Photodermatology, Photoimmunology & Photomedicine

ORIGINAL ARTICLE

Photobiomodulation therapy in breast cancer-related lymphedema: a randomized placebo-controlled trial

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Key words:
breast cancer-related lymphedema; grip strength; limb volume; pain; photobiomodulation therapy

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Accepted for publication:
2 December 2016

Conflicts of interest: The authors declare that there is no conflict of interest. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

SUMMARY

Background

The aim of our study was to examine the effects of photobiomodulation therapy (PBMT) in the treatment of breast cancer-related lymphedema using a compactly designed treatment regime consisting of eight therapy sessions in combination with a cluster laser device covering a total area size of 78.54 cm² over the axillary.

Methods

Forty patients with unilateral lymphedema were enrolled in this double-blind, placebo-controlled trial in order to evaluate effects of PBMT on lymphedema-related pain, quality of life, grip strength and limb volume difference. Subjects received irradiation for ten minutes per session using a cluster laser covering a beam area of 78.54 cm². The applied energy was 384 Joules resulting in an energy density of 4.89 J/cm².

Results

Post-treatment, a 50% reduction in median pain scores and an increase in mean quality of life were observed. Mean grip strength was persistently higher after eight sessions of PBMT compared with pretreatment; however, no statistically significant intergroup differences ($P > 0.05$) were found over the time course.

Conclusion

PBMT using a compactly designed treatment regime in combination with a cluster laser device did not significantly improve quality of life, pain scores, grip strength and limb volume over the time course.

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doi:10.1111/phpp.12284

Lymphedema describes an interstitial accumulation of protein-rich fluid resulting in subsequent inflammation, fibrosis and tissue hypertrophy (1). It is a chronic disease mostly associated with an acquired disorder of the lymphatic vessels and lymph nodes (2). Breast cancer treatments, such as surgery, radiation and chemotherapy, can negatively affect physiological lymphatic function and consequently disrupt lymphatic transport (3). Data regarding incidence and prevalence of breast cancer-related lymphedema (BCRL) in the literature still remain controversial due to inconsistent definitions of lymphedema and a notable amount of different measurement techniques as well as differences in follow-up time.

According to a recently published meta-analysis, more than one in five women who survive breast cancer will develop unilateral arm lymphedema (4). Petrek *et al.* (5) noted an even higher prevalence in a cohort of breast cancer survivors 20 years after diagnosis where 49% of the participants reported the sensation of lymphedema. Frequently reported symptoms of BCRL include pain, substantial functional impairment and psychological morbidity with diminished quality of life (6). It is undoubtedly a serious condition which can lead to severe complications and disability if it remains untreated (2).

Although BCRL is considered incurable, adequate therapy has the potential to substantially slow down its progression (7). Among numerous therapeutic options, complex decongestive therapy (CDT) is nowadays regarded as the basic therapy concept (7). Its effectiveness in reducing lymphedema has been shown in clinical studies (8). Nevertheless, it is also considered time-consuming and requires a high level of compliance. For many patients, CDT is not sufficient to relieve pain and discomfort due to limb swelling. Other therapeutic options, such as intermittent pneumatic compression, are only available in selected hospitals and therapy centres specialized in lymphedema treatment. The demand for additional or alternative therapy options to CDT is persisting and requires further research.

Within the last two decades, photobiomodulation therapy (PBMT), formerly termed low-level laser therapy (LLLT), has become increasingly popular in the supportive care for patients with breast cancer and BCRL (9). In 2014, the North American Association for Laser Therapy (NAALT) and the World Association for Laser Therapy (WALT) defined PBMT as the 'therapeutic use of light absorbed by endogenous chromophores, triggering non-thermal, non-cytotoxic, biological reactions through photochemical or photophysical events, leading to physiological changes'.

Its beneficial effects on tissues and cells, such as relief of pain and stimulation of healing, are nowadays used in many clinical areas (10, 11). Improvements after PBMT have been reported in a variety of medical conditions, for example musculoskeletal disorders (12) and diabetic foot ulcers (13).

