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Effects of gustatory stimulants of salivary secretion on salivary pH and flow in patients with Sjögren's syndrome: a randomized controlled trial

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OBJECTIVES: To compare salivary pH changes and stimulation efficacy of two different gustatory stimulants of salivary secretion (GSSS) in patients with primary Sjögren syndrome.
SETTING: Portuguese Institute for Rheumatological Diseases.
DESIGN: Double-blind randomized controlled trial.
SUBJECTS: Eighty patients were randomized to two intervention groups. Sample size was calculated using an alpha error of 0.05 and a beta of 0.20.
MATERIALS AND METHODS: Participants were randomly assigned to receive a new GSSS containing a weaker malic acid, fluoride and xylitol or a traditionally citric acid-based one. Saliva collection was obtained by established methods at different times. The salivary pH of the samples was determined with a pH meter and a microelectrode.
MAIN OUTCOME MEASURES: Salivary pH variations and counts of subjects with pH below 4.5 for over 1 min and stimulated salivary flow were the main outcome measures.
RESULTS: Both GSSS significantly stimulated salivary output without significant differences between the two groups. The new gustatory stimulant of salivary secretion presented an absolute risk reduction of 52.78% [33.42–72.13 (95% CI)] when compared with the traditional one.
CONCLUSIONS: In Xerostomic Primary Sjögren syndrome patients, gustatory stimulants of salivary secretion based on acid mail only with fluoride and xylitol present similar salivary stimulation capacity when compared to citric acid-based ones, besides significantly reducing the number of salivary pH drops below 4.5. This could be related to a diminished risk for dental erosion and should be confirmed with further studies.
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Keywords: dental erosion; gustatory stimulants; randomized controlled trial; saliva; Sjögren's syndrome

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Introduction

Primary Sjögren syndrome (PSS) is a chronic systemic autoimmune disease of unknown etiology characterized by inflammation of the exocrine glands namely the salivary and lachrymal, without the association of connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, primary biliary cirrhosis, and scleroderma (1, 2). The prevalence of Sjögren's syndrome is estimated between 0.5% and 1.5% predominantly affecting women (female/male ratio being approximately 9:1) and mostly observed in middle-aged individuals (3, 4). The most prevalent symptoms in patients with PSS are dry mouth and dry eye (5, 6), which can equate with significant discomfort and pain from dryness and if left untreated may also lead to complications such as sleep disturbance, difficulties with eating, and speaking that markedly decrease the patient quality of life (6–8). Diminished salivary flow rate in patients with PSS can increase caries and dental erosion risk (9–11). Therefore, measures which stimulate saliva secretion and consequently augment its buffer capacity, have been referred as important factors in preventing dental erosion and promoting remineralization.

Stimulating salivary output in PSS patients who have functioning salivary glands using sugar-free acidic hard candies or commercially free available lozenges for

gustatory stimulation of salivary secretion has been widely used and some patients depend on these products extensively (12, 13). However and albeit, usually sugar free, these gustatory stimulants of salivary secretion (GSSS) are composed of different acids (e.g. citric, tartaric or phosphoric), some of which have been proved to have an intrinsic erosive potential (12, 14–16).

More recently, a new acid xylitol-fluoride-containing GSSS (Xeros^{TM}; Dentaid, Cerdanyola, Spain) has been indicated for use in xerostomic patients, with the claim that its composition is only based on a weaker acid (malic acid) without addition of stronger acids like citric acid which are commonly present in this class of products. Moreover, Xeros fluoride ions and xylitol content could lower the erosive and cariogenic potential of this product (17–20). However, independent studies to assess the efficacy of salivary stimulation of GSSS and its putative erosive potential on xerostomic patients are to our knowledge inexistent but needed.

The aim of this randomized controlled trial was to study the erosive potential and salivary stimulation efficacy of an acidic xylitol-fluoride-containing GSSS (Xeros^{TM}) (malic acid 4.33% w/w), and compare it with a traditional citric acid-added GSSS (SST) (Sinclair Pharma Plc, Godalming, UK) (malic acid 4.2% and citric acid 2.1% w/w) in patients with PSS.

