Efficacy of Melatonin Oral Gel in Reducing Oral Mucositis in Patients with Head and Neck Cancer under Chemoradiation

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Abstract: *Objective*: Oral Mucositis is a significant burden for patients receiving radiation treatment for head and neck cancer. This study aimed to evaluate the efficacy of melatonin oral gel in reducing radiation induced oral mucositis.

Patients and methods: This is prospective, randomized clinical controlled study including locally advanced head and neck cancer patients receiving chemoradiation. The selected participants were recruited into two groups (40 individuals each). Group 1 (melatonin group) will receive 20 mg/ 10 ml /twice per day melatonin gel mouth wash, along with the conventional treatment. Group 2 (control group) will receive conventional treatment only. All participants were evaluated by oral mucositis scale and visual analog scale for pain. Reduced glutathione was quantitated using GSH Colorimetric Assay Kit at base line and on the last day of treatment.

Results: All patients in both treatment groups had low-grade mucositis (grade 1–2). After two weeks, 30% of the patients in the control group had developed severe mucositis (grade 3–4), meanwhile this grade was not reported in melatonin group. At the end of study, 80% of the cases had severe mucositis in the control group compared to the melatonin group (10%) with p value 0.001. At the end of each week, the mean values of pain score were significantly lower in melatonin arm compared to control arm. Also, the mean level of salivary GSH significantly increased in both groups(39.5 ± 2.7 and 29.2 ± 3.85) for the melatonin and control groups, respectively as compared to the baseline value and there were statistically significant differences in Favor to melatonin group (group I; P= 0.001).

Conclusion: Oral mucositis is a clinically critical consequence of chemoradiation. Melatonin significantly reduces pain and irradiation induced mucositits through oncostatic and cytoprotective mechanisms.

Keywords: Melatonin, Oral mucositis, Head and neck cancer, Chemoradiation.

INTRODUCTION

Head and neck cancer (HNC) is the seventh most frequently diagnosed cancer, approximately 660,000 new cases and 325,000 deaths are documented annually [1, 2]. The incidence of the disease is increasing; substantial geographic variations are potentially affected by key risk factors [3].

A multidisciplinary strategy is essential for locally advanced HNC management. Surgery followed by radiotherapy or concurrent chemoradiation and functional organ-preservation strategiessuch as concurrent chemoradiationare main components of management. Platinum-based chemotherapy is the core of concurrent therapy [4].

Radiation-induced oral mucositis (RIOM) is the most common, dose-associated adverse event for patients with HNC under chemoradiation [5, 6]. Dysphagia and pain that result from RIOM may lead to considerable loss of weight and worsening of quality of life. Interruption of radiotherapy due to RIOM can be occurred and negatively impact the effectiveness of the treatment. [7]

Treatment of Oral mucositis (OM) is restricted to symptomatic approaches; no curative or highly effective treatment has been developed [8].

OM is caused by oxidative damage that's mainly triggered by radiotherapy or chemotherapy. The upregulation of oxidative stress signals causes the emission of reactive oxygen species (ROS) with damage of DNA and progressing cell death. Inflammatory cytokines such as IL1b, TNF-a and IL-6 are activated by Increased ROS levels. The resulting inflammation leads to damage and pain of oral mucosa [9].

Melatonin is an ubiquitous methoxyindole (N-acetyl-5-methoxytryptamine) synthesized mainly in the pineal body. Although melatonin is widely known ashormone of darkness" because it promotes sleep, cytoprotection may be the original evolutionary function of melatonin [10, 11]. Melatonin acts as a powerful radical-free scavenger in the extra-pineal organs, which prevents damage to mitochondria [12]. Melatonin and its

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ISSN: 1929-2260 / E-ISSN: 1929-2279/25

metabolites are powerful antioxidants, reducing oxidative stress by different strategies, including direct scavenging of free radicals, neutralize highly reactive oxidants, enhance mitochondrial homeostasis and boost antioxidant enzymes while inhibiting pro-oxidant enzymes. Additionally, melatonin has an anti-inflammatory, immunomodulatory and antitumor effects [13, 14].

