Received: 10 July 2019 | Revised: 13 March 2020 | Accepted: 18 March 2020

DOI: 10.1111/odi.13343

ORIGINAL ARTICLE

ORAL DISEASES WILEY

Topical pilocarpine for xerostomia in patients with head and neck cancer treated with radiotherapy

Raony Môlim de Sousa Pereira[1] | Mônica Danielle Ribeiro Bastos[1] | Maíra Peres Ferreira[2] | Osvaldo de Freitas[2] | Leandro Dorigan de Macedo[3] | Harley Francisco de Oliveira[4] | Hilton Marcos Alvez Ricz[5] | Ana Carolina Fragoso Motta[6] | Ana Paula Macedo[1] | Camila Tirapelli[1] | Vinicius Pedrazzi[1]

[1]Departament of Dental Materials and Prosthodontics, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

[2]Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

[3]Dentistry and Stomatology Division, Ribeirão Preto Clinical Hospital, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil

[4]School of Medicine, Ribeirão Preto Clinical Hospital, University of São Paulo, Ribeirão Preto, Brazil

[5]Ophthalmology, Otolaryngology and Head and Neck Surgery Department, Otolaryngology and Head and Neck Surgery Department, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil

[6]Department of Stomatology, Public Health and Forensic Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

Correspondence
Camila Tirapelli, Department of Dental Materials and Prosthodontics, School of Dentistry of Ribeirão Preto, University of São Paulo, Avenida do Café, s/n, Monte Alegre, Zip Code: 14.040-904, Ribeirão Preto, SP, Brazil.
Email: catirapelli@forp.usp.br

Funding information
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Grant/Award Number: #001; Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant/Award Number: #12/05570-7 and #13/03351-9

Abstract

Objective: To evaluate a pilocarpine spray as a treatment for xerostomia in patients treated with radiotherapy (RT) for head and neck cancer (HNC).

Methods: This was a placebo-controlled, double-blind, crossover clinical trial of patients complaining of dry mouth after RT for HNC. Forty patients were randomly assigned to either placebo or pilocarpine (1.54%) spray and instructed to use three times a day for 3 months. After 1-month washout period, patients were crossed over to receive placebo or pilocarpine. The assessments were salivary flow (Stimulated Whole Saliva Flow – SWSF), xerostomia (Xerostomia Inventory – XI), and quality of life (QoL/Oral Health Impact Profile – OHIP-14), assessed at baseline, 1 hr (only SWSF), and at 1, 2, and 3 months of treatment.

Results: Posttreatment SWFS was not statistically different between pilocarpine and placebo regardless of the treatment sequence (paired *T* test; $p > .05$), except for the SWFS rates at 2 months after therapy. When comparing pilocarpine with placebo in the time points, there was no significant difference ($p > .05$) for QoL or XI. Significant differences in improvement in QoL and xerostomia experience appeared along time for pilocarpine group.

Conclusion: The topical application of pilocarpine spray tested was similar to placebo on SWSF assessments in patients treated with RT for HNC.

KEYWORDS

clinical trial, head and neck cancer, pilocarpine, quality of life, radiotherapy, xerostomia

1 | INTRODUCTION

Xerostomia is a subjective complaint of dry mouth, which may result from hypofunction of the salivary gland related to different causes, including: radiotherapy (RT) for head and neck cancer (HNC) treatment, xerogenic drugs use, and systemic conditions such as Sjögren's Syndrome (SS), AIDS, and Diabetes Mellitus (Dost & Farah, 2013; Tanasiewicz, Hildebrandt, & Obersztyn, 2016). Regardless the cause, it negatively affects the quality of life (QoL), given the frequent reports of dysphagia, dysgeusia, oral discomfort, difficulty speaking, as well as the risk for the development of caries and periodontal diseases, loss of teeth, oral infections, and nutritional disorders (Dost & Farah, 2013; Lastrucci et al., 2017; Wyatt et al., 2016).

Different types of treatment have been suggested for patients with xerostomia to reduce the symptoms and increase the salivary flow (Mercadante, Al Hamad, Lodi, Porter, & Fedele, 2017), including hydration, sugar-free gums, saliva substitute, and systemic sialogogues (Islas-Granillo et al., 2017; Melo Filho et al., 2013); however, treatment of xerostomia remains an unresolved issue. Scientific evidence from randomized clinical trials focusing on the management of xerostomia in HNC patients is scarce and with controversial results (Furness, Worthington, Bryan, Birchenough, & McMillan, 2011). Recent systematic review shows that cevimeline and pilocarpine are the most effective for controlling xerostomia (Cheng et al., 2016; Yang et al., 2016; Mercadante et al., 2017). The latter is one of the most studied salivary gland stimulating method, which consists of a cholinergic sialogogue of muscarinic action predominating for M3 receptors, acting on the postganglionic receptors in cells of the parasympathetic nervous system.

Two clinical trials tested oral pilocarpine against placebo, Johnson et al. (1993) showed that saliva production was improved, but it did not correlate with symptomatic relief, and LeVeque et al. (1993) found postdose improvement in whole and parotid salivary flow. A clinical study used topical pilocarpine as mouthwash in healthy patients who showed the salivary flow increased (Minagi, Ikai, Araie, Sakai, & Sakai, 2018). Another clinical trial proposed pilocarpine in a candy-like pastille in patients with HNC; the results showed that subjective effects were alleviated (Hamlar et al., 1996). In both studies no adverse side effects were reported. Also, topical pilocarpine was tested and showed increased salivary flow in participants on pilocarpine versus placebo after 180 min of use (Taweechaisupapong, Pesee, Aromdee, Laopaiboon, & Khunkitti, 2006).

