Effect of Topical Cryotherapy on Clinical Outcomes of Patients with Breast Cancer Related Lymphedema

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Abstract

Background: Breast cancer-related lymphedema is a prevalent complication of breast cancer treatment. It has a significant negative impact on patients 'physical and psychological well-being and overall quality of life. Cryotherapy gained universal acceptance for its therapeutic effects on controlling various forms of edema when used in conjunction with conservative treatments for patients with lymphedema. **Aim of the study** was to evaluate the effect of topical cryotherapy on the clinical outcomes of patients with breast cancer-related lymphedema. **Subjects and methods:** A quasi-experimental research design was utilized to carry out this study. A purposive sample of 84 adult women who had breast cancer-related lymphedema was divided into two equal groups. **Tools**: Four tools were used to collect data, as follows: Tool I: Patients' demographic characteristics and health-related data; Tool II: Manual circumference measurement, Tool III: Lymphedema tracking tool; and Tool IV: Numerical Rating Scale (NRS). **Results**: The present study showed that there were statistically significant differences between the control and study groups regarding total mean scores of lymphedema-related symptoms and pain scores post-intervention ($P < 0.05$). Moreover, there was a significant improvement in the total mean scores of the patients' arm circumferences in the study group after intervention; wrist measurement improved from 18.15 (1.97) to 16.98 (1.27), forearm from 27.26 (2.84) to 25.49 (2.11), and upper arm from 38.2 (3.36) to 36.17 (2.66). **Conclusion**: The study results indicated that cryotherapy is an effective complementary modality for the treatment of breast cancer-related lymphedema. **Recommendations:** It is recommended to include cryotherapy in physical therapy protocols for lymphedema rehabilitation, develop educational programs and guidelines for safe application in clinical settings, and evaluate long-term effects.

Key words: Topical Cryotherapy, Clinical Outcomes, Breast Cancer-Related Lymphedema

Introduction:

Breast cancer is the most common type of cancer among women and the main cause of cancer-related deaths worldwide. According to the American Cancer Society (ACS) annual report for 2022–2024, more than 4 million women suffered from invasive breast cancer, with an estimated 287,850 new cases detected among women, and 43,250 of them will die in the United States alone in 2023. Precariously, about one in eight women is suspected to have breast cancer in her life-time, and 1 in 39 of them will die. So early detection and timely treatment are life-saving. (1)

Aggressive treatment therapies used for early eradication of breast cancer (e.g., chemotherapy, radiotherapy, hormonal therapy, and surgery) regretfully have many

morbid complications. One of the most serious sequelae of cancer treatment is breast cancer-related lymphedema (BCRL) of the upper extremity, [2,3] that is frequently caused by axillary lymph node dissection or radiation therapy, which are responsible for 10–20% of the risk of developing lymphedema. [4,5] It was estimated that 3-5 million women had BCRL in the US, with 10 million affected worldwide, and approximately one in every three patients was at risk for developing BRCL post mastectomy. [6]

Lymphedema is a group of pathologic disorders that are characterized by an excessive local buildup of protein-rich lymph fluid that may result from disruption or blockage of lymphatic drainage after axillary lymph node dissection, axillary radiation, infection, scarring from wound healing, and compression of the lymphatic by tumors. Eventually, an abnormal swelling in the upper extremity nearby and distal to the treatment site is foreseen and ultimately progresses to BCRL. [3, 7]

Breast cancer-related lymphedema (BCRL) has two forms: early-onset and late-onset lymphedema. Early-onset lymphoedema develops up to 2 months after surgery and is usually temporary. Late-onset lymphedema progresses at any time, usually after 6 months of initial treatment. Lymphedema can develop in four defined stages. Stage (0) is characterized by subclinical swelling that is not visible on clinical examination despite impaired lymph flow. Stage (I) is presented by pitting edema that is considered reversible. In stage II, the edema evolves and becomes brawny, fibrotic, non-pitting, and irreversible. Advanced lymphedema (stage III) develops rarely after breast cancer treatments and is differentiated by cartilaginous hardening, papillomatous outgrowths, and skin hyperkeratosis. [8,9]

Women with BCRL were confronted not only with physical difficulties (i.e., inflammation, pain, edema, arm tightness and heaviness, impaired upper-extremity mobility, function, and overall daily living activities), but also with psychological distress and altered health-related quality of life, in addition to social and economic burdens. [10] In this regard, the National Comprehensive Cancer Network (NCCN) guidelines call for early screening, prevention, education, and intervention for women at risk of developing BCRL. The goal of secondary prevention is to control arm swelling and manage BCRL symptoms. [3, 11]

Going with this context, the oncology nurses who are responsible for caring for the patients with breast cancer should be familiar with the magnitude of this complication and related treatment modalities, assessing patients who are at risk by frequent limb measurement, planning for conservative and alternative treatments, implementing actions, and educating the patients to follow self-care regimens that control symptoms and prevent exacerbation of lymphedema. [12]

Oncology Nursing Society Treatment Guidelines for BCRL include resistive exercises, manual lymphatic drainage, compression pumps, and complete decongestive therapy. [6] Noteworthy, recent evidence-based studies recommended the application of alternative and complementary therapy for its therapeutic benefits and confirmed that many patients prefer it as a non-pharmacological treatment

for controlling BCRL. Nowadays, cryotherapy is the most effective type of complementary therapy and has received much attention in recent research as an unconventional treatment for BCRL. [7, 13, 14] Cryotherapy is a canonical term often used to describe therapeutic procedures involving the application of cold temperatures by ice, cold water, or cold air on an affected part of the body. This treatment modality is recently used; however, its uses date back for centuries to the ancient Greeks and Hippocrates. The principal purposes of cryotherapy are the withdrawal of heat by reducing core and tissue temperatures and the alteration of blood flow associated with slowing sensory nerve conduction. Ultimately, the resulting downstream effects of cold therapy are reducing perception of pain, getting an analgesic benefit, hastening inflammation, and controlling edema. [15, 16, 17]

Furthermore, topical cryotherapy produces cooling to a depth of about 2-4 cm of the skin, ensuing an initial local vasoconstriction that can persist beyond the time of skin temperature normalization and reduces the normal post-ischemic hyperemic response. Skin cooling also causes systemic vasoconstriction, which, together with local vasoconstriction, can decrease interstitial fluid filtration and promote post-capillary fluid reabsorption. These enhanced processes tend to reduce interstitial fluid volume, giving rise to the almost universal acceptance of cryotherapy as a modality for the control of various forms of edema. [18] Therefore, it is reasonable to think that cryotherapy might have a positive effect on the treatment of lymphedema. [14]

Unfortunately, there is little evidence-based research supporting the application of cryotherapy for breast cancer-related lymphedema, and there are controversial reports regarding its therapeutic effects. Consequently, the current study is intended to evaluate the effect of topical cryotherapy on the clinical outcomes of patients with BCRL as evidence-based nursing research that will support the future use of this modality in clinical practice.

