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Evaluation of the Effect of Photobiomodulation on Radiation-Induced Xerostomia in Head and Neck Cancer Patients: A Randomized Clinical Trial

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Abstract

Introduction: Radiotherapy-induced xerostomia is an important side effect of head and neck cancer (HNC) treatment. Photobiomodulation (PBM) is one of the new emerging methods for preventing or reducing this problem. The aim of this study is to evaluate the effect of PBM on radiation-induced xerostomia in HNC patients.

Methods: Thirty-seven patients with HNC who were referred for radiotherapy to Mashhad cancer center. In the case group, an infrared diode laser was used in contact mode on 16 points (covering minor and major salivary glands). The device emitted a wavelength of 810 nm and operated at the power of 200 mW and continuous wave mode. Each area was irradiated for 4 seconds in contact mode with gentle pressure, and the laser energy was 0.8 J with an energy density of 2.85 J/cm^2 at the surface of the probe (spot size, 0.28 cm^2). The total dose was 45.6 J/cm^2. The power density was 714.2 w/cm^2. In the control group, the sham laser device was used. Subjective xerostomia was evaluated through the LENT SOMA scale (LSS). Stimulated and unstimulated saliva was also assessed. Data were analyzed with SPSS ver22 statistical software.

Results: The study included 26 men and 11 women with a mean age of 55.6±15.3 years. In the sixth week, the case group produced more stimulated saliva than the control group (P=0.006). They also had less subjective xerostomia than the control group in weeks four to six.

Conclusion: In the present study, PBM had a preventive effect on stimulated saliva and subjective xerostomia and can be recommended as an adjunctive treatment. Further studies with a higher sample size and the use of a low-level laser in more sessions are needed for definitive comment.

Keywords: Photobiomodulation; Low-level laser; Xerostomia; Head and neck cancer; Hyposalivation.

Introduction

Head and neck cancer (HNC) is the sixth most prevalent type of cancer globally, and it is especially common in some of the less developed nations.[1,2] Currently, standard treatments for HNCs are surgery and radiotherapy with or without chemotherapy, which are always associated with side effects during or after treatment. Oral mucositis and dry mouth are the most frequent side effects.[3]

Although the therapeutic dosages for the treatment of HNCs are typically in excess of 65 Gy, permanent salivary gland (SG) damage can develop after only 24–26 Gy.[4,5] The exact causes of damage are unclear, but some possible factors are impaired secretion of acinar cells, impaired blood flow, oxidative stress and membrane disruption, interference with water secretion signals, and cell death due to reduced secretion.[6-8]

Low saliva production and xerostomia can harm oral hygiene, oral functions, and the quality of life of the patients who suffer from them. They make it hard to taste, chew, swallow, and talk. These patients also have a higher chance of getting oral infectious diseases and tooth decay.[9,10]

There are currently limited effective approaches to preserving or increasing salivary flow, and each of these methods has limitations and short-term effects. The most common treatment for these patients is artificial saliva. However, some types of artificial saliva, besides being expensive and requiring frequent and prolonged application, are potentially erosive for enamel.[11,12]

Another effective method in the treatment of

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xerostomia is the use of Photobiomodulation (PBM). PBM is the application of light for the aim of tissue repair and decreasing inflammation. PBM sends photons to the cell's mitochondria, where they are taken up by cytochrome C oxidase (Cox). This triggers Cox to make more ATP and regeneration of injured cells and tissues.[13] Using PBM on SGs can boost the ducts and epithelial cell mitosis, enhance the protein, raise the glucose use by the cells, and foster cell proliferation as well as blood flow and neoangiogenesis.[13]

While there are a few studies describing the treatment of xerostomia by PBM, there is still no universally agreed clinical management protocol. Some research has involved healthy people or xerostomic patients with other conditions (such as medication use, diabetes mellitus, SG aplasia, and Sjögren's syndrome),[11,12,14-18] so studies on BPM and radiation-induced xerostomia are diminutive.[15,19,20]

