Efficacy of a traditional Persian medicine preparation for radiation-induced xerostomia: a randomized, open-label, active-controlled trial

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ABSTRACT

BACKGROUND: Xerostomia is one of the most common side effects of radiation therapy among patients with head and neck cancers (HNC). However, conventional medicine lacks an effective treatment for radiation-induced xerostomia.

OBJECTIVE: Synthesizing the traditional use of *Alcea digitata* and *Malva sylvestris* with their known beneficial effects from recent studies, we evaluated the efficacy of the herbs in the quality of life (QOL) of HNC patients with radiation-induced xerostomia.

DESIGN, SETTING, PARTICIPANTS AND INTERVENTIONS: This study is a randomized, double-arm, open-label active-controlled clinical trial. We evaluated the effect of *A. digitata* and *M. sylvestris* on QOL of HNC patients with radiation-induced xerostomia compared with Hypozalix (artificial saliva). Patients were enrolled from the Imam Hossein Hospital’s oncology clinic in Shahid Beheshti University of Medical Sciences, Tehran, Iran.

MAIN OUTCOME MEASURES: Primary outcome measures in this trial were changes in patients’ QOL assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module (EORTC QLQ-H&N 35).

RESULTS: Between-group analysis showed that the intervention group patients obtained significantly lower (better) total EORTC QLQ-H&N 35 scores as compared to the control group at the end of the intervention period ($P = 0.007$). Mean scores of dry mouth of EORTC QLQ-H&N 35 was also significantly lower (better) in the intervention group as compared to the control group ($P = 0.017$).
CONCLUSION: Traditional Persian medicine preparation of hollyhocks and common mallow should be considered as a suitable treatment for xerostomia and improving QOL in HNC patients with radiation-induced xerostomia.

TRIAL REGISTRATION: The trial was registered in ClinicalTrials.gov with Identifier: NCT02854358.

Keywords: xerostomia; medicine, Persian traditional; hollyhocks; common mallow; cancer


1 Introduction

Head and neck cancer (HNC) refers to cancers originating in the oral and nasal cavity, paranasal sinuses, pharynx, larynx and salivary glands. HNC is one of the most common cancers worldwide, of which 600 000 new cases are diagnosed annually, and has a high level of mortality.[12]

Although there is a multidisciplinary approach for management and treatment of HNC, radiation therapy is an important treatment, either as an adjunctive method or as the main therapeutic regimen.[26] Xerostomia is one of the most common side effects of radiation therapy among patients with HNC.[5,6]

Xerostomia or mouth dryness is a condition which may be associated with changes in saliva composition and amount.[7] Patients with xerostomia often suffer from impairment of taste, difficulties in speech and swallowing, and dental deterioration. Mouth dryness significantly impairs and has an inverse association with the patients’ quality of life (QOL).[8–10]

Symptom alleviation and prevention of complications are the main therapeutic goals in management of patients with xerostomia.[11–13] Treatment strategies include supplemental mucosal lubrication for the replacement of salivary secretions; using buffering acids to decrease the demineralization of teeth; and the application of antimicrobial agents for prevention of secondary infections.[14,15] However, most treatments are symptom-directed and are not curative, and there is not an effective, curative, allopathic treatment for radiation-induced xerostomia. Hence, many patients seek out complementary and alternative medicine for this condition.[16–18]

Traditional Persian medicine (TPM) is a field of complementary and alternative medicine commonly practiced among Iranian people.[19–24] There are several herbal remedies for the treatment of dry mouth in TPM. [25] Alcea digitata Alef. (hollyhocks) and Malva sylvestris L. (common mallow) are amongst the mucilaginous plants that have long been used in TPM to treat symptoms like dry mouth. [26] A. digitata and M. sylvestris both belong to the family of Malvaceae. [20,27] These medicinal plants are typically used in TPM for their gastrotonic, anti-tussive, mucolytic and antiseptic properties. Moreover, common mallow and hollyhocks have been used for the treatment of stomatitis, aphthous lesions and mucosal inflammations since ancient times.[27–31] Several studies have shown that gargling of hollyhock extract alleviates oral and pharyngeal irritation.[32] Previous studies on hollyhocks and common mallow have shown that they have anti-inflammatory, antimicrobial and antioxidant properties.[33–35] Taking into account both the traditional use of A. digitata and M. Sylvestris, in addition to their scientifically-demonstrated beneficial effects, we decided to design a randomized, controlled clinical trial to evaluate the efficacy of these herbs in enhancing QOL of HNC patients with radiation-induced xerostomia.