Significance of the study

Nowadays, breast cancer is a significant health problem and is considered the main cause of morbidity and mortality worldwide. However, recent treatment technology has improved patients' survival rates. Unfortunately, some of these technologies have negative consequences, and BCRL is one of them. Breast cancer-related lymphedema has physical, psychological, social, and economic burdens on affected patients. In this respect, BCRL gains the attention of clinical communities and research to explore solutions. Recent studies recommended the application of cryotherapy and confirmed its therapeutic effects on controlling symptoms of lymphedema. In the clinical setting, it was observed that cold therapy is a safer, easier-to-apply, less expensive treatment modality to be used in conjunction with conservative treatments for patients with BCRL. Therefore, we tried to evaluate the effect of topical cryotherapy on BCRL.

The aim of the study

To evaluate the effect of topical cryotherapy on the clinical outcomes of patients with breast cancer-related lymphedema.

Research hypothesis

H1: Patients who receive topical cryotherapy would exhibit a significant improvement in lymphedema size compared to patients who do not receive topical cryotherapy.

H2: Patients who receive topical cryotherapy would exhibit a significant improvement in lymphedema-related symptoms compared to patients who do not receive cryotherapy.

H3: Patients who receive cryotherapy would express lower pain intensity compared to patients who do not receive cryotherapy.

Operational definitions

- Cryotherapy is a treatment modality that involves the application of cold temperatures using a skin cooling agent, "moist or dry," on the lymphedema site for a length of time for therapeutic purposes.

- Clinical outcomes of breast cancer-related lymphedema represent the following: lymphedema size and volume change by intervention, which was measured by tool II; BCRL related symptoms, including swelling, arm heaviness, tingling, tenderness, tissue firmness, and level of pain, that were measured by tools III and IV.

Subjects and methods

Research design:

A quasi-experimental research design with a two-group pretest-posttest methodology without randomization allocation was used to investigate the effects of topical cryotherapy.

Settings of the study

The current study was conducted at the inpatient surgical wards along with the outpatient clinics of the Oncology Center affiliated with Egypt's Mansoura University Hospitals. The Oncology Center consisted of two female surgical wards, each ward consisted of five rooms: two big rooms and three small rooms. The big rooms consisted of six beds, and the small rooms consisted of three beds. The Oncology center was founded in 1994, aiming to provide integrated preventive, management, educational, and research services in all oncology disciplines (i.e., Breast, Bone marrow, Blood, and GIT) for Delta and Channel Governorates, with a census of approximately a million people.

Subjects

A purposive sample of 84 conscious adult women was recruited from the aforementioned setting to fulfil the aim of the current study based on the following:

Sample size calculation: The power analysis was done using Open Epi Software (Open Epi.com) to calculate sample size; an anticipated alpha error was 1% (confidence 99%), β error was 5%, and study power was 95%. Upon careful consideration, cooling breast skin leads to a decrease in F4.0 from 3.54 ± 0.72 N to 2.79 ± 0.81 N (**Mayrovitz & Yzer, 2017)**. To account for expected drop-outs, an additional 10 percent were added, so the minimum number of subjects required by considering dropouts for adequate statistical power to test the study model was 84 patients, which were divided into two equal groups.

The total study sample was assigned into two equal groups: a study group consisting of 42 adult women who received the routine hospital's care along with the designed cryotherapy sessions at the affected arm, and a control group consisting of 42 adult women who received the routine hospital's care only.

Participants' inclusion criteria: Adult women aged 18–60 years who had a confirmed diagnosis of either arm lymphedema post-mastectomy (stage 0–1) and were referred for lymphedema treatments, were not engaged in routine

hospital care or any intervention, were able to communicate verbally, and exhibited their willingness to participate in the study.

Participants' exclusion criteria: Women diagnosed with irreversible BCRL (stages II–III), had a local infection, and had a past history of peripheral vascular diseases, connective tissue disorders, and diabetic neuropathy.

Tools for data collection

Four tools were used to collect the significant data for the study.

Tool I: Patients Demographic Characteristics and Health-Related Data Questionnaire

This tool was developed by the researchers after reviewing recent published literature relevant to the study. [10, 19, 20] It was filled only once (pre-intervention) by the researchers and involved two main parts, as follows:

Part-1: Demographic characteristics of the study participants were included: age, level of education, occupation, and residence.

Part-2: Health-relevant data of the study participants was comprised of the following: weight (wt), height (Ht), body mass index (BMI), type and site of operation, post-operative treatment, time of lymphedema development, stages of lymphedema, and routine therapy used.

Tool II: Manual Circumference Measurement

Arm circumferential measurement is a measuring tool used clinically to assess arm size changes, the presence of excess lymph (edema), and the subsequent changes due to either time or treatment. [21] Arm circumference was measured in centimeters (cm) by a calibrated tape measure that was pulled with a constant tension at different points of the arm (wrist, forearm, and upper arm). The inter-limb circumference difference was calculated by taking a number of measurements from the affected arm and comparing them with the other non-affected arm to estimate baseline measurements for comparison pre- and post-intervention.

Tool III: Lymphedema Tracking Tool

The researchers developed this tool after reviewing recent published literature. [18, 22, 23] to assess symptoms of lymphedema such as swelling, arm heaviness, tingling, tenderness, and tissue firmness to compare levels of improvement before and after intervention. The participants were instructed to rate their responses about BCRL-related symptoms using either yes or no questions using a 2-point score (i.e., 0 = No, and 1 = Yes).