PATIENTS AND METHODS

Study Design

This is prospective, randomized, a single-blind, controlled study including locally advancedHNC patients receiving chemoradiotherapy.The study was carried out in Clinical Oncology department, Tanta University, Egypt (from January 2024 to June 2024). This trial was permitted by the Research Ethical Committee of Faculty of medicine, Tanta University (Approval code number: 36264PR562). Each participant submitted a well-informed written consent.

Sample Size

The sample size and power analysis were determined using the 2002 version of Epi-Info, a statistical software by the World Health Organization and the Centers for Disease Control and Prevention in Atlanta, Georgia. The criteria used for sample size calculation were as follows: 95% confidence interval and 86% study power. In the current study, the sample size was found at n=40 in each group.

PATIENT'S SELECTION

Inclusion and Exclusion Criteria

The current study recruited participants with age over 18; PS [0–2] by ECOG; newly diagnosedsquamous cell carcinoma of head and neck; stage III or IV-M0 according to American Joint Committee on Cancer (AJCC 8th edition) [15] prepared for concurrent chemoradiation (definitive or post-operative strategy). The exclusion criteria included patients previously treated with radiotherapy for HNC, distant metastases or palliative RT.

Study Groups and Treatment Strategy

The selected eighty patients were randomized (1:1) and divided into two groups (40 individuals each). Randomization was conducted using a computer software program to generate a series of codes and then placed in sealed envelopes: Group 1 (melatonin group): Subjects received 20 mg/ 10 ml /twice per day melatonin gel mouth wash, along with the conventional treatment. This selected dose is the pharmacological active dose accepted in several randomized and pilot trials to provide maximum antioxidant and anti-inflammatory efficacy. Group 2 (control group): participants received conventional treatment: Subjects received conventional treatment (Benzydamine rinse or/and Diphenhydramine-Lidocaine-Antacid mouthwash).

Pre-treatment Evaluation

All patients underwent a pretreatment evaluation that included careful medical history, medical anddental examination. A comprehensive head and neck examination was performed. All patients underwent a thin-cut contrasted CT neck, and chest CT. Before radiotherapy each patient underwent a detailed intraoral examination to identify and extract any sources of infection. The HNC multidisciplinary team convened to discuss the details of each case and recommend the most appropriate treatment strategies.

TREATMENT DETAILS

Radiotherapy

Intensity-modulated radiotherapy (IMRT) was applied using a 6 MV linear accelerator.Planned target volumes were restricted to international guidelines and depending on anatomic location within the larynx, hypopharynx, oral cavity, and nasopharynx for clinical target volume delineation [16]. A dose of 60 to 70 Gy was planned for the treatment.

Concurrent Chemotherapy

Concurrent systemic treatments were either cisplatin (40mg /m2) on the first day of radiotherapy then weekly through radiotherapy course or carboplatin AUC =2 (for patients can't tolerate cisplatin due to renal impairment or hearing problems. Platinum-based chemotherapy was allowed as neoadjuvant treatment (up to three cycles).

Preparation Melatonin Containing Gel Formulation

The gel formulation was prepared at faculty of pharmacy, Pharmaceutical Technology department, Tanta University, by dispersing carboxymethyl cellulose into a definite volume of distilled water at concentration of 1% w/v. Carboxymethyl cellulose concentration was selected to provide gel of low viscosity suitable for use as mouth wash. This mixture was subjected to

continuous stirring for 15 minutes at room temperature utilizing mechanical stirrer. Melatonin was dispersed in this polymer solution at concentration of 2 mg/ml and stirring process was continued till the drug dissolved. The gel formulation was freshly prepared for each patient and was kept in refrigerator at 2-4oC during the administration period.

