Low level laser therapy versus benzydamin in prevention and treatment of oral mucositis induced by anticancer treatments (clinical and biochemical study)

Terapia a laser de baixa intensidade versus benzidamina na prevenção e tratamento da mucosite oral induzida por terapia oncológica

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ABSTRACT

Objective: In this study, patients undergoing neck and head radiotherapy (RT) with or with no chemotherapy were contrasted to the low-level laser therapy (LLLT) efficacy against benzydamine hydrochloride in treating and preventing oral mucositis (OM) (CHT). **Material and Methods:** This study included 90 individuals with neck and head cancer who were undergoing radiotherapy (RT) individually or in mixture with chemotherapy (CHT), varying in age from 18 to 80 years. Three equal groups were randomly formulated: Group, I patients were using oral care only, Group II patients were using benzydamine hydrochloride mouth rinse, and Group III patients were medicated by using low-level laser therapy. The National Institute of Cancer-Common Toxicity Criteria (NIC-CTC) and the World Health Organization (WHO) were used to rate the severity of OM, and the pain was validated utilizing a visual analog scale (VAS). The salivary level of tumor necrotic factor-α (TNF- α) was assayed. **Results:** As per WHO and NIC, the grade of oral mucositis at the end of cancer treatment was less in the LLLT group than in the other two groups. The alteration in TNF-α level was not significant. The laser group is more liable to have less salivary levels of the pro-inflammatory cytokines TNF- α. **Conclusion**: The incidence of oral mucositis severity has seemed to be reduced due to the prophylactic use of benzydamine hydrochloride and laser therapy protocols. However, laser therapy was more efficient in controlling the shape and progression of OM.

KEYWORDS

Oral mucositis; Photobiomodulation; Radiation therapy; Chemotherapy; Low-level laser therapy; Benzydamine

RESUMO

Objetivo: Neste estudo, pacientes submetidos à radioterapia (RT) da cabeça e pescoço com ou sem quimioterapia foram avaliados quanto à eficácia da terapia com laser de baixa potência (LLLT) versus o cloridrato de benzidamina no tratamento e prevenção da mucosite oral (MO) (CHT). **Material e M**étodos: Este estudo incluiu 90 indivíduos com câncer de cabeça e pescoço submetidos à radioterapia (RT) individualmente ou em combinação com quimioterapia (QT), com idade variando de 18 a 80 anos. Três grupos iguais foram aleatoriamente formulados: os pacientes do Grupo I usaram apenas higiene bucal, os pacientes do Grupo II usaram bochechos com cloridrato de benzidamina e os pacientes do Grupo III foram medicados com terapia a laser de baixa intensidade. Foram utilizados os critérios do National Institute of Cancer-Common Toxicity Criteria (NIC-CTC) e da Organização Mundial da Saúde (OMS) para classificar a gravidade da OM, e a dor foi validada utilizando uma escala visual analógica (VAS). O nível salivar de fator necrótico tumoral-α (TNF-α) foi ensaiado. **Resultados:** De acordo com a OMS e NIC, o grau de mucosite oral ao final do tratamento do câncer foi menor no grupo LLLT do que nos

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outros dois grupos. A alteração no nível de TNF-α não foi significativa. O grupo com tratamento a laser apresentou menores níveis de citocinas pró-inflamatórias TNF-α na saliva. **Conclusão:** A gravidade da mucosite oral parece ser reduzida devido ao uso profilático de cloridrato de benzidamina e protocolos de laserterapia. No entanto, a laserterapia foi mais eficiente em controlar a forma e a progressão da MO.

PALAVRAS-CHAVE

Mucosite oral; Fotobiomodulação; Radioterapia; Quimioterapia; Terapia com laser de baixa intensidade; Benzidamina

INTRODUCTION

Mucosal inflammation is a common acute consequence in cancer patients receiving chemotherapy (CHT). In situations including the neck and head, when the irradiation area includes the salivary glands and oral mucosa, radiotherapy (RT) individually or in mixture with CHT is frequently the medication of choice. Oral mucositis has been documented in head and neck cancer (HNC) patients undergoing CHT and RT treatment with roughly 40% and 80% respectively, whether with or with no CHT [1]. Oral Mucositis (OM) can cause treatment interruption as well as dose-limiting harm [2].

