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Acute inflammatory Response to Manual Lymph Drainage Massage in Breast Cancer Related Lymphedema

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Abstract:

Purpose: To evaluate the effect of manual lymphatic drainage (MLD) on the acute inflammatory response and arm circumference in women suffering from breast cancer-related lymphedema (BCRL).**Methods:** Single-arm study (Pretest – Posttest) design. 35 women with unilateral BCRL were received 1 session of 45 minute of MLD. Inflammatory Markers (IL-6, and CRP), and arm circumference were evaluated before and 24 hours after application of MLD.

Results: Comparing post treatment to pre treatment results, arm circumference was significantly decreased. But, there are no remarkable differences of IL-6 & CRP within the study group.

Conclusion: MLD is a simple, safe and effective procedure in treatment of BCRL which could reduce the arm circumference.

Key words: Manual lymphatic drainage, Breast cancer related lymphedema, Inflammatory markers, Arm circumference.

1.Introduction:

Breast cancer is a serious public health concern since it is the leading cause of cancer-related deaths in women worldwide and the second most frequent cancer type (1).

Lymphedema is a serious consequence of breast cancer surgery (2). It has a bad physical and psychological effect on sufferers. It affects around 15% to 30% of females who have had breast cancer surgery (3,4,5). Breast cancer-related lymphedema (BCRL) happens when the lymphatic system is compromised, resulting in a decreased or slow movement of lymph fluid (6,7).

The degree of axillary node involvement, the technique of breast surgery, and the time of radiation therapy are considered to be associated with BCRL (8).

Because of the fibrotic tissue obstruction caused by radiation, within the radiation field, lymphatic capillaries constrict. Furthermore, radiation inhibits lymph node function and can result in lymphedema (9). Also, superficial scarring secondary to cancer surgery, lead to reduces lymphatic circulation across the scar tissue, resulting in lymphatic accumulation surrounding the scar. (10).

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Furthermore, lymphedema is caused by a local infection following surgery or radiation by increasing the amount of tissues' fluids and cellular contents, exceeding the lymphatic system's transport capacity (9). This decreased lymph flow causes a buildup of protein-rich fluid, which is linked to fibroiss, fat storage, and inflammation in the affected limb (11,12,13).

Complex decongestive therapy (CDT) is the primary therapy for lymphedema and includes a number of manual and safe treatment options such as bandage wrapping, pressure garments, skin care, exercise, and lymphatic drainage techniques. The goal of CDT is to restore the afflicted limb's edema to normal or near-normal levels (14). Manual lymphatic drainage is a soothing massage method that involves periodically contracting lymph vessels (15).

Using MLD promptly after axillary dissection can help to prevent the development of lymphoedema. The goal of this 'safe MLD' is to facilitate lymphatic recanalization following lymph node excision and to remove interstitial tissue water and proteins (16). Women with BCRL may have a unique inflammatory response to MLD due to their compromised lymphatic system. Because the lymphatic system is involved in the synthesis of cytokines and its clearance, the reaction may differ from that of a healthy person. It has been proposed that cytokines can go throw the lymph fluid and affect cytokine levels in addition to the blood. Lymphatic fluid also travels through lymph nodes, which are locations for immune cell clearance. As a result, when injured muscle components travel through lymph nodes, cytokine production may be controlled (17).

It is uncertain, however, whether the ablation of lymph nodes and the accumulation of lymphatic fluid in the BCRL affects the inflammatory response to MLD. As a result, the current study sought to assess the effect of MLD on the acute inflammatory response and arm circumference in women with BCRL. In women with unilateral BCRL, inflammatory markers (IL-6 and CRP) and arm circumference were measured before and 24 hours after MLD treatment.