METHODS OF ASSESSMENT

Clinical Assessment

All patients were clinically assessed by oral mucositis scale and visual analog scale for pain at baseline then weekly after the start of chemoradiation

The severity of oral mucositis was evaluated using the World Health Organization (WHO) grading system, which is based on patient symptoms (pain), functional limitations (difficulty eating), and clinical signs (ulcers, erythema). Grade I:soreness and erythema are present, Grade II: painful erythema and ulcerations thatinterfere with solid diet intake, Grade III: confluent ulceration that interferes with solid diet intake, making a liquid food necessary, and Grade IV: parenteral nutrition is required [17].

- A visual analogue scale (VAS) was used to measure the intensity of the pain:(VAS - 100 mm Horizontal line, with descriptive word no pain at the left side and on the right side very severe pain). Patients were asked to record the specific point on that line representing the daily level of pain severity as they feel and then weekly average were calculated. The score depends on calculation of the distance (in millimeters) from the left end of the line to the point marked by the patient [18].

Immunologic Assessment:

Reduced glutathione was quantitated using GSH Colorimetric Assay Kit (Catalog# ID E-BC-K030-M-48 Elabscience, Wuhan, China). Saliva samples were obtained from the patients, at base line and on the last day of therapy. Calculate the difference in between the measures at each time point which represented the change occur in response to the applied intervention.Saliva samples were obtained by spitting into a sterile Eppendorf tube. Samples were kept at − 80°C in a freezer until colorimetric Assay Reduced glutathione (GSH) in the sample reacts with dithionitrobenzoic acid (DTNB) to produce thio-nitrobenzoic acid and glutathione disulfide. The Nitromercaptobenzoic acid produced has a maximum absorption peak at 420 nm. The optical density was determined spectrophotometrically using a semi-automated clinical chemistry analyzer Erba chem7 (Erba Diagnostics Mannheim GmbH, India).

Statistical Analysis

The Statistical Package for Social Science computer program (SPSS) was used for organization and analysis of the collected data. The mean and SDs were calculated. For intragroup comparisons to baseline values, we used the paired t-test. An independent t-test was employed to assess the statistical differences between the groups.

RESULTS

A total of 80 patients were enrolled in the current study. Patient's characteristics were reported in (Table **1**). Forty patients for each group completed the whole study period without untoward events. The entire datawas well balanced between the two groups. Most of our patients were male (88.75%). Oral cavity was the most common tumor site in our study (38.75%). Sixty-two patients (77.5 %) received cisplatin, and eighteen patients (22.5%) receivedcarboplatin.

In both groups, the mean pain score values were increased compared with baseline in an incremental manner through the six successive week's evaluation periods. By the end of each week, the mean pain score values were significantly lower in melatonin Group compared to control group, Week 1: (1.3 ± 0.46 VS 2 ± 0.45), week 2: (1.5 ± 0.68 VS 2.9 ± 0.39), week 3: (3 ±0.64 vs. 4 ± 0.78) and Week 4-6: (3.7 ± 0.46 VS 5 ± 1.02) with P value of 0.001 (Table **2**)

Mucositis was classified as either low-grade (1-2) or high-grade (3-4) for better comprehensive conclusion. One week after the initiation of radiotherapy, all patients in the two arms had low-grade mucositis (grades 1–2). After two weeks, high-grade mucositis (grades 3–4) was observed in 30% of the control arm, while no patients in the melatonin group developed this severity. By the end of the third week, all patients (100%) in the melatonin group had maintained to have low-grade mucositis (Figure **1**) meanwhile the control grouphad a considerable shift toward high-grade mucositis (80% of patients reaching that severity (Figure **2**). The average severity of oral mucositis was assessed over the period of 4th to 6th weeks and documented, at the end of study, 80% of the participants in the control armdeveloped grades 3-4 mucositis compared to 10% in the melatonin group (10%) with p value 0.001 (Table **3**).