Tool IV: Numerical Rating Scale (NRS)

The NRS was developed by Downie et al. (1978). The purpose of this scale is to assess pain intensity in acute and chronic conditions. This scale consists of an 11-point rating scale (0 to 10), with 0 denoting "no pain" and 10 "the worst possible pain ". The participants were asked to select the single number that best described their pain intensity. [24] The NRS was transformed into a five-point ordinal scale interpreted as follows; "no pain = 0; mild pain = 1-4; moderate pain = 5–7; severe pain = 8 >10; very severe pain = 10. [25]

Validity and reliability of the study tools

Validity: the study tools were tested for content validity by a panel of five experts in the fields of surgical oncology, medical-surgical nursing, critical- care nursing, community-health nursing, and medical biostatisticians. The professional jury reviewed the content of the tools to ensure their inclusiveness, relevancy, simplicity, and applicability. All suggested modifications were calculated and found to be five mistakes in the Arabic translation, which were adjusted, and the final format of the tools was prepared. Reliability: The

proposed study tools were tested by Cronbach's Coefficient Alpha to measure the internal consistency of tool II ($\alpha = 0.75$) and tool III ($\alpha = 0.87$) based on the Strainer study, which reflects that the tools are acceptable and reliable when Cronbach's Alpha =0.70 [26]. For tool V, the test-retest reliability ($r = 0.95$) according to the study done by [27]

Pilot study

Before starting the data collection phase, 10% of the target sample size (eight patients) were interviewed to assess the clarity and applicability of the stated tools and make any necessary modifications before conducting the main study, as well as to estimate the required time needed for completing the questionnaire. Participants included in the pilot study were excluded from the target sample size.

Field Work

Data collection was sustained for 4 months, from the beginning of December 2022 to the end of March 2023. Fieldwork is accomplished through five phases, which are consecutively commenced in order to achieve the aim of the current study.

1. **Preparatory/ development phase**:

The current phase covers the process of stating research problems, formulating hypothesizes, designing the research instruments, and completing administrative preparation for data collection. After the researchers were acquainted with the actual dimension and magnitude of the problem, the study tools were designed. The study tools (I, III) were developed by the researchers after reviewing the relevant literature and used to collect the data for the study, except (II, IV), which were standardized tools used without changing their content. Then the final English version of the tool was translated into Arabic and tested for content validity and reliability. The final Arabic version of the tool was subjected to a pilot study for possible improvement and settled for data collection. Ultimately, written approval to conduct the study was assembled from the pertinent authorities prior to commencing the data collection.

2. **Assessment phase (Pre-test):**

The study procedure was coordinated with health care providers, including nursing staff, after a clear explanation of the aim and nature of the study. Patients who fulfilled the previously mentioned study criteria and attended the study settings during the period of data collection were selected and assigned equally to the study and control groups. Both groups were matched as closely as possible concerning demographic and health related data to secure the homogeneity of the study participants. As a part of the standard pre-intervention assessment (pre-test), before applying topical cryotherapy sessions, each patient of both groups was interviewed individually so as to collect baseline data using all the study tools after explaining the nature and purpose of the study, and obtaining their consent. The time taken to fill out the questionnaire was around 20–30 minutes, as follows:

- The participants demographic data (age, sex, etc.) was obtained from their health records. The health-related data were evaluated as follows: anthropometric measurement (Wt, Ht, BMI) and stage of lymphedema were estimated by the researcher in collaboration with health care providers, and the data concerning type and site of operation, post-operative treatment,

time of lymphedema development, and routine therapy used were collected from patients (Tool I).

- Arm circumference for both groups was measured by a calibrated tape measure that was pulled with a constant tension at the wrist, 10 cm below the elbow, and 15 cm above the elbow on both the affected and non-affected sides based on the recent guidelines [21]. The affected arm size was calculated by subtracting the non-affected side from the affected side before the intervention. After intervention, the comparison of arm measurements was performed only on the lymphedema target site (tool II). Measurements were taken at the selected lymphedematous target site on the arm as well as on the contralateral arm at an anatomically similar site for both groups.
- Subjective complaints of BCRL were evaluated by asking patients about associated symptoms of the affected arm, such as swelling, arm heaviness, tingling, tenderness, and tissue firmness, using Tool III. The participants were asked to rate their level of BCRLs' pain using Tool IV.

3. Planning phase

The current phase was focused on designing the cryotherapy sessions schedule for the participants, which included; date and name of patients, method of skin cooling, application times per day, length of time for each session, procedure steps, and assigned caregiver, which were prepared according to patients' health status, needs, and comfort level based on the data retrieved from the assessment phase.

4. Implementation phase (procedure)

Topical cryotherapy (dry form) was added only for the study group using reusable gel ice packs with straps, which are gel-based. The gel content of the pack provides better cooling power than frozen water, which can be refreezed and used more than once, and the straps secure it in place as much as needed. Moreover, it is manufactured wrapped in cotton cloth, which reduces patient discomfort from direct exposure to cold. The proposed cryotherapy sessions were conducted over six consecutive sessions, three times per day, three days per week, for two weeks, according to standard protocol and recommendations from recent research. [13, 14, 18] Topical skin cooling steps were performed as follows:

- At the beginning of the first session, the researcher introduced herself and explained the objectives of the proposed session and the steps of the procedure for the target woman.
- Wash the skin of the affected arm with normal saline and dry it to avoid infection.
- Apply oil or cream to moisturize the skin before skin cooling.
- A reusable gel ice pack was applied to the affected arm and secured by a strap starting from the hand, wrist, forearm, and shoulder in a distal to proximal direction at each point, which emulates the direction of lymphatic fluid transport and drainage.
- Apply cryotherapy agents for 15-20 minutes, 2-3 times per day, the ideal time for achieving therapeutic effect and avoiding adverse effects from longer exposure according to standard protocol. Each session took approximately 30 to 45 minutes.
- The patient's response to cryotherapy was evaluated, such as discomfort, tolerance, and skin problems, and the

session time was adjusted according to patient tolerance.

- The researcher executed one session per day, and patients or their carers repeated the procedure two times per day after ensuring that they were able to carry out the procedure. Consequently, each patient received regular telephone calls to confirm the adequate application of the intervention.

