Treatment Parameters of Photobiomodulation in the Prevention of Non-surgical Cancer Treatment-Induced Oral Mucositis: A Review of Preclinical Studies

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Abstract

Introduction: The most important side effect after non-surgery cancer treatment (NSCT) is oral mucositis (OM) which degrades the quality of life. Using photobiomodulation (PBM), formerly known as low-level laser therapy (LLLT), in the prevention of NSCT-induced OM was widely studied. Hence, this review evaluates the efficacy of optical treatment parameters behind the working process of PBM in preventing NSCT-induced OM in preclinical studies.

Methods: Using the PubMed, Scopus and Embase databases, the present study systematically reviewed existing preclinical studies for optical treatment parameters of PBM in preventing NSCT-induced OM in experimental models without restriction on the year of publication.

Results: In total, 51 articles were recognized during the search of the literature, and only 16 research papers were included in this review, taking into consideration the inclusion as well as exclusion benchmarks. The reviewed studies showed that a consensus has yet to be reached on the optimal PBM treatment parameters in preventing NSCT-induced OM. However, a wavelength of 660 nm, a power density of 40 mW as well as fluence which ranged between 2 and 6 J/cm² were mostly utilized in the included studies. Furthermore, the severity of NSCT-induced OM was reduced following PBM application with no reported severe side effects.

Conclusion: The efficacy of PBM with the associated optical parameters is a promising strategy in preventing NSCT-induced OM. However, the optimal parameters of PBM need to be investigated.

Keywords: Low-level laser therapy (LLLT); Photobiomodulation (PBM); Oral mucositis; 5-Fluorouracil; NSCT-induced oral mucositis.

Introduction

Oral mucositis (OM) is a painful inflammation and ulceration of the mucosal lining of the inside of the mouth, which often results in a wearing complication associated with cancer regimen.^{1,2} OM is a serious complication of non-surgery cancer treatment (NSCT) modalities. It comes with acute pain, which affects patients' quality of life (drinking, food intake, weight loss, dehydration, and alteration in taste), and dose-limiting factors that damage the oral epithelium.³⁻⁵ The pain and discomfort associated with OM negatively affect patient's ability to take medications, which invariably results in the

prolonged hospitalization, thereby increasing the cost of cancer treatment.^{6,7}

NSCT-induced OM was examined in various experimental models. Chemotherapeutic agents such as 5-fluorouracil (5-FU), methotrexate, and irinotecan were shown to induce mucositis.⁸⁻¹⁰ Thus, many treatment approaches were developed to reduce or prevent severe OM occurrence. One of such therapeutic strategies is the application of photobiomodulation (PBM), also previously called low-level laser therapy (LLLT).^{11,12}

The clinical application of PBM was first established by Mester around the 1960s. This type of modality

restricts the laser irradiation intensity by transmitting low fluence to the target tissues as no heat is generated in this process.¹³ PBM does not increase the tissue temperature due to the power density used, which is much smaller than the intensity needed for photothermal effects to occur.¹⁴ Red light as well as near-infrared light is used in PBM to revive, mend, and restore multiple physiological processes and repair damage from injuries or diseases.^{15,16} Furthermore, Studies showed that PBM increases fibroblast proliferation,¹⁷ which also favours collagen synthesis¹⁸ as well as angiogenesis;¹⁹ in such a case, it reduces cyclooxygenase-2 (COX-2), tissue necrosis factor-alpha (TNF- α) as well as pro-inflammatory cytokines IL-6 and IL-1 β .^{20,21} It also promotes the anti-inflammatory cytokines differentiation, including IL-2, IL-4, IL-8, and IL-10, which acts on the pathway leading to nuclear factor-kappa beta (NF- κ B) signal transduction.²²

In addition to preventing or reducing the incidence of NSCT-induced OM, studies have identified other benefits associated with PBM, including the pain treatment of musculoskeletal, skin lesions healing, and anti-inflammatory effects.²³⁻²⁶ PBM does not work alone as some parameters influence its effectiveness in reducing or preventing NSCT-induced OM. Preclinical studies play vital roles in assessing the efficacy of therapeutic modalities such as PBM. Several experimental studies were conducted investigating the ability of PBM to manage NSCT-induced OM. PBM treatment parameters are crucial to obtain desired outcomes. While numerous studies utilized various parameters, there was no consensus about the optimal parameters. The present systematic review aims to assess the efficacy of the optical treatment parameters behind the working process of PBM to reduce the risk of NSCT-induced OM by considering preclinical studies. These parameters include wavelength, power density, energy density and treatment time. This study will address the following question “what are the common PBM parameters to manage chemotherapy-induced OM?” using PICOS (participants, interventions, comparisons, outcomes, as well as study design).

