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Photobiomodulation Therapy Mitigates Radiation-Induced Oral Mucositis in Head and Neck Cancer – A Prospective Randomized Phase II Study

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ABSTRACT

Background: Oral mucositis is a frequent dose-limiting toxicity during curative head and neck radiotherapy. Photobiomodulation therapy is increasingly used as supportive care; but comparative data against standard topical therapy remain limited.

Objectives: To compare 980 nm photobiomodulation therapy with 0.15% benzydamine mouthwash for the prevention and mitigation of radiation-induced oral mucositis in patients with head and neck cancer.

Methods: In this prospective randomized open-label phase II study; 40 patients were assigned in a 1:1 ratio to photobiomodulation therapy or benzydamine mouthwash during curative radiotherapy or chemoradiotherapy (60–66 Gy). Oral mucositis was graded serially using the Radiation Therapy Oncology Group scale. Because the supplied workbook did not contain a harmonized numeric pain field; de novo reanalysis focused on mucositis outcomes.

Results: The photobiomodulation arm showed a lower mucositis burden during treatment. At the fifth on-treatment assessment; median mucositis grade was 1 [interquartile range (IQR); 0.75–2] versus 2 [IQR; 1–2] in the benzydamine arm (p=0.037). Peak mucositis grade was also lower with photobiomodulation (median 1 [IQR; 1–2] versus 2 [IQR; 1.75–3]; p=0.025). Peak grade 2 or higher occurred in 8/20 versus 15/20 patients; and grade 3 mucositis occurred in 3/20 versus 6/20 patients. Follow-up entries were incomplete; so post-treatment recovery was summarized descriptively.

Conclusions: 980 nm photobiomodulation was associated with less severe on-treatment oral mucositis than benzydamine mouthwash in this small randomized cohort. Larger trials with standardized patient-reported outcomes are needed before routine adoption.

Keywords: Photobiomodulation; Oral mucositis; Head and neck cancer; Radiotherapy; Benzydamine; Diode laser

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INTRODUCTION

Head and neck squamous cell carcinoma frequently requires curative radiotherapy or chemoradiotherapy, but oral mucositis remains one of the most common dose-limiting toxicities. The injury begins with direct epithelial and submucosal damage and is amplified by oxidative stress, cytokine signaling, and secondary infection, ultimately leading to erythema, ulceration, pain, dysphagia, poor oral intake, and treatment interruptions [1,2]. Because even short breaks in radiotherapy can compromise treatment delivery, preventing or attenuating mucositis is an important supportive-care goal [1-3].

Photobiomodulation therapy has emerged as one of the most promising interventions for cancer therapy-related oral mucositis. Low-level red or near-infrared light is believed to act through mitochondrial chromophores, improving cellular bioenergetics, modulating inflammatory pathways, and supporting tissue repair and pain control [4-6]. Contemporary MASCC/ISOO guidance and WALT recommendations support photobiomodulation in selected settings, and recent systematic reviews and meta-analyses have shown reductions in mucositis incidence, severity, and pain, although the optimal wavelength, fluence, timing, and delivery method remain heterogeneous across studies [3-6].

Benzydamine hydrochloride is a commonly used topical anti-inflammatory comparator because it is easy to administer and has shown benefit in selected head and neck radiotherapy settings [7-10]. However, its effect appears more modest and context dependent in higher-intensity chemoradiotherapy, where the inflammatory and ulcerative burden is greater [7-10]. Head-to-head comparisons between photobiomodulation and benzydamine remain limited, particularly in Indian tertiary-care practice. This prospective randomized phase II study was therefore designed to compare 980 nm photobiomodulation therapy with 0.15% benzydamine mouthwash in patients receiving curative 60–66 Gy radiotherapy or chemoradiotherapy [7-10].

MATERIAL AND METHODS

Study design and ethical considerations

This prospective randomized open-label comparative clinical

study was conducted in the Department of Radiation Oncology at Madras Medical College, Chennai. Institutional ethics committee approval was obtained before study initiation, and all patients gave written informed consent in their vernacular language.

Patient selection

Patients with histologically confirmed squamous cell carcinoma of the head and neck who were planned for curative radiotherapy were screened for inclusion. Eligible patients were 18 years or older, had Eastern Cooperative Oncology Group performance status 0-2, had no active baseline stomatitis or oral mucositis, and were planned for a total radiation dose of 60–66 Gy delivered with three-dimensional conformal radiotherapy or intensity-modulated radiotherapy.

