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RESEARCH

Effects of L-glutamine and hyaluronic acid associated with photobiomodulation on oral mucositis: a randomized clinical trial

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Abstract

Objective To investigate whether the application of L-glutamine (L-G) and hyaluronic acid (HA) associated with photobiomodulation (PBM) and the Preventive Oral Care Protocol (POCP) would present similar efficacy as the exclusive use of PBM, associated with POCP, in the prevention and control of severe oral mucositis (OM).

Study design Patients with head and neck cancer undergoing radiochemotherapy (RCT) were randomized into two groups: group A, patients that received PBM + POCP ($n = 24$), and group B, patients that received PBM + POCP + L-G + HA ($n = 24$). OM was assessed using the National Cancer Institute (NCI) and World Health Organization (WHO) scales. The impact of oral health on patients' quality of life and perception of OM symptoms was evaluated. Assessments were made at the 1st, 7th, 14th, 21st, and 30th radiotherapy (RT) sessions.

Results When the severity of OM was assessed according to the WHO scale in the 30th RT, group B showed lower rates of severe OM than group A. There were no differences when using the NCI scale. The impact of oral health on quality of life and the symptoms reported by patients were lower in group B at all times evaluated.

Conclusion The combination of PBM + POCP + L-G + HA resulted in a significantly lower severity of OM than PBM + POCP alone, according to the WHO scale at the 30th RT.

Trial registration Brazilian Clinical Trials Registry—REBEC no. RBR-6ybmgcv. Registration March 27, 2022.

Keywords Oral mucositis · Glutamine · Hyaluronic acid · Photobiomodulation therapy · Radiotherapy · Head and neck cancer

Introduction

Oral mucositis (OM) is a common adverse effect of head and neck cancer treatment due to radiotherapy (RT) or radiochemotherapy (RCT) [1]. OM impairs the masticatory function, quality of life, systemic health, tolerance, and adherence to the treatment. Moreover, severe OM may also be associated with increased mortality rates of cancer patients [2].

Photobiomodulation therapy (PBM) is an important therapeutic modality, considered a standard therapy, for controlling OM and reducing its symptoms [3, 4]. In 2020, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) published guidelines on the effectiveness of complementary therapies for preventing and controlling RCT-induced OM [2]. In addition to PBM, some natural agents, nutritional supplements, and vitamins were suggested, such as the oral use of L-Glutamine (L-G) which may present effectiveness in the treatment of OM [5–9].

In addition to L-G, hyaluronic acid (HA), or sodium hyaluronate, was cited as a natural agent that may be effective in treating and controlling OM. However, few studies have evaluated the effect of HA on the prevention and control of RCT-induced OM [10–12], and there is still lacking sound evidence of its effectiveness [6]. Buchsel [13] suggested that a bioadherent gel containing HA can act in the healing and analgesia of OM by creating a physical barrier over the

Clinical relevance The use of PBM, associated with L-G and HA, may present a supportive therapeutic strategy for patients with oral mucositis receiving treatment for head and neck cancer.

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lesion. Colella et al. [14] observed an acceleration of wound healing and pain reduction in patients with OM when using a spray compound containing a pool of collagen precursor synthetic amino acids combined with sodium hyaluronate. Furthermore, Cirillo et al. [15] suggested that HA promotes less senescence in fibroblasts and keratinocytes, probably due to its action of sequestration of reactive oxygen species.

Although OM is a frequent side effect in patients undergoing cancer treatment, there is still no standardized protocol recommended for these patients [16]. Currently, PBM is an essential therapy for OM control; however, this therapy does not eradicate the occurrence of severe cases or the possibility of interrupting RT [17, 18]. Therefore, actions that associate different therapies, with evidence of effectiveness, should be investigated. Studies that used topical medication exclusively or in association with PBM demonstrated promising results in OM management [19–21]; however, there is no investigation on the association of L-G and HA in the RT-induced OM management or their effect when associated with PBM.

Therefore, this study investigated the effects of L-G and AH in association with a preventive oral care protocol (POCP) and PBM on the prevention and treatment of severe OM and compared the results with the use of PBM and POCP exclusively in patients with head and neck cancer.

Material and methods

Study design and sample

This randomized controlled clinical trial investigated the effects of the association of PBM, L-G, HA, and POCP, compared with PBM and POCP. The study included patients diagnosed with head and neck cancer who underwent RT or RCT. All patients were treated in the Araújo Jorge Cancer Hospital of the Associação de Combate ao Câncer em Goiás (HCAJ-ACCG) from August 2021 to June 2023. The study protocol was previously approved by the local ethics committee (CAAE 48320921.6.0000.0031) and was prospectively registered in the Brazilian Clinical Trials Registry on March 27, 2022 (RBR- 6ybmgcv). All participants agreed to participate in the study and signed an informed consent form. This report followed the CONSORT guidelines [22] for clinical trials.

The number of participants included was based on previous studies that used natural agents or PBM to treat OM [7, 9, 11, 16, 18, 20], which typically included an average of approximately 25 patients per group.

Inclusion and exclusion criteria

It was included patients over 18 years of age, with no sex or ethnicity/skin color/race restrictions, with cancer in the oral cavity, oropharynx, nasopharynx, or hypopharynx, undergoing RT or RCT with a minimum total dose of 60 Gy, 2 Gy per day, with performance status according to the Eastern Cooperative Oncology Group (PS-ECOG) scores 0, 1, or 2 [23].

Exclusion criteria considered patients with tumors in the salivary glands, Sjögren's syndrome, infectious diseases, under palliative RT, with a history of previous oncological treatment in the head and neck region, and individuals diagnosed with lymphoma, melanoma, or skin cancer.

