

# Clinical Applications of Photobiomodulation Therapy in the Management of Breast Cancer-related Lymphedema

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Breast cancer-related lymphedema (BCRL) is characterized by the persistent accumulation of interstitial fluid in the peripheral tissues after treatment for breast cancer. Photobiomodulation (PBM) therapy is widely used as supportive care for patients with BCRL. A search was performed in the PubMed database to find relevant articles published over the last 20 years. Randomized controlled trials that evaluated the efficacy of PBM therapy on BCRL were included. A total of 24 studies were identified through the PubMed database. Seven studies were used for the final analysis, after excluding items that did not meet the duplication and inclusion criteria. Although PBM showed some improvement in reducing arm circumference and the symptoms related to BCRL, the results of the meta-analysis did not show any significant benefit in alleviating lymphedema. Further studies are needed with the recruitment of more participants to evaluate the long-term efficacy and safety of PBM in the management of BCRL.

## Key words

Breast cancer; Lymphedema; Photobiomodulation

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## INTRODUCTION

Breast cancer is the most common cancer and the second leading cause of cancer-related deaths for females in the world.<sup>1</sup> With the increase in the survival rate for breast cancer, the importance of postoperative quality of life has increased.<sup>2</sup> Breast cancer-related lymphedema (BCRL) is a common and serious complication after breast cancer surgery and it results in adverse outcomes in patients, including pain and limited physical function, and negatively affects their quality of life.<sup>3-5</sup> Lymphedema is caused by interruption of the lymphatic drainage system resulting in local accumulation of excess lymphatic fluid in the upper arm.<sup>4,5</sup> Axillary lymph node dissection and adjuvant therapy like radiation and chemotherapy contribute most heavily to risk.<sup>6</sup> A recent meta-analysis reported that the average incidence of arm lymphedema after breast cancer treatment is about 20% in breast cancer survivors.<sup>7</sup>

The optimal treatment for lymphedema is not yet clear. The current standard of care is complex decongestion therapy (CDT), which includes manual lymphatic drainage (MLD), bandaging, skin care, exercise, and the use of compression sleeves.<sup>8</sup> The efficacy of CDT varies widely according to different studies. The combination of MLD with compression bandages has been reported to be probably the most effective method, with excess vol-

ume reductions of up to 38%, based on two randomized controlled trials.<sup>9,10</sup> However, there are limits to these maneuvers.<sup>11</sup> MLD requires regular and frequent intense physical therapy, and the results will depend greatly on the level of experience of the physical therapist. Also, if lymphedema recurs, treatment should be repeated. There is a clear need to develop new, effective and convenient therapeutic interventions to better manage symptoms and psychosocial factors in BCRL patients.

Recently, low-level laser therapy (LLLT), also known as photobiomodulation (PBM) therapy, has been introduced as a potentially useful non-pharmacological treatment modality for BCRL. PBM therapy, approved by the US Food and Drug Administration (FDA) as a therapeutic intervention, is a non-invasive form of phototherapy. It utilizes light wavelengths (range from 650 to 1000 nm) to deliver low irradiance to the target tissue for biological process modulation.<sup>12</sup> PBM has been shown to be a safe technique. Several experimental studies have found that PBM therapy is effective in reducing inflammation, promoting lymph vessel regeneration, improving lymphatic motility, alleviate pain, and preventing tissue fibrosis.<sup>13,14</sup> Previous clinical studies have shown promising effects of LLLT (PBM), when used in addition to conventional therapeutic interventions, for the management of BCRL. The aim of the present review was to evaluate the available