In a systematic review study by Sousa et al, only four studies evaluated the effect of PBM on xerostomia in human subjects with HNCs. Despite the evidence of higher saliva production following PBM, there is no clear guidance on how to apply a laser and what parameters to use. Sousa et al mentioned that further research is necessary to establish standard therapeutic protocols for PBM and xerostomia.[21]

In this placebo controlled clinical trial study, the effect of PBM on SG hypofunction and radiation-induced xerostomia in HNC patients was evaluated. We hypothesized that PBM can preserve and increase SGs' function. To compensate deficits of previous studies, we used a control group and a proposed standard protocol for laser irradiation. Furthermore, both objective and subjective xerostomia were measured, and major and minor SGs were included in the intervention.

Methods and Materials

The present study was a randomized parallel single-blind placebo-controlled clinical trial to evaluate the effect of PBM on SG hypofunction and xerostomia in the patients with HNC undergoing radiation therapy at Reza Medical Center and Imam Reza Hospital, Mashhad, Iran (Both are Main tertiary referral oncology centers in Mashhad, Razavi Khorasan province).

The local ethical committee of Mashhad University of Medical Sciences approved the study protocol (registration number: IR.MUMS.REC.1394.251). The trial is registered in the Iranian Registry of Clinical Trials (identifier: IRCT20080906001216N3). The study enrolled the subjects after assessing the records of all the HNC patients referred to these centers and applying the inclusion and exclusion criteria. The inclusion criteria for these patients were as follows: Patients aged 20-75 years, patients with head and neck tumors that needed radiation therapy covering at least one major SG (mainly the parotid gland), and total radiation dose > 20 Gy.

Exclusion criteria were dissatisfaction of the patient or physician discontent, patients with major and minor SG tumors, individuals with a systemic disease likely to develop xerostomia (diabetes, anxiety, rheumatologic diseases, etc), patients treated with xerostomic drugs (such as antihistamines, antihypertensives, antidepressants, anticholinergic drugs, and opioid analgesics), unstimulated saliva less than 0.1 ml/min at first visit, history of head and neck irradiations, presence of any mucosal lesions at first visit, and unwillingness by the patient to continue the trial.

The present researchers explained the details to the patients and got their signed consent forms. The patients were split into two groups randomly: the case group and the control group. A computer made a random number table to do the randomization.

AZP generated the random allocation sequence, PMM enrolled participants, and ZD assigned participants to interventions. MRM performed the intervention (either laser or placebo). The patients and all investigators except MRM were blinded about the intervention.

The case group included the patients treated with the laser device, and the control group included the same situation except that the device was switched off. Patient's baseline information such as age, sex, occupation, type of cancer, treatment, radiation dose, and number of radiation sessions was recorded.

In the case group, a diode laser (GaAlAs – gallium, aluminum, arsenide – THOR Company, UK) was used in contact mode on 16 points as perpendicular as possible (covering minor and major SGs). The device emitted a wavelength of 810 nm and operated at the power of 200 mW and continuous wave mode. Each area was irradiated for 4 seconds in contact mode with gentle pressure, and the laser energy was 0.8 J with an energy density of 2.85 J/cm^2 at the surface of the probe (spot size, 0.28 cm^2). The total dose per session was 45.6 J /cm^2. The power density was 714.2 mW/cm^2.

A trained person (MRM) who knew the SG anatomy and learned the laser safety protocols did the laser therapy. Both the patient and the operator wore safety goggles.

The laser application areas were selected according to the study which was most similar to our design and also the laser consultant's opinion.[19] Three points were applied to each parotid gland, one point to each sublingual gland, two points to each submandibular gland, and two points to the right and left buccal mucosa.

