Prognostic Value of the Pilocarpine Test to Identify Patients Who May Obtain Long-term Relief From Xerostomia by Acupuncture Treatment

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Background: Xerostomia (dry mouth) is a clinical symptom due to a number of factors, including Sjögren syndrome and radiation treatment to the head and neck region. It has been reported that acupuncture increases the salivary flow rate (SFR) in healthy subjects and in patients with xerostomia. A prognostic tool that would allow the care provider to identify patients who may respond to acupuncture treatment will aid in early intervention and thus lead to normalized SFR or relief of symptoms.

Objectives: To determine the prognostic value of a test using pilocarpine chloride to identify those patients with xerostomia who may achieve a long-term increase in SFR in response to acupuncture.

Design: Cohort clinical study of 10 months’ duration.

Setting: School of dentistry in a large, urban, research institute.

Patients: Thirty-two consecutive patients with xerostomia due to radiation treatment (n = 21) or Sjögren syndrome (n = 11).

Intervention: Salivary flow rates for unstimulated whole saliva and paraffin-chewing stimulated whole saliva were measured before and after the administration of individualized doses of pilocarpine. All patients were then given 24 acupuncture treatments and followed up at 1 and 6 months. The effects of acupuncture treatment on SFR were recorded and response compared with the results of the pilocarpine test.

Main Outcome Measures: Sensitivity, specificity, and positive and negative predictive value of the pilocarpine test based on changes in SFR, defined as a 20% increase or greater, following acupuncture treatment, compared with response to the pilocarpine test.

Results: At the 1-month follow-up, 18 (72%) of 25 patients with a positive pilocarpine test result had defined significant changes in SFR; 4 (67%) of 6 patients with a negative pilocarpine test result had an unchanged SFR. At this point, the sensitivity of the pilocarpine test was 0.90 (95% confidence interval [CI], 0.68-0.99) and the specificity was 0.36 (95% CI, 0.11-0.69). The positive predictive value was 0.72 (95% CI, 0.51-0.88), and the negative predictive value was 0.67 (95% CI, 0.22-0.96). At the 6-month follow-up, 17 (74%) of 23 patients with a positive pilocarpine test result had defined significant changes in SFR; 3 (60%) of 5 patients with a negative pilocarpine test result had an unchanged SFR. At this point, the sensitivity of the pilocarpine test was 0.89 (95% CI, 0.67-0.99), and the specificity was 0.33 (95% CI, 0.07-0.70). The positive predictive value was 0.74 (95% CI, 0.52-0.90), and the negative predictive value was 0.60 (95% CI, 0.15-0.95).

Conclusion: The pilocarpine test was found to have a high sensitivity and good positive predictive value in identifying patients who may respond to acupuncture for the treatment of xerostomia.

PATIENTS AND METHODS

Thirty-two patients with subjective complaints of dry mouth were initially included in the study. All patients were consecutively selected as referred from general dental and medical practices. The only criteria for inclusion were that they complained of dry mouth secondary to SS or radiation treatment and agreed to complete 24 acupuncture treatment sessions over 3 to 4 months, with an additional observation period of 6 months. One patient withdrew from the study because of hospitalization for progression of cancer. Thirty-one of the patients with dry mouth as a sequela of either radiation treatment (20 patients) or SS (11 patients) completed the acupuncture treatment, and 28 completed the study at the 6-month follow-up. The study was approved by the Human Ethics Committee at Karolinska Institute, Huddinge Hospital, Huddinge, Sweden.

In the whole group (N = 31), there were 17 women and 14 men, ranging in age from 43 to 82 years (median, 59 years) and weighing from 45 to 93 kg (median, 64 kg). In the irradiated group, there were 7 women and 13 men, ranging in age from 43 to 82 years (median, 58 years) and weighing from 45 to 93 kg (median, 64 kg). Nineteen patients had undergone radiation treatment to the head and neck region; 18 received a dose between 64 and 66 Gy, and one, 50 Gy. The remaining patient had received 10 Gy as a whole-body dose. These patients had xerostomia between 4 to 18 months since their radiation treatment (median, 9 months).

