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Photobiomodulation Therapy in the Prevention and Treatment of Radiodermatitis in Breast Cancer Patients: Systematic Review

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Abstract

Introduction: Radiodermatitis (RD) is the most common side-effect of radiation therapy, yet its prevention and treatment through photobiomodulation therapy (PBMT) have demonstrated promising results. This study aimed to synthesize the evidence concerning the use of PBMT in managing RD among breast cancer patients undergoing radiation therapy.

Methods: This is a systematic review with no time restrictions, based on the methodology proposed by the Joanna Briggs Institute (JBI), including such databases as PubMed, Cochrane, Web of Science, Scopus, and CINAHL. The studies were selected based on the following inclusion criteria: female participants over 18 years of age and females having breast cancer and undergoing radiation therapy using a three-dimensional technique or an intensity-modulated radiation therapy (IMRT) technique. Two reviewers assessed the methodological quality using the JBI Critical Appraisal Checklist, and the report was described based on PRISMA guidelines.

Results: Red and infrared wavelengths were used. Device power ranged from 1.1 W to 0.08 W for continuous modes and 25 W for pulsed mode, resulting in a 3 and 4 J/cm^2 fluence, applied throughout radiation therapy, leading to a reduced severity in cutaneous reactions.

Conclusion: PBMT can reduce the severity of RD. New clinical trials are required to standardize protocols, given the scarcity of studies for the adopted site and methodological diversity.

Keywords: Radiodermatitis; Photobiomodulation therapy; Breast neoplasms; Radiation therapy; Supportive care.

Introduction

Radiation therapy (RT) consists of a locoregional cancer treatment method that employs ionizing radiation beams in pre-calculated doses according to tumor size for a certain amount of time, producing direct and indirect ionization events that damage cancer cells but may also cause immediate or subsequent alterations in normal tissue.[1,2] Among the most common adverse effects, radiodermatitis (RD) stands out. It affects 95% of patients and usually becomes manifest from the second week of treatment, although skin damage starts after the first exposure to radiation.[3]

RD is caused by a combination of factors related to intense radiation exposure, employed energy, dose and fractionation schedule, size of the exposed surface, and radiosensitization from chemotherapy.[1] In addition, intrinsic patient factors, such as malnutrition, obesity, smoking, underlying vascular disease, and genetic factors with DNA repair deficiencies, may also increase the risk of tissue lesion.[4]

After radiation-induced cell damage, cells die, leading to inflammation and oxidative stress, manifested through erythema, edema, pigmentation changes, loss of body hair, moist or dry flaking caused by the destruction of sweat and sebaceous glands, acute ulceration, pain, burning sensations, and chronic effects such as skin atrophy, telangiectasias, and fibrosis.[1,5,6]

Thus, acute RD prevention and treatment measures require relevant strategies based on reaction degree, including hydration and general skin care, in addition to topical treatments such as corticosteroids, silver sulfadiazine, chamomile compress, lotions composed of essential fatty acids, creams composed of *Aloe vera* and/or *Calendula*, hydrocolloid dressings, and hydrogel, which have proved a considerable therapeutic effect.[6]

Photobiomodulation therapy (PBMT) has been used for RD prevention and treatment, and its deployed energy is absorbed by cytochromes in the mitochondria and converted into energy by the cells, stimulating the acceleration or synthesis of proteins and cell proliferation,

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promoting an anti-inflammatory and analgesic action which accelerates tissue repair.[7]

The cumulative effect of PBMT on tissue repair is well-established, including its application to oncology, and is broadly used for the prevention and treatment of oral mucositis associated with chemotherapy or RT, the treatment of chemotherapy-induced peripheral neuropathy, and osteonecrosis of the jaw.[5] Regarding breast cancer patients, clinical trials have demonstrated its efficacy in treating RD and mastectomy-related lymphedema or local disease progression, with no evidence of side-effects.[7-9]

There is still no consensus on the use of PBMT in RD treatment, which justifies the need for this study, whose objective is to synthesize the evidence available in the literature on the effectivity of PBMT for RD prevention and treatment compared to conventional topical therapies.