The most common adverse side effects of oral pilocarpine include diaphoresis, frequent urination, and nausea. Moreover, patients may have dizziness, headache, and cardiovascular effects what drive for efforts involving experimental topical formulations (Mercadante et al., 2017). Recently, an experimental study with rats testing a topical formulation of pilocarpine showed a significantly sialogogue effect when compared with systemic use, as well as lower side effects when used in high doses of the drug (Santos, Sá, Leite, Freitas, & Nunes, 2014). Based on those findings, this study aimed to evaluate the effectiveness of a new pharmaceutical formulation of pilocarpine spray on salivary flow (SF), experience of xerostomia, and QoL of patients with xerostomia due RT for HNC.

2 | MATERIALS AND METHODS

2.1 | Ethical aspects

This study has been carried out in accordance with Declaration of Helsinki and was approved by the Institutional Review Board of the School of Dentistry of Ribeirão Preto – University of São Paulo (CAAE: 27765714.0.000.5419). All patients provided written informed consent.

2.2 | Sample size, inclusion and exclusion criteria, and study design

The sample size was reached searching on 2016 cancer-free patients assisted with RTX for HNC (2010–2014) that had complaining of xerostomia after treatment. From 216 medical records we excluded patients by death, previous use of xerostomia medication, diseases associated with hyposalivation/xerostomia, and other reasons (Box 1). The primary outcome in this study was SWSF; the expected effect size of topical pilocarpine was an improvement of 50% in SWSF (Bernardi et al., 2002). Considering a double-blind, placebo-controlled and crossover study with a power of 80% and a confidence of 95%, where 28 participants were considered as sample size (G Power, software). Forty patients were included in this trial based on the criteria described in Box 1 (NCT 02982577).

2.3 | Randomization and blinding

Patients were randomized for the initial consultation (T0) by CT using a computer-generated randomization list and distributed in two groups based on the treatment sequence: pilocarpine followed by placebo (sequence 1) and placebo followed by pilocarpine (sequence 2). Patients of sequence 1 used the spray with pilocarpine for 3 months and after 1-month washout period, they used placebo spray for another 3 months. Patients of sequence 2 used the spray with placebo for 3 months and a 1-month washout period, they used pilocarpine spray for another 3 months. Sequently, the blinded operator RMSP received the bottles of sprays produced and blinded by MFP and OF.

2.4 | Pilocarpine and placebo

The 1.54% pilocarpine (Santos et al., 2014) and placebo solutions were prepared by MFP and OF at the Laboratory for Pharmacotechnical Research and Development of the School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo (Brazil), which supplied them in unlabeled plastic bottles of 40 ml. The tested spray composition was as follows: glycerin (6.0%), hydroxypropil methycellulose K100 (0.8%), Nipas solution (0.02% of propylparaben + 0.18% methylparaben in propylene glycol), purified water (qsp, 100%), and pilocarpine (1.54%). The placebo solution had

Box 1 Criteria for inclusion and exclusion of study participants

Inclusion	Exclusion
• Adults ≥ 18 years age; • Both genders; • Lucid; • Diagnosed with HNC and treated for a period of up to 5 years (2010 to 2014) with RT where at least one group of the major salivary glands (parotid, submandibular, or sublingual) were included in the radiation field with a total dose of 50 Gy; • Patient complain of dry mouth at anamnesis and presence of at least two of the followed features (Osailan, Pramanik, Shirodaria, Challacombe, & Proctor, 2011): (a) sticking of an intraoral mirror to the buccal mucosa or tongue; (b) frothy saliva; (c) no saliva pooling in floor of mouth; (d) loss of papillae of the tongue dorsum; (e) altered/smooth gingival architecture; (f) glassy appearance to the oral mucosa (especially the palate); (g) lobulated/deeply fissured tongue; (h) cervical caries (more than two teeth); and/or (i) mucosal debris on palate (except under dentures) • Patients without use of any salivary stimulant or substitute.	• Sensitivity to pilocarpine • Sjögren's Syndrome; • Type 2 diabetes mellitus; • AIDS; • Pregnant or lactating women; • Glaucoma; • Uncontrolled asthma; • Chronic obstructive pulmonary disease; • Renal diseases; • Significant cardiovascular diseases; • Gastrointestinal disorders; • Hepatic insufficiency; • Current use of oral pilocarpine or any other sialogogue agent; • Use of anticholinergic or other drugs potentially associated with an altered salivary flow; • Any psychiatric disorder.

the same composition except for the pilocarpine 1.54%. Each bottle had a number assigned to each participant at the time of randomization, which was unknown to investigators and patients. Box 2 shows patients according to the randomization process, describing their age, gender, HCN site, RT scheme, and surgery type.

2.5 | Interventions

Participants were instructed by RMSP to apply one spray of pilocarpine solution or placebo on each side of the buccal mucosa and one spray on the floor of the mouth every 8 hr. This therapy scheme (pilocarpine 1.54% every 8 hr) corresponded to 5 mg of pilocarpine/day. Adherence was assessed by measuring the residual volume in the spray bottle at each follow-up visit.

2.6 | Parameters assessed

Saliva production was measured by the stimulated whole saliva flow (SWSF) method, using a sialometry kit (Halitus). The test consisted of chewing a mechanical sialogogue (silicone) for 5 min and the saliva produced was collected in a tube; saliva volumes were measured and the salivary flow rate (ml/min) calculated. Xerostomia experienced by the patients was assessed using the Xerostomia Inventory (XI), and QoL was assessed by the Oral Health Impacts Profile (OHIP-14), both validated in Brazil (Almeida, Loureiro, & Araújo, 2004; Barbe et al., 2017; da Mata et al., 2012). SWSF, subjective xerostomia, and QoL were measured at baseline (T0/T0′, pilocarpine and placebo, respectively), and at 1 (T1/T′), 2 (T2/T2′), and 3 (T3/T3′) months after the use of the placebo or policarpine spray in both therapy sequences. SWSF was also measured 1 hr after the spray (T0+/T0+′).