In the SS group, there were 10 women and 1 man, aged 53 to 72 years (median, 63 years), weighing between 51 and 89 kg (median, 63 kg). These patients had had xerostomia between 2 and 20 years (median, 10 years). Seven patients had primary SS, and 4 patients had secondary SS associated with the following diseases: rheumatoid arthritis (n = 2), mixed connective tissue disease (n = 1), and polymyalgia rheumatica (n = 1). Other concomitant conditions were hypothyroidism (n = 4), high blood pressure (n = 4), diabetes (n = 2), gastrointestinal tract disorders (n = 2), and peripheral vascular disorders (n = 3).

The most common concomitant medications were thyroid hormone substitution (n = 4), estrogen (n = 4), sedatives (n = 4), β-receptor blockers (n = 3), angiotensin-converting enzyme inhibitors (n = 2), diuretics (n = 2), proton-pump inhibitor (n = 2), antidepressants (n = 1), and insulin (n = 1). Concomitant medication was not a criterion for exclusion.

In the total group at baseline, 19 of 31 patients (11 of 20 irradiated and 8 of 11 with SS) had measurable quantities of both unstimulated and stimulated whole saliva, and 6 of 20 irradiated patients had a baseline of unmeasurable quantities of both unstimulated and stimulated whole saliva. Two had a baseline of unmeasurable unstimulated saliva but had measurable stimulated saliva, and 1 had a baseline of measurable unstimulated saliva and unmeasurable stimulated saliva. In the SS group, 3 of 11 had a baseline of unmeasurable unstimulated saliva with measurable stimulated saliva.

SALIVARY FUNCTION ANALYSIS

The SFRs were measured for unstimulated and paraffin-chewing stimulated whole saliva using the recognized standard method established by Ericson and Mäkinen.20 Whole saliva was used to provide an adequately large sample for accurate measurement. Also, the collection of whole saliva vs collection from separate glands is more comfortable for the patient and more consistent with general dental/medical practice. Since the quantity of saliva was often too small to be measured in milliliters, all samples were measured by weight in grams (1 mL of saliva weighs approximately 1 g). Each saliva sample was collected over 5 minutes by trained laboratory staff at the same time of day to

as rheumatoid arthritis, scleroderma (progressive systemic sclerosis), systemic lupus erythematosus, biliary cirrhosis, or polymyositis.2-5 Xerostomia is also a common adverse effect of radiotherapy for the treatment of head and neck cancers. Atrophy of salivary glands and dysfunctional changes of the vascular and connective tissues in the gland often lead to decreased salivary secretion in these patients.6,7 Treatment for xerostomia is mainly palliative. There are many ways of alleviating the discomforts of dry mouth, primarily by using saliva substitutes and stimulating the salivary flow by sucking lozenges or by chewing gum. Therapies designed to stimulate secretion may be directed locally or systemically (pilocarpine chloride, anethole trithione, bromhexine hydrochloride).5,8-11 Among the disadvantages of these therapies, however, are that the effects are short lived and application must be frequent.12-15 Adverse effects have also been reported.16-18

Acupuncture as an alternative therapy for xerostomia has appeared in Western medical literature since 1981. In these studies, it was demonstrated that acupuncture may increase salivary flow rate (SFR) in patients with xerostomia associated with disease12-17 and in healthy subjects.18 Subjects observed for up to 11 years have indicated that this improvement can be long lasting.19

Some critics of acupuncture cite the unpredictability and varied outcomes of the therapy as a problem. This may be the result of the broad range and nonspecific screening of patients treated. In an effort to address this problem and to identify those patients with xerostomia whom acupuncture will help, an easy prognostic test was developed using a single dose of pilocarpine. Pilocarpine, often used as a systemic, long-term treatment that can have undesirable adverse effects, was used as an indicator of residual salivary gland function. It was surmised that the presence of some salivary gland function would indicate potential improvement with the stimulation of acupuncture, without the adverse effects found in other modalities. This study determined the prognostic value of a test using pilocarpine to identify those patients with xerostomia whose SFR may increase in response to acupuncture.
avoid circadian variation. The SFR was expressed in grams per minute. All samples were measured with an accuracy of 0.001 g. Protocol was strictly followed to avoid outside influence on normal SFRs. The patients were not allowed to drink, eat, or smoke for at least 60 minutes before salivary testing.

