Impact of Photobiomodulation for Oral Mucositis on Body Weight and Bmi of Patients with Head and Neck Cancer

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Abstract

Purpose

To evaluate the impact of photobiomodulation for oral mucositis on body weight and Body Mass Index (BMI) of patients with head and neck cancer.

Methods

Patients were divided into two distinct groups: Photobiomodulation - PBM ($n = 17$) and SHAM ($n = 19$). Participants in the PBM group received the low-power aluminum gallium arsenide (AsGaAl) laser device with maximum output power of 86.7 mW, wavelength of 660 nm (red) and laser applications at 33 different points of the oral mucosa, on alternate days. Patients in the SHAM group were found to be using the same procedure but with the device turned off. During the first and twenty-fourth session of radiotherapy, participants from both groups underwent an intraoral examination to assess the presence or absence of mucositis and its respective degree according to WHO scale, and were assessed by measuring weight and height and for BMI calculation.

Results

All patients presented significant differences on weight and BMI throughout the study. Patients in the PBM group had less weight loss ($p < 0.01$) and reduced BMI loss ($p < 0.01$) when compared to patients in the SHAM group. PBM did not prevent oral mucositis, however, it decreased its severity ($p < 0.01$).

Conclusion

Photobiomodulation for oral mucositis reduces weight loss and prevented the reduction of BMI in patients who underwent radiochemotherapy treatment for head and neck cancer. Although it did not avoid the appearance of oral mucositis, PBM was able to reduce its degrees, preventing the progress of this condition. Retrospectively registered: <https://data.mendeley.com//datasets/4kd7s49wk4/1>

Introduction

Accelerated weight loss and malnutrition are secondary disorders that frequently affect cancer patients. The prevalence of these conditions is variable and might range from 40 to 80% in individuals with head and neck cancer (HNC) [1] and occur due to local and metabolic changes of large magnitude that are produced by tumor cells, their growth and the secondary effects of antineoplastic treatments [2–6].

The main treatment modalities for HNC are surgery, radiotherapy and chemotherapy which have been

ulcerative character, associated with pain, dysphagia and odynophagia, and complications in diction [7]. This set of manifestations can lead to a state of dehydration due to difficulty in water intake, in addition to lower food intake, resulting in weight loss, negative variation in the Body Mass Index (BMI) and worsening of the individual's nutritional status [8].

The prevention and control of OM is mandatory for nutritional status and the patient's quality of life. Laser therapy or photobiomodulation (PBM) is known to be effective in relieving the pain and inflammatory reaction characteristic of OM, as it has the ability to regulate a variety of metabolic events through photophysical, photobiological and biochemical processes [9–11]. Therefore, PBM could decrease weight loss and BMI reduction by preventing or treating OM.

One way to assess the impact of OM on the nutritional status of individuals is through anthropometric measurements [1]. Regular measurements of weight, height, and other factors that assess body composition, at the beginning, during and at the end of the treatment, are presented as expressive indicators of weight loss and monitoring of nutritional status, being of easy and low-cost application [12, 13].

This study aimed to evaluate the impact of PBM for OM on weight loss and BMI of patients with HNC during the beginning and the end of antineoplastic treatment.

Methods

It was a prospective clinical study, carried out from August 2017 to March 2020, whose population sample included 36 patients with malignant neoplasms in the head and neck region, undergoing exclusive radiotherapy treatment or concomitantly with other therapies, users of a High Complexity Oncology Unit (*Unidade de Alta Complexidade em Oncologia - UNACON*), in the city of Salvador, Bahia, Brazil. The research protocol was approved after ethical analyses (CAAE: 68263317.8.0000.0047). The data that support the findings of this study are openly available in Mendeley Data at <https://data.mendeley.com/datasets/4kd7s49wk4/1>, reference [DOI: 10.176332/4kd7s49wk4.1].

As inclusion criteria, participants were elected at least eighteen years old, who developed or not OM as a side effect of antineoplastic therapies. Individuals with diabetes mellitus and autoimmune diseases were excluded due to difficulties in the tissue repair process, as were those who did not complete the research protocol.