2.Patients and Methods:

2.1. Study participants and recruitment criteria:

Between October 2021 and January 31, 2022, the practical study was finished. Over this period, 35 women with BCRL recruited from the oncology department out-clinic department at Om El Masreen Hospital. Women were eligible for this study if they had ipsilateral axillary lymphadenectomy for unilateral breast cancer and ipsilateral lymphedema with at least a 5% change in limb circumference.

compared to unaffected limbs and had finished radiation or chemotherapy treatment or both minimum six months prior to the study's start date. Women were eliminated from the trial if they had bilateral arm involvement, acute malignant lymphedema during the first three months of therapy, evidence of infection in the afflicted limb (redness, rash, heat, pain), or MLD contraindications (cellulite, deep venous thrombosis, heart failure, uncontrolled hypertension, and renal insufficiency).

2.2. Study Design:

The research was designed as a single-arm study (Pretest – Posttest) with 35 women suffering from unilateral BCRL. Each participant signed a written informed consent form. Also, this study follows declaration of Helsinki recommendations in dealing with human subject studies.

2.3. Methods:

All subjects received 1 session of 45 minute of MLD. MLD is a gentle massage technique that enhances lymph flow by applying gentle pressure and stretch to the tissues. The lymph nodes in the neck and axilla were drained during MLD, as were the axillary anastomoses at the breast and back were stimulated, as well as The lymphatics on the outer side of the shoulder, as well as the arm and hand, were drained from proximal to distal (16).

In the present study, the neck, contralateral and ipsilateral upper quadrants were massaged first, to increase lymph flow. The massage sequence began proximally, with massage strokes were applied in a distal to proximal direction (in the direction of normal lymph flow). After that, the limb was massaged in segments, beginning at the shoulder and working down the limb.

2.4. Outcome measures:

Primary Outcome Measure:

1) The inflammatory markers were the primary outcome measure. A certified phlebotomist took venous blood samples from the nonaffected arm immediately before and 24 hours after the MLD session. IL-6 and CRP levels were measured in the samples. CRP sensitivity was 451 ng/mL, while IL-6 sensitivity was 0.13 pg/mL. For CRP and IL-6, the accuracy was 8.8 percent**.**

Secondary Outcome Measure:

2) The secondary outcome measure was limb circumference measurements. In the clinical setting, circumference (girth) measures are easy, efficient, and more convenient. Circumference measures also provide information on the measurements at the upper-most part of the arm, the site of the lymphedema, and on where changes in girth occur after treatment. The circumference of both arms was measured for the current investigation, beginning at the MCP joints of the fingers, continuing passing throw the hand, and the MCP of the thumb, finally ending at the wrist. In addition, circumference measures were taken at 4-cm intervals from the wrist to the axilla, including the elbow. The percentage difference in total circumference between afflicted and unaffected arms was used to compute arm circumference swelling.

3.DATA ANALYSIS:

Calculation of sample size:

Calculation of sample size:

To eliminate type II error, a preliminary power analysis [power (1−α error P) = 0.95, α = 0.05, effect size = 0.63] determined a sample size of 35 for the study group. This effect size was calculated according after pilot study on 8 subjects considering IL6 as a primary outcome. The power analysis was carried out by G*Power 3.1.9.2 software, using t- test family and statistical test difference between two dependent mean (matched pairs).

Statistical Analysis:

The statistical SPSS Package program version 20 for Windows (SPSS, Inc., Chicago, IL) was used to perform the following statistical procedures:

- Descriptive statistics for quantitative data, such as mean and standard deviation for numerical variables.
- Homogeneity of variance test and test of normality using Shapiro-Wilk test were significant with the p value being less than 0.05. So, we conducted data transformation (using the logarithm). To compare numerical variables before and after therapy, the Wilcoxon signed ranks test was used.
- Significant level: All statistical analyses were significant at $P \leq 0.05$.

4. Results:

At baseline (**Table 1**), This research included 35 women in total, the mean values of age (year) was 57.50 ±6.44 with minimum value 42.00 year and maximum value 69.00 year.

Table (1): Demographic data of patients in study group.

Items	Mean ± SD
Age [Years]	57.5± 6.44
Body mass (kg)	82.2 ± 16.2
Body mass index (kg/ m²)	29.4 ± 7.2
SD: Standard deviation.	