Table 1: Baselinepatient's Characteristics

Patients' characteristics	Melatonin group (No= 40)	Control group (No=40)	All(No= 80)	P value
Age				
Range Median	(40-71) 54.5	(39-72) 53	(39-72) 54	0.425
Gender				
Male Female	35 (87.5%) 5 (12.5%)	36 (90%) 4 (10%)	71 (88.75%) 9 (11.25%)	0.723
Tumor site				
Larynx Hypopharynx Oral cavity Nasopharynx	11 (27.5%) 8 (20%) 16 (40%) 5 (12.5%)	12 (30%) 8 (20%) 15 (37.5%) 5 (12.5%)	23 (28.75%) 16 (20%) 31 (38.75%) 10 (12.5%)	0.995
Stage				
III IVA IVB	10 (25%) 25 (62.5%) 5 (12.5%)	6 (15%) 27 (67.5%) 7 (17.5%)	16 (20%) 52 (65%) 12 (15%)	0.494
Concurrent systemic agent				
Cisplatin Carboplatin	32 (80%) 8 (20%)	30 (75%) 10 (25%)	62 (77.5%) 18 (22.5%)	0.592
Total planned radiation dose (Gy)				
66 Gy 60 Gy 70 Gy	4 (10%) 26(65%) 10(25%)	3 (7.5%) 26(65%) 11(27.5%)	7(8.75%) 52(65%) 21(26.25%)	0.925

Table 2: Pain Score Values in Both Groups

VAS		Melatonin group	Control group	t. test	p. value
Baseline	Range	0 – 0	0 – 0	-	-
	Mean ± SD	0 ± 0.00	0 ± 0.00		
Week one	Range	1 – 2	1 – 3	6.827	0.001*
	Mean ± SD	1.3 ± 0.46	2 ± 0.45		
Week two	Range	1 – 3	2 – 3	11.898	0.001*
	Mean ± SD	1.5 ± 0.68	2.9 ± 0.30		
Week three	Range	2 – 4	3 – 5	6.245	0.001*
	Mean ± SD	3 ± 0.64	4 ± 0.78		
Week four	Range	3 – 4	4 – 7	7.380	0.001*
	Mean ± SD	3.7 ± 0.46	5 ± 1.02		
Baseline & Week one		0.001*	0.001*		
Week one & Week two		0.405	0.001*		
Week two & Week three		0.001*	0.001*		
Week three tosix		0.001*	0.001*		

*Significant value (p< 0.05).

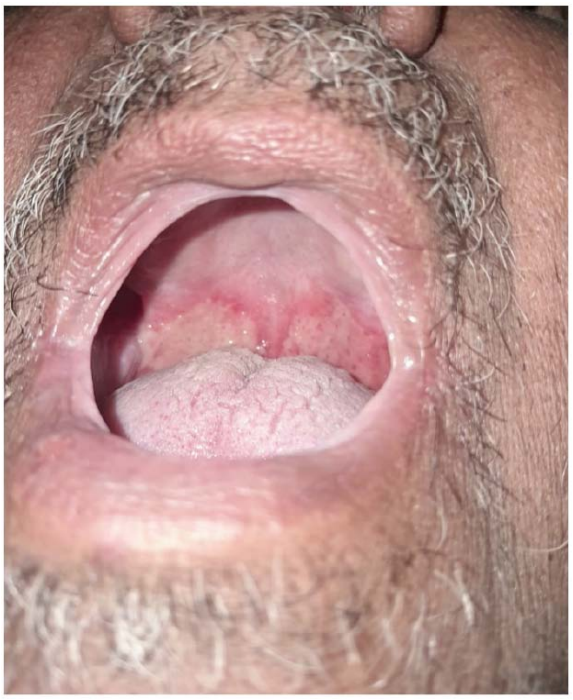

Figure 1: 61-year-old male patient with G2 radiation mucositis in the 3rd week of concurrent chemoradiation for nasopharyngeal carcinoma T2N3 (Melatonin Group).

