The Effect of Acute Xerostomia on Vocal Function

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Objective: To evaluate whether xerostomia can affect vocal function in an experimental model.

Design: Randomized controlled study.

Setting: Academic center.

Subjects: Twenty healthy young men.

Interventions: Glycopyrrolate was administered to induce acute xerostomia in 10 men, and saline was administered to 10 men who served as controls.

Main Outcome Measures: Whole salivary flow rate and dry mouth scale were time-serially measured, and subjective and objective vocal functions were checked before and after treatment. The salivary and vocal functions were compared between groups.

Results: Significant salivary hypofunction and symptoms developed within 90 minutes after the administration of glycopyrrolate. Vocal effort and phonation threshold pressure significantly increased ($P < .005$) and voice range profiles decreased in the xerostomia group ($P = .003$) but not in the control group. Other voice parameters were comparable between groups ($P > .05$). High correlations were also found between salivary and vocal parameters.

Conclusion: Our findings suggest that vocal function can be affected by xerostomia.


XEROSTOMIA, OR DRY MOUTH, is one of common problems that can adversely affect quality of life. It is caused by damage to the salivary glands or by a reduction in salivary flow rates (SFRs). Salivary gland hypofunction and complaints of xerostomia are common in elderly patients. Several conditions, including adverse drug effects, radiotherapy (RT) to the head and neck, dehydration, diabetes, and diseases involving the salivary glands, such as Sjögren syndrome, can produce xerostomia. Xerostomia is associated with oral discomfort and pain, increased rates of dental caries and oral infections, swallowing problems, and diminished or altered taste, all of which can lead to decreased nutritional intake and weight loss.

Xerostomia has been extensively studied in the fields of head and neck oncology and dental research; however, few studies have reported a correlation between xerostomia and vocal function. We previously conducted a retrospective cohort study in which we found that xerostomia that developed after RT to the head and neck affected vocal function. In the study, patients who received wide-field RT to the primary tumor site and the lymphatic system of the entire head and neck, including the salivary glands, were compared with healthy volunteers and with patients with early glottic cancer who received limited RT to the larynx. The group of patients who received wide-field RT showed high xerostomia-related symptom scores and significantly lower whole SFRs than the other 2 groups ($P < .001$). Subjective vocal dysfunction and stroboscopic abnormalities were also observed in the wide-field RT group. Therefore, xerostomia may affect tissue viscosity of the vocal tract as well as oral mucosa and subsequent vocal function. Since the clinical study was completed, we have tried to further clarify whether xerostomia can affect vocal function in an experimental model.

In the present study, we tested the hypothesis that xerostomia can affect subjective and objective vocal functions. First, an acute xerostomia model was created by the administration of glycopyrrolate, a synthetic cholinergic antagonist that is widely used in clinical practice to prevent parasympathetic stimulation and thereby decrease secretions such as saliva. Salivary and vocal functions before and after treatment were compared between the con-
trol group and the glycopyrrolate-induced xerostomia group. The correlation of salivary and vocal functions was also investigated.

METHODS

SUBJECTS AND STUDY DESIGN

Twenty healthy men between 21 and 24 years of age participated in the study. They were normal, nonprofessional speakers and nonsmokers and reported no history of heart disease, elevated blood pressure, glaucoma, asthma, renal diseases, or neurologic, respiratory, hearing, speech, or voice disorders. None of them showed any evidence of oral, nasal, or laryngeal abnormalities on physical examination. They were asked to avoid drinking caffeinated or alcoholic beverages; consuming high-sodium food, drugs, or dehydrating substances; excessive eating or drinking of water; and strenuous use of their voice.

Participants were randomly assigned to either the control group (n=10) or the xerostomia group (n=10). Baseline data were obtained from all participants before treatment: self-perceived salivary and voice scores (checked by 100-mm visual analog scales), whole SFRs, acoustic and aerodynamic analyses, and laryngeal videostroboscopic recordings. Then, the xerostomia group received an intramuscular injection of 0.3 mg of glycopyrrolate (Mobilul; Myungmoon Pharmaceutical Co, Seoul, South Korea), 1.5 mL of a 0.2-mg/mL solution. The control group received an intramuscular injection of 1.5 mL of normal saline. The salivary function was measured every 30 minutes for a period of 3 hours after treatment. The saliva and vocal functions were compared between the 2 groups before and after treatment.

Blood pressure and arterial pulse rates were also measured and then monitored continuously throughout the test session. Emergency support was immediately available in the highly unlikely event of an adverse reaction to the test medication. Informed consent procedures were approved by the Institutional Review Board for Clinical Research, and consent was obtained from all participants in the study.