Allocation, randomization and blinding

Participants were randomly allocated into two groups: A, combined POCP and PBM; and B, combined POCP, PBM, L-G, and HA. An online randomized number generator (www.randomizer.org) created the participant allocation sequence. Block randomization was performed with a 1:1 allocation ratio. Thirteen blocks were generated, with four participants per block. The sequence was generated by an independent collaborator who did not participate in the treatment outcome assessments.

Following the previously generated sequence, the study groups were identified by the letters A and B and placed in opaque envelopes numbered in ascending order from 1 to 52. The envelope with the corresponding group was opened only in the first RT session.

The researcher responsible for outcome assessment was blinded to the patient allocation group and had no contact with the participants. Due to the nature of the therapies adopted, patients could not be blinded. The OM status was evaluated using intraoral photographs. The researcher responsible for statistical analysis was also blinded to the allocation group.

Interventions

Group A: POCP + PBM

Participants in this group underwent PBM concomitant with POCP from the first RT session (baseline) until the end of the RT treatment. A diode laser (GaAlAs and InGaAlP; MMOptics, São Paulo, Brazil) was used, with a wavelength of 660 ± 10 nm, 0.1 watts, 33.3 J/cm^2, 3.33 W/cm^2, a spot area of 0.03 cm^2, 1 J per point, 10 s each point, with photon energy of 1.9 eV, photon fluence of 63.27 p.j/cm^2, and photonic energy of 14.06 E.

The anatomical sites irradiated were the right and left buccal mucosa (10 points on each side), upper (4 points) and lower (4 points) labial mucosa, hard palate (3 points),

soft palate (3 points), lateral aspects of the tongue (10 points on each side), dorsum of the tongue (3 points close to the apex), floor of the mouth (2 points), and lip commissure (1 point on each side) [17–20]. PBM sessions were conducted 5 consecutive days a week, from the first until the last RT session [17–20]. The laser was not irradiated at less than 1 cm when malignant lesions were present or close to surgical or tumor sites.

Participants in this group also underwent the POCP of the Hospital, which consists of maintaining good oral hygiene, drinking at least 1.5 L of water per day, using 0.05% sodium fluoride mouthwash (three times a day for dentate patients) and 0.12% chlorhexidine digluconate (two times a day), elimination of foci of infection, and basic restorative and periodontal dental treatment when necessary [17].

Group B: POCP + PBM + L-G + HA

Participants in group B attended all consultation sessions and received PBM associated with POCP, in addition to L-G and HA. L-G was available in two pharmaceutical forms: an oral solution (Oralcare® Rinse, Wecare, São Paulo, Brazil, registry number at the Brazilian Regulatory Agency (ANVISA): 25351.235165/2019–60) and a gel form (Oralcare® Gel, registry number (ANVISA): 25351.078094/2019–91). The HA was available only as a gel for oral use (OralCare® Gel).

The water-based mouthwash is composed of sorbitol, glycerin, hydroxyethylcellulose, L-G, xylitol, sodium benzoate, potassium sorbate, PEG- 40 hydrogenated castor oil, sodium fluoride (1356.75 ppm of fluorine), and flavoring. Patients were instructed to use 10 mL, in the form of a mouthwash, for 30 s, three times a day, after oral hygiene, during the entire RT. The gel is composed of water, glycerin, hydroxyethylcellulose, sodium benzoate, potassium sorbate, L-G, and hydrolyzed HA. The gel, containing L-G and HA, was available in sachets and was advised to be applied to the entire oral mucosa, which could be swallowed, twice a day throughout the RT.

At the first RT session, participants were provided with 15 sachets and a 250-mL bottle of mouthwash. They were instructed to inform the research team if additional medication was needed for subsequent days. Medication distribution was tracked using a designated form, where the dates and quantities of the delivered medication were recorded, and participants signed to confirm receipt. Participants were advised to store the medication in a dry, well-ventilated place protected from sunlight. They were also instructed to discontinue use and notify the research team if any irritation or side effects occurred. Additionally, they were told to avoid using the mouthwash or gel for at least one hour before PBM sessions.

For ethical reasons, in both groups, PBM was used to enhance the healing process in patients who interrupted RT due to OM symptoms. In these cases, patients were not withdrawn from the study, and daily PBM sessions were offered until RT was resumed. Additional PBM sessions were also offered to patients who completed RT and developed OM, to accelerate healing.

Outcomes

The primary outcome of this study was the incidence of severe OM. In addition, it was evaluated the impact of oral health on patients' quality of life and perception of OM symptoms, adherence to the interventions, and RT interruption due to OM. Clinical and sociodemographic variables, such as tumor type, location, staging, type of treatment, sex, age, skin color, and ethnicity, were retrieved from the medical records.

OM assessment

OM was assessed at the first consultation (immediately before RT) and at the 7th, 14 th, 21 st, and 30 th RT sessions. For each of the periods described, standardized photographs were obtained from the upper and lower labial mucosa, right and left buccal mucosa, hard palate, soft palate, lateral border of the tongue, and floor of the mouth [18, 19].

The ratings of the OM level were carried out by a researcher who was blind to the allocation group and trained and experienced in oral medicine. For the researcher's calibration, the images of ten patients who were not part of the sample of this study were classified. After 90 days, a new classification was carried out, and the Kappa agreement index was 0.92, $p < 0.01$.

To grade the severity of OM, the WHO classification [24] and version 5.0 of the Common Toxicity Criteria of the National Cancer Institute [25] were used. Scores 3 and 4 on the WHO scale and 3, 4, or 5 on the NCI scale were considered severe OM.

Impact of oral health on quality of life

The Brazilian version of the OHIP- 14 (Oral Health Impact Profile) questionnaire [26] was applied to assess the impact of oral health on the participants' quality of life. The sum of the answers obtained was considered as the OHIP- 14 score.