2.7 | Statistical analysis

We analyzed data using per protocol (PP) and intention-to-treat analysis (ITT). SWSF data were analyzed using the paired *t* test with 95% of confidence level, comparing each period of evaluation using Prism 6.0 (Graphpad Statistic Software). XI and OHIP-14 data were analyzed using the IBM SPSS Statistic software, version 20.0. Initially, each variable was submitted to the Shapiro-Wilk normality test ($n < 30$), and showed a non-normal distribution. Thus, the Wilcoxon test was used for comparisons between two groups or two time points, and the Friedman test to compare more than two time points. When comparisons between T0, T1, T2, and T3 showed significant differences ($p < .05$), the Stepwise step-down posttest was applied. For analysis of the results, patients were grouped independently of treatment sequence in placebo-controlled group (C) and pilocarpine (P) group.

3 | RESULTS

3.1 | Patients

A total of 40 patients were enrolled and randomized to receive pilocarpine ($n = 20$) or placebo ($n = 20$) crossing over after a washout period. Figure 1 shows the patient flow though the study. Mean age of the 40 participants was 58.10 years; 29 (72.5%) were men and 11 (27.5%) women.

3.2 | Salivary flow

Means and deviations of the SWFS rate by treatment sequence groups are shown in Figure 2. Considering the PP analysis,

Box 2 **Characteristics of patients by age and gender (A/G), HNC site, radiotherapy scheme, and HCN surgery**

	A/G	HCN site	Radiotherapy	Surgery
Placebo to Pilocarpine	65/M	Amygdala SCC	25 × 180 cGy cervical-facial 6MV; 28 × 180 cGy supraclavicular fossa 6MV; 3 × 180 cGy marrow 6MV; 5 × 200 cGy boost 6MV = 11080 cGy	Radical tonsillectomy right
	63/M	Piriform sinus SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossas; 3 × 180 cGy marrowF2; 10 × 200 cGy neck 6MV = 12080 cGy	-
	53/M	Mouth floor SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 8 × 180 cGy face = 11620 cGy	Segmental hemimandibulectomy
	72/M	Mouth floor SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 13−5 × 200 cGy face = 11080 cGy	Radical command type III left
	56/M	Parotid SCC	32 × 200 cGy PTV1; 32 × 160 cGy PTV2 IMRT = 11520 cGy	Total parotidectomy
	60/F	Retromolar trigone SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 08 × 200 cGy cervical-facial (boost) = 11680 cGy	Excision of malignant lesion of the mouth
	57/M	Amygdala SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 9 × 200 cGy face = 11780 cGy	-
	55/M	Piriform sinus SCC	30 × 180 cGy cervical (PTV1) = 5400 cGy	-
	55/M	Soft palate SCC	25 × 180 cGy cervicalF1; 28 × 180 cGy fossae; 3 × 180 cGy marrow; 7 × 200 cGy boost = 11580 cGy	Resection of soft palate lesion
	62/F	Soft palate SCC	10 × 200 cGy face; 25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 marrowF2 = 12080 cGy	-
	79/M	Carcinoma of acinar cells in the right parotid	32 × 200 cGy right face IMRT = 6400 cGy	Right superficial parotidectomy
	60/M	Tongue border SCC	30 × 180 cGy fase 1 IMRT; 8 × 200 cGy fase 2 IMRT = 7000 cGy	-
	68/F	Cystic adenocarcinoma of the salivary gland	25 × 180 cGy facialF1; 25 × 180 cGy fossae; 10 × 200 cGy boost = 9000 cGy	Excision of malignant lesion of the mouth + segmental hemimandibulectomy
	49/M	Ewing's sarcoma in the pharyngeal space	30 × 200 cGy skull IMRT = 6000 cGy	Surgery of the skull base for benign lesion
	32/F	Amygdala SCC	12 × 200 cGy boost MV; 25 × 180 cGy cérvico-facialF1; 28 × 180 cGy fossas; 3 × 180 cGy medulaF2 = 12480 cGy	-
	63/M	Base of tongue SCC	25 × 180 cGy face; 28 × 180 cGy fossa; 3 × 180 cGy medula; 10 × 200 cGy boost = 12080 cGy	-
	49/M	Nasopharynx SCC	32 × 200 cGy cervical-facial IMRT; 5 × 200 cGy cervical-facial; 5 × 200 cGy fossae; 3 × 200 cGy boost = 9000 cGy	-
	66/F	Parotid SCC	32 × 200 cGy cervical-facial IMRT; 5 × 200 cGy face = 7400 cGy	Left parotidectomy
	66/M	Base of tongue SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 7 × 200 cGy face = 11480 cGy	-
	60/M	Piriform sinus SCC	25 × 180 cGy cervical; 28 × 180 cGy FSC; 3 × 180 cGy marrow; 8 × 200 cGy cervical = 11680 cGy	-

Box 2 (Continued)