2 Materials and methods

2.1 Trial design

This study is a randomized, double-arm, parallel-group, open-label active-controlled clinical trial, conducted from March 2015 to February 2016. In this trial, the authors evaluated the effect of TPM-based prepared medications containing A. digitata and M. Sylvestris on the QOL of HNC patients with radiation-induced xerostomia compared with Hypozalix (artificial saliva). No changes were made to methods after the commencement of the trial.

2.2 Ethical issues

The trial was registered in ClinicalTrials.gov (Identifier: NCT02854358). The trial was in compliance with the Declaration of Helsinki (1989 revision), and also approved by the relevant local research ethics committees (the Office of Research Affairs, the Deputy of Research and Technology and the Shahid Beheshti University of Medical Sciences: reference number 143). All HNC patients who showed symptoms of xerostomia and met the inclusion criteria participated in the study after signing a consent form.

2.3 Participants

Inclusion criteria: men and women with HNC aged 20 to 70 years, who had grade 1 or 2 xerostomia (based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0), finishing radiotherapy at least two months before the study. According to the CTCAE,
the patients who have grade 1 xerostomia are symptomatic (dry or thick saliva) without significant dietary alteration and patients who have grade 2 xerostomia have significant oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft moist foods). Participants needed to be physically and mentally capable of completing the questionnaire. Xerostomia symptoms should have been present for at least four months, and participants were enrolled from the Imam Hossein Hospital’s oncology clinic in Shahid Beheshti University of Medical Sciences, Tehran, Iran. Additionally, signing the informed consent form was required.

Exclusion criteria: history of connective tissue disorder (e.g., Sjogren) or other medical causes of xerostomia (such as diabetes, bowel and renal diseases), using antidepressant drugs, recurrence of cancer, end-stage cancer, pregnancy, lactation, and history of hypersensitivity or allergy to A. digitata and M. sylvestris. The patients who required support in order to take their medications were also excluded.

2.4 Intervention

Explanations for the purpose of the study, the manner of conducting the study, and possible side effects of drugs were all explained to each patient at the start of the study; written informed consent was also obtained. Then, the study questionnaires were filled out by the enrolled patients to assess their symptoms and QOL. Finally, the patients were randomly assigned to receive either TPM preparation (A. digitata and M. sylvestris) as the intervention group, or Hypozalix spray (artificial saliva) as the control group. All patients were asked to take their medication three times per day (before breakfast, lunch, dinner, or before bedtime) for four weeks. Patients in the intervention group received sachets containing 4 g of mixed powder of A. digitata and M. Sylvestris (in a proportion of 1:1). They were asked to mix the contents of a sachet in a glass of boiled water (250 mL) as one dose. After 10 min, when the herbal infusion somewhat cooled, the patients were to sip the entire prepared amount. In the control group, the patients received Hypozalix spray. They were asked to shake the Hypozalix spray before use, and then spray it on all areas of their mouth, tongue, and gums to coat the mucosal membrane of the mouth.

Consumption of less than 70% of the study drugs during the trial was considered to be non-compliance, and such patients were excluded from trial. Because of the nature of the study, the subjects were not allowed to use other saliva substitutes or saliva stimulants during the study.

2.5 Preparation of drugs

The dry flowers of A. digitata and M. sylvestris were purchased from herbal market in Tehran, Iran, and authenticated by a botanist (Voucher number: PM-508 and PM-509, respectively); they were kept at the Herbarium of the Faculty of Pharmacy, Tehran University of Medicinal Sciences, Tehran, Iran. Both herbs were powdered by a micronized steel mill and passed through an 80 mesh-size sieve. The powders were mixed together in a proportion of 1:1 and filled into sachets, weighing 4 g. Each sachet contained 2 g of each herb.

