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Effectiveness of Cold Compression Therapy versus Multi-Waved Locked System Laser on Breast Cancer-Related Lymphoedema: Randomized Controlled Trial

Mohamed H. El Gendy[a], Sherine O. El-Sherif[b], Mohamed A. Abolkasem[c], Shreen R. Aboelmagd[d], Yasser R. Lasheen[a]

[a]Department of Basic Sciences Faculty of Physical Therapy, Cairo University, Cairo, Egypt
[b]Department of Basic Science, Faculty of Physical Therapy, Benha University, Egypt
[c]Department of Clinical Oncology, Kasr Al-Ainy Center of Clinical Oncology & Nuclear Medicine, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt
[d]Department of Woman Health, Faculty of Physical Therapy, Cairo University, Cairo, Egypt

Corresponding author: Mohamed H. ElGendy
e-mail: prof.mgendy@hotmail.com

Abstract

Purpose. This study aimed to compare the effectiveness of Cold Compression Therapy and Multi-Waved Locked System Laser on lymphatic flow, volumetric measurements, and quality of life in breast cancer-related lymphoedema patients. Breast cancer-related lymphoedema is a long-term health problem that often causes pain and disability and interferes with daily activities. It may occur after treatment for breast cancer by surgery and radiation therapy. If left untreated, it can have long-term medical and psychological consequences for patients.

Material & Methods. Sixty-six females with breast cancer-related lymphoedema, with a mean age of 37.4±5.39 years, participated in the study. Subjects were randomly divided into three equal groups using simple randomization via the closed-envelope technique. Group A, consisting of twenty-two female patients, received class 4 multi-wave locked system laser and conventional treatment. Group B, also composed of twenty-two female patients, received cold compression therapy and conventional treatment. Group C, the control group, received conventional treatment only. The three groups were assessed using lymphoscintigraphy for lymphatic flow, measuring tape for limb volume, and the Lymphoedema Life Impact Scale (LLIS) for health-related quality of life assessment. Assessments were conducted before and after treatment.

Results. The results indicated that Group B showed statistically significant improvement over Group A in lymphoscintigraphy ($p<0.001$), limb volume ($p<0.001$), and LLIS questionnaire ($p<0.001$). Group B also showed statistically significant improvement over Group C in lymphoscintigraphy ($p<0.001$), limb volume ($p<0.001$), and LLIS questionnaire ($p<0.001$). However, there was no statistically significant difference between Group A and Group C.

Conclusions. Cold compression therapy significantly improved limb volume and circumference, lymphatic flow, and health-related quality of life in patients with unilateral breast cancer-related lymphoedema compared to the multi-wave locked system laser and conventional treatment.

Keywords: Breast Cancer-related Lymphoedema, Cold Compression Therapy, Multi-waved Locked System Laser, Lymphoscintigraphy.

Introduction

Lymphedema is defined as a gradual abnormal swelling of a limb and the related quadrant of the trunk due to the accumulation of protein-rich fluid in the tissue spaces of the skin (Rockson, 2018). Breast cancer-related lymphedema (BCRL) is a concerning complication that occurs after treatment for breast cancer. It is a chronic disease caused by surgery and radiation therapy involving lymph drainage routes of the breast and axillary areas and is considered a potentially severe and debilitating condition (Rockson, 2018; Keast et al., 2015; Borman et al., 2022).

According to reports, the incidence of BCRL varies and is approximately 20% at one year and increases to 40% at ten years after breast cancer treatment with a cumulative incidence of 28% (Rebegea et al., 2015). Indeed, lymphedema is significantly more likely to occur following axillary lymph node dissection (ALND) than after sentinel lymph node biopsy (SLNB) alone (Wernicke et al., 2013). Lymphedema can develop within days postoperatively and can continue to be present until 11 years after breast cancer treatment (Pappalardo et al., 2021). BCRL is caused by a decreased lymphatic transport capacity and increased lymphatic load (Rezende et al., 2017). A reduction in functioning lymphatic nodes and vessels and increased tissue scarring and fibrosis limit adequate processing of the lymphatic load (Lasinski et al., 2012). This leads to chronic swelling, pain, tightness, heaviness of the involved arm and upper quadrant, impaired limb function, and psychosocial disturbances (Rodríguez et al., 2020). Besides an impact on functional and psychosocial well-being, there can be an additional deleterious effect on patients regarding financial costs (Vrieze et al., 2020).

