

Combined-complex Decongestive Therapy Reduces Volume and Improves Quality of Life and Functional Status in Patients with Breast Cancer-related Lymphedema

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Abstract

Background: The aim of this study was to evaluate the effects of complex decongestive therapy (CDT) in patients with breast cancer-related lymphedema (BCRL), in regard to volume reduction, functional status and quality of life (QoL).

Methods: Fifty patients with unilateral BCRL were included. The demographic variables focusing on lymphedema were recorded. All patients received combined phase 1 CDT including skin care, manual lymphatic drainage, multilayer bandaging and supervised exercises, five times a week for three weeks, as a total of 15 sessions. Patients were assessed by limb volumes and excess volumes according to geometric approximation derived from serial circumference-measurements of the limb, prior and at the end of third week. The functional disability was evaluated by quick disability of arm, shoulder and hand questionnaire (DASH). Quality of life was assessed by the European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) and its breast cancer module (EORTC-QLQ-BR23).

Results: Fifty females with mean age of 53.22 ± 11.2 years were included. The median duration of lymphedema was 12 months. There were 22 patients in stage1, 26 in stage2 and 2 patients in stage3. The mean baseline limb and excess volumes were significantly decreased at the end of therapies ($3262 \pm 753 \text{cm}^3$ vs $2943 \pm 646.6 \text{cm}^3$ and $31.36 \pm 16.5\%$ vs $19.12 \pm 10.4\%$, $p=0.000$, respectively). The DASH and EORTC-QLQ-C30 and BR23 scores were also decreased significantly ($p < 0.05$). The improvements in volumes were related negatively with the duration of lymphedema, and the stage of lymphedema.

Conclusion: In conclusion phase 1 CDT in a combined manner performed daily for 3 weeks, greatly reduces the volumes as well as improves the disability and QoL, especially when performed earlier.

Introduction

Lymphedema is defined as a gradual abnormal swelling of a limb and/or the related quadrant of the trunk due to the accumulation of protein-rich fluid in the tissue spaces of the skin. Upper extremity lymphedema is a concerning complication occurred after treatment for breast cancer. It is a chronic disease caused by surgery and/or radiation therapy involving lymph drainage routes of the breast and axillary areas and considered as a potentially serious and debilitating condition (1,2). If left untreated, the presence of macromolecules, proteases and pro-inflammatory molecules may lead to chronic inflammation, fibrosis and hardening of the skin and eventually prone to infections. These symptoms can result in functional disability, psychosocial problems and impaired quality of life in patients with breast cancer-related lymphedema (BCRL) (3-5).

Lymphedema is a chronic condition that cannot be cured but can be managed. These treatments range from simple exercises to different types of microsurgical techniques (6-12). A variety of physiotherapeutic interventions have been proposed for the control of symptoms and to minimize complication, by reducing upper limb swelling. Complex decongestive therapy (CDT) is the most popular and gold standard of

treatment for patients with lymphedema and comprises two phases. Phase 1 therapy includes education and meticulous skin care, manual lymphatic drainage (MLD), multilayer non-elastic compression bandaging and exercises while phase 2 comprises the continuation of skin care and exercise in addition to self-massage and pressure garments. In the second phase patients may need compression bandaging at night, according to the clinical condition of the patients (7,8,10,11).

CDT is criticized as time consuming, costing and most of the previous studies did not include all items of phase 1 therapy or the intervals of separate components were not standardized (9-15). Many of the studies were retrospective and/or the group sizes were small (12,14-17). In some studies pneumatic compression pumps were added (18-21) or exercises were given as a home based program, not supervised by a therapist (15,22-24). There remains a paucity of evidence that supports the combined application of skin care, MLD, multilayer bandaging and supervised lymphedema exercises, as phase 1 therapy in the initial stage of the treatment (25,26). Recent studies indicated the positive effects of phase 1 CDT on volume reduction, physical function and depression in BCRL patients (23) however there are few studies evaluating the effects of combined CDT on volume reduction, functional status and specific quality of life (QoL) issues (4,16,22). The aim of this prospective study was to evaluate the efficacy of combined phase 1 CDT in a group of patients with BCRL, in regard to volume reduction, functional disability and QoL.

