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EFEKTIVNOST INTRAORALNE I KOMBINOVANE INTRAORALNE I EKSTRAORALNE FOTOBIOMODULACIONE TERAPIJE NA SIMPTOME ORALNOG MUKOZITISA KOJI PRIJAVLJUJU PACIJENTI: RANDOMIZOVANA KONTROLNA STUDIJA

EFFECTIVENESS OF INTRAORAL AND COMBINED INTRAORAL-EXTRAORAL PHOTOBIOMODULATION THERAPY ON PATIENT-REPORTED ORAL MUCOSITIS SYMPTOMS: A RANDOMIZED CONTROLLED TRIAL

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Sažetak

Uvod: *Ova studija je sprovedena s ciljem da uporedi efekte dvaju kliničkih protokola – intraoralnog crvenog lasera i kombinacije ekstraoralnog infracrvenog lasera i intraoralnog crvenog lasera – na skali simptoma oralnog mukozitisa koje prijavljuju pacijenti (engl. Patient-Reported Oral Mucositis Symptoms – PROMS) kod pacijenata na hemioterapiji.*
Metode: *U ovoj prospektivnoj randomizovanoj dvostruko slepoj kliničkoj studiji četrdeset pet pacijenata bilo je raspoređeno u tri grupe, usklađene prema uzrastu, polu, tipu hemioterapije koju primaju i prvobitnom stanju oralnog zdravlja. Grupa 1 je imala samo standardnu oralnu negu, Grupa 2 je pored standardne oralne nege primala i intraoralnu fotobiomodulaciju (engl. Intraoral Photobiomodulation – IOPBM) pomoću diodnog lasera talasne dužine 635 nm, dok je Grupa 3 uz standardnu oralnu negu dobijala i kombinaciju intraoralne terapije laserom od 635 nm i ekstraoralne terapije laserom od 980 nm. Skala simptoma oralnog mukozitisa koje prijavljuju pacijenti procenjivala se nedelju dana i dve nedelje nakon početka hemioterapije.*
Rezultati: *Zabeležene su značajne razlike među grupama na PROMS skali i u jednom i u drugom periodu merenja (p = 0,000). Poređenja parova grupa pokazala su poboljšanje u obema grupama koje su primale fotobiomodulacionu (engl. Photobiomodulation – PBM) terapiju u odnosu na kontrolnu grupu. S druge strane, nije zabeležena statistički značajna razlika između dvaju PBM protokola.*
Zaključak: *Fotobiomodulaciona terapija, bez obzira na to da li se sprovodi samo intraoralnim laserom ili kombinacijom intraoralnog i ekstraoralnog lasera, ima značajnu ulogu u poboljšanju kvaliteta života pacijenata sa gastrointestinalnim karcinomima koji primaju hemioterapiju.*

Ključne reči: *fotobiomodulacija, hemioterapija, simptomi oralnog mukozitisa koje prijavljuju pacijenti*

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Abstract

Background: *This study was conducted to compare the effects of two clinical protocols—intraoral red laser versus a combination of extraoral infrared laser and intraoral red laser—on the Patient-Reported Oral Mucositis Symptoms (PROMS) scale in patients undergoing chemotherapy.*
Methods: *In this prospective randomized double-blind clinical trial, 45 patients were assigned to three groups, matched by age, sex, chemotherapy type, and baseline oral health status. Group 1 received standard oral care alone, Group 2 received standard oral care plus intraoral photobiomodulation (PBM) using a 635 nm diode laser, and Group 3 received standard oral care combined with both intraoral 635 nm and extraoral 980 nm laser therapy. The PROMS scale was assessed 1 week and 2 weeks after the start of chemotherapy.*
Results: *Significant differences were observed between groups on the PROMS scale at both time points (p = .000). Pairwise comparisons showed improvements in both PBM groups compared to the control group, though no significant difference was found between the two PBM protocols.*
Conclusion: *Photobiomodulation therapy, whether with intraoral laser alone or with intraoral and extraoral lasers, has a significant role in improving the quality of life of gastrointestinal cancer patients undergoing chemotherapy.*

Key words: *photobiomodulation, chemotherapy, patient-reported oral mucositis symptoms.*

Introduction

Cancer treatments, including radiotherapy and chemotherapy, are known to profoundly impact patients' quality of life, with numerous studies documenting a general decline from the initiation of treatment onward[1]. Among the most distressing side effects is oral mucositis (OM), a common and debilitating condition that significantly exacerbates the deterioration in health-related quality of life[2,3]. This complication typically arises shortly after the beginning of treatment and persists throughout its duration, causing severe discomfort and impairing daily functioning.