Various photobiomodulation therapy (PBMT) devices exist, ranging from handheld Class 1 and 5-Watt devices to hands-free robotized scanning Class 4 and 75-Watt devices (Chau, 2022). The Class 4 Multi-wave Locked System (MLS®), characterized by synchronized emissions of two wavelengths of 808 nm (in continuous mode) and 905 nm (as pulsed laser light), is a new technique used to increase the effect of laser irradiation (Gworys et al., 2012). Different mitochondrial complexes absorb two emissions and can affect cellular energy metabolism by acting on multiple sites in the cellular respiratory chain at the same time. The super-pulsed laser treats pain and promotes healing; the continuous emissions reduce inflammation and edema (Alayat et al., 2017). Therefore, this device can simultaneously treat pain, inflammation, and edema (Moskal et al., 2015; Peters et al., 2021).

Cryotherapy is a new physical therapy modality for many purposes, including reducing pain, inflammation, and edema. Topical cooling of the skin causes an initial local vasoconstriction (Jan 2020) that reduces the normal post-ischemic hyperemic response caused by tissue indentation loading (Ghanta et al., 2015). Skin cooling also causes systemic vasoconstriction, which, together with local vasoconstriction, decreases capillary-to-interstitium fluid filtration and promotes post-capillary fluid reabsorption (Mayrovitz & Yzer, 2017). These enhanced processes tend to reduce interstitial fluid volume. Therefore, it is reasonable to think that cryotherapy might positively affect the treatment of lymphedema (Askary & Elshazly, 2022; Khanna et al., 2008).

Cryotherapy in combination with Intermittent Pneumatic Compression (IPC), a modality referred to as Cold Compression Therapy (CCT), improves tissue oxygenation, microcirculation, and interstitial fluid circulation, thereby improving soft tissue exchanges (McGuire & Hendricks, 2006). Also, cryotherapy combined with dynamic intermittent Compression decreases the significant risk of skin necrosis (Rashkovska et al., 2014; Rivlin et al., 2014; Mayrovitz & Cassard, 2014; Mendes et al., 2022; Patel et al., 2015). This study was conducted to compare the effectiveness of Cold Compression Therapy and Multi-Waved Locked System Laser on lymphatic flow, volumetric measurements, and quality of life in breast cancer-related lymphoedema patients.

Material and Methods

Participants

This study is a randomized controlled trial approved by the ethical committee of the Faculty of Physical Therapy, Cairo University. Approval from all patients was formally obtained by signing a consent form. This study was conducted at Kasr El-Einy Center of Radiation Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University. Sixty-six female patients with unilateral BCRL were enrolled in this study under the following inclusion criteria: age of patients above 18 years old, history of modified radical mastectomy, chemotherapy and radiotherapy, history or current hormonal treatment, and moderate lymphedema, grade II and III (20–40% increase in extremity volume) patients.

Exclusion criteria were severe co-morbid diseases, the presence of other cancers, cancer recurrence, lymphatic malformation or vascular disease, current chemotherapy and/or radiotherapy, bilateral lymphedema, current metastases, elephantiasis, infection, lymphangitis carcinomatosa, cellulitis, venous thrombosis, or congestive heart failure, and musculoskeletal disorders affecting the upper extremity.

Methods

Patients were divided randomly into three groups: Group (A): study group included 22 female patients who received class 4 MLS laser therapy for the affected arm plus the convention-

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al treatment for BCRL, Group (B): study group included 22 female patients who received CCT for the affected arm plus the conventional treatment for BCRL, and Group (C): control group included 22 female patients who received the conventional treatment for BCRL only. The clinical severity of lymphedema was determined using Cheng Lymphedema Grading (CLG), a 5-grade system based on the circumferential difference between the lymphedematous limb and the uninvolved contralateral limb (Cheng et al., 2021). The five grades are as follows: grade 0 (<9%), grade I (10%–19%), grade II (20%–29%), grade III (30%–39%), and grade IV (>40%) (Cheng et al., 2021). All subjects were familiarized with the study's objectives, equipment, and procedures and received sessions five times per week for four weeks.

