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Patient-related outcomes in Sjögren syndrome treated with stimulants of salivary secretion: Randomized clinical trial

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Abstract

Objectives: To investigate the impact of gustatory stimulants of salivary secretion (GSSS) on Sjögren's syndrome patients' self-perception of xerostomia, oral health-related quality of life (OHRQoL) and salivary secretion.

Methods: A total of 110 Sjögren's syndrome patients were randomly allocated to be treated with either a malic acid lozenge or a citric acid mouthwash and then crossed over. Before and after the interventions, the Xerostomia Inventory 5 (SXI-5-PL) and the Oral Health Impact Profile (OHIP-14-PT) questionnaires (both in the Portuguese language) were administered to patients. Unstimulated, mechanical and gustatory-stimulated salivary flows were determined. Repeated measures and between-subject analyses were performed. Statistical significance was set at 5%.

Results: After the intervention and within each group, both GSSS elicited a reduction in the SXI-5-PL and OHIP-14-PT scores and an increase in salivary output, significant in the malic acid lozenge group. The malic acid treatment resulted in a greater effect size and percentage improvement than citric acid mouthwash. The malic acid lozenge also produced a significant greater salivary output than the citric acid rising solution.

Conclusions: In Sjögren's syndrome patients, lozenges containing malic acid increased saliva production and xerostomia relief, resulting in improved quality of life.

KEYWORDS

patient-reported outcomes, quality of life, questionnaire, saliva, xerostomia

1 | INTRODUCTION

Saliva is critical for intra-oral homeostasis. People with hyposalivation have greater susceptibility to oral infections, dental decay and dental erosion (Fox et al., 2008; Furness, Worthington, Bryan, Birchenough, & McMillan, 2011; Villa, Connell, & Abati, 2014). Moreover, hyposalivation is responsible for the difficulties in performing oral functions such as speaking or eating. Many of those affected tend to isolate themselves and have poorer quality of life (Rusthen et al., 2017; Sasportas et al., 2013). Major causes of diminished salivary flow are medications, head and neck radiation and Sjögren's syndrome (Furness et al., 2011; Turner, 2016; Villa et al., 2014).

Primary Sjögren's syndrome (PSS) is a systemic, chronic, autoimmune disease of unknown cause, provoking inflammation of the salivary glands, among other exocrine glands, without any other systemic disease (Kassan & Moutsopoulos, 2004). It affects predominantly

This trial is registered in clinicaltrials.gov with number NCT03578900.

middle-aged women and has a prevalence of between 0.5% and 1.5% (Patel & Shahane, 2014; Sugai et al., 2009). The most common signs and symptoms of this condition are dry mouth and dry eyes (Fox, 2005; Mathews, Kurien, & Scofield, 2008), which can cause significant pain and discomfort and, if left untreated, may also lead to complications such as insomnia, corneal lesions and difficulties with eating and speaking and a greater risk of caries and dental erosion risk (Al-Hashimi, 2007; Cornec et al., 2017; López-Jornet & Camacho-Alonso, 2008; Rusthen et al., 2017).

Frequently, the exocrine involvement in PSS extends even beyond the lachrymal and salivary glands since it may include the gastrointestinal and respiratory system (Al-Hashimi, 2001; Brito-Zerón et al., 2016). All of these conditions can compromise general and oral health-related quality of life (OHRQoL; Cornec et al., 2017; Stewart, Berg, Cha, & Reeves, 2008).

Owing to the multisystem involvement in PSS, management of the disease requires a multidisciplinary approach. From the oral medicine perspective, the management of PSS includes saliva stimulation and mucosal lubrication along with remineralization procedures in dentate patients in order to minimize the xerostomia consequences (Singh & Tonk, 2011; Villa et al., 2014).

Pharmacological sialagogues such as muscarinic agonists like pilocarpine have been used as first-choice agents for xerostomia management (Salum, Medella-Junior, Figueiredo, & Cherubini, 2018). However, these drugs have secondary effects and pharmacological interactions, which limit their use in many situations (Salum et al., 2018). Therefore, alternative methods for increasing salivation and intra-oral lubrication with fewer secondary effects and a better cost-effectiveness ratio have emerged (Furness et al., 2011; Shiboski, Hodgson, Ship, & Schiødt, 2007; Villa et al., 2014; Vitali, Palombi, & Cataleta, 2010; Zandim, Tschoppe, Sampaio, & Kielbassa, 2011). Among those, gustatory stimulants of salivary secretion (GSSS)—such as sugar-free acidic hard candies, acidic custom-made solutions or commercially available lozenges for stimulation of salivary secretion—have been widely used, and some patients depend on these products extensively (da Silva Marques et al., 2011). Recent studies have suggested that these products are effective if some functional gland tissue remains (Gómez-Moreno et al., 2014, 2013; da Mata et al., 2009; da Silva Marques et al., 2011).

However, and despite the fact that several studies have investigated the efficacy of these products in increasing salivary secretion, little is known about these effects on xerostomia or oral health-related quality of life (OHRQoL; Gómez-Moreno et al., 2014, 2013; da Mata et al., 2009; Niklander et al., 2017; da Silva Marques et al., 2011; Thomson, Lawrence, Broadbent, & Poulton, 2006). The aim of this study was to compare the efficacy of two commonly used GSSS in improving salivary flow and patient OHRQoL.