A socioeconomic questionnaire was used to collect individual data about patient's health lifestyle, treatment modality (radiotherapy with chemotherapy/surgery), location and tumor staging. Anthropometric measurements were performed throughout the treatment, being a mandatory criterion. Welmy® anthropometric scale was used to this procedure. BMI was calculated by measuring weight and height, applied in the formula $BMI = \text{weight}/\text{height}^2$. The results were categorized following the World Health Organization (WHO, 2006) [14] classification for adults, and the Pan-American Health Organization (PAHO, 2006) [15] classification for children and adolescents (under 60 years old).

To assess the percentage of speed of involuntary weight loss (SIWL) as a function of time, the classification criteria of Blackburn et al., 1977 [16] was used, calculated using the formula:
$$SIWL(\%) = \frac{Initialweight(Kg) - currentweight(Kg) \times 100}{Initialweight(Kg)}$$

Patients were randomly allocated into two distinct groups, PBM (n=17) and SHAM (n=19). In the PBM group, the low-power aluminum gallium arsenide (AsGaAl) laser device (Twin Flex®, MM Optics, São Carlos, Brazil) with maximum output power of 86.7 mW, tip area active device of 0.03 cm² (measurement performed by the team = 0.1246 cm²), wavelength of 660 nm (red), was applied to specific points of the oral mucosa, three times a week on alternate days. The dosimetry used at each application point was 1J for 10 seconds, total energy of 33J. Thirty-three equidistant laser application points were delineated in the oral cavity, excluding the tumor site, with at least 5cm of safety margin. The laser was applied to the upper and lower lips (03 points each), right and left buccal mucosa (03 points each), hard and soft palate (03 points each), buccal floor (01 point), right and left lateral edge of the tongue (03 points on each side), back of the tongue (06 points), labial commissure (02 points), according to the protocol proposed by Scully (2009) [17].

For individuals of SHAM group, the laser device was positioned in the same molds as the PBM group, however, without light emission. The analyzes took place in sessions 1 and 24 of radiotherapy, when, in each session, the patients were submitted to weighing and intra-oral physical examination to analyze the presence of OM. The severity of OM was assessed according to the WHO scale (1979) [18].

For statistical analysis of the data, the freeware R, version 4.0.1 (2020) was used. To verify the normality of data distribution, the *Shapiro-Wilk* test was used. In intragroup analysis, the *t-student* was used for paired samples, in the case of continuous variables, and the *McNemar-Bowker* test for categorical data. In the intergroup comparison, *t-student* test was used for continuous data, *Mann-Whitney* for continuous data with non-normal or ordinal distribution, and Fisher's exact test for categorical data. Comparisons were made between the beginning (1st session) and the end (24th session) of cancer treatment. The significance level adopted for this study was 5%.

Results

The socioeconomic analysis in the study demonstrated an average age of 54.4 years (±13.06). Most of the population was male, married, self-declared brown, with primary education and with a family income of up to 01 minimum wage. The majority of the studied population was composed of individuals with drinking and smoking habits, with a predominance of tumor location in the oropharynx, in stage IV and under a therapeutic regimen of radiotherapy concomitant with chemotherapy (Table 1).

Table 1
Population characterization regarding
socioeconomic data, lifestyle, tumor characteristics
and treatment modality, in absolute numbers and
percentages.