Treatment started on the first day of radiation therapy. Stimulation was performed three times a week for 4 consecutive weeks, just before radiation therapy. Thus, PBM sessions were exactly before radiation therapy for four weeks, and the patients were followed weekly, until the end of radiation therapy (six weeks). Saliva collection was performed on the first day of radiotherapy (before

PBM) and every week (before the session). The patients were asked not to eat, drink water, chew gum, or use any saliva stimulant for 90 minutes prior to saliva collection. First, unstimulated saliva was collected. Saliva samples were collected between 9 and 12 a.m. in a room with natural light. The patients gathered saliva in their mouths and then spit into a test tube. This was repeated every 60 seconds during 5 minutes. The test tube was well shaken, the volume of saliva was measured in milliliters, and then the saliva was poured into the cotton which was on the scale and the amount was recorded in grams.[13,16] Then stimulated saliva was also collected weekly. Saliva stimulation was performed in 0, 30, 60, 90, and 120 seconds by 2% citric acid swabbed on the lateral border of the tongue, 5 times stimulation during 2 minutes.

Furthermore, subjective xerostomia was assessed through the LENT SOMA scale (LSS) every week before the third weekly session, totally for 4 weeks.[22] In the LSS, xerostomia was evaluated using grades from 1 to 4. No dryness was also recorded as grade 0. The grades were recorded as follows: Occasional dryness (grade 1), partial but persistent dryness (grade 2), complete dryness non-debilitating (grade 3), and complete dryness debilitating (grade 4).[23]

Statistical Analysis

Differences between the groups were assessed using the independent-samples t-test (for normally distributed variables) and the Mann Whitney U test (for non-normally distributed variables). Also, the dependent *t* test (for normally distributed variables) and the Wilcoxon test (for non-normally distributed variables) were used for internal comparison of the groups. The repeated measure test was used to determine changes during the study due to repeating variables. The significance level was set at ≤ 0.05 for all tests.

Results

In this study, a total of 44 patients were enrolled. One patient in the case group and one patient in the control group were excluded in the first week due to non-cooperation. Subsequently, in the second week, one subject in the case group due to drug administration and four patients in the control group because of oral mucositis and inability to provide saliva sampling were excluded. Therefore, 37 patients including 17 patients in the case group and 20 subjects in the control group ended the trial (Figure 1).

In addition, in weekly follow-up sessions, in the fifth week, radiation therapy was terminated in two patients in the case group and one patient in the control group. In the sixth week, one patient in the case group and three patients in the control group failed to be followed up. These patients finished the PBM trial (4-week PBM regimen), so the results are shown in Figure 1.

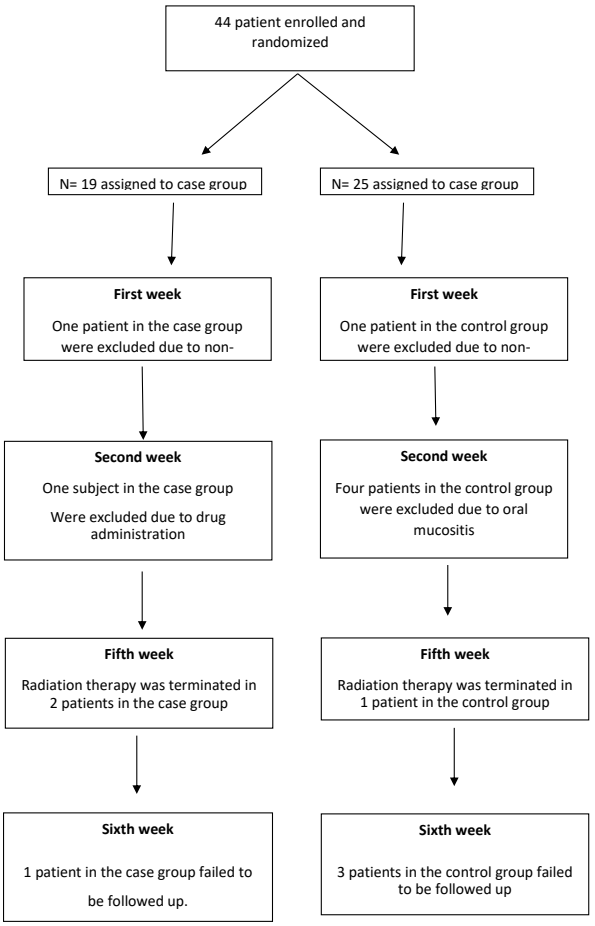

Figure 1. Subjects Enrollment in the Study

In this study, the patients were matched in terms of sex, age, type of cancer, fields of radiation (unilateral or bilateral), overall radiation dose, and combination of radiation therapy with chemotherapy. All subjects had cisplatin in their chemotherapy regimen. In squamous cell carcinoma (SCC) patients, 5-fluoro uracil was added to this regimen. In terms of the main variables of the study, including stimulated and unstimulated saliva and degree of subjective xerostomia, the two groups were also matched. Baseline characteristics of the subjects are provided in Table 1.