The translated version of the PROMS scale was used to assess the patient's perception of OM symptoms [17, 19, 27]. The participant was asked to indicate the score for each item on a visual analogue scale. The sum of the items was used as the final score of the PROMS scale.

Before the session, the questionnaires were applied at the first consultation and 7th, 14 th, 21 st, and 30 th RT, by the researcher responsible for PBM therapy.

Treatment adherence assessment

Regarding adherence to the established protocols (group A or group B), participants were analyzed using the MMAS- 8 questionnaire [28] in the same periods previously described. The score obtained was classified as low adherence (< 6), moderate adherence (6–7), or high adherence (8).

Statistical analysis of data

The Kolmogorov–Smirnov test was used to test the normality of data. The Pearson chi-square test was used to associate categorical variables, and the Mann–Whitney test was used to compare numerical variables. The weighted Kappa test was performed to evaluate the intra-examiner agreement of OM classifications. Patients who missed more than five PBM sessions, died, or withdrew during treatment were excluded from the analysis. The IBM-SPSS version 21.0 program (IBM, SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The significance level considered was 5%.

Results

One hundred forty-seven patients were considered eligible for the study, 52 were recruited, and 48 were analyzed and randomized, with 24 in each group (Fig. 1). Most participants were male ($n = 34$; 70.8%), with a mean age of 57.42 years, smokers ($n = 31$; 64.6%) and alcoholics ($n = 23$; 47.9%). The main anatomical site affected was the oropharynx ($n = 24$; 50%), and RCT was prescribed for most participants ($n = 31$; 64.6%). It was observed that dysphagia was an initial symptom more commonly reported in

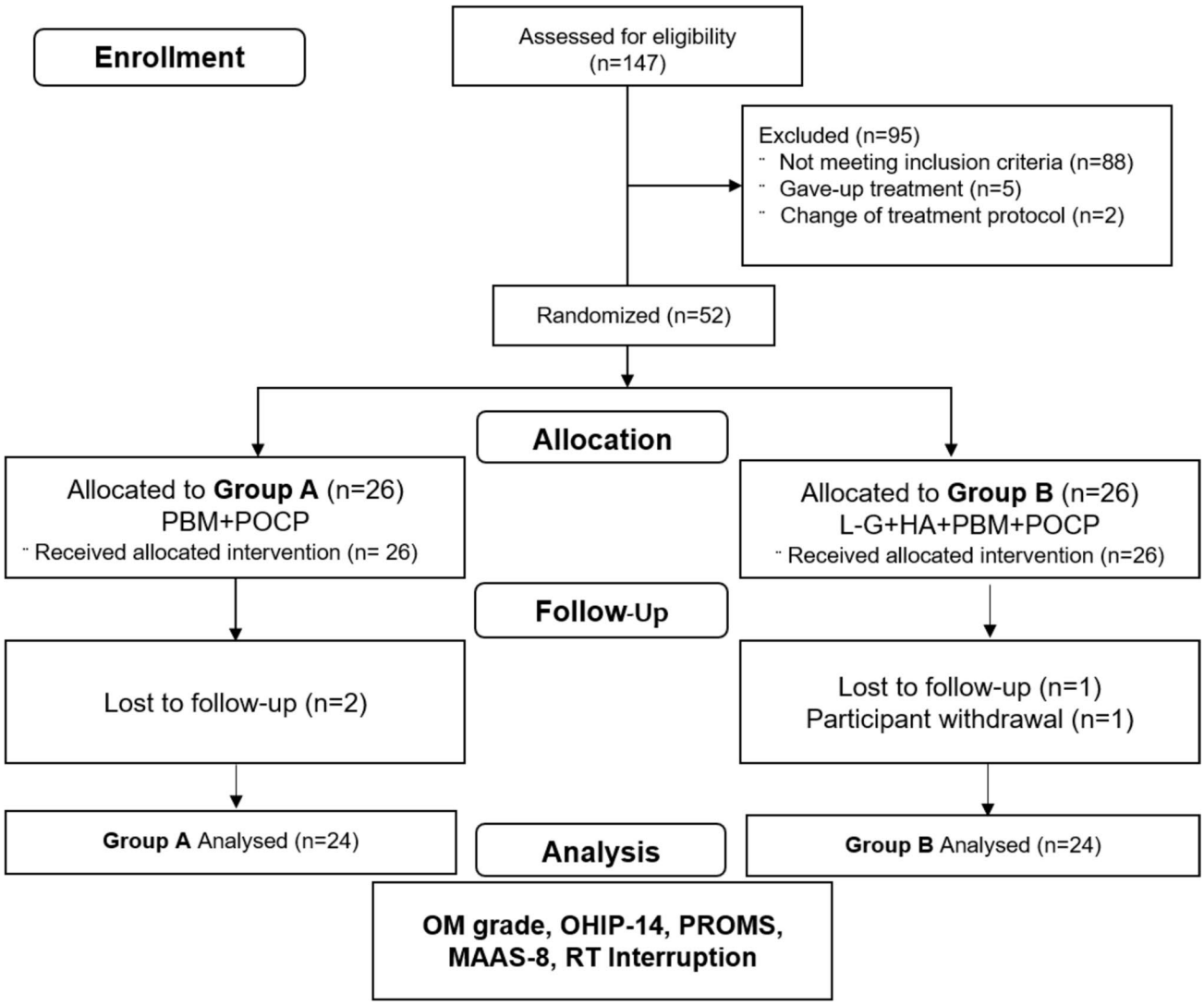

Fig. 1 Flowchart of the study

patients of group B ($n = 21$; 87.5%) than in group A ($n = 12$; 50%). The baseline clinicopathological features of the participants are summarized in Table 1.

Regardless of allocation group, none of the participants experienced or reported major side effects. Some reports to the main researcher described that the patient in group B felt nausea while using L-G or HA; however, other participants reported relief when using the mouthwash and/or gel.