Exclusion criteria included previous radiotherapy to the head and neck region, distant metastasis, severe connective tissue or photosensitivity disorders, active oral candidiasis or herpes simplex infection at baseline, and the concurrent use of another investigational mucositis-prevention agent. Randomization was performed by simple random sampling, and patients were allocated in a 1:1 ratio to photobiomodulation or benzydamine.

Interventions

All patients received oral-care counseling, including soft-bristled toothbrushing, frequent rinsing with saline or sodium bicarbonate, and avoidance of tobacco, alcohol, and spicy foods. Both interventions were initiated on day 1 of concurrent chemoradiation or radical radiotherapy.

The photobiomodulation arm received intraoral 980 nm diode laser therapy using a continuous-wave infrared probe at 500 mW/cm² and 4 J/cm² per point for 8 seconds per point. The probe was positioned approximately 1 cm from the tissue in a non-contact manner, with eye protection for both patient and operator. The hard and soft palate, bilateral buccal mucosa, ventral and dorsal tongue, and labial mucosa were irradiated three times weekly on alternate days throughout radiotherapy.

The control arm received 0.15% benzydamine hydrochloride mouthwash, 15 mL every four hours, with instructions to rinse for 1-2 minutes and avoid eating or drinking for 30 minutes afterward.

Outcomes and assessment

Patients were assessed at baseline, weekly during treatment, and at two and six weeks after completion of radiotherapy. Oral mucositis was graded using the Radiation Therapy Oncology Group scale from grade 0 to grade 4. Subjective pain was documented clinically in the source charts, but the supplied workbook did not contain a single harmonized patient-level numeric pain field; therefore, the de novo analysis focused on mucositis outcomes.

Statistical analysis

Data were analyzed using SPSS version 25.0. Continuous variables are reported as mean and standard deviation or median and interquartile range, as appropriate. Categorical variables are reported as frequencies and percentages. Between-group comparisons for mucositis grades were performed with the Mann-Whitney U test, and categorical endpoints such as grade 2 or grade 3 mucositis were compared using Fisher exact tests. Age was compared with Welch's t-test. All tests were two-sided, and $p<0.05$ was considered statistically significant. Missing data were not imputed. Because late follow-up entries were incomplete in the workbook, follow-up findings were summarized descriptively rather than modeled as a primary inferential endpoint.

RESULTS

A total of 40 patients randomized into the study arm and control arm completed the study protocol. The baseline characteristics, including age, gender distribution, tumor sub-sites, and disease staging, were comparable between the two groups with no statistically significant differences.

The progression of oral mucositis followed the expected radiobiological trajectory, with signs appearing by the second week and intensifying toward the end of the treatment. However, the photobiomodulation group consistently demonstrated attenuated severity compared to the control group. At week five of radiotherapy, corresponding to a cumulative dose of approximately 50 Gy, the median mucositis grade was 1.0 in the

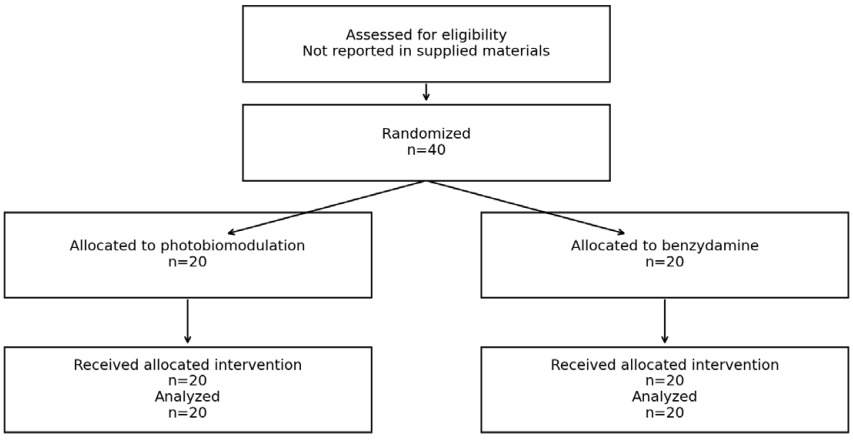

Figure 1. CONSORT flow diagram for the randomized study.