Methods

This study recruited patients who had breast cancer-related lymphedema and submitted for treatment and rehabilitation between January 2014 and January 2016, to the lymphedema unit of the Physical Medicine and Rehabilitation Department, in a university hospital. The inclusion criteria were as follows: 1) age being between 18-65, 2) having unilateral breast cancer surgery 3) a volume difference depended to the circumferential measurements between the affected and unaffected upper extremities of more than 10%, 4) having completed chemotherapy and/or radiation therapy 5) complied and fully attended CDT five times per week for 3 weeks. Patients were excluded according to the following criteria: 1) patients with edema before breast cancer treatment, 2) patients with history of contralateral breast cancer, 3) medical history comprising other causes of lymphedema 3) having recurrence or metastasis of breast cancer 4) having contraindicated condition for CDT (renal insufficiency, congestive heart failure, infection, thrombosis, thyroid or abdominal disease, severe vascular disease, etc), 5) having had prior any therapy for lymphedema. All the patients agreed to participate in the study. Written informed consent was obtained prior to the study from all subjects. Approval for the study was granted by the non-invasive clinical research ethical committee of our University and the study was conducted in accordance with the principles of Declaration of Helsinki.

Demographic properties comprising age, gender, body mass index, education, marital status, occupation, regular exercise habit, hand dominancy, lesion site were recorded. Breast cancer treatments (type of surgery, histopathological diagnosis, cancer stage, adjuvant treatments like radiation therapy, chemotherapy, hormonal therapy) were determined in all patients.

The presence of lymphedema was assessed by inter-limb volume difference (> 10%) based on the serial circumferential measurements in both affected and non-affected extremities (27). For circumferential measurements subjects sat straight on a chair with their arms relaxed by their sides and elbows straight. Both arms were measured at each test date. Circumferential measurements were performed by a standard 1 inch retractable tape, starting at the level of ulnar styloid, at 4 cm intervals along the arms and converted to an approximate arm volume to enable estimation of volume (28,29). Calculation of the limb segment volumes (millimeter) was undertaken using a simplified truncated cone formula. Excess limb volume comparing affected and unaffected limbs and difference in excess volume (The excess limb volume is expressed as a percentage of the unaffected limb volume indicating how much larger the affected limb is compared to the unaffected limb) were calculated (29). Every patient was assessed by the same physiotherapist.

Lymphedema characteristics including duration of lymphedema, type of lymphedema (subclinical, reversible, spontaneous irreversible, elephantiasis) initial side (proximal, distal), positivity of Stemmer sign were assessed. The stages of lymphedema are categorized according to International Society of Lymphology (ISL) (27). ISL staging ranges from 0 to III and involves two criteria: the "softness" or "firmness" of the limb (reflecting fibrotic soft tissue changes) and the outcome after elevation. Within stages I through III, severity based upon volume differences is assessed as mild (<20 percent increase), moderate (20 to 40 percent increase), or severe (>40 percent increase). Stage "0" lymphedema is a subclinical or latent condition where swelling is not evident despite impaired lymphatic transport. QoL was assessed by the Turkish version of European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its breast cancer specific complementary measure (EORTC QLQ BR23) (30). EORTC-QLQ-C30 is a 30 item self-administered cancer specific questionnaire designed to measure QoL in the cancer population. The assessment is comprised of nine domains (physical, role, cognitive, emotional, social, fatigue, pain, nausea and vomiting) categorized as global health status, functional scale and symptom scales (31). EORTC-QLQ-Br23 is a 23 item self-administered breast cancer specific questionnaire, usually administered with the EORTC-QLQ-C30, designed to measure QoL in breast cancer population at various stages and with patients with differing treatment modalities. The assessment is comprised of eight domains (body image, future perspective, sexuality domains, arm symptoms, breast symptoms and systemic therapy side effects, hair loss) categorized as functional scales and symptom scales (31).

Functional disability of the affected extremity was evaluated by quick disability of arm, shoulder and hand questionnaire (DASH) (32). It is a self-report questionnaire evaluating the patients' symptoms and functional tasks associated with limitations of the arm, shoulder and hand. It is validated for Turkish population with upper limb problems. It contains 11 items and results in a score ranging from 0-100 with higher scores indicating more functional disability (33).

All the patients underwent a standard protocol of CDT comprising skin care, manual lymphatic drainage, short-stretch multilayer bandaging and lymphedema exercises, five sessions per week for a duration of three weeks in the outpatient lymphedema unit, by an experienced certified lymphedema therapist. All

