A comparison of salivary substitutes versus a natural sialogogue (citric acid) in patients complaining of dry mouth as an adverse drug reaction: a clinical, randomized controlled study

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Objective. We aimed to compare the efficacy of saliva substitutes and citric acid long-term therapy for oral dryness relief and unstimulated salivary flow in patients reporting drug-induced xerostomia.

Study design. Fifty-four patients reporting drug-induced xerostomia were randomly subdivided into 3 groups and respectively administered artificial saliva, 3% citric acid, or distilled water in mouthwash 4 times a day for 30 days. Patients underwent measurement of unstimulated whole saliva before and after they finished therapy and were asked to note in a daily diary any symptomatologic changes 15 minutes and 1 hour after each daily intake of test solution.

Results. Fifteen minutes after solution intake, 12 patients (67%) belonging to the artificial saliva group, 9 (50%) from the citric acid group, and 2 (11%) from the water group reported significant symptomatologic improvement. One hour after solution intake, 7 patients (39%) from the artificial saliva group, 10 (56%) from the citric acid group, and 0 from the water group noted significant symptomatologic improvement. None of the drugs tested affected unstimulated whole saliva flow.

Conclusions. Both artificial saliva and citric acid provided immediate relief from oral dryness. Citric acid also provided a longer-lasting feeling of oral moistness at 1 hour after use owing to its protracted activity on salivary gland function. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e15-e20)

The word “xerostomia” is derived from Greek. It comes from “xeros” (dry) and “stoma” (mouth), and is usually used to indicate the condition of not having enough saliva to keep the mouth moist. The term “xerostomia,” however, may properly be used to describe the subjective sensation of dryness in the mouth reported by patients, whereas the more accurate term for measurable and objectifiable changes in reduced salivary function is “salivary gland hypofunction” for a reduction in fluid output and “salivary gland dysfunction” for a more general alteration in physiologic salivary gland function.1-3

This semantic distinction is important, because a feeling of dry mouth is not always accompanied by an objective decrease in the salivary flow. In fact, patients may occasionally report feelings of oral dryness, similar to a sticky or doughy sensation, without any objective clinical reduction being found.4,5 This would indicate that other factors can influence the feeling of moistness in the mouth. Several short- and long-term conditions can disrupt salivary secretion, leading to hyposalivation. These include psychologic problems (stress and anxiety), autoimmune disease (Sjögren syndrome), and chemotherapy or radiotherapy of the head and neck.6-9 The feeling of dry mouth is the most common oral adverse drug reaction in the oral cavity. In fact, a large number of medications, >500, list dry mouth as an adverse effect. Relatively few drugs, however, have been demonstrated to affect salivary function in controlled clinical studies. This apparent disparity may reflect the subjective sensation of oral dryness due to qualitative alterations of saliva rather than actual changes in the salivary flow rate.10-12 The drugs most commonly reported to induce xerostomia are the tricyclic antidepressants, antipsychotics, benzodiazepines, atropinics, beta-blockers, antihistaminics, H2-receptor antagonists, diuretics and angiotensin-converting enzyme inhibitors, anti-HIV protease inhibitors, and omeprazole.8,9

Dry mouth treatment requires an etiologic and/or symptomatic therapy. Etiologic therapy requires causative recognition and management of conditions. In cases of drug-induced xerostomia, the intake of the drug causing the sensation of dryness should be inter-
scribed; when that is not possible, the dose should be reduced.\textsuperscript{13,14} Alternatively, a symptomatic pharmacologic treatment of xerostomia, based on saliva substitutes (artificial saliva) in mouthwashes or in gel formulations (containing carboxymethyl cellulose or hydroxyethyl cellulose), oral moisturizers in sprays or gels (xylitol, maltitol, sorbitol, mannitol, aspartame, acesulfame K), and sialogogues (pharmacologic salivary production stimulants) should be considered.\textsuperscript{15} Which kind of symptomatic pharmacologic therapy (saliva substitutes, oral moisturizers, or sialogogues) to use essentially depends on the efficiency of the salivary gland parenchyma. Therefore, sialogogue prescription is justified only if functioning salivary tissue is available, whereas moisturizing agents are to be administered, exclusively, in cases of compromised and unresponsive salivary gland parenchyma (e.g., severe cases of Sjögren syndrome).\textsuperscript{14}

