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Effectiveness of a recent topical sialogogue in the management of drug-induced xerostomia.

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Abstract

Objectives: Use of certain drugs is the most common aetiology of xerostomia. Systemic sialogogues provide a longer effect than topic ones, but also induce relevant side effects. Topical sialogogues, as malic acid, allow a safe use as they induce no systemic side-effects or pharmacological interactions, being especially interesting in cases of mild hyposalivation and oral dryness, mainly the chronic use of xerostomizing drugs. The aim of this study was to evaluate the clinical effect of 1% malic acid in patients affected by xerostomia due to antihypertensives or antidepressants.

Study Design: 10 patients with drug-induced xerostomia were prospectively evaluated before and after using malic acid spray during three weeks. Xerostomia Inventory (XI) was used to evaluate subjective improvement. Unstimulated and stimulated salivary flow rates were determinated.

Results: Severity significantly decreased, from 38.22 to 31.00 points ($p = 0.011$) after using the product. 77.8% of subjects did not complain about xerostomia at the end and 66.6% achieved an improvement > 6 points. Unstimulated flow rate singnificantly increased, from 0.163 to 0.226 mL/min ($p = 0.021$) at the third week.

Conclusions: 1% malic acid spray induces some improvement in the management of mild and reversible xerostomia. Carrying out of randomized controlled trials is justified according to this study.

Key Words: *Xerostomia, malic acid, antihypertensive agents, antidepressant agents.*

Introduction

The association of a decrease of salivary flow rates and the altered composition of saliva, as a consequence of salivary gland hypofunction leads, in most cases, to subjectives complaints or oral dryness (xerostomia). Saliva is indispensable in maintaining oral health (1). Decreases in the amount of saliva or its quality may produce difficulties in swallowing, alteration of the taste perception, or a higher risk of developing oral diseases as caries, *C. albicans (Candida albicans)* infection (2) and also periodontal disorders (3).

Use of certain systemic drugs is the most common aetiology of xerostomia (4). Drug-induced xerostomia is temporary, lasting to the end of pharmacological treatment, and usually presenting mild-to-moderate severity. It has been described more than 500 drugs, among 42 pharmacological groups, inducing oral dryness (5). Other aetiologies as head and neck radiotherapy or Sjögren's syndrome are related with severe hyposalivation, but its prevalence is not as frequent as intake of these drugs.

Antidepressants are the most important drugs inducing xerostomia, mainly tricyclic antidepressants (6). Therefore, selective serotonin reuptake inhibitors (SSRI) has also been related with xerostomia, specially when combined with benzodiazepines (7). Diuretics are also one of the most xerostomizing drugs. Chronic intake of diuretics increases nearly six times the incidence of xerostomia (6). Other antihypertensives as beta-blokers (8) or angiotensine-converting enzyme inhibitors have also been reported as xerostomic drugs, producing dry mouth in about 13% of patients (9).

There is a wide spectrum of approaches in the management of xerostomia, from the classical ones, either salivary stimulants or saliva substitutes and artificial salivas, to the most recent as lingual nerve electrostimulation (10), sodium channel blockers or acupuncture (11). Available treatments nowadays are not truly effective. Thus, an ideal approach of treatment should be long-lasting (xerostomia worsen specially during the night), salivary stimulant, leading to normal salivary flow rates, with a topic activity, without side-effects (systemic or caries) and accepted by the patient. Systemic sialogogues provide a longer effect than topic ones. Nevertheless, these drugs induce relevant side effects due to the parasympathetic induction as nausea, rhinitis, sweating, flushing and frequent polyuria (12). Topical salivary stimulants, as organic acids (malic, citric or ascorbic acid) have a very transient effect. Furthermore, these substances allow a safe use as they induce no systemic side-effects or pharmacological interactions, being especially interesting in those cases of mild hyposalivation and oral dryness, mainly the chronic use of xerostomizing drugs.

The objective of this study was to evaluate the clinical effect of 1% malic acid, as a topical sialogogue, in patients affected by drug-induced xerostomia due to chronic treatment with antihypertensives or antidepressants.