patients were educated for lymphedema including skin care and maintenance of healthy body weight and delivered a written lymphedema brochure for general advices in the first day of the treatment. The MLD consisted of four basic techniques (stationary circle, rotary, pump and scoop techniques) and, was performed in a proximal to distal direction with light skin strokes, with duration of 45 minutes. Cervical area, abdominal area, anterior trunk, and posterior trunk anastomoses were covered in a standard manner. Finally the whole limb was massaged from proximal to distal parts of the extremity (34). After the MLD, short-stretch multilayer bandages were performed and changed daily except the weekends. A cotton tube stockinet was placed on the arm at first, then finger bandaging was applied. A layer of padding bandage was placed on the hand and wrapped around the arm. Four short stretch bandages (6,8,10,12 cm in width) were sequentially placed around the limb with the first starting at the hand, the second at the wrist, and the third and fourth starting below the elbow. Multiple layer compression bandages were applied such that the most compression was at the distal parts and the compression decreased gradually moving to proximal sites. All subjects were provided individualized active exercise program 20 minutes per day under the supervision of an experienced physiotherapist, including diaphragmatic breathing exercise, neck and shoulder stretching, hand pumping and non-isometric strengthening of arm muscles, in order to help facilitate lymphatic flow and improve strength and range of motion. The exercises were performed with the bandages.

The difference in volumes, excess volumes, QoL and functional assessment scores were evaluated at baseline and after the phase 1 CDT in all patients. The primary outcomes were the reduction in volumes and excess volumes, between the arms while the secondary outcomes included functional disability and QoL scores. The related factors with improvement of the lymphedema were also determined in all patients.

Statistical analysis

Descriptive statistics were used to examine the frequency distributions and calculate the scores of scales and subscales, and defined with mean \pm standard deviation, median and percentage values. The continuous variables have been tested for each group for normal distribution using the Shapiro Wilk test. Student t test or Mann Whitney test were used compare differences in quantitative variables before and after the study. The relationship between improvement of volume differences and QoL scores, Lymphedema symptoms and arm disability scores were assessed using Pearson's correlation for parametric data and with spearman's rho (correlation) for nonparametric data. All tests of statistical significance were two sided and considered statistically significant at $p < 0.05$. Analyses were conducted by SPSS 21.0 statistical package.

Results

Between January 2014 and January 2016, a total of 134 females were screened among the patients who were referred to lymphedema rehabilitation unit for the treatment of lymphedema. 73 patients were not

found to be eligible according to inclusion and exclusion criteria, 11 patients did not agree to take part in the study. Therefore 50 patients were enrolled to the study.

The demographic and clinical properties are shown in Table 1. The median age was 47 years (range 28-62), and mean of body mass index was 29.8 kg/m². A majority of participants in both groups were married, overweight, mostly graduated from primary and high school, and housewives. Approximately half of subjects had completed high school and university. Concerning breast cancer treatments, the most common type of surgery was modified radical mastectomy followed by radical mastectomy and lumpectomy. The majority of the subjects were treated with chemotherapy, radiation therapy and hormonal therapy.

Regarding lymphedema, 54% of the patients had their dominant side affected by lymphedema, while 46% of the patients had their non-dominant side affected. Lymphedema developed after a mean of 4.1 years from surgery. The median duration of lymphedema was 12 months. The mean inter-limb volume difference among women with lymphedema was 31% at baseline. A majority of participants were categorized as grade 2 followed by grade 3 lymphedema (moderate to severe). There were 22 (44%), 26 (52%) and 2 (4%) patients with lymphedema stage 1, 2 and 3 respectively. The lymphedema type was reversible in 42% and spontaneous irreversible in 58% of the patients and most of the patients had grade 2 lymphedema.

Seventy percent of patients had symptoms for lymphedema comprising paresthesia and/or heaviness at the involved arm. The lymphedema characteristics are shown in Table 2.

After 3 weeks of CDT treatment, arm volumes were compared with baseline levels. The volumes and excess volume differences, functional and quality of life scores in regard to baseline and after therapy levels are shown in Table 3. There were significant improvements in volumes, excess volumes, functional scores and QoL scores and sub-scores at the end of therapies.

We determined a significant negative relationship between the improvement of volume difference and duration of lymphedema ($p=0.016$, $r=-0.34$), as well as grade ($p=0.000$, $r=-0.516$) and type ($p=0.041$, $r=-0.29$) of lymphedema. No correlation was found between improvements in volumes and QoL or functional disability scores.

