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PHYSIOTHERAPY IN UPPER LIMB LYMPHEDEMA AFTER BREAST CANCER TREATMENT: A RANDOMIZED STUDY

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ABSTRACT

Our aim was to compare the responses of physical treatment with or without manual lymphatic drainage (MLD) in lymphedema after breast cancer treatment in a Brazilian population. This was a controlled clinical trial with lymphedema secondary to breast cancer treatment patients that were randomized into either: Group 1 consisting of MLD, skin care, bandaging and remedial exercises; or Group 2 using skin care, bandaging and remedial exercises. Sixty-six patients were randomized and 9 were excluded during the first phase, resulting in a total of 57 patients eligible for analyzes with 28 in Group 1 and 29 in Group 2. The first phase of treatment had an average duration of 24 days (±12.38) and final volume excess average (VE) between limbs was 494.51ml, corresponding to 29.18% of the initial volume. Volume reduction was highly significant, independent of the intervention ($p<0.001$), and both treatments led to an average of percentage volume excess reduction (PVER) of 15.02%. Patients with incomplete range of motion and lymphatic-related fibrotic tissues showed a statistically significant reduction in the percentage of volume excess ($p=0.010$; $p=0.009$). The presence of arm paresthesia was associated with the lowest therapeutic response ($p=0.024$). Both treatment groups demonstrated absolute and relative reductions of excess limb volume, and the addition of MLD did not significantly increase the therapeutic response in women with lymphedema after breast cancer.

Keywords: lymphedema, breast cancer, randomized trial, treatment, Manual Lymphatic Drainage

The recent increase in breast cancer incidence and more aggressive treatments employed in advanced stages are common situations in countries like Brazil, and these factors are likely to result in higher prevalence of upper limb lymphedema (1,2). Worldwide, the incidence and prevalence of lymphedema after axillary dissection for breast cancer treatment ranges from 0 to 22% and 6% to 49%, respectively, depending on the criteria used for lymphedema definition, time of follow-up, treatment approach and population studied (2-4).

For most lymphedema patients, Decongestive Physical Therapy (DPT) is widely accepted as an effective treatment (3,5-7) even though scientific evidence is still poor. Whereas external compression has been demonstrated to have beneficial effects in upper limb lymphedema treatment, the importance of manual lymphatic drainage

(MLD), either alone or combined with compression, is uncertain and lack of good scientific evidence of clinical usefulness challenges the real role of MLD (8-12).

This study aimed to compare the therapeutic responses of physical treatment with or without manual lymphatic drainage in lymphedema after axillary lymphadenectomy for breast cancer treatment.

METHODS

A controlled clinical trial was undertaken in the outpatient clinic of the National Cancer Institute (Rio de Janeiro, Brazil) and included women who underwent unilateral axillary lymphadenectomy and presented a circumference difference of at least 3cm as compared to the correspondent area of the contralateral limb, six or more months after surgery. Patients with active disease, current chemotherapy or radiation treatment, hypertension, congestive heart disease, presence of inflammatory signs in the swollen limb, previous history of allergic reaction to the material used for compressive bandaging, and patients who underwent any compressive therapy in the previous three months were excluded.

Data recorded for each patient were: age, body mass index, diabetes, shoulder range of motion, breast operation, level of axillary clearance, histopathological classification, neoadjuvant therapies, lymphedema staging, duration of edema, and history of previous infections or treatments. Subjective data related to the arm (pain, heaviness, discomfort, and social reclusion) and expectation towards the lymphedema treatment were also recorded.

After providing informed consent, patients were initially randomized in three treatment groups: Group A (MLD, skin care, bandaging and remedial exercises), Group B (soft touch, skin care, bandaging and remedial exercises), and Group C (skin care, bandaging and remedial exercises). The soft touch was performed as a sliding touch on the upper limbs and chest area. After preliminary evaluation during patient recruitment, no difference was observed between Groups B and C, so they were joined in a single group for further analysis. Patients from those groups together with new randomized patients were separated in Groups 1 and 2, MLD and no MLD groups, respectively.