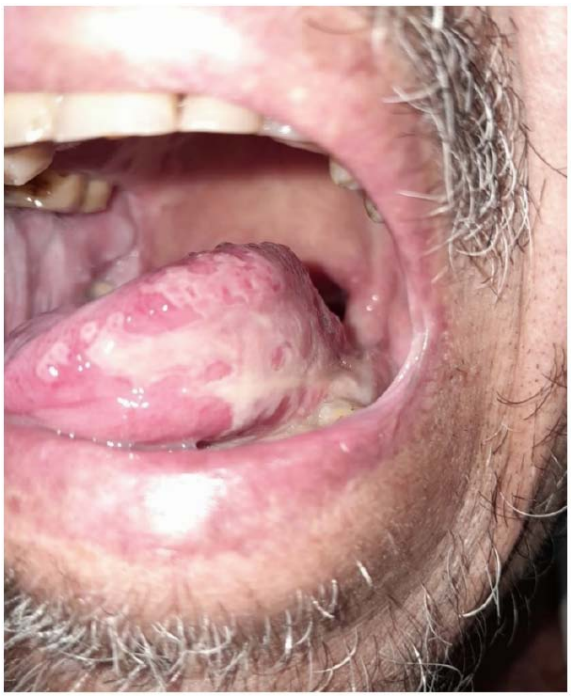

Figure 2: 56-year-old male patient with G3 mucositis in the end of 3rd week of concurrent chemoradiation for oral tongue cancer T3N0 (Control Group).

Table 3: Oral Mucositis in Both Groups

Oral Mucositis		Melatonin group		Control group		X2 test	p. value
		N	%	N	%		
Baseline	0	40	100	40	100	-	-
Week one	1 – 2	40	100	40	100	-	-
Week two	1 – 2	40	100	28	70	14.118	0.001*
	3 – 4	0	0	12	30		
Week three	1 – 2	40	100	8	20	53.333	0.001*
	3 – 4	0	0	32	80		
Week four-six	1 – 2	36	90	0	0	65.455	0.001*
	3 – 4	4	10	40	100		

*Significant value (p< 0.05).

Table 4: Change in GSH level in Both Group

GSH		Melatonin group	Control group	t. test	p. value
Baseline	Range	23 – 30	22 – 33	0.171	0.865
	Mean ± SD	26.3 ± 2.41	26.2 ± 2.83		
Last day	Range	35 – 44	25 – 39	13.901	0.001*
	Mean ± SD	39.5 ± 2.70	29.2 ± 3.85		
t. test		23.168	3.983		
p. value		0.001*	0.001*		

*Significant value (p< 0.05).

Table 5: Other Radiation Induced Toxicity

Toxicity	G 1-2		P	G3-4		P
	Melatonin group	Control group		Melatonin group	Control group	
Dry mouth	20 (50%)	28 (70%)	0.068	24 (60%)	31 (77.5)	0.091
Dysgeusia	16 (40%)	23 (57.5%)	0.117	6 (15%)	3 (7.5)	0.288
Dysphagia	8 (20%)	14 (35%)	0.133	5 (12.5%)	9 (22.5)	0.239
Decreased appetite	16 (40%)	13 (32.5%)	0.485	2 (5%)	0 (0)	0.150
Odynophagia	18 (45%)	22(55%)		10(25%)	13(32.5%)	0.458

At baseline, before radiotherapy treatment began, the salivary GSH levels were (26.3 ± 2.41 and, 26.2 ± 2.82) pg/ml for themelatonin group and control group respectively, with a statistically insignificant difference (P = 0.865). At the end of study period, there was a statistically significant increase in the mean level of salivary GSH for both groups (39.5 ± 2.7 and 29.2 ± 3.85) for the melatonin and control groups, respectively) as compared to the baseline value and the differences between the two arms was significant in favor to melatonin group (P= 0.001) (Table **4**).

Other radiation induced adverse events (dry mouth, dysgeusia, dysphagia and odynophagia) were assessed and reported in both groups. Grade 3-4 odynophagia was numerically lower in melatonin arm (25% of patients) compared to control arm (32.5%). The difference was not significant between both arms regarding the other adverse events (Table **5**).