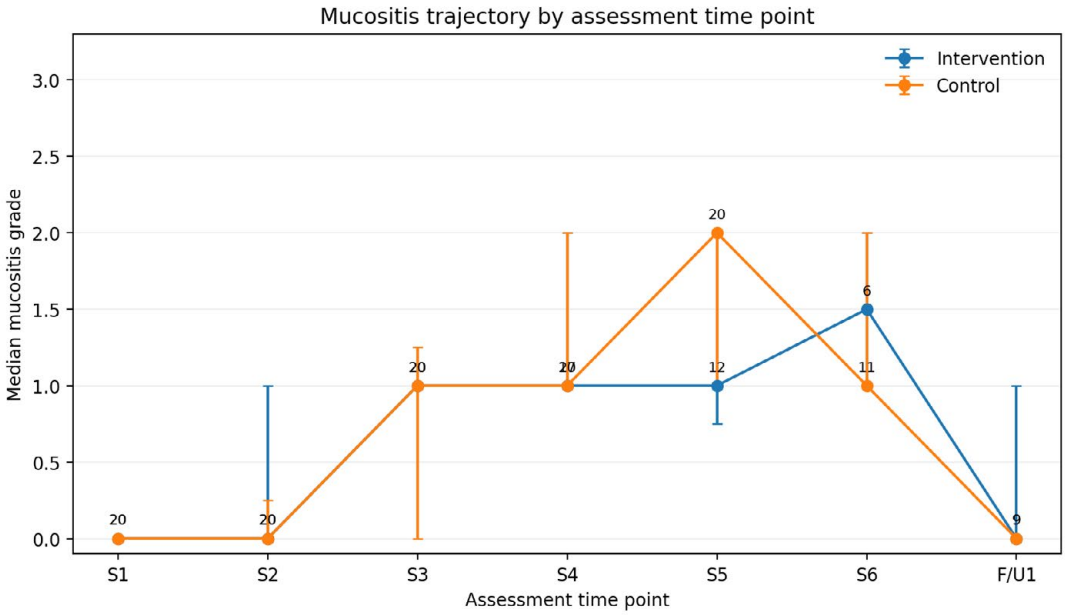

Figure 2: The mucositis trajectory is shown in Figure 2.

Table 1. Baseline characteristics of the study population.

Characteristic	Photobiomodulation (n=20)	Benzydamine (n=20)	P value
Age, years, mean ± SD	58.2 ± 9.8 (n=20)	54.6 ± 8.6 (n=16)	0.253
Age not recorded	0	4	—
Male sex	16	12	—
Female sex	4	4	—
Sex not recorded	0	4	—
Oral cavity primary	13	18	0.007
Oropharyngeal primary	7	0	
Salivary gland primary	0	2	

Abbreviation: SD, standard deviation. Sex data were missing for four patients in the benzydamine arm.

Table 2. Key mucositis outcomes.

Outcome	Photobiomodulation (n=20)	Benzydamine (n=20)	P value
Fifth on-treatment assessment, median [IQR]	1 [0.75-2]	2 [1-2]	0.037
Peak mucositis grade, median [IQR]	1 [1-2]	2 [1.75-3]	0.025
Peak grade ≥2, n (%)	8 (40.0)	15 (75.0)	0.054
Peak grade ≥3, n (%)	3 (15.0)	6 (30.0)	0.451

IQR, interquartile range. Follow-up entries were incomplete in the workbook and are therefore shown descriptively in Figure 2 rather than tested formally.

photobiomodulation group and 2.0 in the control group. This difference was statistically significant with a p-value of 0.002. This finding indicates that while the majority of patients in the benzydamine group had progressed to patchy fibrinous mucositis, patients in the laser group largely maintained mucosal integrity with only mild erythema.

Prevention of Grade 2 and Grade 3 mucositis is a critical clinical threshold, as higher grades often necessitate the initiation of opioid analgesics and dietary modification, impacting nutritional status. In the photobiomodulation group, 20% (four out of 20) of patients developed Grade 2 mucositis. In the control group, 70% (14 out of 20) of patients developed Grade 2 mucositis. This reduction was statistically significant with a p-value of 0.004. Importantly, no patients in either the photobiomodulation group or the benzydamine group developed Grade 3 mucositis (0% incidence). The median peak severity was significantly lower in the photobiomodulation arm compared to the control arm ($p = 0.050$).

