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Original

Impact of 1% malic acid spray on the oral health-related quality of life of patients with xerostomia

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Abstract: Dry mouth sensation, also known as xerostomia, is a common clinical problem with an increasing prevalence. Although recent studies have reported promissory results of malic acid, none have evaluated the impact of malic acid on the oral health-related quality of life (OHRQoL) of patients with xerostomia. Thus, this study aimed to evaluate the impact of 1% malic acid, combined with fluoride and xylitol, on the OHRQoL of patients with xerostomia. We enrolled 70 patients and randomly allocated them into two groups: the intervention group (applied topical sialogogue with 1% malic acid) and the control group (applied a placebo). We assessed the OHRQoL and severity of xerostomia before and after treatment with the Spanish version of the Oral Health Impact Profile-14 questionnaire (OHIP-14sp) and a visual analogue scale (VAS), respectively. In addition, stimulated and non-stimulated salivary flow rates before and after treatments were also measured. In total, 60 patients completed the study. According to the VAS, both sprays significantly improved dry mouth sensation ($P < 0.001$). However, OHIP-14sp total scores decreased significantly in the intervention group from 20.8 ± 10.4 to 16.5 ± 9.5 ($P < 0.001$), indicating an improvement in the OHRQoL. No significant differences were observed in the control group ($P > 0.05$). Furthermore, non-stimulated salivary flow rates significantly increased in the intervention group from 0.25 ± 0.22 to 0.33 ± 0.33 mL/min ($P < 0.001$). Overall, this study demonstrated that malic acid improves the OHRQoL and dry mouth sensation in patients with xerostomia.

Keywords: xerostomia; dry mouth; malic acid; oral health-related quality of life.

Introduction

Saliva is an essential fluid in the human body for the maintenance of oral tissues and oral health. Alterations in the amount or quality of saliva induce several changes in the oral cavity, including predisposition to caries, infections, altered taste, halitosis, dysphagia, dysarthria, lack of retention of dentures, and dry mouth sensation (1,2).

Dry mouth sensation, or xerostomia, is a subjective symptom characterized by a decline in the salivary flow rate or alteration in the chemical composition of saliva (3). Xerostomia is a common clinical problem, with an increasing prevalence; the estimated prevalence is 0.9-64.8% (4,5). Xerostomia can be a symptom of various disorders and can be attributed to several causes such as medications, head and neck radiotherapy, chemotherapy, Sjögren's syndrome, and psychological illness (5-8). Despite its cause, xerostomia has been reported to adversely affect the oral health-related quality of life (OHRQoL) (5,9-11). Willumsen et al. reported that xerostomia affects the quality of life by interfering with speech, taste, and mood (12). Moreover, patients with dry mouth are prone to having dental caries, periodontal

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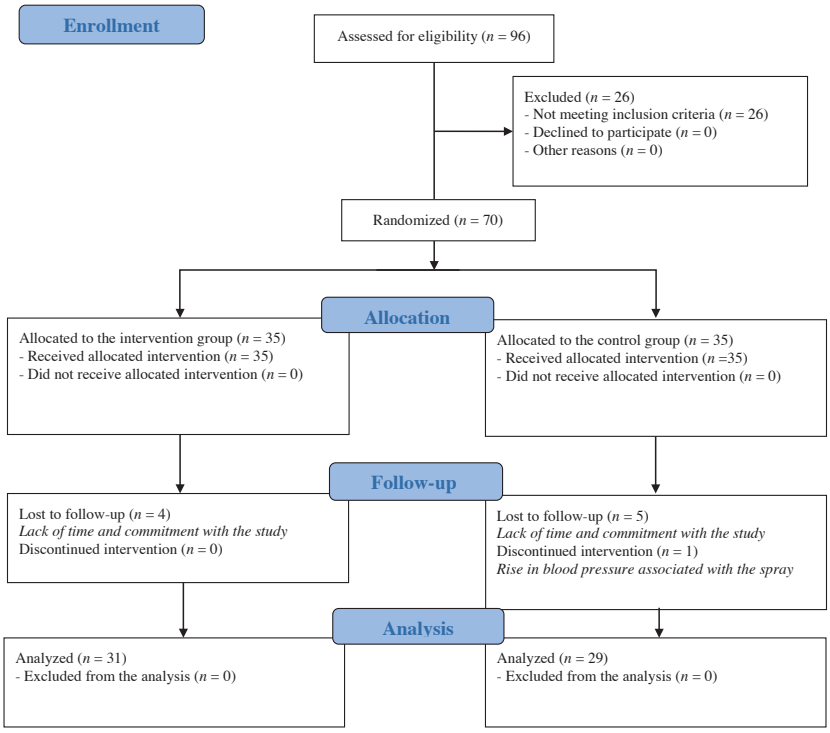