Procedures

Instrumentation. The lymphatic flow was assessed by lymphoscintigraphy using a dual-headed gamma camera (Symbia, Siemens Healthineers, Erlangen, Germany). A measuring tape was used to assess circumferential limb measurements, which were used to calculate total upper limb volume. HRQL was assessed by administering the Lymphedema Life Impact Scale (LLIS).

The ASA M6 laser device, provided by ASA s.r.l, emitted a class 4 MLS laser. The BioCryo Cold Compression System Model #SC-2004-C was administered sequentially, combining gradient pneumatic compression and cryotherapy.

Outcome Measures. Initially, demographic data and patient characteristics were collected, including age, weight (kg) (measured to the nearest 0.1 kg using a standard weight scale), and height (cm) (measured to the nearest 0.1 cm with the subject standing erect against a vertical scale).

The lymphatic flow was assessed by lymphoscintigraphy, which was performed using a dual-headed gamma camera (Symbia, Siemens Healthineers, Erlangen, Germany). Anterior, posterior, and spot images of both upper extremities were acquired 5-10 min and one hour after an injection of 0.5 mL MBq of technetium-99m-labeled human serum albumin (Vrieze et al., 2020). The injections were performed subcutaneously into the first web space of both hands. The patients squeezed a rubber ball to improve the transport of the radiopharmaceuticals. The results of the lymphoscintigraphy were interpreted by two nuclear medicine specialists blinded to other clinical characteristics (Vrieze et al., 2020). The following four findings were evaluated: (1) uptake of axillary LNs (not visible or visible), (2) uptake of the primary lymphatic vessel (not visible or visible), (3) uptake of the collateral lymphatic vessel (not visible vs. visible), and (4) presence of dermal backflow (not visible or visible) (Rockson, 2018). Figure 1 shows representative images of the upper extremity lymphoscintigraphy. The lymphoscintigraphy images were divided into three groups and classified into four stages: normal lymphatic drainage (L-0) or partial obstruction (P-1, P-2, and P-3) (Vrieze et al., 2020):

- Normal drainage (L-0): identification of prominent uptake of proximal lymph nodes and linear lymphatic duct from distal to proximal.
- Partial obstruction occurs with a reduced number of proximal lymph nodes or the presence of intermediate lymph nodes in the elbow or popliteal area and is further subclassified into three stages:
  - P-1: distal linear lymphatic ducts without dermal backflow;
  - P-2: engorged distal linear lymphatic ducts with dermal backflow in the proximal or distal lymphedematous limb;
  - P-3: engorged lymphatic ducts with entire

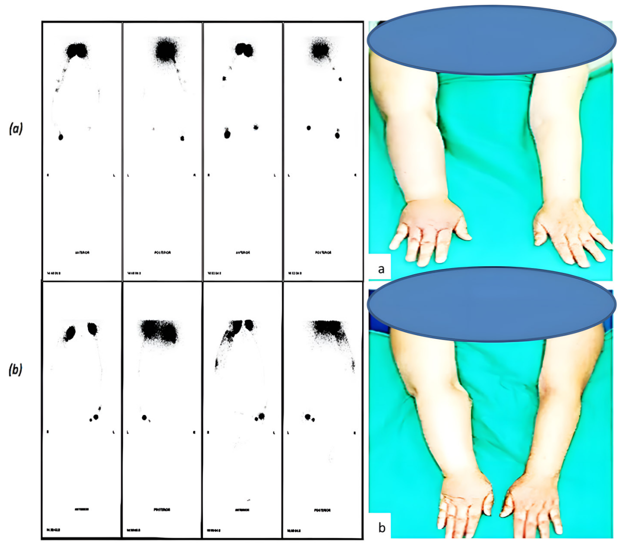

Figure 1. Lymphoscintigraphy images in patients with breast cancer-related upper extremity lymphoedema. A stage P-1. b stage P-2.

dermal backflow.