Our *a priori* hypothesis was that the malic acid-based GSSS increases salivary secretion and is safer regarding dental erosion when compared with a traditional citric acid-based GSSS.

Materials and methods

Study participants

Study participants were recruited between March and April 2010 from the Portuguese Institute for Rheumatological Diseases. Recruitment was supervised by research assistants.

The inclusion criteria for entry into the trial were: (i) Primary Sjögren syndrome diagnosis according to the American-European Consensus Group; (ii) unstimulated whole saliva flow <0.1 ml/min; (iii) stimulated whole saliva flow >0.2 ml/min and (iv) more than 18 years of age.

Written informed consent was obtained from all eligible participants at the first stage of screening and before study admission. All patients had a full medical history and saliva samples were collected at the Portuguese Institute for Rheumatological Diseases or at the Oral biochemistry and Biology Research Group (GIBBO) laboratory. The study protocol was approved by the local institutional ethical committees and was completed accordingly to the guidelines of Good Clinical Practice and conducted in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

Study protocol and intervention

This randomized controlled study, with two parallel groups, was carried out between May and August 2010.

Visit 1

During visit 1 inclusion criteria were verified for each participant. Unstimulated and mechanical-stimulated whole saliva flow rate were measured (5 min collection per sample) to demonstrate some residual salivary function and a full medical history was performed to screen any clinically significant condition and medication.

Upon screen, patients were then consecutively randomly allocated to one of two groups named A and B accordingly to a computer-generated randomization software (GraphPad QuickCalcs Web site: http://www.graphpad.com/quickcalcs/randomize1.cfm accessed March 2010). Both GSSS were transferred by foreign personnel into two identical opaque flasks labeled A and B containing respectively, either the GSSS Dentaid which was considered the new GSSS group (N) or the traditional GSSS which was considered as the citric acid group (C). A code for randomization was kept in an opaque envelope in a safe environment and opened only at the end of the study. Data were analyzed by a third party blinded to the allocation results, which were at that point referred as treatment A or B in the SPSS worksheet (SPSS 16.0, Inc., Chicago, IL, USA).

From there, participants were instructed that 24 h before saliva collection they should discontinue the use of any drug with muscarinic agonist action (Pilocarpine) and to present themselves between 8 and 11 am at the laboratory the following weeks. The participants were told to refrain from eating, drinking (except water) for 2 h and should wait at least 1 h after brushing prior to the investigation to minimize effects of the diurnal variability in salivary composition (visits 2 and 3) (12, 21, 22).

Visit 2

Upon arrival at the laboratory, participants were instructed to brush their teeth with a given medium soft-bristled manual toothbrush (Akzenta, Lugano, Switzerland) and a dentifrice (Aquafresh Extreme Clean, GlaxoSmithKline, Brentford, UK), and wait for 1 h.

Unstimulated whole saliva flow rate (baseline value) was measured in duplicate by a method described by Navazesh et al. (15 min collection per sample) (23).

Mechanical-stimulated salivary secretion rate was measured by a previously established method (12).

The saliva buffer capacity was determined by a modified method from Kitasako, and described by Mata et al. (12, 24).

Masticatory stimulation of saliva was done in order to determine the individual mechanical-stimulated salivary secretion capacity as this is considered an important baseline characteristic, which was afterwards used to evaluate the homogeneity of salivary function capacity between the two groups. Salivary buffering capacity was determined as it can act as confounding variable since it has been widely considered as a major salivary factor with influence on dental enamel protection.

Visit 3

Upon arrival at the laboratory participants were again instructed to brush their teeth with a given toothbrush

and dentifrice and wait for an hour. Resting salivary secretion, GSSS stimulated salivary secretion and erosive potential were determined by previously established methods. For the determination of predictive risk for dental erosion we recurred to a simple marker namely the amount of time of exposition (min) to salivary pH below 4.5, and a contingency table compiling the counts of subjects with pH drops below 4.5 for over 1 min was obtained.