**Table 1.** Characteristics of included studies

Study	Number of subjects	Treatment design	Control group	Follow up	Evaluation outcomes
Baxter et al. (2018) <sup>16</sup>	PBM = 8, control = 8	2 times per week for 6 weeks + BCRL conventional therapy	BCRL conventional therapy	6 weeks, 12 weeks	Limb circumference, perceived symptoms, psychological impacts, activity disability
Kilmartin et al. (2020) <sup>17</sup>	PBM = 11, control = 11	2 Times per week for 8 weeks + CDT	Inactive PBM + CDT	3 months, 6 months, 12 months	Lymphedema symptoms, symptom distress, limb volume, adherence rates
Rinder et al. (2013) <sup>2</sup>	PBM = 15, PBM + MLD = 15, control = 16	20 min of PBM, 20 min of MLD	Compression bandaging	Post-treatment immediately (final treatment)	Extracellular fluid and arm volume, physical and psychological symptoms and skin condition, QOL
Storz et al. (2017) <sup>18</sup>	PBM = 20, control = 20	2 times per week for 4 weeks	Inactive PBM	4 weeks, 8 weeks, 12 weeks	Pain, mood state, QOL, grip strength, limb volume difference
Lau and che-ing (2009) <sup>19</sup>	PBM = 11, control = 10	3 times per week for 4 weeks	No treatment	4 weeks	volumetry, tonometry, DASH questionnaire symptoms
Carati et al. (2003) <sup>20</sup>	PBM = 33, control = 33	2 blocks of PBM, separated by an 8 week rest period	1 block of sham therapy, followed by and 8 week rest period and then 1 block of PBM	Post-treatment 1 month, 2 months	Perimetry, bioimpedance, tonometry, shoulder range of movement, self-reports
Ahmed Omar et al. (2011) <sup>21</sup>	PBM = 29, control = 29	3 times per week for 12 weeks	Inactive PBM + exercise, education	4 weeks, 8 weeks, 12 weeks	Limb circumference, shoulder morbidity, grip strength

PBM, photobiomodulation; BCRL, breast cancer-related lymphedema; CDT, complete decongestive therapy; MLD, manual lymphatic drainage; QOL, quality of life; DASH, disabilities of the arm, shoulder and hand.

literature regarding the effectiveness and safety of PBM therapy for the treatment of BCRL.<sup>13-15</sup>

## SUMMARIES OF INDIVIDUAL STUDIES

A search was performed in the PubMed database without period restriction and limited in the English language. The selected keywords were ("Low-level laser" OR "photobiomodulation" OR "phototherapy") AND ("lymphedema" OR "lymphoedema") And ("breast cancer"). The author also provided a hand search of the references of the selected studies to identify other possible relevant studies. The articles included should necessarily be presented with full access to the text. We verified those articles that presented titles and summaries that approached the subject of this research, as well as methodology, results, and relevance for its practical application. In total, 24 studies were identified through the PubMed database. After excluding duplicates and those which did not meet the inclusion criteria, 7 studies were finally included. A summary of included studies is presented in Table 1 and laser treatment parameters are summarized in Table 2.

### PBM versus conventional therapy

Baxter et al.<sup>16</sup> recruited 17 participants with BCRL and randomized them into the two groups: (1) PBM + BCRL conventional therapy or (2) BCRL conventional therapy alone. Treatment adherence was high in the PBM group (88.9% of participants completed all treatments). Retention rates were 88.9% for the PBM group and 100% for the control group at both 6 and 12 weeks post-randomization. All participants who completed PBM therapy indicated that they were satisfied with the treatment. No serious adverse reactions were reported in this study. In

general, the results show a trend toward improvement in symptoms (limb circumference differences, perceived symptoms, and psychological impacts) from baseline to the primary endpoint in both groups. There was a numerically larger improvement in BCRL psychological impacts (except for anxiety) in the PBM group. However, this study did not have the power to investigate effectiveness between groups, and the small sample size along with the variability of the mean values at stated time points may explain these findings.

Kilmartin et al.<sup>17</sup> evaluated the effectiveness of PBM as a complementary treatment to complete decongestion therapy (CDT) for 12 months after treatment for lymphedema in breast cancer patients. Participants (n = 22) were randomly assigned to either an active PBM group or an inactive PBM, control group. Active PBM was administered to participants twice a week at the beginning of each CDT session. Outcome measures included lymphedema symptoms, symptom pain, and limb volume by an infrared perometer. Significantly fewer participants in the active PBM group (55.6%) compared to the placebo group (83.3%) reported one or more symptoms of lymphedema ( $p = 0.012$ ) 12 months after the intervention. Significantly, more patients in the active laser group (44.4%) reported fewer than 2 limb mobility symptoms at 12 months after intervention compared to the placebo group (33.3%) ( $p = 0.017$ ). The active PBM group had a statistically significant improvement over time from baseline to 12 months post-intervention, from 73 to 11% of symptom pain of sadness ( $p = 0.005$ ) and from 36 to 0% of self-perception ( $p = 0.030$ ). Limb volume did not decrease significantly. This trial demonstrated significant benefits of complementary PBM in alleviating symptoms and improving emotional distress in breast cancer patients with lymphedema.