In recent years several models have been done to provide clinical care to patients who are at a greater developing serious oral mucositis risk. Even though various anti-mucositis medications have been explored, the number of high-quality preventive and therapeutic choices for OM is rather limited [3].

Increases in proinflammatory cytokines are linked to mucositis development and are thought to act a function in the damage progression and signaling pathways [4]. Before tissue damage is visible, the tumor necrotic factor-α(TNF-α) levels rise. Furthermore, the oral mucositis' severity is correlated with the level of proinflammatory cytokine production, and inhibiting cytokine production improves the course of oral mucositis [5].

The oral environment and bacteria are believed to have a significant function in the development of mucositis. Basic oral hygiene is known to be important in preventing OM and enhancing patient comfort [6].

Benzydamine is a local anti-inflammatory medication that also acts as an analgesic and anesthetic. Its action is equivalent to that of non-steroidal anti-inflammatory drugs (NSAIDs); however, it targets local inflammation causes

rather than systemic physiological systems. It can work on inflammation and pain by interacting with various inflammation pathways. Also, because it suppresses TNF-α generation, benzydamine has been demonstrated to limit the production of proinflammatory cytokines [7]. It was recently suggested in the MASCC/ISOO instructions by the International Society of Oral Oncology and Multinational Association of Supportive Care in Cancer because it is one of the most crucial medications for preventing RT-associated mucositis [8].

Furthermore, the MASCC/ISOO has issued guidelines that recommend low-level laser therapy (LLLT) as an surrogates' way for preventing and controlling OM induced by antitumor treatment or irradiation. Phototherapy is the low-level or low-powered light sources usage to treat damaged areas. It is used to hasten the healing process while also reducing pain and inflammation [9]. This non-thermal, non-invasive treatment allows for the control of a broad range of biological processes. The cell absorbs photon energy, which causes a photochemical reaction. Cells must receive a biphasic dosage for biological procedures to occur (light's optimal dose for any particular uses). Low amounts of light stimulate and repair tissues far better than greater levels of light, according to a biphasic dosage response. Phototherapy can thus be used to help with wound healing, tissue restoration, and tissue death prevention [2].

The current trial to our knowledge was not done recently in such an extensive manner to evaluate the mucositis both clinically and by using proinflammatory mediator TNF-α as a biomarker after using benzydamine hydrochloride 0.15% and low-level laser therapy (LLL) in the avoidance and medication of OM during the cancer treatment in neck and head cancer cases. The laser device that was utilized in this study was a semiconductor laser (Soft Laser SL–202, 870 nm Petrolaser, Russia).

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The low-level laser parameter used was Ga–Al–As diode, semiconductor laser 870 nm wavelength, power 60 mW, and energy density of 6 J/cm2, that locate within the near-infrared or red infrared spectrum region (632, 670, and 870 nm), with a mean power density between 5 and 150 mW/cm2, the laser does not generate any thermal impacts, due to the lower power usage, and as the related area is larger, the heat dispersed and generates a bio stimulating and anti-inflammatory impact within the cell [9].

MATERIAL AND METHODS

Study setting and population

This comparative study was performed at the Oral Medicine, Periodontology, Oral Diagnosis, and Dental Radiology Department, Faculty of Dental Medicine, Assuit branch Al-Azhar University from October 2021 till February 2022. Where ninety (90) individuals with neck and head cancer medicated with RT associated or not with CHT enrolled in this study were pointed from South Egypt Cancer Institute (35 males and 55 females) with age range 18-80 years once the approval of the hospital ethical committee.

Ethical statement

The study method was authorized by the moral committee, Faculties of Dental Medicine, Al-Azhar University in the Research Ethics Committee as trial number (AUAREC20020048-12). All eligible individuals were informed of the character, possible risks, and advantages of their enrollment within the study and obtained their informed consent.

Trial registration

With conformity to the Helsinki Declaration, the trial was signed up in ClinicalTrials.gov Protocol Registration and Results System with ID: NCT05034068.

Inclusion criteria

Patients have to suit all of the proceeding criteria to be considered for this study: male and non-pregnant female individuals diagnosed with neck and head cancer. The patients had been scheduled for a head and neck radiation procedure at the hospital, which included Intensity-modulated radiation therapy (IMRT).