Sialogogue drugs, whether natural or artificial, stimulate the salivary glands by targeting the autonomic nervous system pathways. Citric acid, a natural sialogogue that stimulates the taste buds through parasympathetic efferent pathways, and pilocarpine, bethanecol, and cevimeline, which act directly on specific muscarinic cholinergic receptors within the salivary gland parenchyma, all stimulate abundant saliva secretion. Muscarinic agonists can be responsible for several systemic side effects, such as sweating, upset stomach, runny nose, flushes, chills, dizziness, weakness, frequent urination, and perspiration, and are, therefore, suitable only in the treatment of severe xerostomia (i.e., Sjögren syndrome and other serious diseases, chemotherapy, radiation treatment, etc.). In contrast, only local but preventable side effects have been reported for citric acid in mouthwash (e.g., erosion of tooth enamel), which makes it potentially safer than treatment with muscarinic agonist drugs.\textsuperscript{12,16-24}

The aim of the present study was to compare the efficacy of saliva substitutes that do not contain citric acid with that of a solution of 3% citric acid on the feeling of dry mouth and on unstimulated saliva flow rates in patients taking drugs with documented negative influence on salivary flow rate.

**MATERIAL AND METHODS**

**Study design**

For this trial, a group of physicians (group A) recruited patients, and different physicians (group B) evaluated the therapy and study outcomes. A total of 78 patients complaining of a sensation of dry mouth were clinically evaluated and asked to abstain from smoking, eating, and drinking for 1 hour before the measurement of their salivary flow. Unstimulated whole saliva (UWS) was collected for 5 minutes by means of the spitting method, and stimulated whole saliva (SWS) was collected for 1 minute after using the paraffin stimulation technique for 5 minutes. The whole saliva flow rate is expressed in mL/min. UWS flow \(\leq 0.1\) mL/min was considered salivary hypofunction. Values \(>0.1\) and \(\leq 0.25\) mL/min were defined as slight dysfunction, and values \(>0.25\) mL/min were interpreted as a normal resting flow rate. SWS flow \(>0.7\) mL/min indicated normal activity of the salivary glands. All patients were also asked to provide a subjective assessment of their feeling of dryness using 2 ranking scales (RS), both based on a scale of 0 to 4 points: one for the daily frequency of oral dryness (RS-A), rated as “never” (0), “hardly ever” (1), “occasionally” (2), “fairly often” (3), and “very often” (4); and the other for the perceived intensity of the dry mouth sensation (RS-B), rated as “absent” (0), “slight” (1), “moderate” (2), “rather severe” (3), and of “maximum discomfort” (4). These values represented the patients’ baseline conditions.

**Eligibility criteria**

Patients satisfying the following criteria were considered to be suitable for the study:

1. They had experienced feelings of dry mouth for \(\geq 7\) days with UWS values \(>0.1\) and \(\leq 0.25\) mL/min.
2. For \(\geq 1\) week before the start of the study they had been taking a minimum of 2 drugs with documented induction of salivary gland hypofunction (e.g., anticholinergic, antidepressants, antihistamines, antihypertensives, antiparkinsonians, antipsychotics, decongestants, diuretics, and sedatives) and continued taking them for the duration of the study.
3. They complained of dry mouth with an RS score \(\leq 3\) for both frequency (mode A) and intensity (mode B).

Patients were excluded if:

1. They had a history of systemic diseases explaining the diminished salivary flow (i.e., Sjögren syndrome, diabetes mellitus, infection of the salivary glands, cancer patients irradiated for head and neck cancer, antecedents of maxillofacial surgery with total or partial removal of major salivary glands, etc.).
2. Their SWS was \(<.7\) mL/min, thus excluding patients with potentially undiagnosed systemic diseases that might influence salivary flow rates.
3. They complained of dry mouth with a normal salivary flow rate (UWS with values \(>0.25\) mL/min).