Variables	n (36)	%
Gender		
Male	28	77.8
Female	08	22.2
Age group (years)		
20 - 39	05	13.9
40 - 59	19	52.8
60 – 79	12	33.3
Marital status		
Single	08	22.2
Married	25	63.9
Separated	01	2.7
Widowed	02	5.6
Skin color		
White	04	11.1
Brown	17	47.2
Black	13	36.1
Indigenous	02	5.6
Education		
Illiterate	02	5.6
Incomplete basic education	15	41.7
Complete basic education	06	16.6
Complete high school	13	36.1

Variables	n (36)	%
Family income (minimum wage)		
Up to 01	14	38.9
From 02 – 05	12	33.3
None	05	13.9
Social security	05	13.9
Alcohol consumption		
Yes	30	83.3
No	06	16.7
Smoking		
Yes	27	75
No	09	25
Alcohol consumption + smoking		
Yes	25	69.4
No	11	30.6
Tumor location		
Oral cavity	10	27.7
Oropharynx	13	36.1
Larynx	09	25
Other	04	11.2
Tumor staging		
I	06	16.7
II	04	11.2
III	05	13.8
IV	16	44.5
Undefined	05	13.8
Therapeutic scheme		
Radiotherapy	09	25
Radiotherapy + chemotherapy	23	63.8

Variables	n (36)	%
Surgery + radiotherapy	04	11.2

All patients, from both groups, lost weight and reduced their BMI. The PBM group had a statistically significant mean weight loss and BMI of 2.72 kg (± 2.2) ($p < 0.001$) and 1.05 kg/m² (± 0.83) ($p < 0.001$), respectively, when comparing the 1st and 24th radiotherapy sessions. The SHAM group had a significantly higher mean weight loss and BMI, 5.71 kg (± 3.45) ($p < 0.001$) and 2.11 kg/m² (± 1.23) ($p < 0.001$), respectively (Table 2).

Table 2
Body weight loss in kilograms (Kg) and BMI (Kg/m²) according to the use or not of PBM, between 1st and 24th session, represented by mean and standard deviation.

	PBM	<i>p</i> value	SHAM	<i>p</i> value
Weight 1st session	65,82 Kg ($\pm 13,96$)	<0,001*	66,29 Kg ($\pm 11,19$)	<0,001*
Weight 24th session	63,09 Kg ($\pm 13,77$)		60,57 Kg ($\pm 10,1$)	
BMI 1st session	24,37 Kg/m ² ($\pm 6,07$)	<0,001*	24,54 Kg/m ² ($\pm 3,27$)	<0,001*
BMI 24th session	23,32 Kg/m ² ($\pm 5,78$)		22,44 Kg/m ² ($\pm 3,00$)	

When comparing the groups, the difference between the 1st and 24th radiotherapy sections was calculated, thus using the delta weight and delta BMI. Thus, it was possible to notice that the PBM group had a significantly lower weight loss (2.72 Kg $\pm$ 2.2), compared to the SHAM group (5.71 Kg $\pm$ 3.45) ($p = 0.004^*$). When the BMI was evaluated, the PBM group showed a smaller reduction (1.05 Kg/m² $\pm$ 0.83) when compared to the SHAM group (2.11 Kg/m² $\pm$ 1.23) ($p = 0.005^*$) (Table 3).

Table 3
Influence of the use of photobiomodulation on body weight (Kg) and BMI (Kg/m²), between the 1st and 24th radiotherapy session.

Groups	Delta weight	<i>p</i> value	Delta BMI	<i>p</i> valor
PBM	2.72 Kg (± 2.2)	<0,001*	1.05 Kg/m ² (± 0.83)	0.005*
SHAM	5.71 Kg (± 3.45)		2,11 Kg/m ² (± 1.23)	

Regarding to OM, a total of 82.4% of the individuals in the PBM group had mucositis, while in the SHAM group, 68.4% of the participants were affected by this side effect ($p = 0.451$). For the analysis of the

It was noticed that individuals affected by this side effect had

greater weight loss (4.85 kg $\pm$ 3.1) and BMI (1.14 kg/m² $\pm$ 1.89) when compared to those without it, with 2.65 Kg ($\pm$ 3.3) for weight loss and 1.03 Kg/m² ($\pm$ 1.59) for BMI reduction. Regarding the PBM group, the weight loss for patients with mucositis, represented by the delta weight, was 1.9 kg (0.7-7.9), compared to the SHAM group, which was 5.8 kg (5.1-7.9) (p=0.87). For the BMI, the delta of the PBM group was 0.69 Kg/m² (0.47-2.9) and for the SHAM group it was 2.18 Kg/m² (1.9- 2.94) (p= 0.87).