According to the LSS, subjective xerostomia was not statistically significant in the two groups in the first, second and third weeks (*P* values: 0.117, 0.132, and 0.132 respectively). In the fourth, fifth and sixth weeks, the patients in the case group had significantly lower xerostomia than the control group (*P* values: 0.010, 0.04, 0.038 respectively) (Table 2).

At the end of radiotherapy, 23.5% of the patients in the case group and 75% in the control group had grade 3 xerostomia, which showed less discomfort and disability of the subjects in the case group. In general, it can be said that the number of patients experiencing grade 3 xerostomia during radiotherapy in all weeks was lower in the case group than in the control group (Table 2).

The mean of stimulated and unstimulated saliva in the case and control groups are given in Table 3.

The mean of stimulated saliva from the fourth week in the case group had always been higher than the control group, and in the case of unstimulated saliva, from the first week the average of saliva in the case group had always been higher than the control group, but these differences were not statistically significant until the fifth week. In the sixth week, the amount of stimulated saliva was statistically significant between the two groups ($P=0.006$).

The process of changes in stimulated and unstimulated saliva in grams during radiation therapy in two groups is shown in Figures 2 and 3.

According to Figure 2, however, the average stimulated saliva in the case group in the first, second and third weeks was lower than in the control group; there was an increasing trend from the fourth week, while in the control group, the downward trend continued uniformly from the beginning to the end of radiation therapy.

Discussion

Radiation affects SG in many ways. It causes atrophy of acinar cells, parenchymal loss, dilation of ducts, loss of secretion in acinar cells, and invasion of inflammation cells like lymphocytes and plasma cells. These can result in atrophy and fibrosis.[24] PBM can modify some of these changes and help to prevent some adverse effects of radiation.[9,12,13,20]

We studied how PBM affects SG hypofunction and xerostomia in HNC patients getting radiation therapy.

Our results revealed that PBM can increase stimulated saliva, especially in the 6th follow-up session. Furthermore, PBM alleviated subjective xerostomia in the case group in the fourth, fifth and sixth weeks.

Overall, there are only a few studies about the effect of low-level lasers on xerostomia, especially radiation-induced xerostomia. Similar studies were carried out by de Oliveira Lopes et al,[12] Oton-Leite et al,[18] Gonnelli et al,[20] Palma et al,[16] González-Arriagada et al,[19] and Simões et al,[14] who investigated the effect of low-level lasers on patients undergoing radiotherapy.

Previously, various types of low-level lasers with different wavelengths have been investigated, [8,9,13,16,19,20] and only in studies by Pezelj-Ribarić et al[15] and Saleh et al,[8] the Ga-Al-As low-level laser was applied. While low-level lasers with wavelengths of 630-685 nm have been investigated in previous studies, [12,14,15,18,22] here we used the Ga-Al-As low-level laser with a wavelength of 810 nm, due to its higher penetration depth (3 cm) and better absorption effects.