Methods

This systematic review adopted the methodology proposed by The Joanna Briggs Institute (JBI),[10,11] registered in the PROSPERO platform under protocol CRD42021231565.

Question of the Review

The PICOT strategy (Participants, Intervention, Comparison, Outcome, and Type of study) was employed to search for the articles,[12] as described below. It aimed to answer the following question: What is the effectivity of PBMT for the prevention and treatment of RD in breast cancer patients undergoing radiation therapy compared to conventional topical therapy?

Eligibility Criteria

Participants

The included studies contained female participants over 18 years old, with a breast cancer diagnosis, and they were undergoing adjuvant or neoadjuvant radiotherapy, using a three-dimensional technique and/or an intensity-modulated radiation therapy (IMRT) technique.

Intervention

Studies assessing the effectivity of PBMT in RD treatment and prevention were selected to compose the sample of this review. Studies which did not specify the employed protocol were excluded.

Comparison

There is no standard treatment protocol for RD prevention and treatment in the literature. Therefore, the therapies that were adopted to compare and to assess intervention effectivity with PBMT were topical products commonly used as creams, generally containing *Aloe vera*, *Calendula*, vitamin E, and corticosteroids, among other substances or dressings.

Outcomes

The results of interest were the reductions of RD severity degree, measured by currently available assessment scales: Common Toxicity Criteria (CTC) and/or Radiation Therapy Oncology Group (RTOG).

Type of Study

The types of studies examined were randomized controlled trials (RCT), published in English, Portuguese, or Spanish, with no time restriction.

Search Strategy

The search strategy was applied from January to May 2021. Initially, a preliminary search was performed on the Cumulative Index of Nursing and Allied Health Literature (CINAHL), identifying keywords and descriptors to be used, which were combined with the Boolean operators "AND" and "OR", guiding the search on the included electronic databases: Medical Literature Analysis and Retrieval System (MEDLINE via PubMed), Cochrane, Web of Science, Scopus, and CINAHL.

Thus, representing the participants (women with breast cancer undergoing radiotherapy), the terms "Breast cancer" OR "Breast neoplasm" AND "Radiotherapy" OR "Radiation therapy" were used. For the intervention (photobiomodulation therapy), the terms "Photobiomodulation Therapy" OR "Low-Level Light Therapy" OR "Low-Level Laser Therapy" were used, whereas for the outcome (Radiodermatitis) "Radiodermatitis" OR "Radiation-Induced Dermatitis" were used.

Finally, a search was performed on the references of the selected articles and on the grey literature, including the CAPES database of theses and dissertations and clinical trial protocol platforms such as the World Health Organization International Clinical Trials Registry Platform and Brazilian Registry of Clinical Trials (Registro Brasileiro de Ensaios Clínicos - ReBEC).

Study Selection

The references were exported to the Mendeley Reference Manager, in which duplicates were removed. For study selection, two independent reviewers assessed the titles and abstracts of the identified references based on the previously established inclusion criteria, and potentially eligible studies were fully read and critically assessed. All divergencies between the two reviewers were solved by a third researcher. The search results, presented in Figure 1, were organized based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[13]

