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Comparative Evaluation of Low-Level Laser Therapy and Pilocarpine Hydrochloride on Stimulated Salivary Flow in Patients with Head and Neck Cancer Undergoing Radiochemotherapy: A randomized clinical trial

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Aim: To evaluate the effects of low-level laser therapy (LLLT) and pilocarpine hydrochloride (Salagen) on stimulated salivary flow in patients with head and neck cancer undergoing radiochemotherapy. Furthermore, this study aims to provide the first comparative analysis of the protective effects of these two treatment modalities.
Materials and methods: This clinical study consisted of 16 head and neck cancer patients, 10 females and 6 males, aged between 18 and 62. The patients were randomly assigned to two groups: one received low-level laser therapy (810 nm and 650 nm), and the other was given pilocarpine hydrochloride (5 mg Salagen tablets, three times daily). Stimulated saliva was collected at three points: before radiochemotherapy (R1), immediately after the final session (R2), and three months later (R3). Data were analyzed with SPSS ver26 statistical software.
Results: The study involved 10 females and 6 males, with a mean age of 41.75. Participants in the Salagen group demonstrated a statistically significant increase in stimulated saliva in R3 compared to those in the laser group. Additionally, the results indicated a statistically significant decrease in stimulated saliva in R3 compared to R1 within the laser group.
Conclusion: This study demonstrated that Salagen effectively prevents significant hyposalivation when administered concurrently with radiochemotherapy in head and neck cancer patients. In contrast, the low-level laser therapy (LLLT) protocol employed in this study could not prevent the decline in stimulated salivary flow caused by radiochemotherapy. Furthermore, the findings highlight the superiority of Salagen in mitigating severe hyposalivation associated with radiochemotherapy, compared to the LLLT protocol utilized in this research.

Keywords: Radiochemotherapy, Low-Level Laser Therapy, Pilocarpine Hydrochloride, Hyposalivation, Head and Neck Cancer

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Introduction

Head and neck cancer (HNC) is the seventh most prevalent cancer worldwide, originating from the mucosal epithelium in various regions, including the lips, nasal cavity, oral cavity, sinuses, pharynx, larynx, and salivary glands. [1,2] Treatment approaches vary based on the stage and severity of the disease, ranging from surgery and radiotherapy (RT) for early-stage cancers to Radiochemotherapy (RCT) for locally advanced cases. [3] Chemotherapy (CT) agents are drugs specifically designed to target cancer cells. They inhibit or poison these malignant cells to prevent them from dividing rapidly or to eliminate them during the division process. Although chemotherapy effectively targets the fast growth of cancer cells, it can also affect normal cells with a high turnover rate, such as those in hair follicles, bone marrow, and the epithelial cells lining the digestive tract. This leads to a variety of side effects. Similarly, radiotherapy aims to deliver a focused dose of radiation to the tumor while minimizing damage to surrounding healthy tissues. [4]

Standard radiation therapy doses for advanced cancers typically range from 50 to 70 Gy. These doses are delivered in fractionated amounts of 2 Gy per day over five days, resulting in a total of 10 Gy per week for 5 to 7 weeks. [5] Research suggests that glands exposed to radiation doses below 26 Gy exhibit time-dependent recovery, while those exposed to higher doses experience irreversible damage, leading to a range of complications. [4,6] Therefore, although Radiochemotherapy is an effective treatment, it causes many reversible acute oral problems, including oral mucositis (OM), dysphagia, dysgeusia, candidiasis, and malnutrition. [5] And irreversible chronic complications such as xerostomia (the subjective sensation of dry mouth) and hyposalivation (decreased saliva flow). [7]