2 | MATERIALS AND METHODS

This was a crossover randomized clinical trial, conducted between 1 January 2013 and 31 December 2016. It was designed to test the superiority of a new GSSS and also aimed at studying the effects of two different GSSS on the patient's self-perception of xerostomia and OHRQoL. A marketed GSSS in the form of a malic acid- and fluoride-containing lozenge (malic acid 4.33% w/w) from Xeros® system (Dentaid) and a citric acid-based hospital custom-made rinsing solution (citric acid 0,07% w/v with glycerine (15%) and deionized water as solvents) were used as trial arms. The a priori hypotheses were, first, that in adult patients with PSS, the use of GSSS in the form of a malic acid-containing lozenge or a customized rinsing solution containing citric acid improves xerostomia self-perception, OHRQoL and salivation; and second, that, in adult patients, these stimulants differ in the xerostomia self-perception, OHRQoL and salivary secretion.

2.1 | Study participants

Participants were recruited from the Portuguese Rheumatology Institute by research assistants from the Faculdade de Medicina Dentária da Universidade de Lisboa. Informed consent was obtained. The inclusion criteria for entry into the trial were as follows: (a) solely Primary Sjögren syndrome diagnosis (American-European Consensus Group); (b) unstimulated salivary flow (USF) <0.1 ml/min; and (c) more than 18 years of age. All participants provided a full medical history. Excluded were pregnant women, users of complete removable denture and those who were non-fluent in the Portuguese language. These patients were already under medical care, with no experiences of treatments for dry mouth with the exception of pilocarpine, which was suspended, and they had no other mucosal diseases. The ethical committees of the participating institutions approved the study protocol (IRB No. 121002, October 2012), which is in accordance with the Helsinki Declaration as revised in 2013.

2.2 | Intervention

2.2.1 | Visit 1

Eligibility was assessed for each participant, and a Decayed, Missing, Filled Teeth index score was determined (Broadbent & Thomson, 2005). USF and mechanical salivary flow (MSF) of whole saliva rate were measured with a technique described in previous studies (da Mata et al., 2009; da Silva Marques et al., 2011). After screening, participants were randomly allocated to one of the two groups (A or B) according to QuickCalcs (GraphPad Software).

Since the two products used different delivery systems, concealment of allocation from the participants and clinicians was not possible. However, the data collected were analysed by a third party blinded to the allocation with the treatments referred to only A or B.

Participants were instructed to discontinue the use of any drug with muscarinic agonist action (manly pilocarpine) 24 hr before saliva collection and to present themselves between 2 and 4 p.m. at the laboratory the following week. The participants were told to refrain from

eating, drinking for 2 hr and to wait at least 1 hr after brushing, with a manual toothbrush, with a toothpaste already applied (Medibase®), prior to the appointment to minimize effects of diurnal variability in salivary composition (da Mata et al., 2009; Moritsuka et al., 2006).

2.2.2 | Visit 2

Upon arrival at the laboratory, participants were instructed to brush their teeth as previously described. The Portuguese versions of the Xerostomia Inventory 5 (SXI-5-PL) and the Oral Health Impact Profile (OHIP-14-PT; Amaral, Marques, Thomson, Vinagre, & da Mata, 2018a; Amaral, Sanches, et al., 2018b) questionnaires were administered to the patients for establishing their baseline values before the usage of one of the systems. The original SXI is a questionnaire comprising five questions from which the respondent can choose from three available answers. The scores are summed, with the result representing the degree of xerostomia the participant feels. The OHIP-14 questions are divided into seven domains each measuring a different dimension, briefly: functional limitation (Q1 and Q2), physical pain (Q3 and Q4), psychological discomfort (Q5 and Q6), physical disability (Q7 and Q8), psychological disability (Q9 and Q10), social disability (Q11 and Q12) and handicap (Q13 and Q14). The score is calculated by adding the score of the respective questions, and as such, each domain has a total possible score of eight. The highest possible score equates to 56 indicating a very poor quality of life.

Both questionnaires were administered using a standardized format. The participants were encouraged to give the answer that immediately came to mind. Participants were also encouraged to ask the interviewer to repeat the question if any aspect of the question was not understood.

USF and MSF of whole saliva at the same time were determined following established methods (da Mata et al., 2009; da Silva Marques et al., 2011). USF was collected over a 15-min span, while MSF was determined by chewing a paraffin tablet (CRT Buffer; Ivoclar Vivadent), and the saliva was collected to preweighed volumetric tubes at the 2, 4, 6, 8, 10, 15 and 20 min' mark (to determine salivary flow variation during GSSS use) and the tubes again weighed with stimulated salivary flow rate determined in ml/min.

Finally, the system allocated to the patient was delivered for use in the following fortnight (Period 1) with the manufacturer's instructions. Both the acid malic lozenge and citric acid mouthwash were used four times a day for 2 weeks. Patients were instructed to apply the acid malic lozenge on the dorsal surface of the tongue until completely dissolved. On the other hand, patients were instructed to rinse the mouth for 1 min, before spitting, to apply the citric acid mouthwash.