5. Evaluation phase (post-test)

At the final step of data collection after cryotherapy sessions, the researcher evaluated the effect of cryotherapy on the clinical outcomes of patients with BCRL. All outcome measurements were undertaken prior to the intervention and at the end of six intervention sessions for a follow-up period of two months, passing through the study tools (II–IV) as follows:

- The first phase of evaluation (post-test 1) was conducted after two weeks at the end of the intervention for both groups.
- The second phase of evaluation (post-test 2) was conducted after four weeks for both groups.
- The third phase (follow-up/ post-test3) was conducted after 8 weeks of intervention for both groups.
- Both study and control groups received routine hospital care according to Oncology center protocol as follows; anti-inflammatory drugs, anti-edematous therapies, and resistance exercise. After data collection was accomplished, the researcher provided the control group with cryotherapy guidelines to be involved in their routine care, striving to achieve justice in receiving the same care for both groups.

Ethical Considerations

The Ethical Committee for Scientific Research of Faculty Nursing, Mansoura University, Egypt, approved the study (IRP: ref. no. P.0331). Official approval to carry out the study was obtained from the Mansoura University Hospital authorities before conducting the current study after describing the nature and objective of the study. Informed consent (verbal and written) was obtained from the participants after illustrating the study's aim, advantages, and risks. Voluntary participation, withdrawal from the study at any time, and the patients' rights to refuse to participate in the study without adverse effects on their care were assured. Privacy was absolutely ascertained, data confidentiality was secured by coding the data, and the researchers confirmed that the data would be used only for research purposes.

Statistical analysis

The collected data were coded and entered into the statistical package for social sciences (SPSS) version 20. Qualitative data was presented as percentages. Quantitative data were described as mean/SD, as appropriate. The study data were tested for normality by the Kolmogorov-Smirnov test. For normally distributed variables, RM-ANOVA for the comparison of more than two related groups was used to indicate an actual difference between mean scores. While an independent T test was used to indicate the difference between the mean scores of the two different groups. Chi-square, Monte-Carlo, and Fisher exact were utilized for comparison between two nominal variables. All tests were performed at a level of significance where (P-value

equal to or less than 0.05 was considered to be statistically significant.

Results

Table (1): Baseline characteristics of the studied groups : This table reveals that the mean age of control and study groups were 40.33(3.26) and 42.23(2.53) respectively. Regarding educational level 40.5% and 47.6 % of control and study groups were illiterate respectively and 88.1%, 95.2 % of control and study groups were housewives respectively. Concerning residence 71.4% and 66.7% of control and study groups were lived in rural area respectively. The mean body mass index of control and study groups were 34.35(4.86) and 34.81(4.45) respectively. There were no statistically significance differences of baseline characteristics between control and study groups.

Figure (1): Types of postoperative treatment in control and study group : Presents that 50 % and 61.9% of patients were received hormonal therapy post-operative in control and study groups respectively. While 45.2 % and 28.6 %were received chemotherapy post-operative in control and study groups respectively.

Figure (2): Comparison between control and study groups related to time of lymphedema developed postoperative: This figure shows that 33.3 % and 31% of patients, lymphedema was developed after one year postoperative in control and study groups respectively. While 26.2 % and 31% of them lymphedema developed after 4 to 6 weeks postoperative in control and study groups respectively. There was no significantly difference related to the time of lymphedema developed between the control and study groups (p=0,900).

Figure (3): Comparison of lymphedema stages between control and study groups pre-intervention: This figure clarifies that 61.9 % and 69% of patients were in stage 1 of lymphedema in the control and study groups, respectively. While 38.1% and 31% of them were in stage 0 of lymphedema in the control and study groups, respectively. There was no statistical significance between the control and study groups (P = 0.491) related to lymphedema stages pre intervention.

Table (2): Comparison between affected and unaffected arm measurements in the control and study groups pre-intervention: This table reveals that there were statistically significant differences between the affected and unaffected arms in the control group and study group before intervention.

Table (3): Comparison of the lymphedema signs between the control and study groups before, after 2 weeks, after 1 month, and after 2 months of intervention: This table portrays the distribution of patients according to signs of lymphedema in the control and study groups. It was noticed, there was a significant decrease in hotness and localized swelling as signs of lymphedema after two weeks in the study group. While all of the lymphedema signs decreased after one month in the study group and disappeared after two months. There were statistical differences between the control and study groups related to signs of lymphedema after one month and after two months of intervention.

Table (4) Affected arm measurement in the control and study groups before, after 2 weeks, after 1 month, and after 2

months of intervention: This table reveals that there were no statistically significant differences in different arm measurements (wrist, forearm, and upper arm) at baseline between the control and study groups (p = 0.542, 0.700, and 0.567, respectively). There were statistically significant differences in different arm measurements (wrist, forearm, and upper arm) related to time within subjects (p = 0.000*). Also, there were statistical differences between the control and study groups after two weeks, after one month, and after two months related to previous items.

Figure (4): Comparison of tissue firmness pre, after 2 weeks, after 1 month, and after 2 months between the control and study groups: This figure portrays that 61.9 % and 71.4% of patients suffered from tissue firmness in the control and study groups, respectively, pre-intervention. There was no statistical significance (P = 0.355) between the control and study groups pre-intervention. While after 2 months, 33.3% and 7.1% of them suffered from tissue firmness in the control and study groups, respectively. There were statistically significant differences between the control and study groups after 2 weeks, after 1 month, and after 2 months (p =0.048, 0.013, and 0.003), respectively.

Table (5): Comparison of pain scores in control and study groups before, after 2 weeks, after one month, and after 2 months of intervention: This table reveals that there were no statistically significant differences in pain score (p = 0.683) at baseline between the control and study groups. There were statistically significant differences in pain score (p = 0.000*) related to time within subjects. Also, there were statistical differences between the control and study groups after two weeks, after 1month, and after two months related to the previous item.

Figure (5): Pain level in the control and study groups before, after 2 weeks, after one month, and after 2 months of intervention: This figure illustrates that 76.2% and 69% of patients suffered from moderate pain in the control and study groups, respectively, pre-intervention. It was noticed that the level and severity of pain decreased in the study group compared with the control group after 2 months of intervention, where 28.6% and 61.9% had no pain in the control and study groups, respectively.

