Clinical Oral Medicine

Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment

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OBJECTIVE: To determine the long-term effects of acupuncture in patients with xerostomia of different etiologies and the influence of additional treatment.

DESIGN: Retrospective study.

SUBJECTS: Seventy patients, between the ages of 33 and 82, with xerostomia due to primary and secondary Sjögren's syndrome, irradiation and other causes were included. The median duration of xerostomia was 32 months.

METHODS: Salivary flow rates (SFR) for whole unstimulated and stimulated saliva were used as indicators of effects of treatment. Data from 67/70 patients were analyzed 6 months following a baseline course of 24 acupuncture treatments using two-way ANOVA. Patients data up to 3 years were also compared by those who chose to receive additional acupuncture treatment vs those who did not. These data were analyzed descriptively.

RESULTS: Statistically significant differences in unstimulated and stimulated salivary flow rates \( (P < 0.01) \) were found in all etiological groups after 24 acupuncture treatments and up to 6 months follow-up compared to baseline. Three years observation of these patients showed that patients receiving additional acupuncture treatment had a consistently higher median SFR in both unstimulated and stimulated saliva compared to patients who chose not to continue acupuncture. The upper limits of the interquartile range were also higher.

CONCLUSIONS: This study shows that acupuncture treatment results in statistically significant improvements in SFR in patients with xerostomia up to 6 months. It suggests that additional acupuncture therapy can maintain this improvement in SFR for up to 3 years.

KEYWORDS: xerostomia; acupuncture; treatment; alternative; long-term

Introduction

Xerostomia (dry mouth), a decreased production or total lack of saliva secretion, is a common clinical phenomenon, and is present in about 40% of adults over the age of 50 years (Sreebny et al., 1992). Associated clinical problems include difficulty in speaking, eating and swallowing, decreased sense of taste, ulceration or soreness of the mouth, greater incidence of fungal infections, poor denture retention, and rapid progress of dental caries. Xerostomia is a common side effect of many medications, but may also be due to therapeutic irradiation, autoimmune disease and endocrinological disorders. Sjögren’s syndrome (SS) is one of the systemic diseases that causes salivary dysfunction and dry mouth. SS is an autoimmune exocrinopathy involving, in particular, the salivary and lacrimal glands. It may occur alone, as primary Sjögren’s syndrome (PSS), or as secondary Sjögren’s syndrome (SSS), if it is in association with an autoimmune disorder or a variety of connective tissue diseases such as rheumatoid arthritis (RA), scleroderma (progressive systemic sclerosis), systemic lupus erythematosus (SLE), biliary cirrhosis, or polymyositis (Moutsopoulos et al., 1980; Vitali et al., 1994; Fox and Saito, 1994; Fox, 1997). Xerostomia is also common following irradiation 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 (Dreizen et al., 1976; Greenspan, 1990).

The ‘normal’ course of xerostomia is poorly described. There are only a few published studies that observe whole salivary flow rate (SFR) for more than 1 year in patients with xerostomia. Markitziu et al. (1992), followed 14 patients who received radiation for head and neck cancer for 5 years. Jonsson et al. (1993) investigated, on two occasions, patients with primary and secondary Sjögren’s syndrome for 11–112 months. A common observation in these patients was that xerostomia never generally spontaneously improved but was associated with a gradual decrease in salivary gland function.

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 gum chewing. Therapies designed to stimulate secretion may be directed locally or systemically (pilocarpine, anethole trithione, bromhexine) (Schuller et al, 1989; Rhodus and Schuh, 1991; Fox et al, 1991; Le Veque et al, 1993; Fox, 1997).

Among the disadvantages of these therapies, however, are that the effects are short-lived and application must be frequent (Schuller et al, 1989; Sreebny et al, 1992). Adverse effects have also been reported, such as sweating, urinary frequency, rhinitis, dyspepsia and others (Schuller et al, 1989; Sreebny et al, 1992).

Acupuncture as an alternative therapy for xerostomia has appeared in western medical literature since 1981. In observational studies, it was demonstrated that acupuncture may increase SFR in patients with xerostomia associated with disease (Pierminova et al, 1981; Goidenko et al, 1985; Blom et al, 1992, 1996; Somova et al, 1993) and in healthy subjects (Dawidson et al, 1997a). However, other than one case report (Blom et al, 1993a) that described two irradiated patients who were followed for 2 years, there are no published studies on long-term effects of acupuncture treatment in patients with xerostomia.