In 2023, a systematic review by Potrich et al. highlighted the consistent association between the onset of OM and a decline in quality of life across all examined studies[1]. These findings emphasize the critical need for effective interventions to prevent and manage OM, aiming to improve patients' overall well-being during cancer treatment.

Photobiomodulation (PBM) therapy, a non-thermal light-based intervention utilizing non-ionizing sources such as lasers, LEDs, and broad-spectrum light within the visible and infrared spectrum, has emerged as a promising strategy. By engaging endogenous chromophores, PBM triggers photophysical and photochemical events at various biological levels, facilitating therapeutic outcomes[4].

Several studies have demonstrated the efficacy of PBM in both preventing and treating OM, in patients undergoing PBM reporting notable improvements in quality of life compared to control groups[5–10]. In 2021, Martins et al. utilizing the PROMS questionnaire, confirmed that severe OM corresponded to lower quality of life scores in placebo groups, further validating the therapeutic potential of PBM[11]. However, despite its promise, the use of PBM for the treatment or prevention of OM is still in its early stages and faces challenges in clinical practice, particularly regarding the lack of a standardized protocol. Considerable variability has been observed between studies in terms of irradiation parameters[12].

Therefore, this study was conducted to compare the effects of two clinical protocols—intraoral red laser versus a combination of extraoral infrared laser and intraoral red laser—on the PROMS scale in patients undergoing chemotherapy

Materials and Methods

Trial Registration and Ethics approval

This clinical trial was officially registered in the ISRCTN registry under the identifier ISRCTN70634383 on July 24, 2023 (https://doi.org/10.1186/ISRCTN70634383).

Ethical Approval was obtained from Scientific Research Council at Damascus University (Damascus University, Damascus, 00963, Syria; +963 11 33923000; president@damasuniv.edu.sy), ref: 2027 on 18/01/2023. Also, all participants in this study provided a signed, informed consent.

Inclusion Criteria

The study included patients diagnosed with digestive tract cancer undergoing their first chemotherapy cycle at Albairouni Hospital in Damascus, Syria. Participants were required to have a similar risk for oral mucositis and receive either the FOLFOX regimen (leucovorin calcium, fluorouracil, oxaliplatin) or the XELOX regimen (oxaliplatin, capecitabine). Additional eligibility criteria included a neutrophil count of ≥ 1500 cells/µL, a platelet count of ≥ 100,000 cells/µL, clinically healthy oral mucosa, and a Karnofsky Performance Status (KPS) score above 60[13].

Exclusion Criteria

Patients were excluded if they had a history of head or neck radiotherapy, oral malignant or potentially malignant lesions, oral infections or bleeding, or diabetes. Patients already using any oral mucositis prevention strategies or those unable to comply with study requirements were also excluded.

Intervention

Participants were randomly allocated into three groups prior to initiating chemotherapy:

• Group 1 participants received standard oral care instructions, including guidance on brushing, flossing, rinsing, and dietary recommendations[14].

• Group 2 participants received intraoral PBM therapy using a diode laser (635 nm, 100 mW, 4 J/cm²) in addition to the oral care instructions. The treatment was applied to multiple sites in the oral cavity, including the buccal mucosa, labial mucosa, tongue, floor of the mouth, and soft palate.

• Group 3 participants received the same oral care and intraoral PBM therapy as Group 2, with the addition of extraoral PBM therapy administered via a diode laser (980 nm, 100 mW, 4 J/cm²) at six predefined neck points[15] (Table 1).

The six neck points for extraoral PBM are anatomically defined as follows:

• The top two points are located just below the jawline, approximately 1–2 cm lateral to the midline of the chin on each side.

• The middle two points are situated about 3–4 cm below the top points, near the larynx and close to the neck's midline.

• The bottom two points are positioned near the base of the neck, approximately 3–4 cm below the middle points.

Table 1. Laser parameters used

	Wavelength nm	Power Density mW/cm^2	Time per Spot, s	Energy Density J/cm^2	Spot Size cm^2	No. of Sites	Duration
Intraoral PBM	635	200	20	4	0.5	24	Before the start of the first chemotherapy session (on the same day)
Extraoral PBM	980	200	20	4	0.5	6	Before the start of the first chemotherapy session (on the same day)

Patient-Reported Oral Mucositis Symptom Scale

The PROMS scale assesses the most common symptoms experienced by patients who develop oral mucositis, including oral pain, difficulty speaking due to mouth pain, speech restriction, difficulty eating solid foods, difficulty eating soft foods, eating restriction, difficulty drinking, drinking restriction, difficulty swallowing, and taste changes. These symptoms are presented as ten questions, each accompanied by a 10 cm visual analog scale (VAS). Patients indicate the point on the scale that corresponds to the extent to which oral mucositis affects their daily activities and quality of life. The final score is calculated as the sum of the individual scores from all ten questions, with higher scores indicating more severe oral mucositis and, consequently, a poorer quality of life. The maximum possible score is 100[16].