The radiation protocol sessions were 5 days / week, 2Gy per fraction, with an overall dosage of 70 Gy delivered in 7 weeks (35 sessions), either alone or in conjunction with CHT. The CHT was to be performed using cisplatin, a medication with a minimal toxicity potential to somatic cells, and the risk of OM would be the same in all groups [10].

Exclusion criteria were as shown

Karnofsky performance status (KPS) lower than 60% [11], hypersensitivity to benzydamine if detected, or any common non-steroidal anti-inflammatory drugs, individuals were eliminated if they had lockjaw, any prior medical circumstances (s) defective wound healing.

Sample size calculation and power analysis

The power analysis was used to calculate the sample size using the G Power method (Ver. 3.192 copy right 1992-2020). A power calculation was utilized to measure the sample size. The significance thresholds were experimented at $\alpha = 0.05$ (type I error) and $\beta = 0.20$ (type II error) to detect a significant difference (ϱ) of 1 cm between groups when the alteration in the National Institute of Cancer—Common Toxicity criteria (NIC-CTC) RT-caused oral mucositis scale was used as the primary result variable, with a 95% confidence interval. As a consequence, the needed sample size for this experiment was determined to be 25 individuals in each group, with 0.97% actual power.

Randomization and blindness

The patients were divided using a block randomization method, in which all of the subjects were similar in regards of age, tumor site, oncology treatment, and cancer stage. Patients and Outcomes Assessors were both blinded in this study.

The patients grouping

Thirty individuals were treated with oral care in the first group. Thirty individuals were treated with 0.15% benzydamine hydrochloride in the second group. Thirty patients were medicated with low-level laser therapy in the third group.

Oral mucositis treatment protocols

Patients were provided thorough information on how to maintain excellent oral hygiene and

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were given an intensive oral care program depending on the dental lesions medication before cancer therapy. Study evaluations were carried out before cancer treatment and every week until the treatment was completed. Oral sites were checked at each visit, and scores were assigned to each site depending on the mucositis's degree.

In the first group, oral hygiene recommendations included brushing two times a day, flossing, and alcohol-free mouthwashes following oral hygiene. Oral analgesics and local anesthetics could be used if needed during RT.

Patients in the second group were instructed to wash with 15 ml of benzydamine solution 2 min/4-8 times each day till the end of cancer therapy. If patients have any troubles, they will be able to dilute the solution 1:1 or 1:2 with water (for example, burning sensations). The third group was given laser irradiation during cancer treatment triplicate within a week on alternate days, shortly prior the radiation therapy sessions. The laser device tip was cleansed with 70% alcohol. The trigger sites were irradiated with a Ga–Al–As diode semiconductor laser (Soft Laser SL–202, 870 nm PETROLASER, RUSSIA) operating in continuous wave mode (CW) with a customized probe with a spot size of 0.55 cm2 and power (P) of 60 mw in direct contact with the tissue. To avoid the tumor site, irradiation was done intra-orally. The laser irradiation was done as a preventative measure in the buccal mucosa and lateral aspect of the tongue (ten points on the left and right sides), hard and soft palate, and the dorsal aspect of the tongue (three points), the floor of mouth (two points), and labial commissure (on both sides at one point). It's important to remember that the surgical area (with the tumor excised) was not included in the laser field. Individuals in the laser group who established grade II mucositis stopped the preventative protocol and started curative laser therapy, which consisted of continuous laser treatment of 870 nm wavelength, 60 mW power, and 6 J/cm^2 energy density delivered in all ulcerated areas of the oral mucosa, spot size =0.55 cm2.

Mucositis assessment

The severity and extent of OM were evaluated according to (WHO) as symptoms evaluation, and (NIC-CTC) as extension evaluation respectively,

and the pain was rated according to a visual analog scale (VAS).WHO scale (symptoms evaluation) [12]: (0) no symptoms or signs [1], oral discomfort and redness [2], solid and liquid diets can be tolerated, oral redness and ulcers [3], oral ulcers only liquid diet can be tolerated [4], oral nutrition is not possible. NIC-CTC (extension evaluation) [13]: (0) patients with no obvious changes to the oral mucosa [1], erythema [2], ulcers up to 1.5 cm diameter [3], ulcers more than 1.5 cm diameter [4], ulcers with bleeding and necrosis may found. VAS (pain tolerance scale) [14]: The lack of pain is 0, while the maximum discomfort is 10.