Methods

Search Procedure

This study was to perform a preclinical small animal review in line with systematic reviews and meta-analyses due to the statement of preferred reporting items (PRISMA).²⁷ The electronic database search of PubMed, Embase and Scopus was carried out in April 2020 for research papers investigating the efficacy of PBM against chemotherapy-induced OM by considering experimental animal models, without a restriction on the year of publication. The search keywords were as follows: “low-level laser therapy” and “oral mucositis” and “animals”. Furthermore, manual screening of the references of the retrieved studies was conducted to obtain relevant studies.

Inclusion Criteria

This systematic review was in terms of PICOS: Participants: animals; Intervention: LLLT; Comparisons/control type: chemotherapy

treated animals only; Outcome variables: wavelength, power density, energy density and treatment time; and Study design: experimental studies.

The inclusion criteria of the retrieved articles were as follows: the studies investigating PBM efficacy of LLLT to prevent chemotherapy-induced OM, published in the English language, the research articles which used chemotherapy, and experimental papers with their complete texts available.

Exclusion Criteria

Studies were exempted using these benchmarks: research articles that did not use chemotherapy, articles that were not published in the English language, clinical studies, conference abstracts, letters, review articles, editorials, unpublished data, as well as research studies without complete texts available.

Selection of Eligible Study

The articles retrieved from the electronic database and manual searches were added to EndNote software to remove identical articles. Thereafter, retrieved studies were reviewed by three authors for eligibility. Finally, 16 preclinical articles were selected using the inclusion as well as the exclusion benchmarks.

Extraction of Data

The authors checked the information extracted from the eligible studies included in the present review. The following information was carefully obtained from each included study: first author name, subject, sample size, NSCT dose, the laser type, wavelength, power, energy, time, as well as spot size. Furthermore, these data were summarized and presented in a tabular form.

Results

Literature Search

The flow chart of the included articles in this systematic review is shown in [Figure 1](#) following the PRISMA statement.²⁷ The breakdown of the initial search of 51 articles in total is as follows: 48 articles from PubMed, Scopus and Embase and 3 articles obtained from a manual search. Furthermore, 41 articles were engaged after the removal of identical articles. Thereafter, following careful examination and screening of their titles and abstracts as well as applying the inclusion and exclusion criteria, a further 18 articles were excluded. The full texts of the remaining 23 records were assessed. We excluded three articles for non-English language publication, and four articles were further removed for not having full texts. 16 articles were finally considered for review.

Figure 1. The Flow Chart of the Included Articles in this Systematic Review Following PRISMA Statement.

Study Characteristics

The studies that were reviewed were published between the years 2007 and 2019, and the summary of these studies is presented in a tabular form (Table 1). Furthermore, the studies were carried out using Sprague-Dawley, Wistar albino, golden/syrian hamsters, mice and rats with a sample size ranging from 8-150. All the studies utilized NSCT as the subjects received 5-FU intraperitoneally. Out of the 16 included studies, 8 studies used NSCT doses of 65-100 mg/kg, 2 studies used 40-80 mg/kg and 2 studies used 40-60 mg/kg. The laser type mostly used in the included studies is InGaAlP as 7 out of the 16 studies used this. Four studies employed the Nd: YAG diode laser and 3 studies utilized a light-emitting diode (LED). The optical parameters of PBM used in the included studies, such as wavelength, power density, energy density as well as treatment time, were extracted and extensively discussed.

Discussion

The Wavelength of LLLT in Preclinical Studies

The laser device has a specific purpose as its use is dependent on the wavelength as well as the output power. Specifically, the wavelength is a factor to be considered in terms of tissue penetration depth. Photoacceptors show distinct responsiveness to individual wavelengths of light. The most effective PBM wavelength ranges from 600 nm to 1100 nm²⁸ as this is the optical window in tissue.^{29,30}

Several experimental studies have reported several PBM wavelengths in the prevention of NSCT-induced

OM (Table 1). The wavelength of 660 nm was mostly utilized.^{19,21,31-39} Only one study used 630 nm.⁷ Moreover, higher wavelengths such as 808 nm,³³ 810 nm,^{31,40} 940 nm,⁴¹ 970 nm,⁴² 980 nm,³¹ and 1064 nm,³⁶ were also utilized. Due to outcomes, smaller differences in wavelengths (632–970 nm) had potent therapeutic effects. However, the larger wavelength of 1064 nm did not show a significant impact. Moreover, wavelengths varying between 632.8–685 nm (visible red) were shown to be effective in preventing NSCT-induced OM at energy densities less than 2 J/cm².⁴³