Discussion

Lymphedema is one of the most common complication of breast cancer causing disruption of lymphatic vessels due to axillar node dissection and/or radiation therapy (34). CDT causes a reduction of edema by facilitating lymphatic circulation and defined as the gold standard for treatment of this multifactorial morbidity (6-8,10). There is not a standard protocol for CDT. MLD and compression bandaging in the intensive phase may be applied alone, together or combined with pressure pumps or compression garments. The intervals of different procedures can be changed from two times a week to everyday for four weeks (4-9,12-25). In our study we performed CDT in a combined manner with skin care, MLD,

multilayer bandaging and supervised lymphedema exercises, and determined a significant reduction in volumes and excess volumes. In addition we have found significant improvements in functional and QoL scores which indicate the positive effects of CDT on disability and QoL. Good reduction in lymphedema through CDT has been reported by previous studies with wide reduction ranges from 22% to 73% (10,12,13,17,26,35). Hwang et al (12) retrospectively investigated the effect of CDT in 59 patients with BCRL and reported a volume reduction from 41.9% to 28.8%, as from severe lymphedema to moderate lymphedema. Forner Cordero et al indicated 71% volume reduction in their lower extremity lymphedema patients by CDT including MLD, pneumatic device and multilayer bandaging (36). In our study most of the patients had mild to moderate lymphedema and we determined a volume reduction from 31% to 19%. Noh et al (17) investigated volume reduction in arm lymphedema patients and reported a volume reduction from 20.9 % to 16.3%, related with quality of life. Gradalski et al (26) obtained 47% edema volume reduction within the intensity phase of CDT. Several studies evaluated the effects of CDT but assignments to components of CDT, were not uniform and standardized in most of the studies. The sessions also differed in whether the compression between sessions supplied by bandaging or compression garment. Sometimes the exercise component of CDT was included, sometimes it was not (10,12-23). In our study we have performed MLD, multilayer short-stretch bandaging and supervised exercises along with meticulous skin care, five times a week for 3 weeks. The initial intensive phase is performed daily until maximal volume reduction and normalization of tissue texture is achieved. Then the patients were enrolled to the second phase of CDT and were prescribed compression bandages. It appears that the degree of reduction may be different according to the method of assessing lymphedema and may be due in part to differences in study protocols.

Lymphedema is a potentially debilitating problem and can produce significant impairments on functional status and QoL. Several studies have reported the benefit of CDT in patients suffering BCRL, especially regarding a reduction in the excessive volume (12,14,21,22,23). There are few studies in the literature assessing the effects of CDT in regard of functional disability and quality of life (4,9,16,21,22,37). In most of the studies the quality of life was assessed by generic instruments like SF-36 (3,16,17,22). Evidence from systematic reviews concluded that CDT was effective and had a positive impact on QoL in patients with varying severity of lymphedema (4,9,10,16,21,22). Karadibak et al (21) assessed the effects of CDT in patients with BCRL after 12 weeks of treatment program, once per day, 3 days per week and concluded that CDT could decrease edema and increase quality of life. Pekyavaş et al (16) investigated the effects of CDT and kinesiio-taping and found that CDT was effective therapy especially combined with kinesiio-taping, respecting the functional status and QoL. In another systematic review CDT was found to be effective in reducing lymphedema and has a positive impact on QoL in patients with varying severities of lymphedema whether early or late onset (10). In our study we have assessed the QoL with a specific instrument for breast cancer, apart from previous studies and determined an improved quality of life at the end of phase 1 CDT therapy.

Earlier studies have shown that, a reduction in the size of the upper extremity, was associated neither with the quality of life nor with the upper extremities function (36-38). Vignes et al (37) found that the chronicity of lymphedema was a predictive factor of response when the response was measured in the

absolute value of reduction in lymphedema volumes. Forner Cordero et al (36) determined that stage of lymphedema and compliance to bandages were found to be predictive factors of response. Our results were similar to previous studies that we could not indicate a relationship between improvement in volumes and QoL and functional disability scores. Instead we determined a significant relation with duration, stage and grade of lymphedema and improvements in volumes, similar to some previous studies (36,37). Knowledge of potential factors that influence CDT outcome would help clinicians develop care plans. Intensive early treatment for patients with BCRL is essential for the reduction of edema. As a result of CDT, reduction in lymphedema volume can lead to improvement in functional status and QoL.

The main limitations of our study are the short term, un-controlled and observational study design, but previous long term studies showed a similarity between volumes at post CDT and at 24 months suggesting that volumes at post CDT may be used to predict a long term outcome (12,13,38). Long term results were out of our focus, further studies may be planned in order verify the long term continuing effects of this treatment.

Another potential limitation was the use of circumferential tape measurements to calculate arm volumes. Previous work has found strong correlation between calculated and direct volume measures (29,39). Despite standardized procedures for circumferential measurements, variance in arm volumes may be high. Potentially more reliable and expensive measures such as perometer were not available in our unit. But the point that each measurement taken in a patient was done by the same physiotherapist may make the measurements clinically acceptable and strong. Another limitation is that most of the patients had grade 2 lymphedema which may not allow generalization of the study results to patients with severe lymphedema. But strengths of our study include the prospective nature, relatively large size of study group, the combined contribution of MLD, multilayer bandaging and supervised exercises, to achieving good outcomes in regard to both functional disability and QoL in addition to volume differences.