Oral mucositis

All participants presented signs and symptoms of OM from the 7 th RT. However, the mean OM score remained below 3 in all assessments, evaluated using WHO or NCI scales. Considering the WHO scale, OM scores were lower in group B in the 30 th RT compared to group A. For the NCI scale, lower degrees of OM were observed in the 7 th RT in group A compared to group B (Table 2).

When OM was dichotomized into severe and non-severe, the results demonstrate that in the 30 th RT, the incidence of severe OM, assessed by the WHO scale, was lower in group B (2/8.3%) when compared to group A (12/50%) (Fig. 2a). No statistically significant differences were found for the assessment of dichotomous OM when using the NCI scale (Fig. 2b).

Impact of oral health on quality of life

The OHIP- 14 results demonstrated that oncological treatment worsens patients' quality of life, regardless of the allocation group. However, the impact of oral health on quality of life was lower in group B, which was statistically significant in all periods evaluated except baseline. The PROMS evaluation demonstrated similar results (Table 3).

The assessment of the OHIP- 14 domains demonstrated that group B presented lower scores in the domains relating to psychological disability (domain 5) and disability (domain 7) at baseline. During RT, this group presented lower scores in all domains assessed (Fig. 3).

Adherence to treatment

Participants showed moderate or high adherence to the interventions. However, group B had more patients with high adherence to treatment, especially at the end of cancer treatment. In the 21 st RT, 13 (54.2%) participants in group B showed high adherence, while in group A, this number was 5 (20.8%) ($p = 0.036$; chi-square). In the 30 th RT, in group B, the number of participants with high POCP adherence increased to 15 (62.5%), while it remained stable in group A (5/20.8%) ($p = 0.011$; chi-square test).

RT interruption due to OM

There was no statistical difference between the groups when comparing the number of patients that interrupted RT due to OM symptoms. This was also observed in the length of interruption. It was noted that of the 48 participants evaluated, 11 participants (22.9%) interrupted RT due to OM symptoms, 6 (25%) participants in group A, and 5 (20.8%) in group B ($p = 0.730$; chi-square test). The interruption usually occurred around the 20 th RT session. The mean length of RT interruption was 8 days in group A, while in group B, it was 9 days ($p = 0.502$; Mann–Whitney test). There was no statistically significant association between RT interruption due to OM symptoms and adherence to treatment. During the days of treatment interruption, all patients received additional PBM sessions to control symptoms. Table 4 presents data on RT interruption.

Discussion

OM is a complex inflammatory condition in all patients undergoing RT in the head and neck region. Therefore, this trial aimed to investigate whether the combination of PBM and products based on L–H and HA could positively impact severe cases of this condition. The results indicate that this combination effectively manages severe OM and correlates with a reduced impact of oral health on patients' quality of life.

PBM is well-established as a treatment modality for OM [3, 4] and one of the most used therapies [30]. This study relies on the well-established approach of PBM and basic oral care in managing OM in patients treated for RT or RCT for head and neck cancer [3, 4, 31]; however, we expand this approach by incorporating topical agents, aiming to evaluate whether this combination can enhance the clinical outcome since severe cases of OM can still occur and compromise cancer treatment. The association of PBM with natural products may be promising, as recently demonstrated by Martins et al. [19], in which the association between PBM and a curcumin-based product (FITOPROT) showed potential in reducing the number of severe cases of MO. Thus, looking for novel anti-inflammatory agents that are effective in controlling and treating OM, L-G and HA associated with PBM and POCP were tested, and the results showed a significant reduction in the number of severe cases when the association was used. This effectiveness may be related to the potential of L-G [32] and HA [16, 33] in ulcer healing, added to the well-established clinical effects of the PBM [3, 4].

L-G is a precursor of a free primary amino acid necessary for protein synthesis, involved in gastrointestinal mucosa cell replication [32]. Meanwhile, HA may act as a physical barrier to protect and hydrate ulcerated surfaces [34] and may

Table 1 Baseline clinical-demographic and pathological data of the patients

Variable	Total *n* (%)	Group A *n* (%)	Group B *n* (%)	*p*-value*
Age (mean ± s.d.)	57.42 ± 11.30	57.96 ± 10.67	56.88 ± 12.10	0.741
Sex				
Female	14 (29.2)	6 (25)	8 (33.3)	0.525
Male	34 (70.8)	18 (75)	16 (66.7)	
Tabagism				
Yes	31 (64.6)	15 (62.5)	16 (66.7)	0.940
No	11 (22.9)	6 (25)	5 (20.8)	
Former	6 (12.5)	3 (12.5)	3 (12.5)	
Alcoholic				
Yes	23 (47.9)	12 (50.0)	11 (45.8)	0.585
No	8 (16.7)	5 (20.8)	3 (12.5)	
Former	17 (35.4)	7 (29.2)	10 (41.7)	
Site				
Oral mucosa	3 (6.3)	2 (8.3)	1 (4.2)	0.635
Tongue	19(39.6)	9 (37.5)	10(41.7)	
Floor of mouth	1 (2.1)	1 (4.2)	0	
Oropharynx	24 (50)	11 (45.8)	13 (54.2)	
Hypopharynx	1 (2.1)	1 (4.2)	0	
Local pain				
Yes	28 (58.3)	14 (58.3)	14 (58.3)	1.000
No	20 (41.7)	10 (41.7)	10 (41.7)	
Otalgia				
Yes	17 (35.4)	8 (33.3)	9 (37.5)	0.763
No	31 (64.6)	16 (66.7)	15 (62.5)	
Dyspnea				
Yes	3 (4.2)	1 (4.2)	1 (4.2)	1.000
No	46 (95.8)	23 (95.8)	23 (95.8)	
Dysphagia				
Yes	33 (68.8)	12 (50)	21 (87.5)	0.052
No	15 (31.3)	12 (50)	3 (12.5)	
Odynophagia				
Yes	27 (56.3)	12 (50)	15 (62.5)	0.383
No	21 (43.8)	12 (50)	9 (37.5)	
Lymphadenopathy				
Yes	28 (58.3)	16 (66.7)	12 (50)	0.242
No	20 (41.7)	8 (33.3)	12 (50)	
Oral Bleeding				
Yes	2 (4.2)	0	2 (8.3)	0.149
No	46 (95.8)	24 (100)	22 (91.7)	
Stage T				
T1	0	0	0	0.472
T2	16 (33.3)	9 (37.5)	7 (29.2)	
T3	16 (33.3)	6 (25)	10 (41.7)	
T4	16 (33.3)	9 (37.5)	7 (29.2)	
Nodal metastasis (N)				
N0	21 (43.8)	7 (29.2)	14 (58.3)	0.186
N1	14 (29.2)	9 (37.5)	5 (20.8)	
N2	12 (25)	7 (29.2)	5 (20.8)	
N3	1 (2.1)	1 (4.2)	0	