2.2.3 | Visit 3

Upon arrival at the laboratory, participants were again instructed to brush their teeth and wait for an hour. USF and gustatory-stimulated salivary flow (GSF) of whole saliva were determined by established methods (da Mata et al., 2009; da Silva Marques et al., 2011). GSF instead of using the paraffin tablet used the stimulants being tested, and due to their different natures, different instructions were supplied. As such, the participants were instructed to place the lozenge on the dorsal surface of the tongue and to signal when it completely dissolved. In the citric acid mouthwash group, the participants were instructed to rinse with a volume of 20 ml for 1 min and to spit out without rinsing with water, and then, GSF was collected.

The OHIP-14-PT and SXI-5-PL questionnaires were again applied, and instructions were given for the following washout period (15 days) in which the participant should resume their normal routine. The rationale for this washout period was that gustatory stimulants of salivary secretion (GSSS) have a very short-term effect, which disappears rapidly upon GSSS withdrawal. Moreover, Sjögren's syndrome is a chronic condition with patients experiencing heavy xerostomia with marked effects, and thus, symptoms reappear quickly when the GSSS is removed.

2.2.4 | Visit 4

The participants were delivered both questionnaires to establish their new baseline values. USF and MSF were also determined. The crossover was applied, and the system not used the first time was allocated to the participant (Period 2).

2.2.5 | Visit 5

Finally, after 15 days of use the participants were again administered both questionnaires and USF and GSF determined.

2.3 | Statistical analysis

Data were analysed using SPSS 23.0 statistics software (SPSS_Inc). From a previous study, the authors of the XI-5 have determined 4 to be the minimal important difference (MID) of the total score (Thomson et al., 2011). From a pilot study, we anticipated the standard deviation (*SD*) of the total XI score to be three (da Mata et al., 2012). Therefore, recruiting 40 participants per group would allow the detection of a difference of two (50% of the putative MID) units in the total XI score between groups with a power of 80% and an alpha of 5% with a possible attrition of 20%.

Normality of distribution was evaluated using the Shapiro–Wilk test for normality of distribution ($\alpha = 0.05$). The data sets were normally distributed. The *t* tests were performed with equal variances not assumed.

Primary outcomes were defined as the variation in xerostomia's self-perception scores measured with the total SXI-5-PL questionnaire and the scores obtained in the OHIP-14-PT questionnaire (total score and subdomains) before and after the administration of the

TABLE 1 Demographic and oral parameter data of both groups in sample population

	Malic acid lozenge group		Citric acid mouthwash group	
	Mean	95% CI	Mean	95% CI
Age	**58.5**	**55.3–61.8**	**59.5**	**56.5–62.6**
Gender				
Female	66		68	
Male	1		1	
Academic degree				
Pregraduate degree	53		54	
Professional/technical degree	2		2	
Bachelor degree	8		8	
Postgraduate degree	4		5	
Occupational status				
Employed	26		27	
Unemployed	10		9	
Student	1		1	
Retired	30		32	
Own residence				
Yes	52		52	
No	15		17	
Marital status				
Single	5		5	
Married	45		45	
Cohabiting partners	1		1	
Divorced	7		8	
Widow	9		10	
Unstimulated salivary flow (ml/min)	0.04	0.04–0.05	0.05	0.04–0.05
Mechanical stimulated salivary flow (ml/min)	0.53	0.41–0.64	0.52	0.42–0.63
DMFT index	18.4	16.8–20.1	18.4	16.9–20.0

interventions. Partial scores for each domain were obtained, and total score was calculated by adding up the partial scores as previously described.

Questionnaires were obtained at each visit as described earlier. Secondary outcome was defined as the salivary flow variation and total salivary output produced. Fisher's exact test was used to test for differences among categorical variables, *Z* test was used to test differences between groups whenever expressed as proportions, and independent or paired *t* tests were used as appropriate (namely, in all before/after within-subject analysis) to test for differences between and within groups, respectively.

Since it is widely accepted that simpler expression of aggregate scores and assessing statistical significance of differences in patient-related outcomes (PROs) are insufficient for result description and interpretation, score change distribution, effect sizes (ES; calculated by the Glass Δ equation; Fan & Konold, 2010; Ialongo, 2016), standardized response mean (SRM) and standard error of measurement (*SEM*) were calculated as recommended in TsakosAllen, Steele, and Locker (2012). ES and SRM were considered as small (<0.3), moderate (0.3–0.8) or large (≥0.8) effect.

A general linear univariate model was carried out to determine the contributions of the putative explanatory variables that we have accounted for with possible effect on the outcomes. These are depicted in Table 1 as intervention product (acid malic lozenge or citric acid mouthwash), period of administration (before or after crossing over), professional status (from stable employment to retired), marital status (from married to divorced), academic qualification (from undergraduate degree to postgraduate degree), residency situation (owner or not), wearer of removable dental prosthesis (wearer or not) and periodontal status (presence of periodontal disease or not) on primary and secondary outcomes. Since the bivariate approach does not account for any effects of the crossover design (assuming random distribution about the true treatment effect), this model enabled the possibility of accounting

for period effects, period by treatment interaction, carryover and patient by period interaction (Khalessi, Pack, Thomson, & Tompkins, 2004). Multiple pairwise tests with the Bonferroni correction were applied to all levels of each predictive variable in the univariate model between the two intervention groups, and significance was set at $\alpha = 0.05$ (Supporting information 1).

