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REVIEW ARTICLE

Low-level laser therapy in secondary lymphedema after breast cancer: systematic review

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Abstract Complex physical therapy is the main treatment for the secondary lymphedema after breast cancer. The low-level laser therapy (LLLT) has been used in order to stimulate lymphangiogenesis, encourage lymphatic motility, and reduce lymphostatic fibrosis. However, these factors could also favor the development of recurrence and metastasis. The objective of this study is to discuss the use of LLLT in the treatment of lymphedema after breast cancer. This study utilized a systematic review on the use of LLLT in the treatment of lymphedema after breast cancer. Evaluating quality of articles was conducted through the PEDro scale. Of the 41 articles identified, four were considered to be of high methodological quality (score≥5). The low-level laser in the axillary region was performed in all studies. The control group was not similar across studies. The results presented showed that there was a reduction in limb volume in the group subjected to low-power laser when compared with other treatments. No studies have evaluated the risk of metastasis or relapse in the irradiated areas. Because no studies have included the complex physical therapy as the comparison group, we cannot claim that laser treatment is the best efficacy or effectiveness in lymphedema treatment after breast cancer. No studies have evaluated the hypothesis that the LLLT can increase the risk of recurrence or metastasis. Therefore, the questions about the safety of this procedure in cancer patients remain.

Keywords Breast neoplasm · Low-level laser therapy · Physiotherapy · Lymphedema

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Introduction

The overall increase in incidence of breast cancer and significant morbidity related to its treatment has raised renewed attention to the management of arm lymphedema in recent years. The onset of lymphedema secondary to breast cancer treatment often leads to a chronic condition of functional disability, disfigurement, and inflammatory attacks [1] and even conservative approaches to treat breast cancer, like sentinel lymph node sampling and selective axillary clearance, have failed to erradicate lymphatic complications. Moreover, incidence of lymphedema can affect up to one out of four treated patients [2].

According to the Consensus Document of the International Society of Lymphology, complex physical therapy (CPT), consisting two phases of treatment involving a combination of four components: skin care, manual lymph drainage, compression therapy, and remedial exercises, is the recommended conservative approach to reduce limb volume in most patients [3]. However, not all facilities dealing with breast cancer patients offer the recommended treatment and several alternative modalities of lymphedema treatment have been reported [4–6].

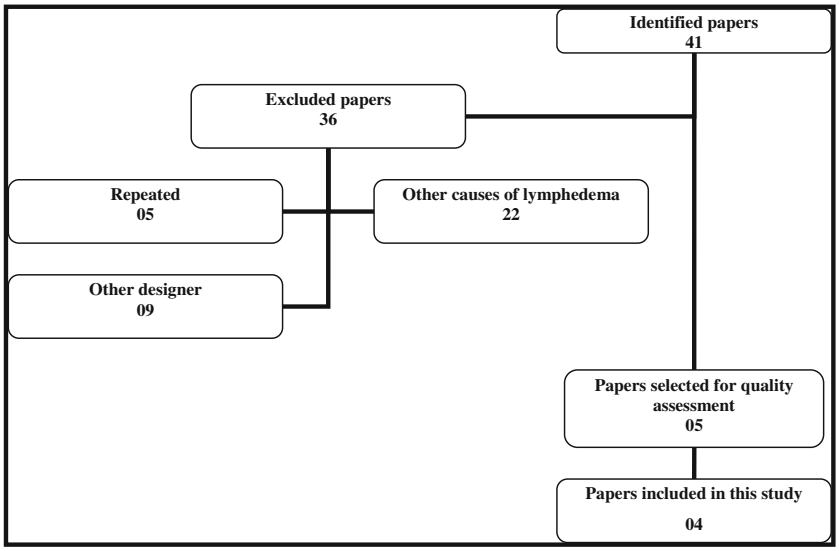

Fig. 1 Identification of papers in databases

Recently, low-level laser therapy (LLLT) has been suggested as a possible useful treatment for lymphedema. Its described mechanisms of volume reduction include promotion of lymphangiogenesis and lymphatic motility stimulation, with no significant changes in tissue architecture. LLLT would also improve overall lymphatic flow and reduce interstitial fibrosis which accompanies lymph stasis [7]. However, such proposed impact of enhanced lymphatic drainage in promoting metastasis in these patients is still unknown, even though some studies have examined its action in different tumoral cell lines [8–13] and LLLT has been shown to underexpress extracellular matrix proteins responsible for cell adhesion which could be related with metastasis [14].