Hyposalivation occurs when the glandular tissue of both major and minor salivary glands is destroyed and replaced by fibrous tissue that infiltrates lymphocytes and plasma cells. [8,9] The extent of damage to the glandular cells largely depends on the cumulative doses of radiation received. During the first week of treatment, saliva flow typically decreases by 50–60% in the first week of RT, dropping to approximately 20% after seven weeks, with continued reduction for months post-treatment. [10] The loss of saliva's essential functions, such as natural oral cleaning, pH regulation, and remineralization of enamel, leads to symptoms such as dysphagia, dysarthria, dysgeusia, and increased dental caries. Ultimately, these complications severely impact patients' quality of life. [4] To improve the quality of life for head and neck cancer patients undergoing Radiochemotherapy and enhance their salivary flow, we found that this depends on the extent of residual salivary gland function. For patients with preserved glandular tissue, sialogogues like pilocarpine and, or chewing sorbitol-containing gum, can stimulate salivary production. However, for patients with complete glandular destruction, saliva substitutes may help maintain oral moisture. Additional options include acupuncture to boost saliva production, low-power laser therapy, and herbal remedies. [4,7]

Pilocarpine hydrochloride (Salagen) is a Para sympathomimetic agent approved by the FDA for treating Sjögren's syndrome and radiation-induced xerostomia. It stimulates muscarinic acetylcholine receptors (M3R) on exocrine glands, promoting smooth muscle contraction and increased saliva secretion. The systemic administration of pilocarpine has shown efficacy at doses ranging from 2.5 to 10 mg, with an optimal dose of 5 mg three times daily. However, side effects such as sweating, headaches, nausea, and diarrhea may limit its use [11.12.13]. Several studies have suggested that concomitant use

of pilocarpine with radiotherapy helps maintain unstimulated saliva flow. [14,15] In contrast, other studies have not shown a significant therapeutic effect of pilocarpine in treating xerostomia induced by radiotherapy. [16,17] Also, Photobiomodulation therapy (PBMT), Previously known as low-level laser therapy (LLLT), is a novel approach to managing xerostomia. By activating photoreceptors in the mitochondrial respiratory chain, PBMT increases ATP production, promoting tissue repair, inflammation control, and pain relief (as shown in [18] that low-level LASER therapy with the use of Michigan splint showed a reduction in the pain associated with TMD). Additionally, a previous study indicated that PBMT has a protective effect on cells subjected to ionizing radiation. [13] Animal studies have shown that PBMT not only stimulates saliva flow but also helps regulate saliva formation and control oxidative mechanisms, reducing inflammation. [19,20] Clinically, PBMT has shown promise in mitigating hyposalivation when used alongside RT [21]. However, inconsistencies in study protocols have led to mixed results regarding its efficacy. [22,23]

Despite the potential of pilocarpine and PBMT, the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) have found insufficient evidence to recommend these interventions during RT for HNC patients. [24] Therefore, it was necessary to enrich the medical literature with more studies on the effectiveness of both pilocarpine hydrochloride and low-power laser and compare them in preventing dry mouth caused by radiochemotherapy.

Materials and methods

This study was conducted at Damascus University, specifically in the Faculty of Dentistry, Department of Oral Medicine, as well as at Al-Biruni University Hospital in the Department of Radiotherapy, from 2022 to 2024. The study protocol received approval from the Ethics Committee of Damascus University and was conducted as a randomized clinical trial, involving a cohort of 16 patients with head and neck cancer who will receive radiochemotherapy. Based on data from Louzeiro et al. (2020) [22], the standard deviation was estimated at 0.11. Using Minitab (version 19) to calculate the required sample size for a power of 90%, it was determined that 13 participants were necessary. To account for potential withdrawals, an additional three patients were included as a contingency. Informed consent was obtained from all participants after they were informed about the research procedures and conditions. The patients were then randomly assigned to two groups using the website (www.randomizer.org):

The first group: is the Salagen group, which included 8 patients who were given pilocarpine hydrochloride 5 mg in the form of coated tablets, known commercially as Salagen, from the beginning of their radiochemotherapy until its end.

The second group: is the Low-level laser therapy (LLLT) or the PBMT group, which included 8 patients who were given diode laser three times a week from the beginning of radiochemotherapy until its end.