Material and Methods

This study has been accepted by the university of Granada Ethics Committee on Research. All the measurements and intervention were undertaken with the understanding and written consent of each subject. The investigation was designed as a single-blinded pilot study including 10 patients suffering for xerostomia as a consequence of chronic administration (more than two months prior to the intervention) of antidepressive and/or antihypertensive medication (diuretics, beta-blokers and/or angiotensin-converting-enzyme inhibitors).

Patients recruitment and intervention

Patients with xerostomia attending to the university of Granada School of Dentistry were evaluated. Recruitment of patients was made consecutively, including subjects in treatment with antidepressive or antihypertensive drugs and excluding any other aetiologies of hyposalivation (Sjögren's syndrome, radiotherapy, diabetes,…). There was no restriction about age, gender and oral conditions (edentulism, denture wearers,…) After performing anamnesis on recruited subjects, the following question was presented to each patient. "How often do you feel dry mouth?" Response options were "never", "occasionally", "frequently" or "always". On each occasion, those who said "frequently" or "always" were considered xerostomia (13).

The intervention consists on the at-home application of a topical sialogogue containing 1% malic acid (Xeros Dentaid Spray©, Dentaid, Barcelona, Spain) during three weeks. Each patient used the product as many times as they consider necessary. The spray was presented to the subjects without any brand name. Thus, the patients did not know which product they were being treated with (single-blinded).

Measures

Xerostomia Inventory (XI) test was used to obtain subjective information about the severity of xerostomia before and after treatment with malic acid (14). This 11-item survey is considered a valid tool to evaluate changes in xerostomia severity after an intervention (15,16). Higher scores of XI mean worse xerostomia. A decrease in XI score ≥ 6 points from baseline was accepted as a partial response (PR). Differences <6 points but >3 points were defined as minor response (MR). No response (NR) was defined as a decrease of <3 points after intervention (15).

As secondary measurements, whole salivary flow rates were assessed in all patients. Saliva was collected on a pre-weighed 20-mL plastic container. Unstimulated flow rate was obtained by the spit method every 30 seconds during 15 minutes. Collection tubes were weighed (in 0.001g) using a precision scale (Cobos M-150, Cobos, Barcelona, Spain) and expressed as mL/min, as

previously described (17). Stimulated whole saliva was obtained by chewing 1-g piece of paraffin wax during over a period of 6 minutes. Saliva collected during the first minute was discarded, and then collected into the container every 30 seconds (18). Either XI or sialometries were assessed always at the same time (09:00 a.m. to 11:00 a.m) to avoid any circadian variation. Before the evaluation, patients were told not to eat, nor drink, nor smoke, nor brush their teeth from one hour prior the visit.

Statistical analysis

All the analyses were performed using SPSS software v17.0 (SPSS INC., Chicago, IL, USA). The primary endpoint was to test for differences between XI scores at baseline and at the end of the study (week 3). Wilcoxon signed rank test was applied as the data were not normally distributed. Same test was used for the analysis of salivary flow rates. Level of significance for all tests was set at 0.05 and 90% power.

Results

A total of 10 subjects (9 female, 1 male) with drug-induced xerostomia were recruited in our study. One of the patients increased three times the dosage of xerostomic drug (from 25 mg/d maprotiline to 75 mg/d maprotiline) during the follow-up. Thus, this subject was discarded for the statistical analysis, resulting in a final sample of 9 subjects, size enough for the preliminary study we expected. Three patients were being treated with antidepressants, five with antihypertensives, and one patient were receiving antidepressive and antihypertensive drugs (Table 1). Mean age of the sample was 50.33 ± 7.31 years-old and participants used the sialogogue 3.67 ± 1.41 times per day, needing a new application after 406 ± 397 min as shown in Table 2.