Table (1) Baseline characteristics of the studied groups (N = 84)

Items	**Control (n=42) N (%)**	**Study (n=42) N (%)**	**P value**
Age			
18<30	2(4.8)	2 (4.8)	0.757[a]
30<40	11(26.2)	7(16.7)	
40<50	13(31)	13 (31)	
50 and more	16 (38.1)	20 (47.6)	
□ **(SD)**	40.33(3.26)	42.23(2.53)	
Educational level			
Illiterate	17 (40.5)	20 (47.6)	0.718[a]
Read and write	9 (21.4)	10 (23.8)	
Secondary	11 (26.2)	10 (23.8)	
University	5(11.9)	2 (4.8)	
Occupation			
Housewife	37 (88.1)	40 (95.2)	0.236[b]
Administrative work	5 (11.9)	2 (4.8)	
Residence			
Urban	12 (28.6)	14 (33.3)	0.637[c]
Rural	30 (71.4)	28 (66.7)	
Weight □ (SD)	91.12(13.57)	92.9 (12.3)	0.529 [d]
Height □ (SD)	162.81(4.33)	163.36 (4.28)	0.562[d]
Body mass index (BMI) □ (SD)	34.35 (4.86)	34.81 (4.45)	0.657[d]

a: Monte Carlo **b**: Fisher's Exact **c**: chi square **d**: Independent T test

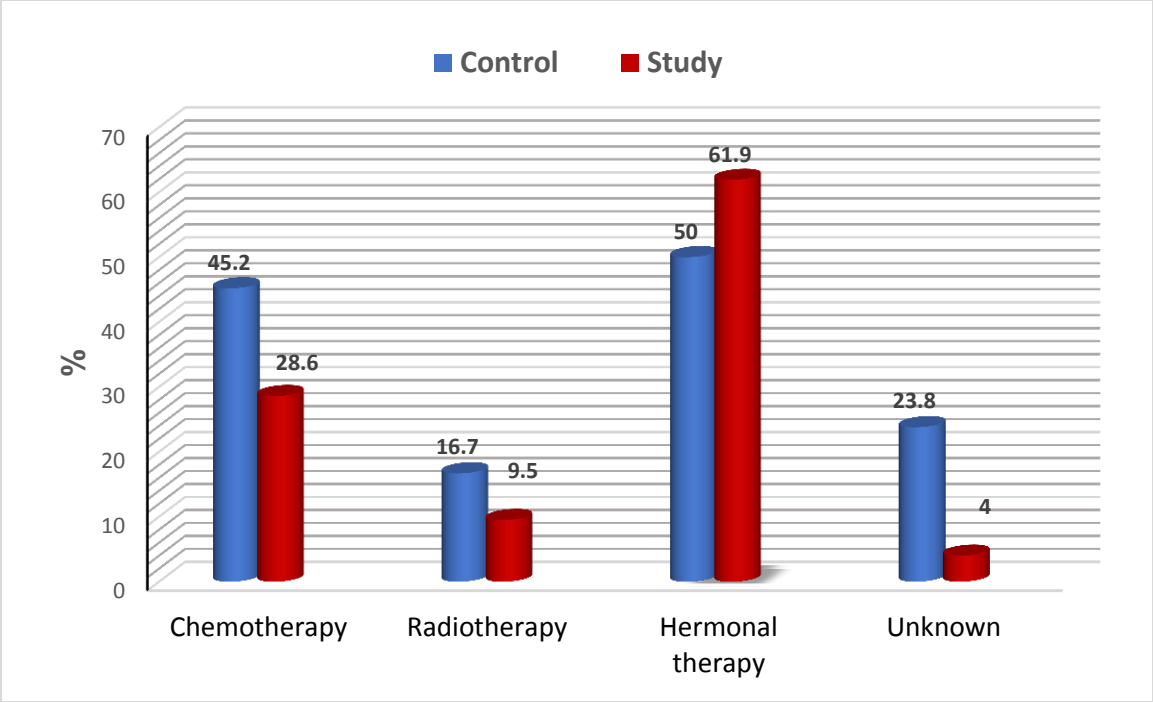

Figure 1: Types of postoperative treatment in control and study group (n=84)

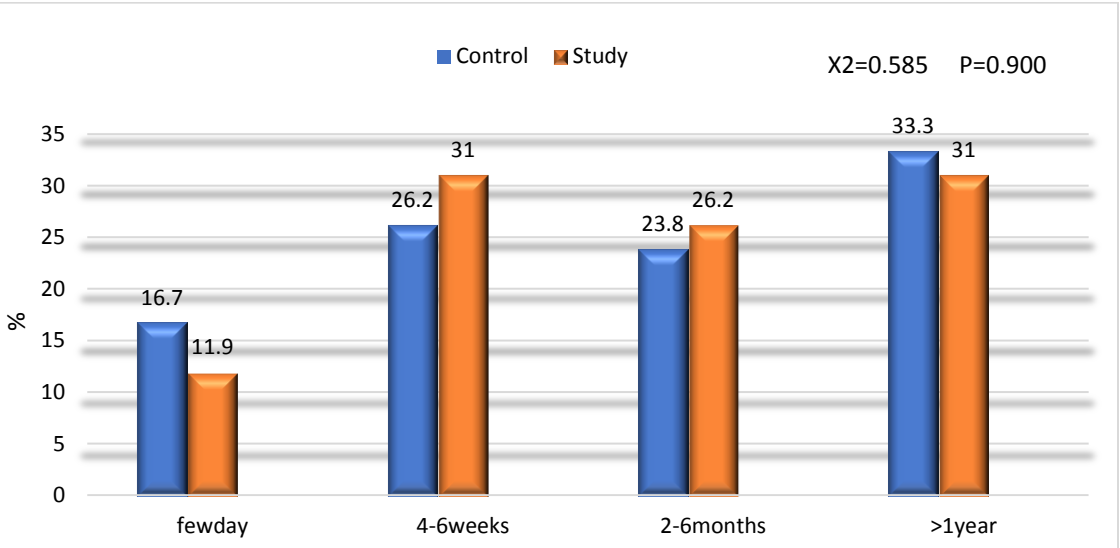

Figure 2 :Comparsion between control and study groups related to time of lymphedema developed postoperative (n=84)