	A/G	HCN site	Radiotherapy	Surgery
Pilocarpine to placebo	59/M	Tongue SCC	25 × 180 cGy face; 3 × 180 cGy marrow; 28 × 180 cGy fossa; 5 × 200 cGy boost = 11080 cGy	Partial glossectomy
	57/M	Tongue SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 10 × 200 cGy boostF3 6MV = 12080 cGy	-
	68/M	Soft palate SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 10 × 200 cGy neck = 12080 cGy/28 × 180 face IMRT = 5040 cGy	Excision of malignant lesion of the mouth
	52/M	Hypopharynx SCC	25 × 180 cGy cervical-facialF1 6MV; 28 × 180 cGy FSC 6MV; 3 × 180 marrowF2 6MV; 10 × 200 cGy neck = 12080 cGy	-
	62/F	Carcinoma ex-parapharyngeal adenoma	25 × 180 cGy facialF1; 25 × 180 cGy fossae; 10 × 200 cGy face (boost) = 11000 cGy	Resection of left parapharyngeal tumor
	63/F	Hard palate SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2 6MV; 8 × 200 cGy boost 6MV = 11680 cGy	Excision of malignant oropharynx lesion
	56/M	Base of tongue SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy FSC; 3 × 180 marrowF2; 8 × 200 cGy boost = 11680 cGy	-
	46/M	Base of tongue SCC	25 × 180 cGy cervicalF1; 28 × 180 cGy fossae; 3 × 180 marrowF2; 10 × 200 cGy face = 12080 cGy	Partial glossectomy
	53/F	Nasopharynx SCC	25 × 180 cGy face IMRT = 4500 cGy	-
	52/M	Base of tongue SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 10 × 200 cGy face = 12080 cGy	-
	53/F	Hard/soft palate SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 10 × 200 cGy boost = 12080 cGy	-
	52/M	Soft palate SCC	25 × 180 cGy face; 28 × 180 cGy fossaF1; 3 × 180 cGy marrowaF2; 10 × 200 cGy cervical (boost) = 12080 cGy	-
	46/M	Hypopharynx SCC	16 × 180 cGy cervical-facialF2 6MV; 22 × 200 cGy cervical-facialF1 6MV; 25 × 200 cGy fossae 6MV; 3 × 200 cGy marrowF2 6MV = 12880 cGy	-
	74/M	Piriform sinus SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 8 × 200 cGy cervical(boost) = 11680 cGy	Excision of malignant larynx lesion
	41/F	Nasopharynx SCC	25 × 180 cGy face IMRT = 4500 cGy	-
	74/M	Mouth floor SCC	25 × 180 cGy cervical-facialF1; 28 × 180 cGy fossae; 3 × 180 marrowF2; 7 × 200 cGy face = 11480 cGy	-
	56/M	Oropharynx SCC	35 × 200 cGy cervical; 20 × 200 cGy cervical-facial IMRT = 11000 cGy	-
	62/M	Soft palate SCC	25 × 180 cGy cervicalF1; 28 × 180 cGy fossae; 3 × 180 cGy marrowF2; 7 × 200 cGy boost = 11480 cGy	-
	46/M	Soft palate SCC	25 × 180 cGy cervical-facialF; 28 × 180 cGy fossae; 3 × 180 marrow2; 9 × 200 cGy face = 11880 cGy	-
	64/F	Submandibular gland epithelial carcinoma	25 × 180 cGy cérvico-facialF1; 28 × 180 cGy fossas; 10 × 200 cGy boost = 11540 cGy	Left submandibulectomy