To date, it has not been clear which laser parameters are most effective in salivary function preservation. We used an 810 nm Ga-Al-As laser with the following characteristics: power: 200 mW, laser energy: 0.8 J, energy density: 2.85 J/cm^2 with a total dose of 45.7 J/cm^2, power

Table 1. Baseline Characteristics of the Study Participants

Characteristics	Case Group (n=17)	Control Group (n=20)
Age (mean±SD)	54.1±15.4	57±15.18
Gender		
Male	3	8
Female	14	12
Tumor location		
Larynx	7 (41.2%)	3 (15%)
Pharynx	5 (29.4%)	9 (45%)
Mouth	3 (17.6%)	6 (30.0%)
Others	2 (%10)	2 (11.8%)
Type of tumor		
Nasopharyngeal carcinoma	5	9
Laryngeal cancer	7	3
Oral squamous cell carcinoma	3	6
Others	2	2
Average radiation dose (Gy)	61.8±11.3	62.3±9.4
Salivary glands involved in radiotherapy field		
Parotid, submandibular, and sublingual	10 (58.8%)	9 (45%)
Parotid, submandibular	7 (41.2%)	9 (45%)
Parotid	0 (0%)	2 (%10)

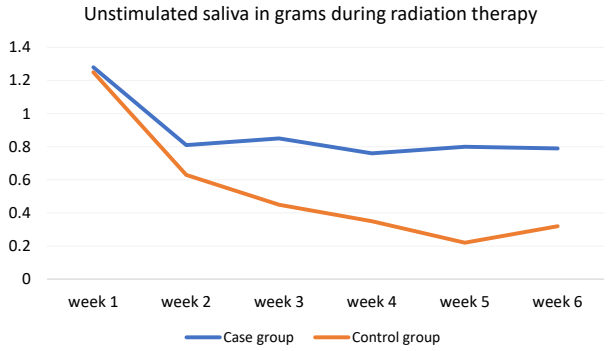

Figure 2. The Process of Changes in Unstimulated Saliva in Grams During Radiation Therapy in Two Groups

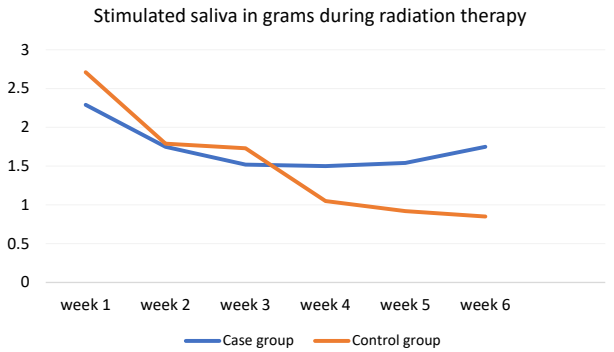

Figure 3. The Process of Changes in Stimulated and Unstimulated Saliva in Grams During Radiation Therapy in Two Groups

Table 2. Subjective Xerostomia in the Control and Study Groups Using LSS Questionnaire During the Course of Radiation Therapy

Grade of Subjective Xerostomia	Case Group						Control Group					
	Normal	Occasional Dryness (Grade 1)	Partial but Persistent Dryness (Grade 2)	Complete Dryness Non-debilitating (Grade 3)	Debilitatingdryness (Grade 4)	Lost to Follow Up	Normal	Occasional Dryness (Grade 1)	Partial but Persistent Dryness (Grade 2)	Complete Dryness Non-debilitating (Grade 3)	Debilitatingdryness (Grade 4)	Lost to Follow Up
First visit (before radiotherapy)	14 (82.4%)	3 (17.6%)	0 (0)%	0 (0)%	0 (0 %)	-	17 (85.0%)	3 (15.0%)	0 (0)%	0 (0)%	0 (0)%	-
week 1	3 (17.6%)	12 (70.5%)	1 (5.8%)	1 (5.8%)	0 (0 %)	0 (0 %)	1 (5%)	10 (50%)	7 (35%)	1 (5%)	0 (0 %)	0 (0 %)
week 2	1 (5.8%)	8 (47.0%)	7 (41.1%)	1 (5.8%)	0 (0 %)	0 (0 %)	0 (0 %)	4 (20%)	7 (35%)	9 (40%)	0 (0 %)	0 (0 %)
week 3	0 (0 %)	4 (23.5%)	10 (58.8%)	3 (17.6%)	0 (0 %)	0 (0 %)	0 (0 %)	2 (10%)	5 (25%)	13 (65%)	0 (0 %)	0 (0 %)
week 4	0 (0 %)	4 (23.5%)	8 (47.0%)	5 (29.4%)	0 (0 %)	0 (0 %)	0 (0 %)	2 (10%)	2 (10%)	16 (80%)	0 (0 %)	0 (0 %)
week 5	0 (0 %)	1 (5.8%)	10 (58.8%)	4 (23.5%)	0 (0 %)	2 (11.7%)	0 (0 %)	1 (5%)	1 (5%)	17 (85%)	0 (0 %)	1 (5%)
week 6	0 (0 %)	1 (5.8%)	9 (64.2%)	4 (23.5%)	0 (0 %)	3(17.6%)	0 (0 %)	0 (0%)	1 (5%)	15 (75%)	0 (0 %)	4 (16%)