The PROMS scale was assessed at two time points:

• One week after the first chemotherapy session

• Two weeks after the first chemotherapy session

Statistical Analysis

The Chi-square test was utilized to compare the clinical and demographic characteristics of participants across the three study groups. To verify the normality of parametric variables, the Kolmogorov–Smirnov test was conducted. Subsequently, a one-way analysis of variance (ANOVA) was applied to compare the mean values among the three groups at each time point. For evaluating pairwise differences between the two time periods separately, a paired sample t-test was performed.

Results

Our study included 45 patients, who were equally distributed into three groups matched for age, sex, type of chemotherapy and oral status before treatment.

Statistically significant differences were observed among the three groups after one week of follow-up (p = .000). Pairwise comparisons revealed significant differences between the control group and both the intraoral laser group (p = .002) and the combined intraoral and extraoral laser group (p = .000). However, no statistically significant differences were detected between the two laser groups (p = .071) (Figure 1).

After two weeks of follow-up, statistically significant differences were observed among the three groups (p = .000). Pairwise comparisons revealed statistically significant differences between the control group and both the intraoral laser group and the intraoral-extraoral laser group (p = .003 and p = .000, respectively). However, no statistically significant difference was observed between the two laser groups (p = .059) (Figure 2).

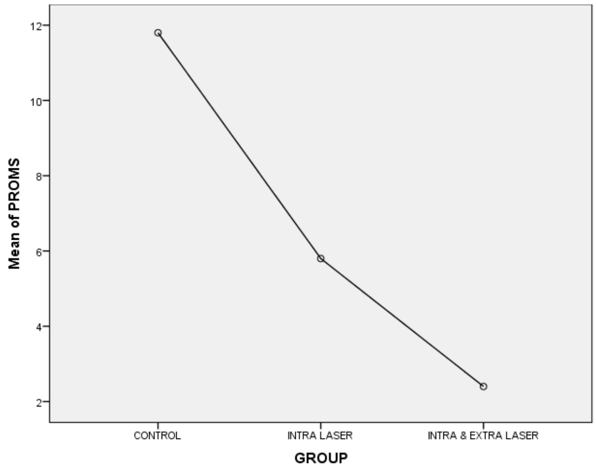

Figure 1. Mean PROMS scores after one week of follow-up

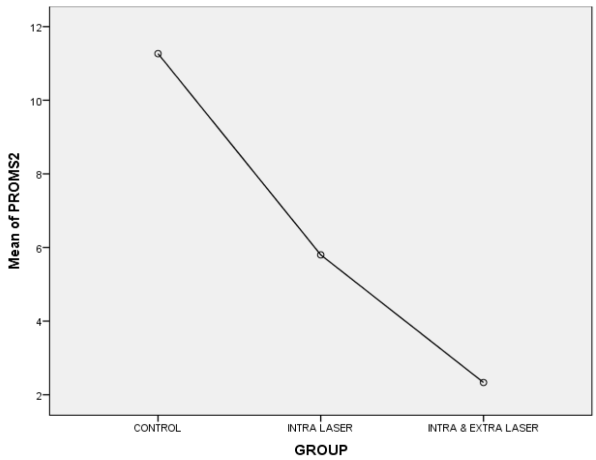

Figure 2. Mean PROMS scores after two weeks of follow-up

In detail, differences were observed among the three groups regarding pain, difficulty eating hard foods, difficulty eating soft foods, difficulty drinking, difficulty swallowing, and taste changes. However, no statistically significant differences were observed among the three groups concerning difficulty speaking, eating restriction, or drinking restriction after one week and two weeks of follow-up (Table 2).

In pairwise comparisons between each group, significant differences were observed regarding pain, difficulty eating solid foods, difficulty eating soft foods, and taste alterations between the control group and both laser groups.

Statistically significant differences were noted between the two laser groups concerning the consumption of both solid and soft foods, while no significant differences were observed regarding pain and taste alterations.

Regarding difficulty drinking and difficulty swallowing, no statistically significant differences were found when comparing the control group with the intraoral laser group. However, significant differences were observed when comparing the control group with the combined intraoral and extraoral laser group, as well as when comparing the two laser groups.