DISCUSSION

Mucositis is a well-known side effect that frequently accompanies radiation therapy (RT) and chemoradiation (CRT) in patients undergoing treatment for HNC [19]. Mucositis is usually clinically evident during the second or third week of RT, associated with pain and ulceration that negatively affect oral intake and nutrition. Preventive strategies are needed to minimize radiotherapy induced mucositis [20].

The current study is a randomized clinical controlled trial, which evaluates the effectiveness of melatonin in minimizing incidence and duration of radiation-induced mucositis and pain. Also, to assess, immunologically, the reduced glutathione levels in saliva during the treatment period.

The rationale for using melatonin in this study is based on its positive aspects: it is endogenouslyproduced, plays a regulatory role in many physiological processes. Melatonin also, acts as an immunomodulatory agent,itreduces radiation toxicity by inhibiting pro-inflammatory cytokine production [21, 22].

In our study the pain score was significantly lower in participants who received melatonin, our results are also consistent with prior research thatdemonstrated potent analgesic actions of melatonin [23]. Although the exact mechanism of melatonin's analgesic effects has not yet been clarified, numerous explanations have been proposed.One of the most compelling mechanisms connects it to beta-endorphins and nociception [24].

Our results aligned with those of Elsabbagh *et al*., who reported significant reduction of the painful oral lesions by the end of 6th week of radiotherapy for participants who received melatonin, clarifying the possible analgesic effect of melatonin [25].

Many approaches had been investigated to reduce pain related to oral mucositis such as Doxepin rinse and Diphenhydramine-Lidocaine-Antacid Mouthwash. The doxepin rinse or Diphenhydramine-Lidocaine-Antacid Mouthwash significantly decreased pain linked with radiation mucositis (by 11.6 points and 11.7 points respectively versus 8.7 points in the placebo group), but associated with burning, unpleasant taste, and drowsiness [26]. In our study, the melatonin rinse was tolerable and comfortable for most patients. No direct comparison was done between melatonin and doxepin rinse or Diphenhydramine-Lidocaine-Antacid Mouthwash.

By the 3rd week of radiotherapy, 30% of patients who didn't receive melatonin had developed grade 3–4 mucositis, meanwhile none of the melatonin group developed grade3-4. At the end of study, the control group has shown a higher percent (80%) of severe mucositis compared to the melatonin group (10%) (p= 0.001), our results are matched with the study by Lozano *et al*., which showed a significantly lower incidence of severe mucositis (44% vs. 78%; P = 0.02)

and a reduced duration (0 vs. 22 days; P = 0.022) in the melatonin arm compared to the controlled arm [27]. These favorable results can be explained by the role of melatonin as an anti-inflammatory and as a cytoprotective agent. Melatonin acts as strong free radical scavenger of ROS. Additionally, melatonin interferes the inflammatory pathway triggered by radiotherapy induced oral mucosal damage and decrease the production of proinflammatory chemicals (IL1b, TNF-a and IL-6). Also, melatonin stimulates body's own antioxidative enzyme such as glutathione peroxidase.

The rate of other adverse events (dry mouth, dysgeusia, dysphagia and odynophagia) was reported in both groups. The reported difference was not significant, although odynophagia was numerically lower in melatonin arm 25% of patients compared to 30% in control arm in agreement with Lozano study and support the evidence of the analgesic effect of melatonin [27].

Our study is limited by the small number of participants and the absence of subgroup analysis. Specific subgroups including concurrent systemic therapy, definitive CRT versus postoperative CRT and tumor subsites should be involved in More comprehensive large phase III clinical studies to analyze the efficacy and safety of melatonin rinse as a preventive and therapeutic approach for radiation-induced mucositis and pain. In general, the overall results of the current study consistent with the published data suggesting the protective role of melatonin against cell damage caused by radiotherapy.

CONCLUSION

Oral mucositis is a major challenge for patients undergoing radiation therapy treatment for head and neck cancer. At the molecular level, chemoradiation-induced mucosal damage is related to emission of ROS. Melatonin is a potentially effective prophylactic and/or therapeutic strategy for oral mucositis by inhibition of this pathway.