Methodological Quality Assessment

The methodological quality of the eligible studies

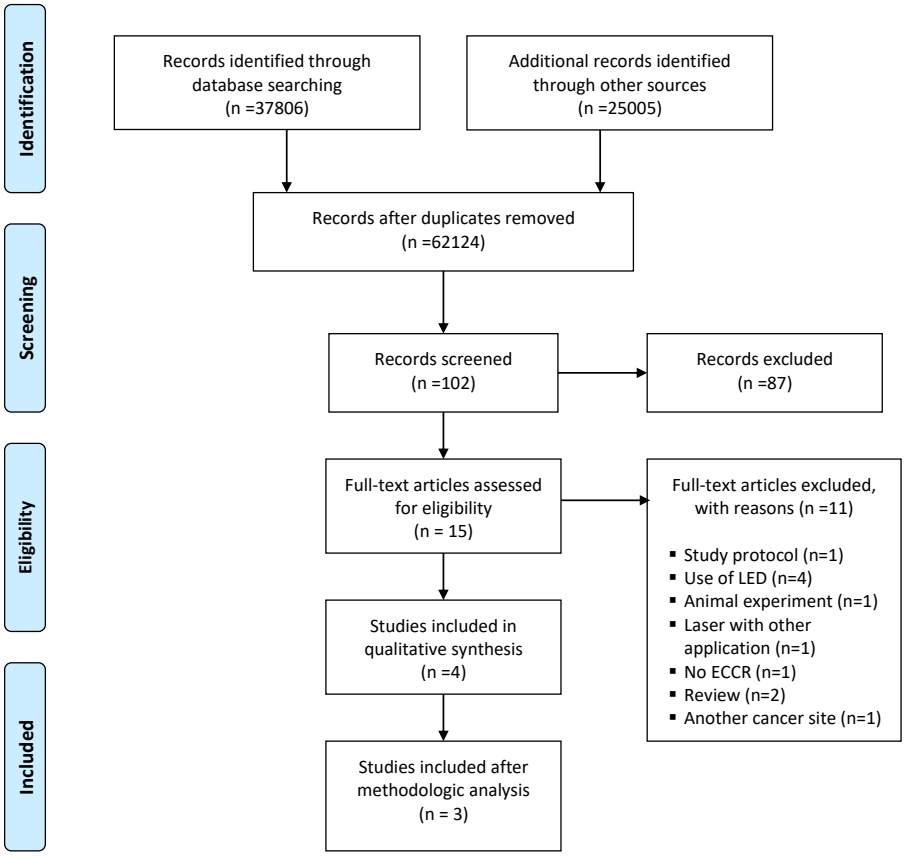

Figure 1: Search Strategy According to PRISMA Flowchart Adapted from Moher et al[13]

was assessed by two independent reviewers, with the participation of a third reviewer when there were divergencies. To do so, the critical assessment tool of JBI, entitled the JBI Critical Appraisal Checklist for Randomized Controlled Trials, was used.[10] It contains thirteen assessment items which encompass information on randomization, allocation, blinding, intervention and follow-up, statistical analysis of the results, and study design, with the options "yes", "no", "unclear", and/or "not applicable", which represent low risk, high risk, or uncertain risk of bias.

The cut-off point established for assessing methodological quality was nine, representing 70% of all thirteen items which were assessed, according to the instrument. After critical assessment, the studies which did not meet the defined quality limit were excluded.

Data Extraction and Synthesis

For data extraction, two independent reviewers used an instrument elaborated by the authors, which contemplates information of the studies, such as authors, country of origin, participants, setting, design, intervention, comparator, methods of analysis, and important results for the research question and study objectives.

Due to variations in the protocols used in the studies, it was not possible to perform a meta-analysis. Therefore, the results of the review were presented through a qualitative synthesis of the included studies. For the construction of the review report, the steps suggested by PRISMA were respected.[13]

Results

A total of 37 806 articles were identified in the first search in the electronic databases, in addition to 25 005 studies from other sources. After duplicates were removed and the titles and abstracts were read by the reviewers, 102 studies on the theme under study were pre-selected, fifteen of which were eligible for full reading, and only four of them were selected to comprise the sample. However, after the assessment of methodological quality, one of the studies, characterized by low methodological quality and a high risk of bias related to the absence of randomization of study participants and no blinding, was excluded. Figure 1 presents the flow diagram with the search results and details of the study selection process.