Table 1 (continued)

Variable	Total *n* (%)	Group A *n* (%)	Group B *n* (%)	*p*-value*
Distant Metastasis (M)				
M0	38 (79.2)	19 (79.2)	19 (79.2)	0.287
M1	2 (4.2)	2 (8.3)	0	
MX	8 (16.7)	3 (12.5)	5 (20.8)	
Overall cancer staging**				
II	8 (16.7)	3 (12.5)	5 (20.8)	0.434
III	16 (33.3)	7 (29.2)	9 (37.5)	
IVa	21 (43.8)	11 (45.8)	10 (41.7)	
IVb	1 (2.1)	1 (4.2)	0	
IVc	2 (4.2)	2 (8.3)	0	
Histological grade (WHO)				
I	25 (52.1)	15 (62.5)	10 (41.7)	0.162
II	22 (45.8)	8 (33.3)	14 (58.3)	
III	1 (2.1)	1 (4.2)	0	
Surgery				
Yes	18 (37.5)	9 (37.5)	10 (41.7)	0.551
No	30 (62.5)	15 (62.5)	14 (58.3)	
Neck dissection				
Yes	14 (29.2)	7 (29.2)	7 (29.2)	1.000
No	34 (70.8)	17 (70.8)	17 (70.8)	
Treatment				
RCT	31 (64.6)	15 (62.5)	14 (58.3)	0.268
Surgery + RT	2 (4.2)	0	2 (8.3)	
Surgery + RCT	15 (31.3)	9 (37.5)	8 (33.4)	
Chemotherapy				
Yes	45 (93.8)	24 (100)	21 (87.5)	0.074
No	3 (6.2)	0	3 (12.5)	
Chemotherapy cycle				
Weekly	29 (60.4)	15 (62.5)	14 (58.3)	0.194
Every 21 days	16 (33.3)	9 (37.5)	7 (29.2)	
Not performed	3 (6.2)	0	3 (12.5)	
RT type				
3D	7 (14.6)	3 (12.5)	4 (16.7)	0.683
IMRT	41 (85.4)	21 (87.5)	20 (83.3)	

Abbreviations: *IMRT* intensity-modulated radiation therapy, *RCT* radiochemotherapy, *RT* radiotherapy, *WHO* World Health Organization

*Mann–Whitney test for age and chi-square test for the other variables for comparison between groups

**According to the American Joint Committee on Cancer. Lip and Oral Cavity, 2017 [29]

prevent mucosal injuries through the inactivation of reactive oxygen species produced during the RCT [15]. In the oral cavity, endogenous HA supports the structural integrity and homeostasis of tissues that regulate osmotic pressure and tissue lubrication [33] acting as a protective barrier over the ulcerated oral mucosa. HA can repair tissues and promote cell proliferation by regulating inflammatory responses, promoting re-epithelialization, improving the healing process, and reducing the size of damaged areas of the oral mucosa [16]. In vitro studies suggest that HA may have a pro-repair effect by inhibiting NF-kB, controlling the inflammatory process, promoting earlier angiogenesis, and assisting in collagen repair [35]. Furthermore, it can prevent apoptosis, inhibit oxidative stress, and suppress inflammatory cytokines in human and murine model mucosal cells [36].

Clinical trial results demonstrate L-G effectiveness in reducing both the symptoms and the severity of OM [37–39]. There is evidence, from systematic reviews, that suggests that L-G can control and treat RT-induced OM in patients with head and neck cancer [6–9, 40] and may also