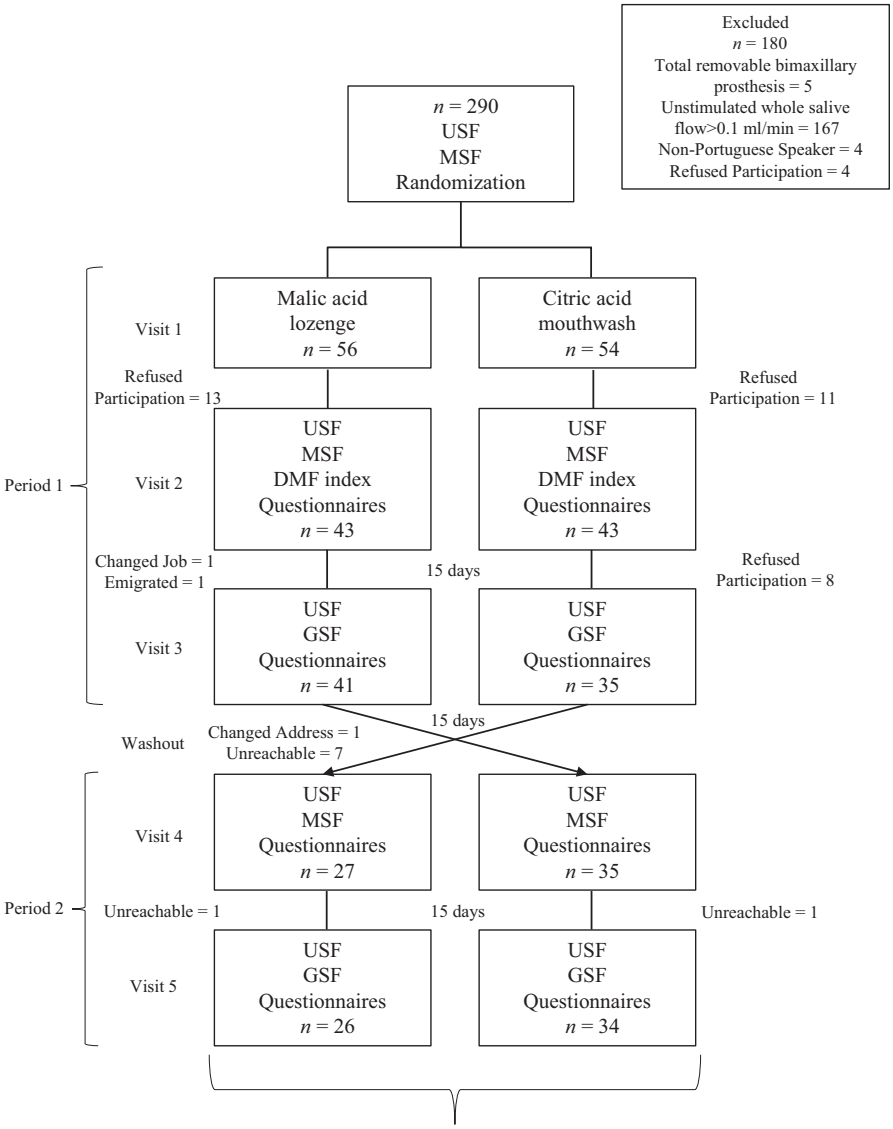
3 | RESULTS

Eligible participants were screened, and a total of 110 were enrolled. Randomization assigned 56 participants to the malic acid lozenge group and 54 to the citric acid mouthwash group. Losses to follow-up and their reasons are described in Figure 1. Recruited participants' demographic characteristics are summarised in Table 1.

After follow-up losses, in the malic acid group, 41 participants in Period 1 and 26 in Period 2 completed the study, for a total of 67 participants. In the citric acid group, 35 participants in Period 1 and 34 in Period 2 completed the study, for a total of 69 participants.

3.1 | Self-perception of xerostomia (SXI-5-PL) and oral health-related quality of life (OHIP-14-PT)

Summary data on the SXI-5-PL are presented in Table 2. There were no significant differences between groups whether at baseline or at the end of the study. In the malic acid lozenge group, there



	Period 1	Period 2	Total
Malic acid lozenge	41	26	67
Citric acid mouthwash	35	34	69

FIGURE 1 Study design and participation

TABLE 2 Mean and standard deviation for total score in the SXI-5-PL questionnaire before and after usage of both systems and standard error measurement (*SEM*), standard response mean (SRM) and effect size (ES) in the score variation

	Malic acid lozenge (*n* = 67)						Citric acid mouthwash (*n* = 69)					
	Before	**After**	**Δ Score**	***SEM***	**SRM**	**ES**	**Before**	**After**	**Δ Score**	***SEM***	**SRM**	**ES**
	$\bar{x}$ *SD*	$\bar{x}$ *SD*	$\bar{x}$ *SD*	1	**−0.5**	**−0.4**	$\bar{x}$ *SD*	$\bar{x}$ *SD*	$\bar{x}$ *SD*	0.7	−0.1	−0.1
Total score	12.5 (2.3)	11.7 (2.6)	−0.8* (1.7)				12.4 (2.4)	12.2 (2.2)	−0.2 (1.4)			

Note: In bold, we have the moderate effect size values, which appear in the malic acid lozenge group only (>0.3).