Methodological Quality

The results referring to the assessment of the methodological quality of the three studies included in the review are presented in Table 1. All demonstrated high methodological quality, with a score over 85%. Participants' randomization into treatment groups, generated from a random sequence through specific software, as well as blinding such allocation, was

Table 1. JBI Critical Appraisal Results for Randomized Controlled Trials

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	%
Censabella et al[14]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	85
Costa[5]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	92
Robijns et al[15]	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	85
Total %	100	100	100	33	0	100	100	100	100	100	100	100	100	-

Note: Y = Yes; N = No; U = Unclear.
Q1 = Was true randomization used for assignment of participants to treatment groups?
Q2 = Was allocation to treatment groups concealed?
Q3 = Were treatment groups similar at baseline?
Q4 = Were participants blind to treatment assignment?
Q5 = Were those delivering treatment blind to treatment assignment?
Q6 = Were outcome assessors blind to treatment assignment?
Q7 = Were treatment groups treated identically other than the intervention of interest?
Q8 = Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?
Q9 = Were participants analyzed in the groups to which they were randomized?
Q10 = Were outcomes measured in the same way for treatment groups?
Q11 = Were outcomes measured in a reliable way?
Q12 = Was appropriate statistical analysis used?
Q13 = Was the trial design appropriate, and any deviations from the standard RCT design accounted for in the conduct and analysis of the trial?

performed for all the selected studies, with a detailed description of the process, which was one of the required criteria for study selection.

Participant blinding to intervention application was conducted only in one study,[5] whereas blinding of the professional responsible for intervention application was not performed for any of the studies. This is due to the singularity of this technology, which requires a professional who is qualified to use it, as well as understanding who should and should not receive therapy so as to set application parameters. On the other hand, the researchers who were responsible for result assessment were blinded in the three studies, which were measured in the same way for all groups in a reliable manner and used appropriate statistical analyses so as to reduce bias.

Characteristics of the Included Studies

The included studies corresponded to RCTs investigating the effectivity of PBMT in the prevention and/or treatment of RD related to radiation therapy applied to breast cancer patients. The publications were in Portuguese[5] and English[14,15] and were published from 2015 to 2019. Only one study was conducted in Brazil,[5] and the others were conducted in Belgium.[14,15]

A total of 286 women were included in the three studies, and 142 of them received PBMT intervention. For the inclusion, female patients over eighteen, with a proposal of adjuvant RT after conservative surgery[14,15] and/or mastectomy with no reconstruction[5], were considered. The exclusion of women with previous breast radiation, concomitant chemotherapy, and metastasis, in addition to the exclusion of women under a hyperfractionation regime and collagen alterations, was common in the three studies.[5]

In relation to the histopathological type of tumor in the total sample, invasive ductal carcinoma was the most prevalent (n = 229; 80%); 23% of the cases (n = 65) were stage I, 39% (n = 111) were stage II, and 13% (n = 37) were stage III. Considering previous treatment, 72% (n = 206) received hormone therapy; 68.5% (n = 196) received chemotherapy; and 19% (n = 54) received monoclonal antibody therapy.

RT was an adjuvant indication in all studies, using the linear accelerator with an emission of 50 Gy to 60 Gy, set to 25 Fr to 30 Fr, considering a 16 Gy boost set to 8 Fr.[14,15] Topical therapies standardized in the institutions where the studies were carried out were considered comparative therapies due to the absence of a gold standard in the scientific literature, as synthesized in Table 2.