Absolute risk reduction was calculated as the difference ±95% CI between the C and N groups event rates (25). Number needed to treat is expressed as the inverse ratio of the absolute risk reduction (25).

Outcomes

Primary outcome

Time of GSSS induced pH drop below 4.5 expressed in minutes as the mean ± 95% CI. Additional analyses were done to calculate association measures like the absolute risk reduction (ARR) and number needed to treat (NNT).

Secondary outcomes

GSSS induced salivary pH variations expressed as the mean ± 95% CI of the three pH measures obtained from salivary samples at defined time points.

GSSS stimulated salivary flow expressed in ml/min as the mean ± 95% CI of stimulated salivary flow obtained at different time points.

Overall stimulated salivary flow was calculated and expressed in ml/min as the mean ± 95% CI of the total volume of stimulated saliva divided by the total time of each experiment which is 20 min.

Salivary stimulation output defined as the difference between GSSS until complete dissolution of the lozenge and basal salivary flow or the difference between mechanical and basal salivary flow, expressed as ml/min.

Sample size

According to previous results published by our group employing GSSS on salivary pH of healthy adults (12) we expected the control event rate of counts of subjects with pH drops below 4.5 for over 1 min to be at least 95%.

To compare event rates in the two groups using a Fisher exact test, to detect a difference of 25% between groups with a power of 80% and significance level of 0.05, 30 patients per group need to be enrolled. Enrolling 40 patients per group would allow an attrition bias of 25%.

Statistics

All data analysis was carried out according to a pre-established plan. Data and analyses were computed using a computer statistical package (SPSS v.16; SPSS Inc.). Discrete data were analyzed using Fisher exact test and direct 95% CI analysis.

Means of salivary flow, salivary pH, and time of pH drop below 4.5 were analyzed with paired or independent Student's *t*-test or ANOVA and *post hoc* (Tamhane's) tests as appropriate. Two-sided significance tests were used throughout.

Results

Participant follow-up and baseline characteristics

A total of 80 persons were selected for participating in the study (Fig. 1). They were randomly assigned to one of the two study groups and followed until the end of study. Eight patients were lost to follow-up. Patients with SS are predominantly female, with onset of symptoms and diagnosis typically occurring in middle age (2, 26, 27) which is consistent with enrollment in this study (100% women with the patient with the youngest age of 35 years old). The baseline characteristics of the subjects of the two groups are shown in Table 1. Chi-squared test and Student's *t*-test were employed for testing differences between categorical and continuous variables respectively. No differences ($P > 0.05$) were seen between baseline characteristics of the two groups.

Salivary pH variations

Figure 2 shows the results for salivary pH changes over time expressed as mean ± 95% confidence intervals. In both groups the GSSS induced a significant ($P < 0.05$, paired Student's *t*-test) drop in salivary pH followed by a slow recovery which for both groups failed to return to basal levels after 20 min.

The N group produced less accentuated pH drops during the GSSS dissolution which were statistically significantly different ($P < 0.05$, independent Student's *t*-test) compared with C group during the initial 8 min.

Figure 3 shows the mean time of salivary pH below 4.5 in minutes (TSB) (±95% CI) for overall and subgroups based on saliva buffer capacity for each group. Within each group (N or Control) salivary high buffer capacity produced inferior TSB values when compared with medium or low salivary buffer capacity subgroups, but the differences were not statistically significant (ANOVA plus *post hoc* Tamhane's test $P > 0.05$).

When comparing the mean TSB between the two study groups (N and Control) for overall, medium and high buffer capacity subgroup, the N group produced significantly diminished TSB values compared with control ($P < 0.05$ independent *t*-test). Table 2 shows the contingency table for number of participants in each group with TSB values above 1 min. From Table 2 the ARR and NNT were extrapolated with respective 95% CIs to give a quantitative association measure of the reduction in the risk of the GSSS driving the salivary pH for values under 4.5 for over 1 min.