MEASUREMENT OF SALIVARY FLOW AND XEROSTOMIA

Unstimulated and stimulated whole saliva samples were collected over a 2-minute period using saliva sampling tubes (Salivette; Sarstedt, Leics, England) according to a previously reported modified swab method. Briefly, each subject was asked to swallow in order to empty his mouth; he then placed the polyester swab in the floor of his mouth and rolled it around the oral cavity for exactly 2 minutes, absorbing saliva from all major and minor salivary glands. Stimulated whole saliva samples were also collected from each subject after 2% citric acid was applied to the dorsal surface of the anterior tongue at 30-second intervals. The saliva volume was estimated by centrifuging the saliva sampling tube at 1000 g for 5 minutes. The SFR was determined by dividing the volume of saliva by the collection time. All subjects refrained from eating, drinking, and smoking for a minimum of 90 minutes before saliva collection and were seen in the morning. No subject had a history of taking medication to reduce salivation.

Self-perceived scores for dry mouth were obtained from the participants. The scores rated symptoms on a 100-mm visual analog scale, with higher scores indicating greater dryness or stickiness. The salivary flow and xerostomia scores were measured in each subject before and every 30 minutes for a period of 3 hours after the administration of saline or glycopyrrolate.

VOCAL FUNCTION

Voice quality was blindly assessed by 2 laryngologists via acoustic and aerodynamic analyses, vocal effort rating, and stroboscopic examination. Each subject’s voice was recorded during phonation of the vowel /a/ at comfortable pitch and intensity levels using a microphone at a constant 10-cm distance from the mouth and evaluated with speech analysis and transcription software (Speech Studio; Laryngograph Ltd, London, England). Acoustic parameters included fundamental frequency, jitter, shimmer, and harmonics-noise ratio. Voice range profiles of pitch and loudness were recorded by asking each participant to produce low and high pitches at different loudness levels. Aerodynamic data were obtained from each subject and analyzed using a handheld transducer module (Aerophone II for Windows; F-J Electronics, Vedbaek, Denmark). Each subject was asked to sustain a phonation for as long as possible. Maximal phonation time and average airflow were measured during sustained a production. Subglottal pressure was measured by repetition of the vowel-consonant-vowel train /api/ at comfortable pitch and intensity levels.

Phonation threshold pressure (PTP), the minimum subglottic pressure required to initiate and sustain vocal fold oscillation, was estimated from oral pressure using a method detailed and validated elsewhere. Three pressure peaks were examined from the midpoint, excluding the first and last peaks. Adjacent pressure peaks were within 1 cm H2O of each other, and the shape of the waveforms was acceptable. The PTP estimates were derived by averaging adjacent pressure peak values to determine the midpoint interpolated between the peaks. This averaging process yielded 10 subglottic pressure values for each assessment. These 10 values were averaged to produce the estimated PTP value. Differences in PTP across trials that were less than or equal to 0.1 cm H2O were considered to be within measurement.

For the phonatory effort rating, participants were asked to read J. K. Rowling’s “Harry Potter” aloud at a comfortable loudness level for 20 minutes. Then, the self-perceived efforts for speaking were measured by 100-mm visual analog scales, with extremes labeled “no effort” and “extreme effort.”

The larynges of all subjects were examined, and images were digitally recorded into a laryngograph precision system (Laryngograph Ltd) using a rigid stroboscope. Two laryngologists blindly evaluated the larynx, including parameters of vibratory closure pattern, supraglottic activity, presence of mucus, color, mucosal wave, amplitude, and symmetry, according to a stroboscopic evaluation form. The 6 parameters were rated on a 100-mm visual analog scale from normal to abnormal. The judges were encouraged to compare the experimental images with other normal laryngeal images that had been seen by 2 other examiners.

All vocal tasks were performed before and after the administration of saline or glycopyrrolate. The task values before and after treatment were compared between groups.

STATISTICAL ANALYSIS

The t test was used to compare continuous variables between groups, and the paired t test was used to compare paired samples before and after treatment, using a commercially available software package (Version 11.0; SPSS Inc, Chicago, Ill). The data of each group were expressed as mean±SEM. Correlation between whole SFRs, dry mouth scores, and variables with statistical significance was analyzed using the Pearson correla-
Whole SFRs significantly decreased after the administration of glycopyrrolate ($P<.001$) (Figure 1). Pretreatment levels of unstimulated and stimulated SFRs were 0.56 mL/min and 1.78 mL/min, respectively; they decreased to half their pretreatment levels within 30 to 60 minutes after injection and reached their lowest levels at 90 to 120 minutes after injection (0.03 mL/min and 0.24 mL/min, respectively). However, the SFRs of the controls did not change after saline injection. The posttreatment values of the SFRs were significantly different between groups ($P<.001$). Dry mouth scores significantly increased from 30 minutes after the administration of glycopyrrolate and reached the highest levels within 2 hours ($P<.001$), while they did not change after saline injection (Figure 2). There was a significant difference in the posttreatment values between the 2 groups ($P<.001$). The average dry mouth score was 84 after glycopyrrolate injection. The body weight and blood pressure readings of all participants did not change during the experiment.