Limb volume was assessed using manual circumferential measurements, and limb volume was calculated using the volume of a cylinder formula. With the upper limb held straight toward the floor, limb circumferences were measured at 4 cm intervals, from the level of knuckles to 44 cm proximally. A volume of cylinder formula was then used to calculate limb volume (Ghanta et al., 2015; Jan 2020). Volume of a cylinder: The limb was viewed as a series of cylinder-shaped segments. The volume of each segment = C^2/π; C is the circumference at the midpoint of a segment with a length of 4 cm. Total limb volume was determined by the sum of the segment volumes (Ghanta et al., 2015; Jan 2020).

HRQL was assessed using The LLIS questionnaire, which uses the 5-point Likert scale. Each item has a possible score of 0-4, corresponding to the phrases. Participants chose the number corresponding to how true each statement had been for them during the last seven days. The total percent impairment score, where a higher score indicates a worse outcome, was calculated by adding the subscale scores, dividing by the maximum possible score (68), and multiplying by 100 (Williams & Whitaker, 2015; Wiser et al., 2020).

Conservative Treatment for BCRL. All the patients underwent a combined protocol of complete decongestive therapy (CDT) comprising skin care, manual lymphatic drainage, short-stretch multilayer bandaging, and lymphedema exercises (Borman et al., 2022; Lasinski et al., 2012).

a. Skin care and general instructions:

All patients were educated on lymphedema, including skincare and maintaining a healthy body weight, and provided with a written lymphedema brochure for general advice on the first day of treatment (Borman et al., 2022).

b. MLD (Manual Lymphatic Drainage):

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, lasting 45 minutes (Lasinski et al., 2012).

c. Compression short-stretch multilayer bandages:

After the MLD, short-stretch multilayer bandages were applied and changed daily except on the weekends. First, a cotton tube stockinet was placed on the arm, followed by finger bandaging. A padding bandage was placed on the hand and wrapped around the arm. Four short stretch bandages (6, 8, 10, and 12 cm in width) were sequentially placed around the limb (Lasinski et al., 2012).

d. Lymphedema exercises:

All subjects were given an individualized active exercise program, 20 minutes per day, including diaphragmatic breathing exercises, neck and shoulder stretching, hand pumping, and non-isometric strengthening of arm muscles to help facilitate lymphatic flow and improve strength and range of motion. The exercises were performed with bandages (Lasinski et al., 2012).

MLS laser. Class 4 MLS® was used with the robotized head covering the whole area from axilla to hand on the affected arm. Duration: 10 min, with Frequency: 1500 Hz, Duty ratio: 50%, Energy density: 9 J/cm², and Irradiance: 15 mW/cm² (Alayat et al., 2017; Moskal et al., 2015).

CCT. Each patient was seated comfortably, sliding the arm through the internal cavity of the garment. The cryo garments have a water-based gel that maintains a constant 40°F skin interface temperature. The BioCryo Cold Compression System with four sequentially inflated chambers was adjusted to create a pressure of 60 mmHg, with an overall cooling time of about 12-15 minutes (Askary & Elshazly, 2022). Patients were instructed to wear light clothing, light bandages, clean hosiery, or stockinettes underneath garments for hygienic purposes and to prevent skin irritation.

Statistical analysis

All statistical analyses were performed using the statistical package for social studies (SPSS) for Windows, version 27 (SPSS, Inc., Chicago, IL). Alpha level set at 0.05. A split-plot ANOVA was conducted for volumetric measurement and Lymphoedema Life Impact Scale (LLIS) questionnaire, with time (pretest, posttest) as the within-subject factor and Group (Group 1, Group 2, Group 3) as the between-subject factor. Data was summarized using frequency (count) and relative frequency (percentage) for categorical data. The non-parametric Marginal Homogeneity Test was used to compare lymphoscintigraphy pre- and post in each group. For comparing categorical data, the Chi-square (χ^2) test was performed. The exact test was used when the expected frequency was less than 5.