AAR and NNT are presented only for overall TSB over 1 min values in the two main arms of this study. The N group presented an ARR of 52.78% [33.42–72.13 95% CI]. For TSB values over 1 min when compared with the control group the NNT was 2 (3–1 95% CI), meaning that for each two patients who took a N group GSSS an episode of TSB over 1 min was avoided.

Taken together these results suggest that the N GSSS presented a very significant diminished risk for lowering the salivary pH under 4.5 for prolonged times when compared with the control.

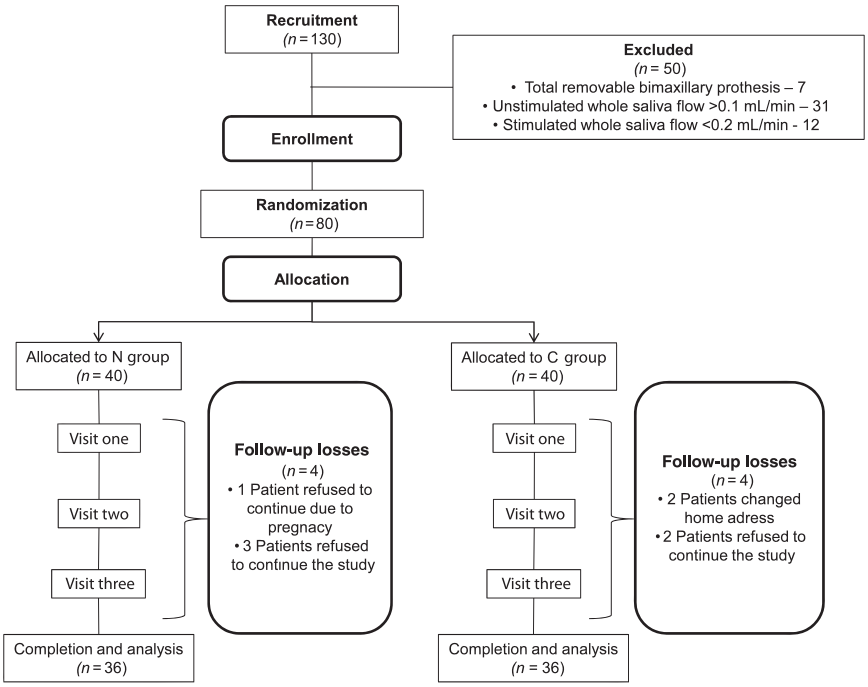

Figure 1 Study design diagram.

Table 1 Baseline characteristics, gender distribution and mean ± 95% CI for baseline characteristics

	N	*C*
Gender		
Male	0	0
Female	36	36
Age (years)	56.17 [52.37–59.96]	60.69 [56.82–64.57]
Non-stimulated salivary flow (ml/min)	0.066 [0.049–0.083]	0.066 [0.048–0.083]
Mechanical-stimulated salivary flow (ml/min)	0.44 [0.35–0.54]	0.42 [0.32–0.52]

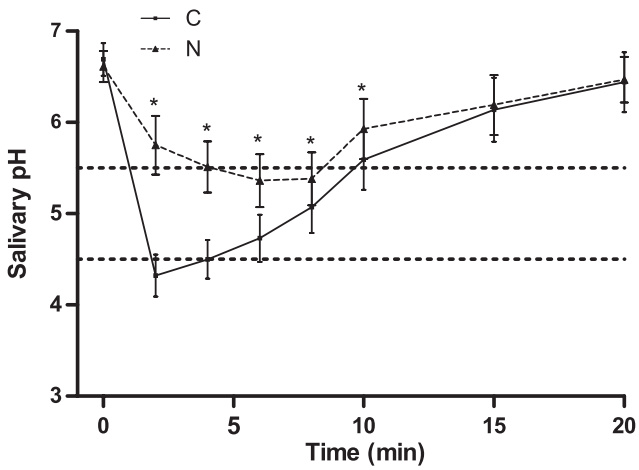

Figure 2 Mean (±95% CI) recordings of salivary pH changes induced by different gustatory stimulants of salivary secretion (GSSS). Traces are typical 40 experiments from 40 subjects. In both groups the GSSS induced a significant ($P < 0.05$, paired Student's *t*-test) drop in salivary pH levels followed by a slow recovery.