The objective of this retrospective study was to determine the long-term effect of acupuncture in patients with xerostomia. This was evaluated first in patients with xerostomia of different etiologies (Sjögren’s syndrome, irradiated, and unclassified ‘other’), and then in patients with additional appropriate acupuncture vs those with only an initial course of acupuncture treatment.

Materials and methods

The material comprised patients treated and observed during the period 1986–1998.

Seventy patients with xerostomia due to primary and secondary Sjögren’s syndrome (SS) (n = 25), irradiation (irradiated) (n = 38), and unclassified causes (‘other’) (n = 7) were included in the study. All patients had been referred for acupuncture treatment for xerostomia from dental and medical practices within a large, urban area. Demographic and baseline information of the total population and by etiology can be found in Table 1. No patient was receiving any pharmaceutical for the treatment of xerostomia (no additional group), or other causes, such as work, family (five patients). Of these patients 17/49 were lost to follow-up because: of death or metastases (11 patients); deterioration in other diseases eg, RA (six patients); some were improved to the extent that they were satisfied with the outcome obtained (eight patients); lack of improvement (14 patients); or other causes, such as work, family (five patients). Of the 32 patients who chose not to receive additional treatment (49 patients) did so because: they moved out of the area (five patients); of death or metastases (11 patients); deterioration in other diseases eg, RA (six patients); some were improved to the extent that he was satisfied with the outcome obtained; lack of improvement (five patients); or other causes, such as work, family (three patients).

Of the 21 patients who received additional acupuncture treatment (additional group), 11 were in the SS group, eight were in the irradiated group and two were in the ‘other’ group (see Table 2). There were 11 women and 10 men, with a median of age of 61 years (range 33–67 years). Of the 32 patients who chose not to continue acupuncture therapy for treatment of their xerostomia (no additional group), eight were in the SS group, 20 were in the irradiated group and four were in the ‘other’ group. There were 20 women and 12 men, with a median of age of 55 years (range 35–73 years).

‘Other’ group included seven patients with different etiologies: there were five patients with: ‘unknown reason’

**Table 1** Baseline characteristics of all patients (n = 70)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 70)</th>
<th>Irradiated (n = 38)</th>
<th>SS (n = 25)</th>
<th>Other (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>60.5</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Range</td>
<td>33–82</td>
<td>37–82</td>
<td>53–72</td>
<td>38–73</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>26</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>40</td>
<td>12</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Dur. of xerostomia, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>13.5</td>
<td>96</td>
<td>48</td>
</tr>
<tr>
<td>Range</td>
<td>4–276</td>
<td>4–186</td>
<td>24–276</td>
<td>18–120</td>
</tr>
<tr>
<td>Radiation doses, Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (whole body)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>4</td>
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<tr>
<td>64</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>66–68</td>
<td>4</td>
<td></td>
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</tbody>
</table>

SS, Sjögren’s syndrome; Dur, duration; Gy, Gray, measurement of radiation dose.
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Table 2 Comparison between objective and subjective changes in saliva secretion after initial acupuncture treatment and 6 months follow-up

<table>
<thead>
<tr>
<th>Subjective changes</th>
<th>Objective changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>improvement</td>
</tr>
<tr>
<td>Irradiated</td>
<td></td>
</tr>
<tr>
<td>n = 38 (8 add)</td>
<td>20 (7 add)</td>
</tr>
<tr>
<td></td>
<td>6 (1 add)</td>
</tr>
<tr>
<td>SS</td>
<td></td>
</tr>
<tr>
<td>n = 25 (11 add)</td>
<td>12 (4 add)</td>
</tr>
<tr>
<td></td>
<td>1 (1 add)</td>
</tr>
<tr>
<td>‘Other’</td>
<td></td>
</tr>
<tr>
<td>n = 7 (2 add)</td>
<td>5 (2 add)</td>
</tr>
<tr>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>n = 70 (21 add)</td>
<td>37 (13 add)</td>
</tr>
<tr>
<td></td>
<td>7 (2 add)</td>
</tr>
</tbody>
</table>

The needles were stimulated manually until the appearance of needle reaction (DeQi), a subjective feeling of numbness, soreness, distension around the point, warmth, or a radiating sensation originating from the needled point. When DeQi was achieved, the needles were left in situ for 20 min. The needles used were Chinese, stainless-steel (Cloud & Dragon), sterile for single use, with the dimensions 0.30 × 40 mm, 0.30 × 30 mm or 0.30 × 15 mm. The treatments were given at the School of Dentistry, Karolinska Institute.