density: 714.2 W/cm^2. In this study, 16 points were irradiated for 4 seconds.

Gonnelli et al used a 660 nm, 40 mW, 10.0 J/cm^2 laser on 22 points intraorally and a 780 nm, 15 mW, 3.8 J/cm^2 laser on 16 extraoral points.[20] It seems that both protocols can be effective in salivary function preservation. Furthermore, Colaco et al mentioned that 2–4 J/cm^2 is suitable for prophylactic purposes of PBM.[25] Zecha et al proposed 750-830 nm, 20 mW/cm^2 – 80 mW/cm^2 for extraoral and 630–680 nm, 20 mW – 150 mW IR laser diodes or LED Cluster for Intra-oral application with 3 J/cm^2 dose on at least 3 extra-oral sites targeting major SGs and 6 intraoral sited targeting minor SGs.[26] It can be noted that further studies in this field is needed to achieve more data.

Other studies have performed PBM on SG hypofunction due to other issues.[11,16,23,27-29] Wibawa et al showed an increase in stimulated saliva and a change in saliva quantity by the 940-nm indium-gallium arsenide-phosphide low-power semiconductor diode laser, 4 J/cm^2 dose on major SGs in diabetic patients. In their study, stimulated saliva did not show any significant change.[23]
In all previous studies, the method for measuring and quantifying saliva was the volumetric sialometric method (mL), by which stimulated and unstimulated saliva is measured in "mL per 5 minutes".[8,9,20,12-15,18]

However, in our study, due to the accuracy of measurement, salivary measurement in the sialometric method was performed based on weight (g). Due to the fact that the saliva of the patients, especially in the follow-up visits, was sticky, stringy or thick, and in many cases contained bubbles, the liquid level could not be accurately measured in milliliter. Therefore, digital scales with an accuracy of 0.01 g were used to measure saliva.

We measured the saliva amount from the start of radiotherapy and then every week by weight in both groups. The results showed that the case group had more unstimulated saliva than the control group on the follow-up visits, but this difference was statistically significant. For stimulated saliva, the results showed a significant difference between the case group and the control group in week six. Thus, even though the laser did not keep or increase saliva levels in these patients, it prevented a strident drop in saliva level.

Previous studies have shown positive and significant results in both stimulated and unstimulated saliva increase after low-level laser therapy in patients undergoing radiation therapy.[14,19]

Pezelj-Ribarić et al also reported an increase in unstimulated saliva.[15] However, this study has been performed on idiopathic dry mouth shown to have a reversible cause. The present study evaluated the effects of a low-level laser on the patients undergoing ionizing destructive radiation.

Furthermore, subjective xerostomia in the case group

Table 3. Stimulated and Unstimulated Saliva During the Course of Radiation Therapy