*Means statistically significant at $p < .05$

TABLE 3 Mean and standard deviation for each domain in the OHIP-14-PT questionnaire and total score before and after usage of both systems and standard error measurement (*SEM*), standard response mean (SRM) and effect size (ES)

	Malic acid lozenge (*n* = 67)						Citric acid mouthwash (*n* = 69)					
	Before	**After**	**Δ Score**				**Before**	**After**	**Δ Score**			
Domains	$\bar{x}$ *SD*	$\bar{x}$ *SD*	$\bar{x}$ *SD*	***SEM***	**SRM**	**Effect size**	$\bar{x}$ *SD*	$\bar{x}$ *SD*	$\bar{x}$ *SD*	***SEM***	**SRM**	**Effect size**
Functional limitation	3.1 (1.8)	2.8 (2)	−0.3 (1.4)	0.6	−0.2	−0.2	2.9 (2)	2.7 (1.8)	−0.1 (1.4)	0.7	−0.1	−0.1
Physical pain	3.7 (1.7)	3.2 (1.8)	−0.8* (1.4)	0.6	−0.6	−0.5	3.8 (2.1)	3.3 (1.9)	−0.4(2)	0.7	−0.3	−0.2
Psychological discomfort	4.5 (2.2)	3.2 (2.4)	−1.3* (2.3)	0.7	−0.6	−0.6	4.4 (2.7)	3.8 (2.6)	−0.6(2.4)	0.9	−0.3	−0.3
Physical disability	2.7 (2.0)	2.2 (2)	−0.4 (1.6)	0.7	−0.3	−0.2	2.7 (2.4)	2.3 (2.2)	−0.4(2.1)	0.8	−0.2	−0.2
Psychological disability	3.0 (1.9)	2.5 (1.7)	−0.5* (1.4)	0.6	−0.4	−0.3	2.9 (2)	2.6 (1.9)	−0.3(1.9)	0.7	−0.2	−0.2
Social disability	2.2 (2)	1.8 (1.9)	−0.3 (1.6)	0.7	−0.2	−0.2	2.6 (2.1)	2.3 (2.1)	−0.3(1.9)	0.7	−0.2	−0.2
Handicap	2.4 (1.9)	2.0 (1.9)	−0.4* (1.4)	0.6	−0.3	−0.2	2.8 (2.2)	2.4 (2.1)	−0.4 (2)	0.7	−0.2	−0.2
Total Score	21.5 (10)	17.8 (10)	−3.7* (7.4)	3.3	−0.5	−0.4	22 (12.2)	18.9(11.4)	−3.1* (8.9)	4.0	−0.3	−0.3

*Means statistically significant at $p < .05$.

was a significant improvement in the SXI-5-PL total score before and after the intervention, whereas in the citric acid mouthwash, no differences were observed. Considering the primary outcome (variation in xerostomia's self-perception scores), there was a significant difference between the two groups with the malic acid lozenge group showing a greater improvement in self-perception of xerostomia. The SXI-5-PL total score ES and SRM were moderate in the malic acid lozenge group while small in the citric acid mouthwash group.

Table 3 presents the results for the dimensional and total OHIP 14 scores. There were no significant differences between both groups at baseline and the end of the study ($p < .05$, *t* test). Within the malic acid lozenge group, there was a significant improvement between the baseline and the end of the study for the physical pain, psychological discomfort, psychological disability and handicap dimensions and also for the total OHIP14 scores, whereas functional limitation, physical and social disability showed no differences (paired *t* test). In the citric acid mouthwash group, only the total OHIP14 score showed a significant difference between the baseline and the end of the study. Considering the primary outcome (variation in OHIP scores), there were no significant differences between groups. However, with respect to ES, SRM and *SEM* for OHIP-14-PT, considering the malic acid lozenge group, the ES and SRM ranged from small to moderate with the highest effect sizes (corresponding to moderate) observed for the physical pain and psychological discomfort dimensions and the total score. Conversely, in the citric acid mouthwash group, the SRM and ES showed only small values.

Table 4 shows the percentage distribution (95% CI) of improved, no change and deterioration response scores for the SXI-5-PL and OHIP-14-PT. Despite the fact that a greater percentage of improved responses was observed in the malic acid lozenge group (except for the Social Disability OHIP-14-PT dimension) than in the citric acid mouthwash group, no significant differences were found between groups (*Z* test for proportions). Within each group and considering the SXI-5-PL total score, the malic acid lozenge group showed a significant increase in the percentage of improved responses relative to the deteriorations score. No significant differences were found between improvement and deterioration scores in the citric acid mouthwash group. Concerning the OHIP-14-PT, although an increase in improvement scores was registered within both groups, in the malic acid lozenge group there was a significant difference in the percentage of improved responses for total score and every dimension (excepting for social disability) from the deterioration score. In the citric acid mouthwash group, there were only differences in the percentage of improved responses for the total OHIP score and the dimensions such as physical pain, psychological discomfort and physical disability ($p < .05$ *Z* test for proportions).