Fig. 1 Study CONSORT flowchart.

disease, and burning sensation, also contributing to the deterioration of the OHRQoL (13).

Because therapies for xerostomia are highly variable, treatment must be selected according to the cause and severity of dry mouth. Although topical agents are the most prevalent treatment options, as they relieve symptoms with no or little side effects, no substantial evidence proves their efficacy in relieving the dry mouth sensation (14). Acidic substances, such as malic and citric acid, have been used as salivary stimulants, but their use has been discontinued because of their demineralizing effect (13). Several studies have demonstrated that 1% malic acid, in combination with xylitol and fluoride, exerts no or little effect on tooth demineralization and maintains its properties as a salivary stimulant (15). In fact, recent studies have demonstrated promissory results of 1% malic acid; they have reported an increase in salivary flow and a reduction in dry mouth sensation (16-18). Nevertheless, none of these studies have evaluated the impact of 1% malic acid on the OHRQoL in patients with xerostomia.

The present study aimed to investigate the impact of a topical sialogogue spray containing 1% malic acid, combined with fluoride and xylitol (Xeros Dentaid Spray; Dentaid, Barcelona, Spain), on the OHRQoL of patients with xerostomia.

Materials and Methods

Participants and study design

In this study, we enrolled 70 patients with xerostomia who attended a dental clinic of the Dentistry Faculty of Andres Bello University (Viña del Mar, Chile) between 2014 and 2015. This study was approved by the Ethical and Scientific Committee of the Dentistry Faculty of Andres Bello University (approval number 026, 2014). This research was conducted in full accordance with the World Medical Association Declaration of Helsinki. The study was designed as a double-blind randomized clinical trial according to the guidelines established by The CONSORT Statement (http://www.consort-statement.org/consort-statement/).

We randomly distributed patients with xerostomia into two groups of 35 and 35 individuals (treatment and control group, respectively), which were balanced in terms of age and salivary flow rates (Fig. 1). Randomization was performed by an investigator not involved in this study through a specific webpage (http://www.randomization.com/) using the method of randomly permuted blocks, setting 35 subjects per block and two labels, A and B, for the intervention and control group, respectively. Moreover, randomization was kept in a sealed envelope in an unknown place for examiners till the end of the study.

The inclusion criteria in this study were that participants had to be over 18 years and have dry mouth according to

a previously established question (see measurements). In contrast, patients who have had topical or systemic treatment for xerostomia in the last 3 months or had history of head and neck radiotherapy, chemotherapy, and/or any systemic disease reported to produce hyposalivation (Sjögren's syndrome, scleroderma, hepatitis C, HIV, sarcoidosis, rheumatoid arthritis, polyarteritis nodosa, systemic sclerosis, or lupus erythematosus) were excluded from this study.

We obtained written informed consent from all eligible individuals who agreed to participate in this study. Furthermore, data were collected by personal interviews and clinical examination, which were conducted at the dental clinic and were recorded in a specially designed questionnaire.