At 3 hours after treatment, the self-perceived scores for vocal effort increased slightly in the control group and significantly in the xerostomia group (Table 1). There was a significant difference in the scores between the 2 groups ($P=.004$). Voice range profiles of pitch and loudness decreased significantly in the xerostomia group ($P=.003$); the changes were more prominent in the highest levels of fundamental frequency and loudness. The maximal phonation time and average airflow did not significantly change after treatment ($P>.05$). Only the PTP increased in both groups, and statistical significance was found only in the xerostomia group. The videostroboscopic changes after treatment were not significant in either group ($P>.05$). Only incomplete closure or posterior gap of the glottis was seen slightly more often in the xerostomia group after treatment, but the difference between the 2 groups was not significant ($P>.05$).

On correlation analysis of SFRs, dry mouth scores, and above-mentioned variables with statistical significance, all variables showed a strong correlation with both unstimulated and stimulated SFRs and dry mouth scores (Table 2). Also, the dry mouth scores showed a high correlation with the whole SFRs.

The administration of glycopyrrolate induced significant xerostomia and reductions in resting and stimulated whole SFRs. In 2 previous studies, the resting SFR that appeared to trigger dryness was less than 0.2 mL/min, or a loss of about 50% of salivary flow, in individuals with normal salivary function; a similar rate was also observed in the present study. The onset of dryness occurred between 30 minutes and 1 hour after the antisialogogue was administered. There was a high correlation in the relationship between dry mouth and reduction of the resting SFR ($r=-0.877$) in our study. Significant salivary hypofunction and xerostomia symptoms were successfully produced within 2 hours after the administration of glycopyrrolate ($P<.001$). Therefore, the vocal functions were checked 3 hours after administration.

The present study revealed that some subjective and objective voice parameters changed significantly with the induction of salivary hypofunction. Among the voice parameters, phonatory effort scores, voice range profiles, and PTPs were significantly affected by xerostomia ($P<.05$). Other acoustic, aerodynamic, and laryngostroboscopic values were slightly lower in the xerostomia group than in the control group after treatment, although none reached statistical significance. The increases in vocal effort and PTPs may have been caused by viscosity change in the vocal tract as well as in oral
The PTP, which is the minimum tracheal pressure required to initiate vocal fold oscillation, is directly proportional to vocal fold tissue viscosity.\(^{15,16}\) The viscosity within the vocal folds is reportedly inversely related to hydration.\(^{16}\) It may be also affected by the use of medications such as cholinergic antagonists, which can cause salivary hypofunction. The PTP increases with the use of anticholinergic medication also seems to contribute to changes in perceived effort in phonation.\(^9\) It has been suggested that osmotic gradients across the mucosa and superficial drying of vocal fold mucosa can cause increases in PTP and vocal effort.\(^9\) Glycopyrrolate reduces salivary flow rate and subsequent mucosal wetness. The drug-induced salivary hypofunction may induce decreases in the mucosal wetness of vocal folds as well as oral mucosa.

The decreases in the extremes of voice range profiles achieved after the glycopyrrolate treatment may result from increased vocal effort and fatigue. Yiu and Chan\(^8\) found that subjects who sang continuously without drinking water and tasking rests showed significant changes in the jitter measure and in the highest pitch that they could produce while singing. In the present study, the significant changes in voice range profiles in the xerostomia group seem to have been affected in part by salivary hypofunction \((P<.05)\). Also, increased emotional and physical fatigue resulting from water restriction and multiple tasking during the experiment may have contributed to vocal fatigue and to the change in the vocal ranges, especially in the subjects in the xerostomia group who had an intense feeling of dry mouth.