Table 2 Oral mucositis in the periods evaluated

	OM score	WHO, *n* (%)					NCI, *n* (%)				
		Initial	7 th RT	14 th RT	21 st RT	30 th RT	0 RT	7 th RT	14 th RT	21 st RT	30 th RT
Group A ($n = 24$)	**0**	24 (100)	9 (37.5)	0	0	0	24 (100)	0	0	0	0
	1	0	7 (29.2)	3 (12.5)	2 (8.3)	1 (4.2)	0	11 (45.8)	7 (29.2)	4 (16.7)	2 (8.3)
	2	0	8 (33.3)	20 (83.3)	17 (70.8)	11 (45.8)	0	1 (4.2)	1 (4.2)	2 (8.3)	2 (8.3)
	3	0	0	1 (4.2)	3 (12.5)	10 (41.7)	0	12 (50)	16 (66.7)	18 (75)	20 (83.3)
	4	0	0	0	2 (8.3)	2 (8.3)	0	0	0	0	0
	Mean (s.d.)	0	0.96 ± 0.86	1.92 ± 0.41	2.21 ± 0.72	2.54 ± 0.72	0	2.04 ± 1.00	2.38 ± 0.92	2.58 ± 0.78	2.75 ± 0.61
Group B ($n = 24$)	**0**	24 (100)	14 (58.3)	0	0	0	24 (100)	1 (4.2)	0	0	0
	1	0	5 (20.8)	5 (20.8)	3 (12.5)	3 (12.5)	0	17 (70.8)	7 (29.2)	3 (12.5)	0
	2	0	5 (20.8)	18 (75)	19 (79.2)	19 (79.2)	0	1 (4.2)	2 (8.3)	3 (12.5)	3 (12.5)
	3	0	0	0	0	2 (8.3)	0	5 (20.7)	15 (62.5)	18 (75)	21 (87.5)
	4	0	0	1 (4.2)	2 (8.3)	0	0	0	0	0	0
	Mean (s.d.)	0	0.63 ± 0.82	1.88 ± 0.61	2.04 ± 0.69	1.96 ± 0.46	0	1.42 ± 0.88	2.33 ± 0.92	2.63 ± 0.71	2.88 ± 0.34
	p value*	-	0.163	0.511	0.283	0.002	-	0.028	0.833	0.842	0.329

*Mann–Whitney test for comparison between groups in the evaluated time

Abbreviations: *NCI* National Cancer Institute, *WHO* World Health Organization

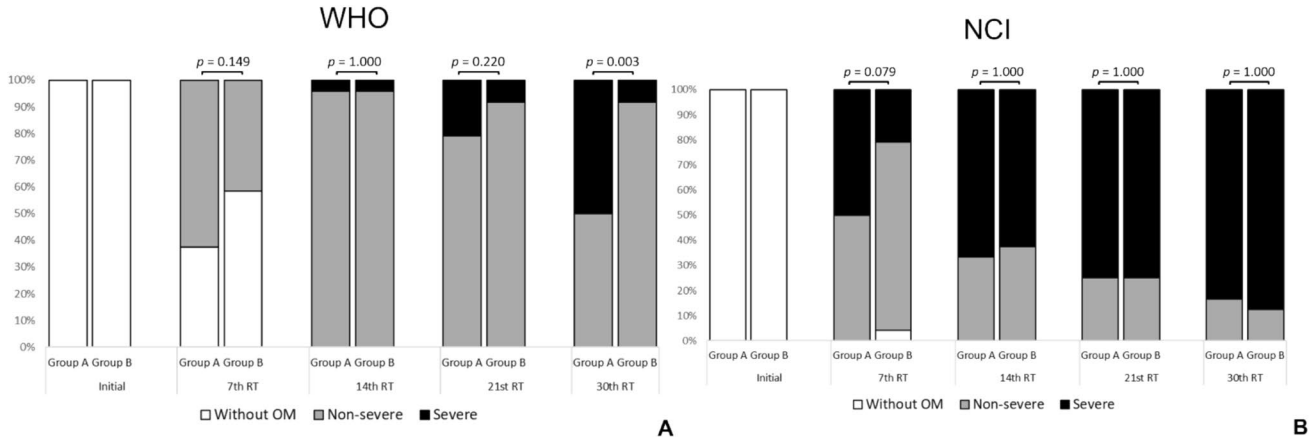

Fig. 2 Dichotomized oral mucositis on the periods evaluated. In (**A**) and (**B**) severe and non-severe oral mucositis according to the WHO and NCI scales respectively. *p* values referring to the Chi-square test

Table 3 OHIP- 14 and PROMS scores in the different periods evaluated. Results expressed as median (minimum and maximum)

Questionnaire	RT session	Group A ($n = 24$)	Group B ($n = 24$)	*p* value*
OHIP- 14	Baseline	11.69 (1.40–16.03)	8.30 (1.94–17.90)	0.063
	7 th RT	12.32 (2.89–20.49)	8.51 (4.00–18.20)	0.008
	14 th RT	15.07 (7.55–20.49)	11.46 (4.45–16.07)	< 0.0001
	21 st RT	17.40 (8.78–26.29)	12.86 (8.20–16.43)	< 0.0001
	30 th RT	20.31 (8.87–26.70)	13.70 (5.04–20.49)	0.001
PROMS	Baseline	15 (0–38)	10 (0–43.00)	0.176
	7 th RT	25.50 (7.00–48.00)	10 (1.00–51.00)	0.003
	14 th RT	41.5 (14.00–71.00)	25.50 (8.00–63.00)	0.001
	21 st RT	56.5 (27.00–85.00)	33 (12.00–69.00)	< 0.0001
	30 th RT	65.5 (31.00–95.00)	40 (22.00–68.00)	< 0.0001

*Mann–Whitney test for comparison between groups in the same radiotherapy session

Abbreviations: *OHIP* Oral Health Impact Profile, *PROMS* Patient-Related Oral Mucositis Symptoms; *RT* radiotherapy

reduce symptoms related to this side effect [41]. Meanwhile, HA has been studied in the treatment of OM mainly in the form of a gel associated with polyvinylpyrrolidone (Gelclair) [42] or as a spray associated with amino acids (Mucosamin) [15]. Gelclair may present limited effectiveness in controlling symptoms related to RT-induced OM in head and neck cancer patients [10, 11]. Meanwhile, Nasrollahi et al. [12] suggest that Mucosamin effectively prevents severe OM in patients with oral cavity cancer treated with RT. Additionally, Agha-Hosseini et al. [16] compared the use of a mouthwash containing HA, vitamin E, and triamcinolone with one containing only triamcinolone in patients with RT-induced OM and found that the rate of severe OM in participants who were treated with the medication containing HA was lower.