Sample size calculation

We calculated the sample size using Stata software v11.2 and the sample size tool (StataCorp LP, College Station, TX, USA). We set the significance level and power of the study at 5% and 95%, respectively. Proportions were obtained per Gomez et al. (17,18). Based on these settings, the minimum sample size required was 15 patients for each group.

Interventions

In the intervention group, patients received a topical spray comprising 1% malic acid, 10% xylitol, and 0.05% sodium fluoride (Xeros Dentaid Spray; Dentaid). In the control group, patients received a placebo topical spray comprising 10% xylitol and 0.05% sodium fluoride. Each formulation was placed into identical opaque flasks and labeled according to randomization by personnel unrelated to this study. Patients in both groups were instructed to use the spray on demand for 2 weeks, with a maximum of eight applications per day and record the daily number of applications in a diary. We controlled patients during that period to ensure correct use and resolve possible problems with the sprays. Furthermore, patients were advised to interrupt the treatment and call investigators in case they felt insecure or experienced unpleasant symptoms upon the use of the solutions.

Measurements

Xerostomia

We assessed the presence of xerostomia with the following question, as reported elsewhere (19): "How often do you feel that your mouth is dry?". Participants could select from the following answers: "never", "sometimes", "usually", or "always". Those who answered "usually" or "always" were considered to have xerostomia (19).

The severity of xerostomia was assessed using the visual analogue scale (VAS), which comprised a 10-cm horizontal line with a "0" and "10" marked on each extreme. A score of 0 indicated "no xerostomia" and 10 indicated the "worst imaginable xerostomia". All patients were asked to draw a vertical line perpendicular to this horizontal line to reflect their symptom severity. We evaluated and recorded the distance between the vertical line and the zero extreme to obtain the VAS score for each patient (20).

Evaluation of impact on the quality of life

The OHRQoL was assessed using the Spanish version of the Oral Health Impact Profile-14 questionnaire (OHIP-14sp) before and after the treatment. OHIP-14 is a 14-item questionnaire designed to assess self-reported functional limitation, discomfort, and disability attributed to oral conditions. Despite being a short questionnaire, the OHIP-14sp has been proven to be reliable, sensitive to changes, and have adequate cross-cultural consistency (21). We evaluated the OHIP-14sp according to the following dimensions: functional limitation, physical pain, psychological discomfort, physical incapacity, psychological incapacity, social incapacity, and social disadvantage. The answers were assessed using a Likert-type evaluation scale with five points as follows: never = 0; rarely = 1; sometimes = 2; repeatedly = 3; and always = 4. Of note, the OHIP-14sp scale ranges from 0 to 56. The lowest scores represent a satisfactory perception of an individual's oral conditions and, therefore, a higher satisfaction and better quality of life.

Salivary flow rate

We assessed stimulated and non-stimulated salivary flow rates before and after treatment using the spitting method. All patients were instructed to refrain from eating, drinking, smoking, and oral hygiene procedures for a minimum of 60 min before the procedure. Samples were collected in the morning hours, between 9:30 and 11:30 am, always in the same room under similar room temperatures. The collection time for stimulated and non-stimulated whole salivary flow was 5 min. First, non-stimulated whole saliva was collected. Patients were instructed to spit into a tube for 5 min, and the amount of saliva was measured using a graduated syringe. Then, stimulated whole saliva was collected after a break of 3 min using the mastication method. Patients were asked to chew a wax cube of 15 × 10 mm for 1 min at their own pace and then to spit into a tube for 5 min. Wax residues were eliminated using a filter paper before quantification using a graduated syringe.

Table 1 Age, gender, OHIP-14sp total score, VAS score and the mean number of applications of both groups at baseline and 2 weeks after treatment

Variables	Intervention group	Control group
Sample size	31	29
Age (years)	54.6 ± 14.9	49.2 ± 14.9
Gender		
Male	5	3
Female	26	26
OHIP-14sp total score		
Baseline	20.8 ± 10.4	22.3 ± 12.2
Final (2 weeks after treatment)	16.5 ± 9.5*	22.6 ± 12.2
OHIP-14 difference	4.4 ± 8.2*	− 0.2 ± 9.8
VAS score		
Baseline	56.6 ± 20.3	58.2 ± 21.5
Final	28.5 ± 22.0*	33.7 ± 18.3*
No. of daily applications	2.47 ± 1.54*	3.55 ± 1.72

*Statistically significant results with $P < 0.05$.