TNF-α assessment

TNF- concentrations were measured in (μg\ml) using a commercial enzyme-linked immunosorbent assay (ELISA) test (Sunred Biological Technology Co., Ltd, Baoshan District, Shanghai, China) at baseline, 7th, 21st, and 35th radiation sessions [15].

Saliva sample collection:

The Navazesh spitting method was used to collect saliva samples(2ml) from all groups at one session before chemoradiotherapy treatment (CRT) and at the 7th,21st, and 35th appointments during the cancer radiation therapy [15]. Cases were not allowed to drink or eat anything for an hour prior the saliva collection procedure. The specimens were kept frozen at -70° C until TNF- levels were determined and it was measured in picograms per milliliter (pg/ml).

Statistical analysis

SPSS software version 24 was used to create the graph and collect the data (SPSS Inc., Chicago, Il., USA). The ANOVA test is utilized to compare two groups at different intervals and to compare the baseline reading to subsequent readings within the similar group. A paired sample t-test was utilized to compare two groups in related samples.

RESULTS

Patients' characteristics

Ninety patients that were diagnosed with cancer treated by different anti-cancer modalities, participated in this study. Every 30 patients

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completed a study in every group. There were no substantial variations between the groups as per tumor site, age, cancer treatment protocol, or cancer stage (Figure 1) (Table I).

Gross observations

Gross observation showed normal oral mucosa in the first week of cancer therapy in all groups. In the 2nd, 3rd, and 4th weeks variation grades III was noticed in the control group, while in the second and third groups showed variation between grades I, II respectively. The last three weeks of anti-cancer gross observation showed a decrease in the progression of oral mucositis towards a higher grade in the second and third groups. Also, immediate relief of pain after each laser therapy session and a considerable

progression in the oral mucositis healing was noted (Figure 2A-C).

Clinical evaluation

As per the WHO, a less mean of oral mucositis (OM) scores was noted in the laser group during the radiotherapy (RT) duration. No significant variations was noted between groups (P>0.05) at week 4, moderate significance difference (P <0.001) at week 2&6, and highly significant difference (P<0.005) at week 7. During the RT treatment, it was observed that 23.3% in the oral care group represent grade IV oral mucositis (OM) at the end of RT, and it was presented in 6.7% of patients in the benzydamine group, however, grade IV OM was not presented in the laser group. Also, at the termination of medication OM grade III happened in 26.7% of individuals
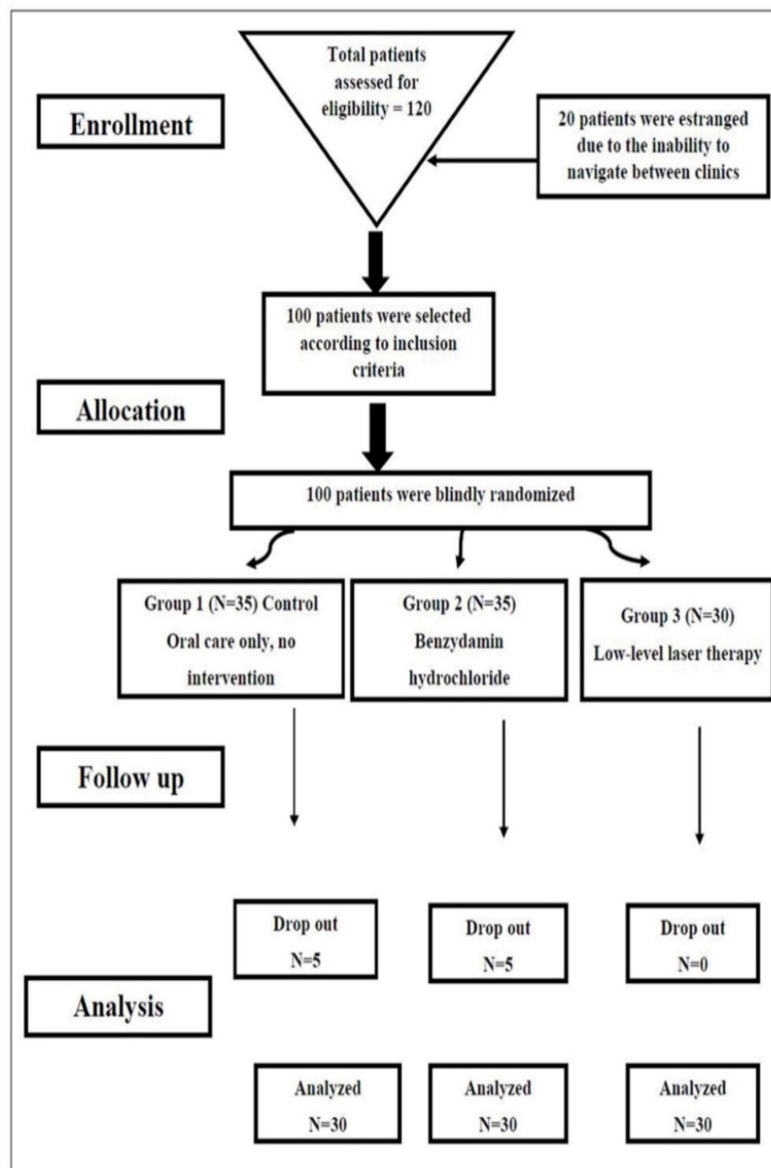