Interestingly, lower rates of severe OM in patients who used L-G and AH were demonstrated when using the WHO scale, but not for the NCI scale. It is important to highlight that these scales are similar, reliable, and reproducible and have been recommended as instruments for assessing OM in clinical studies with head and neck cancer patients [43]. However, the NCI scale does not specifically assess solid food intake capacity but food intake in general.

The results based on the WHO scale suggest that, despite the presence of ulcerated lesions, participants in group B exhibited greater tolerance to solid foods. This finding is consistent with the outcomes in domain 1 of the OHIP- 14. We hypothesize that the gel and mouthwash contributed to improved oral cavity lubrication, thereby facilitating food intake. Due to that, the efficacy of the topical agents in the management of OM was more evident when assessed using the WHO scale, but not when using the NCI scale. We believe that the results on the NCI scale should be interpreted carefully. This suggests that L-G and HA may improve functional outcomes (e.g., swallowing) rather than lesion severity alone. Notably, most patients in group B experienced dysphagia at the beginning of

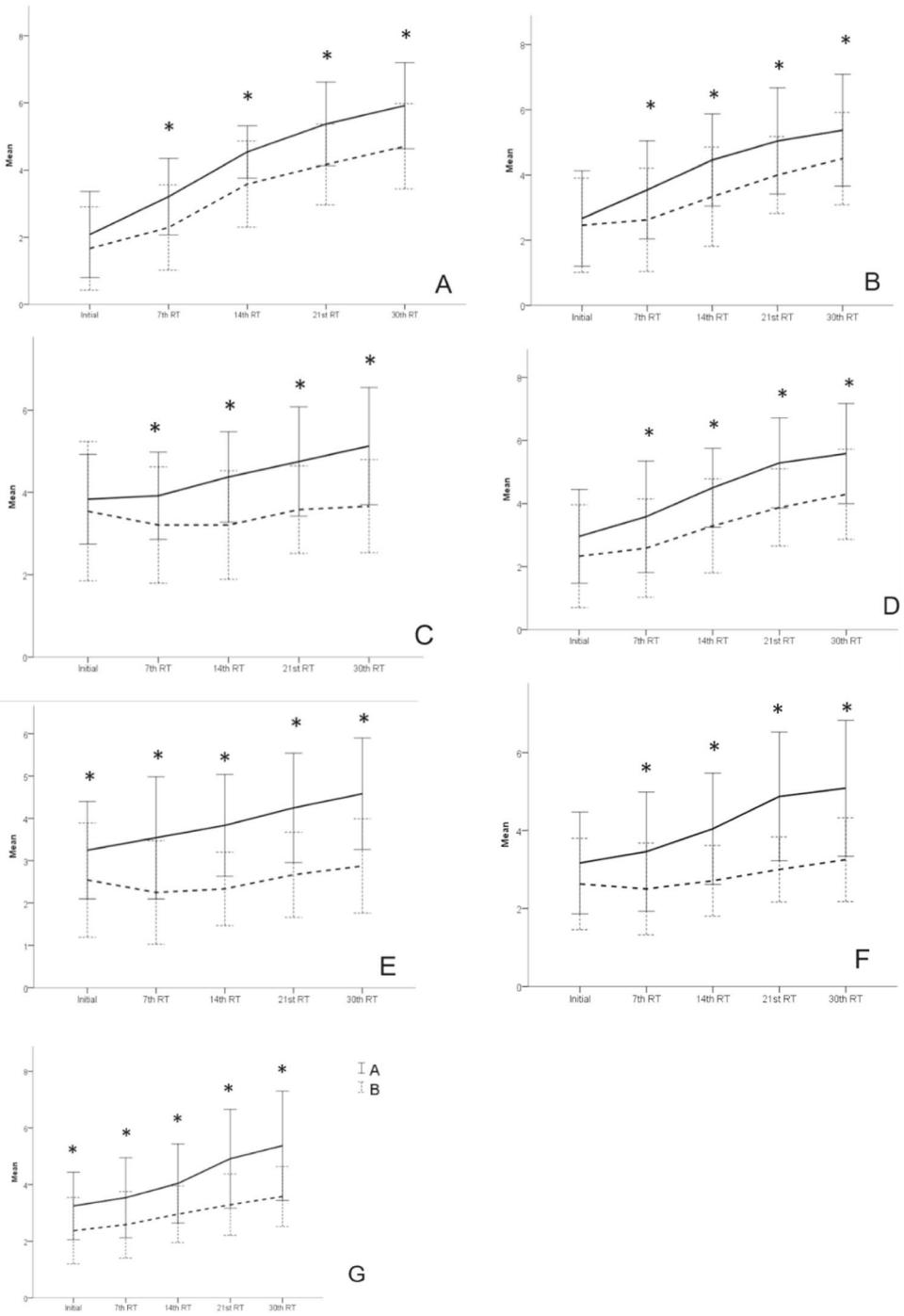

Fig. 3 OHIP-14 scores in each domain. OHIP-14 domain scores, values expressed as mean ± s.d. In (**A**) Functional limitation, in (**B**) physical pain, (**C**) psychological discomfort, in (**D**) physical disability, in (**E**) psychological disability, in (**F**) psychological disability, and in (**G**) disability. Continuous line: group A; Dashed line: group B. *Indicates a statistically significant difference between groups, Mann-Whitney test

treatment; although there was not a significant difference, this symptom is known to substantially impact quality of life [44]. Thus, this result reinforces the importance of cautious interpretation. Nevertheless, during oncological treatment, PROMS and OHIP- 14 scores related to swallowing function were better in patients using L-G and HA in combination with PBM and POCP, compared to group A.