All saliva collections and further measurements in this study were performed by three different examiners. Thereafter, standardization and calibration were performed among the examiners. Of note, Lin's concordance agreement was 0.97.

Outcomes

In this study, the primary outcome was to assess the effect of 1% malic acid on the OHRQoL, defined as the difference between the baseline total OHIP-14sp scores and post-treatment total OHIP-14sp scores. Results were expressed as mean ± standard deviations.

The secondary outcome was salivary flow stimulation, defined as the difference between the stimulated and non-stimulated salivary flows before and after treatment, expressed as mL/min. Both primary and secondary outcomes were measured 2 days after patients finished the 2-week treatment, whether with the placebo or malic acid spray (Xeros Dentaid Spray).

Statistical analysis

The data were analyzed using Microsoft Excel v.2007 (Microsoft Corporation, Redmond, WA, USA) and R-Cran 3.1.1. (The R Foundation, Vienna, Austria). For independent and related samples, we used the Kolmogorov-Smirnov and Wilcoxon signed-rank test, respectively. $P < 0.05$ was considered statistically significant. Patients who did not complete the study were excluded from the statistical analysis.

Results

We enrolled 70 patients in this study who were randomly allocated to the intervention and control groups. Ten patients (control group, 6; intervention group, 4) did not complete the study and were thus excluded from the statistical analysis. Of these 10 patients, nine were lost to follow-up because of the lack of time and commitment to the study. The remaining patient (from the control group) discontinued the intervention because he associated one application of the placebo with a rise in blood pressure. Hence, 60 patients completed this study (control group, 29; intervention group, 31; Fig. 1). No patient reported any adverse effect. No significant differences were observed between the mean ages and group ($P > 0.05$) or between gender and group ($P > 0.05$).

While xerostomia was correlated with drug use in 47 patients (78.3%), it was associated with idiopathic causes in the remaining 13 patients (21.7%). The most commonly used medications in this study were antihypertensives, followed by antidepressants, anxiolytics, antihistaminics, and hypoglycemic agents. Furthermore, the average number of drugs consumed by patients with drug-related xerostomia was 2.5.

Table 1 summarizes the mean ages, gender distribution, OHIP-14 score before and after treatment, VAS score before and after treatment, and mean number of applications in both groups. According to the VAS, both sprays significantly improved xerostomia ($P < 0.001$), but only the spray containing 1% malic acid (Xeros Dentaid Spray) significantly improved the OHRQoL ($P < 0.001$). The difference in the OHIP-14sp total score pre-post treatment between the groups was statistically significant ($P < 0.05$). Patients in the intervention group reported a decrease in all seven dimensions from the OHIP-14sp after the treatment, with statistically significant differences for physical pain ($P < 0.001$), physical incapacity ($P < 0.05$), and social disadvantage ($P < 0.05$; Fig. 2). Conversely, patients in the control group had no statistically significant decrease in any of the dimensions; in fact, three dimensions (physical pain, physical

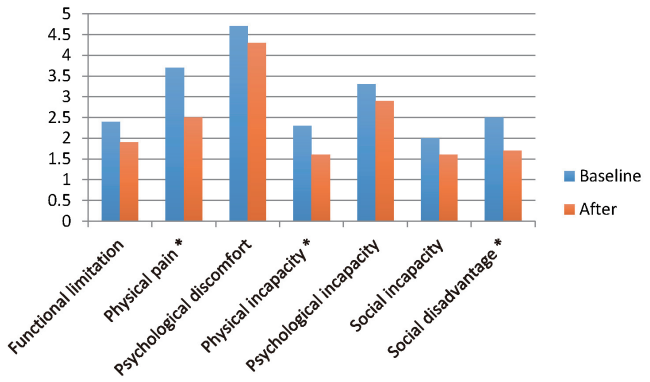

Fig. 2 OHIP-14sp scores per dimension for the intervention group at baseline and 2 weeks after treatment. *Statistically significant results with $P < 0.05$.