In all studies, the scale of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) was used to assess RD, associated with the Radiation therapy-Induced Skin Reaction Assessment Scale (RISRAS), Dermatology-specific quality of life (Skindex-16),[14] and Common Toxicity Criteria for Adverse Events (CTCAE).[5] The following devices were also used: Tewameter® TM300 to determine transepidermal water loss; Corneômetro® to measure skin hydration level; and Mexameter® MX18, a reflectance spectrophotometer to verify skin pigmentation (for example, melanin and erythema).[15]

RTOG and CTCAE are the most used scales in clinical practice. The first has been used in oncology for more than 25 years and is graded as follows: grade 0 (no reaction); 1 (faint erythema, dry desquamation, epilation, decreased sweating); 2 (tender or bright erythema, patchy moist desquamation, moderate edema); 3 (confluent, moist desquamation other than skin folds, pitting edema); and 4 (ulceration, hemorrhage, necrosis).[16,17] The CTCAE scale is currently on version 5.0 and assesses adverse events grouped by the anatomic site and graded from 1 to 5 in increasing order of toxicity.[18,19] The category RD is part of the subgroup "Injury, poisoning, and procedural

Table 2. Summary of the Characteristics of the Studies Included in the Review

Author	Year/ Sample	Radiotherapy Details	Intervention	Comparative Therapy	Instruments	Assessment	Results
Censabella et al [14]	2018 / N=120	Linear accelerator (6-15 mV photon), with dose of 50 Gy of 25 fraction (Fr)+16Gy (8 Fr *boost*)	Laser applied 2 days a week, immediately after the RT session, over 7 weeks.	Flamigel 3x/day starting at the first day of RT and Mepilex, if painful skin reactions and/or moist desquamation.	RTOG and RISRAS	First day of RT, at a RT dose of 40 Gy, and at the end of RT (total dose 66 Gy).	At the end of RT the severity of the skin reactions (RTOG≥2) was higher in *CG than **IG (30% vs. 6,7%, for CG and IG, respectively; *P*=0,004).
Costa, M. [5]	2015 / N=45	Linear accelerator, with dose of 50 Gy, of 25 Fr to 30 Fr (if *boost* applied).	Laser applied over 5 weeks, from monday to friday, until 12 h before RT session.	Cream based on chamomile 10% and silicone, with pH 5.5% (50 g), applied 3x/day.	CTCAE and RTOG	Weekly and 3 months after the end of RT	There was no significant difference between groups regarding radiodermatitis-free survival (*P*=0,729) or pain reduction (*P*=0,257).
Robijns et al [15]	2019 / N=120	Linear accelerator, with dose of 50 Gy (25 Fr)+16 Gy (*boost* 8 Fr)	Laser starting at the first day of RT, applied 2 days a weekright after the RT session, over 7 weeks (14 sessions).	Flamigel 3x/day from first day of RT and secondary coverage with Mepilex if desquamation or local pain.	- RTOG - Tewameter® TM300 (transepidermal water loss)+Corneômetro® (skin hydration)+Mexameter® MX18 (skin pigmentation).	Three moments: First RT session, at 40 Gy dose and at 66 Gy dose.	- Erythema and pigmantatiom higher in CG at the end of RT (*P*=0,016 and *P*=0,019, respectively), less skin hydration in CG at 40Gy dose (*P*=0,036) and increase of transepidermal water loss in both groups, being a little lesser in IG at the end of RT (*P*=0,05); - Lower incidence of RTOG≥2 in IG at the end of RT (*P*=0,004);

Note: *CG=Control group; **IG=Intervention group.

complications".

The scale RISRAS encompasses objective and subjective aspects of patient perception of RD, with a total score from 0 to 36, with a field for patient-reported symptoms and another field for health professional assessment.[20] Skindex-16 assesses the patient's quality of life related to general cutaneous changes and is divided into symptoms, emotional state, and physical/functional performance. Assessment is conducted through an analog numeric scale (0=never bothered to 6=always bothered) applied to 16 items.[21]

Review Findings

The first study,[14] performed with the laser Multiwave Locked System (MLS®), has shown no significant difference between the groups in the distribution of RD grades in the dose equivalent to 40 Gy. However, when the RT ended, the severity of the cutaneous reactions of both groups was different ($P=0.004$), and the control group (CG) showed 30% of RD with RTOG classification ≥ 2, compared to only 6.7% in the intervention group (IG). In addition, 3.4% of CG patients had displayed grade 3 RTOG, which was absent for the IG. The objective score of RISRAS confirmed these results, in which there was a reduction of the subjective scores of the IG and maintenance in the CG. The objective and total scores increased in the 40 Gy dose and at the end of the CG treatment, indicating increased RD severity in the CG throughout treatment. In addition, the subjective score Skindex-16 showed that the patient's quality of life was significantly better in the IG than in the CG.