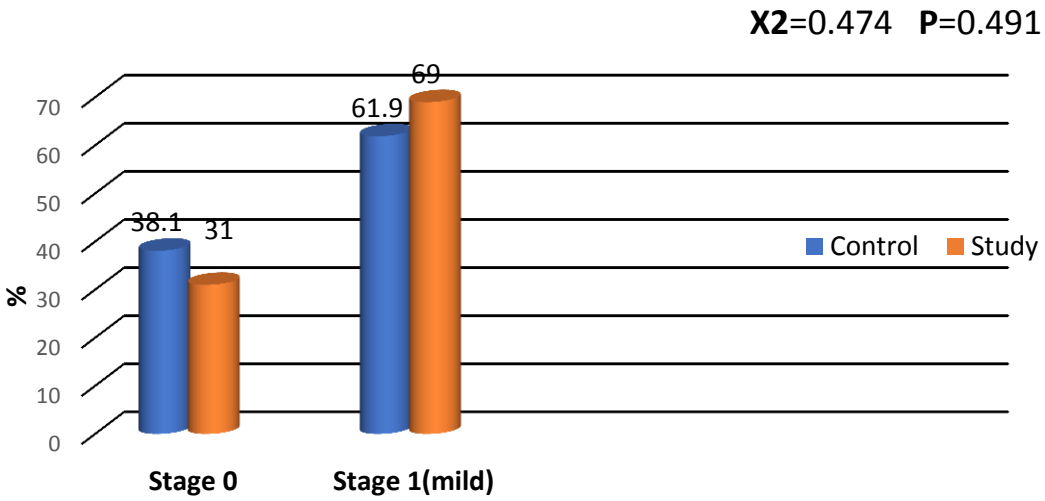

Figure 3 : comparsion of lymphedema stages between control and study group pre intervention (84)

Table (2) Comparison between affected and unaffected arm measurements in control and study group before intervention (N = 84)

Arm measurement	Groups			
	Control (N=42)		Study (N=42)	
	Unaffected	Affected	Unaffected	Affected
Wrist	□ (SD)		□ (SD)	
	17.12(1.22)	18.31(1.87)	17.11(1.28)	18.15(1.97)
	T=3.375 **P =0.001***		T=2.870 **P =0.005***	
Forearm	26.11(1.8)	27.51(2.68)	25.92(1.86)	27.26(2.84)
	T=2.860 **P =0.006***		T=2.631 **P =0.01***	
Upper arm	36.22(2.84)	38.62(2.62)	36.24(2.98)	38.2(3.36)
	T=3.373 **P =0.001***		T=2.992 **P =0.004***	

T: Independent T test P (significance)

Table (3) Comparison of the lymphedema signs between control and study group before, after 2weeks, after one month and after 2 months of intervention (N = 84)

Items	**Control group**	**Study group**	**Test of significance**	
	N (%)	**N (%)**	FE	P
Pre-intervention				
Redness	12 (28.6)	9 (21.4)	.571	0.615
hotness	20 (47.6)	22(52.4)	.190	0.827
Edema (all arm)	31 (73.8)	31 (73.8)	0.00	1.000
Swelling (localized)	13 (31)	7 (16.7)	2.363	0.200
Tenderness	34 (81)	38 (90.5)	1.556	0.350
Numbness	37 (88.1)	38 (90.5)	0.124	1.000
Tingling	27 (64.3)	29 (69)	0.214	0.817
After 2 weeks				
Redness	12 (28.6)	6 (14.3)	2.545	0.183
hotness	20 (47.6)	0	26.250	0.000*
Edema (all arm)	31 (73.8)	31 (73.8)	0.000	1.000
Swelling (localized)	13 (31)	4 (9.5)	5.974	0.028*
Tenderness	34 (81)	27 (64.3)	2.934	0.141
Numbness	37 (88.1)	10(23.8)	0.819	0.548
Tingling	27 (64.3)	23(54.8)	0.791	0.505
After one month				
Redness	6(14.3)	0	6.462	0.026*
hotness	20(47.6)	6 (14.3)	10.918	0.002*
Edema (all arm)	24 (57.14)	14 (33.3)	4.805	0.048*
Swelling (localized)	11 (26.2)	2 (4.8)	7.372	0.013*
Tenderness	13 (31)	5(11.9)	4.525	0.033*
Numbness	16 (38.1)	2 (4.8)	13.859	0.000*
Tingling	19 (45.2)	9 (21.4)	5.357	0.036*
After 2 months				
Redness	0	0	NA	
hotness	14 (33,3)	0	16.8	0.000*
Edema (all arm)	16 (38.1)	4(9.5)	9.450	0.004*
Swelling (localized)	10 (23.8)	1 (2.4)	8.473	0.007*
Tenderness	9 (21.4)	0	10.080	0.002*
Numbness	10 (23.8)	0	11.351	0.001*
Tingling	10 (23.8)	2(4.8)	6.222	0.026*

FE: Fisher's Exact Test **NA:** *Not applicable* ***P*:** *(significance)*

Table (4): Affected arm measurement in control and study group before, after 2weeks, after one month and after 2 months of intervention (N = 84)

Items	Time				P^a -value	
	Pre- test	**After two weeks**	**After one month**	**After 2 months**	Within subjects	Between subjects
	□ **(SD)**	□ **(SD)**	□ **(SD)**	□ **(SD)**		
Wrist cm						
Control group	18.31(1.87)	18.30 (1.93)	18.1(1.79)	17.71(1.78)		
Study group	18.15 (1.97)	18.05(2)	17.03(1.3)	16.98(1.27)	**0.000***	**0.009***
P^b	0.542	0.018*	0.003*	0.033*		
Forearm cm						
Control group	27.51(2.68)	27.12(2.82)	27.2(2.56)	26.75(2.56)		
Study group	27.26(2.84)	26.45(1.87)	26.06(2.19)	25.49(2.11)	**0.000***	**0.030***
P^b	0.700	0.001*	0.032*	0.016*		
Upper arm cm						
Control group	38.62(2.62)	38.61(3.05)	38.21(2.65)	37.42(2.89)		
Study group	38.2(3.36)	37.68(2.42)	36.94(2.66)	36.17(2.66)	**0.000***	**0.064**
P^b	0.567	0.031*	0.031*	0.042*		