Figure 1 - Showing study flow diagram.

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Table I - Patient's characteristic and comparisons between groups using ANOVA test and Chi-square test

Item	Group "1"	Group "2"	Group "3"	p-value
· Age "years	45±19	58±14	51±14	P=0.375
· Tumor site:				
Buccal mucosa	10(33.33%)	12(40.0%)	9(30.0%)	
Tongue	7(23.33%)	9(30.0%)	11(36.67%)	P=0.273
Oropharynx	5(16.67%)	3(10.0%)	6(20.0%)	
Others	8(26.67%)	6(20.0%)	4(13.33%)	
· Oncology treatment:				
RT	5(16.67%)	4(13.33%)	7(23.33%)	
Surgery and RT	7(23.33%)	5(16.67%)	5(16.67%)	P=0.351
CHT and RT	14(46.67%)	18(60.0%)	16(53.33%)	
Surgery, CHT and RT	4(13.33%)	3(10.0%)	2(6.67%)	
· Cancer stage:				
Stage II	5(16.67%)	6(20.0%)	5(16.67%)	
Stage III	15(50.0%)	17(56.67%)	18(60.0%)	P=0.438
Stage IV	10(33.33%)	7(23.33%)	7(23.33%)	
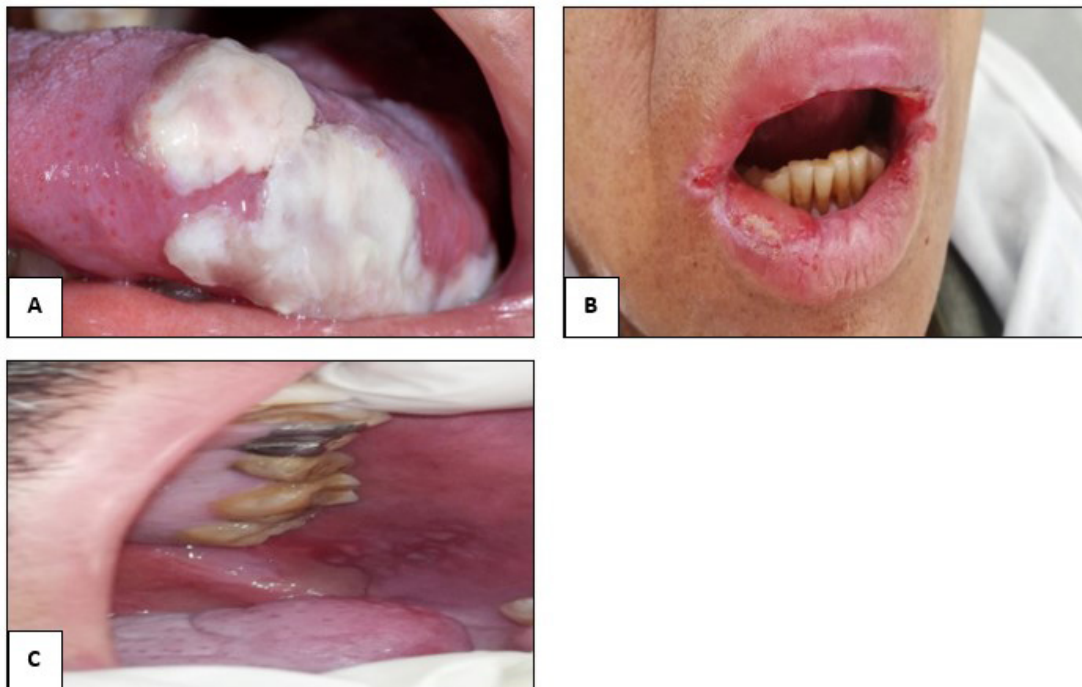
Figure 2 - Showing gross observation in all patients in the 7th and last weeks of cancer therapy, in oral care group with grade III oral mucositis (A), benzydamin group with grade II oral mucositis (B) & laser group with grade I oral mucositis (C).