Hypozalix (artificial saliva, solution, spray bottle, 100 mL; BIOCODEX Pharmaceutical Co. France, distributor in Iran: Behin Paad Pharmaceutical Co.), containing sodium carboxymethyl cellulose, which is prescribed as a routine drug for the treatment of xerostomia in oncology clinics of Iran, was used as the control in this study.

2.6 Analysis of the prepared powder

Since A. digitata and M. sylvestris are rich in mucilage and phenolic compounds, the swelling index and total phenolic content were determined in the prepared mixture. The swelling index of the powder was 13%, determined by the volume in millimeter and taken up by the swelling of 1 g of herbal mixture after addition of water. The total phenolic content of A. digitata and M. sylvestris mixture was 0.198 mg catechin per gram of dry weight (determined by the Folin Ciocalteu method in a colorimetric assay). Moreover, total ash and acid-insoluble ash were measured by ignition method. In this study, the total ash was 16%, acid-insoluble ash was 3%, and microbial contamination was < 101.5 CFU/mL (colony-forming unit per milliliter). Finally, after a quality and quantity control process of microbial control in the control laboratory of the Faculty of Pharmacy, Tehran University of Medicinal Sciences, the powders of both plants were mixed together in a proportion of 1:1 and kept in sachets weighing 4 g.

2.7 Outcome measures

Primary outcome measures in this trial were changes in the patients’ QOL assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module (EORTC QLQ-H&N 35). Our study utilized the Persian version of the EORTC QLQ-H&N 35, which was translated, validated and used by Sahba et al.99 previously. This questionnaire is a site-specific symptom and functional assessment tool, which consists of 24 questions. It is filled out by patients and evaluates the patients’ QOL during the previous week and 4 weeks after the intervention. Six general domains including pain, swallowing, senses of smell and taste, speech, eating, and social contacts before and after the study were assessed. The specific domains covered by the questionnaire are: four items related to mouth opening, dry mouth, sticky saliva and cough. The score of each domain was obtained from the total scores of related questions. All of the scales and single-item measures range from 1 to 5. A high score shows a high level of problems and lower QOL. Any observed adverse event was considered to be a secondary outcome.
2.8 Safety assessment

All of the enrolled patients (in both groups) were inquired about any adverse reactions at the follow-up visit. They were specifically asked about gastrointestinal side effects (such as abdominal pain, diarrhea and/or constipation), aphthous lesions and mucositis.

2.9 Randomization

Sixty eligible patients were randomized in two parallel groups, the intervention group and the control group. A randomized list was generated using Microsoft Excel version 15\textsuperscript{®} with block randomization method (non-stratified, with the same block lengths) as previously described by a statistician.\textsuperscript{37,38} Then, the patients were assigned to two groups by the secretary of the oncology clinic, who used the generated block randomization list sequentially. Only statisticians were blind to the allocation of the patients.

2.10 Follow-up

All patients were followed by a physician on the 10th day after the intervention, by phone, and were visited again at the end of the fourth week after the intervention by the oncologist.

2.11 Statistical methods

By investigation of previous studies, the sample size was calculated by considering two-sided significance level of 0.05 and 0.80 power.\textsuperscript{39,40} Finally, by considering a probable 25% drop-out rate, the sample size was calculated to need a total of 60 patients (30 patients in each group). The collected data were analyzed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) software (Version 15). Statistics are represented by mean ± standard deviation or number (percentage). Chi-square, and paired and independent samples t-test were conducted for data analysis. The significance level of less than 0.05 was set for all cases. Intention-to-treat was applied for data analysis.

3 Results

3.1 Study flow and baseline characteristics of the patients

From March 2015 to February 2016, a total of 98 patients were assessed for eligibility. Of this number, 60 who met the inclusion criteria and were willing to participate were included in the study. Thirty patients were allocated to the intervention group and 30 were allocated to the control group. Only one patient in the control group stopped Hypozalix use due to nausea and four patients in the intervention group stopped TPM preparation use due to nausea, gastric upset and polyuria (Figure 1).