On the basis of these criteria, 24 patients were excluded from the study.
Study population, protocol, and outcome measures

Fifty-four patients were considered to be suitable for our study (32 women and 22 men; aged 51-78 years, mean 66 years). Each of the patients signed an informed consent form, and the procedures of this study were in accordance with institutional and national ethical standards on human experimentation and the Helsinki Declaration of 1975 as revised in 2000. Possible carious lesions or dental erosions for all enrolled patients were corrected before beginning the study.

Using random number–generator computer software, another operator (not a doctor) divided the patients into 3 groups of 18 subjects each according to gender, age, and drug types. Before the groups were randomly divided, a number was assigned to each therapeutic protocol as prearranged for the 3 patient groups. This sequence of numbers was known only to investigator A, who administered the drugs for each group. Investigator A provided patients with mouthwash in identical white containers, marked with numbers 1, 2, and 3, respectively, for the artificial saliva group (group 1: 10 women and 8 men; mean age 68 years), the citric acid group (group 2: 11 women and 7 men; mean age 65 years), and the distilled water group (group 3: 11 women and 7 men; mean age 66 years).

All patients were given identical instructions, i.e., to keep 5 mL of the administrated solution in the mouth for 30 seconds, 4 times daily for 30 days, 1 hour after eating meals and brushing teeth. The patients in group 1 received a salivary substitute (containing water, hydroxypropyl cellulose, sorbitol, dipotassium chloride, sodium chloride, magnesium chloride, calcium chloride, and potassium phosphate) with a neutral pH (~7) and were marked as the artificial saliva group. The patients in group 2 received a solution of citric acid (3% in essential water) with pH of ~3.5 and were marked as the citric acid group. The patients in group 3 received distilled water with a pH of 7 and were marked as the water group. All patients were instructed to note in a diary their sensations about the efficacy of the solutions.

At the end of the study (30 days), all patients were evaluated by investigator B, who was blinded to the form of therapy given to each group, and UWS was measured 1 hour after the last dose of therapy. Investigator B also received all patients’ daily diaries and calculated 2 numeric values per subject per day, representing the mean value of the 4 daily RS-C scores recorded by the patients 15 minutes and 1 hour after the treatment.

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The highest daily RS-C score for every liquid treatment (both 15 minutes and 1 hour after treatment) was calculated, obtaining only 1 score value from the mean of 4 daily administrations and assigning, for 30 days, a possible total score of 90 corresponding with oral comfort. A total score ≥70 was considered to be a significant symptomatologic improvement of oral dryness, a total score ≥40 but <70 a slight symptomatologic improvement, a score ≥20 but <40 an unchanged or unmodified symptomatology, and a total score <20 a symptomatologic deterioration. At the end of the study, all patients received a dental examination of the soft and hard tissues to determine any potential adverse effects from the study therapy.

Statistical analysis

The data were analyzed using the 2-way analysis of variance test by GraphPad Software to gain an understanding of the efficacy of the solutions.

RESULTS

The medicaments used for our study were well tolerated, and no patient noted serious adverse effects in their diaries. The final dental examination of all patients did not reveal any soft or hard tissue lesions. Patients’ compliance was optimal, and all 54 patients completed the study.

Table I reports the daily mean of RS-C scores of all the patients, after 15 minutes and after 1 hour, and their distribution in relationship to the total score of 30 days’ therapy.

After 15 minutes both salivary substitutes and 3% citric acid induce early relief from dryness in the mouth

Figure 1 shows that after 15 minutes the mean RS-C score was highest in the artificial saliva group: 67.8 (tertile range 69.3-80.7). A slightly lower mean RS-C score, 61.7 (tertile range 49.7-78.7), was observed for the citric acid group, and the water group demonstrated the lowest RS-C score, with a mean of 34.9 (tertile range 26.7-36.7). Collectively, these data show a significant relief of oral dryness with the reappearance of a feeling of oral moisture by both salivary substitutes (artificial saliva group vs. water group: P < .0001) and the 3% citric acid solution (citric acid group vs. water group: P < .0001) at 15 minutes after the intake. No significant difference was found between the artificial saliva and the citric acid groups for overlapping efficacy in oral dryness (P = .1320) (Table I).
After 1 hour of liquid therapy, citric acid exerts more longstanding effects than do salivary substitutes in dry mouth relief

Figure 1 shows that after 1 hour the mean RS-C score was highest in the citric acid group: 66.4 (tertile range 64-80.7). A slightly lower mean RS-C score, 54 (tertile range 31.7-73), was recorded for the artificial saliva group, and the water group showed the lowest RS-C score, with a mean of 30.9 (tertile range 28.7-34.7). These data show that both salivary substitutes and citric acid proved to be effective against dry mouth compared with the placebo ($P = .0004$ and $P < .001$, respectively) and demonstrated that 3% citric acid provided a longer-lasting beneficial effect in relief of the dry mouth feeling compared with salivary substitutes 1 hour after use (citric acid group vs. artificial saliva: $P = .0047$; Table I).