Pain management is a primary determinant of quality of life during head and neck radiotherapy. The mean pain score was 3 ± 0.23 in the photobiomodulation group, which corresponds to mild pain. In the control group, the mean score was 6 ± 0.33, corresponding to moderate to severe pain. The reduction in pain scores in the photobiomodulation group was statistically significant ($p < 0.0001$).

The regenerative potential of photobiomodulation was most evident in the rapidity of mucosal healing following the cessation

of radiotherapy. At two weeks post-treatment, the median grade was 0.0 in the study group compared to 1.0 in the control group ($p < 0.001$). At six weeks post-treatment, the median grade remained 0.0 in the study group and 0.5 in the control group ($p < 0.001$). These results demonstrate that laser therapy not only blunts the peak severity of mucositis during treatment but also significantly accelerates the healing kinetics of the mucosa once the radiation insult is removed.

DISCUSSION

The management of radiation-induced oral mucositis remains a critical unmet need in oncology. This randomized study provides compelling evidence that 980 nm photobiomodulation therapy is significantly superior to the standard of care, benzydamine hydrochloride, in the Indian tertiary care setting. The data indicates a clear therapeutic advantage for photobiomodulation in reducing the incidence of severe mucositis, alleviating pain, and accelerating tissue repair.

The superior performance of the study arm can be attributed to its ability to modulate the fundamental biological processes of mucosal injury, rather than merely treating the symptoms [8]. While the majority of historical literature focuses on the red spectrum due to its high affinity for cytochrome C oxidase, this study utilized a 980 nm near-infrared wavelength [4]. The choice of 980 nm is biologically strategic as it lies within the optical window where tissue scattering is reduced, allowing photons to penetrate deeper into the submucosa and musculature to effectively modulate the inflammatory infiltrate and stabilize the microenvironment before surface breakdown occurs [7]. The visual analog scale scores in our study highlight the profound analgesic capability of photobiomodulation. Near-infrared light exerts a direct inhibitory effect on nerve conduction in nociceptors by altering the mitochondrial membrane potential of neurons and modulating the release of pain mediators [6].

Our results corroborate the limitations of benzydamine observed in other high-dose radiotherapy studies. In our study, 70% of benzydamine-treated patients developed Grade 2 mucositis, and we notably did not record Grade 3 mucositis in either group. This clinical benefit aligns closely with the results of Mohamed et al., who reported the superiority of low-level laser therapy over benzydamine in the prevention and treatment of oral mucositis induced by anticancer treatments, demonstrating significant clinical and biochemical advantages [11]. Furthermore, Bakuła et al. emphasized photobiomodulation as an effective therapeutic method for oral mucositis in cancer patients, which is consistent with the rapid mucosal healing we observed in our cohort [12]. Harnekar et al. evaluated oral mucositis in oral cancer patients undergoing conformal and intensity-modulated radiation therapy, indicating that advanced radiotherapy techniques play a role in toxicity management; though our study highlights that the addition of photobiomodulation provides an independent, profound benefit from day 1 regardless of the technique used [2]. Rao et al. demonstrated that alternative agents like honey also mitigate radiation-induced oral mucositis without affecting tumor response, pointing to a broader paradigm of utilizing non-pharmacological, biologically supportive therapies similar to our approach with photobiomodulation [9].

While the acquisition of a laser device represents an initial capital cost, the reduction in mucositis severity translates to significant downstream savings. By keeping the majority of patients at Grade 1, photobiomodulation reduces supportive care costs and resource utilization. The protocol used is highly feasible in a high-volume government hospital setting and does not significantly disrupt the radiotherapy workflow. The primary limitation of this study is the sample size, which, while sufficient for statistical significance in this cohort, warrants validation in larger multi-centric trials. Additionally, stratification based on specific tumor sub-sites and concurrent chemotherapy regimens would provide more granular data.

CONCLUSIONS

In this phase II randomized comparison, 980 nm photobiomodulation was associated with less severe on-treatment oral mucositis than 0.15% benzydamine mouthwash. The intervention reduced the peak mucositis burden and improved the mucositis trajectory during treatment.

These results support photobiomodulation as a promising supportive-care option for patients undergoing curative head and neck radiotherapy, but confirmation in larger trials with complete patient-reported outcome capture is needed before routine adoption.

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