**Table 2.** Photobiomodulation treatment parameters

Study	Device type/Model	Wavelength (nm)	Application duration and number of sessions	Application area(s)
Baxter et al. <sup>16</sup>	Direct contact; LightForce EX LTS-1500	980	1 min/spot	10 points from axilla to wrist on the affected arm
Kilmartin et al. <sup>17</sup>	Direct contact; RianCorp LTU 904H	904	1 min/spot	10 sites in the axilla and a portion of the chest wall
Rinder et al. <sup>2</sup>	Direct contact; RianCorp LTU 904H	904	20-30s per point, in each treatment grid (~20 min total) 10 sessions (average)	Not specifically stated: "grids for the areas to be treated were identified"
Strorz et al. <sup>18</sup>	Non-contact mode; TIMELAS Vital	980	10 min per session	Axillary
Lau and cheing <sup>19</sup>	Scanning 50 cm above skin; Comby 3 Terza Serie, Model D	808 905 × 2	20 min 12 session	Entire axilla (144 cm <sup>2</sup> )
Carati et al. <sup>20</sup>	Direct contact; RianCorp LTU 904H	904	1 min/spot; 17 min/session	17 spots, 2 cm apart in axilla
Ahmed Omar et al. <sup>21</sup>	Direct contact; RianCorp Ga-As laser	904	2 min/spot; 20 min	3 spots antecubital fossa, 7 spots axilla (0.2 cm <sup>2</sup> /spot)

Ridner et al.<sup>2</sup> randomized controlled trial (RCT) was performed on 46 women with unilateral BCRL, randomized to one of three treatment groups: (1) PBM + compression bandage, (2) MLD + compression bandage, or (3) combined MLD/PBM + Compression bandages. For the PBM group, the median duration of lymphedema was 27 months (IQR: 6, 58). The median, interquartile range, and effect size for each group of limb volume were reported. All three groups showed clinically and statistically significant volume reductions ( $p < 0.001$ ), but no statistically significant intergroup differences were found (circumference  $p = 0.422$ ). The largest reported effect size was for the difference in circumference between the two PBM groups. The authors suggest that PBM followed by compression bandage may be effective in reducing volume compared to MLD or composite MLD/PBM, followed by compression bandage. However, since each group received a compression bandage after the procedure, the beneficial effect of the compression bandage itself cannot be ignored. Assessment of upper extremity (UE) pain/pain was included as part of the Lymphedema Symptom Intensity and Pain Scale-Arm (LSIDS-A). The effect size for UE pain compared to baseline immediately after final treatment was 0.24 for the MLD group, -0.31 for the PBM group, and -0.07 for the MLD + PBM group. No intergroup comparisons for UE pain/pain were performed, however, there were no significant differences between groups for total LSIDS-A scores.

### PBM versus sham laser

Storz et al.<sup>18</sup> evaluated the effects of PBM therapy on lymphedema-related pain, quality of life, grip strength and limb volume difference with forty patients. After treatment, a 50% decrease in central pain score and an increase in the average quality of life was observed. Mean grip strength was consistently higher after 8 sessions of PBM therapy compared to pretreatment. However, there were no statistically significant between-group differences ( $p > 0.05$ ) over time.

In 21 women with BCRL, Lau et al.<sup>19</sup> investigated the effect of PBM in RCT compared to a waitlist control group. In the PBM group ( $n = 11$ ), a mean decrease of 16% in arm volume immediately after treatment ( $84.2 \pm 8.5\%$ ,  $p < 0.0001$ ) and a mean decrease of 28% after 4 weeks of treatment ( $71.9 \pm 6.3\%$ ,  $p < 0.0001$ ). In the control group, arm volume increased on average by 6% after 4 weeks of treatment ( $106.0 \pm 4.3\%$ ,  $p < 0.0001$ ). Although differences between groups at 4 weeks post-intervention follow-up ( $p = 0.044$ ) did not reach Bonferroni-corrected statistical significance (set to  $<0.017$ ), Lau et al. suggest that PBM may

be useful in conjunction with other treatments and reduce the need for expensive and labor-intensive treatments.

Carati et al.<sup>20</sup> performed a two-component crossover study. The first was a double-blind, randomized, sham (placebo) controlled crossover trial of 9-session cycles of PBM ( $n = 26$ ) versus sham PBM treatment ( $n = 27$ ). After 1 cycle of PBM, no significant differences in volume were found and there were no significant differences between groups. The second component of the test is designed to compare one and two cycles of the PBM. After completing the crossover phase, 11 participants in the original sham laser group (unblinded) received a second 9-session cycle of PBM treatment, and data were pooled to increase the number of participants receiving both cycles of active PBM to 37. There was no statistically significant decrease from baseline in mean affected limb volume after 2 cycles of PBM therapy immediately after treatment ( $p = 0.442$ ), 1 month after treatment ( $p = 0.119$ ), or 3 months after treatment ( $p = 0.061$ ), although volume was decreased. However, compared with the sham group, the 2-cycle PBM group showed a significant decrease in mean limb volume at 3 months after treatment ( $89.7 \pm 46$  ml decrease vs.  $32.1 \pm 3.4$  ml increase;  $p = 0.017$ ). At 2 to 3 months after the second PBM block, 31% of participants had a clinically significant decrease ( $>200$  ml) in affected limb volume ( $p = 0.01$ ) compared to 4% in the sham group. Pain was not reported as an independent outcome.