The mean age of the study participants was (50.60 ± 14.53) and (50.26 ± 15.40) years in the intervention group and the control group, respectively. This did not show any significant difference between the groups (\(P = 0.60\)). None of the baseline characteristics of the patients had significant difference between the two groups (Table 1).

In both groups, the most common type of HNC that led to dry mouth was nasopharynx malignancy. There was no significant difference between the study groups in total scores of the EORTC QLQ-H&N 35 at the beginning of
the study \( (P = 0.81) \). Specific cancer-related data of the patients in the study groups are shown in Table 2.

### 3.2 Clinical response

Regarding within-group changes in the mean values of outcome measures (i.e., comparing before and after the intervention mean values in each group), there was significant improvement in the QOL domains of pain, swallowing, speech, and eating in the intervention group (Table 3). The control group also showed significant improvements in these domains except for pain, which did not improve.

Regarding between-group analysis, the patients obtained significantly lower total EORTC QLQ-H&N 35 scores in the intervention group (36.83 ± 6.17) compared to the control group (38.76 ± 6.09) at the end of the intervention \( (P = 0.007) \). Details of the scores in each domain are

### Table 1  Baseline characteristics of the patients and associated factors in the study groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention group ( (n = 30) )</th>
<th>Control group ( (n = 30) )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± standard deviation, years)</td>
<td>50.60 ± 14.53</td>
<td>50.26 ± 15.40</td>
<td>0.60</td>
</tr>
<tr>
<td>Male/female ( (n) )</td>
<td>18/12</td>
<td>23/7</td>
<td>0.16</td>
</tr>
<tr>
<td>Smoker/non-smoker ( (n) )</td>
<td>5/25</td>
<td>6/24</td>
<td>0.73</td>
</tr>
<tr>
<td>Alcohol user/non-user ( (n) )</td>
<td>1/29</td>
<td>0/30</td>
<td>0.31</td>
</tr>
<tr>
<td>Artificial teeth user/non-user ( (n) )</td>
<td>6/24</td>
<td>8/22</td>
<td>0.54</td>
</tr>
</tbody>
</table>

### Table 2  Specific cancer-related data of the patients in the study groups

<table>
<thead>
<tr>
<th>Cancer-related data</th>
<th>Intervention group ( (n = 30) )</th>
<th>Control group ( (n = 30) )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of tumor ( (n) )</td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>14</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mouth cavity</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Parotid</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Concomitant chemotherapy with radiotherapy</td>
<td>25/5</td>
<td>23/7</td>
<td>0.51</td>
</tr>
<tr>
<td>Severity of xerostomia assessed by VAS ( (mean ± standard deviation) )</td>
<td>5.50 ± 1.50</td>
<td>5.43 ± 1.40</td>
<td>0.85</td>
</tr>
<tr>
<td>Total score of EORTC QLQ-H&amp;N 35 ( (mean ± standard deviation) )</td>
<td>36.83 ± 6.17</td>
<td>38.76 ± 6.09</td>
<td>0.81</td>
</tr>
</tbody>
</table>

VAS: visual analogue scale; EORTC QLQ-H&N 35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module.

### Table 3  Changes in scores of general domains of EORTC QLQ-H&N 35 before and after the intervention

<table>
<thead>
<tr>
<th>Group</th>
<th>( n )</th>
<th>EORTC QLQ-H&amp;N 35 scores (mean ± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td>Interv</td>
<td>30</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( P ) value</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( P ) value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( P ) value (inter groups after treatment)</td>
</tr>
</tbody>
</table>

EORTC QLQ-H&N 35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module.
presented in Table 3.

Regarding mean scores of dry mouth of EORTC QLQ-H&N 35 after the intervention, there was a significantly lower score in the intervention group than the control group ($P = 0.017$). No significant differences were observed between the two groups when it came to the mean scores of sticky saliva, difficulty in mouth opening, and cough after the study ($P = 0.215, 0.215, \text{and} \ 0.542$, respectively) (Table 4).