The frequency of the treatment was 3 times a week for all groups. Two physiotherapists trained in lymphedema treatment were responsible for every treatment session and assessment. Treatment protocol consisted in two phases. In the first phase, both groups received skin care, compressive bandaging and remedial exercises. Group 1 had additional 30 minutes of MLD, according to Vodder technique. Patients entered the second phase of treatment when their volume reduction plateaued for one week regardless of which Group they were enrolled in. The second phase was the same for both groups and consisted of skin care, exercises, and fitted standard or custom made elastic garments.

Volume (V) was calculated by the truncated cone formula with circumferences obtained at 7, 14, and 21cm under and 7, and 14cm above the cubital fold at time of randomization, after each treatment session, and at each follow-up visit. Volume excess (VE) was considered to be the volumetric difference between affected and contra lateral arm and calculated volume excess percentage (VEP) (VEP= (VL-VS/VL)* 100), where VL is the limb volume with lymphedema and VS is the healthy contralateral limb volume. Final VE reduction was considered the main outcome.

Absolute volume excess reduction (AVER) and percentage volume excess reduction (PVER) were also calculated for both limbs. Descriptive analysis of the population was performed using central tendencies for continuous variables and frequency for categorical variables. Mean volumetric reduction of the limb at the end of intervention was used to analyze main outcome for

TABLE 1
Initial Clinical Characteristics and Lymphedema Volume

Clinical characteristics	Initial volume (VE) (ml) Mean	P value
Post-operative time until lymphedema onset		
≤ 2 years	822.53	0.457
> 2 years	724.64	
Duration of lymphedema		
≥ 2 years	898.53	**0.005**
< 2 years	511.02	
Age		
< 50 years	818.93	0.824
≥ 50 years	771.16	
Body mass index		
< 29.9	632.33	**0.014**
≥ 30.0	947.65	

both groups, considering statistical significance <0.05. In order to identify predictive factors to treatment response, one-way ANOVA was performed using a p value 0.05.

This study was approved by the Ethics Committee on Research of the National Institute of Cancer and registered under the number 011/07.

PATIENTS

Sixty-six patients were randomized, 30 allocated to Group 1 and 36 to Group 2. Nine patients were excluded for treatment interruption during the first phase, making 57 patients eligible for analyzes, 28 in the MLD Group 1 and 29 women in Group 2 without MLD.

Mean age of population at the beginning of study was 62 years and most patients were overweight or obese (average BMI 29.75). Mean post-operative time before lymphedema onset was 37 months and mean duration of edema at the randomization was 61 months. Previous infections were reported by 38.6% with three episodes as average.

Before treatment, volume excess (VE) between upper limbs was 776.16 ml, corresponding to a volume excess percentage (VEP) of 44.2%. Initial excess volume of lymphedema was associated with body mass index and duration of lymphedema (*Table 1*).

Regarding feelings about the affected arm, 12.3% of the patients avoided wearing short sleeves, 29.8% felt ashamed of the limb, and 8.8% reported absence of social activities. Subjective symptoms included heaviness in 77.2%, altered sensation in 68.4%, and shoulder dysfunction in 15.8%. Pain was a complaint for 35.1% of the patients.

All variables showed no significant difference among groups, except for duration of edema before treatment; Group 1 (with MLD) presented lymphedema for 41 months whereas in Group 2 (without MLD), for 79 months (*Table 2*) (p=0.023).

RESULTS

The first phase of treatment for the combined groups consisted of an average duration of 24 days (±12.38) and final volume excess average (VE) between limbs was 494.51ml, corresponding to 29.18% of the initial volume. Group 1 patients needed 21.54 days to complete the first phase of treatment (AVER of 292.20 ml and PVER of 14.53%). Group 2 patients needed 27.34 days (AVER of 271.46 ml and PVER of 15.49%). There was no significant statistical difference