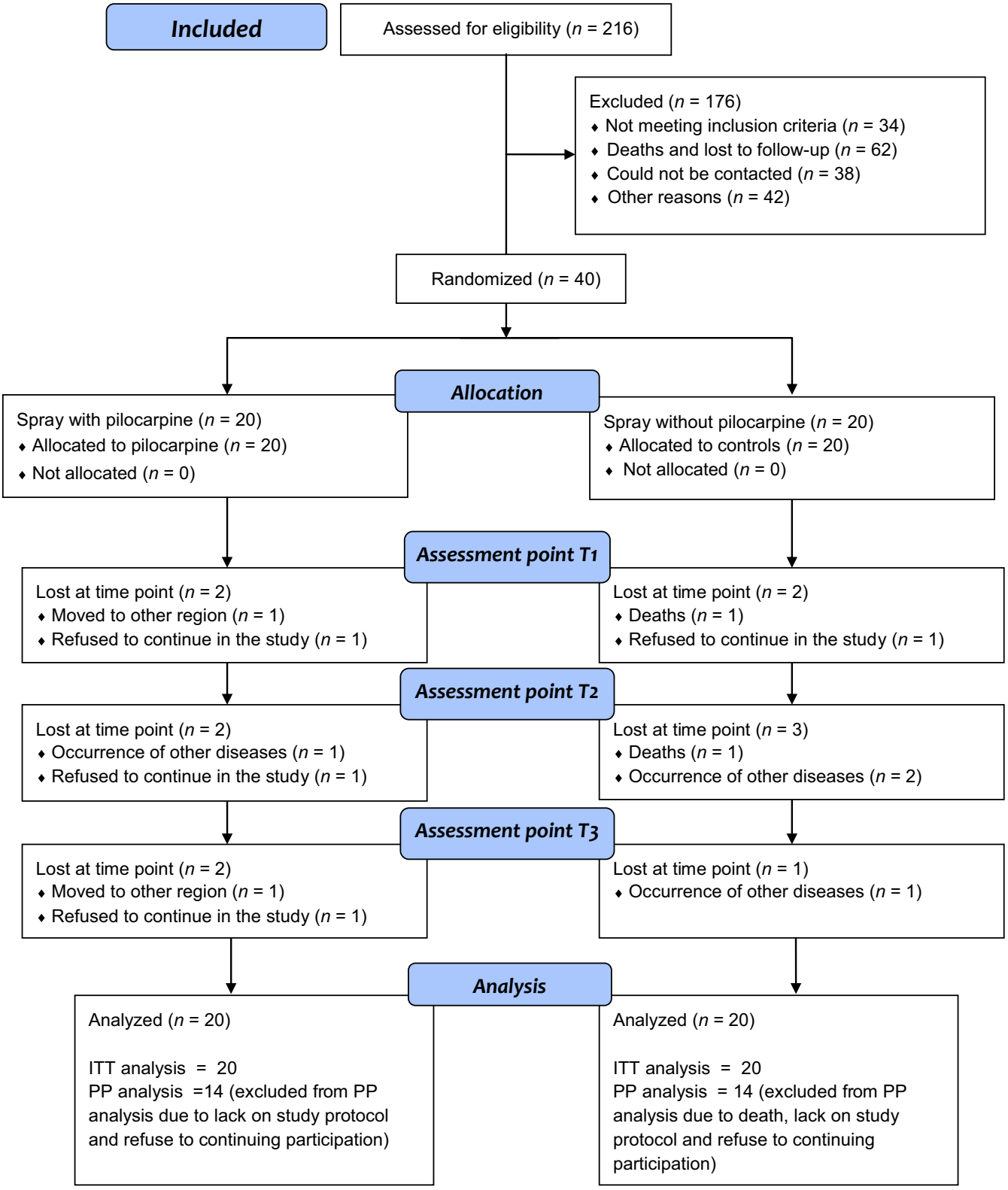

FIGURE 1 Study flowchart. *Occurrence of health problems that prevented patients from attending the monthly assessment appointments of the study [Colour figure can be viewed at wileyonlinelibrary.com]

posttreatment SWFS was not statistically different between pilocarpine and placebo regardless of the treatment sequence (paired *T* test; $p > .05$), except for the SWFS rates at 2 months of therapy: SWSF was higher at T2P (0.61) than at T2C (0.32). On ITT analysis the same was observed, there was no difference between pilocarpine and placebo regardless of the treatment sequence.

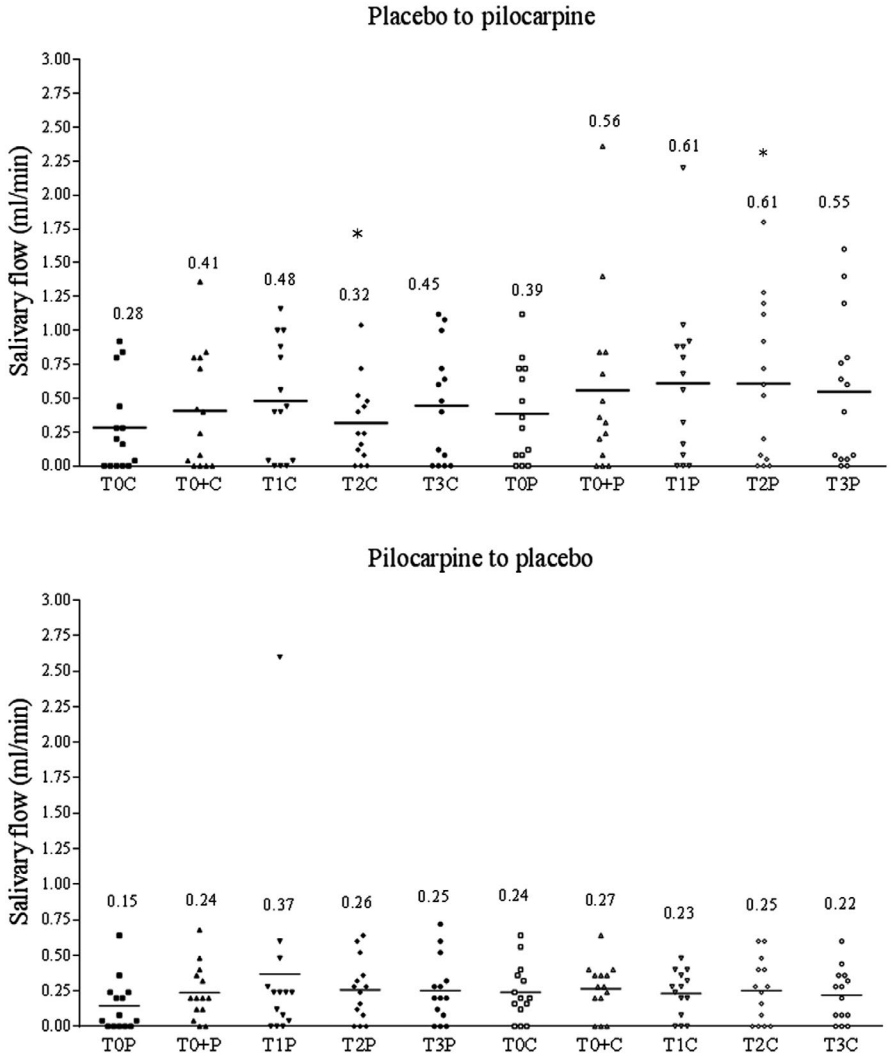

FIGURE 2 Graphic illustration of stimulated whole saliva flow rate along with the study for the 28 patients who participated in the entire study period. The symbol (*) refers to statistically significantly different (p = .032) means

3.3 | Xerostomia Inventory and OHIP-14

XI and OHIP-14 scores are illustrated on Figure 3. Overall, when comparing pilocarpine with placebo in the time points, for both PP and ITT analysis, there was no significant difference (p > .05) for most of the OHIP-14 questionnaire domains (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap); the same pattern was observed for XI scores.