The 660 nm wavelength utilized in most of the studies can be attributed to the fact that the wavelength increases reactive oxygen species (ROS) if applied before or after the oxidative stimulus.⁴⁴ Besides, it has better absorbance in haemoglobin, closer to tissue cell resonant frequency, and has the ability to influence mitochondrial enzyme activity such as CCO-2,^{45,46} which eventually increases adenosine triphosphate (ATP) level synthesis as well as the mitochondrial activity.⁴⁶ This same wavelength, when used in the LED therapy, increases cell proliferation and migration.⁴⁷

In a study by Campos et al³³ involving 150 hamsters, 100 mg/kg and 65 mg/kg doses of chemotherapy were administered on day 1 and day 3 respectively. Furthermore, a combination of three wavelengths (LED, 635 nm; PBM, 660 nm and HPL [high power laser], 808 nm) were used. Their results showed a positive outcome in the LED and LLLT groups in which they observed a decrease in the level of TNF- α on day 7, and the mucosa was totally healed after 10 days. Findings from their study

Table 1. Summary of PBM Treatment Parameters for The Prevention of NSCT-induced OM in Animal Studies

First Author	Subject	Sample Size	NSCT Dose (mg/kg)	Laser Type	Wavelength (nm)	Power (mW)	Energy (J/cm ²)	Time (s)	Spot Size
Alinca et al ⁴⁰	Sprague-Dawley rats	8	65–100	Diode laser	810	0.0003	18.75	5	0.08 cm ²
Bayer et al ⁴¹	Sprague-Dawley rats	8	65–100	Diode laser	940	0.001	7.14	20	2.8 cm ²
Bostancikliglu et al ³⁶	Adult Wistar-Albino rats	28	65–100	Nd-YAG;	1064	0.00025	8	9	0.28 cm ²
				Diode laser;	980	0.0001	8.3	10	0.12 cm ²
				Diode laser;	810	0.00025	8.04	9	0.28 cm ²
				Diode laser;	660	0.0001	8	60	0.75 cm ²
Campos et al ³³	Golden Syrian hamsters	150	65–100	LED;	635	120	1.3	10	1 cm ²
				InGaAlP;	660	40	6	6	0.04 cm ²
				GaAlAs;	808	0.001	10	10	-
Cotomacio et al ³²	Syrian hamsters	18	65–100	MMOptics®:					
				Laser 1;	660	40	6	6	0.04 cm ²
				Laser 2;	660	40	25	25	0.04 cm ²
				Laser 3;	660	40	24	6	0.04 cm ²
Cruz et al ³⁴	Hamsters	54	65–100	Low-power-laser	660	40	120	2*	0.037 cm ²
Curra et al ³⁵	Golden Syrian hamsters	96	65–100	InGaAlP	660	40	6	6	0.04 cm ²
Franca et al ¹⁹	Hamsters	24	65–100	GaAlAs	660	30	1.2	40	2 mm ²
Freire et al ³⁷	Golden Syrian hamsters	40	60–90	InGaAlP laser;	660	40	4.8	30	4 mm ²
				LED;	670	150	4	16	0.5 cm ²
Lara et al ⁴⁸	Wistar rats	45	50–60	GaAlAs	780	70	4	NR	NR
Lopes et al ²¹	Hamsters	48	40–80	InGaAlP					
				L1;	660	35	E _t = 10.48 J	16	600 µm
				L2;	660	100	E _t = 11.12 J	6	600 µm
Lopes et al ³⁹	Hamsters	48	40–80	InGaAlP					
				L1:	660	35	E _t = 10.48 J	16	600 µm
				L2	660	100	E _t = 11.12 J	6	600 µm
Lopes et al ³⁸	Hamsters	72	40–60	InGaAlP	660	40	6.6	6	0.036 cm ²
Ottaviani et al ⁴²	Mice	32	60	Diode laser;					
				LPLT:	635	2.5	0.375	30	0.5 cm ²
				HPLT:	970	5	375	30	0.5 cm ²
Sacono et al ⁷	Golden Syrian hamsters	32	60–90	LED	630	160	12	37.5	0.8 cm ²
Thieme et al ³¹	Rats	54	40–60	InGaAlP					
				IO (CW):	660	100	6	2.4	0.04 cm ²
				EO(PM):	810 + 980	2000	6.11, 12.22	15, 30	4.91 cm ²