TABLE 2
Characteristics of Groups 1 and 2 at Randomization

Characteristics	Group of treatment Group 1 (With MLD)	Group 2 (Without MLD)	Total	P value
Age	62.16 (9.06)	63.55 (10.98)	62.87(10,02)	0.604
Lymphedema onset (months)	38.53 (48.61)	36.45 (62.47)	37.47(55.60)	0.889
Volume excess (VE)	757.63 (509.74)	794.05 (480.19)	776.16 (490.19)	0.782
Volume excess percentage (VEP)	40.65 (24.75)	47.63 (28.71)	44.20 (26.83)	0.330
Lymphedema duration (months)	41.84 (35.29)	79.30 (77.57)	60.90 (62.98)	0.023
Inflammatory attacks	2.71 (3.30)	2.87 (2.70)	2.82 (2.80)	0.909
Body Mass Index	30.44 (5.14)	29.08 (5.97)	29.75 (5.57)	0.361

Values in average (sd)

TABLE 3
Therapeutic Responses for Lymphedema Volume Excess Reduction Between Treatment Groups With and Without MLD at the End of the First Phase of Treatment

Therapeutic Responses	Group of treatment Group 1 (With MLD)	Group 2 (Without MLD)	Total	P value
Treatment duration (days)	21.54 days (11.15)	27.34 days (13.03)	24.49 days (12.38)	0.076
VE (ml)	465.42 ml (323.60)	522.59 ml (311.46)	494.51 ml (315.95)	0.500
AVER (ml)	-292.21 ml (251.60)	-271.46 ml 227.57)	-281.65 ml 237.75)	0.745
VEP (%)	26.11% (16.79)	32.14% (17.13)	29.18% (17.09)	0.186
PVER (%)	-14.53% (11.68)	-15.49% (14.72)	-15.02% (13.21)	0.787
Pain Reduction (AVS)	-1.54 (3.43)	-1.17 (3.24)	- 1.35 (3.31)	0.682

VE: volume excess; AVER: absolute volume excess reduction; VEP: volume excess percentage; PVER: percentage volume excess reduction; AVS: analogical visual scale; MLD: Manual Lymph Drainage.

between groups (*Table 3*). Volume reduction was highly significant for both groups ($p<0.001$), but there was not a significant difference between them (*Fig. 1*). Both treatments led to an average of percentage volume excess reduction (PVER) of 15.02% (*Table 3, Fig. 2*).

Subjective feelings of great improvement in swelling were reported by 73.7% of the patients. Overall treatment acceptance by patients was good. They found it worthwhile and would voluntarily undergo additional treatment (91.2% and 98.2%, respectively). Pain improvement was reported by 35.1% of the patients, but 8.8% reported increased pain at the end of the first phase of treatment. The active shoulder function was improved after lymphedema therapy with MLD in 10.5% and without MLD in 3.5%. The results showed no statically difference between the intervention groups and subjective feelings and symptoms (*Table 4*).