The results of the multivariate analysis are shown in Table 5. The order in which the treatment was administered had no effect on the outcomes. Moreover, there were no significant interactions between the period and the intervention for any of the outcomes. The intervention significantly affected all of the outcomes except for the variation in the OHIP-14-PT total score. No other predictive variable showed a significant effect on the outcomes or produced differences between groups (pairwise comparisons).

3.2 | Salivary secretion

Figure 2 summarises the mean (±95% CI) salivary flow changes over a 20-min span. In both groups, the GSSS elicited a significant increase in the salivary flow followed by a progressive decrease but recovering basal levels only after the 20-min period. The malic acid lozenge group produced a significantly higher salivary output than the citric acid mouthwash group at the 4, 6, 8, 10, and 15 min' mark ($p < .05$). Dissolution corresponds to the time when the patient reported the complete elimination of the lozenge.

TABLE 4 Percentage distribution (95% CI) of improved (+, questionnaire score presents better OHRQoL), no change (=) and deterioration (−) in both questionnaires

	Malic acid lozenge ($n = 67$)			Citric acid mouthwash ($n = 69$)		
ΔScores	+ % (95% CI)	= % (95% CI)	− % (95% CI)	+ % (95% CI)	= % (95% CI)	− % (95% CI)
Total XI 5 score	45* (30–53)	40 (28–52)	15 (6–24)	38 (26–49)	36 (25–47)	26 (16–36)
Functional limitation	42* (30–54)	33 (22–44)	25 (15–35)	33 (22–44)	46 (34–58)	21 (11–29)
Physical pain	58* (46–70)	27 (16–38)	15(7–24)	50* (39–63)	28 (17–39)	22 (12–31)
Psychological discomfort	54* (42–66)	30 (19–41)	16 (7–25)	48* (36–60)	33 (22–44)	19 (10–28)
Physical disability	43* (31–55)	46 (34–58)	11 (3–17)	33* (22–44)	48 (36–60)	19 (10–28)
Psychological disability	40*(28–52)	44 (31–55)	16 (7–25)	38 (27–50)	39 (28–51)	23(13–33)
Social disability	34(23–45)	42 (30–54)	24 (14–34)	38 (27–50)	38 (27–50)	24 (14–34)
Handicap	43* (31–55)	33 (22–44)	24 (14–34)	38 (27–50)	33 (22–44)	29 (18–40)
Total OHIP−14 Score	72* (61–83)	5 (0.3–12)	23 (12–32)	62* (51–73)	6 (0.4–12)	32 (21–43)

*Means statistically significant at $p < .05$.

TABLE 5 Effect of predictive variables on changes in SXI-5-PL and OHIP-14-PT score variation and total salivary output, outcome of general model analysis

Model	Coefficient	Standard error	*t* statistic	*p* value
ΔTotal SXI−5-PL score				
Intercept	−1.89	2.64	−0.72	.48
Product treatment time periods	0.01	0.59	0.12	.99
Treatment group	−1.01	0.47	−2.15	.03*
Professional status	0.66	0.62	1.06	.29
Marital status	−0.45	1.49	−0.30	.77
Academic qualification	0.99	1.56	0.63	.53
Residency situation	0.13	0.42	0.31	.76
Wearer of removable dental prosthesis	0.81	1.18	0.69	.49
Periodontal status	−0.34	0.44	−0.78	.43
ΔTotal OHIP−14-PT				
Intercept	0.35	13.70	0.03	.98
Product treatment time periods	−5.40	3.07	−1.76	.08
Treatment group	−3.85	2.44	−1.57	.12
Professional status	1.38	3.22	0.43	.67
Marital status	3.76	7.71	0.49	.63
Academic qualification	−4.01	8.09	−0.50	.62
Residency situation	4.59	2.16	2.12	.06
Wearer of removable dental prosthesis	0.36	6.1	0.06	.95
Periodontal status	0.28	2.28	0.12	.9
Total salivary output				
Intercept	0.21	0.28	0.73	.47
Product treatment time periods	−0.03	0.07	−0.48	.63
Treatment group	0.16	0.07	2.42	.02*
Professional status	0.01	0.11	0.01	.99
Marital status	0.41	0.17	2.39	.06
Academic qualification	−0.01	0.19	−0.6	.96
Residency situation	0.06	0.06	1.08	.28
Wearer of removable dental prosthesis	−0.39	0.25	−1.56	.12
Periodontal status	−0.11	0.07	−1.58	.12

*Means statistically significant at $p < .05$.

Figure 3 presents mean (±95% CI) salivary output for GSF and MSF. GSSS elicited salivary output was significantly greater in the malic acid lozenge group than in the citric acid mouthwash group. Moreover, in the citric acid mouthwash group, salivary output was significantly smaller than the mechanical induced output, whereas for the malic acid lozenge group, no differences were detected ($p < .05$, *t* test).