Subject	Drugs
1	**Amitriptyline**, acetaminophen.
2*	**Maprotiline**, acetaminophen, omeprazole, naproxen, levothyroxine.
3	**Telmisartan**, chondroitin sulfate.
4	**Torasemide**, ebastine, omeprazole, alprazolam.
5	**Paroxetine**, levothyroxine, alprazolam.
6	**Indapamide**, levothyroxine, simvastatin.
7	**Chlortalidone, carvedilol**, tamsulosin, chondroitin sulfate, bromazepam.
8	**Citalopram, captopril**, levothyroxine, acetylsalicylic acid, omeprazole.
9	**Citalopram**, ibuprofen, pantoprazole
10	**Bisoprolol**

Bold: xerostomic drugs: antidepressants or antihypertensives (diuretics, beta-blokers and/or angiotensin-converting-enzyme inhibitors)

*: Discarded patient

Table 1. *Chronic pharmacological treatment of the patients.*

Sample size (N)	9	
Age (years)	50.33 (7.31)	
Gender		
Male	1 (11.1 %)	
Female	8 (88.9 %)	
XI score		
Baseline	38.22 (7.80)	
Final (three weeks)	31.00 (7.22) *	p = 0.011
XI difference	7.22 (5.52)	
Number of applications/ day	3.67 (1.41)	
Effect duration (min)	406 (397)	

Mean (standard deviation).

*: $p < 0.05$

Table 2. *Age, gender, XI score and effect duration of the participants.*

At baseline, mean XI score was 38.22 ± 7.80 points. At the end of the study, XI score significantly decreased to 31.00 ± 7.22 points (p = 0.011), resulting a reduction of 7.22 ± 5.52 points (Figure 1). 88.9% of patients eviden-

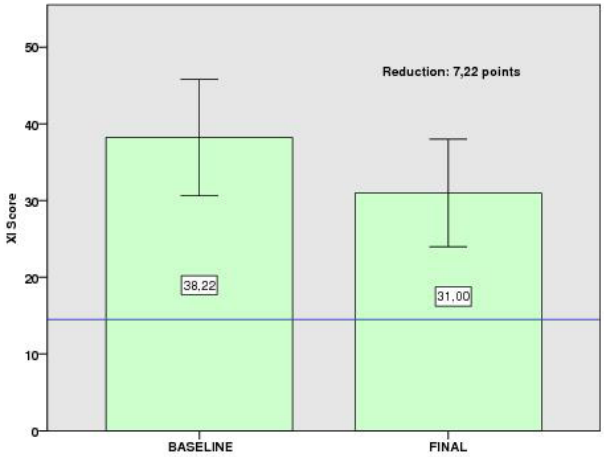

Fig. 1. *Mean and standard deviations of XI score of the participants. Differences greater than 6 points are considered "partial response" to the product. Blue line shows the symptom threshold (14.5 points).*

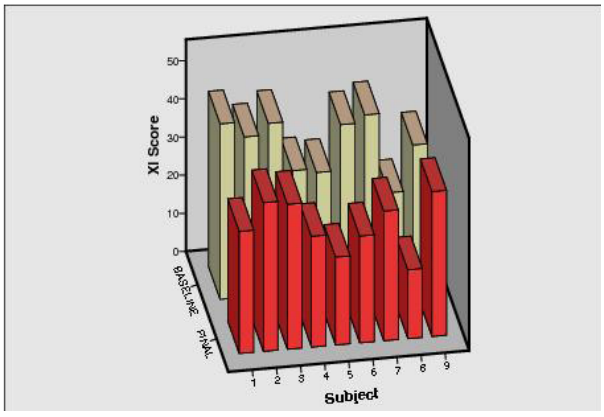

Fig. 2. *Individual XI score. Individual progress of each participant in the study*

	Baseline	*Final (three weeks)*	
Unstimulated (mL/min)	0.163 (0.101)	0.226 (0.088) *	p = 0.021
Stimulated (mL/min)	0.574 (0.292)	0.734 (0.245)	p = 0.051

Mean (standard deviation).
*: $p < 0.05$

Table 3. *Unstimulated and stimulated salivary flow rates of the participants.*

ced some improvement after the treatment with 1% malic acid. 66.6% of patients achieved an improvement > 6 points (partial response). None of the participants got worse their initial situation after the intervention. 77.8% of patients did not complaint about xerostomia after being treated with the sialogogue (Figure 2).