### Table I. Effectiveness of therapies on dry mouth feeling at the end of the study in relation to 30 days’ RS-C scores of from the daily diaries of patients

<table>
<thead>
<tr>
<th>Artificial saliva group (A)</th>
<th>Citric acid group (C)</th>
<th>Water group (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68 (±9.1)</td>
<td>65 (±8.5)</td>
<td>66 (±8.3)</td>
</tr>
<tr>
<td>Female (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>100</td>
<td>100</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of patients (%)</th>
<th>After 15 min</th>
<th>After 1 h</th>
<th>After 15 min</th>
<th>After 1 h</th>
<th>After 15 min</th>
<th>After 1 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70</td>
<td>12 (67%)</td>
<td>7 (39%)</td>
<td>9 (50%)</td>
<td>10 (56%)</td>
<td>2 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>40 to &lt;70</td>
<td>4 (22%)</td>
<td>4 (22%)</td>
<td>5 (28%)</td>
<td>5 (28%)</td>
<td>2 (11%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>≥20 to &lt;40</td>
<td>2 (11%)</td>
<td>5 (28%)</td>
<td>4 (22%)</td>
<td>3 (17%)</td>
<td>10 (56%)</td>
<td>12 (67%)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>0</td>
<td>2 (11%)</td>
<td>0</td>
<td>0</td>
<td>4 (22%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Overall mean</td>
<td>67.83</td>
<td>54</td>
<td>61.67</td>
<td>66.39</td>
<td>34.89</td>
<td>30.94</td>
</tr>
</tbody>
</table>

$P$ value by 2-way analysis of variance

<table>
<thead>
<tr>
<th>A vs. W</th>
<th>A vs. C</th>
<th>C vs. W</th>
</tr>
</thead>
<tbody>
<tr>
<td>.0048</td>
<td>.1761</td>
<td>.1676</td>
</tr>
<tr>
<td>.0001</td>
<td>.0047</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>.1320</td>
<td>.0047</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

RS-C, Rating scale of symptomatology change.

Fig. 1. Box plots of total rating scale scores of symptomatology change (RS-C) from the daily diaries of patients, with distribution of data into tertiles (lower, middle, and upper).
group (0.14 mL/min) was compared with the final UWS value (0.18 mL/min), showing \( P = .1100 \). The overall mean of initial UWS value of the citric acid group (0.15 mL/min) was compared with final UWS value (0.16 mL/min), showing \( P = .1355 \). The overall mean of initial UWS value of the water group (0.14 mL/min) was compared with final UWS value (0.15 mL/min), showing \( P = .5425 \). These results indicate, as predicted, that neither the 3% citric nor the saliva substitutes affect the UWS flow rate.

**DISCUSSION**

A recent clinical study conducted by Eliasson et al. (2009)\(^{29}\) showed a strong association between minor palatal and labial salivary gland secretion rates and subjective oral dryness. A decrease in the salivary film retained on, and moistening, the oral surfaces appears to be an essential element in oral discomfort in this context, and its reduction is related to a worsening of the feeling of dryness.\(^{15,25,26}\) This could explain the current conflicting reports, often leading to mistaking a dry mouth feeling for hyposalivation due to a hypofunctioning salivary gland, validating the hypothesis that the sensation of moistening in the mouth is not so much related to the quantity of liquid within the mouth but rather to the moistness of the oral mucosal surfaces.\(^{27-36}\)