Results

Comparing the demographic characteristics of the subjects of the three groups revealed no significant difference between the groups in the mean age, weight, height, and BMI (Body Mass Index) ($p>0.05$), as shown in Table 1.

i. Lymphatic Flow

As shown in Table 2, there was no significant difference in CLG pretreatment between the three groups ($p=0.394$). At the same time, there was a significant difference in the CLG classification posttreatment posttreatment between the three groups ($p=0.001$). There was a statistically significant improvement in CLG posttreatment com-

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Table 1. Descriptive statistics for the mean age, weight, height, and body mass index of the three groups

Variable	Group A (X±SD)	Group B (X±SD)	Group C (X±SD)	f-value	p-value
Age (years)	37.1 ± 5.88	37.5 ± 5.39	37.6 ± 6.07	1.474	0.237
Weight (Kg)	73.3 ± 7.35	76.1 ± 8.48	74.1 ± 6.10	0.828	0.441
Height (m)	1.635 ± 0.051	1.636 ± 0.067	1.640 ± 0.052	0.045	0.955
Body mass index (Kg/m^2)	27.4 ± 1.92	28.4 ± 2.09	27.5 ± 1.38	1.927	0.153

Table 2. Frequency (count), relative frequency (percentage), and p-values for lymphatic flow pre and posttreatment of the three groups

Lymphatic Flow	MLS group (Count, %)	CCT group (Count, %)	Control group (Count, %)	P-value
Pretreatment				
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.394
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	
2	6 (27.3%)	9 (40.9%)	5 (22.7%)	
3	16 (72.7%)	13 (59.1%)	17 (77.3%)	
PosttreatmentPosttreatment				
0	0 (0.0%)	11 (50.0%)	0 (0.0%)	< 0.001
1	3 (13.6%)	8 (36.4%)	0 (0.0%)	
2	9 (40.9%)	3 (13.6%)	10 (45.5%)	
3	10 (45.5%)	0 (0.0%)	12 (54.5%)	
P value	0.003	<0.001	0.025	

Table 3. Comparison between each two groups for lymphoscintigraphy posttreatment

Comparison	P-value	Significant
Group A vs. Group B	<0.0001	S
Group A vs. Group C	0.326	NS
Group B vs. Group C	<0.0001	S

Table 4. Mean and p-values for volumetric measurement pre and posttreatment of the three groups

Group	Volumetric Measurement in cm^3 Pre (X±SD)	Volumetric Measurement in cm^3 Post (X±SD)	MD	% of Change	t-value	P-value	Sig
Group A	2770.56±367.36	2583.29±367.12	−187.267	-6.76%	14.912	<0.0001	S
Group B	2589.11±433.97	2183.69±342.08	−405.422	-15.66%	6.210	<0.0001	S
Group C	2810.40±344.14	2669.28±317.95	−141.11	-5.02%	10.552	<0.0001	S
f-value	2.079	12.558151					
P-value	0.134	0.00001					
Sig	NS	S					

X: Mean SD: Standard deviation MD: Mean difference p value: Probability value S: Significant NS: Non-significant

pared to pretreatment in all three groups: group A (p=0.003), group B (p<0.001), and group C (p=0.025).

The Chi-square (χ^2) test was performed to find the statistical difference between groups. There were significant differences between groups A and B (p=0.0001) in favor of group B and between groups B and C (p=0.0001) in favor of group B. There was no significant difference between groups A and C (p=0.326), as shown in Table 3.

ii. Volumetric Measurements

As shown in Table 4, there was no significant difference between the three groups' pretreatment regarding the volumetric measurements (p=0.134). In comparison, there was a significant difference in the mean values of volumetric measurements posttreatment between the three groups (p=0.001). There was a significant decrease in the volumetric measurements in the study and control groups posttreatment compared with pretreatment (p=0.001).

As observed in Table 5, a post hoc test to find the statistical difference between groups in the mean values of volumetric measurements t, there were significant differences between groups A and B (p=0.001) in favor of group B, groups B, and C (p=0.001) in favor of group B, while there was no significant difference between groups A and C (p=0.88).

Table 5. Post hoc test for the mean values of volumetric measurement posttreatment

Comparison	Mean Difference	P-value	Significant
Group A vs. Group B	−399.6	<0.0001	S
Group A vs. Group C	−85.9	0.88	NS
Group B vs. Group C	−485.59	<0.0001	S

iii. LIIS Questionnaire

Table 6 showed that there was no significant difference in the mean values of the LIIS questionnaire pretreatment between the three groups (p=0.430837). However, there was a significant difference in the mean values of the LIIS questionnaire posttreatment between the three groups (p=0.001). There was a significant decrease in LIIS in both study groups and the control group posttreatment compared with pretreatment (p=0.001).