in the oral care group,33.3% of individuals in the benzydamine group, and 13.3% of the individuals in the laser group. OM begin to appear in the 2nd week of RT where the oral care group presented 70% grades I and 10% grade II, compared to 50% grade I and 6.7% grade II in the benzydamine group, while in laser group grade I presented in 33.3% of patients and 3.3% of patients presented grade II (Figure 3A).

Extension evaluation

The laser group also expressed lower scores of NIC-CTC throughout the RT medication. There was a significant variation (P <0.05) between the oral group, benzydamine group, and laser group at weeks 3, 4&5, also there was a moderate significance difference (P<0.001) at weeks 2, 6 and a highly significant difference (P<0.000) at week 7 with an increase in mean value at a different interval. At the

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end of treatment (35 th session) the prevalence of grade II OM according to NIC was 16.7% in the oral care group, 50% in the benzydamine group, and 36.7% in the laser group. The prevalence of grade III OM was 56.7% in the oral care group, 43.3% in the benzydamine group, and 40% in the laser group.

The prevalence of grade IV OM in the last week of treatment was 26.7% in oral care, 6.7% in the benzydamine group. Grade IV was not represented in the laser group at the termination of the RT and grade I was recorded in 23.3% of patients in the last week of RT (Figure 3B) (Table II).
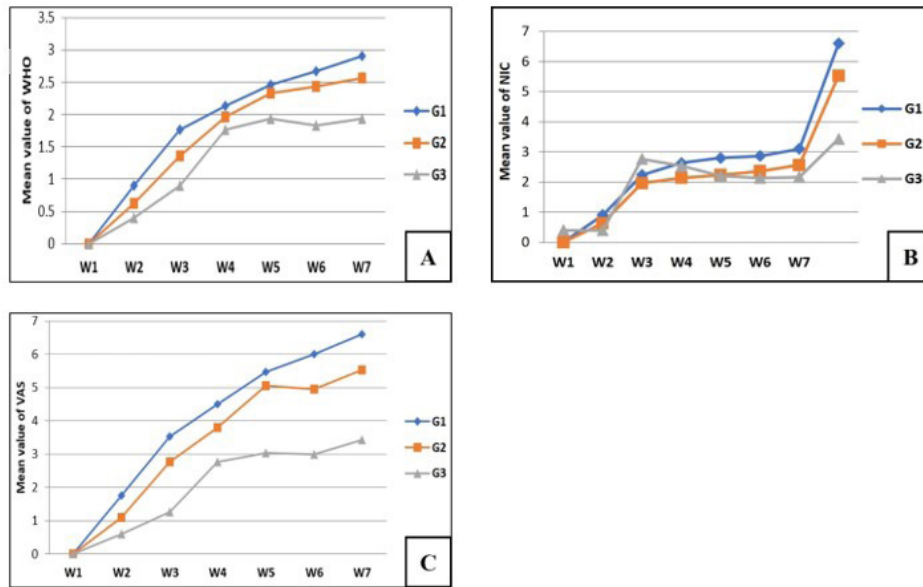

Figure 3 - Mean values of WHO (A), NIC (B), and VAS (C) in different groups. Abbreviations W; week, G-1; Control, G-2; benzydamine, G-3; Laser.