P^a: Repeated measure ANOVA **P^b:** Independent T test P*; significance

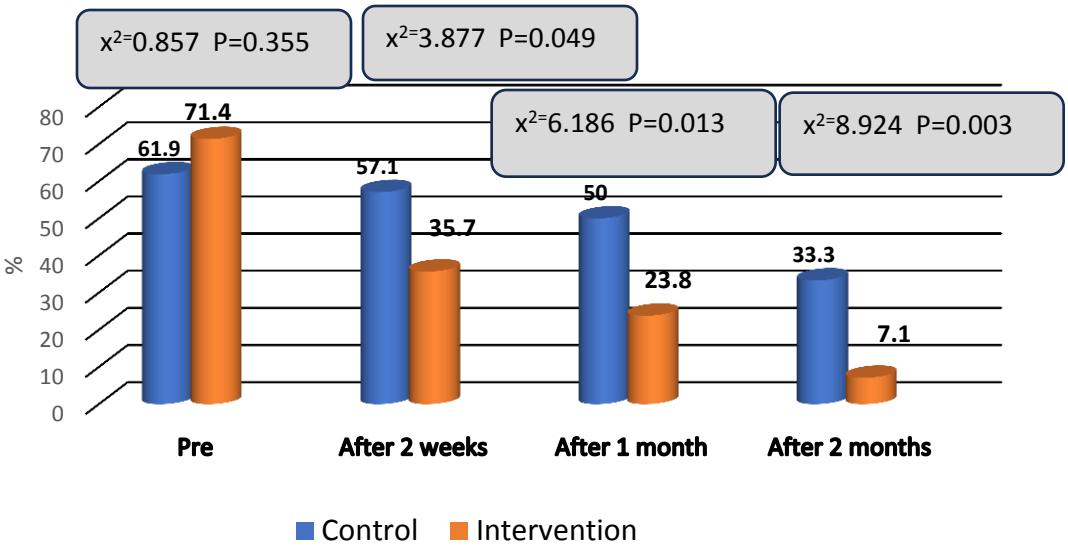

Figure 4 :Comparison of tissue firmness pre , after 2 weeks ,after 1 month ,and after 2 months between control and study group

Table (5): Comparison of pain scores in control and study groups before, after 2weeks, after one month and after 2 months of intervention (N = 84)

Items	Time				P^a -value	
	Pre- test	**After two weeks**	**After one month**	**After 2 months**	Within subjects	Between subjects
	□ **(SD)**	□ **(SD)**	□ **(SD)**	□ **(SD)**		
Pain score						
Control group	6.93(1.22)	6.93(1.18)	5.2(1.69)	2.82(2.54)	**0.000***	**0.000***
Study group	6.8(1.54)	5.12(1.65)	3.3(1.37)	0.76(1.14)		
P^b	0.683	0.000*	0.000*	0.000*		

P^a: Repeated measure ANOVA **P^b:** Independent T test P*; significance

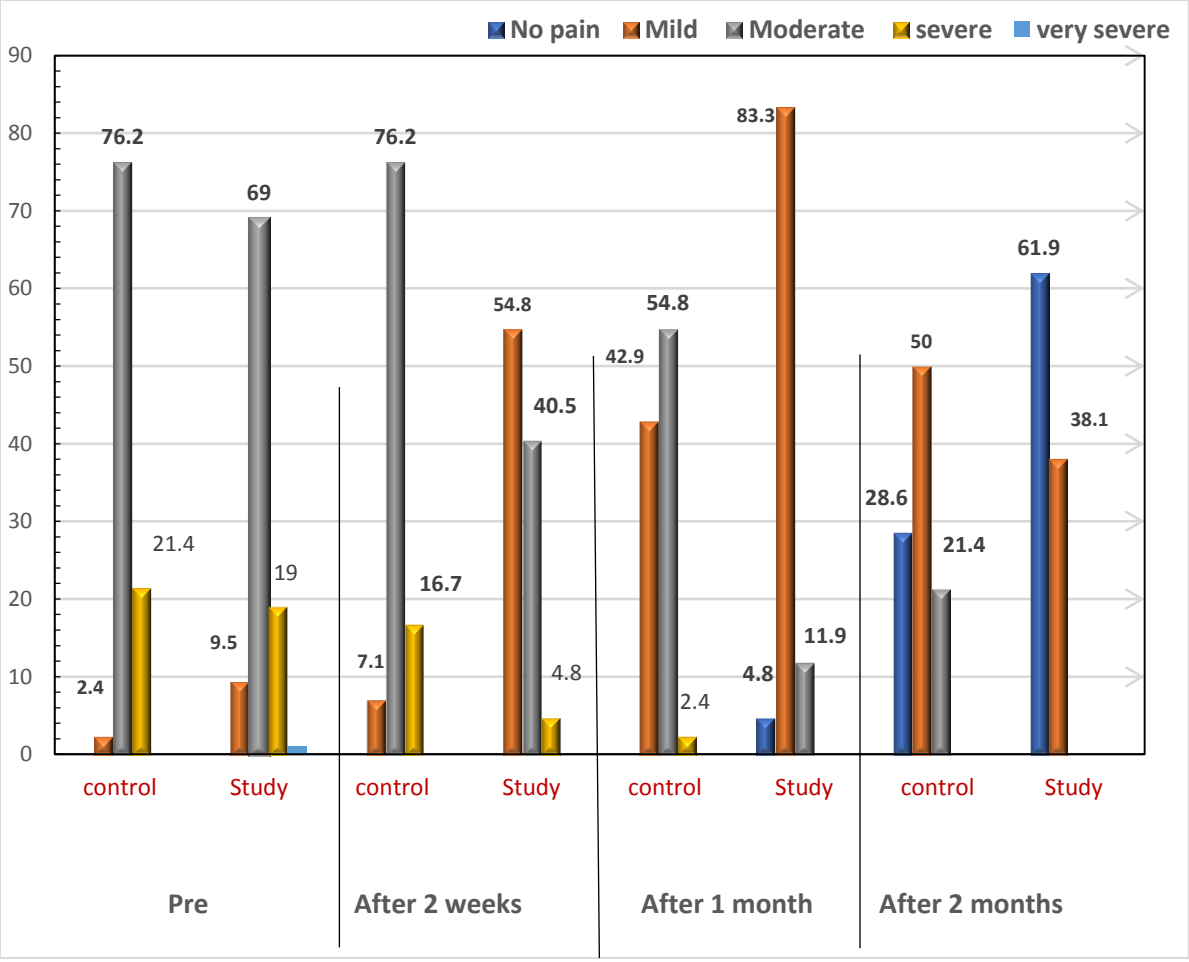

Figure (5): Pain level in control and study group before, after 2weeks, after one month and after 2 months of intervention