Salivary secretion

Figure 4 shows the results for mean ± 95% CI of salivary flow changes over time. In both groups the acidic lozenges elicited a significant ($P < 0.05$, paired Student's *t*-test) increase in the salivary flow followed by a progressive decrease but only reaching basal levels after the 20-min period. Dissolution corresponds to the time when the patient refers the complete elimination of the lozenge in the oral cavity. Figure 5 shows mean (±95% CI) for basal, GSSS stimulated and paraffin-stimulated salivary flow for each group. There were no significant ($P > 0.05$, independent Student's *t*-test) differences between the two groups for basal or stimulated salivary flow. Figure 6 shows the effects of the stimulants (mechanical or GSSS) on the output for both groups of the study. Within each group (N or Control) GSSS induced an higher output while the dissolution of the lozenge occurs when compared to mechanical stimulation, but differences were only statistically significant ($P < 0.05$, independent Student's *t*-test) for Group C.

Taken together the results suggest that N and Control presented a similar capacity in stimulating salivary secretion which was higher than mechanical stimulation in the same subjects.

Discussion

The results of this double-blind randomized controlled study, with two parallel groups, show that the use of GSSS in PSS patients can stimulate salivary secretion. Also, both GSSS induce salivary pH drops leading to the suggestion that under certain circumstances and in

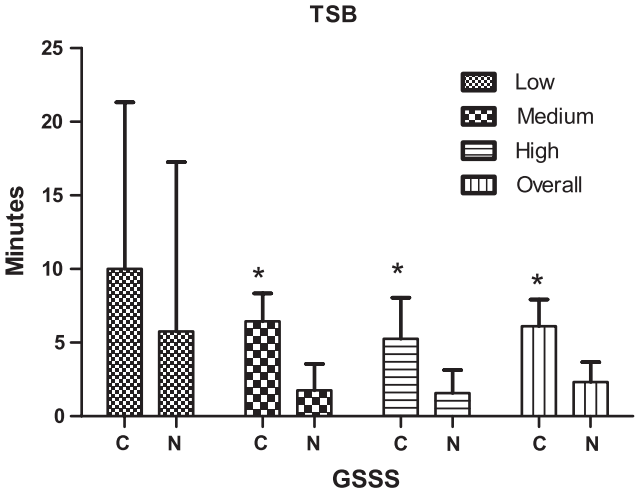

Figure 3 Bar charts showing the mean time of salivary pH below 4.5 in minutes (±95% CI) for overall and subgroups based on saliva buffer capacity for each group. When comparing the mean TSB between the two study groups (N and Control) for overall, medium and high buffer capacity subgroup, the N group produced significantly diminished TSB values compared with control ($P < 0.05$ independent *t*-test).

Table 2 Frequency distribution for number of participants in each group with salivary pH records below 4.5 for over 1 min. The absolute risk reduction and number needed to treat were extrapolated with respective confidence intervals to give a quantitative association measure of the reduction in erosion potential risk

pH below 4.5 for over 1 min			
	Present	*Absent*	*Total*
Group C	30	6	36
Group N	11	25	36
Total	41	31	72

susceptible patients it may represent an increased risk for dental erosion.

However, the ARR for the N group of 52.78% and the NNT of 2 indicate that for every two GSSS used of the N type an episode of effective salivary pH drop under 4.5 for over 1 min may be avoided compared with C type. Moreover, both types of GSSS tested in this trial elicited saliva stimulation with the same magnitude and pattern indicating similar efficacies in saliva stimulation and presented a higher capacity for chemical or gustatory saliva stimulation when compared with mechanical stimulation, although the differences were only statistically significant for Group C.

Thus, taken together the results of this study indicate that GSSS of the N type possess a more favorable risk benefit ratio when compared with the C type GSSS.