Salivary flow rates also improved after treatment. Unstimulated flow rate (UFR) significantly increased from 0.163 mL/min at baseline to 0.226 mL/min (p = 0.021) at the third week (Table 3). Stimulated flow rate (SFR) also increased from 0.574 mL/min to 0.734 mL/min (p = 0.051), but the difference was not statistically significant (Figure 3).

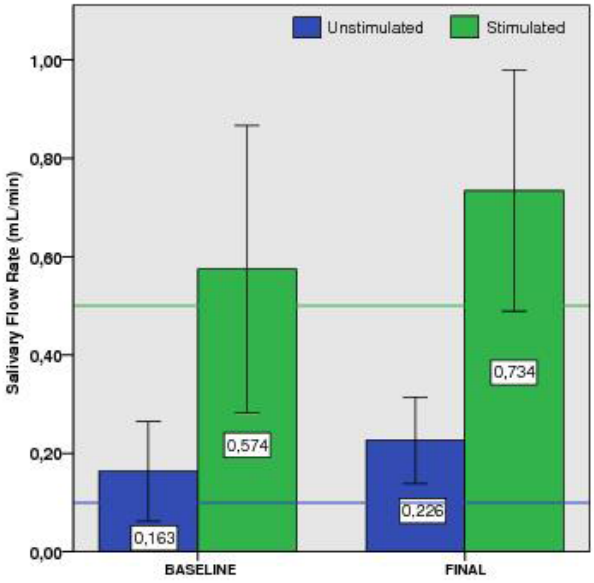

Fig. 3. *Mean and standard deviations of salivary flow rates. Blue (unstimulated) and green (stimulated) lines show the hyposalivation threshold.*

A third of participants were initially categorized as hyposalivation patients (UFR < 0.1 mL/min) (19). All of them exceeded the hyposalivation threshold after the intervention, with relevant increases (multiplying from two to seven times) of their initial rates. The other two-thirds had a reduced salivation (between 0.1 and 0.3 mL/min) at the beginning. They improved their unstimulated rates, but the increases were between 13% and 58%, except one of them who suffered a reduction of 21% (Figure 4).

Regarding stimulated rates, 44.4% of the participants were initially considered as hyposalivation patients (SFR

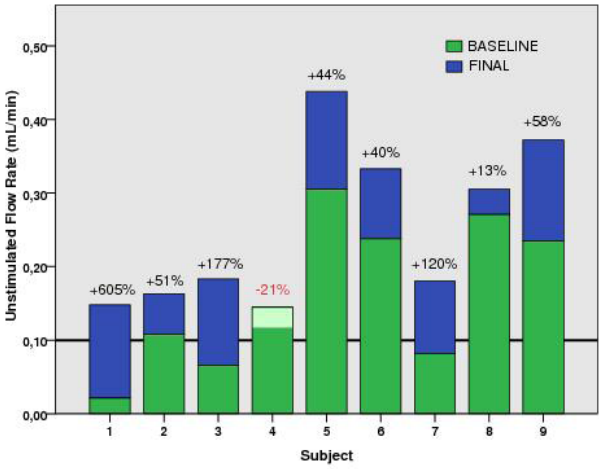

Fig. 4. *Individual progress of unstimulated flow rates of each participant. Black line shows hyposalivation threshold (0.100 mL/min). Percentages on the bars indicate increase/decrease after using the product.*

< 0.5 mL/min) (19). Half of these duplicated their rates after three weeks. The other half, as patients with SFR > 0.5 mL/min, increased their rates in a minor extension (5.7% to 19.5%) or slightly decreased (-6.4% to -8.4%).

Discussion

Topical treatment with 1% malic acid, when applied onto the oral mucosa, is shown to improve the oral dryness felt by the patients and also their unstimulated flow rates, based on previous results. The use of acid substances to induce the salivation reflex is not recent. However, chronic application of these sialogogues, as citric acid, is related with a higher risk of caries, due to de acidic dental erosion over the dentin (20). In 1980, Anneroth *et al.* (21) found similar effects after using 0,06 mg ascorbic or malic acid chewing-gums, containing sorbitol and mannitol. These products were dropped out because of their demineralizing effect on human dentin, not only related with high doses of acid, but also to the product appearance (chewable) which allowed a prolonged contact onto the dental surfaces.