On the first visit, the patient was informed of the nature and aims of the study, and verbal consent was received. Within the next 2 weeks, the baseline SFR for unstimulated and paraffin-chewing stimulated whole saliva was determined by calculating the mean of 2 measurements taken. Also during this time, 2% pilocarpine chloride (Tika Läkemedel AB, Lund, Sweden; pilocarpine solution for ophthalmic use), 0.7 mg in 1 drop of solution for every 10 kg of body weight, or part thereof, was administered by mouth in 20 mL of water. Figure 1 shows the full procedure of the pilocarpine test. Neither the staff performing the salivary measurements nor the patient was aware of the exact nature of the pilocarpine administered. After 45 minutes, SFR was measured for both unstimulated and paraffin-chewing stimulated whole saliva. The pilocarpine test was considered to be positive if either or both the stimulated and unstimulated SFR increased or decreased 20% or greater from baseline. It was considered negative if there was none or a less than 20% increase or decrease in all of the above SFRs.

Acupuncture treatment was then administered in 2 series of 12 treatments each, given as 2 treatments per week. These 2 series were given over the next 3 months. The patient was observed for 6 months following the second acupuncture series. Unstimulated and stimulated saliva was measured at the 1- and 6-month follow-up visits. The SFR was considered to be changed if there was an objective increase of 20% or greater from baseline. It was considered unchanged if there was no or less than 20% increase from baseline.

At the 6-month follow-up, the sensitivity of the pilocarpine test was 0.89 (95% CI, 0.67-0.99) and the specificity was 0.33 (95% CI, 0.07-0.70). The positive predictive value was 0.74 (95% CI, 0.52-0.90). In other words, 74% (17/23) (after 1 month, 72% [18/25]) of the patients with a positive pilocarpine test result responded to acupuncture treatment, and these effects are statistically significant. The negative predictive value was 0.60 (95% CI, 0.15-0.95).

When the data were organized by etiology (SS vs irradiated patients) and compared, it was found that the pilocarpine test was about equally prognostic in both groups in identifying patients who may respond to acupuncture.

The only 2 adverse effects of the pilocarpine reported were a mild cough lasting no more than 5 minutes after pilocarpine administration and, in another patient, general abdominal discomfort lasting a few hours.

Qualitative findings were also recorded. Six patients noted that saliva became more fluid and found an improvement in taste. Two patients reported a considerable reduction in nausea, and 2 an improvement in appetite, both of which led to a cessation of weight loss. Three patients reported increased moisture of the eye, and 7 said that color and temperature in extremities im-

Table 1 shows the median SFR and interquartile range for the total group at baseline and at the 1- and 6-month follow-up visits. Patients with positive or negative pilocarpine test results compared with a change or no change in SFR following acupuncture treatment are described in Table 2. At the 1-month follow-up, 18 (72%) of the 25 patients with a positive pilocarpine test result had a significant (≥20%) defined change in SFR; 4 (67%) of the 6 patients with a negative pilocarpine test result had an unchanged SFR. At the 6-month follow-up, 17 (74%) of 23 patients with a positive pilocarpine test result had a significant defined change in SFR; 3 (60%) of 5 patients with a negative pilocarpine test result had an unchanged SFR.

The evaluation of the reliability of the pilocarpine test at the 1-month follow-up indicated that the sensitivity of the pilocarpine test was 0.90 (95% CI, 0.68-0.99) and the specificity was 0.36 (95% CI, 0.11-0.69). The positive predictive value was 0.72 (95% CI, 0.51-0.88), and the negative predictive value was 0.67 (95% CI, 0.22-0.96).

ACUPUNCTURE TREATMENT

All acupuncture treatment was performed by one of us (M.B.), who is certified in classic Chinese acupuncture according to traditional Chinese medicine and has 14 years of experience. The classic acupuncture points21,22 stimulated during treatment were in the head, hands, and legs. Points were chosen locally from the head region (ST 3, ST 5, ST 6, ST 7, SI 17, LI 18, TE 17, and GV 20) and as distal points (H 7, P 6, L 13, L 14, LI 11, TE 5, ST 36, SP 6, GB 41, LR 3, K 3, and K 5) (Figure 2). Five to 8 points were chosen on the head, face, and distal points specific to the particular complaints and the general health of each patient. The needles were stimulated manually until the appearance of needle reaction (De Qi), a subjective feeling of numbness, soreness, distension around the point, warmth, or a radiating sensation originating from the needle point. When De Qi was achieved, the needles were left in situ for 20 minutes. The needles used were Chinese, stainless steel (Cloud & Dragon, Swzhou, China), sterile for single use, with the dimensions 0.30 × 40, 0.30 × 30, or 0.30 × 15 mm.