4 | DISCUSSION

In this crossover, double-blind, placebo-controlled clinical trial, we tested a spray formulation of 1.54% pilocarpine solution for topical use. SWFS, QoL (OHIP-14), and experience of xerostomia (XI) were not statistically different between pilocarpine and placebo regardless of the treatment sequence.

Comparison of results between clinical trials on the management of xerostomia in RT patients is a complex task, as reported by a recent meta-analysis (Mercadante et al., 2017), especially because not all clinical trials assessed salivary flow. In this context, our results are different from those found in studies that tested topical pilocarpine (mouthwash) and showed increased salivary flow in HNC patients (Nikles et al., 2015; Tanigawa et al., 2015). Studies showed increased saliva production in short periods of time after administration of systemic and topical pilocarpine (Pfizer Canada Inc, 2010; Kim, Ahn, Choi, Jung, & Kwon, 2014; Bernardi et al., 2002). The efficacy of both topical and systemic pilocarpine on salivary production in patients with hyposalivation has been reported (Ma, Rivers, Serra, & Singh, 2019; Mercadante et al., 2017). The topical application of pilocarpine appears to be an advantage in avoiding the side effects that systemic pilocarpine can have (Tanigawa et al., 2015). In this study, despite the lack of statistical significance on both per protocol or intention-to-treat data analysis, SWSF increased when individual cases were analyzed. At sequence 2 (placebo followed by pilocarpine), we observed after 1 hr of pilocarpine use a SWSF mean of 0.39 ml/min going to 0.61 ml/min. It can suggest that topical pilocarpine can have good results on the salivary flow increase depending on the patient profile, then, the cost-benefit of indicate it, need to be considered.

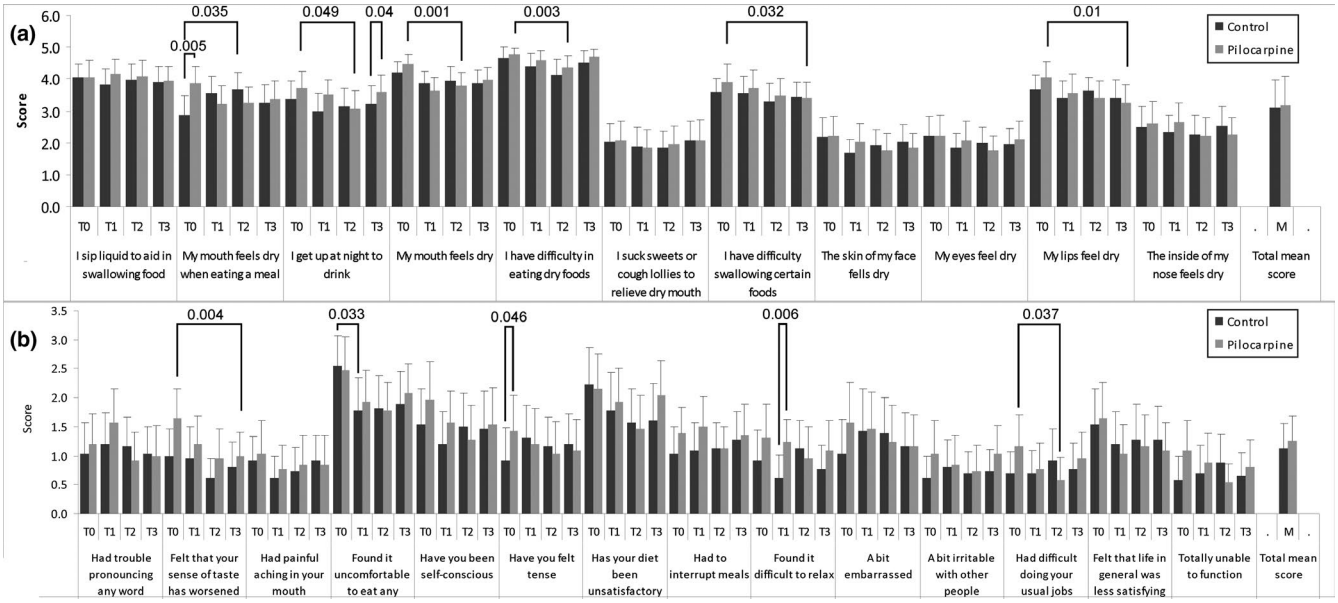

FIGURE 3 Graphic illustration of the Xerostomia Inventory (a) and Oral Health Impact Profile (OHIP-14) (b) mean values for each question over the study for the 28 patients who participated in the entire study period

In this study observing Figure 3 we noticed that pilocarpine was not significantly better than placebo on XI and QoL at the same time points. Nevertheless, we found statistical significance along the time. For example, on XI, comparing patients using pilocarpine along time (T0 × T3) statistical significance was found for "I get up at night to drink"; "my mouth fells dry"; "I have difficulty in eating dry foods"; and "I have difficulty in swallowing certain foods", suggesting an improvement in the xerostomia experience. The same patterns are seen for patients using pilocarpine (OHIP-14) in "Felt that you sense of taste has horsed" (T0 × T3) and "had difficult doing your usual jobs" (T0 × T2). Controversially, we observed a decrease in QoL for patients using pilocarpine when compared with placebo at same time point expressed for "Found difficult to relax" (T1). Subjective parameters such as quality of life and xerostomia experience can receive influence from several parameters, and maybe the overall patients profile – aged men, most of them living about 100 km of distance of the hospital, being low-income citizen, dependent of health-care people; with low educational level – had influenced. And indeed, sometimes, any professional care can have effect; for example, a clinical trial reported improved xerostomia-related symptoms (but not salivary flow rate) by spraying olive oil in patients with drug-induced xerostomia (Navarro Morante, Wolff, Bautista Mendonza, & López-Jornet, 2017).