Multiple studies have been conducted to evaluate its effectiveness in the treatment of BCRL (14–21). Omar *et al.* (18) reported an increase in grip strength and shoulder mobility as well as a reduction in limb volume in more than 90% of the participants in their study. In another trial, 31% of the participants had a clinically significant reduction in the volume of their affected limb approximately 2-3 months after LLLT (14). One study demonstrated a 28% cumulative reduction in arm volume one month after completing 12 sessions of LLLT (21). E Lima *et al.* (22) came to the conclusion that LLLT showed favourable results in reducing limb volume in comparison with placebo therapy, no intervention and other methods such as pneumatic compression.

The majority of formerly conducted studies used small tip lasers with treatment heads measuring less than 0.5 cm^2 in size (14, 15, 18, 20). Their usage implies time-consuming manual-guided application on multiple points, often with the help of additional tools, such as a plastic guide with a grid, to ensure reproducibility. To facilitate this elaborate and time-costly practice, we used a cluster laser on a single area.

To our knowledge, cluster lasers covering the whole axillary have rarely been used in this setting. Corollary, information on adequate dosing parameters for this purpose is limited. In 2010, the WALT published dosage- and scientific recommendations such as 'WALT standard for conduct of randomized controlled trials' (23, 24). Those recommendations include common conditions such as arthritis and tendinopathies, but no data are provided for BCRL.

Another point to address is the frequency of sessions per week and the number of total treatment sessions. In general, either daily treatment for two weeks or treatment every other day for 3-4 weeks is recommended (23). Using a cluster laser and a compactly designed treatment regime, we intended to dramatically cut the total number of necessary sessions to make treatment better applicable in daily routine care.

The aim of our study was to examine the effects of PBMT in the treatment of BCRL using a compactly designed treatment regime in combination with a cluster laser device. Our outcome variables included lymphedema-related pain, life quality, grip strength and limb volume difference.

MATERIALS AND METHODS

Patient selection

Our study was performed at the Center for Palliative Medicine and Pain Therapy at Saarland University Medical Center. Forty women with at least a three-month history of unilateral arm lymphedema after treatment for breast cancer were enrolled in our trial. Participants had undergone either modified radical mastectomy or breast-conserving surgery. To determine nodal status, axillary dissection or sentinel lymph node biopsy was performed. The ethics committee approved the study protocol in 2013 and patients were recruited between December 2013 and August 2015. Participants signed an informed consent after being informed about the study details and all following procedures were in accordance with the Helsinki Declaration of 1975 (as revised in 2008).

Patients with medical conditions that made PBMT prohibitive (current metastases, pregnancy, photosensitivity, continuing radiotherapy, chronic inflammatory diseases, history of severe trauma) were excluded from the study. Subjects were randomized to either the active laser group (n = 20) or the placebo laser group (n = 20) using generated computerized random number lists from which the subject allocation sequence was obtained. Although the placebo laser device contains an inactivated, functionless laser, both devices are similar in terms of weight, emitted sounds and optical appearance to guarantee strictly controlled double-blinded conditions.

Study protocol

Participants received irradiation with the cluster laser device 'TIMELAS Vital' (Schwa-medico, medizinische Apparate Vertriebsgesellschaft mbH, Ehringshausen, Germany), equipped with 16 continuous-wave laser diodes with an average power output of 40 mW each. All diodes were continuously activated, emitting at a wavelength of 980 nm (near infrared light) and delivering a total power output of 640 mW. Each one covered a 'point' with a spot size of 4.9 cm^2 on the skin and treatment time was ten minutes per session. The energy applied per 'point' was 24 and 384 Joules over the whole axillary, respectively, giving an energy density of 4.89 J/cm^2.

Irradiation was performed in non-contact mode two times a week for four weeks. All patients were advised to continue their daily limb exercises and routine in regard to skin care. Safety googles were compulsory for all attendants. Calibration was performed at the beginning of the study and every three months consecutively to ensure correct optical output. Table 1 provides all information in accordance with Carroll's and Jenkins' recommendation on how to report photomedicine dose and beam parameters in clinical studies (25).