Table II - Distribution and Comparison of oral mucositis grades (0, I, II, III, IV) of NIC-CTC scale between different groups (G1,G2, G3)

Grade in group	Week1	Week2	Week3	Week4	Week5	Week6	Week7
· 0							
G1	30(100%)	6(20.0%)	0	0	0	0	0
G2	30(100%)	13(43.3%)	0	0	0	0	0
G3	30(100%)	19(63.3%)	10(33.3%)	3(10.0%)	0	0	0
· 1							
G1	--	21(70.0%)	10(33.3%)	3(10.0%)	3(10.0%)	2(6.7%)	0
G2	--	15(50.0%)	10(33.3%)	4(13.3%)	4(13.3%)	4(13.3%)	0
G3	--	10(33.3%)	15(50.0%)	4(13.3%)	6(20.0%)	9(30.0%)	7(23.3%)
· II							
G1	--	3(10.0%)	6(20.0%)	11(36.7%)	9(30.0%)	7(23.3%)	5(16.7%)
G2	--	2(6.7%)	8(26.7%)	9(30.0%)	12(40.0%)	13(43.3%)	15(50.0%)
G3	--	1(3.3%)	3(10.0%)	11(36.7%)	15(50.0%)	10(33.3%)	11(36.7%)
· III							
G1	--	--	11(36.7%)	10(33.3%)	9(30.0%)	14(46.7%)	17(56.7%)
G2	--	--	6(20.0%)	14(46.7%)	11(36.7%)	11(36.7%)	13(43.3%)
G3	--	--	2(6.7%)	10(33.3%)	6(20.0%)	9(30.0%)	12(40.0%)
· IV							
G1	--	--	3(10.0%)	6(20.0%)	9(30.0%)	7(23.3%)	8(26.7%)
G2	--	--	4(13.33%)	3(10.0%)	3(10.0%)	2(6.7%)	2(6.7%)
G3	--	--	0	2(6.7%)	3(10.0%)	2(6.7%)	0
p-value	--	P<0.02*	P<0.00***	P=0.834n.s	P=0.183n.s	P<0.04*	P<0.00***

*, **, *** = low, moderate, high significant difference, respectively; n.s = no significant difference.

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Pain evaluation

In the laser group, the pain scores' lower mean value was noticed during the RT treatment. Throughout the whole RT medication, very severe pain was noted in the oral care group with a mean value (7±0.47), and a lower mean score for severe pain (6±0.33) was noted in the benzydamine group, while mild pain was reported in the laser group with mean value (3±0.23). The mean value of pain by VAS in all groups during the weeks of radiation therapy (RT) is presented in (Figure 3C).

TNF- α assessment

At baseline, the RT's 7th, 21st, and 35th sessions, salivary TNF- α levels were measured in salivary level for the oral care, benzydamine, and laser groups. The alteration in TNF- α level following medication was not substantial for the entire group of patients. In the OM's ulcerative phase (session 21), the laser group had reduced proinflammatory cytokines TNF-α's amounts as the mean was (14±6) and at the end of RT it was (10±3) while in the oral care group the mean was (35±7) in session 21 and (30±5) in the last session, and in the benzydamine group the mean in session 21 was (3±4) and in the last session, the mean was (29±6). However, there is no statistically significant difference observed at any of the time-points assessed (P>0.05 for all contrasting) (Figure 4).

DISCUSSION

Head and neck tumors, and oral-maxillofacial tumors, are examples of the most common types of tumors. Radiotherapy (RT) has become one of the most p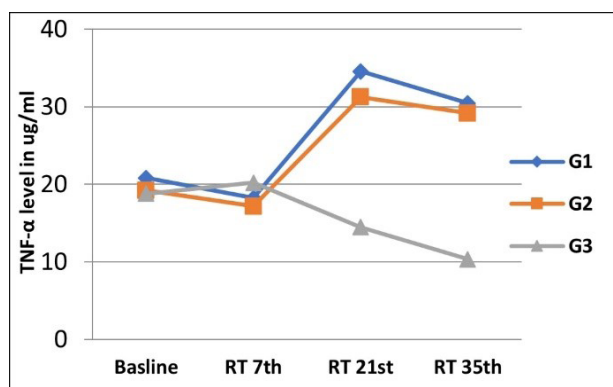opular treatments for HNC patients in recent years. For HNC patients, a common radiation regimen consists of a daily dose of 2Gy for 5–7 weeks, for an overall cumulative dose of 60–70Gy [16].

The treatment of radiation-caused oral mucositis is usually focused on the symptoms, the medicated of complex infections, and the stimulation of mucositis healing. There are a variety of preventative and treatment strategies available right now. Oral mucositis can be avoided by maintaining good oral hygiene, proper dietary support, and modern RT techniques [17].