Recent research reported that a suitable administration format, as spray format, which allows a fast and temporary contact on the oral mucosa, combined with a suitable formulation could decrease the demineralizing potential as the salivary stimulant effect remains unchanged (22,23). The use of 4.7% malic acid spray, combined with fluorures/xylitol, on 60 healthy subjects induced a significant drop in salivary pH levels which recovered

after 20 minutes. Although pH decreased immediately after the application of an acid, when administering this acidic xylitol-fluoride-containing salivary stimulant, minimum pH did not reach the hydroxyapatite critical level (pH = 5,5), while a no xylitol-fluoride-containing stimulant reached a pH score lower than 5,5 (24). Thus, combination of malic acid with xylitol/fluorides on spray seems to be a safe option as topical sialogogue.

Oral dryness is a common complaint we often can find among older adults in dental office. There is a wide spread of etiologies, different degrees of severity and reversible/irreversible course of xerostomia. Also there is available a large spectrum of different treatments in the management of xerostomia. Thorough diagnosis of the underlying etiology and salivary hypofunction is very important in order to choose the best treatment option in each patient, as each approach provides advantages and disadvantages and, nowadays, none of them is truly effective.

Acidic xylitol-fluoride-containing salivary stimulants are an interesting option in the management of mild and reversible xerostomia, mainly due to xerostomic drugs. These products, used as topical sialogogues, provides a short-term effect increasing unstimulated flow rates immediately and reaching basal levels after 20 minutes (24) although patients do not feel the need of a new application until six to seven hours later, based on this preliminary study. Radiotherapy on head and neck or Sjögren's syndrome are less frequent etiologies, but they are much more present in the literature because of their severity and irreversible degenerative processes over salivary glands. Topical stimulants of the salivation may not be the correct choice in these cases, since it is necessary a stronger induction through systemic administration, mainly parasympathomimetic drugs as pilocarpine or cevimeline among others (25). These drugs provides a more long-lasting effect, but also inducing relevant side effects, as flushing, sweating or nausea, so they should be administered with caution (12). Even when the residual salivary function is very low, it is recommended the use of salivary substitutes and artifitial salivas (26).

After reviewing the recent literature, it is found a large amount of papers about the efficacy and feasibility of different treatments, especially systemic stimulants and artificial salivas. However, we could hardly find scientific evidence about topical sialogogues and, always based on an objective approach, by determination of salivary flow rates. It is also necessary to evaluate the improvement felt by the patient, by subjective approach. This point of view is almost absent when studying the classical therapies (sialogogues and substitutes) (1,18), but often appears in those papers evaluating new options as acupuncture (15,27,28). Among different available questionnaires and visual analogue scales (VAS), we used XI (14) since it is an easy, fast and no technical system. Furthermore, this 11-item questionnaire appears to be a valid multi-item method for measuring the severity of the symptoms of dry mouth in clinical and epidemiologic studies (16,29).

Results obtained show a significant increase of unstimulated flow rate after using the stimulant, in acordance with da Mata *et al.* (24) when applied in healthy subjects. There is no evidence about effectiveness of topical salivary stimulants in patients complaining for xerostomia. In regards of subjective improvement, it cannot be found similar papers to compare. Researchers have left investigation about this topic because of the caries-inducing role of acidic susbtances when they were not well-formulated. Once improved this therapy, new research is expected in the next years.

A preliminary study, as presented, is not evidence enough to state the effectiveness of the product. Furthermore, sample size was very small, nine patients. Presented results show some benefit after using malic acid spray. New effort is needed in carrying out a randomized controlled clinical trial, where this product will be compared with a control (placebo) and using a larger sample size. Conclusions on this kind of research will help us to state if really malic acid may be an adequate approach of treatment in drug-induced xerostomia.

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