In this context, the aim of this systematic review is to ascertain the usefulness of LLLT in lymphedema treatment and discuss the safety of its use in cancer patients.

Materials and methods

We performed a systematic review in the databases LILACS, MEDLINE, PEDro, PubMed, and SCIELO for articles published in Portuguese, Spanish, and English using, individually or combined, the keywords: physical therapy modalities, physical therapy, lymphedema, breast neoplasms, and low-level laser therapy.

Table 1 Quality assessment according to PEDro criteria

Author Item	Carati et al. [16]	Kaviani et al. [17]	Maya et al. [19]	Kozanoglu et al. [18]	Lau et al. [7]
Eligibility criteria were specified	Yes	Yes	Yes	Yes	Yes
Subjects were randomly allocated to groups	Yes	Yes	Yes	No	Yes
Allocation was concealed	Yes	No	No	Yes	Yes
The groups were similar at baseline regarding the most important prognostic indicators	Yes	Yes	No	Yes	Yes
There was blinding of all subjects	Yes	Yes	No	No	Yes
There was blinding of all therapists who administered the therapy	Yes	Yes	No	Não	Não
There was blinding of all assessors who measured at least one key outcome	Yes	No	No	Não	Yes
Measures of at least one key outcome were obtained from more than 85 % of the subjects initially allocated to groups	Yes	No	Yes	Yes	Yes
All subjects for whom outcome measures were available received the treatment or control condition as allocated or data for at least one key outcome was analyzed by "intention to treat"	No	No	No	No	No
The results of between-group statistical comparisons are reported for at least one key outcome	Yes	Yes	Yes	Yes	Yes
The study provides both point measures and measures of variability for at least one key outcome	Yes	No	Yes	Yes	Yes
Total PEDro Scale	09	05	04	05	08
Included	Yes	Yes	No	Yes	Yes

The following criteria were used to include studies for further assessment:

- Study design: clinical trials (intervention studies)
- Eligible population: women with lymphedema secondary to breast cancer treatment;
- Intervention: treatment with LLLT used as an intervention in the treatment group.
- Control group: there was no restriction in the control group (placebo, other drug regimens, lack of intervention);
- Outcome of primary interest: changes in volume or perimetry of the affected limb before and after the intervention.

Data collection

Data were collected using a standardized form containing information about: author and year of publication, number of participants, the protocol of LLLT used, the control group, outcomes evaluated, and main results.

Quality assessment of the methods of included studies

Quality of the articles was evaluated using the physiotherapy evidence database scale (PEDro). When unavailable from the original source, articles were reviewed employing the same methodology used in PEDro [15]. Articles were included whenever they scored at least 5 out of 10 points in the scale.

Results

Forty-one studies were found matching our keyword search in the selected databases and 36 articles were excluded for not meeting the inclusion criteria (Fig. 1).

Among the five eligible papers for this systematic review, quality assessment according to PEDro database was available for four publications [16–19] and one of them [19] did not reach the minimum score required to be included in this review. The article which was not evaluated in the PEDro database [7] was considered of high methodological quality and included in this analysis (Table 1).

Considering all four studies, 75 patients were submitted to LLLT and 74 subjects were considered as controls. The control groups were not similar in the studies. Among those who used the placebo as a comparison (inactive laser), Carati et al. [16] used it only in the first treatment cycle but added active laser protocol in the second cycle. Kaviani et al. [17] used two cycles of inactive laser in the control group. The pneumatic compression was the control used by Kozanoglu et al. [18] and Lau et al. [7] compared their results with a group with no intervention (Table 2).