STATISTICAL ANALYSIS

Sensitivity, specificity, and positive and negative predictive values were calculated to compare the results of the pilocarpine test before acupuncture with the results of acupuncture after 1 month and after 6 months.

To analyze the effect of the pilocarpine test and the effect of 24 acupuncture treatments, we decided to dichotomize the change in SFR, “changed” (≥20% changed from baseline) and “unchanged” (unchanged or changed <20% from baseline). The probability for improvement was then calculated together with the 93% confidence interval (CI). If the CI did not cover 0.5, we concluded that there was a statistically significant improvement from baseline.
system and influenced by the sensory nervous system. The function of the salivary glands is controlled by the autonomic nervous system. Acupuncture on the salivary glands. The function of the glands was determined before and after a pilocarpine test. After this test, all patients were given 24 acupuncture treatments. Salivary secretion was determined to be either changed or unchanged from baseline at the 1- and 6-month follow-up visits. The results of the pilocarpine test were then compared with the SFRs at the above time points. Of the patients with a positive pilocarpine test result, 72% (18/25) showed significant change in SFR at the 1-month follow-up. At 6 months, 74% (17/23) of these patients indicated a change. Of the patients with a negative pilocarpine test result, 67% (4/6) did not have a significant change in SFR at 1 month and 60% (3/5) did not at 6 months.

The results showed that there was a strong positive correlation between the response to pilocarpine and the response to acupuncture. This may be explained by some similarity in the physiologic actions of pilocarpine and acupuncture on the salivary glands. The function of the salivary glands is controlled by the autonomic nervous system and influenced by the sensory nervous system.

**COMMENT**

In the present study, 31 patients with xerostomia as a sequela of radiation treatment or SS were observed. Salivary secretion was determined before and after a pilocarpine test. After this test, all patients were given 24 acupuncture treatments. Salivary secretion was determined to be either changed or unchanged from baseline at the 1- and 6-month follow-up visits. The results of the pilocarpine test were then compared with the SFRs at the above time points. Of the patients with a positive pilocarpine test result, 72% (18/25) showed significant change in SFR at the 1-month follow-up. At 6 months, 74% (17/23) of these patients indicated a change. Of the patients with a negative pilocarpine test result, 67% (4/6) did not have a significant change in SFR at 1 month and 60% (3/5) did not at 6 months.

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Pilocarpine Test

Step 1. The unstimulated whole saliva is collected by having the patient passively flow saliva into a graduated cylinder for 5 minutes.

Step 2. The patient chews a paraffin piece for 1 minute, swallowing the saliva.

Step 3. Stimulated whole saliva is collected by having the patient chew a paraffin piece and spit into a graduated cylinder for 5 minutes.

Evaluation

Step 9. The unstimulated and stimulated saliva collected is measured in milligrams and/or milliliters.

Step 10. The unstimulated whole saliva from step 1 (baseline) is compared with that from step 6 (pilocarpine test), and the stimulated saliva from step 3 (baseline) with step 8 (pilocarpine test). The prognosis is positive if either or both postpilocarpine SFRs increase or decrease 20% or greater from baseline. The prognosis is negative if both postpilocarpine SFRs are unchanged or change less than 20% from baseline.

The basic equipment required was four 10-mL graduated cylinders, 4 small funnels, a timer, and scales. Supplies per test were 2 paraffin pieces and 2% pilocarpine chloride solution (0.7 mg in 1 drop of solution). The entire test takes approximately 70 minutes. SFR indicates salivary flow rate.

**Figure 1.** Concise step-by-step description of the pilocarpine chloride test. The basic equipment required was four 10-mL graduated cylinders, 4 small funnels, a timer, and scales. Supplies per test were 2 paraffin pieces and 2% pilocarpine chloride solution (0.7 mg in 1 drop of solution). The entire test takes approximately 70 minutes. SFR indicates salivary flow rate.