As observed in Table 7, post hoc test to find the statistical difference between groups in the mean values of LIIS questionnaire posttreatment, there were significant differences between groups A and B (p<0.001) in favor of group B and between groups B and C (p=0.0001) in favor of group B. At the same time, there was no significant difference between groups A and C (p=0.192).

Discussion

Lymphoedema is a significant healthcare problem in several countries. It is a hot spot due to its long-term physical and psychosocial effects on the patient if left untreated. The present study compared the effectiveness of Cold Compression Therapy and Multi-Waved Locked System Laser on lymphatic flow, volumetric measurements, and quality of life in breast cancer-related lymphoedema patients. The results indicated that local cryotherapy combined with intermittent compression therapy, called CCT, positively affects BCRL treatment, as shown by comparing pretreatment and posttreatment. Posttreatment improvement in the lymphatic flow and HRQL and decrease in limb volume of group B posttreatment. The primary result of the present study was the finding that the application of cryotherapy in addition to compression therapy (CCT) on the lymphoedematous and hardened limb led to a reduction in limb volume, improved lymphatic flow and quality of life, and released tissue fibrosis as judged by decreasing the circumferential measurements and improved lymphatic flow.

The primary hemodynamic effect is a blood flow reduction attributable to cold-induced vasoconstriction (Alvarez et al., 2006) and, to a lesser degree, to increased blood viscosity (Çinar et al., 2001). Such precapillary vasoconstriction tends to reduce fluid transport from capillary to inter-

Table 6. Mean and p-values for LIIS questionnaire pre and posttreatment of the three groups

Group	LIIS Questionnaire Pre (X±SD)	LIIS Questionnaire Post (X±SD)	MD	t-value	P-value	Sig
Group A	73.13±13.2	58.55±13.024	14.586	19.8294	<0.0001	S
Group B	68.25±17.04	36.89±11.53	31.359	14.9775	<0.0001	S
Group C	73.195±12.467	65.582±12.485	7.614	7.1964	<0.0001	S
f-value	0.85	32.17				
P-value	0.430837	<0.0001				
Sig	NS	S				

X: Mean SD: Standard deviation MD: Mean difference p value: Probability value S: Significant NS: Non-significant.

Table 7. Post hoc test for the mean values of LIIS questionnaire posttreatment

Comparison	Mean Difference	P-value	Significant
Group A vs. Group B	21.6545	<0.0001	S
Group A vs. Group C	7.0318	0.192	NS
Group B vs. Group C	−28.6864	<0.0001	S

stitium and also promotes post-capillary fluid reabsorption due to an associated decrease in venous intravascular pressure. This cooling-related reduction in tissue water could potentially contribute to net tissue softening (Askary & Elshazly, 2022). Another possible mechanism whereby tissue hardness may have been reduced is via a direct cooling effect on the skeletal muscle contractile state. Such changes have been reported to occur (García-Manso et al., 2011). It is also possible that a rapid pain-reducing effect of cooling mediated indirect skeletal muscle relaxation (Leff et al., 2007; Koc et al., 2006).

Average cooling-induced temperatures achieved on the arm (23.7 °C) would have caused altered sensory nerve activity via effects mediated by transient receptor potential (TRP) channels located in the sensory nerve endings (Voets et al., 2004). Cooling to temperatures of 30 °C to 15°C, as in the present case, causes specific voltage-gated TRP channels (TRPM8) to open about the amount of the temperature decrease, causing increased inward calcium current. This causes an increase in the tonic firing rate of cold-sensitive A afferent nerve fibers (Park & Kim, 2013). Although the altered nerve firing rate mainly provides sensory feedback, the possibility of a mechanical effect on tissue via other potential pathways cannot be entirely excluded. When tissue is softened by cryotherapy, as has been observed in the present study, it becomes more pliable, and the combination with compression therapy can ease fibrosis management through more profound levels of myofascial lengthening and scar tissue release, resulting in the release of restricted lymphatic structures and improved lymphatic flow.