Patients with no OM in the PBM group had a delta weight equal to 1.5 kg (0.2-2.35), while for the SHAM group the delta weight was 2.7 kg (1.6-5.1) (p=0.300). For the BMI analysis, the PBM group had a delta BMI of 0.66 Kg/m² and the SHAM group was 1.2 Kg/m² (0.53-1.9) (0.1-0.87) (p=0.300), with no statistically significant difference (Table 4).

Table 4

Influence of OM on weight (Kg) and BMI (Kg/m²), between 1st and 24th session, in patients submitted or not to photobiomodulation.

Patients with mucositis (q1-q3)	GROUP PBM		p value	GROUP SHAM		p value
	DELTA WEIGHT	DELTA BMI		DELTA WEIGHT	DELTA BMI	
	1.9 Kg (0.7-7.9)	0.69 Kg/m ² (0.47- 2.9)	0.87	5.8 Kg (5.1-7.9)	2.18 Kg/m ² (1.9-2.94)	0.3
Patients with no mucositis (q1-q3)	1.5 Kg (0.2-2.35)	0.66 Kg/m ² (0.1-0.87)	0,87	2.7 Kg (1.6-5.1)	1.2 Kg/m ² (0.53-1.9)	0.3

However, when analyzing the severity of OM, it is clear that the PBM group had a lower severity, mostly grades 1 and 2, when compared to the SHAM group, which in turn, predominantly presented grades 2 and 3 (p = 0.004*).

It was also evaluated the SIWL during the 24 radiotherapy sessions, that is, approximately 1 month. Participants in the PBM group showed a percentage of weight loss of 4.7%, which was classified as acceptable. In the SHAM group, however, the percentage of weight loss was 8.5%, which determines a severe weight loss. Regarding the BMI classification, changes were noted during the treatment. For the initial BMI, the PBM group had 41.7% of individuals in the normal weight/adequate weight category and 23.5% in the underweight category. The SHAM group, in turn, presented 47.4% for the overweight category and 36.8% for normal weight/adequate weight, with no statistically significant difference between groups (p = 0.216). For the final BMI of the PBM group, the eutrophic/adequate weight category represented 47.1% of the patients, while the low weight category represented 29.4% of the individuals. The SHAM group had 73.7% of patients in the normal /adequate weight category and 15.8% for low weight. However, this difference was not statistically significant between groups (p=0.259). For the general analysis of both groups, the categories that presented the highest quantity of individuals for the initial BMI were eutrophic/adequate weight with 38.9% and overweight with 33.3%. For the final BMI, the categories were

eutrophic/adequate weight with 61.1% and low weight with 22.2% of the total number of individuals participating in the study (Table 5).

Table 5
Influence of photobiomodulation on the classification of BMI* in the 1st and 24th radiotherapy session.

INITIAL BMI (categories)	PBM		SHAM		Total		<i>p</i> value
	n	%	n	%	n	%	
Eutrophic/adequate weight	07	41.2	07	36.8	14	38.9	0.216
Overweight	03	17.6	09	47.4	12	33.3	
Obesity	03	17.6	01	5.3	04	11.1	
Underweight	04	23.5	02	10.5	06	16.7	
FINAL BMI							0,259
Eutrophic/adequate weight	08	47.1	14	73.7	22	61.1	
Overweight	02	11.8	02	10.5	04	11.1	
Obesity	02	11.8	-	-	02	5,6	
Underweight	05	29.4	03	15.8	08	22.2	
* According to the WHO (2006) and PAHO (2002) criteria.							

Discussion

In this study, the therapeutic effects of PBM for radiochemotherapy-induced OM and its clinical implications to nutritional status in patients with HNC were evaluated. This study is innovative because it highlights the role of PBM in the improvement of nutritional impacts caused by OM.