Participants in the study were aged 18 years or older and underwent head and neck irradiation using the Varian Halcyon radiotherapy system. The minimum radiation dose was 50 Gy, delivered at least to the parotid and submandibular glands. Patients included in the study had not previously received radiotherapy or chemotherapy within the past two months and had a Karnofsky Performance Scale score exceeding 60. Exclusion criteria encompassed patients with tumors in the parotid or submandibular glands, floor of the mouth, or blood. Patients with Sjögren's syndrome, autoimmune diseases, diabetes, or

significant uncontrolled cardiac, renal, pulmonary, or visual conditions, as well as other chronic diseases that could interfere with the evaluation of Pilocarpine's safety and efficacy, were excluded. Additionally, individuals taking tricyclic antidepressants, antihistamines with anticholinergic effects, beta-blockers, or those using Pilocarpine for ophthalmic purposes were not eligible for the study.

Clinical Intervention Steps

A detailed medical and medication history was obtained to confirm inclusion and exclusion criteria, followed by a clinical examination to treat any acute oral conditions or mucosal lesions outside the study period, minimizing complications from cancer treatment.

Patients were instructed on oral hygiene practices and advised to avoid hot or spicy foods. For prophylactic measures, Nystatin 100,000 IU was prescribed, along with Benzydamine hydrochloride (15 mg) mouthwash, which should be used four times daily for 30 seconds during radiochemotherapy.

The first group received Salagen (pilocarpine hydrochloride), 5 mg coated tablets, taken three times daily, one hour before meals. The drug took effect one hour after administration and lasted for three hours [25], continuing from the first day of radiochemotherapy (R1) until treatment ended (R2).

The second group received PBMT (LLLT) directly before the start of the first radiochemotherapy session (R1) and continued three times weekly until the end of radiochemotherapy (R2).

The low-level laser protocol used in this study was based on the method described by Louzeiro and colleagues [22], with some modifications to suit the AsGaAl diode device (PIOON model MER-G10) available at the Department of Oral Medicine, Damascus University (Fig.1)

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Figure 1: Diode laser device used in this research from PIOON company

The biostimulation protocol for the application consists of the following steps: Intraoral application on Minor salivary glands with a wavelength of 650 nm, a power of 40 mW, a time of 25 s, a Spot size of 0.5 cm2, an energy density per point 2 j/cm2, a power density of 80 mW/cm2, and one joule per point, and power density of 80 mW/cm2, in continuous waves and contact mode on the following points: A point on each labial commissure, 8 points on the upper labial mucosa, 8 points on the lower labial mucosa, 12 points on each buccal mucosa, 12 points on the hard palate, 4 points on the soft palate, 6 points on the ventral surface of the tongue, 6 points on each border of the tongue, and 4 points on the mouth floor. For the extraoral application targeting the parotid and submandibular glands, the protocol utilized a wavelength of 810 nm, a power of 400 mW, a time of 17.5 s, a Spot size of 2.54 cm2, an energy density per point 2.7 j/cm2, 7 joules per point, and power density of 185 mW/cm2, in continuous waves and contact mode on the following points: 6 extraoral points on each parotid gland. 3 extra-oral points on each submandibular gland. In the sublingual gland, the same laser device is applied as the following: wavelength 810 nm -power 100 mW -energy 3.5 j/cm2- duration 17.5 s -for each point 1.75 J – power density

of 200 mW/cm2- spot size 0.5 cm2, on the following: 2 intra-oral points on each sublingual gland.

The stimulated salivary flow rate (sSF) was recorded during three distinct periods: R1, immediately before the patient's first session of radiochemotherapy; R2, immediately after the patient's last session; and R3, at a three-month follow-up. During the monitoring sessions, the stimulated salivary flow rate (sSF) was studied according to the following protocol: Patients were asked to refrain from eating or drinking for one hour before the examination (water was allowed). They rinsed their mouths with distilled water for 30 seconds to reduce bacterial load. Also, Saliva samples were collected in the morning between 8 AM and 11 AM in a quiet, well-ventilated, and warm room. Participants swallowed any saliva in their mouths, leaned forward slightly, and chewed a 1 cm by 1 cm piece of nylon for 5 minutes to collect saliva. Afterward, they spat the saliva into a pre-weighed 15 ml graduated plastic tube without removing the nylon piece (Fig.2). This was repeated three times, and the nylon piece was then disposed of, completing the 15-minute saliva collection.

