($p>0.05$) (Table 2).

Table 1. Demographic characteristics of patients.

	CDT	CDT+PCT	CDT+PCT+LLT	PCT+LLT	P
Age (mean± SD) (years)	61.28±9.56	56.88±10.79	57.38±8.55	53.50±9.99	0.83
Gender (n) (M/F)	23/2	24/1	44/1	22/0	0.46
Education level (n)					0.78
İlliterate	1	0	0	0	
Elementary school	12	10	18	9	
Middle or high school	11	13	26	13	
College	1	2	1	0	
Marital status (n)					0.76
Married	18	21	35	20	
Single	3	3	5	0	
Widowed	4	1	5	2	
Activity level (n)					0.09
Sedentary	0	0	2	1	
Walks for pleasure	13	9	13	10	
Regular exercise (3/week)	5	14	25	8	
Athletic (<4/week)	7	2	5	3	
Dominant hand (right) (n)	20	20	34	19	0.88

CDT: Complex decongestive therapy, PCT: Pneumatic compression therapy, LLT : Low intensity laser therapy, SD: Standart deviation, M: Male, F: Female

Table 2. Clinical characteristics of patients.

	CDT	CDT+PCT	CDT+PCT+LLT	PCT+LLT	P
Post-op duration (mean±SD) (months)	62.36±57.58	74.68±50.26	66.47±53.58	76.23±107.95	0.38
Number of chemotherapy cures (mean±SD)	7.36±7.32	5.96±2.83	6.73±4.54	4.73±2.12	0.64
Number of radiotherapy sessions (mean±SD)	24.24±9.54	24.80±9.75	25.71±9.20	27.09±6.06	0.58
HT patients (n, %)	13(52)	14(56)	26(57.7)	7 (31.8)	0.39
Duration of HT (mean±SD) (months)	12.88±18.66	14.60±19.65	16.87±20.59	5.09±11.04	0.60
Duration of LE (mean±SD) (months)	3.92±7.76	2.72±5.50	15.67±34.41	18.18±40.88	0.59

CDT: Complex decongestive therapy, PCT: Pneumatic compression therapy, LLT: Low intensity laser therapy, SD: Standart deviation, HT: Hormonotherapy, LE: Lymphedema

Table 3. Lymphedema treatment data.

	CDT (n=25)	CDT+PCT (n=25)	CDT+PCT+LLT (n=45)	PCT+LLT (n=22)	P
LE volume (mean±SD)					
BT	2871.76±802.17	3017.20±772.111	2884.49±791.43	2471.18±618.01	0.09
AT	2522.68±458.53[*a]	2653.52±830.99[*a]	2606.69±611.95[*a]	2462.05±720.70	-
Δ	-0.102±0.09	-0.118±0.161	-0.083±0.081	-0.007±0.118	<0.001[*b]

*CDT: Complex decongestive therapy, PCT: Pneumatic compression therapy, LLT: Low intensity laser therapy, LE: lymphedema, BT: Before treatment, AT: After treatment, Δ: Delta value (posttreatment volume- pretreatment volume/pretreatment volume), [a]Wilcoxon signed rank test, [b]Kruskal-Wallis test, NS: Not significant, SD: standart deviation, [*a]: p<0.001 (pre-post treatment difference)*

Our analysis within groups suggested statistically significant reduction in the average volume of the upper limbs in nearly all the groups (for CDT, p<0.01; for CDT+PCT, p<0.001, for CDT+PCT+LLT, p<0.001) except Group 4 (p>0.05) (Table 3). Besides, the results of post-hoc analysis between groups demonstrated a significant difference by means of delta limb volume (posttreatment volume-pretreatment volume/pret-

reatment volume) ($p<0.001$). We noted that PCT+LLT group caused the statistical difference. The delta values in this group were significantly lower compared to other groups. For intergroup comparisons, p values for delta values were as follows; CDT + PCT + LLT with CDT + PCT, $p = 1.000$; CDT+ PCT with CDT, $p=1.000$; CDT+ PCT with LLT + PCT, $p<0.001$; CDT+PCT + LLT with CDT, $p=1.000$; CDT+PCT+LLT with LLT+ PCT, $p<0.001$; and CDT with LLT+ PCT, $p<0.05$.

Treatment -related side effects or worsening in patients conditions were not observed. The patients did not use any medication for lymphedema during their treatments.

DISCUSSION

In this study, we investigated the effects of different therapy protocols in BCRL patients; and, with the exception of the PCT+LLT group, we were successful in reducing arm volume in all groups. The delta values obtained after the treatment showed a significant difference between the groups and the difference originated from the PCT+LLT group (the delta values in this group were significantly lower compared to other groups).

Lymphedema is a condition that can create problems in many aspects for the patient. Sensory deficits, pain, loss of strength, movement restrictions, tendency to infections and skin sensitivity may develop in the arm affected by lymphedema[5]. This, in turn,it hinders patient's performance in their activities of daily living or necessitates receiving more help. In this respect, it is important to figure out which treatment can be administered to patients with least cost and most satisfactiory outcomes[12,13].