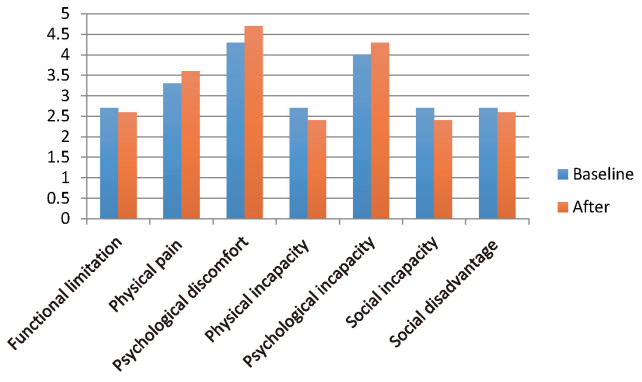

Fig. 3 OHIP-14sp scores per dimension for the control group at baseline and 2 weeks after treatment.

Table 2 Stimulated and non-stimulated salivary flow rates at baseline and 2 weeks after treatment

	Intervention group	Control group
Stimulated salivary flow rate		
Baseline	1.30 ± 0.79 mL/min	1.45 ± 1.11 mL/min
Final (2 weeks after treatment)	1.48 ± 0.81 mL/min	1.36 ± 1.11 mL/min
Unstimulated salivary flow rate		
Baseline	0.25 ± 0.22 mL/min	0.28 ± 0.28 mL/min
Final	0.33 ± 0.33 mL/min*	0.31 ± 0.30 mL/min

*Statistically significant results with $P < 0.05$.

discomfort, and physiological incapacity) registered an increase, which was not statistically significant ($P > 0.05$; Fig. 3).

Furthermore, non-stimulated salivary flow rates significantly increased after the 2-week treatment in the intervention group ($P < 0.001$). The control group, however, revealed a small increase, which was not statistically significant ($P > 0.05$; Table 2). Although the intervention group reported an increase in stimulated salivary flow rates after the treatment, the difference was not statistically significant ($P > 0.05$; Table 2).

Discussion

The most commonly used agents for the treatment of dry mouth are salivary stimulants and/or substitutes. Nevertheless, not much evidence supports any treatment to be more effective than the other (14,22). Hence, the selection of the agent is primarily based on the clinical experience or by allowing patients to decide which one works the best for them, which could be both expensive and frustrating. Usually, topical treatments are preferred over systemic treatments because of their fewer side effects, easy administration, and acceptance by patients. The use of topical salivary stimulants based on acidic substances, such as citric, tartaric, or phosphoric acid, is not new; however, their use has been questioned because of their intrinsic erosive potential, which is contra-productive in patients with reduced salivary flow (23,24), thereby increasing the risk of caries (25). In contrast, the use of weaker acid-based salivary stimulants, such as malic acid, combined with fluoride and xylitol, has been shown to reduce the risk of lowering the salivary pH under the hydroxyapatite critical level (5.5) when compared with stronger acids (citric acid) having no impact on tooth demineralization, even with relatively high concentrations (4.7%) (15). Malic acid is an organic acid found in fruits, such as pears and apples, and can be obtained for commercial use by chemical synthesis (26). Malic acid stimulates salivary flow by dissociating into H^+ ions when mixed with water and becoming hydronium ions (H_3O^+), leading to saliva secretion to neutralize the acid formation (17). Recently, a new spray formulation containing 1% malic acid, 10% xylitol, and 0.05% fluoride (Xeros Dentaid Spray) has been proven to be clinically safe and efficient in reducing xerostomia and increasing salivary flow rates in patients with dry mouth secondary to drugs (16-18,27). Nevertheless, its ability to improve the OHRQoL has not been investigated, and

patient-centered outcome measures, such as the quality of life, are considered as vital outcome measures in the evaluation of any treatment or health-related intervention (28,29). Hence, the present study assessed the effect of 1% malic acid on the OHRQoL.