No statistically significant differences were observed when comparing the two follow-up periods ($p = .473$) (Figure 3).

Table 2. Mean scores of PROMS items among the three groups

		One week			Two weeks		
		Mean	Standard Error	Sig	Mean	Standard Error	Sig
Pain	Control Group	2.67	.422	.000	2.40	.363	.000
	Intraoral Laser Group	.53	.256		.47	.274	
	Intra-Extraoral Laser Group	.60	.289		.40	.235	
Difficulty Speaking	Control Group	.13	.133	.553	.00	.000	1
	Intraoral Laser Group	.00	.000		.00	.000	
	Intra-Extraoral Laser Group	.07	.067		.00	.000	
Speech Restriction	Control Group	.00	.000	1	.00	.000	1
	Intraoral Laser Group	.00	.000		.00	.000	
	Intra-Extraoral Laser Group	.00	.000		.00	.000	
Difficulty Eating Hard Foods	Control Group	3.13	.401	.000	2.80	.296	.000
	Intraoral Laser Group	1.60	.363		1.47	.350	
	Intra-Extraoral Laser Group	.60	.235		.60	.254	
Difficulty Eating Soft Foods	Control Group	1.07	.228	.000	1.07	.228	.000
	Intraoral Laser Group	.53	.192		.53	.192	
	Intra-Extraoral Laser Group	.00	.000		.00	.000	
Eating Restriction	Control Group	.00	.000	.376	.00	.000	.376
	Intraoral Laser Group	.20	.200		.20	.200	
	Intra-Extraoral Laser Group	.00	.000		.00	.000	
Difficulty Drinking	Control Group	.93	.300	.017	.93	.300	.017
	Intraoral Laser Group	.67	.252		.67	.252	
	Intra-Extraoral Laser Group	.00	.000		.00	.000	
Drinking Restriction	Control Group	.00	.000	1	.00	.000	.376
	Intraoral Laser Group	.00	.000		.13	.133	
	Intra-Extraoral Laser Group	.00	.000		.00	.000	
Difficulty Swallowing	Control Group	1.27	.371	.006	1.13	.363	.013
	Intraoral Laser Group	.80	.279		.80	.279	
	Intra-Extraoral Laser Group	.00	.000		.00	.000	
Taste Changes	Control Group	2.67	.303	.003	2.73	.267	.001
	Intraoral Laser Group	1.47	.291		1.47	.291	
	Intra-Extraoral Laser Group	1.13	.350		1.00	.352	

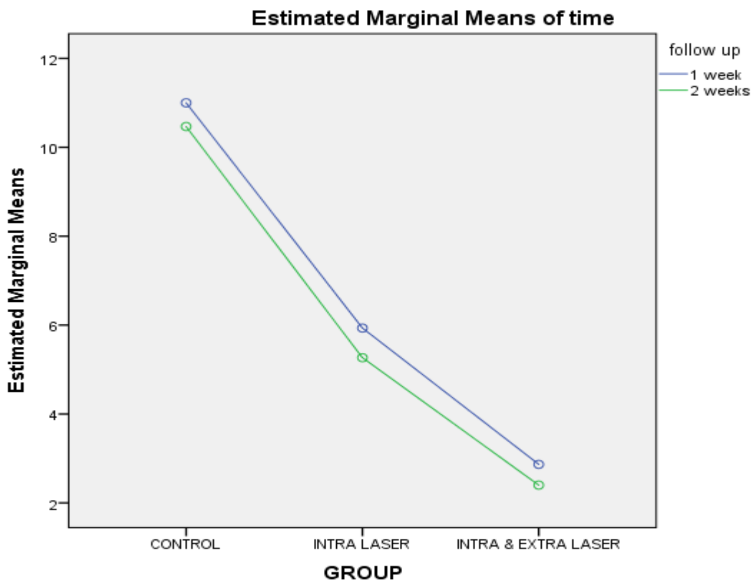

Figure 3. Mean scores of PROMS items after one week and two weeks of follow-up

Discussion

In our study, we compared two PBM protocols. The first protocol employed intraoral irradiation at a wavelength of 635 nm, following the guidelines established by the World Association for Laser Therapy (WALT)[17]. The second protocol combined intraoral red laser therapy with extraoral infrared laser application to effectively target deeper tissues, such as the oropharynx15. Both protocols adhered to the power settings recommended by Bensadoun et al.[18] and followed the energy density parameters suggested by Cronshaw et al.[19], ranging from 2 to 5 J/cm² for lesion prevention and tissue healing. We observed that the PROMS scale, was better in the PBM group, whether the laser was applied intraorally alone or both intraorally and extraorally. This improvement can be attributed to the role of PBM in reducing the incidence of OM and xerostomia, which subsequently alleviates symptoms such as pain, difficulty eating, dysphagia, taste changes, and other physical and psychological consequences that impact patients' quality of life.