The results of this study are important and new. Dental erosion is a growing concern in modern civilizations and a structured literature search conducted shows that the number of publications is increasing (28).

GSSS for stimulation of saliva are sold over the counter in a considerable number of countries. Up-to-date studies on the erosive potential of these products are lacking. This study was designed as a randomized controlled trial which is recognized as producing the

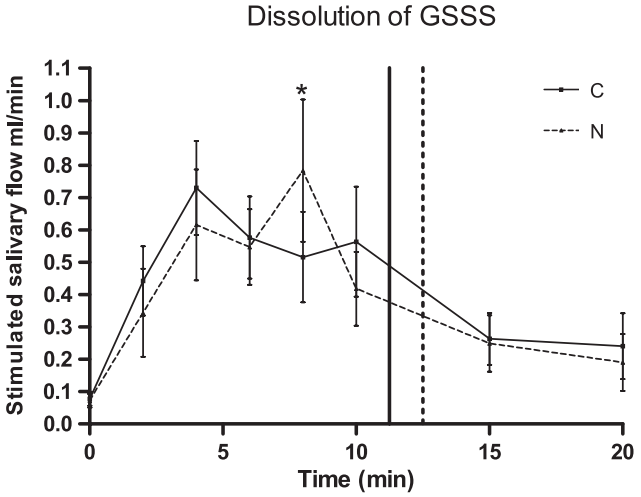

Figure 4 Mean (±95% CI) of salivary flow changes over time during stimulation with gustatory stimulants of salivary secretion. In both groups the acidic lozenges elicited a significant ($P < 0.05$, paired Student's *t*-test) increase in the salivary flow followed by a progressive decrease but failed to reach basal levels after the 20-min period. There were no significant differences between the two GSSS regarding the time needed to the lozenges dissolve in the mouth.

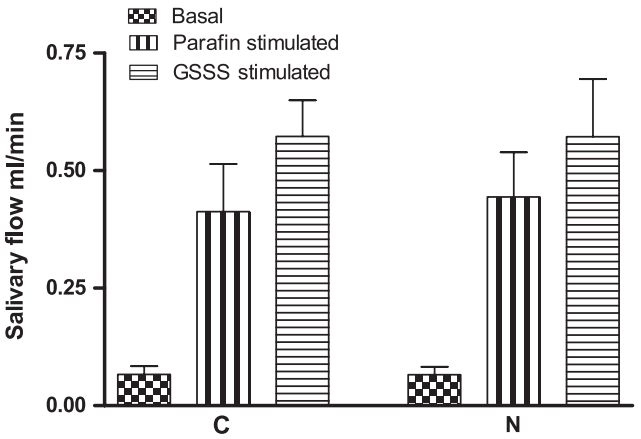

Figure 5 Mean (±95% CI) for basal, gustatory stimulants of salivary secretion-stimulated and paraffin-stimulated salivary flow for each group. There were no significant ($P > 0.05$, independent Student's *t*-test) differences between the two groups for basal or stimulated salivary flow. Note also that there were no significant ($P > 0.05$, independent Student's *t*-test) differences between lozenge-stimulated salivary flow and paraffin chewing mechanical-stimulated flow for both groups.

best sound evidence. The study arms shared homogeneity, demographic and functional characteristics, and power calculations ensured that an adequate number of subjects were enrolled. Management of xerostomia is important for the patient's quality of life and may prevent consequent oral diseases (13, 29, 30). Whenever possible, increasing the amount of saliva in the mouth should be achieved in those individuals who have functioning salivary glands by means of the use of sugar-free hard candies or lozenges, sugar-free chewing gum, or by the use of a muscarinic agonist (13, 29, 31, 32). However fluoride-xylitol-containing lozenges may have additional benefit when compared to muscarinic agonists and their adverse effects (4, 13, 29, 30, 32).