The statistical analysis by The Wilcoxon signed ranks test found that there was a significant (P = 0.02; P < 0.05) decrease in arm circumference post treatment compared to pretreatment. But no remarkable differences (P = 0.648 & 0.874; P > 0.05) between post treatment and pretreatment of IL-6 & CRP within study group. (**table 2**).

5. Discussion:

Manual lymphatic drainage (MLD) massage is universally acknowledged as a safe and effective lymphedema treatment. [18]. MLD is a set of specialized movements used to increase lymph flow and reabsorption by acting as a pump on the skin. It improves muscular tissue flexibility and increases parasympathetic tone by acting on the autonomous nervous system.

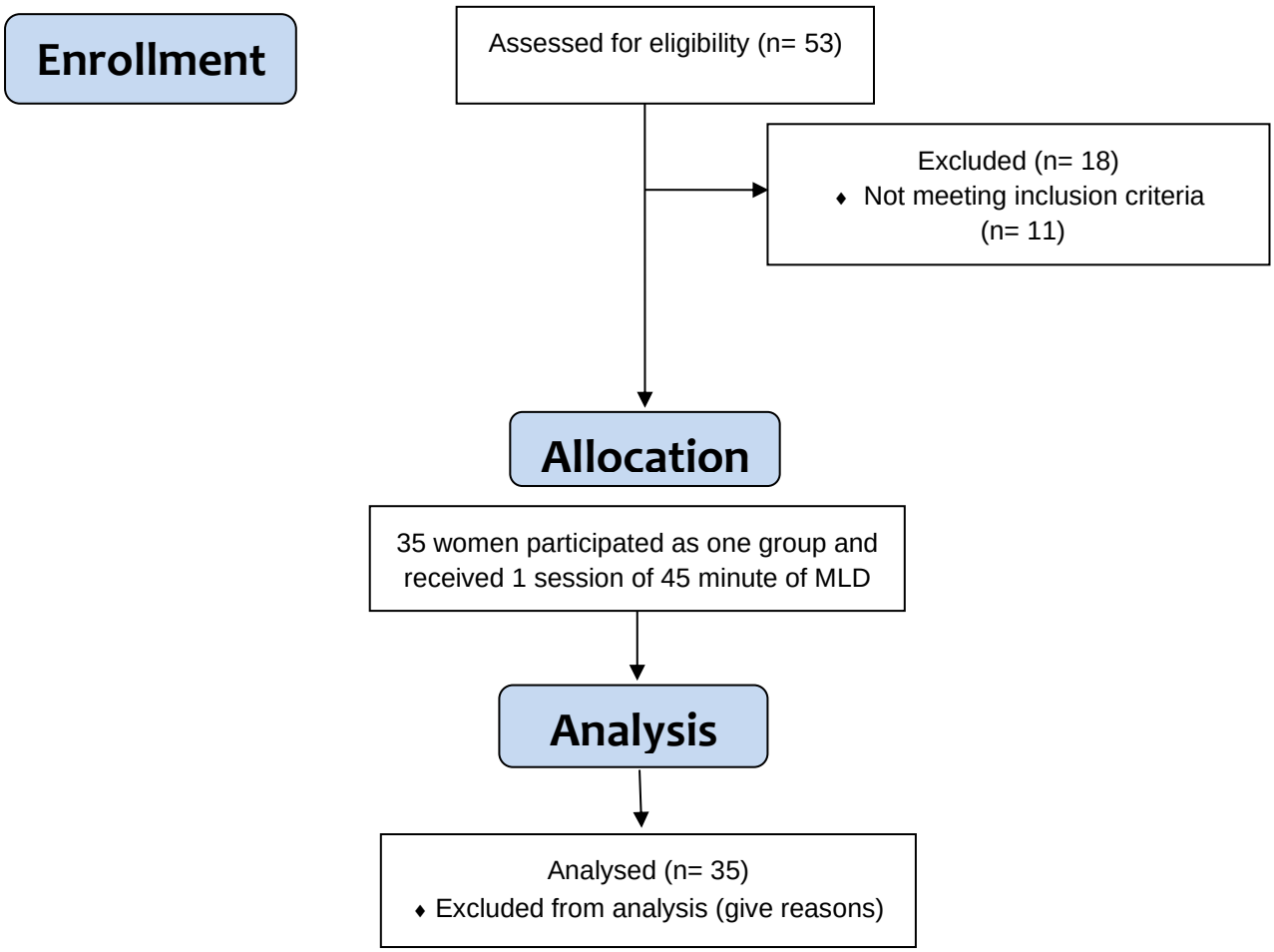

Figure (1): Study flow chart.