These findings align with several studies, such as the study conducted by Malta et al. in 2022, which demonstrated that PBM improved overall health status and quality of life in breast cancer patients undergoing chemotherapy[20]. Similarly, the study by Gautam et al. conducted in 2013, which investigated patients with head and neck cancer undergoing combined chemotherapy and radiotherapy, found that PBM was effective in enhancing patients' subjective experiences with OM and improving their overall quality of life[8]. Likewise, in 2023, Silva et al. reported that PBM improved the quality of life in head and neck cancer patients treated with radiotherapy[21]. Our results also agree with the 2021 findings of Martins et al., which indicated that higher PROMS scores were associated with severe OM in the placebo group, resulting in a reduced quality of life[11].

Our only discrepancy was with the 2011 study by Djavid et al., which did not find any impact of PBM therapy on the quality of life of cancer patients who received PBM therapy[22].

Regarding swallowing changes, the PBM protocol combining intraoral red laser and extraoral infrared laser demonstrated greater efficacy compared to intraoral red laser alone in preventing chemotherapy-related swallowing dysfunction. Notably, no statistically significant effect was observed for the intraoral red laser alone when compared to the control group. These findings can be attributed to the enhanced effectiveness of PBM when the intraoral red laser and the extraoral infrared laser are combined. This combination maximizes the benefits of both laser types and improves targeting of potentially affected tissues. PBM not only prevents inflammation and alleviates pain associated with oral mucositis but also helps manage excessive fibrosis. Furthermore, it reduces irritation in key areas such as the base of the tongue, pharyngeal and laryngeal muscles, and the sympathetic nerve plexus, which are critical in the development of dysphagia[23]. Our results align with those of de Lima et al., obtained in 2012, who observed improvement in severe dysphagia in the intraoral PBM group (660 nm, 10 mW, 2.5 J/cm²) among patients with head and neck cancer[24]. In contrast, our findings differ from those of Gautam et al., obtained in 2012, who used intraoral PBM only (632.8 nm, 24 mW, 0.3 J/cm²) and reported that PBM reduced the incidence of acute dysphagia, the need for total parenteral nutrition, and the use of opioids23. Regarding the combined use of intraoral and extraoral laser therapy, our findings align with the case report by El Mobadder, Farhat, and Nammour in 2019, where the use of a 980 nm diode laser both intraorally and extraorally proved effective in managing dysphagia as a side effect of hormone therapy in a cancer patient[25]. Similarly, in a case series conducted by El Mobadder et al. in 2019, the application of PBM intraorally and extraorally, this time using red laser wavelengths, demonstrated efficacy in managing cancer treatment-induced dysphagia[26].

Regarding taste changes, we observed that both PBM protocols were effective in preventing chemotherapy-induced taste alterations. This finding aligns with the 2022 study by Malta et al., which evaluated the efficacy of PBM in preventing dysgeusia in breast cancer patients undergoing treatment with doxorubicin-cyclophosphamide (AC). That study reported less taste loss, better quality of life, and a reduction in the incidence of cachexia, loss of appetite, diarrhea, oral mucositis, and vomiting[20].

Recent studies have begun to explore the effects of photobiomodulation (PBM) on voice, but the field remains in its infancy[27,28]. Furthermore, no study has specifically investigated the effect of PBM on chemotherapy-induced voice changes. In our study, we did not observe any impact of PBM on voice, possibly due to the relatively short follow-up period, which may not have been sufficient to allow for the development of noticeable voice-related issues. Overall, the lack of research on PBM's effect on voice could be attributed to its classification as a secondary concern, often overshadowed by more prominent issues such as xerostomia and oral mucosal ulcers.

Study limitations

One limitation of this study is the relatively short follow-up period, which restricted our ability to assess long-term outcomes. Additionally, a longer follow-up could introduce potential confounding factors, as patients experiencing side effects might receive various interventions, such as pain management, potentially influencing the precise evaluation of PBM therapy's effectiveness in preventing oral complications. Furthermore, the study's small sample size and the inherent difficulty in standardizing non-surgical treatments across patients may have influenced the consistency of the findings.

Conclusion

Photobiomodulation therapy, whether with intraoral laser alone or with intraoral and extraoral laser, has a significant role in improving the quality of life of gastrointestinal cancer patients undergoing chemotherapy.

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