Abbreviations: NSCT, non-surgery cancer treatment; Nd-YAG, neodymium-doped yttrium aluminium garnet; LED, light-emitting diode; InGaAlP, indium-gallium-aluminium-phosphide; GaAlAs, gallium aluminium-arsenide; Et, total energy; LPLT, low-power laser therapy; HPLT, high-power laser therapy; IO, intraoral; EO, extraoral; CW, continuous wave mode; PM, pulse mode; NR, not reported; *, time reported in minutes.

showed that the LED (635 nm) and LLLT (660 nm) are effective in reducing OM severity by speeding up the tissue restoration mechanism and preventing the action of inflammation. This result was similar to studies carried out by Curra et al,³⁵ Freire et al,³⁷ and Franca et al.¹⁹ In these studies, a wavelength of 660 nm was utilized, with their results showing that LED/PBM therapy at this wavelength stimulated the process of repair and reduced the severity of OM by activating the NF-κβ pathway. Studies^{38,39,42} also showed similar results at wavelengths of 660 nm and 970 nm.

In a study by Bostancikliglu et al,³⁶ 28 adult Wistar-Albino rats received 100 mg/kg and 65 mg/kg doses of chemotherapy on days 1 and 3 respectively, in addition to a combination of different LLLT wavelengths (660, 810, 980, and 1064 nm). A substantial reduction in gene

expressions was observed at wavelengths of 660, 810 and 980 nm. A similar outcome for a wavelength of 780 nm was obtained in a study by Lara et al⁴⁸ in which the laser group was not really effective in preventing OM in rats. In a later study by Cruz et al,³⁴ this same wavelength (660 nm) was found to be effective in ameliorating OM severity, but application time was extended.

Power Density Used in Preclinical Studies

In the prevention of NSCT-induced OM, PBM power ranging from 5–2000 mW was utilized in numerous studies. It was shown that lower power density is more effective than higher power density.⁴⁹ However, when the power density is insufficiently coupled with a shorter treatment time, no meaningful effect will be recorded, and at the same time when a large amount of power

density is applied at a much higher treatment time, this leads to inhibitory effects.^{30,50} This suggests that there must be a balance between too low power/time and high power/time so as to achieve a much beneficial effect on the tissue. Moreover, we may have a situation whereby the low power density is given at a much longer treatment time, thereby leading to many beneficial effects rather than inhibitory as the wavelength, the type of tissue and the pulse parameters can influence this effect.

Furthermore, 40 mW was commonly used^{32-35,37,38} followed by 100 mW–160 mW.^{7,21,31,33,37,39} A study by Freire et al³⁷ compared an LED (670 nm, 150 mW) and a Laser (660 nm, 40 mW) for the control of OM following NSCT induction. Their results showed that both the laser and the LED effectively stimulated the process of repair and reduced OM lesions and their development.

In another study, Ottaviani and colleagues⁴² compared low-power laser therapy (LPLT; 635 nm, 2.5 mW) and high-power laser therapy (HPLT; 970 nm, 5 W). They observed that both LPLT and HPLT, specifically the HPLT, enhanced and speeded up the healing action of OM. They concluded that the HPLT healed and enhanced the process of inflammation as compared to LPLT.

In a later study by Campos and colleagues, three different light therapy protocols were compared to treat NSCT-induced OM (LED: 635 nm, 120 mW; LLLT: 660 nm, 40 mW; and HPL: 808 nm, 1 W).³³ Their results indicated that the LED and LLLT treatment were foremost in reducing OM severity. Moreover, it accelerated the repair process of tissue and decreased the process of inflammation. Furthermore, a study by Lopes et al. compared two laser power densities of 35 mW and 100 mW.²¹ Their result indicated that the 35 mW laser showed a peak OM severity reduction than the 100 mW laser by a significantly lower level of COX-2 staining. In their study, the low-intensity laser therapy reduced OM severity by reducing COX-2 levels and its associated inflammatory response. In a further study by the same researchers, it was reported that PBM at 16 s time of application reduced OM severity by increasing collagen.³⁹ Hence, it can be implied that PBM promotes wound healing and possesses an anti-inflammatory effect as it supports the reduction in neutrophil infiltrate.