Salivary function analysis

The salivary flow rates were measured for unstimulated whole saliva (UWSFR) and paraffin-chewing stimulated whole saliva (SWSFR) using the recognized standard method established by Ericson and Mäkinen (1986). Whole saliva was used in order to provide an adequately large sample for accurate measurement. Since the quantity of saliva was often too small to be measured in millilitres, all samples were measured by weight in grams (1 mL of saliva weighs approximately 1 g). Each saliva sample was collected over 5 min by trained laboratory staff at the same time of day to avoid circadian variation. The SFR was expressed in grams per minute. All samples were measured to an accuracy of 0.001 grams. The patients were not allowed to drink, eat or smoke for at least 60 min before salivary testing. Protocol was strictly adhered to in order to avoid outside influence on normal salivary flow rates.

Statistical methods

Patient data for UWSFR and SWSFR up to 6 months observation following initial treatment were organized by etiology. A two-way analysis of variance (ANOVA) with repeated measures on one factor was used to analyze the salivary flow rate (SFR) in unstimulated and stimulated saliva over seven time points before and during 4 months of acupuncture (AP) and during the 6 months of observation. Etiology group was identified as the Group effect (irradiated, SS, and ‘other’) and Time as the repeated factor. The Group × Time interaction in the ANOVA refers
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Figure 1 Acupuncture points used during treatment

...to the statistical test of whether the mean response profile for one etiology group is the same as for another group.

In case of significant interaction, simple effects were examined, i.e., effects of one factor holding the other factor fixed. When the F-ratio for the factor Time was significant, planned comparisons were performed between the repeated measures. The *P* values were then corrected according to the Bonferroni procedure. If the correlations between each pair of repeated measures were not the same (test of sphericity), the degrees of freedom (d.f.) of the F-tests associated with the Time factor were reduced by multiplying each of the d.f. by the ‘Greenhouse and Geiser epsilon’. The SFR in stimulated saliva data were log-transformed in order to meet the requirements for an adequate ANOVA (Kirk, 1995).

Patient data for UWSFR and SWSFR up to 3 years were organized by whether or not the patients received additional acupuncture treatment. The long-term follow-up (3 years) of these patients were analyzed by descriptive statistics because there was no random allocation of patients to the two treatment regimens.

Results
The general outcome of the long-term effects of acupuncture in xerostomic patients show that acupuncture treatment resulted in an increased unstimulated (UWSFR) and stimulated (SWSFR) salivary flow.

Six-month observation by etiology
Unstimulated SFR (UWSFR). The Group × Time interaction was significant between the three groups, *F* (7236) = 7.00, *P* < 0.001. Further analysis of the interaction revealed a significant difference between the irradiated and SS groups versus the ‘other’ group, concerning the increase of SFR across time, *F* (4236) = 13.4, *P* < 0.001. There was no significant difference between the irradiated and SS groups across time, *F* (4236) = 0.66, *P* = 0.61. Tests for
simple effects showed that the irradiated, SS and ‘other’ groups have significantly higher salivary flow rates in unstimulated saliva after 24 AP compared to baseline, \( P < 0.01, P < 0.01 \) and \( P < 0.001 \), respectively. The same results could be demonstrated after 12 acupuncture treatment compared to baseline. No statistically significant differences could be demonstrated between 3-month follow-up and 6-month follow-up, compared to the last acupuncture treatment in the SS and irradiated groups. However, patients in the ‘other’ group did display significant increases in SFR from the last acupuncture treatment to 6-month follow-up, \( P < 0.05 \) (Figure 2).

**Stimulated SFR (SWSFR)**

The Group × Time interaction was not significant between any of the three groups, \( F(7207) = 1.84, P = 0.08 \). This analysis did reveal a significant effect for time for all three groups, \( F(3207) = 11.8, P < 0.001 \). Post hoc comparisons demonstrated significantly higher salivary flow rates in all three groups in stimulated saliva after 12 acupuncture treatments and after 24 acupuncture treatments, compared to baseline, \( P < 0.001 \), and \( P < 0.001 \), respectively. No statistically significant differences could be demonstrated between 3- and 6-month follow-up, compared to the last acupuncture treatment (Figure 2).