In the study conducted with the InGaAlP laser,[5] the intervention and control groups were similar in all studied variables. There were 24 events of RD with RTOG ≥ 2 and only three cases of grade 3 RD. There was no significant difference between the groups regarding RD-free survival ($P=0.729$) or in relation to pain reduction ($P=0.257$), although it was lower in the CG after 90 days. In relation to the risk of developing grade ≥ 2 RD, age over 45 years and breast size over 5 cm were significant factors ($P=0.007$ and $P=0.005$, respectively).

The third study,[15] also performed with the Multiwave Locked System (MLS®) laser, showed further radiation-related skin alterations in the CG. There was an increase in the presence of erythema and pigmentation in both groups throughout the RT, which was significantly higher in the CG than in the IG at the end of radiation (erythema: $P=0.016$; pigmentation: $P=0.019$). When considering hydration of the radiated skin, there was, throughout treatment, a reduction in hydration in both groups, which was slightly lower in the IG in the dose equivalent to 40 Gy, compared to the CG ($P=0.036$). Finally, upon the assessment of the transepidermal water loss, a reduction was noticed in both groups in the 40 Gy dose; however, when RT was terminated, it increased in both groups and was slightly lower in the IG when compared to the CG ($P=0.05$).

Therefore, after 40 Gy, about 90% of CG and IG

demonstrated RTOG 2, followed by RTOG 3 manifested in 6.7% of CG and 5% of the IG. After 66 Gy, 26.7% of the CG were RTOG 2 and 3.3% were RTOG 3, compared to 6.7% RTOG 2 and no RTOG 3 in the IG ($P=0.004$). Furthermore, women with voluminous breasts [>800 cm^3] were shown to have a 4 times higher chance of presenting moist desquamation ($P=0.017$, 95% CI, OR 1.290-12.936),[15] and the CG had a 6 times higher chance of developing RD compared to the IG ($P=0.003$, 95% CI, OR 1.881-19.82). The characteristics of the lasers used in the interventions are detailed in Table 3.

Discussion

In vitro and *in vivo* studies have shown that PBMT affects all phases of the wound-healing process, and its role in the modulation and production of various growth factors and cytokines, also involved in the RD mechanism, is fundamental to understanding its use.[15]

Red and/or infrared light photons are absorbed by cytochrome c oxidase, a mitochondrial chromophore, leading to the dissociation of nitric oxide and a consequent increase in blood flow due to its vasodilator action. This dissociation increases the transportation of the mitochondrial electrons, increasing the production of adenosine triphosphate, responsible for the biostimulant effect of the laser. This leads to a short explosion of reactive oxygen species, responsible for the bio-inhibitory effect of the laser, which causes alterations in the cell redox potential and activates photosensitive ion channels, enabling the entrance of Ca^{2+} ions into the cells. The transcription factors are then activated, such as the nuclear factor kappa B (NF- κB) and activator protein 1 (AP-1), which induce transduction and photo signal amplification. This may then increase growth factor production, cell proliferation, cell mobility, anti-inflammatory molecule production, adherence, and extracellular matrix deposition.[15,22]

In oncology, the use of PBMT was strengthened after evidence from studies proving the absence of any tumor stimulus. *In vitro* studies have shown contrasting results, with biostimulation and bio-inhibition depending on wavelength and dose.[23] *In vivo* studies conducted on animals have shown the absence of tumor growth.[24-26] Other studies, the first comparing animal groups undergoing RT with and without the application of PBMT[27] and the second applying PBMT to stimulate hair growth in leukemic rats presenting chemotherapy-induced alopecia,[28] did not show tumor progression or differences regarding global survival.