In addition, the tissue softening likely reduces pressure on muscles and muscle spindles in those areas where the fibrosis affects muscle. This helps normalize sensory nerve communication and muscle-length feedback to the central nervous system and assists with stretching therapy during treatment. Perhaps equally significant to the various physical and physiological effects is the psychological impact of rapid tissue softening and the associated decrease in pain that improves the patient's outlook for recovery (Askary & Elshazly, 2022). Askary and Elshazly (2022) have conducted a study to investigate the effect of adding local cryotherapy of the upper limb to the traditional physical therapy program, which includes pneumatic Compression, MLD, and exercises (breathing, circulatory, and ROM of the upper limb) on fibrotic points in the upper limb using ultrasonography and on the volume of the arm using circumferential measurements of preselected points in the upper limb, in patients with postmastectomy lymphoedema. The results of this study came in agreement with our study, as it proved that adding local cryotherapy had a positive effect on the fibrotic points, with a significant decrease in their thickness and a significant decrease in the circumferential measurements of the upper limb.

In concurrence with our study, Mayrovitz and Yzer (2017) also stated that topical surface cooling of lymphoedematous and fibrotic regions led to a reduction in hardness and fibrotic tissue by about 24% to 28% as judged by reduced local indentation forces. This study considered that when tissue is softened by local cooling, the tissue becomes more pliable, and the clinician can facilitate more profound levels of myofascial lengthening and scar tissue release, releasing restricted lymphatic structures and improving lymphatic flow. Ojeh et al. (2020) suggested that both pressure therapy and cryotherapy can be used to treat and manage keloids, hypertrophic scars, and fibrotic tissues, as increased pressure in combination with cryotherapy to the scar surface reduces perfusion and decreased oxygen to the location of injury reduces collagen synthesis. It is also thought that pressure increases apoptosis, reduces scar hydration, stabilizes mast cells, and decreases angiogenesis, which agrees with the findings of our study that cryotherapy combined with compression therapy releases the fibrotic tissues and improves the lymphatic flow. However, Scialoia and Swartzendruber (2020) reported in their review that the RICE (Rest, Ice, Compression, Elevation) protocol for acute musculoskeletal injuries treatment is a myth and wholly predicated upon unsubstantiated reports dating back over four decades, which was also recanted in 2015 by its founding father. They suggested that when topical cooling (ice) is applied to damaged tissues, it acts as a vasoconstrictor. This physiological response impedes the transport of inflammatory chemicals and neutrophils to the site of trauma and delays healing (Mirkin, 2014; Khoshnevis et al., 2015).

They also purported that icing could produce more damage to the body's tissues due to the prolonged period of vasoconstriction, as the blood vessels will remain constricted after icing regardless of whether the ice is being applied. As a result of the reduced blood flow, the tissue is subjected to a hypoxic (low oxygen) environment, which can result in tissue death and permanent nerve damage (Mirkin, 2014; Khoshnevis et al., 2015). It should be noted that this review's scope differed from our study, as they were concerned about the effect of ice and Compression on acute musculoskeletal injuries. On the contrary, our study focused on stage II and III lymphoedema, characterized by chronic edema and fibrotic tissues that restrict lymphatic flow, causing more congestion and hardening of the limb. Besides, this review did not conduct a proper systematic review with no meta-analyses. So, it can be considered as an opinion of the authors, not evidence-based guidelines supported by research. The second result of the present study was the finding that the administration of class 4 MLS laser in conjunction with MLD, compression therapy, and exercises to the whole area from axilla to hand on the lymphoedematous arm resulted in decreasing the limb volume and releasing tissue fibrosis as judged by decreasing the circumferential measurements and improved lymphatic flow.

PBMT is a nonionizing light-based conservative therapy (Mahmood et al., 2022). Photons of a specified wavelength penetrate skin tissue to give low rays and doses to the targeted area in laser treatment or PBMT (Mahmood et al., 2022; Karu, 2007). However, biochemical changes at the cellular level are the critical mechanism for employing PBMT. Fibroblasts, osteoblasts, lymphocytes, and smooth cells are all altered during the therapy. The cytochromes, cytochrome oxidase, and flavin dehydrogenases in the mitochondrial respiratory chain absorb the rays, causing changes in the reduction-oxidation reaction (REDOX) state of the cytoplasm and mitochondria, which leads to increasing the levels of adenosine triphosphate (ATP) (Karu, 2007). After ATP synthesis, an increase in metabolic energy triggers a subsequent critical process for cellular repair and downregulation of pain and inflammation (Karu, 2007; Moskal et al., 2015). Furthermore, intracellular signaling and cytokine activation allow for various responses, including the development of new lymphatic vessels, the release of growth factors, and metabolic upregulation (Alayat et al., 2017; Moskal et al., 2015). As a result, PBMT helps enhance the immune system by facilitating the drainage of excess protein-rich fluid and increasing macrophage formation (Karu, 2007).