Table 2 Characteristics of included studies

Study	Number of subjects	Treatment design	Control Group	Similar interventions among groups	Follow-up	Evaluation of outcomes
Carati et al. [16]	LLLT=33 Control=33	2 blocks of LLLT, separated by an 8-week rest period	1 block of sham therapy, followed by an 8-week rest period and then 1 block of LLLT	1 block of LLLT	1 block of therapy (active or placebo), followed by an 8-week rest period and then 1 block of LLLT	Perimetry; bioimpedance; tonometry; shoulder range of movement; self-reports
Kaviani et al. [17]	LLLT=6 Control=6	3 times a week for 3 weeks. After an 8-week interval, the same treatment protocol was repeated for another 3-week period (18 treatment sessions)	Patients similarly received sham irradiation under strictly controlled double-blinded conditions	Not applicable	Assessed before and during the treatment at weeks 3, 9, 12, 18, and 22	Limb circumference; pain score; range of motion; heaviness of the affected limb
Kozanoglu et al. [18]	LLLT=25 Control=25	20-min therapy for 4 weeks and consisted of 12 sessions	2 h of intermittent pneumatic compression therapy for 4 weeks (20 sessions)	Active range of motion, elevation, and pumping exercises, hygiene, and skin care	Pre and post treatment and follow-up at 3, 6, and 12 months	Limb circumference; pain in range of motion of the upper extremity joints; grip strength;
Lau et al. [7]	LLLT=11 Control=10	LLLT was 3 times a week for 4 weeks	No treatment. Follow-up after 4 and 8 week for reassessment	Skin care, MLD, and gentle upper limb mobilization exercises	Before and after the treatment period and at the 4-week follow-up	Volumetry; tonometry; DASH questionnaire symptoms

LLLT low-level laser therapy; *DASH* disabilities of the arm, shoulder, and hand; *MLD* manual lymph drainage

Table 3 Clinical characteristics of the patients included in the studies

Study	Mean age (±SD)		Mean weight at start of trial (±SD)		Lymphedema duration (months) (±SD)		Excess limb volume at start of trial[a]	
	LLLT	Control	LLLT	Control	LLLT	Control	LLLT	Control
Carati et al. [16]	63 years (±2)	65 years (± 2)	76 kg (±2)	76 kg (±3)	98 months (±15)[b]	43 months (±9)[b]	888 mL (±108)	645 mL (±72)
Kaviani et al. [17]	54 years (±10)	49 years (±12)	-	-	7 years (±4)	6 years (±5)	180 cm (±18)	166 cm (±17)
Kozanoglu et al. [18]	45 years (±10)	51 years (±10)	-	-	19 months (±30)	21 months (±27)	19 cm (±6)	17 cm (±10)
Lau et al. [7]	51 years (±9)	51 years (±9)	62 kg (±86)	62 kg (±12)	43 months (±1)	36 months (±9)	448 mL (±146)	426 mL (±167)

[a] Affected limb volume−unaffected limb volume

[b] A significant statistical difference was found between the groups

The treatment period varied from 3 to 4 weeks for each cycle and follow-up ranged from 1 to 12 months. Volume reduction of the limbs as a major endpoint for the studies was also measured by different methods: perometry, bioimpedance [16], circumference of the upper limbs [17, 18], and water displacement [7]. In two studies, changes in tissue hardening were also assessed by tonometry [7, 16]. Analysis of subjective feelings as pain, restriction of movement, difficulty in daily activities, and heaviness was included in all studies (Table 2).

Treatment and control groups were similar in all studies included in this systematic review except for lymphedema duration in one study [16] (Table 3). Treatment protocol and physical laser characteristics (type, output, and power) varied widely in all four studies making it difficult to compare among them. In all studies, the axilla was targeted and one of them included treatment of the cubital fossa [18]. Table 4 summarizes the methods of the studies.