Male individuals, with an average of 40 years or more, low education and income levels, with alcohol drinking habits and/or smokers characterize the population of patients diagnosed with HNC [19–23]. Regarding skin color, the findings of this study differ from literature data, which demonstrates prevalence in white individuals [24, 25]. However, according to the Brazilian Institute of Geography and Statistics (IBGE) (2019) [26], the territorial contingent of the Bahian population is predominantly marked by African descendants, which would justify the large percentage of brown and black participants.

Gonçalves et al. (2018) [27] demonstrated, similarly to our study, a predominance of tumor location in the oropharynx and stated that tumors in this region are often diagnosed late and in advanced stages, due to difficulties in the examination and scarcity or non-perception of signs and symptoms. Casati et al. (2012)

most commonly diagnosed for HNC are the oral cavity,

oropharynx and larynx, as they are structures in direct contact with the risk factors of tobacco and alcohol. The involvement of these anatomical structures culminates in a high functional impairment, thus promoting greater sequelae to the nutritional and health status of this population.

Weight loss is often an unavoidable condition for the cancer population [28]. For patients with HNC, this loss happens very quickly, affecting 80% of diagnosed patients. Invariably, one of the main outcomes of this condition is malnutrition [29]. Advanced stages and combined therapeutic regimens are more likely to have negative nutritional impacts, in particular, the reduction or total incapacity of oral food intake. In addition, these large are tumors that can cause obstructions in the oral feeding route and demand enhanced energy and metabolic supply for its growth [30]. The combined therapy, acting locally and systemically, can induce or exacerbate potentially harmful side effects, such as OM, xerostomia, poor oral cavity condition, anatomical and functional mechanical obstructions, malabsorption, constipation, diarrhea, emesis, nausea, dysgeusia, dysphagia and pain [31]. These conditions are listed as predisposing factors for weight loss and lead to worsening of nutritional status and prognosis, in addition to a decrease in quality of life [32, 33].

For individuals who were affected by OM it was noticed that there was a deficit in body weight and BMI. Using a similar methodology, Goobo et al. (2014) [13] demonstrated analogous results regarding the use of PBM in the prevention and treatment of OM, and its effects on body weight and BMI of patients with HNC, however, that the type of laser used by the authors has a higher power and a wavelength of 970 nm. According to the authors, the equipment was used in an unfocused manner, with the goal of obtaining biomodulatory effects, however, they did not indicate whether any device was used for this purpose, or what was the distance between the equipment and the oral mucosa. It is also important to emphasize that defocused high-power laser acts by decreasing the tissue vaporization effect, thus resulting in increased incision diameter and, thus, reduction its depth, a primary property of this category of lasers [34, 35]. MASCC/ISOO recommends the use of low-power laser for the prevention and treatment of OM, due to its therapeutic properties of positive biostimulation, anti-inflammatory, analgesia and healing, without causing harm or toxicity reactions in its use [11]. The visible red light from the low-intensity laser is readily absorbed by endogenous chromophores. It acts by triggering biological reactions, which are not thermal nor cytotoxic, through photochemical, photophysical and photobiological events, leading the cell metabolism to beneficial physiological changes. The mechanism of action of PBM is related to its action on the cytochrome c oxidase (CcO) complex, acting in the facilitated transport of electrons in the mitochondrial respiratory chain. This transport provides an increase in the transmembrane proton concentration gradient, which will boost the production of adenosine triphosphate (ATP) whose bioavailability will be increased to promote the functions of cell metabolism [36]. In this study, PBM was not able to prevent OM. There was, however, a reduction in the severity of the condition. The greater the gravity of mucositis, the greater the amplification of its symptoms and the greater the interference with the individual's ability to feed orally and with the nutritional status. According to Sonis (2007) [37], OM is an inflammatory reaction marked by the participation of cytokines with a pro-inflammatory profile. Thus, the greater the pro-inflammatory gradient concentration, the greater painful symptomatology and,

Loading [MathJax]/jax/output/CommonHTML/jax.js body weight and BMI. It is believed, that PBM reduced the

severity of OM by decreasing the production of inflammatory cytokines, preventing the evolution to more advanced stages. Findings of severe SIWL for patients in the SHAM group indicate that they were more vulnerable to the effects of OM than individuals in the PBM group. The assessment of SIWL is an important parameter for understanding weight variations as a function of time, as it is possible to measure the severity of weight loss, identifying the risk and the various stages of malnutrition [8, 16].