Furthermore, PBMT is an emerging therapeutic modality for treating cutaneous fibrosis. PBMT would act on the cellular plan as a modulator of the reactions causing the pathology. PBMT would reduce the rate of proliferation and migration of fibroblasts, would inhibit pro-fibrotic cytokines and their related pathways like that of TGF-beta, and would decrease the synthesis and deposition of collagen (Moskal et al., 2015).

Only one single-case study by Perkins et al. (2017) investigated the effect of class 4 MLS laser combined with MLD, compression therapy, and IPC on limb volume and quality of life of a 36-year-old female patient over four weeks. This study concluded that this combination of MLS laser therapy and the conventional treatment of lymphoedema regarding limb size, tissue mobility, and patient activity level achieved optimal patient outcomes. It also suggested that this case's results show the efficacy of PBMT in lymphoedema treatment, given its potential high impact on patient quality of life. This proves our results, as decreased fibrotic tissues and improved excess protein-rich fluid drainage led to the encouragement of lymphatic flow, decreased arm volume, and improved quality of life. The results of the current study suggested no significant difference between the effect of class 4 MLS laser therapy in addition to the conventional therapy for lymphoedema and the effect of the conventional therapy alone on limb volume, lymphatic flow, and quality of life. These results agreed with Baxter et al. (2018), as they reported conflicting evidence from systematic reviews on the effectiveness of PBMT over conventional therapy (e.g., compression bandage, pneumatic Compression, and manual lymphatic drainage) in limb circumference reduction and pain relief in short-term follow-ups. They also reported that evidence from systematic reviews and meta-analyses on using PBMT for other conditions has shown that effect sizes are often more significant at the long-term follow-up assessments than directly at the end of the PBMT intervention. Fully powered RCTs with more extended follow-up periods are needed to inform the effectiveness of PBMT in the management of BCRL (Baxter et al., 2018).

Conclusion

Study results prove that CCT is a compelling new modality in the treatment and rehabilitation of BCRL. It should be added to the lymphoedema physical therapy rehabilitation protocol to improve patient outcomes over conventional treatment alone.

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Authors details

Mohamed H. El Gendy
https://orcid.org/0000-0001-9996-5344,
Department of Basic Sciences Faculty of Physical Therapy, Cairo University, Cairo, Egypt.

Sherine O. El-Sherif
https://orcid.org/0009-0006-9822-6666,
Department of Basic Science, Faculty of Physical Therapy, Benha University, Egypt.

Mohamed A. Abolkasem
https://orcid.org/0009-0005-5354-1569,
Department of Clinical Oncology, Kasr Al-Ainy Center of Clinical Oncology & Nuclear Medicine, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt.

Shreen R. Aboelmagd
https://orcid.org/0009-0005-9849-8445,
Department of Woman Health, Faculty of Physical Therapy, Cairo University, Cairo, Egypt.

Yasser R. Lasheen
https://orcid.org/0009-0000-3547-3885,
Department of Basic Sciences Faculty of Physical Therapy, Cairo University, Cairo, Egypt.

Author's contribution
Conceptualization, M.H.E., S.O.E., and Y.R.L.; methodology, M.A.A., S.R.A.; M.A.A., S.R.A., and S.O.E., ; check, M.H.E., M.A.A., S.R.A., and Y.R.L.; formal analysis, S.R.A.; investigation, M.A.A., S.R.A.; resources, SRA; data curation, MHE, MAA, SRA, and YRL; writing - rough preparation, S.R.A.; writing - review and editing, M.A.A. and Y.R.L.; visualization, S.O.E.; supervision, M.H.E. and Y.R.L.; project administration, M.H.E.; All authors have read and agreed with the published version of the manuscript.