Energy Density Used in Preclinical Studies

Energy density is the most potent parameter in laser PBM as it estimates the actual energy received by the target tissue. This is often referred to as the fluence (J/cm²) which means the dose; however, some scholars also referred to energy in joules as dose.³⁰

The energy of a laser involved depends solely on the wavelength of the laser, the state and depth of the target tissue, tissue type, pigmentation, acute or chronic problem as well as the treatment technique used (i.e. contact and non-contact modes). Moreover, the laser

radiation is determined by its power density (also known as irradiance), power, time and treatment intervals.⁵¹ In the same vein, it has been stated that there is a high degree of proof indicating that the irradiance and the fluence are the key variables for the efficacy of PBM.⁵²

Furthermore, it is better noted that PBM is biphasic as this is used to illustrate the dose expected as a response to light at the cellular level. This implies that when insufficient energy is applied, there will be no response showing that the threshold has not been reached. On the other hand, when higher energy is applied, bioinhibition will occur.^{50,52} PBM also favours lower doses in wound healing by accelerating the cutaneous tissues as a result of biphasic dose response.⁵³

Several preclinical studies have reported several energy densities of PBM in preventing NSCT-induced OM. The energy densities used range from 1.2 to 375 J/cm². The energy density of 6 J/cm² was mostly utilized.^{32,33,35,38} Higher doses of energy densities, 18.75 J/cm²,⁴⁰ 25 J/cm²,³² 120 J/cm²,³⁴ as well as 375 J/cm²,⁴² have also been used. Thieme et al³¹ compared the effect of intraoral (IO) with 6 J/cm² of fluence (continuous wave mode) and extraoral (EO) at the fluence of 6 J/cm² as well as 12 J/cm² (pulsed mode) diode laser irradiation on OM induced by 5-FU in rats. PBM accelerated the healing process without a reduction in the level of ROS generated. It also showed higher antioxidant levels. Furthermore, the protein damage marker was greatly reduced in the EO 6 J/cm² LLLT protocol. The EO diode laser showed positive effects as compared with the IO in OM-induced rats. EO with an energy density of 6 J/cm² showed the most promising results among the EO protocols. Moreover, promising outcomes were also observed from studies by Campos et al³³ (at 6 J/cm² and 660 nm), Bayer et al⁴¹ (at 7.14 J/cm² and 940 nm), Cotomacio et al³² (6 J/cm² showed better result at a wavelength of 660 nm), and Curra et al³⁵ (6 J/cm² and 660 nm), in which the activation of NF-κB pathway greatly reduced the severity of OM lesions. Furthermore, in most of the preclinical studies reviewed, fluence of 4 J/cm² and 6 J/cm² had a better treatment response and reduced the prevalence as well as the level of OM severity induced by chemotherapy. However, PBM with the fluence of 24 J/cm² and 25 J/cm² at a 660 nm wavelength could not ameliorate the incidence of NSCT-induced OM unlike the result obtained at 6 J/cm² using the same wavelength by Cotomacio et al.³² Similarly, in a study by Cruz et al,³⁴ energy density of 120 J/cm² did not show a promising effect in reducing the severity of NSCT-induced OM.

Treatment Time

This is the allowed interval through which the energy is delivered to the target tissue when it is exposed to light.⁵⁴ When the treatment time is too short, the effect may not be meaningful, and applying a longer time does not

necessarily mean that a beneficial effect will be achieved, rather this may lead to inhibitory effects.^{30,55} To achieve a beneficial effect, the time of application needs to be well balanced between the power density and the fluence.

The treatment time of the PBM device is relative to the mode of application of the device (either punctual or scan mode). Franca et al¹⁹ reported a total time of application of 40 s per day. In most studies, application times ranging from 6 - 60 s were utilized.^{34,36, 40-42} Furthermore, the majority of the studies used the PBM therapy devices in the continuous wave mode,^{21,31-34,38,39,41, 42} while Bostancikloglu et al³⁶ and Thieme et al³¹ utilized the combination of both continuous wave and pulsed modes. No study has reported the application time effect of different PBM devices on the treatment of NSCT-induced OM.

Conclusion

For the effective control of NSCT-induced OM, treatment parameters of PBM, including wavelength, power density, energy, energy density and time of application, play key roles, thereby ensuring that the therapeutic benefits following NSCT are maximized. Moreover, from reviewed preclinical studies, a consensus has yet to be reached on the optimal treatment parameters of PBM for the prevention of NSCT-induced OM; however, the wavelength of 660 nm, the power density of 40 mW and fluence ranging between 2 and 6 J/cm² were mostly utilized. Most included preclinical studies had variation in laser devices, wavelength, energy and time. Thus, there would be a need for future studies investigating the optimal treatment parameters of PBM. Furthermore, more comparative studies on these parameters would open up more insights.

Most importantly, the treatment parameters of PBM were productive in ameliorating the OM severity induced by chemotherapy with minimal side effects. However, future preclinical studies using larger sample sizes would be more desirable. Finally, the efficacy of PBM with the associated treatment parameters is a promising strategy in preventing OM induced by chemotherapy.

Ethical Considerations

Not applicable.

Conflict of Interests

The authors declared no conflicts of interest.

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