Figure 2: The stimulated salivary flow was collected from head and neck cancer patient

The salivary flow rate was calculated in one minute by subtracting the previously calculated weight of the empty tube from the weight of the tube filled with saliva by using a digital scale with an accuracy of 0.01 g (Fig.3), then dividing the result by the duration of saliva collection (15 minutes)

Figure 3: The digital scale used to measure stimulated saliva

Comprehensive data for groups were recorded and organized in Excel files to facilitate subsequent statistical analysis and evaluation.

Results

This study involved 16 patients with head and neck cancer undergoing radiochemotherapy, who were included into two groups: 8 received pilocarpine hydrochloride (50%) and 8 underwent low-level laser therapy (50%). Also, the sample included 6 males and 10 females, with an average age of 41.75 years

The arithmetic mean of the stimulated saliva flow index (sSF) was calculated for the two study groups across the three study periods (R1, R2, R3), as presented in Table 5. A paired t-test was performed to assess the significance of differences in sSF index means during the pre-treatment phase (R1). The analysis revealed no statistically significant differences between the groups prior to treatment.

The change in the stimulated saliva flow index (Δ sSF) was also analyzed across

treatment periods. The results indicated no statistically significant differences in (Δ sSF) between the groups for the intervals R1-R2 and R1-R3. However, a statistically significant difference was observed in the change between R2-R3, favoring the salagen group (Table 1).

Table 1: Results of the T-Student test to assess the significance of changes in the sSF index between groups during the studied periods.

periods	research groups	Mean Δ sSF	Value T	P Value
R2-R1	Salagen	−0.25	−0.762	0.459
	PBMT	−0.133		
R3-R2	Salagen	0.188	3.053	**0.009***
	PBMT	−0.133		
R3-R1	Salagen	−0.063	1.622	0.127
	PBMT	−0.256		

The effect of time on sSF index values was further analyzed within each study group using repeated-measures one-way ANOVA. Statistically significant differences were identified across the periods in the PBMT group. Pairwise comparisons, adjusted using the Bonferroni correction, revealed that the sSF index values in R3 were significantly lower than those in R1, with no other pairwise comparisons showing significant differences (Table 2).

Table 2: Results of the Bonferroni correction on the period effect for sSF values in the low-level laser group (PBMT).

research group	group (I)	group (J)	difference between Means (I-J)	P Value
PBMT	R1	R2	0.133	0.762
		R3	0.265	**0.019 ***
	R2	R3	0.133	0.386

Discussion

Head and neck cancer involves malignant tumors in the nasal and oral cavities, sinuses, lips, pharynx, larynx, and salivary glands. Standard treatments include radiotherapy, chemotherapy, and surgery, often combined according to cancer stage and patient factors. [26] While effective, these therapies frequently result in debilitating side effects that compromise patients' quality of life. The most prevalent are mucositis, xerostomia, dysgeusia, dysphagia, masticatory muscle spasms, and candidiasis. [27]

Xerostomia, or dry mouth, is primarily caused by radiation-induced damage to salivary glands, impairing their ability to secrete saliva and altering its composition. The severity of xerostomia depends on factors such as the total radiation dose, the extent of glandular tissue exposed, and whether radiotherapy is combined with chemotherapy. [28] Various interventions have been proposed to enhance salivary gland function, including gustatory and mechanical stimulation (e.g., chewing sugar-free sweet-sour gum) and pharmacological treatments like cholinergic agents such as pilocarpine and cevimeline. These agents are considered first-line options for xerostomia management in head and neck cancer patients. [7,29] However, their use is limited in some regions due to significant side effects. [29] Saliva substitutes, frequent water intake, and non-saline mouth rinses are additional supportive measures. [30]

In recent years, photobiomodulation therapy (PBMT), employing low-level laser therapy (LLLT), has shown promise in alleviating radiation-induced xerostomia. Studies indicate its potential to preserve salivary flow and improve the quality of life for cancer patients. [22,31] However, a systematic review by Souza et al. identified only four studies specifically addressing PBMT's efficacy in managing xerostomia in head and neck cancer patients. While some evidence supports increased salivary flow post-PBMT, the lack of standardized application protocols and parameter settings highlights the need for further research and consensus on treatment guidelines. [32] Given the varying outcomes reported for LLLT in

preventing xerostomia, further investigation into its effectiveness in this context is essential. Meanwhile, pilocarpine, marketed as Salagen, has demonstrated efficacy in managing xerostomia during and after radiochemotherapy, though the limited number of studies on its preventive role during treatment underscores the need for additional research.