A recent systematic review performed with 27 studies, which included several types of cancer, assessed the safety of the use of PBMT in the management of the main toxicities related to oncological treatment, suggesting that the use of this therapy was safe and that no tumor margin alterations were identified.[29] Moreover, clinical trials have shown no adverse effects after therapy and demonstrated an improvement in overall survival related to the reduction of these side effects, such as oral mucositis,[30-32] RD[14,15] and lymphedema,[33] associated with the reduction of inflammation and pain, promotion of tissue reparation, reduction of fibrosis, and nerve regeneration.[34]

The PBMT can be applied using a laser diode (LD), the topic of this review, or light-emitting diodes (LED), using red and/or infrared wavelength, ranging from 620 to 1000 nm.[22] Some of the studies identified in the literature have used an LED, with an emphasis on two remarkable clinical trials: the first applied a daily LED (25 W, 590 nm, pulsed light, 0.15 J/cm^2) one hour from the RT, prospectively, in nineteen breast cancer patients, undergoing post-quadrantectomy IMRT. Upon comparing the results with the retrospective CG (n=28), the LED was shown to significantly reduce RD with an RTOG≥2.[35]

The second study applied an LED (590 nm, 25 W, pulsed mode, 0.15 J/cm^2) to breast cancer patients after mastectomy or quadrantectomy, before and after each RT session, throughout the treatment, and up to seven days

Table 3. Photobiomodulation Therapy Irradiation Parameters

Parameters	Study		
	Censabella et al [14]	**Costa[5]**	**Robijns et al [15]**
Laser type	Multiwave Locked System (MLS®)	Photon Laser III – Indium/Gallium/ Aluminum/ Phosphorus (InGaAlP)	Multiwave Locked System (MLS®)
Wavelength (nm)	808 nm – 905 nm	660 nm	808 nm – 905 nm
Operating mode	Continuous and pulsed	-	Continuous and pulsed
Irradiance (W/cm^2)	0.168 W/cm^2	-	0.168 W/cm^2
Energy (J/point)	-	3 J/point	-
Fluence (J/cm^2)	4 J//cm^2	108 J/cm^2	4 J/cm^2
Power (W)	25 W (pulsed) and 1.1 W (continuous)	0.08 W	25W (pulsed) and 1.1W (continuous)
Beam area (cm^2)	19.635 cm^2	-	19.635 cm^2
Timing and anatomical location	467.27 seconds in breast, axilla and inframammary fold	35 points, with 38 s per point (22 min of treatment)	420-720 s for breast, 68 s for axilla and 103 s for inframammary fold
Application technique	5 cm above the skin	Contact, 2 cm distance between points	5 cm above the skin

after. However, no statistically significant differences were identified between the groups.[36] In another prospective intervention, conducted on women with breast cancer submitted to conformation or 3D RT (n = 70), 25 patients received a prophylactic LED (1390 mW, 660 + 850 nm, 44.6 mW/cm^2, 0.15 J/cm^2, twice a week), showing that PBM reduced the incidence of severe RD when compared to the CG (n = 45).[37]

The first study with PBMT using LD emission described the case of three breast cancer patients after mastectomy, who developed RT-induced cutaneous ulcers. They were submitted to three LD sessions per week (30 mW, 632.8 nm, 3 mW/cm^2, 30 J/cm^2, three times a week), and the results showed that the laser accelerated the healing process of the cutaneous wounds.[38]

The DERMIS trial has investigated the therapeutic effect of LD on seventy-nine post-quadrantectomy breast cancer patients treated with RT. The therapeutic application of the laser (25W + 1.1 W, 808-905 nm, 168 mW/cm^2, 4 J/cm^2, twice a week), which started with a dose equivalent to 40Gy of RT fractionation, prevented RD from increasing severity and improved patients' quality-of-life after treatment.[39] This study was excluded from this review due to the methodological quality score, which did not achieve the mean established by the authors of the present review.