MLD was discovered to be beneficial in the treatment of secondary lymphedema when used immediately following cancer surgery of the breast, during the first phases of BCRL or as a maintenance tool (19).

MLD is hypothesized to soften fibrosis and enhance lymph outflow into venous circulation by increasing superficial lymphatic contraction and rerouting lymphatic fluid into nearby functional lymph arteries (2, 20). MLD and exercise improve microcirculation, lymph drainage, lymph angiogenesis, and reduce inflammatory markers in BCRL women (21).

The following were the study's findings: (1) no significant variations in inflammatory markers (IL6 & CRP) before and post 24 hours MLD application (2) substantial decrease in arm circumference with statistically significant difference in arm circumference post treatment compared to pretreatment.

According to the current study, there may be no change in the inflammatory response 24 hours after MLD administration in women with BCRL. The findings of this study are consistent with prior research, which found that MLD reduces arm circumference (2, 22, 23). Furthermore, MLD has been shown to be just as effective as PNF for reducing arm circumference in BCRL patients (24).

Our findings are consistent with earlier studies that indicate a significant decrease in the diameter of the afflicted arm 24 hours post a high-load resistance training programme. The exact mechanisms underlying this are unclear; nevertheless, higher hydrostatic pressure is thought to enhance lymph return (25).

Table (2): Comparison between (Mean ± SD) values of outcome measured variables pre- and post-treatment:

Variable		MLD	(P value)
		Mean ± SD (Median)	
Arm circumference	Pre	6.73 ± 5.79	Non-sig
	Post	5.66 ± 6.11	(P = 0.02).
IL6	Pre	2.23 ± 4.29	Non-sig
	Post	1.93 ± 3.99	(P =0 .684).
CRP	Pre	7.56 ± 5.36	Non-sig
	Post	7.26 ± 5.96	(P = 0.874).

****: Statistically significant difference within in comparison to pretreatment values P-value <0.05.**
SD: Standard deviation. Pre: before treatment measures. Post: after 24 hours of treatment measures

This is, to the best of our knowledge, the first research to investigate whether MLD influences the inflammatory response in breast cancer women with lymphedema. The study examined two blood markers of inflammation in response to MLD. The current study contributes to the corpus of information by demonstrating that MLD does not cause inflammation in lymphedematous breast cancer survivors. This study supports previous results that MLD did not worsen lymphedema of the affected limb. The improvement in the affected limb's arm circumference 24 hours after MLD supports the conclusion that MLD did not produce significantly elevated inflammation in the current study. The findings of this study agreed with those of Cormie et al., who discovered that Upper body resistance training did not result in a greater 24-hour inflammatory response in women with impaired upper limb lymph flow after breast cancer (26).

Limitations and recommendations:

Despite the fact that MLD has been shown to be useful in the treatment of BCRL, more research into its impact on the inflammatory response is needed. However, our study has some limitations. First, blood samples were only evaluated 24 hours after MLD was applied. As a result, we can't rule out the possibility that the lack of a substantial difference between pre and post treatment is due to cytokine clearance prior to blood withdrawal. Second, MLD application was limited to 1 session. As a result, we recommend future experiments include long duration of MLD application. Even if our findings show promising results, more clinical research is required to discover a more therapeutic potential of MLD and to recognize its effects.

Conclusion:

According to prior discussions of these findings and a review of academic research related to the current study, MLD is a straightforward, safe, and effective method for the treatment of BCRL that did not result in a substantial rise in IL6 or CRP as inflammatory mediators.

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