The results showed that the association of medications with L-G and HA, associated with PBM and POCP, is associated with a lower impact of oral health on the participants' quality of life and lesser OM symptoms. Besides that, there were improved quality-of-life scores despite no reduction in RT interruptions. This may reflect a lower impact of OM on the overall quality of life, contributing to better adherence to the oncological treatment regimen. It is important to note that the therapeutics adopted in this study did not influence RT interruption since no difference was observed between the groups evaluated, suggesting that the association of the topical

Table 4 Data from patients who interrupted radiotherapy due to symptoms of oral mucositis

Patient	Group	Sex	Tumor site	T-stage	Type of RT	Daily dose (Gy)	WHO OM grade	NCI OM grade	RT session that interrupted	Treatment adherence	Days interrupted	PBM sessions during interruption
1	A	M	Tongue	T2	IMRT	2	2	1	19 th	Low	8	6
2	A	M	Oropharynx	T3	IMRT	2.18	3	3	22 nd	Low	7	5
3	A	M	Oropharynx	T2	IMRT	2.18	2	3	20 th	Low	7	5
4	A	M	Oropharynx	T4	IMRT	2.18	3	2	18 th	Moderate	7	5
5	A	M	Oropharynx	T3	IMRT	2.08	4	3	23 rd	High	7	5
6	A	M	Tongue	T4	IMRT	2.085	4	3	23 rd	High	12	8
7	B	M	Tongue	T3	IMRT	2.18	4	3	21 st	Low	10	7
8	B	F	Tongue	T2	IMRT	2	2	3	18 th	Low	12	8
9	B	F	Tongue	T3	IMRT	2	2	2	21 st	Moderate	7	5
10	B	M	Oropharynx	T3	IMRT	2.18	2	3	19 th	Moderate	3	3
11	B	M	Oral mucosa	T4	3D	2	2	3	18 th	High	13	9

Abbreviations: *F* feminine, *IMRT* intensity-modulated radiation therapy, *M* male, *NCI* National Cancer Institute, *OM* oral mucositis, *PBM* photobiomodulation therapy; *POCP* Preventive Oral Care Protocol, *RT* radiotherapy, *WHO* World Health Organization

medications with PBM may not favor RT interruption. It was observed that, of the 11 patients who interrupted RT due to OM symptoms, 8 exhibited low or moderate adherence to therapeutic OM control protocols. Since OM is also related to the loss of the patient's general quality of life [45, 46], it is suggested that dental support throughout the patient's oncological treatment should be guaranteed, favoring control of adverse effects of RT, less impact on the quality of life, better control of oral health, and less interruption rates [17].

This study presents limitations that need to be addressed, for example, the trial was designed to compare the standard intervention (PBM) and a novel intervention. Considering this, it does not include a placebo group, as the effectiveness of individual interventions has already been studied in past investigations [3, 4, 6, 10, 12, 39]; however, this prevents definitive conclusions about the independent efficacy of HA and L-G. It is important to note that the association of PBM and the other medications is mandatory due to ethical reasons since the ethical research committee would not approve a study with a sham-PBM. The sample size, the single-center design, and heterogeneity in tumor stages and treatment protocols may introduce potential confounding of the study, may limit the generalizability of the present findings, and may reduce statistical power for secondary outcomes, such as the RT interruption result. Additionally, although not statistically significant, baseline differences in dysphagia may represent a potential source of bias and may affect the generalizability of the findings, particularly regarding quality-of-life scores. Moreover, we believe that the topical agents did not impair the PBM properties since patients were recommended to use the L-G and HA at least 1 h prior to each session. Nonetheless, despite the limitations, the findings of this study are promising and may serve as a foundation for future research aimed at optimizing preventive and therapeutic approaches for OM in patients undergoing RT.

In the present study, we demonstrated that the association of L-G and HA-based components with PBM and POCP prevented more severe cases of OM, when evaluated by the WHO scale, at the end of treatment than PBM exclusive; therefore, we suggest that therapies should be combined to reduce the risk of developing OM in its severe form, as well as to control its symptoms and their impact on the patient's quality of life. Furthermore, we suggest that the WHO scale may be more suitable for evaluating patients using topical agents than the NCI scale. It remains a challenge to develop a unique formulation that contains the two active ingredients investigated, L-G and AH, reducing the number of medications used during cancer treatment. Furthermore, economic studies on the association of therapies must be conducted to verify whether it is more cost-effective than the exclusive use of PBM and POCP. Future studies that expand the number of patients treated with this regimen are necessary to confirm these findings.

Conclusion

The association of L-G and HA to PBM and POCP is related to a lower incidence of severe OM, as assessed by the WHO scale in the 30 th RT session, and a lower impact of oral health on quality of life in patients undergoing RT for oral cavity and oropharynx cancer. However, no statistically significant differences were observed when the OM was evaluated using the NCI scale; this emphasizes the need for further validation of these results across standardized assessment instruments.

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Author contributions E.F.M., C.R.L., N.M.A.F., and D.A.C.A. were responsible for the study concepts and design. R.W.S, A.F.L.M, D.A.C.A, S.S.S.N., V.H.L.O.M., M.M.O., and A.F.O.L. were responsible for data acquisition, analysis, and interpretation. S.S.S.N., M.M.O, and A.F.O.L. did the quality control of data. Statistical analysis were performed by A.F.L.M. and C.R.L. R.W.S., A.F.L.M., and S.S.S.N. were responsible for the manuscript preparation. All authors reviewed the manuscript and agree with it submission.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Declaration of AI-assisted technologies in the writing process During the preparation of this work, the authors used Grammarly (Sep 07 version) from Grammarly, Inc. (https://app.grammarly.com) to specifically review grammar and spelling. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. No large language models/tool/service were used to analyze and draw insights from data as part of the research process.

Ethics approval This study was approved by the Araujo Jorge Cancer Hospital Ethics Committee under number 4,898,517 (CAAE: 48320921.6.0000.0031).

Consent to participate All participants signed an informed consent to participate of this study.

Competing interests The authors declare no competing interests.

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