In all studies, LLLT showed favorable results in limb volume reduction as compared with the control group, especially in longer periods of follow-up. Also, significant decrease in tissue hardness was observed in two studies where it was considered as an endpoint. LLLT failed to show improvement of subjective symptoms in all but one study. Results are shown in Table 5. No adverse reactions were reported. None of the articles referred to any increase in cancer dissemination after treatment. However, that was not included as a scope for the selected studies.

Table 4 Technical features of laser used in the included trials

Study	Laser type/model	Local	Treatment time	Laser output/power density/dose
Carati et al. [16]	RianCorp LTU 904H	17 points centered at 2-cm intervals in the axilla	1 min each point, 1 7 min per session, 3 times a week, 3 weeks	300 mJ over 17 points (5.1 J in total), dosage of 1.5 J/cm2
Kaviani et al. [17]	GaAs diode laser system, Mustang-024	5 points in the axillary region	3 times a week, 3 weeks, 2 period (18 sessions)	10 W at 890 nm wavelength in pulsed mode (frequency 3,000 Hz, pulse width 130 ns, emission power 4 mJ/s). 0.7 cm^2 each point of axillary region was 1 J (energy density 1.5 J/cm2)
Kozanoglu et al. [18]	GaAs 904-nm laser devise (Eletronica Pagani IR27/4)	3 points on the antecubital fossa and at seven points on the axilla	20 min, 3 times a week, 4 weeks (12 sessions)	2800 Hz , 1.5 J/cm2
Lau et al. [7]	Comby 3 Terza Serie, Model D; ASA S.r.l	Axillary region of the affected side	20 min, 3 times a week, 4 weeks (12 sessions)	Wavelength of 808 nm and two emitting at a wavelength of 905 nm. The average output of the head source was 500 mW (808 nm) and 24 mW (905 nm). Each with pulsed emission at a frequency varying from 1 to 10,000 Hz (905 nm) and continuos emission at 1 to 1.500 Hz (808 nm).

Table 5 Effect of the treatment of studies included in systematic review

Author	Effect of the treatment		
	Arm volume	Tonometry	Symptoms
Carati et al. [16]	Mean affected limb volume at 3 months after 2 cycles of treatment was significantly less than after placebo treatment (89.7 vs 32.1 mL; $P=0.017$). There were no significant differences found between active and placebo groups immediately after cessation of the treatment. Thirty-one percent had a clinically significant reduction in their affected limb volume 2–3 months after treatment with 2 cycles of LLLT treatment.	There were significant decreases in tonometry readings (indicating increased tissue hardness) in participants receiving placebo or one cycle of LLLT treatment over the duration of the trial. Significant hardening of the affected arm were reported immediately after treatment with 2 cycles of LLLT, but at 3 months after treatment there was a significant increase in tissue tonometry reported in the affected upper arm ($P=0.025$).	There was no difference found between placebo or either of the active treatment regimens.
Kaviani et al. [17]	The total reduction in circumference in LLLT group was greater than in the sham group in all sessions except week22[a].	-	The reduction of pain score at each session compared to pretreatment status in the laser group was more than in the sham group except in the weeks3 and 9[a]. The differences between range of motion and heaviness scores at each session and baseline scores had a similar pattern in both groups[a].
Kozanoglu et al. [18]	The reduction in the limb circumference was greater in LLLT group than that in control group at posttreatment ($P=0.04$) and at 12 months ($P=0.02$).	–	No significant differences were detected with respect to pain scores and grip strength between the two groups in all follow-up.
Lau et al. [7]	In the laser group, the change in arm volume decreased from 448.2 to 320.9 mL at 4-week follow-up ($p=0.00$). The control group showed a significant increase, from 426.0 to 447.0 mL ($p=0.00$) at the 4-week follow-up. By the follow-up session, the laser group had a 28 % cumulative reduction in the arm volume in contrast to a 6 % increase in the control group ($p=0.044$).	The laser group demonstrated a significant increase in tonometry readings at sites 1, 2, and 4 ($p=0.000$; $p=0.002$; $p=0.000$). Upon the follow-up session, there was a 33.2 % cumulative increase in tonometry reading at site 1 and a 15.2 % cumulative increase at site 2 and 4, with significant between-group difference found at sites 1 and 4 even after adjustment ($p<0.017$).	In the laser group, the mean DASH scores decreased significantly from 36.9 to 24.9 at the follow-up session ($p=0.040$), but not in control group ($p=0.338$). Upon the 4-week follow-up, the laser group demonstrated a 37 % cumulative reduction in DASH scores, compared to a 7 % cumulative increase in DASH scores for the control group ($p=$not significant).