Percentage volume excess reduction (PVER) was considered to identify associated

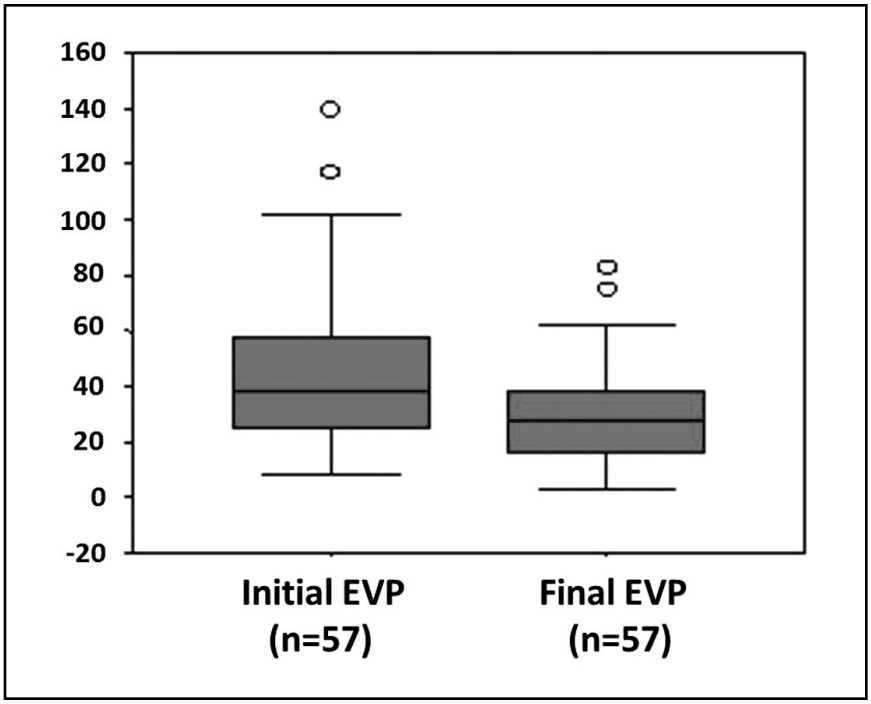

Fig. 1. Box-and-whisker graph displaying volume excess percentage (VEP) reduction after the first phase of treatment for both Groups. Boxes highlight 2nd and 3rd quartile with line indicating the median value. Range is indicated by whiskers and there are two outliers at each time point.

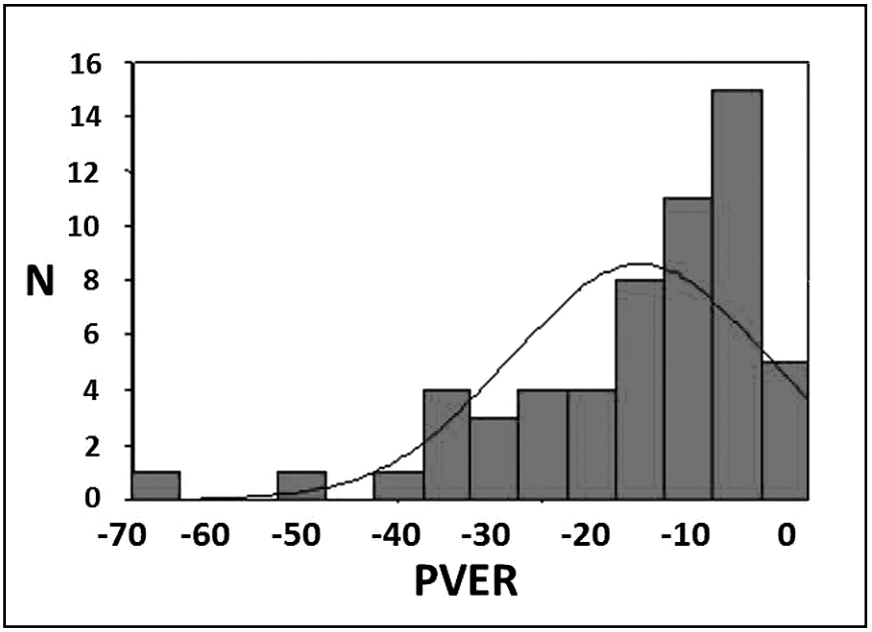

Fig. 2. Percentage volume excess reduction (PVER) at the end of the first phase of treatment for both treatment Groups combined.

TABLE 4
Feelings and Symptoms at the End of First Phase of Treatment for Groups 1 and 2 (Percentage)

Therapeutic Responses	Group of treatment (%) Group 1 (With MLD)	Group 2 (Without MLD)	Total	P value
Swelling reduction				
Poor or Moderate	13.3	6.7	20.0	0.460
Very much	33.3	46.7	80.0	
Treatment worthiness				
Not much and Moderate	3.5	5.3	8.8	0.517
Very much	45.6	45.6	91.2	
If necessary, would repeat treatment				
No	1.8	-	1.8	0.491
Yes	47.3	50.9	98.2	
Pain				
No pain	26.3	29.8	56.1	0.776
Pain reduction	19.3	15.8	35.1	
Pain worsening	3.5	5.3	8.8	
Shoulder function				
Normal range before and after treatment	38.6	45.6	84.2	0.190
Range improved after treatment	10.5	3.5	14.0	
Range remained incomplete	-	1.8	1.8	

factors related to the outcome. At the beginning of the lymphedema therapy, patients with incomplete range of motion and lymphostatic fibrosis showed a statistically significant reduction in the percentage of volume excess. The presence of arm paresthesia was associated with worst therapeutic response. The previous oncologic treatments and clinical variables did not affect the limb volume reduction (*Table 5*).