AUTHOR CONTRIBUTIONS

Writing; Fatma Gharib and Asma M Elkady.Data collection: Fatma Gharib, Doaa A Yousef and Mona M Watany. The study has been read and accepted by all authors.

FUNDING

There was no external financial support for this study.

CONFLICTS OF INTEREST

None.

REFERENCES

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71(3): 209-249. https://doi.org/10.3322/caac.21660

[2] Johnson D E, Burtness B, Leemans C R, Lui V W Y, Bauman J E, Grandis J R. Head and neck squamous cell carcinoma. Nat Rev Dis Primers 2020; 6: 92. https://doi.org/10.1038/s41572-020-00224-3

[3] Thomas S J, Penfold C M, Waylen A, Ness A R. The changing aetiology of head and neck squamous cell cancer: A tale of three cancers? Clin Otolaryngol 2018; 43: 999-1003. https://doi.org/10.1111/coa.13144

[4] Sharma A, Kumar M, Bhasker S, Thakar A, Pramanik R, Biswas A. An open label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial). J Clin Oncol 2022; 40; 16S. https://doi.org/10.1200/JCO.2022.40.16_suppl.6004

[5] Liu S, Zhao Q, Zheng Z, Liu Z, Meng L, Dong L, et al. Status of treatment and prophylaxis for radiation-induced oral mucositis in patients with head and neck cancer. Front Oncol 2021; 11: 642575. https://doi.org/10.3389/fonc.2021.642575

[6] Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Front Oncol 2017; 7: 89. https://doi.org/10.3389/fonc.2017.00089

[7] González Ferreira JA, Jaén Olasolo J, Azinovic I, Jeremic B. Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: review of the literature. Rep Pract Oncol Radiother 2015; 20(5): 328-339. https://doi.org/10.1016/j.rpor.2015.05.010

[8] Davy C, Heathcote S. A systematic review of interventions to mitigate radiotherapy-induced oral mucositis in head and neck cancer patients. Support Care Cancer 2021; 29: 2187. https://doi.org/10.1007/s00520-020-05548-0

[9] Elad S, Cheng KKF, Lalla RV, arom N, Hong C, Logan RM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2020; 126: 4423. https://doi.org/10.1002/cncr.33100

[10] Cardinali DP, Hardeland R. Inflammaging, metabolic syndrome and melatonin: a call for treatment studies. Neuroendocrinology 2017; 104: 382-97. https://doi.org/10.1159/000446543

[11] Kopustinskiene DM, Bernatoniene J. Molecular Mechanisms of Melatonin-Mediated Cell Protection and Signaling in Health and Disease. Pharmaceutics 2021; 13(2): 129. https://doi.org/10.3390/pharmaceutics13020129

[12] Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res 2016; 61: 253-78. https://doi.org/10.1111/jpi.12360

[13] Farhood B, Goradel NH, Mortezaee K, Khanlarkhani N, Salehi E, Nashtaei MS, et al. Melatonin as an adjuvant in radiotherapy for radioprotection and radiosensitization. Clin Transl Oncol 2019; 21(3): 268-79. https://doi.org/10.1007/s12094-018-1934-0

[14] Çakir ZÜ, Demirel C, Kilciksiz SC, Gürgül S, Zincircioğlu SB, Erdal N. Melatonin can ameliorate radiation-induced oxidative stress and inflammation-related deterioration of bone quality in rat femur. Inflammation 2016; 39(3): 1134-40. https://doi.org/10.1007/s10753-016-0347-x

[15] Forastiere AA, Ismaila N, Wolf GT. Use of larynx-preservation strategies in the treatment of laryngeal cancer: American Society of Clinical Oncology Clinical Practice Guideline Update Summary. J Oncol Pract 2018; 14: 123-128. https://doi.org/10.1200/JOP.2017.027912