Ahmed Omar et al.<sup>21</sup> RCT was performed comparing PBM ( $n = 25$ ) and sham laser ( $n = 25$ ). Of the 58 women initially randomized, 8 were lost for follow-up (4 women in each group): 1 with cellulitis and 3 with non-adhesion from the PBM group withdrew. In the sham group, 2 patients withdrew with cellulitis and 2 with non-adhesion. The mean duration of lymphedema was 13.98 months ( $\pm 2$  months). Limb circumference was significantly decreased in the PBM group compared to baseline at each time point ( $p < 0.05$ ). There was a significant within-group decrease ( $p < 0.05$ ) in limb circumference in the sham group, except at week 4. Differences between groups, with a greater reduction in the PBM than in the sham group, were significant at weeks 8, 12, and 16 ( $p < 0.01$ ). The authors concluded that PBM may be effective in reducing arm circumference in BCRL patients, and the results could last up to 16 weeks.

## DISCUSSION

The laser is an electromagnetic radiation from the light amplification by stimulated emission of radiation generated in a resonant optical cavity from an active medium

and an excitation source.<sup>22</sup> The PBM has been used as a resource for physical therapy in different clinical settings. As a relatively novel therapeutic tool for the treatment of BCRL, PBM has gained increasing popularity since its approval by the US FDA in 2007.

The underlying mechanism of using low-levels light for therapeutic tool includes light absorption, targeting and activating cytochrome oxidase in the mitochondrial membrane, leading to greater consumption of cellular oxygen and ultimately increased metabolic energy production, which is used for cellular repair.<sup>23</sup> Research of the use of this laser at the low-intensity wavelength suggest effects at the cellular level with stimulation of lymphocytes and local fluid circulation,<sup>24</sup> and stimulation of macrophage cells and the immune system which decrease the risk of infection.<sup>25</sup>

Over the past two decades, several RCTs<sup>2,16-22</sup> and observational studies<sup>26,27</sup> have been published in this area. Decreased limb volume in women with BCRL is associated with improved mobility and quality of life. It may also be reasonable to expect that a decrease in swelling in the arm could result in changes in the quality or texture of the skin (such as fibrosis) or concomitant pain severity. Treatments that contribute to a significant reduction in swelling should be considered as viable treatment options in BCRL management.<sup>15</sup>

A reduction in volume change between the affected and unaffected arms was determined in four trials evaluating the outcome of PBM in BCRL patients.<sup>17-20</sup> In meta-analysis using three trials, the combined standardized mean difference (SMD) of arm volume was 0.04 (95% CI: -0.32 -0.41) after treatment and -0.53 (95% CI: -1.10 -0.04) at 1 month after treatment. No significant difference in arm volume was observed between the PBM groups and the control groups after the treatment period.<sup>3</sup> Many trials demonstrated that treatment with PBM resulted in reduction of pain felt by women with BCRL.<sup>2,16-18</sup> However, evidence for PBM-induced pain reduction in BCRL is not available as no significant differences in pain reduction were observed in the meta-analysis.<sup>3</sup> This is thought to be the reason why studies used different pain score. And other potential causes of BCRL pain include musculoskeletal disorders, cervical neuropathy, brachial plexopathy, neuropathy (e.g., chemotherapy-induced peripheral neuropathy), post-mastectomy pain syndrome, and bone metastases, which also cannot be ignored. Regarding harm, there were no apparent differences in adverse treatment-related events in PBM versus control groups across studies, but important contraindications and precautions for PBM should be considered when

using this modality. In the study, PBM did not increase the risk of cellulitis, however, patients must undergo appropriate medical management when they observe the symptoms and signs of cellulitis.<sup>15</sup>

## CONCLUSIONS

Although the results of meta-analysis did not show significant benefit in relieving lymphedema, PBM demonstrated a slight improvement in reducing arm volume and symptom-related BCRL like pain without any complications. Overall, there were some limitations in the studies, and these must be considered in future studies. In conclusion, further well-designed trials are needed to confirm the long-term efficacy and safety of PBM in BCRL management.

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