Patient assessment

To evaluate therapy effects, subjective and objective parameters were measured pretreatment and after completion of the whole laser cycle. Follow-up sessions were performed at four, eight and twelve weeks after completion, respectively. Regarding subjective parameters, we focused on QOL and pain sensation. Numerous studies outlined the substantially lowered health-related QOL in patients with BCRL (26, 27). Life quality was determined using two standardized questionnaires: McGill Quality of Life Questionnaire (MQOL) and the German version of the Multidimensional Mood State Questionnaire (MMSQ).

Table 1. Intervention, dose and beam parameters

Intervention	
Number of total treatment sessions	Eight sessions
Frequency of sessions per week	Two sessions per week
Interval between treatments	At least 2–3 days
Anatomical location	Axillary
Application procedure	Stationary in non-contact mode
Dose and beam parameters	
Wavelength	980 nm
Spectral width	≤3 nm
Pulse parameters	Continuous-wave laser
Number of diodes in total	16
Average power output in mW per single diode	40 mW
Average power output in mW in total*	640 mW
Treatment time in seconds	600 s
Single spot size on the skin in cm^2	4.9 cm^2
Total beam area on the skin in cm^2	78.54 cm^2
Average energy dose delivered in Joule per point	24 J
Average energy dose delivered in Joule in total	384 J
Power density	8.14 mW/cm^2
Energy density	4.89 J/cm^2

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Women suffering from BCRL frequently complain about loss of power in the arm and reduced hand grip strength that is easily fatigued with use (28). Patients were assessed for changes in difference in limb volume and grip strength. A reduction in limb volume and mobilization of accumulated lymphatic fluid may contribute to a better range of motion and an increase in lost grip strength.

Limb volume was calculated non-invasively from circumference measurements using a flexible measuring tape. This classical disc method, first described by Kuhnke in 1976, involves repetitive measurements at 4-cm intervals along the arm beginning at the ulnar styloid process and ending at the medial axillary fold (29). After circumference of the extremity is determined at all reference points, the obtained values are squared and added to each other. The resulting sum is then divided by π. The obtained value represents the volume of the extremity in cm^3.

$$V\text{total} = \frac{(C_1)^2 + (C_2)^2 + (C_n)^2}{\pi}$$

$$\Delta V = V\text{affected} - V\text{normal}$$

Finally, the difference in volume (ΔV) between the affected and the unaffected limb is calculated. Hereby, a decrease in limb volume difference (ΔVpretreatment > ΔVpost-treatment) indicates therapy success. As accumulated lymphatic fluid is mobilized, the volume of the affected extremity approaches closer to the volume of the healthy extremity. Measurements were performed with patients in prone position, and participants were asked to relax their arms by their sides with elbows straight. The measuring tape was put tightly around the arm, strictly avoiding tissue indentation. This method is widely spread in clinical routine and considered sufficiently accurate, provided it is used consistently (30).

Grip strength was measured using Trailite TL-LSC100, a portable handheld dynamometer. Patients were asked to sit upright on a chair with a back. Further instructions included an adducted shoulder, flexed elbow (90°) and forearm in neutral rotation position. Participants were asked to press 5 seconds and the first attempt was always discarded.

Life quality was determined using two standardized questionnaires including MQOL and the German version of the MMSQ. MQOL employs 16 items and five subscales (31). Each question uses a 0–10 scale with anchors at each end. For a better overview, an overall score which can range from 0 to 10 was calculated from the means of the five subscales. Since all questions have a 2-day frame, MQOL is considered especially useful in the evaluation of interventions on QOL. MMSQ consists of three subscales with eight items each (32). An item is represented by an adjective that characterizes different moods. In addition to that, there are five answer categories for each item ranging from 'definitely not' to 'very much'. Patients are asked to mark for each adjective the answer that represents best the actual intensity of their mood status. The total score for each subscale ranges from 8 to 40, and thus, the overall score ranges from 24 to 120. To assess lymphedema-related pain, 'faces pain scale-revised' was used (33).