4 Discussion

In the present trial, we evaluated the effectiveness of a TPM preparation containing $A. \ digitata$ and $M. \ sylvestris$ on QOL of HNC patients with radiation-induced xerostomia via an open-label randomized active-controlled clinical trial. Study participants were HNC patients suffering from radiation-induced xerostomia. The study group taking TPM preparations experienced improvement in more areas of their xerostomia-associated symptoms as well as QOL, as compared to the group using Hypozalix spray.

Several studies have been done on the effectiveness of herbal medicines on dry mouth. Murakami et al. showed effects of some Chinese herbs on salivary fluid secretion in an animal study. Jiang et al. evaluated the efficacy of Chinese herbs on the salivary glands of patients with HNC during radiotherapy. Our previous report, also, showed the effect of Persian herbs on dry mouth. Although the mechanism of action of these herbs is not clear, they may reduce xerostomia via increased salivary secretion or the maintenance of mucosal water content in the oral cavity. However, some studies have shown that improvement in xerostomia is not necessarily due to increasing salivary flow rate and may be attributable to other factors, such as improvements in psychological status or hormonal changes. According to the TPM references, increasing moisture content (based on humoral theory) in the body is the key point for the treatment of dry mouth; consequently, mucilaginous herbs could be effective for this purpose. Mucilaginous herbs that generally have a high content of wetness based on TPM view increase the flexibility of tissues in the body. When flexibility increases, the movement of muscles becomes easier and glands have better function. Along this line of thinking, the mouth and tongue will be able to move more easily and salivary glands will have better function. Hollyhocks and common mallow act as mucilaginous herbs in our study. This is similar to increasing salivary mucin, and as such, they have moisturizing, lubricating, and antimicrobial effects. Therefore, these herbs could be potentially suitable for alleviation of dry mouth symptoms in patients with xerostomia. Hollyhocks is used in conjunction with common mallow by TPM practitioners because they believe that these herbs have a synergistic effect and more effectively increases moisture in the body. Another consequence of using hollyhocks and common mallow simultaneously is that the necessary dosage for each herb decreases and, consequently, there is decreased probability of side effects. Some patients reported adverse events such as gastric upset and nausea while using the TPM preparation in this trial, but these effects can be explained according to TPM references. TPM deems the herbal preparation that was used in this study to have a cold nature, which could cause gastric upset especially in patients who also have a cold temperament.

There are some limitations of this study that should be taken into account. The main one is the small sample size. Although functional status of the patients was assessed by EORTC QLQ-H&N 35, as a reliable and valid tool, another limitation was the lack of objective outcome measures for assessment of the patients’ salivary secretion. In addition, because this was an open-label study, both study participants and administrators may have been biased in their evaluations. Another methodological problem was that this study

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>EORTC QLQ-H&amp;N 35 scores (mean ± standard deviation)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Difficulty in mouth opening</td>
</tr>
<tr>
<td>Intervention</td>
<td>30</td>
<td>Before</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
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<tr>
<td></td>
<td></td>
<td>$P$ value</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>Before</td>
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<tr>
<td></td>
<td></td>
<td>After</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P$ value</td>
</tr>
</tbody>
</table>

EORTC QLQ-H&N 35: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Head and Neck Module.
lacked a placebo group, which may help to clarify the effectiveness of the TPM preparation for xerostomia. Moreover, considering the chronic nature of radiation-induced xerostomia and patients’ long-term need for medication, long term investigations are needed; this means longer duration of follow-up might result in different findings on the efficacy and safety of TPM preparation in patients with radiation-induced xerostomia. Finally, the lack of dose adjustment or multiple dose evaluation of the TPM preparation in this present study was yet another limitation, and these parameters should be evaluated in future studies.

5 Conclusion

TPM preparation (hollyhocks and common mallow) should be considered a suitable treatment for xerostomia and improving QOL in HNC patients with radiation-induced xerostomia.

6 Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

21 Zohalinezhad ME, Imanieh MH, Samani SM, Mohagheghzadeh