DISCUSSION

Possible methodological problems encountered in this study include the loss to follow-up of 6%. Our analysis leads us to believe that this would not compromise results due to the standardization among intervention groups. Randomization was able to distribute, across the intervention groups characteristics that can influence limb volume reduction including age, lymphedema onset, volume excess, number of infections, and obesity. The only variable which was more frequent in Group 2 (without MLD) was lymphedema duration (chronicity); however, at bivariate analyses there was no influence at therapeutic response. Therefore, groups were comparable in relation to the outcome that should be assessed, minimizing possible selection biases.

Independently of intervention group, treatment was able to reduce volume excess and pain intensity. Considering patient´s feelings after lymphedema treatment, most of them reported improvement of swelling and that it was worth undergoing treatment and if it was necessary, they would have it again. Such facts reinforce the idea that even with possible bandaging discomfort, women accepted treatment due to the outcome results.

Taking into consideration volume excess reduction, results show that the treatment carried out (with or without MLD) promoted an absolute reaction of 281ml and 15% percentage reduction. Other intervention and observational studies using CPT have also reported a statistically significant decrease of limb volume after treatment (5,7,8,13,14).

TABLE 5
Reduction in Percentage of Volume Excess Reduction (PEVR) in Relationship to Patient Characteristics Before Initiation of Lymphedema Therapy for Both Groups Combined

Variable	PEVR	
	Mean	P value
Active shoulder flexion		
Incomplete range	25.21	0.010
Normal range	13.11	
Feeling heaviness in the arm		
No	14.82	0.951
Yes	15.08	
Arm pain		
No	15.12	0.942
Yes	14.85	
Lymphostatic fibrosis		
No	9.57	**0.009**
Yes	18.70	
Winged Scapula		
No	12.43	0.076
Yes	18.66	
Arm Paresthesia		
No	20.78	**0.024**
Yes	12.36	
Site of surgery		
Right	15.21	0.927
Left	14.88	
Previous arm infection		
No	14.40	0.626
Yes	16.24	
Number of lymph nodes removed	15.32	0.771
≥ 15	14.12	
< 15		
Lymph node status		
Positive	13.08	0.353
Negative	16.19	
Type of surgery		
Mastectomy	15.79	0.347
Conservative	10.29	
Histopathologic stage (TNM)		
Advanced (≥ II B)	14.73	0.987
Initial (< II A)	14.68	
Adjuvant radiotherapy		
No	15.21	0.817
Yes	14.21	
Adjuvant chemotherapy		
No	16.53	0.494
Yes	14.29	

We have observed that there was no meaningful statistical difference between groups with and without MLD in relation to therapeutic responses (absolute and relative volume excess reduction). McNeely et al (15) completed a randomized clinical trial with women who had lymphedema for an average of 20 months also with compression bandaging with and without MLD and found no meaningful statistically significant difference (PVER) between intervention groups. In another randomized clinical trial of women with lymphedema who underwent compression sleeve wearing and home exercises with and without MLD, no volume reduction difference was observed between intervention groups (16). However, different results were obtained in a randomized clinical trial carried out with 77 women treated with compressive bandaging and exercises with and without MLD. The investigators reported reduction percentages of 55.7% in the group with MLD and 36% in the group without MLD ($p<0.05$) (17). Available data indicate that CPT shows very satisfactory results in limb volume reduction, and it can be considered as a standard treatment for lymphedema secondary to breast cancer. Although no statistical significance was found among the groups that did or did not have MLD as treatment component in the present study, we cannot conclude that MLD inclusion does not help therapeutic answer and, in fact, our data demonstrates a trend for fewer treatments days with the addition of MLD (*Table 3*) as well as a trend for shoulder function improvement with MLD (10.5% c.f. 3.5%).