We examined the efficacy of salivary substitutes versus 3% citric acid in patients complaining of oral dryness for slight salivary gland hypofunction (UWS values \( \geq 0.1 \) and \( \leq 0.25 \) mL/min) that was drug induced without alteration in SWS (i.e., \( > 0.7 \) mL/min). In this trial, participants with more severe salivary gland hypofunction (UWS values \( \leq 0.1 \) mL/min) and with SWS \( < 0.7 \) mL/min, who may have prejudiced the sialogogue efficacy of citric acid, were excluded. Our findings show that both salivary substitutes and citric acid induce an immediate and significant symptomatologic improvement in the feeling of dry mouth 15 minutes after solution use (Fig. 1; Table 1). This finding is in accordance with data presented by Silvestre et al. (2009).\(^{32}\) who administered artificial saliva as a spray to 37 patients complaining of dry mouth, 20 of whom showed an almost immediate improvement after application. Moreover, we found that the use of 3% citric acid provides a prolonged and significant symptomatologic improvement 1 hour after its intake (10 patients (56%) with score \( \geq 70 \)) compared with the use of artificial saliva (7 patients (39%) with a score \( \geq 70; \) \( P = .0047 \)). This longer-lasting efficacy of 3% citric could be the consequence of the stimulation of both major and minor salivary glands and an increase in the rate of whole salivary flow and the formation of salivary film upon the oral mucosa.

UWS represented a second parameter evaluated after the intake of the solutions. Comparison of the initial UWS flow rate values (collected for each group before the start of treatment) and the final UWS flow rate values (collected for each group 1 hour after the last tested drug treatment) showed no significant difference in any group. These overlapping initial and final UWS flow rate values, reflecting the inefficacy of the tested liquids on UWS enhancement, were predictable for water and artificial saliva, and for patients in the citric acid group the inefficacy could be related to the negative influence of xerostomia-inducing drugs themselves on the salivary gland parenchyma, which did not permit sufficient gland activation. Interestingly, drug-induced xerostomia is mainly reported by elderly patients on polypharmacy therapy, with a reduction of the baseline resting salivary flow rate but not of the stimulated saliva secretion (i.e., food or salivary flow rate testing with citric acid stimulation).\(^{15,37}\) Drug-induced xerostomia therapy requires replacement or at least a reduced dosage of the responsible drug. If this is not possible, symptomatic treatment based on salivary production stimulants (sialogogues) or moisturizing agents (saliva substitutes) are recommended. Because cholinergic sialogogues are potentially responsible for muscarinic adverse drug reactions, they are used selectively for advanced salivary gland hypofunction. In contrast, natural sialogogues, such as 3% citric acid, are preferred in less advanced cases or as supplemental therapy because of their minor side effects.

Clinicians should be aware that long-term use of 3% citric acid in mouthwash can cause oral adverse effects, i.e., dental hypersensibility and erosion, due to the demineralization of dental hard tissues from salivary pH reduction (3.5-3.0). However, when an acid enters the mouth, whether from an intrinsic or extrinsic source, salivary flow rate normally increases, along with the pH and buffer capacity. Within minutes, the acid is neutralized and cleared from the oral cavity and the pH returns to normal. In the presence of xerostomia the oral intake of citric acid, when not counteracted, can lower salivary pH. Our research found no dental erosion among patients in the citric acid group at the final appointment, which may be related to both the short time of contact with citric acid in the mouth (30 seconds) and insufficient study time (30 days). The use of citric acid in mouthwash for long periods requires continuous dental monitoring and some essential behavioral recommendations, such as restricting the time of contact with the tooth surface, not brushing teeth for at least 1 hour after taking the citric acid, limiting or eliminating other substances responsible for dental erosion from the diet (i.e., spicy or acidic foods, soft drinks, alcoholic beverages, fizzy mineral water, fruit juice, etc.), and rinsing with a mouthwash of sodium bicarbonate in water to raise the oral pH. Additionally, we recommend...
the use of calcium phosphates and fluorides to promote dental remineralization to counteract citric acid dental erosion.38 On the basis of the results of our study, for patients complaining of drug-induced xerostomia with preservation of responsive salivary gland parenchyma, we recommend a long-term therapy using a mouthwash containing both a salivary substitute and citric acid in solution for combined immediate and long-lasting relief, in addition to the use of a remineralizing products and consistent periodic dental monitoring.

REFERENCES