4 | DISCUSSION

The findings of this trial strongly suggest that gustatory stimulants of salivary secretion (GSSS) can diminish xerostomia and improve OHRQoL. In relation to the second hypothesis of the study, it is also suggested that, in participants with SS, the use of GSSS containing malic acid (relative to a GSSS in a form of a rinsing solution) produces improvements in xerostomia and OHRQoL. The findings also confirm that GSSS are effective in stimulating salivation, with the lozenge group being significantly more effective in stimulating salivary secretion. Therefore, the findings of this investigation strongly suggest that the GSSS in the form of malic acid-containing lozenge is more effective than a citric acid-based rinsing solution.

GSSS are important because they represent an interesting alternative to systemic pharmacological stimulants such as pilocarpine, which have pharmacological interactions and numerous side effects.

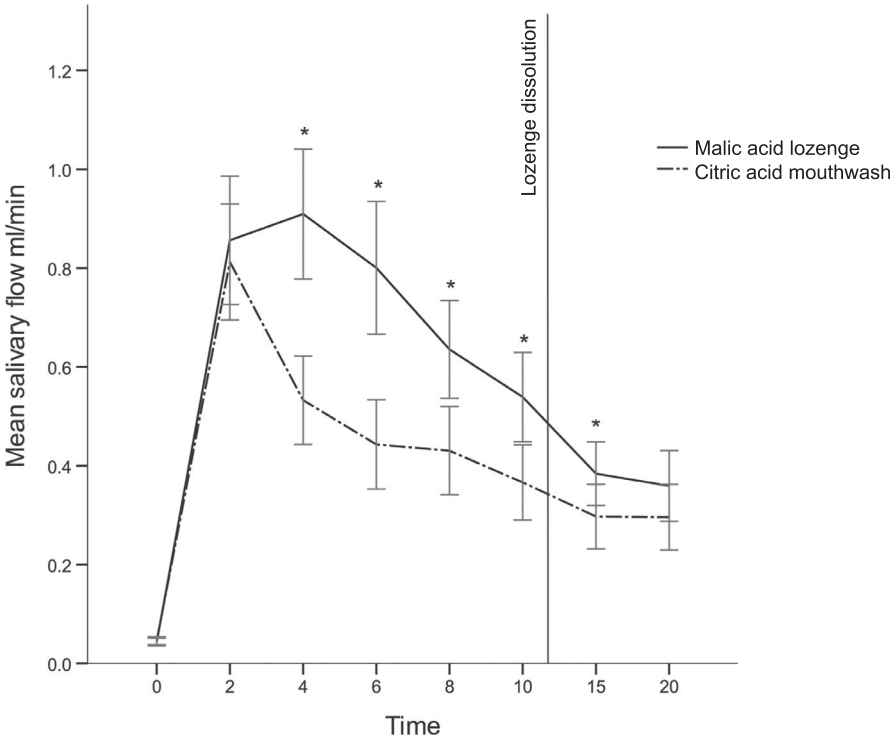


FIGURE 2 Mean (±95% CI) gustatory salivary flow (ml/min) over time in the malic acid lozenge and citric acid mouthwash group collected in visit 3 and 5. *Means statistically significant at $p < .05$

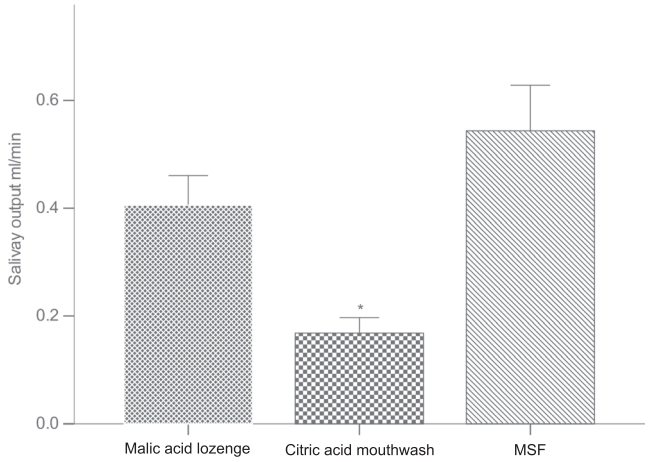


FIGURE 3 Mean (±95% CI) salivary output produced by both gustatory and mechanical stimulation of salivary secretion (GSF and MSF). *Means statistically significant at $p < .05$

In Portugal, several national institutions and hospitals provide xerostomia patients with a custom-based critic acid-based rising solution to stimulate saliva. However, many patients have difficulties in accessing the institution on regular basis and need other therapeutic options. Marketed GSSS in a form of lozenges are obtained easily over-the-counter. Previous studies suggested both malic and citric acid lozenges to be equally effective in stimulating salivation (da Mata et al., 2009; da Silva Marques et al., 2011). Differently, in this study the malic acid lozenges were more effective than the citric acid solution in stimulating saliva. It may be that using a solution instead of lozenge may produce less mechanical salivary stimulation. However, this was an effectiveness RCT with a pragmatic approach aiming at comparing established practices. One concern about the use of GSSS in dentate patients is its erosion potential due to the acidic nature of these products. Nevertheless, previous authors have suggested that malic acid had a significantly lower risk for erosion than citric acid (da Silva Marques et al., 2011). Moreover, malic acid-based lozenges also include fluoride, and this may promote increased remineralization and a more favourable benefit-to-harm ratio (da Silva Marques et al., 2011).