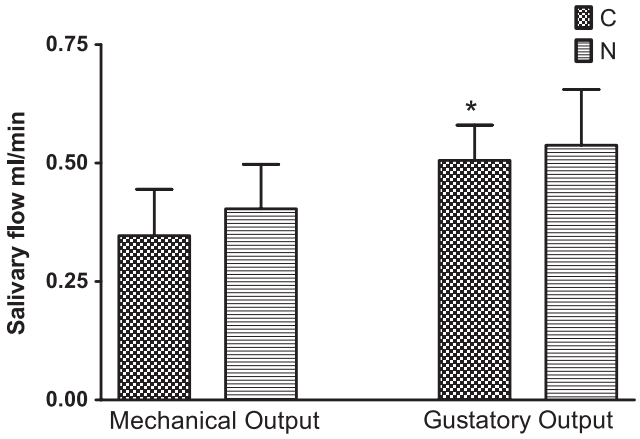

Figure 6 Mean (±95% CI) stimulated salivary output from gustatory stimulants paraffin stimulation. Between the study arms there were no statistically significant differences when stimulated outputs were compared (independent *t*-test, $P > 0.05$). Note also that there were significant ($P < 0.05$, independent Student's *t*-test) differences between mechanical and gustatory output for Group C.

Nevertheless, GSSS due to its acidic nature may in itself possess an intrinsic potential for dental erosion as it has been suggested to occur with other acidic candies and medicinal products (11, 15, 33–36) or in more recent studies performed by our group (12).

In this study we investigated the effects of two gustatory stimulants on the salivary secretion and salivary pH variations. For each patient, unstimulated, mechanical-stimulated, and GSSS-induced salivary flow was determined and a standardized protocol was used to reduce variations due to patients factors (21, 22). Our results, regarding salivary stimulation revealed the competence of both test materials in increasing salivary output even above the patient's mechanical salivary stimulation thus confirming the comparable efficacy in saliva stimulation for both groups. The results of this study also show that this type of GSSS presents an increase on salivary secretion of the same magnitude as traditional citric based GSSS but a significant absolute risk reduction in inducing salivary pH drops below 4.5, which can be indicative of a reduction in dental erosion potential when compared with those used in the control group.

Salivary pH is not a measure of effective dental erosion, but it is correlated with dental erosion potential and decreased salivary pH values have been referred in several studies as being a predictive risk factor for dental erosion and may be considered a proximal surrogate marker for dental erosion (12, 15, 37, 38). However, it is also true that dental erosion is a multifactorial disease and other behavioral, chemical, and biological factors must be accounted for besides salivary hydrogen concentration. The erosive potential of an element depends among others on its titrable acidity, acid dissociation constant (pKa), calcium, phosphate and fluoride content, and chelating properties (39, 40). Both GSSS employed in this study include malic acid in its composition with similar quantities. Nevertheless, the traditional GSSS used in C group has additionally citric acid in its composition. Malic or citric acid are organic acids and have a complex behavior in aqueous solutions like saliva, in which they exist as a mixture of hydrogen ions, acid anions (e.g. citrate) and undissociated acid molecules, with the amounts of each determined by the acid dissociation constant and the pH of the solution (14). Moreover, they exhibit chelating properties and can subtract calcium from mineralized tissues by direct interaction of its carbon skeleton. The chelating capacity is usually measured by the calcium association constant. When compared to malic acid citric acid presents an higher dissociation and calcium association constants indicating that citric acid has a more damaging potential to enamel when compared to malic acid from both perspectives of acid attack and calcium bonding affinity (14). Therefore, GSSS of N type with no citric acid in its composition could nominally possess an instrinsic diminished erosive potential.

On the other hand, the GSSS used in the N group belong to a new type of salivary stimulants, which include fluoride and xylitol in its composition. Several *in vitro* studies have demonstrated that the presence of fluoride and/or xylitol compounds in enamel potential erosive media can inhibit its erosion effect (17–20, 41–45). The mechanisms behind this effect are not clear but may be related to direct buffering effect from fluoride ions or via fluoride ion participation in ionic force lowering undersaturation balance regarding HA. However in a recent clinical study where the erosive potential of a similar GSSS as the one used in the N group was tested, it was suggested that the addition of fluoride had little to no effect on the erosive potential, and that the use of fluoride in these type of products was beneficial only where caries prevention was concerned (46).