The PBM protocol recommended to prevent OM is the use of a low-power laser with a wavelength of 660nm, energy density of 6.2J, in 72 application points, 10 seconds per point, during 03 days a week, alternately [11]. Other studies [38–42] presented different PBM protocols, which ranged in energy density from 1J to 6J, with application points from 09 to 58 points, alternating to continuous and different conductive media. Previous data from our group [43], whose PBM protocol included low-power AsGaAl laser, 660nm, 86.7 mW, energy density of 2J, applied to 28 points in the oral cavity for 3 seconds at each point, was also unable to prevent the emergence of OM. However, as observed in this study, the severity of OM was reduced. These laser peculiarities make the studies difficult to be compared, not invalidating, however, the relevance of its findings.

The anthropometric measurements, mainly through assertive and quick methods such as measuring body weight, checking the variation of body weight and calculating the BMI, as well as its classification, is extremely important for the early diagnosis of the most frequent nutritional disorders in cancer patients. This quick identification can help in counseling and possible nutritional interventions, preventing nutritional damage, thus providing a better prognosis for these patients [13, 31].

Previous data [32, 33], showed a strong correlation between pre-treatment BMI and weight loss, however, the findings are conflicting as they show divergences in relation to the BMI classification. For the first study, it is stated that individuals classified as overweight, before starting antineoplastic therapy, are more likely to maintain or have less reduction in body weight during treatment, reducing possible interruptions, because their immune function is not compromised, when compared to individuals with low weight and obesity, and, therefore, overweight individuals tend to have better results for quality of life and future nutritional status. On the other hand, for Zhao et al. (2015) [33], overweight or pre-treatment obesity was a predisposing factor for weight loss, when compared to eutrophic individuals. This condition was justified by the tendency of professionals to prescribe nutritional supplements for low weight and eutrophic patients, aiming at the recovery or maintenance of body weight. This practice, however, is not performed with overweight and obese patients, making their weight loss more evident.

Our study had limitations related to the sample size, that can interfere the absence of statistical significance when evaluating the influence of PBM on the initial and final difference in body weight and BMI, according to the presence or absence of OM, as well as in the classification of BMI. It was observed, however, that the numerical difference in the group of patients with OM who underwent PBM was expressive, both for the difference in weight loss and for the difference in BMI, when compared to individuals in the control group. The treatment of cancer patients has some particularities, such as

interruption due to worsening side effects, indisposition and death, which end up substantially reducing the sample size.

Conclusion

PBM for OM reduced weight loss and prevented the reduction of BMI in patients undergoing radiochemotherapeutic treatment for HNC. Although it did not prevent the occurrence of OM, PBM was able to reduce its severity, preventing the evolution of the condition.

Declarations

Funding: Nothing to declare.

Conflict of Interest: The authors declare that they have no conflict of interest.

Availability of data and material: <https://data.mendeley.com//datasets/4kd7s49wk4/1>, reference [DOI: 10.176332/4kd7s49wk4.1].

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. CAAE: 68263317.8.0000.0047

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable

Code availability: Not applicable

Authors' contribution: This is an original study and all authors contributed to the study conception, design, and approved the final version of the manuscript. Amanda de Sousa Melo and Camila Lima Andrade participated the text writing and the experiment's execution. Juliana Borges de Lima Dantas, Alena Ribeiro Alves Peixoto Medrado, Gabriela Botelho Martins and Hayana Ramos Lima collaborated in the experiment's execution, article review assay, english proofreading and critical review. Manoela Carrera guided all stages of the work and participated in the text writing and review.

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