	Stimulated Saliva (g)			Unstimulated (g)		
	Case Group	**Control Group**	***P* Value**	**Case Group**	**Control Group**	***P* Value**
First visit (before radiotherapy)	4.53 ± 1.43	4.24 ± 0.76	0.42	2.61 ± 0.9	2.79 ± 0.76	0.46
Week 1	2.29 ± 1.27	2.71 ± 0.64	0.21	1.28 ± 0.92	1.25 ± 0.65	0.92
Week 2	1.75 ± 0.49	1.79 ± 0.74	0.49	0.81 ± 0.86	0.63 ± 0.67	0.65
Week 3	1.52 ± 0.99	1.73 ± 0.45	0.810	0.85 ± 0.85	0.45 ± 0.83	0.104
Week 4	1.5 ± 0.84	1.05 ± 0.51	0.092	0.76 ± 0.90	0.35 ± 0.53	0.213
Week 5	1.54 ± 0.86	0.92 ± 0.97	0.092	0.80 ± 0.01	0.22 ± 0.45	0.311
Week 6	1.75 ± 0.77	0.85 ± 0.61	0.006	0.79 ± 0.68	0.32 ± 0.48	0.057

was lower than in the control group, and a significant difference was observed in the fourth, fifth and sixth weeks.

Subjective evaluation of xerostomia has only been studied in a limited number of studies, most of which have generally assessed the extent of pain and discomfort with the *visual analogue scale* (*VAS*) criteria.[12,13,18] To the best of our knowledge, only in Arbabi and colleagues' study, [22] the LSS was used, and in Saleh and colleagues' study,[8] Oral Health Impact Profile-14 (OHIP-14) was utilized for the evaluation of oral xerostomia.

In the current study, the LSS questionnaire was used to examine xerostomia more precisely. In addition, response to the LSS is easier for the patient compared to other scales. In previous studies, the VAS criteria in the case group also showed a significant improvement, which is similar to our study.[12,19]

Wibawa et al also tested how low-level laser therapy affects saliva production in diabetic patients. They used VAS criteria and found that low-level laser therapy reduced dry mouth in diabetic patients with low saliva.[23]

Saleh et al used VAS and OHIP-4 to measure xerostomia, but they did not find any significant improvement. However, their study is not similar to ours because they applied laser therapy 6 months after radiation therapy ended.[8] In addition, González-Arriagada et al tested the effectiveness of low-level laser therapy for acute side effects of head and neck radiotherapy. They found no difference in xerostomia between groups.[19] These differences and contradictions in the studies may be because of different methods of measuring xerostomia, different types of low-level lasers, and diverse numbers of laser therapy sessions.

One concern that may arise when using lasers in cancer patients is whether the laser parameters have negative effects on HNC cells. There are many articles that have addressed the safety of this wavelength of laser in treating cancer complications such as oral mucositis, dysphagia, dysgeusia, dermatitis, and trismus, and they have found that it is generally safe.[30-32] However, more research is required and the benefits must outweigh the possible disadvantages

Our study has some limitations. Firstly, the sample size is small, so the results must be generalized with caution. Secondly, although we made attempts to collect saliva based on a standard protocol, it is impossible to eradicate the effect of intense stress of patients which in turn will affect saliva secretion. Lack of laser equipment in cancer centers and transportation issues were other limitations that caused the loss of some cases. Some oncologists did not contribute to patient referral due to some concerns.

We have some suggestions for future surveys. To begin with, we can irradiate more points on major SGs. If specialized small oral probes are designed, more points on minor SGs beneath oral mucosa (except anterior palate and gingiva) can be irradiated since minor SGs have a more prominent role in the unstimulated salivary flow rate. In addition, a longer follow-up may show more differences in trial groups. Also, methods for SG activity such as scintigraphy may reflect the effect of PBM more precisely.

Conclusion

This study showed that the Ga-Al-As low-level laser at an 810 nm wavelength could greatly avoid a serious decrease in saliva production and xerostomia in HNC patients. Therefore, Ga-Al-As low-level laser therapy could be suggested as an adjunctive treatment. More research with a bigger sample size and more sessions of low-level lasers is required for a final conclusion.

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Authors' Contribution

Data curation: Mahdokht Rashed Mohassel.
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Investigation: All authors.
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Supervision: Pegah Mosannen Mozaffari, Zahra Delavarian.
Writing–original draft: All authors.
Writing–review & editing: All authors.

Competing Interests

The authors have no competing interests in this study.

Ethical Approval

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences under registration number: IR.MUMS.REC.1394.251

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