Most probably the fact that the N group GSSS is based on a weaker acid composition, may explain the milder effect on pH drop.

In this study the primary outcome chosen regarding dental erosion risk was the salivary pH drop, although this is not a direct measure of effective erosion and could be viewed as a weakness. Several studies have measured effective dental erosion mainly related to acidic drinks by the use of intra-oral appliances with dental enamel or HA discs or by profilometry among other techniques (47–52). More recently, some studies have been conducted where the erosive potential has been evaluated by calculation of under saturation of saliva regarding HA (29, 46, 53–55). In fact in a recent clinical trial it was suggested that the use of GSSS of the N type is safe regarding dental erosion, since no salivary undersaturation towards hydroxiapatitis was attained in a group of xerostomic head and neck irradiated patients, and these are in agreement with our present findings (46). The main criticism regarding the use of salivary pH variation alone is that because salivary pH is considered an important predictor risk factor for dental erosion, it does not account for other interfering biological factors affecting effective dental erosion such as resting or stimulated flow and buffering capacity of saliva.

Salivary flow is an important biological factor in acid dilution and clearance. In a previous study from our group, similar GSSS were compared using a young and

healthy population (12). In the present study, a PSS population was used and xerostomia and diminished resting salivary flow were considered as inclusion criteria. In both studies the GSSS employed stimulated salivary secretion without significant differences between products. However in comparison PSS patients salivary output was substantially reduced when compared to healthy patients. Also, pH drops were more pronounced and prolonged, and even more accentuated in the citric acid GSSS group, in the xerostomic patients recruited to the present study when comparing to our previous findings from previous reports (12). These results may be explained by the diminished salivary flow elicited in PSS patients which could conduct to an impaired acid clearance and prolonged acid contact with dental hard tissues.

Also, in this study, we investigated, as baseline characteristics, the buffering capacity of saliva for every subject by established methods and studied its interactions with the primary outcomes. Within each arm of the study, subjects with low buffer capacity presented a diminished stimulated salivary output and an elevated TSB when compared with subjects with high buffer capacity, although the later was not statistically significant. When comparing the study outcomes between groups N and C for the different buffer capacities same type of associations could be drawn when considering the overall study samples. The relationship between buffer capacity, acid clearance, and effect upon salivary pH agrees with previous findings by other authors, namely from studies on acidic candies (15, 29, 35, 46, 53–55). Moreover, despite the protective effects of high buffering, the results of this study show that even in the high buffering subgroup, traditional GSSS such as the ones used in C group still have the ability of producing sustained salivary drops. Even further, the proportion of patients with low buffer capacity in this study was elevated when compared to the distribution of this property in healthy populations, which was also reflected in sustained and prolonged times of salivary pH under 4.5. Thus, the results of this study suggest that PSS patients have a clear significant impairment whereas oral acid clearance is concerned, and are therefore more vulnerable and susceptible towards dental erosion.

In this study, we did not measure the occurrence of dental erosion, nor measured undersaturation regarding HA. We measured salivary pH over time which is a simple marker for dental erosion potential of these products. Nevertheless, and although not definitive, the results of this study are indicative that new GSSS present a more favorable cost benefit ratio, with significant absolute risk reduction for prolonged and sustained salivary pH drops while maintaining an efficient stimulation of salivation.

Finally, the fact that the GSSS used in this study had different aspects, smell and taste impaired complete masking. However, the outcomes measured were objective and masking was maintained for the third party who made calculations based on groups defined only as group A or B. Therefore, actions were undertaken to compensate and minimize study weaknesses which did not in our view compromise study quality and validity.

In conclusion, the results of this study suggest that acidic lozenges can be effective in stimulating salivary secretion in patients with xerostomia. New GSSS based on malic acid only and with fluoride and xilitol in its composition produce milder and swifter salivary pH drops when compared to citric acid-based ones. This could represent a lower erosive potential, but further studies should try to determine the real effects of these products in dental erosion.

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