Stimulated Salivary Flow Analysis

Our study found a significant decrease in stimulated salivary flow within the PBMT group between the R1 and R3 time points. These results are consistent with previous[13], which indicated a notable reduction in stimulated salivary flow two months after treatment compared to the flow during treatment among patients receiving LLLT. However, our findings differ from Simões, A. et.al study [33] which reported no significant reduction in salivary flow. This discrepancy may be attributed to differences in treatment approaches; the patients received radiotherapy alone, while our cohort underwent radiochemotherapy. Furthermore, Simões, A. et.al Study assessed salivary flow before the initiation of treatment and compared it to post-treatment outcomes, lacking long-term follow-up.

When comparing the two study groups, the salagen group showed a significant increase in stimulated salivary flow between R2 and R3, with flow rising three months post-treatment, while the PBMT group experienced a decrease.

The effectiveness of Salagen can be attributed to pilocarpine's mechanism of action, which involves binding to cholinergic receptors, triggering biochemical cascades that increase intracellular calcium ion release, smooth muscle contraction around salivary glands, and enhanced saliva secretion. Therefore, the use of Salagen (pilocarpine hydrochloride tablets) has been approved as a treatment for dry mouth caused by damage to some secretory cells in the salivary glands due to radiation therapy in both Europe and the United States of America. [34] In our study, the concurrent use of Salagen with radiochemotherapy likely preserved salivary gland function by reducing cell apoptosis, contributing to the gradual recovery of salivary flow three months post-treatment. This aligns with Al-Zahrani's 2024 study [35] on pilocarpine, which showed enhanced salivary flow and reduced xerostomia during radiotherapy. However, our findings contrast with another study [36] that found no improvement in salivary flow one year after radiotherapy, possibly due to patients in that study receiving radiotherapy alone.

To interpret the findings for the low-power laser group, it is important to consider that while LLLT has the potential to stimulate the cellular respiratory chain, enhance the production of cyclic adenosine triphosphate (ATP), and activate various biochemical responses—such as anti-inflammatory effects, tissue repair, and increased blood supply [37]—the spectral absorption characteristics of cellular chromophores in oral mucosal tissues vary significantly. Specifically, the absorption coefficient of water, which constitutes approximately 75% of these tissues, is nearly five times higher at a wavelength of 830 nm compared to 685 nm. [38] This variation may influence treatment efficacy. Furthermore, the lack of standardized PBMT protocols for stimulating salivary gland secretion has led to inconsistent outcomes across studies. In this research, we adapted a PBMT protocol from a previous study [22] and modified it to align with the specifications of the laser device used at Damascus University's Oral Medicine Department. Consistent with the reference study, we observed a sustained decline in salivary flow following radiotherapy. Conversely, other research [39] has reported improved salivary flow post-

radiotherapy, with significant differences compared to control groups. These discrepancies can likely be attributed to differences in laser application protocols, such as the use of an 810 nm wavelength targeting all salivary glands, as well as radiation doses exceeding 20 Gray.

Conclusion

Our findings underscore that Salagen effectively prevents significant hyposalivation when administered concurrently with radiochemotherapy in patients with head and neck cancer. In contrast, the LLLT protocol employed in this study could not prevent the stimulated hyposalivation. Furthermore, Salagen has the superiority in mitigating severe hyposalivation associated with radiochemotherapy, compared to the LLLT protocol utilized in this research. Additional research with larger sample size and different low-level laser protocols is needed for a definitive conclusion.

Funding

This study was self-funded by the authors.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethical Committee of the Faculty of Dental Medicine, to the Declaration of Helsinki ethical principles for medical research and was approved by the ethics committee at Damascus University, number 3779 .

All participants provided informed consent prior to participation.

Competing Interests

The authors declare no conflicts of interest related to this study

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