[a] *P* value not reported

Discussion

The laser is an electromagnetic radiation from the light amplification by stimulated emission of radiation, produced in a resonant optical cavity from an active medium and a source of excitation [20]. The LLLT has been used as a resource for physical therapy in different clinical settings [21]. Among the types of laser, the most widely used in clinical practice are the helium–neon (HeNe) and gallium–arsenide (GaAs) [22].

In cancer patients, the laser has been used in prevention and treatment of mucositis induced by radiotherapy and chemotherapy [23]. It is also employed in postoperative complications of breast cancer, in order to stimulate lymphangiogenesis, enhance lymphatic motility, stimulate macrophages and immune system, and reduce fibrosis [24]. However, these effects could possibly favor recurrence and metastasis development [25–28].

Inclusion of studies was performed based on the criteria of the PEDro scale. However, this scale does not classify the external validity of the studies nor considers the magnitude of the effects of the treatments, thus it cannot be considered as a reliable source for evidence of the results [15].

Several aspects must be taken into account in assessing the applicability of the LLLT in clinical practice for patients

with lymphedema after breast cancer treatment (external validity): generalizability of results, definition, and evaluation of outcomes and benefits of treatment [29].

Considering the generalization of results, this systematic review was used as selection criteria studies in women with lymphedema after breast cancer. Therefore, the results cannot be generalized to other populations.

About the outcomes studied, all items included limb volume reduction as the main outcome, although the method used was not uniform. Also studied were the tissue resistance (tonometry), range of motion, related symptoms of the limb, and reported difficulties in performing daily activities.

The best methodological design of a clinical trial to assess the efficacy of a new treatment is to compare the treatment under test to the standard method employ to manage the clinical problem [30]. For lymphedema after breast cancer treatment, the best scientific evidence supports the approach by complex decongestive physiotherapy and compression [3, 6, 24, 31–33]. However, no study has targeted such design.

Therefore, the results of this systematic review are to be cautiously interpreted due to the inherent methodological limitations of the analyzed studies, like the small sample sizes of the included studies, the lack of definition of the used dose and power density in several studies, and the lack of two important qualitative parameters, i.e., blindness and concealed allocation to groups. Because of these limitations, the meta-analysis could not be performed.

Future research must be performed to establish some unclear issues regarding laser therapy in patients with lymphedema after breast cancer treatment, particularly the time of laser application, number of treatment sessions, energy settings, power density, and dose. In addition, future studies must include, as a comparison group, the standard lymphedema treatment (complex physical therapy) in order to ascertain the laser role in lymphedema treatment. Additionally, longer follow-up is necessary to evaluate the occurrence of side effects or adverse reactions related to laser exposure.

Conclusion

The LLLT showed favorable results in reducing limb volume as compared to placebo, no intervention, and pneumatic compression. However, studies comparing LLLT with the standard approach recommended to treat most patients with lymphedema after breast cancer treatment were not reported. Therefore, it is not possible to ascertain the role of LLLT alone or combined with complex physical therapy in this group of patients. As no studies have evaluated the hypothesis whether LLLT can increase the risk of recurrence or metastasis, this procedure should be employed cautiously in cancer patients.

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