Conclusion

This study which has shown that phase 1 combined CDT, resulted in a marked decrease in the affected limb volumes and excess volumes as well as improved function and QoL, is one of the relatively largest prospective studies, performed by combined components of CDT, to date. Also this study indicated that the duration, stage and grade of lymphedema correlated with the improvement in volume which means that the earlier the treatment begins the greater is the success of the therapy.

In conclusion phase 1 CDT in a combined manner performed daily for 3 week, can greatly reduce the volume as well as improve the disability and impaired QoL by this condition. The results of this study will contribute to setting treatment approaches in clinical practice and the knowledge from this study can be implemented into the early treatment of patients with combined components of phase 1 therapy.

Abbreviations

BCRL: Breast cancer-related lymphedema

CDT: Complex decongestive therapy

MLD: Manual lymphatic drainage

QoL: Quality of life

ISL: International Society of Lymphology

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire, EORTC QLQ BR23: its breast cancer specific complementary measure

DASH: Quick disability of arm, shoulder and hand questionnaire

Declarations

Ethics approval and consent to participate: Ethical approval was taken from Hacettepe University ethical committee (HU-2014-201) and consents to participate was taken from each patient.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' contributions: PB designed the study and written the study, AY has performed the clinical examinations and measurements and contributed to writing. SY has analyzed and interpreted the patient data, API performed the CDT therapies

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Tables

Table 1. The demographic and clinical variables of the patients

	n=50
Age (years) (mean±SD)	53,22± 11,20
BMI (kg/m ²) (mean±SD)	29,84± 4,45
Normal n (%)	8 (16%)
Overweight n (%)	33 (66%)
Obese n (%)	9 (18%)
Education	
Illiterate	1 (%2)
Primary school	25 (%50)
High School	9 (%18)
University	15 (%30)
Marital status- married	
Single	6 (%12)
widow	4 (%8)
Occupation - housewife	
Worker	9 (%18)
Retired	11 (%22)
Exercise habit yes	
No	36 (%72)
Type of surgery-	
radical Mastectomy	1 (%2)
modified radical	38 (%78)
mastectomy	10 (%20)
lumpectomy	
Breast cancer stage 1	
2	23 (%46)
3	13 (%26)
Histopathologic diagnosis	
Infiltrative ductal	33 (%66)
Infiltrative lobular	5 (%10)

	Before therapy	After therapy	p
	N=	N=	
Volumes (cm³) (mean±SD)	3262±753,0	2943±646,6	,000
Excess volume (%) (mean±SD)	31,36±16,5	19,12±10,4	,000
DASH	38,14±19,04	31,26±17,51	,002
EORTC-QLQ-C30			
Functional Scales QoL			
Physical functioning	69,99±17,65	74,06±20,23	,003
Role functioning	75,72±21,57	76,08±28,24	,002
Emotional functioning	69,56±22,37	73,00±25,53	,000
Cognitive functioning	76,81±23,68	76,80±25,69	,000
Social functioning	68,84±28,67	79,71±27,41	,000
Symptom Scales QoL			
Fatigue	43,71±20,20	32,60±23,11	,071
Nausea and vomiting	11,23±23,05	6,15±16,61	,000
Pain	27,53±21,14	20,65±23,61	,002
Dyspnoea	15,94±21,93	12,31±21,49	,001
Insomnia	26,81±33,42	16,66±27,88	,005
Appetite loss	15,21±24,04	10,86±21,14	,786
Constipation	15,94±23,02	14,49±25,96	,000
Diarrhoea	12,59±22,79	5,92±12,88	,090
Financial difficulties	26,08±30,56	23,18±27,09	,000
Global health status	58,33±22,36	67,39±23,94	,013
EORTC-QLQ-BR23			
Functional scales			
Body image	69,69±24,87		,000
Sexual functioning	11,40±18,46	76,51±23,24	,037
Sexual enjoyment	8,88±19,78	11,40±19,28	,006

Future perspective	48,49±28,61	15,55±24,77	,018
Symptom scales		54,55±28,26	
Systemic therapy side effects	25,54±16,72		<i>,054</i>
Breast symptoms	20,27±18,58	19,46±10,88	,330
Arm symptoms	46,44±23,67	12,49±16,55	,049
Upset by hair loss	20,82±35,35	34,33±20,27	,103
		33,32±43,64	

DASH: Disability of arm, shoulder and hand questionnaire, QoL: Quality of life, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire, EORTC QLQBR23: its breast cancer specific complementary measure