Despite the fact that previous studies have suggested that GSSS are effective in stimulating salivary secretion, to our knowledge very few studies have looked upon the effects of these products on PROs (Ní Ríordáin et al., 2015). In this study, however, interpreting the PROs must be done with caution since due to the bidirectional nature of scores, a simple comparison of aggregate answers may be insufficient to provide accurate information about the real meaning of the data (Tsakos et al., 2012, 2010). It is why we followed several recommendations for reporting and interpreting PROs in longitudinal studies (Tsakos et al., 2012).

Where the primary outcomes are concerned, the malic acid-based lozenges produced a significant improvement in the SXI-5-PL and a greater proportion of improvement for every item in both SXI-5-PL and OHIP-14-PT than the citric acid mouthwash.

Moreover, the GSSS in form of a lozenge produced a larger effect on PROs, with ES and SRM for the SXI-5-PL and OHIP-14-PT ranging from small to moderate, while they were very small to small for the citric acid mouthwash. Moreover, SRM and ES were similar in magnitude, which indicates that the Cohen threshold may be used (Middel & van Sonderen, 2002; Tsakos et al., 2012). In the lozenge group, the variations of the measurements before and after the intervention were larger than the standard error of measurement (*SEM*) for the

physical pain, psychological discomfort domains and OHIP-14-PT total score, while in the mouthwash group, the variation was always smaller than the *SEM*. This may imply that the effect in the lozenge group is more consistent and reliable since the findings in the mouthwash group can hardly be dissociated from measurement error.

One important measure in explaining longitudinal data related to QoL is the minimal important difference (MID), which has been defined as the value scored in the domain of interest, in which patients perceive a beneficial improvement and which would mandate a change in the patient's management(Barrios et al., 2015; Revicki, Hays, Cella, & Sloan, 2008; Tsakos et al., 2012, 2010; Wyrwich, Nienaber, Tierney, & Wolinsky, 1999). The MIDs for the SXI-5 and OHIP-14 have been reported to be four and five, respectively (Locker, Jokovic, & Clarke, 2004; Thomson et al., 2011). However, other authors have suggested that the MID would correspond to the *SEM* and this was observed to hold for patients with cancer and periodontitis (Wyrwich, 2004). It is also known that the MID of the same instrument may differ considerably with the condition affecting the patients. There are no determinations for the MID in SS patients. These patients experience extreme xerostomia, and it could be argued that small changes can be highly perceived, which would lower the MID. If one considers the MIDs proposed by Thomson and Locker (Locker et al., 2004; Thomson et al., 2011) respectively for the SXI-5-PL and OHIP-14-PT, the findings of this study are well under the MID values for both products. However, if considering Wyrwich rules where the MID tends to be equal to the standard error of measurement and in this case the lozenge group results were quite above the MID but not for the mouthwash group (Wyrwich, 2004), the lozenge group produced similar and greater changes above the MID for the SXI-5-PL and some categories of the OHIP-14-PT, respectively. However, independently of the type of calculation in the mouthwash group results remained well under MID.

Another important finding is that the biggest effect and score difference were obtained in the malic acid lozenge group for the psychological discomfort dimension of the OHIP-14-PT. This is noteworthy because it has been suggested that patients with xerostomia experience an increased prevalence of anxiety and depression (Lopez -Jornet et al., 2016). In the malic acid lozenge group, the difference was nearly twice the MID, suggesting that the GSSS from this group provide considerable improvement in this dimension. From this perspective, this investigation also provides important information towards the establishment of a MID in SS patients.

This study has some limitations. Masking the intervention was not possible since products were completely different. However, the data were analysed by a third party who received a spreadsheet without identifying the study groups. Future studies should consider longer follow-up times to verify the longer-term stability of the findings due to the chronic nature of the condition. The external validity of the study is somewhat narrow since only PSS patients were recruited. It would be interesting to extend this study to other populations and for more RCTs to be designed and conducted. However, whereas SS is concerned, this was a classical SS population to whom these findings can be generalized.

In conclusion, GSSS can stimulate saliva, provide xerostomia relief and improve QoL. Lozenges containing malic acid and fluoride are more effective than citric acid-based rinsing solutions at producing greater saliva stimulation and xerostomia relief and providing an improved quality of life, especially where psychological comfort is concerned.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Professor António Mata was the principal investigator responsible for the study. He mentored the study design and proceeded to write the final version of the manuscript in collaboration with Professor Murray Thomson. Professor Duarte Marques was the study coordinator and supervised all aspects of the implementation and development of this study. Professor. João Amaral, Dr. Ruben Pereira, Dr. Filipe Barcelos and Dr. Filipe Vaz Patto carried out the diagnostic and recruitment of patients as well as data collection and its analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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