[16] Grégoire V, Evans M, Le QT, Bourhis J, Budach V, Chen A, et al. Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: Airo, caca, dahanca, eortc, georcc, gortec, hknpcsg, hncig, iag-kht, lprhht, ncic ctg, ncri, nrg oncology, phns, sbrt, somera, sro, sshno, trog consensus guidelines. Radiother Oncol 2018; 126: 3-24. https://doi.org/10.1016/j.radonc.2017.10.016

[17] Iovoli AJ, Turecki L, Qiu ML, Khan M, Smith K, Yu H et al. Severe Oral Mucositis After Intensity-Modulated Radiation Therapy for Head and Neck Cancer. JAMA Netw Open 2023; 6: e2337265. https://doi.org/10.1001/jamanetworkopen.2023.37265

[18] Huskisson EC, Jones J, Scott PJ. Application of Visual-Analogue Scales to the Measurement of Functional Capacity. Rheumatol Rehabil 1976; 15: 185-7. https://doi.org/10.1093/rheumatology/15.3.185

[19] Sunaga T, Nagatani A, Fujii N, Hashimoto T, Watanabe T, Sasaki T. The association between cumulative radiation dose and the incidence of severe oral mucositis in head and neck cancers during radiotherapy. Cancer Rep (Hoboken) 2021 Apr; 4(2): e1317. https://doi.org/10.1002/cnr2.1317

[20] Ariyawardana A, Cheng KKF, Kandwal A, Tilly V, Al-Azri AR, Galiti D, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer 2019; 27: 3985. https://doi.org/10.1007/s00520-019-04888-w

[21] Vriend J, Reiter RJ. Melatonin feedback on clock genes: A theory involving the proteasome. J Pineal Res 2015; 58: 1-11. https://doi.org/10.1111/jpi.12189

[22] Tuli HS, Kashyap D, Sharma AK, Sandhu SS. Molecular aspects of melatonin (MLT)-mediated therapeutic effects. Life Sci 2015; 135: 147-157. https://doi.org/10.1016/j.lfs.2015.06.004

[23] Tchekalarova J, Ivanova N, Nenchovska Z, Tzoneva R, Stoyanova T, Uzunova V, et al. Evaluation of neurobiological and antioxidant effects of novel melatonin analogs in mice. Saudi Pharm J 2020; 28(12): 1566-1579. https://doi.org/10.1016/j.jsps.2020.10.004

[24] Wang J, Gu J, Ma F, Wei Y, Wang P, Yang S, et al. Melatonin Induces Analgesic Effects through MT2 Receptor-Mediated Neuroimmune Modulation in the Mice Anterior Cingulate Cortex. Research (Wash D C) 2024; 7: 0493. https://doi.org/10.34133/research.0493

[25] Elsabagh HH, Moussa E, Mahmoud SA, Elsaka RO, Abdelrahman H. Efficacy of Melatonin in prevention of radiation-induced oral mucositis: A randomized clinical trial. Oral Dis 2020; 26(3): 566-572. https://doi.org/10.1111/odi.13265

[26] Sio TT, Le-Rademacher JG, Leenstra JL, Loprinzi CL, Rine G, Curtis A, et al. Effect of Doxepin Mouthwash or Diphenhydramine-Lidocaine-Antacid Mouthwash vs Placebo on Radiotherapy-Related Oral Mucositis Pain: The Alliance A221304 Randomized Clinical Trial. JAMA 2019; 321(15): 1481-1490. https://doi.org/10.1001/jama.2019.3504

[27] Lozano A, Marruecos J, Rubió J, Farré N, Gómez-Millán J, Morera R, et al. Randomized placebo-controlled phase II trial of high-dose melatonin mucoadhesive oral gel for the prevention and treatment of oral mucositis in patients with head and neck cancer undergoing radiation therapy concurrent with systemic treatment. Clin Transl Oncol 2021; 23(9): 1801-1810. https://doi.org/10.1007/s12094-021-02586-w

Received on 22-08-2025 Accepted on 19-09-2025 Published on 31-10-2025

https://doi.org/10.30683/1929-2279.2025.14.21