Understanding the involvement of cytokines in the etiology of RIOM may aid in the development of management methods. The proinflammatory cytokines TNF- α and IL-6 have been examined and done in multiple studies, all of which have shown an elevation in TNF-a and IL-6 levels [18-20].

The role of TNF- α as a biomarker for RIOM was the focus of the current study. At the end of the treatment, there was no significant change in TNF- levels in any of the groups (35th session). The laser group, on the other hand, had proinflammatory cytokines TNF-α's in a lower level than the other two groups. This variations, however, was not statistically substantial at any of the endpoint intervals of time examined [4,20,21].

In this study, the first group received dental care and proper oral hygiene measures. Maintaining good oral hygiene improves this condition by alkalinizing the mouth, lowering the risk of oral mucositis during cancer treatment [22].

The present study evaluated laser therapy for OM in individuals undergoing traditional radiation therapy methods and the findings recommended that the prophylactic laser therapy application could decrease the total risk of serious OM, these findings are in line with those of some other investigations [23,24]. As for therapeutic laser therapy in the current study, it appeared to have no significant impact on the severe OM's remission, these findings are parallel to a treatment protocol published in 2016, where they found that low-level laser therapy significantly reduced the grade of OM, xerostomia, and pain in a group of patients receiving cancer radiation [18]. Another trend similar to our study noted that the OM's mean grades were significantly less in laser-medicated cases than in the control group and the prevalence of higher grades of OM was less in the laser group patient [25,26].

Figure 4 - Mean value of TNF-α (µg\ml) in different groups.

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Our results combined the preventive and treatment impacts of laser therapy in cases obtaining therapy for a variety of neck and head tumors, providing the outcomes of a prior study [27], which only supplied conclusions as per the prophylactic impact of laser therapy. Moreover, our finding is parallel with a meta-analysis that involved an overall number of 30 research studies from 8 countries, with both prophylactic and medicated impacts evaluated [25].

In the present study, the results indicated a decrease of erythema and ulceration in the benzydamine group contrasted to the control group as there was a significant difference ($P<0.05$) at duration (3, 5, 6) weeks and there was a high significance difference at week 7, and these findings go parallel with a study published in 2015 that advised the utilization of benzydamine for the avoidance of OM in cancer individuals following a radiation therapy's moderate dose [28]. Benzydamine was investigated in another study that found no statistically substantial difference in the number of patients with oral mucositis, although it did lessen the pain intensity and duration of oral mucositis. Furthermore, benzydamine delays oral mucositis progression [29]. Another trial done on benzydamine found a significant difference in reducing grade III oral mucositis in patients receiving RT doses (>50 Gy) [30].

Systematic reviews and meta-analyses have demonstrated that from each of all of the records adopted for the medication of pain or oral mucositis ensuing from cancer medication, benzydamine mouthwash, and low-level laser therapy with basic standard oral care, showed a statistically significant benefit [30].

More inflammatory mediators are required to be studied to gain knowledge about the function of laser therapy and benzydamine in the reduction of radiation-induced oral mucositis. Also, more research has the necessity to develop the biological processes by which the laser enhances wound healing and lowers pain, as well as to validate the laser therapy impact in OM in individuals who are receiving traditional chemotherapy treatments. More sophisticated random controlled studies focused on laser parameters and laser therapy schedules, as well as the possibility of combining low-level laser therapy with other mucositis treatment modalities, are also necessary.

CONCLUSION

In individuals medicated with RT and/or CHT, photobiomodulation with LLLT lowers the prevalence, discomfort, and radiation-caused oral mucositis' severity. Furthermore, the data extremely support and suggest the prophylactic utilization of benzydamine hydrochloride to reduce OM in cancer-treated patients following a moderate dose of radiation therapy.

Author's Contributions

NHM: Conceptualization, Investigation, Original Draft Preparation, Project Administration. AMK: Methodology, Investigation, Visualization. MFE: Supervised the finding of this work, Review & Editing. ASSM: Contribute in sample collecting, Formal Analysis. AIAEHG: Review & Editing, Supervision, Formal Analysis.

Conflict of Interest

The authors have no ownership, financial, or other form of personal conflict of interest in any of the products, services, or companies mentioned in this article.

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Regulatory Statement

All provisions of the local human subjects oversight committee rules and policies, as well as any local and institutional regulations and instructions that govern IRB operation, were followed in this investigation.

The approval code of this study is: AUAREC20020048-12

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