Manual lymph drainage is about pace, tensioning, and muscle as well as connective tissues compression by means of therapist´s touch which helps to improve circulation. It stimulates lymphatic and venous flow, enhancing

metabolism muscle tissue elasticity, and promotes relaxation by increasing parasympathetic nervous system activity and the sympathetic nervous system activity reduction. Such benefits, that were not assessed in the current study, can contribute in reducing anxiety, sleeping improvement and treatment adherence (14,18-20).

Women who underwent lymphedema treatment (both groups) showed reduction in pain intensity, in accordance with data obtained by Hamner and Fleming (14). Thus, aside from pain intensity, studies indicate that CPT promotes reduction in pain threshold in patients with lymphedema. However, more studies are necessary to assess whether pain reduction is a consequence of interstitial fluid reduction or it is due to placebo effect. We have verified an improved range of motion of the shoulder in women treated for lymphedema with or without MLD, which is compatible with Diden et al (21).

Vignes et al (22) reported observational studies in 357 women with lymphedema of approximately 5.8 years duration and VEP of 59% who underwent complex physical therapy (MLD, compressive bandaging, exercises and skin care) in order to examine predictor factors for therapeutic success. After treatment, mean percentage reduction (PVER) was 36% and univariate analysis demonstrated that longer lymphedema duration (chronicity) and higher BMI before treatment was related to the absolute reduction of volume excess, but they also did not find any association with these variables in the percentage of volume reduction (PVER).

Forner-Cordeiro et al (12) carried out an observational study which aimed to verify predictor factors of therapeutic treatment in 171 women who underwent MLD, pneumatic compression therapy, and compression taping. The population was composed of women with VEP 35% at the beginning of the treatment and average of 4-year-duration of lymphedema. They found the average reduction after treatment was 71.7% and multivariate analysis (linear regression) demonstrated that the best predictor factors were: presences of venous insufficiency; lower VEP at the beginning of the treatment; higher tolerance for bandaging; and undergoing treatment in the fall portion of the year. Other authors have also reported better volume reductions after treatment for patients who have a shorter duration of lymphedema (9,13).

The association among therapeutic response, chronicity, and lymphedema is not yet clear. Limbs with lymphedema, lymphatic stasis or lymph stasis, are always subject to local immunity deficiency which generates risks for developing infections (erysipelas). This occurs due to factors such as increasing blood capillaries and tissues, lingering transportation time of macrophages and lymphocytes, and protein antibodies present in the interstitium which allow microorganisms to remain in the local tissue and therefore limiting exposure and time for antibodies to act. Furthermore, interstitial fluid in lymphedema presents high protein levels which become an excellent location for propagation of infection. Thus, recurrent infections can excessively increase the risk of increasing lymphedema and this along with scarred and incompetent lymph vessels from infections can both increase lymphatic demands and decrease lymphatic transport capacity (23,24).

Age can also play an important risk factor for lymphedema. As lymph transportation capacity decreases in aging, a higher risk for developing edema also occurs. However, the influence of age on therapeutic response for lymphedema has not yet been reported in the literature (25,26).

This study has as its main advantages a prospective design, randomization among groups, and the fact that it is the first randomized study in a Brazilian population with lymphedema after breast cancer. However, due to intervention characteristics, it was not possible for the patients, therapists, or evaluators to be blinded and biases could have been introduced in the assessment of treatment effects. Additional limitations

include a relatively small sample size and the difficulty in performing linear regression due to the non-normality of average reduction variables (PVER).

CONCLUSION

Independent of the type of treatment in Groups 1 and 2, there was an absolute and relative reduction of excess limb volume and intensity of pain, as well as improved range of motion. Manual lymphatic drainage did not significantly increase the reduction of volume excess in women with lymphedema after breast cancer. It did demonstrate a trend for fewer treatments days as well as for shoulder function improvement. Further studies with a larger sample size and with increased maintenance phase and follow-up length are needed to verify effectiveness of manual lymphatic drainage treating lymphedema secondary to breast cancer.

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