**Three-year observation of patients with or without additional acupuncture treatment**

Figures 3 and 4 display the medians and interquartile ranges, with outliers and extremes, of UWSFR and SWSFR for those patients with (additional) or without (no additional) additional acupuncture treatment.

The patient data up to 3 years were reviewed based on patients who continued with additional acupuncture treatment as needed, and those who had no additional acupuncture treatment beyond 6 months. The patients were analyzed descriptively, including 10 time points from baseline up to 3 years follow-up. In UWSFR, both groups at baseline have medians of zero (Figure 3). After the initial acupuncture course and up to 3 years, it was observed that patients who chose additional treatment had consistently higher median SFR than patients who chose not to continue acupuncture treatment. The upper limit of the interquartile range are also higher in the additional group, compared to the no additional group.

In SWSFR, there was a tendency toward an improvement in the additional group. Although the baseline medians may be considered similar, the median SFRs were consistently higher at each time point up to 3 years in the additional group. The upper limits of the interquartile ranges are noticeably greater, compared to the no additional group (Figure 4).

**Subjective changes**

Subjective information on alleviation of symptoms of oral dryness was assessed. After 6 months follow-up, after initial acupuncture treatment, the results show that the subjective improvement was largely paralleled by an objective increase in salivary secretion. Forty-four of the 70 patients reported subjective improvement. In seven of those patients a subjective improvement was reported even though a measurable increase in salivary secretion was not detected. Information is presented in Table 2.

**Side effects**

The side effects of acupuncture observed in this study were hematoma at the acupuncture points and fatigue following the first treatments.

**Discussion**

Earlier studies have shown that acupuncture can improve salivary secretion in xerostomic patients (Blom et al, 1992, 1996). There have been, however, no published studies looking at the long-term effects of acupuncture in xerostomic patients; nor have there been any studies including more than 38 patients. In this retrospective study, our purpose was to investigate the long-term effects of acupuncture in a larger population of xerostomia patients and investigate if any beneficial effects could be achieved by additional acupuncture treatments.

SFR for unstimulated and chewing-stimulated whole saliva was observed in 70 patients with xerostomia. Patient data regarding SFR were analyzed by etiology at 6 months following an initial course of acupuncture treatment. Patient data up to 3 years were then analyzed by whether or not patients received additional acupuncture treatment beyond the initial course.

Analysis of the patient data by etiology at 6 months showed significant increases over time within every etiological group for both unstimulated and stimulated saliva. This is supportive of previous results (Blom et al, 1992, 1996) showing significant improvement in SFR in patients with xerostomia of various etiologies.

In UWSFR (Figure 2), patients in the irradiated and SS groups responded similarly, however, the ‘other’ group showed a much greater response. In SWSFR (Figure 2), patients in all groups responded similarly. This may be explained by functional disturbance vs structural damage of the salivary gland as the underlying cause of the xerostomia. In SS and irradiated patients there is more often, and to a greater degree, structural damage caused by inflammation and radiation. In the unclassified group (‘other’), the underlying cause is probably a functional disturbance, which is more likely to respond with an SFR that approaches normal range.

It was also observed that the significant changes that occurred did so after the first 12 treatments. However, in many patients, a slight decrease in SFR can be seen between the two treatment periods. Based on clinical experience, it is MB’s opinion that the second series of 12 acupuncture treatments is necessary to stabilize the initial improvement and maintain it for 6 months and beyond. This benefit appears to be consistent across etiologies included in the study.

The findings in the patient data up to 3 years suggest that supportive acupuncture treatment, given as needed over a long-term period, helps to maintain the initial increase in SFR as a response to acupuncture treatment in these patients. In some patients, it can also continue to improve SFR. These long-term benefits on salivary secretion are probably related to the cumulative effects over time of the
release of neuropeptides, which affect blood flow and also have anti-inflammatory properties and a trophic influence on the salivary gland tissue (Andersson and Lundeberg, 1995; Dawidson et al, 1997b, 1998a, 1998b).