CDT is a method accepted as a standard in LE treatment today[3]. Various studies have investigated the efficacy of CDT in treating, and preventing development of post-mastectomy lymphedema[3,14-16]. While a large portion of the studies where different techniques and dosages were used have focused on the cumulative outcomes of CDT, a few of them have dealt with the efficacy of individual components. In their retrospective study assessing the efficacy of a 4-week CDT on 119 patients (56 with one-sided LE in the upper extremity), Boris et al.[17] found 62.6% reduction in the arm volume compared to baseline. In one of their recent studies, Noh et al.[14] explored the efficacy of CDT on edema and quality of life in 35 patients with upper extremity LE, and reported at the end of their study significant improvements in quality of life (QoL) when they assessed QoL using SF-36 (Korean version) and LE volumes. Besides Yamamoto et al.[18] reported that the post-CDT median volume reduction in upper extremities was 328.7 ml, the rate of median volume reduction being 58.9%. Similar to other studies, we also found in our study that there was significant volume reduction in both groups that received CDT alone and the other groups that received CDT as part of their treatment.

Although an adequate control of edema is achieved with CDT in most of the patients, some patients need additional treatment options. One of these is the pneumatic pump. PCT reactivates the pumping action of muscles and removes the fluid from the interstitial space with the effect of pressure.

A number of clinical trials have sought to explore the benefits of PCT in patients with BCRL[19,20]. Haghighat et al.[20] compared the results of the patients who were administered PCT and MLD for 30 minutes a day for 10-15 weeks to those of the patients who received CDT alone and reported that the use of CDT alone or in combination with PCT significantly reduced limb volume in patients with BCRL. Similarly, Uzkeser et al.[21] randomly divided 31 patients with BCRL into CDT and CDT+PCT treatment groups. They have reported rmedian reductions in arm volume were 500 ml (range: 60-2,160 ml) and 480 ml (range: 0-1,410 ml) for experimental and control groups respectively. There was no significant difference between the two groups[21]. In a study where Dini et al.[22] compared a pneumatic compression group to a control group that received no treatment at all, the patients in the PCT group received a treatment of five 2-hour sessions per week for two weeks repeated after a five-week

interval. Although they found a reduction in the measurements of the circumferences of extremities in the treatment group at the end of their study, it was not statistically significant. A recent meta-analysis including seven randomized controlled trials with 287 patients revealed that PCT use may alleviate lymphedema, but there is no significant difference between routine management of lymphedema with or without pneumatic pump[23]. We did not evaluate the effectiveness of the pump alone in our study, but we found significant volume reductions in the CDT + PCT and CDT + PCT +LLT groups where pump therapy was part of the treatment. However, lack of any significant difference between the CDT and CDT + PCT groups was also one of our findings, which mean that adding pump to the treatment did not produce any additional contribution.

LLT has been reported as another alternative for the treatment of BCRL in the literature. LLT is an effective, inexpensive, painless, easily applied and also a less time-consuming therapy. By increasing the pumping rate and regeneration of lymphatic vessels, laser therapy accelerates lymph flow, diminishes pain and softens fibrous tissue and surgical scars[24]. Looking at the publications on this therapy, we see that it has been insufficiently evaluated in BCRL. A recent review analyzing studies about this topic, which have rarely been published has reported statistically and clinically significant reductions in extremity volume after treatments that included laser therapy compared to those that did not include the laser therapy[10]. The authors mentioned about heterogeneity of patient characteristics, study designs and treatment regimens in studies, thus indicating that the efficacy and relative utility of laser therapy for BCRL is unknown.

In their randomized controlled study, Ridner et al.[25], assigned 46 patients with BCRL' to three different groups regarding their treatment protocol; (1) LLT + compression bandaging, (2) MLD + compression bandaging, or (3) combined MLD/LLT + compression bandaging. All three groups showed clinically and statistically significant volume reductions ($p<0.001$); however, no statistically significant difference between groups was found (circumference $p=0.422$). In another study, Kozanoglu et al.[26] compared LLT with PCT; consequently, they have reported statistically significant reduction in extremity circumferences compared to baseline in the two groups immediately after treatment ($p<0.001$), at 3 months ($p<0.001$), and at 6 months (PCT group $p<0.01$; LLT group $p<0.05$). Besides, recovery was greater in the laser therapy group compared to the PCT group immediately post-treatment ($p<0.05$) and at twelve-month follow-up ($p<0.05$).

We had 2 groups in our study where laser was involved. From these, the CDT+PCT+LLT group proved to produce significant volume reduction compared to pretreatment. However, we also found that there was no significant difference between this group and the groups without laser. Such reduction did not reach to the level of significance in the PCT+LLT group. The delta values after the treatment showed that the significant difference between the groups originated from the PCT+LLT group where less volume reduction was obtained compared to other groups. Although there was not a significant difference, the baseline volumes of the patients in the PCT+LLT group being less than those of the other groups might have effected the results. Based on the previous studies, we know that greater the baseline extremity volumes of patients, the more they respond to treatment.

There are some limitations in our study. The most important ones are that our study was retrospective and it lacked a benefit-cost analysis and a long-term follow-up of the patients. Nevertheless, it can be distinguished as being the first study where so many different therapy protocols were compared. The other strong characteristics is that the study has a large sample size and the treatment is applied to the patients by the same physiotherapist using a standard approach.

CONCLUSION

Although treatment of LE using CDT is successful, there is a need for further studies where its efficacy

is compared to other methods because CDT is expensive and hard to tolerate for patients. That is the reason why we compared in this study the efficacies of different therapy protocols in LE. We observed that CDT alone and the PCT and LLT in combination with CDT were effective. However, since the pump and laser therapies result in significant volume reduction only when they are used in combination with CDT, we cannot conclude that they are effective treatments when used alone. We believe that there should be studies comparing LLT and PCT to CDT, and there is also a need for large-scale, prospective studies with long follow-up periods to confirm our study results and to identify the best combination therapy.

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