Statistical analysis

Statistical analysis was performed using SPSS Statistics (Statistical Packages for the Social Sciences), version 22 (IBM Corporation, Armonk, NY, USA). Baseline group differences of continuous variables were assessed using two-sample *t*-test (if normally distributed) or Mann–Whitney *U*-test (if asymmetrically distributed). Given an approximately normally distributed variable, results are shown as mean with the respective standard deviation (SD). Results of non-normally distributed variables are listed as median with the corresponding interquartile range (IQR). Differences in categorical variables were examined using the chi-squared test or Fisher's exact test. All tests were two-sided and a P-value <0.05 was considered statistically significant.

GEE method (generalized estimating equations) was used, in order to evaluate the effectiveness of PBMT on the primary and secondary outcome(s). An exchangeable working correlation matrix was chosen and probability distribution was either 'normal' or 'gamma'. Furthermore, outlier data were excluded from our analysis. This approach is considered an extension of generalized linear models to longitudinal data analysis using quasi-likelihood estimations. The coefficient of the independent group variable reflects the mean difference between the active laser group and the placebo group regarding the investigated outcome variable.

RESULTS

A CONSORT flowchart of our study is shown in Fig. 1. Forty-three women were assessed for eligibility; however, one woman declined to participate and two women did not meet the inclusion criteria. The remaining forty women were randomized to the both treatment arms. Each group contained 20 subjects. Subjects with poor adherence to therapy (defined as missing more than one

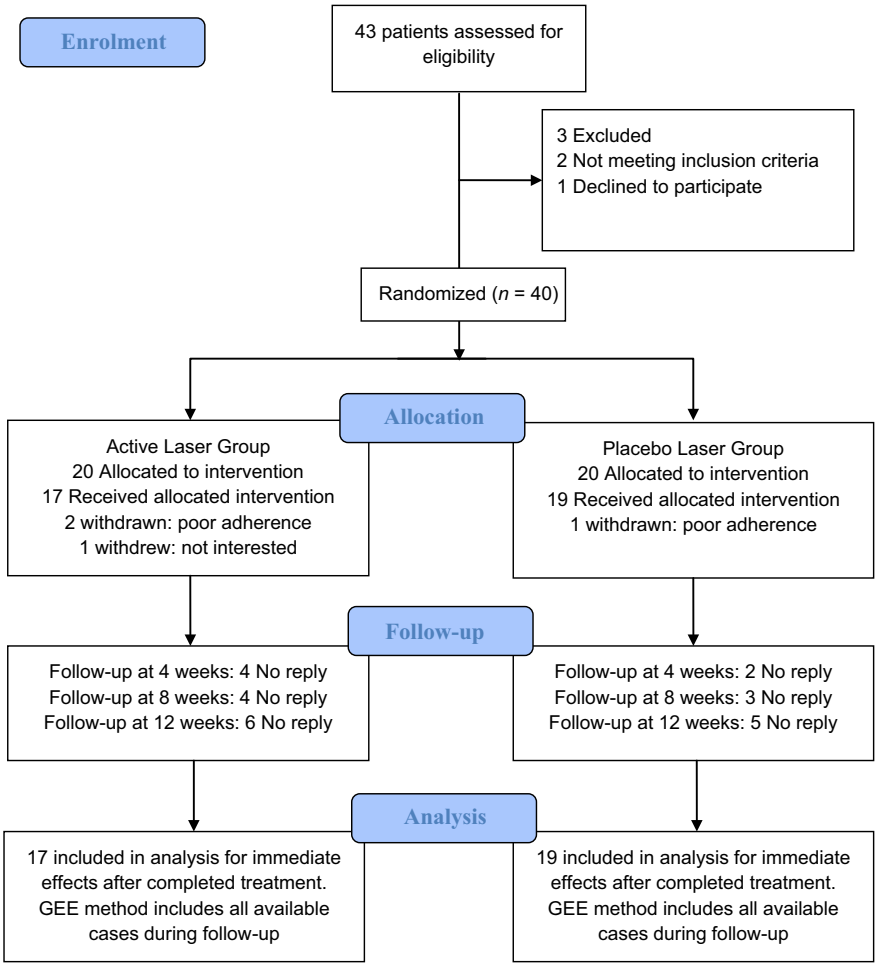

Fig. 1. CONSORT flowchart.

session) were excluded from the trial. Three women had to be withdrawn from the study due to poor adherence and one lost interest in our trial. Thirty-six women completed all sessions and entered follow-up period.