**Figure 2.** Acupuncture points used during treatment were localized in the head, hands, and legs.

Noxious mechanical stimuli to the oral area, such as pinching the tongue, were found to produce copious reflex salivation in anesthetized rabbits. The magnitude of the reflex response was also influenced by the site of the stimulation, the front of the oral cavity inducing greater amounts of saliva than other facial regions, and the face more than other parts of the body. Cervical sympathectomy reduced the salivation induced by pinching the oral tissues from the ipsilateral submandibular gland by 18%, and transection of the ipsilateral chorda tympani containing the parasympathetic nerves to the salivary glands caused an 80% decrease. This suggests that the pain-salivary reflex depends heavily on the parasympathetic innervation of the chorda tympani, and to some extent on the sympathetic innervation. Takahashi et al. found the secretory and vasodilatory responses evoked by somatic stimulation (by electrically stimulating the cut end of the lingual nerve after sectioning the chorda tympani) to be mediated via activation of the autonomic nervous system and by a parasympathetic mechanism. Murakami et al. electrically stimulated the chorda tympani to identify salivary neurons in the lower brainstem of anesthetized cats. The response from groups II and III afferent fibers of the trigeminal nerve in activating salivary efferent neurons indicates the importance of afferent input from the oral region. It is also possible that the afferent nerves may contribute to the salivary secretion through axon reflexes.
Pilocarpine is a well-known cholinergic parasympathomimetic agent that acts primarily on muscarinic receptors in the target organ. One mechanism through which it increases salivary secretion is by increasing smooth muscle tone in salivary glands. As a cholinergic agonist, pilocarpine may also stimulate acetylcholine release, leading to an increased salivary secretion rate.

Although the physiologic mechanisms of acupuncture are only partly understood, acupuncture is known to affect the parasympathetic and sympathetic nervous system via input in group III and IV afferent fibers. This information can then affect the parasympathetic and sympathetic nervous capacity of the salivary glands. This information can then be used to determine the appropriateness of acupuncture and bring the patient to early intervention. It can also be applied in counseling the patient about realistic expectations of that therapy. In addition, this study indicates that pilocarpine individualized to the patient's body weight can be administered with a minimum of adverse effects. It can be carried out quickly and easily within a normal clinical routine.

Today, there exists in the literature 3 randomized controlled trials evaluating the efficacy of acupuncture in patients with xerostomia. These studies demonstrate that acupuncture may induce some relief of xerostomia. Based on our findings from this most recent report, we believe a randomized controlled clinical trial of the efficacy of acupuncture for the relief of xerostomia is needed. Prior to randomization to active acupuncture or "sham" acupuncture, the patients should be stratified based on the response to the pilocarpine test and the clinical condition of SS or irradiation.

In conclusion, our results show that the pilocarpine test is a good prognostic tool for easily predicting if acupuncture treatment may be successful in patients with xerostomia. A randomized trial within prognostic subgroups must be done if acupuncture is to be scientifically evaluated for effectiveness.

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Table 1. Salivary Flow Rate for Unstimulated and Paraffin-Chewing Stimulated Whole Saliva*

<table>
<thead>
<tr>
<th>Examination</th>
<th>Baseline</th>
<th>Time After the Last Acupuncture Treatment</th>
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<tbody>
<tr>
<td></td>
<td>1 mo (n = 28)</td>
<td>6 mo (n = 28)</td>
</tr>
<tr>
<td>Unstimulated saliva</td>
<td>0.005 (0.000-0.060)</td>
<td>0.024 (0.000-0.140)</td>
</tr>
<tr>
<td>Stimulated saliva</td>
<td>0.032 (0.002-0.340)</td>
<td>0.070 (0.004-0.560)</td>
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* Values are given as median (interquartile range).

Table 2. Patients' Response to the Pilocarpine Test vs Change or No Change in SFR Following Acupuncture Treatment*

<table>
<thead>
<tr>
<th>Positive Pilocarpine Chloride Test Result</th>
<th>Changed SFR After Acupuncture</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>1 mo (n = 31)</td>
<td>18</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>6 mo (n = 28)</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
</tbody>
</table>

* SFR indicates salivary flow rate.

REFERENCES