In our study, other acoustic, aerodynamic, and strobolaryngoscopic parameters did not significantly change after the induction of xerostomia \((P>0.05)\). The objective perturbation measures seem to be less affected by salivary hypofunction. The findings, except for the stroboscopic ones, were the same as those reported in our earlier study as well as in other previous clinical studies.\(^5,18\) The differences in the stroboscopic findings may be the result of the difference in subjects: the present study included only healthy young men, but the prior study included patients who had received RT to the head and neck. The laryngeal mucosa of patients who have undergone RT usually becomes edematous, swollen, and dry and contains sticky secretions.\(^5\) However, it may be difficult to believe that the drug-induced temporary salivary hypofunction mimicks the apparent

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**Table 1. Differences in Vocal Parameters Between Control and Xerostomia Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n = 10)</th>
<th>Xerostomia Group (n = 10)</th>
<th>P Value†</th>
<th>P Value‡</th>
<th>P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre*</td>
<td>Post*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonatory effort§</td>
<td>4 ± 3</td>
<td>11 ± 3</td>
<td>.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acoustic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F0, Hz</td>
<td>113 ± 5</td>
<td>115 ± 6</td>
<td>.74</td>
<td></td>
<td>.82</td>
</tr>
<tr>
<td>Jitter, %</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.2</td>
<td>.90</td>
<td></td>
<td>.69</td>
</tr>
<tr>
<td>Shimmer, %</td>
<td>2.7 ± 0.9</td>
<td>3.3 ± 1.2</td>
<td>.71</td>
<td></td>
<td>.33</td>
</tr>
<tr>
<td>HNR, dB</td>
<td>24.1 ± 0.9</td>
<td>23.1 ± 0.7</td>
<td>.69</td>
<td></td>
<td>.74</td>
</tr>
<tr>
<td>Voice range</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.23</td>
</tr>
<tr>
<td>F0, Hz</td>
<td>426 ± 18</td>
<td>405 ± 13</td>
<td>.29</td>
<td>448 ± 22</td>
<td>.003</td>
</tr>
<tr>
<td>Loudness, dB</td>
<td>44.4 ± 1.3</td>
<td>42.8 ± 1.1</td>
<td>.16</td>
<td>45.5 ± 1.6</td>
<td>.003</td>
</tr>
<tr>
<td>Aerodynamic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>MPT, s</td>
<td>19.8 ± 1.2</td>
<td>17.0 ± 1.2</td>
<td>.13</td>
<td>19.9 ± 1.5</td>
<td>.26</td>
</tr>
<tr>
<td>Average airflow, mL/s</td>
<td>125 ± 12</td>
<td>118 ± 15</td>
<td>.72</td>
<td>120 ± 14</td>
<td>.79</td>
</tr>
<tr>
<td>PTP, cm H2O</td>
<td>4.8 ± 0.2</td>
<td>5.4 ± 0.2</td>
<td>.12</td>
<td>5.0 ± 0.2</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: F0, fundamental frequency; HNR, harmonics-noise ratio; MPT, maximum phonation time; PTP, phonation threshold pressure.

*Mean ± SEM, obtained before (pre) and at 3 hours after (post) administration of saline (control group) or glycopyrrolate (xerostomia group).

†Analyzed by paired t test.

‡Analyzed by t test. Values were obtained from comparison of the posttreatment values between control and xerostomia groups.

§Rated according to a 100-mm visual analog scale.

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**Table 2. Correlations Among Whole Salivary Flow Rate, Dry Mouth Score, and Significant Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unstimulated</th>
<th>Stimulated</th>
<th>Dry Mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value</td>
<td>r Value*</td>
<td>P Value</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>&lt;.001</td>
<td>-0.88</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Vocal effort</td>
<td>.03</td>
<td>-0.56</td>
<td>.01</td>
</tr>
<tr>
<td>Change of F0 range</td>
<td>.03</td>
<td>-0.58</td>
<td>.004</td>
</tr>
<tr>
<td>Change of loudness range</td>
<td>.05</td>
<td>-0.52</td>
<td>.02</td>
</tr>
<tr>
<td>PTP</td>
<td>.004</td>
<td>-0.69</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviations: F0, fundamental frequency; PTP, phonation threshold pressure.

*Pearson correlation coefficients.
mucosal or secretory changes of the vocal tract observed in the irradiated patients.\textsuperscript{5}

CONCLUSIONS

Our findings suggest that vocal function can be affected by xerostomia. However, voice is multifunctional; therefore, many factors can affect vocal function, and we acknowledge that only 1 causative factor is insufficient to explain voice dysfunction. We are also aware that the changes observed in our study may be different from those that occur after RT to the head and neck, as RT not only decreases salivary flow but also causes structural changes in tissues. However, our data suggest that salivary hypofunction may be closely related to some vocal changes. Although the clinical significance of the changes in vocal effort, PTP, and voice range profiles at the extremes may not be great, a subtle change in vocal function can affect the daily life of normal speakers as well as those who use their voice in a professional capacity. The present study findings confirm those of our previous study regarding the correlation between xerostomia and vocal function.\textsuperscript{5} Therefore, a change in vocal function needs to be considered in patients who undergo RT and who may have many problems related to xerostomia or salivary hypofunction.

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