Other studies have shown the efficacy of lasers in RD control for head and neck cancer patients submitted to RT. A case study was performed with two grade 3 RD patients throughout RT. Two lasers were applied daily, both with 660 nm, 1 J/point, for every 1.5 cm (the first, with a dose of 27.77 J/cm^2, 25 seconds/point, 40 mW, and beam area of 0.036 cm^2; the second, with a dose of 35.71 J/cm^2, 100 mW, 10 seconds/point, and beam area of 0.028 cm^2). In the first patient, RD was reduced to grade 2 in 48 hours and to grade 1 in 6 days. For the second, it was reduced to grade 1 after 4 sessions and to grade 0 after seven sessions.[40] A recent clinical trial (DERMISHEAD trial) performed with 46 participants with head and neck cancer patients undergoing RT, controlled by the application of a placebo laser, demonstrated a significant reduction in severe RD (RTOG ≥ 2) in the group receiving MLS® laser (25 W + 1.1 W, 808 + 905 nm, 168 mW/cm^2, 4 J/cm^2, twice a week).[41]

There is a wide variation in the parameters of application and treatment; however, current evidence shows that PBMT in the red or near-infrared spectrum (630–905 nm) is safe and efficient in the management of various complications of oncological therapy and can be applied throughout radiotherapy and/or up to 30 days after.[22,26,42]

A correct choice of dosimetry is crucial for the efficacy of this therapy and is determined by radiation parameters, which include the wavelength, power, fluence or energy density, and pulse structure, and treatment parameters, which include the dose or energy per point, time, treatment schedule, and anatomic site.[15] It should be emphasized that fluence corresponds to the energy deposited on a particular area, which is directly proportional to the device power and duration of application and inversely proportional to the beam area.

In the main studies using a laser diode, the fluence was 3 and 4 J/cm^2, with device power ranging between 1.1 W and 0.08 W for continuous modes and 25 W for pulsed mode.[14,15,41] However, the fluence must be calculated according to the power of the employed devices. In Brazil, for example, the main available devices present an effective power of 100mW or 0.1W, that is, a lower power than those employed by devices internationally, which would imply a higher fluence for the corresponding dose.

Strengths and Limitations

Although the evidence of PBMT for RD management is limited, a rigorous and transparent methodological design was employed for the selection of eligible studies, which were randomized and methodologically sound. In addition, all phases of the study search, selection, and assessment were conducted by two reviewers, with the participation of a third reviewer. As a limitation, language restrictions are emphasized since the literature in languages other than Portuguese, English, or Spanish was excluded, in addition to the reduced number of studies comprising the sample.

Implications for Nursing

Ionizing radiation emitted in radiation therapy causes structural and functional skin alterations, in addition to local inflammatory processes.[3] Thus, considering the impact of RD on patients' quality of life as well as on therapy adherence and continuation, PBMT is described by the literature as a preventive and therapeutic agent since the therapeutic properties of the laser accelerate tissue healing, in addition to anti-inflammatory control and local analgesia.[7] Therefore, the application of a laser from the first fraction of radiation therapy until the end of the treatment is considered, with beneficial results for the reduction of RD severity and accelerated resolution.

Conclusion

The available evidence shows that PBMT may effectively reduce RD severity. Studies related to this theme are still scarce and those available have divergent methodologies, which limits recommendations. Other noteworthy aspects include the lack of information on the employed parameters, the diversity of skin care protocols adopted by different institutions, and difficulties with blinding the device operator, and sometimes the patient, which increases the risk of bias, hindering the comparison of results among diverse trials and possibly limiting inferences. Given these factors, further studies are

suggested to focus on controlled and randomized designs with well-described parameters, favoring the implementation of lasers for RD management.

Conflict of Interests
The authors declare that there are no conflicts of interest.

Ethical Considerations
Not applicable.

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