Demographic characteristics and baseline data are shown in Table 2. No significant differences between trial arms ($P > 0.05$) were found. The age of the participating women ranged from 41 to 79 years with a mean age of 61.06 ± 9.66 years in the active laser group and 59.37 ± 10.16 years in the placebo group. In both groups, median pain intensity was 4 at baseline. QOL measured using MMSQ and MQOL was slightly higher in the active laser group than in the sham group (82.75 vs. 79.88 and 6.43 vs. 6.28). Regarding grip strength, both groups were nearly identical. Median limb volume difference was higher in the placebo group (160.46 ml/cm³) than in the active laser group (91.63 ml/cm³); however, this difference was not statistically significant.

Post-treatment, median pain intensity declined in both groups (Table 3). A median pain intensity of 2 was observed in both groups, which constitutes a reduction of 50% compared with baseline. With one exception in the active laser group (month 3), measured pain intensity remained at this level.

QOL increased in the active laser group and a peak in MMSQ was noticed immediately after treatment, while mean MQOL score reached its peak after one month of follow-up. Data revealed an increase in mean MMSQ score by 2.75 points while MQOL score increased by 0.4 points.

Additionally, an increase in grip strength was observed in both groups. Mean grip strength was persistently higher after eight sessions of PBMT. In the active laser group, a maximum was observed after two months of follow-up, which, compared with baseline measurements, constituted an increase of approximately 13.5%. Furthermore, a reduction in median limb volume

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Table 2. Baseline characteristics of patients

	Active laser (n = 17)	Placebo laser (n = 19)	P-value
Age (years), Mean ± SD	61.06 ± 9.66	59.37 ± 10.16	0.61
Age at initial diagnosis (years), Mean ± SD	56.12 ± 8.85	53.17 ± 11.42	0.40
Breast-conserving therapy	11 (64.7%)	12 (63.2%)	0.90
(Modified) Radical mastectomy	6 (35.3%)	6 (31.6%)	0.90
Radiotherapy, n (%)	14 (82.4)	16 (84.2)	0.65
Chemotherapy, n (%)	13 (76.5)	14 (73.7)	1.00
Hormonal therapy, n (%)	14 (82.4)	14 (73.7)	1.00
Pain intensity, Median (IQR)	4 (2)*	4 (4)*	0.33
Multidimensional Mood State Questionnaire, Mean ± SD	82.75 ± 17.22*	79.88 ± 19.70*	0.66
McGill Quality of Life Questionnaire, Mean ± SD	6.43 ± 1.27	6.28 ± 1.04	0.69
Grip Strength, Mean ± SD	21.38 ± 5.98*	21.36 ± 4.18*	0.99
Limb volume difference, Median (IQR)	91.63 (368.18)*	160.46 (298.67)*	0.13

*Based upon available cases. Baseline group differences of continuous variables were assesses using two-sample t-test or Mann–Whitney U-test whereas differences in categorical variables were examined using the chi-squared test or Fisher's exact test.