The major strength of this study was that we evaluated the use of topical pilocarpine by a prospective randomized, placebo-controlled, and crossover study. In addition, we were able to assess objective and subjective variables over the whole study period, which made it possible to determine short- and long-term effects of the tested sprays. Some limitations of this study: the inclusion of patients with different types of HNC, treated with different types/schemes of RT, and the lack of a precise delimitation of the irradiated area that could be a bias for the objective analysis. In addition, we included patients with so low SWSF at baseline that it cannot be measured and such condition was maintained along the study time points. Finally, we did not evaluate whether there was mucosal absorption of pilocarpine, and the occurrence of side effects was determined based on clinical parameters.

5 | CONCLUSION

In conclusion, this study demonstrated that topical (spray) application of pilocarpine 1.54% solution was similar to placebo on SWFS, xerostomia experience, and quality of life assessments in patients treated by RT for HNC.

ACKNOWLEDGEMENTS

Professor Dr. Lívio César Cunha Nunes and Professor Dra. Laisa Lis Fontinele de Sá from the Federal University of Piauí for the donation of pilocarpine for the manufacture of the sprays. Financial support: grant #12/05570-7 and #13/03351-9, São Paulo Research Foundation (FAPESP) and CAPES Grant #001.

CONFLICTS OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

We would like to inform that CT, VP, LDM, and ACFM worked on study design; HFO, HMAR, ACFM, and LDM manage the patients at

the Medical School Hospital, RMSP and MDRB collected data, OF and MFP produced and blinded the products tested; APM and CT analyzed data. All authors revised the paper critically and approved the submitted version.

ORCID

Maíra Peres Ferreira https://orcid.org/0000-0002-0385-6416
Ana Carolina Fragoso Motta https://orcid.org/0000-0002-3887-9239
Camila Tirapelli https://orcid.org/0000-0001-5020-6515

REFERENCES

Almeida, A. A., Loureiro, C. A., & Araújo, V. E. (2004). Um estudo transcultural de valores de saúde bucal utilizando o instrumento OHIP-14 (Oral Health Impact Profile) na Forma Simplificada. Parte I: Adaptação cultural e lingüística. *UFES Revista De Odontologia*, *6*, 6–15. https://doi.org/10.21722/rbps.v6i1.10632

Barbe, A. G., Heinzler, A., Derman, S. H. M., Hellmich, M., Timmermann, L., & Noack, M. J. (2017). Hyposalivation and xerostomia among Parkinson's disease patients and its impact on quality of life. *Oral Diseases*, *23*(4), 464–470. https://doi.org/10.1111/odi.12622

Bernardi, R., Perin, C., Becker, F. L., Ramos, G. Z., Gheno, G. Z., Lopes, L. R., … Barros, H. M. (2002). Effect of pilocarpine mouthwash on salivary flow. *Brazilian Journal of Medical and Biological Research*, *35*(1), 105–110. https://doi.org/10.1590/s0100-879x2002000100015

Cheng, C. Q., Xu, H., Liu, L., Wang, R. N., Liu, Y. T., Li, J., & Zhou, X. K. (2016). Efficacy and safety of pilocarpine for radiation-induced xerostomia in patients with head and neck cancer: A systematic review and meta-analysis. *The Journal of the American Dental Association*, *147*(4), 236–243. https://doi.org/10.1016/j.adaj.2015.09.014

da Mata, A., da Silva Marques, D. N., Freitas, F., de Almeida Rato Amaral, J. P., Trindade, R., Barcelos, F., & Vaz Patto, J. M. (2012). Translation, validation, and construct reliability of a Portuguese version of the Xerostomia Inventory. *Oral Diseases*, *18*, 293–298. https://doi.org/10.1111/j.1601-0825.2011.01879.x

Dost, F., & Farah, C. S. (2013). Stimulating the discussion on saliva substitutes: A clinical perspective. *Australian Dental Journal*, *58*, 11–17. https://doi.org/10.1111/adj.12023

Furness, S., Worthington, H. V., Bryan, G., Birchenough, S., & McMillan, R. (2011). Interventions for the management of dry mouth: Topical therapies. *Cochrane Database of Systematic Reviews*, (12), CD008934. https://doi.org/10.1002/14651858.CD008934.pub2

Hamlar, D. D., Schuller, D. E., Gahbauer, R. A., Buerki, R. A., Staubus, A. E., Hall, J., … Martin, M. R. (1996). Determination of the efficacy of topical oral pilocarpine for postirradiation xerostomia in patients with head and neck carcinoma. *Laryngoscope*, *106*(8), 972–976. https://doi.org/10.1097/00005537-199608000-00011

Islas-Granillo, H., Borges-Yáñez, A., Fernández-Barrera, M. Á., Ávila-Burgos, L., Patiño-Marín, N., Márquez-Corona, M. D. L., … Medina-Solís, C. E. (2017). Relationship of hyposalivation and xerostomia in Mexican elderly with socioeconomic, sociodemographic and dental factors. *Scientifics Report*, *17*(7), 40686. https://doi.org/10.1038/srep40686

Johnson, J. T., Ferretti, G. A., Nethery, W. J., Valdez, I. H., Fox, P. C., Ng, D., … Gallagher, S. C. (1993). Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *The New England Journal of Medicine*, *329*, 390–395. https://doi.org/10.1056/NEJM199308053290603