When indicating treatment for xerostomia, it is crucial to identify the underlying cause. If xerostomia is caused by a disease that is known to destroy the salivary gland acini (such as advanced cases of Sjögren's syndrome or post-head and neck radiotherapy), it is unlikely that patients will benefit from a salivary stimulant; in fact, they are more likely to benefit from a salivary substitute. In this study, we only included patients in whom xerostomia was associated with a specific type of drug or idiopathic causes. In both cases, xerostomia is considered to be reversible, as there is no glandular damage. Hence, patients are likely to benefit from a topical stimulant, such as malic acid.

Plenty of evidence confirms that xerostomia negatively affects the OHRQoL (5,10,30). Patients using a spray containing 1% malic acid, 10% xylitol, and 0.05% fluoride (Xeros Dentaid Spray) demonstrated a statistically significant increase in their OHRQoL compared with that in patients using the placebo. All seven dimensions from the OHIP-14sp revealed an improvement in the intervention group, with statistically significant differences for physical pain, physical incapacity, and social disadvantage. Gerdin et al. (9) and Thomson et al. (30) reported that physical pain and physical incapacity dimensions exert a significant impact on the OHRQoL of patients with xerostomia, which is in accordance with our results. When analyzing xerostomia with the VAS, both groups reported statistically significant improvement, which is in discordance with the studies of Gomez-Moreno et al. (17,27) who reported a statistically significant difference just for the malic acid group. This discordance can be attributed to several reasons. One could be that xylitol in the placebo group could have some salivary stimulant activity because of its sweetness, acting as an "active placebo" (18), thereby decreasing the severity of xerostomia without improving the OHRQoL. Söderling et al. revealed that chewing gums with xylitol significantly increased the salivary flow rate compared to chewing gums without xylitol, suggesting an independent effect of xylitol on salivary flow (31). Nevertheless, Giertsen et al. established no effect of xylitol or fluoride on the salivary flow rate (32). However, none of these authors assessed the effect of xylitol on xerostomia itself. Another explanation could be that patients from the control group used the spray more significantly than patients from the intervention group, which can increase the placebo effect because of the willingness of patients to improve their clinical condition by using the treatment more often (18).

As reported earlier, an increase was noted in the non-stimulated salivary flow rates (which was statistically significant) and the stimulated salivary flow rates (which did not reach statistical significance) in the malic acid group. Our results correspond to those of previous studies, with the primary difference being that these studies reported statistically significant differences in both stimulated and non-stimulated salivary flow rates (15,17,27). The significant improvement in the OHRQoL observed in the intervention group could be attributed to an increase in both non-stimulated and stimulated salivary flow rates. Only an increase in the non-stimulated salivary flow rate was statistically significant, and the increase in the stimulated salivary flow rate almost reached statistical significance ($P = 0.055$). Hence, it is likely that its increase also contributed to the improvement in the OHRQoL, as reported in the literature (15,17,27).

This study has some limitations. First, most patients included in this study were females; this indicates that xerostomia is more common in females than in males (5). Nevertheless, as groups were balanced regarding gender and age, not many differences were present between groups. Second, we recognized that it would have been ideal to assess xerostomia using a specially designed questionnaire, such as the xerostomia inventory; however, a Spanish, validated version of such a questionnaire was not available during this study period.

This clinical trial demonstrates that a topical salivary stimulant containing 1% malic acid improves the OHRQoL and dry mouth sensation in patients with drug-induced or idiopathic xerostomia.

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Conflict of interest

The authors declare no conflict of interest.

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