Table 3. Post-treatment and follow-up evaluations

	Active laser (n = 17)	Placebo laser (n = 19)	P-value
Pain intensity (Range: 0–10), Median (IQR)			
Pretreatment	4 (2)*	4 (4)*	0.33
Post-treatment	2 (6)*	2 (2)*	
Month 1	2 (2)*	2 (3)*	
Month 2	2 (2,5)*	2 (6)*	
Month 3	4 (4)*	2 (6)*	
Multidimensional Mood State Questionnaire (Range: 24–120), Mean ± SD			
Pretreatment	82.75 ± 17.22*	79.88 ± 19.70*	0.66
Post-treatment	85.50 ± 15.09*	79.75 ± 15.70*	
Month 1	78.55 ± 17.37*	81.00 ± 11.97*	
Month 2	80.23 ± 21.52*	74.80 ± 16.93*	
Month 3	81.09 ± 23.05*	76.33 ± 15.54*	
McGill Quality of Life Questionnaire (Range: 0–10), Mean ± SD			
Pretreatment	6.43 ± 1.27	6.28 ± 1.04	0.69
Post-treatment	6.83 ± 1.52	5.90 ± 0.9	
Month 1	7.00 ± 1.73*	6.77 ± 1.22*	
Month 2	6.65 ± 1.70*	6.00 ± 1.10*	
Month 3	6.58 ± 2.12*	6.28 ± 1.30*	
Grip Strength, Mean ± SD			
Pretreatment	21.38 ± 5.98*	21.36 ± 4.18*	0.99
Post-treatment	21.42 ± 4.65*	22.87 ± 5.30*	
Month 1	22.82 ± 4.79*	24.73 ± 5.40*	
Month 2	24.25 ± 4.92*	23.56 ± 6.10*	
Month 3	23.65 ± 3.98*	24.90 ± 5.78*	
Limb volume difference, Median (IQR)			
Pretreatment	91.63 (368.18)*	160.46 (298.67)*	0.13
Post-treatment	82.99 (328.41)*	84.03 (351.97)*	

*Based upon available cases.

difference was noticed, but this reduction was higher in the sham group than in the active laser group (76.43 cm^3 vs. 8.64 cm^3).

GEE analysis was performed to evaluate the effectiveness of PBMT over the time course for grip strength, difference in limb volume and QOL; however, no

Table 4. GEE analysis results

	Regression coefficient	Standard error	95% confidence interval	*P*-value
Multidimensional Mood State Q. (Probability distribution: normal)				
Placebo laser	0.076	5.430	−10.567 to 10.720	0.988
McGill Quality of Life Questionnaire (Probability distribution: normal)				
Placebo laser	−0.158	0.400	−0.947 to 0.631	0.694
Grip Strength (Probability distribution: normal)				
Placebo laser	1.187	1.730	−2.204 to 4.578	0.493
Limb volume difference (Probability distribution: gamma)				
Placebo laser	48.210	75.972	−100.69 to 197.11	0.526

Reference group: active laser group.

statistically significant intergroup differences were found (Table 4).

DISCUSSION

The aim of our study was to examine the effects of PBMT in the treatment of BCRL using a cluster laser device in combination with a compactly designed treatment regime consisting of only eight therapeutic sessions.

A median pain intensity reduction of 50% was observed in both groups after completion of the whole laser cycle. With one exception in the active laser group, pain intensity remained at this level. Additionally, data revealed an increase in QOL after completion of the treatment. Mean grip strength was continuously higher after eight sessions of PBMT compared with pretreatment. After two months of follow-up, an increase of approximately 13.5% in grip strength was observed in the active laser group. We also observed a slight reduction in limb volume difference; however, the reduction in the active laser group was less pronounced. Results from Table 4 suggest that there were no statistically significant ($P > 0.05$) intergroup differences regarding these outcome variables over the time course. Neither adverse events nor any harm related to this study has been reported by our participants.

According to a meta-analysis by Omar *et al.* (34), moderate to strong evidence exists for the effectiveness of LLLT in BCRL. An energy dose of 1-2 J/cm² per point applied to several points covering the fibrotic area was found to reduce limb volume following BCRL (34). Another meta-analysis revealed similar findings, showing moderate strength evidence supporting LLLT in the management of BCRL, especially in regard to pain and volume reduction (35).

Various theories about how PBMT precisely affects lymphedema have been postulated; however, a detailed description would go beyond the scope of this paper. According to Carati *et al.* (14), lymphatic drainage through the axillary region is restored by tissue softening and by reduction of fibrosis and scarring. The efficacy of LLLT in softening surgical scarring and fibrous tissue has been shown in another study unrelated to BCRL (36). Its pain reducing effects have been documented in various retrospective studies and meta-analyses (11, 37).

Reviewing the results of our own study, the applied treatment regime showed only minor improvements in regard to our primary and secondary outcome variables. No statistically significant intergroup differences were found regarding our main outcome variables over the time course. Several possible influencing factors are going to be systematically discussed below.