Kim, J. H., Ahn, H. J., Choi, J. H., Jung, D. W., & Kwon, J. S. (2014). Effect of 0.1% pilocarpine mouthwash on xerostomia: Double-blind, randomised controlled trial. *Journal of Oral Rehabilitation*, *41*, 226–235. https://doi.org/10.1111/joor.12127

Lastrucci, L., Bertocci, S., Bini, V., Borghesi, S., De Majo, R., Rampini, A., … Gennari, P. G. (2017). Late toxicity, evolving radiotherapy techniques, and quality of life in nasopharyngeal carcinoma. *Radiology Medical*, *122*(4), 303–308. https://doi.org/10.1007/s11547-016-0722-6

LeVeque, F. G., Montgomery, M., Potter, D., Zimmer, M. B., Rieke, J. W., Steiger, B. W., … Muscoplat, C. C. (1993). A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *Journal of Clinical Oncology*, *11*, 1124–1131. https://doi.org/10.1200/JCO.1993.11.6.1124

Ma, S. J., Rivers, C. I., Serra, L. M., & Singh, A. K. (2019). Long-term outcomes of interventions for radiation-induced xerostomia: A review. *World Journal of Clinical Oncology*, *10*(1), 1–13. https://doi.org/10.5306/wjco.v10.i1.1

Melo Filho, M. R., Rocha, B. A., Pires, M. B. O., Fonseca, E. S., Freitas, E. M., Martelli Júnior, H., & Santos, F. B. G. (2013). Quality of life of patients with head and neck cancer. *Brazilian Journal of Otorhinolaryngology*, *79*(1), 82–88. https://doi.org/10.5935/1808-8694.20130014

Mercadante, V., Al Hamad, A., Lodi, G., Porter, S., & Fedele, S. (2017). Interventions for the management of radiotherapy-induced xerostomia and hyposalivation: A systematic review and meta-analysis. *Oral Oncology*, *66*, 64–74. https://doi.org/10.1016/j.oraloncology.2016.12.031

Minagi, H. O., Ikai, K., Araie, T., Sakai, M., & Sakai, T. (2018). Benefits of long-term pilocarpine due to increased muscarinic acetylcholine receptor 3 in salivary glands. *Biochemical and Biophysical Research Communications*, *503*(2), 1098–1102. https://doi.org/10.1016/j.bbrc.2018.06.125

Navarro Morante, A., Wolff, A., Bautista Mendonza, G. R., & López-Jornet, P. (2017). Natural products for the management of xerostomia: A randomized, double-blinded, placebo-controlled clinical trial. *Journal of Oral Pathology & Medicine*, *46*(2), 154–160. https://doi.org/10.1111/jop.12487

Nikles, J., Mitchell, G. K., Hardy, J., Agar, M., Senior, H., Carmont, S.-A., … Currow, D. (2015). Testing pilocarpine drops for dry mouth in advanced cancer using n-of-1 trials: A feasibility study. *Palliative Medicine*, *29*(10), 967–974. https://doi.org/10.1177/0269216315585473

Osailan, S., Pramanik, R., Shirodaria, S., Challacombe, S. J., & Proctor, G. B. (2011). Investigating the relationship between hyposalivation and mucosal wetness. *Oral Diseases*, *17*(1), 109–114. https://doi.org/10.1111/j.1601-0825.2010.01715

Pfizer Canada Inc (2010). *Salagen*. Kirkland, 40f. Bula.

Santos, G. A. S., Sá, L. L. F., Leite, J. R. S. A., Freitas, R. M., & Nunes, L. C. C. (2014). Technological development and evaluation on sialagogue activity of a spray-like liquid formulation of pilocarpine. *African Journal of Pharmacy and Pharmacology*, *8*(35), 868–874. https://doi.org/10.5897/AJPP2014.4027

Tanasiewicz, M., Hildebrandt, T., & Obersztyn, I. (2016). Xerostomia of various etiologies: A review of the literature. *Advances in Clinical Experimental Medicine*, *25*(1), 199–206. https://doi.org/10.17219/acem/29375

Tanigawa, T., Yamashita, J., Sato, T., Shinohara, A., Shibata, R., Ueda, H., & Sasaki, H. (2015). Efficacy and safety of pilocarpine mouthwash in elderly patients with xerostomia. *Special Care in Dentistry*, *35*(4), 164–169. https://doi.org/10.1111/scd.12105

Taweechaisupapong, S., Pesee, M., Aromdee, C., Laopaiboon, M., & Khunkitti, W. (2006). Efficacy of pilocarpine lozenge for post-radiation xerostomia in patients with head and neck cancer. *Australian Dental Journal*, *51*, 333–337.

Wyatt, G., Pugh, S. L., Wong, R. K. W., Sagar, S., Singh, A. K., Koyfman, S. A., … Berk, L. (2016). Xerostomia health-related quality of life: NRG

oncology RTOG 0537. *Quality of Life Research*, *25*(9), 2323–2333. https://doi.org/10.1007/s11136-016-1255-0

Yang, W., Liao, G. Q., Hakim, S. G., Ouyang, D. Q., Ringash, J., & Su, Y. X. (2016). Is pilocarpine effective in preventing radiation-induced xerostomia? A systematic review and meta-analysis. *International Journal of Radiation Oncology Biology Physics*, *94*(3), 503–511. https://doi.org/10.1016/j.ijrobp.2015.11.012

How to cite this article: Pereira RMDS, Bastos MDR, Ferreira MP, et al. Topical pilocarpine for xerostomia in patients with head and neck cancer treated with radiotherapy. *Oral Dis*. 2020;26:1209–1218. https://doi.org/10.1111/odi.13343