Clinical studies of acupuncture present inherent problems associated with the design of satisfactory controls such as placebo, conducting double-blind trials, and randomization (Vincent and Richardson, 1986; Haker and Lundeberg, 1990; Thomas and Lundeberg, 1994; cf. Thomas, 1995). Generally speaking, all manual treatment methods (eg, acupuncture, massage) have the same problem with the design of placebo in control groups. The use of superficial/sham acupuncture as control in our previous studies (Blom et al, 1992, 1996) proved to be disadvantageous. Every needle insertion in the skin resulted in some degree of afferent sensory stimulation. In another study (Blom et al, 1993b), we observed that in some patients the superficial needling (used as placebo) resulted in changes in blood flux. This suggests that in some patients even superficial acupuncture is a strong enough stimulus to induce neuropeptide release.
and to cause changes in blood flux. According to several studies, superficial or sham acupuncture should be used as another form of sensory stimulation and not as placebo (Macdonald et al, 1983; Vincent and Richardson, 1986; Haker and Lundeberg, 1990; cf. Thomas, 1995).

Although there was no control group in this study, some light can be shed on the long-term results when looking at the ‘natural course’ of xerostomia in these diseases. Markitziu et al (1992) observed 14 patients after radiation—seven of whom had received doses of >60 Gy for head and neck cancer—and followed them for 5 years. There were no significant differences in mean SFRs over the

Figure 3  Unstimulated salivary flow rates (UWSFR) from baseline to 3 years in patients with and without additional acupuncture treatment. N, number of patients; AP, acupuncture treatment; 1,2 One to 2 weeks’ interval between 1st and 2nd measurement.
course of the study. The yearly mean SFRs for the first 3 years of observation (which corresponds to our 3-year observation) were \(0.028 \pm 0.014\), \(0.025 \pm 0.010\), and \(0.030 \pm 0.025\), respectively. These findings were not significant. Jonsson et al (1993) investigated 37 patients with primary (PSS) \((n = 20)\) and secondary (SSS) \((n = 17)\) Sjögren’s syndrome for 11–112 months (PSS mean months: 28.8 ± 10.9; SSS mean months: 50.41 ± 24.21) measuring SWSFR on two occasions and comparing the two. There were no significant changes in SFR between the two observations. The result of these two studies, when compared to our findings, suggest that acupuncture treatment induced a
greater response in SFR than what may be seen in the ‘natural course’. This is only a suggestion, however, and cannot take the place of a randomized, controlled study.

Another disadvantage of this long-term analysis is the low number of patients, even though the population at 70 was larger than in any other study of this problem, to date. This is an inherent problem in the study of xerostomia, which can include very sick patients. Due to the length of this study, there was a predictable inconsistency of data due to disease progression, psycho-social influences, and death.

When observing the data on an individual basis, one can see that certain patients initially responded well to acupuncture, and that these patients continued to respond over time. At the same time some patients did not respond initially and continued not to respond. Only rarely did patients, who initially responded, obtain significantly decreased SFR, and if so, this could often be explained by concomitant illness. This raises the issue of proper identification through initial screening of patients who may respond to acupuncture. Patients who have salivary gland tissue damaged by inflammation (eg, Sjögren’s syndrome), atrophy of salivary glands, or dysfunctional changes of the vascular, and connective tissues in the glands due to radiation therapy, may respond to acupuncture treatment, depending on how much residual salivary gland tissue and functional capacity is present. The appropriate application of acupuncture in these patients, however, is still in the process of being defined. Since the initiation of this long-term study, Blom et al (1999) have designed and evaluated a prognostic test using pilocarpine to identify just these patients. This test is based on the oral administration of pilocarpine solution, in strictly individualized doses. Before and after its administration SFR for unstimulated and paraffin-chewing stimulated whole saliva is determined. The Pilocarpine Test was considered positive if SFR changed by ≥20% from baseline.

These findings showed that patients with a positive response to a pilocarpine challenge were more likely to respond to acupuncture. A test of this type, if it had been available at the time these patients initiated their care, may have ultimately provided clearer findings in this study.

The next logical step, based on these findings, is to conduct a randomized trial of acupuncture, including two prognostic subgroups, as defined by the Pilocarpine Test, and a control group. In addition, the xerostomic patients could be stratified by etiology, eg, Sjögren’s syndrome, post-radiation therapy, etc. It would also be interesting to investigate if there are any site or stimulation specific effects.

Conclusions

This study shows that 24 acupuncture treatments result in statistically significant improvement in SFR in patients with xerostomia in the long-term up to 6 months. It suggests that additional appropriate acupuncture treatment can maintain this improvement in SFR up to 3 years.

Acknowledgements

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References