To achieve positive results, a well-conceived therapy schedule and an adequate laser configuration are necessary. In this study, a laser emitting continuous waves (CW) at a wavelength of 980 nm was used. In terms of reaching deep target tissues, it is known that LLLT in CW mode of operation is inferior to pulsed wave mode of operation (38). Although CW lasers are said to be limited to 2 cm in their therapeutic efficient penetration, this still seems appropriate to affect BCRL. Undoubtedly, a pulsed wave laser would have been more suitable; nevertheless, this point might not explain our results to full satisfaction.

Another aspect that has to be mentioned is the irradiated anatomical area. Although cluster lasers usually cover larger areas than simple tip lasers, still only one area was irradiated in our study. Study protocols of previously conducted trials included the irradiation of an additional anatomical area along the affected arm such as the antecubital fossa (17, 18). As BCRL affects the whole limb, the administration on multiple points may consequently lead to better results.

Participants received eight therapy sessions with an irradiation time of ten minutes each. The energy applied per 'point' was 24 Joules and 384 Joules over the whole axillary respectively, giving an energy density of 4.89 J/cm². A too high amount of total energy applied per

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point could be a possible explanation for our results. It is particularly worth mentioning that we increased the energy dose in order to cut the total amount of sessions. So it is hard to determine, whether the applied doses are really too high or whether the amount of sessions is simply insufficient.

Former conducted studies included a larger number of total treatment sessions along with a higher frequency of sessions per week. While a total amount of 18 sessions is often found in the literature (14–16), Omar *et al.* (18) treated patients up to three times a week for twelve subsequent weeks, resulting in a total of 36 sessions. We consequently cannot exclude that using the same dose parameters along with more treatment sessions and at a higher frequency would have led to better results.

Even though it is alluring to apply higher energy doses to achieve desired results quicker, one should always keep in mind the main findings of Arndt-Schulz Law, a frequently quoted model to describe dose-dependent effects of PBMT/LLLT (39, 40). This concept states that weak stimuli slightly accelerate vital activity, stronger stimuli raise it further, but a peak is reached and even stronger stimuli suppress it (41). We assume that in treating chronic conditions such as lymphedema, the application of our chosen energy dose and density simply constituted a too strong stimulus in a too short time frame.

Although these widely accepted concepts are known to proficient and experienced users, it is hard to determine specific values for an adequate stimulus. After all, not for nothing it is recommended to start with weak stimuli and to slightly increase the applied energy dose. However, this is hardly possible in the context of a RPCT because dosage changes during the trial are not compliant with ethical guidelines.

The limitations of our study include a too small number of patients because of the long-term follow-up and missing measurements of limb volume difference during the follow-up period. The likelihood that an improvement in limb volume difference does not manifest itself immediately after eight sessions cannot be excluded. Furthermore, a third treatment arm with a laser configuration that is known to have beneficial effects is missing in our study.

As a consequence, we are not able to list our own evidence for the effectiveness of PBMT in reducing BCRL. No statistically significant ($P > 0.05$) intergroup differences were found regarding our main outcome variables over the time course. Further well-designed studies including more patients and treatment arms are required to determine which combination of dosage and beam parameters is best used to reduce BCRL.

SUMMARY STATEMENT

We examined the effects of photobiomodulation therapy in the treatment of breast cancer-related lymphedema using a compactly designed treatment regime consisting of eight therapeutic sessions in combination with a cluster laser device covering the whole axillary area. Instead of the manual and time-costly application of a tip laser on multiple anatomical areas, we intended to facilitate this process using a therapeutic regime that is better applicable in daily routine care. Unfortunately, PBMT using the compactly designed treatment regime described above did not significantly improve quality of life, pain scores, grip strength and limb volume over the time course.

AUTHOR CONTRIBUTIONS

MAS, BG, SG, RM: performed the research; MAS, SG, RM, SB: designed the research study; SB: contributed essential reagents or tools; MAS, RM, JS: analysed the data and statistical analysis; MAS, BG, SG: wrote the manuscript.

ETHICAL APPROVAL

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Furthermore, informed written consent was obtained from all patients for being included in the study.

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