Discussion

Breast cancer-related lymphedema is a prevalent complication of breast cancer treatment and manifests as upper limb swelling. [28] It is a chronic condition that may lead to lifelong impairment of the affected upper extremity. [29] It has a significant negative impact on physiologic and psychological well-being. Moreover, greater restrictions on activity lead to poor quality of life (QOL) and make patients more prone to cellulitis. Lymphedema is incurable and progressive. [30]

Furthermore, persistent lymph stasis creates a condition of chronic inflammation that contributes to fibrosis and fatty deposition in the subcutis of the affected limb. Therefore, more attention should be paid to the management of BCRL in order to improve the patient's clinical outcomes and health-related quality of life. Topical cryotherapy is used as a new physical modality for the treatment of BCRL in order to decrease pain, inflammation, and edema. [31, 32] So, the current study investigated the effect of topical cryotherapy on the clinical outcomes of patients with breast cancer-related lymphedema.

Regarding demographic and medical data, the present study revealed that there was no statistically significant difference between the two groups regarding all items of baseline characteristics. This data emphasizes the strength of the study in eliminating the assignment bias of participants to groups by randomization.

Regarding the types of treatment received after mastectomy, the current study indicated that 50 % and 61.9% of patients received hormonal therapy postoperatively in the control and intervention groups, respectively. These findings are in agreement with **Refaat Elmaadawy et al., (2022)** [33] who found that 55% of women received hormonal therapy after mastectomy. These findings related to endocrine therapies are the main treatment strategies for the clinical management of hormone-dependent breast cancer, improve prognosis and decrease the risk of recurrence in patients with positive human epidermal growth factor receptor 2 (HER2) **(Alataki & Dowsett, 2022)**. [34]

In reference to the development of lymphedema, the present study revealed that, lymphedema developed in 33.3 % and 31% of patients after one year postoperatively in the control and intervention groups, respectively. These findings were consistent with **McDuff et al., (2019)** [35] who reported that, the risk of lymphedema peaked between 12–30 months postoperatively; however, the time course varied depending on the treatment received.

Regarding arm measurement, the present study showed that there were statistical differences between the control and study groups regarding different arm measurements after two weeks, after one month, and after two months post-intervention. These findings were supported by **Askary& Elshazly, (2022)** [14] who demonstrated that there was a significant decrease in thickness and circumferential limb difference at the wrist, below the elbow, and above the elbow in

intervention group compared with control group. In contrast, these findings disagree with **Hemmati, Rojhani-Shirazi, Zakeri, Akrami, & Salehi Dehno, (2022)** [36] who revealed that, changes in limb circumference at the end of the treatment were not significantly different at any measured point among the studied groups. From the researcher's point of view, this may be related to the measurement method used in the study, and aside from topical cryotherapy, combined therapies are required to produce a significant change in arm measurement.

In relation to signs of lymphedema, the current study revealed that there were statistical differences between the control and study groups regarding signs of lymphedema in terms of hotness and localized swelling after 2 weeks, after one month, and after 2 months of intervention, where most of the lymphedema signs disappeared after 2 months in the intervention group compared with the control group. These findings agree with **Askary& Elshazly, (2022)** [14] who reported that, skin cooling initially leads to local vasoconstriction, leading to decreasing redness, hotness, and edema. In addition to **Jan, (2019)** [37] who revealed that local cooling decreases interstitial fluid volume, inflammation, and fibrosis.

Concerning tissue firmness, the current study revealed a statistically significant difference between the control and intervention groups, and there was a significant improvement in the intervention group. These findings are in harmony with **Mayrovitz & Yzer, (2017)** [18] who demonstrated that topical surface cooling of lymphedematous and fibrotic regions led to a reduction in tissue hardness as judged by reduced local indentation forces.

As regards pain scores, the present study demonstrated statistically significant differences in pain score levels between the control and intervention groups, and there was a decrease in the mean pain score level at different times due to intervention. This agrees with **Mayrovitz& Yzer, (2017)** [18] who stated that skin cooling of the upper limb softens lymphedematous and fibrotic tissue by about 24% to 28%. This tissue softening leads to decreased pressure on the underlying nerve ending and decreased input to the sensory nerves that interrupt the pain cycle.

Conclusion

According to the findings of the current study, it can be concluded that topical cryotherapy is an effective complementary modality for the treatment of breast cancer-related lymphedema by improving the clinical outcomes of the affected patients. It was evident that cold therapy had led to significant improvements in lymphedema size, associated symptoms, and pain intensity scores.

Recommendations

- Including cryotherapy in physical therapy protocols for lymphedema rehabilitation.
- Developing an educational programs and guidelines for safe application of cryotherapy in clinical settings
- Developing educational programs for patients and nurses to enhance their

knowledge about topical cryotherapy as a modality for lymphedema management
- Perioperative education of patients regarding risk-reduction strategies as well as signs and symptoms of lymphedema
- Rigorous clinical trials are needed to address the effect of early detection and rehabilitation of lymphedema after breast cancer treatment.
- Randomized controlled trials with a larger sample size can be conducted to assess the long-term effects of topical cryotherapy on patients with BCRL.

Limitation of the study

The current study has some limitations. Firstly, the follow-up for patients was limited to two months, and the long-term effects needed 3-6 months follow up. Secondly, the study was carried out at one cancer center; so its findings cannot be generalized. Finally, there was a scarcity of evidence-based research on cryotherapy.

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Conflicts of interest

The authors declare that there was no conflict of interest regarding the study.

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