Efficacy of BioXtra Spray and Mouthwash in Patients with Radiation-induced Xerostomia: A Randomized Clinical Trial

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ABSTRACT

Aim: Xerostomia is an important complication following radiotherapy for head and neck regions producing serious discomfort for patients. Symptomatic treatments for the disease include strict oral hygiene and use of artificial saliva substitutes. The present study compared the efficacy of BioXtra spray and mouthwash in the relief of radiotherapy-induced xerostomia in patients referred to Imam Khomeini Hospital, Tehran University of Medical Sciences.

Materials and methods: In a cross-over randomized clinical trial, BioXtra spray and mouthwash were used by 20 patients for 2 weeks with a 1 week wash-out period. The ease of application and the patients' acceptance of the products were obtained using 100 mm visual analog scale (VAS) and dichotomous scales. We used SPSS version. 18.0 to analyze our data considering level of significance less than 0.05.

Results: Both forms of BioXtra showed similar effect in reducing oral dryness and its complications. The mean VAS was 33.2 for spray and 34.5 for mouthwash. Majority of our patients reported improvements in xerostomia after using spray (85%) and mouthwash (70%), respectively. The patients' acceptance of both modalities was similar and they showed equal tendency to continue the treatments. No significant differences in symptoms relief as well as judgment of the regimens were found between groups.

Conclusion: BioXtra spray and mouthwash are similarly effective in reducing the symptoms of postradiotherapy xerostomia.

Keywords: Xerostomia, Radiation therapy, BioXtra.


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INTRODUCTION

Radiotherapy (RT) is a treatment modality which is regularly used in the treatment of the head and neck cancers (HNC). This method destroys tumor cells and also we can expect undesirable effects on normal tissues.1 Salivary glands are often involved in the head and neck cancer radiotherapy field because of their position. Radiotherapy destroys salivary gland parenchyma and as a result we can expect varying degrees of xerostomia. This phenomenon is usually permanent. Irreversible effects happen at total dosage of greater than 5000 cGy.2

Saliva has an important protective role against oral disease. It is necessary for lubrication, regulation of the oral cavity flora, teeth demineralization and maintaining soft and hard tissue integrity.3,4

Xerostomia, or dryness of the mouth, can cause oral discomfort and pain, difficulty in mastication and swallowing, speech problems, and impairment of taste and smell. It may also lead to an increased risk of dental caries or oral infections. As a result, nutrition intake can be affected with subsequent weight loss. So xerostomia is a major health issue in these patients.5

Xerostomia can be managed symptomatically. Dental caries and oral infections can be prevented appropriately by strict oral hygiene, fluoride agents and antimicrobials. Systemic sialogogues such as pilocarpine, cimevline, anethole trithione and bethanechol could stimulate salivary secretion from remaining functional salivary acini. These agents have side effects on patients with systemic disease.6 However, in the absence of functioning tissue, wetting agents or saliva substitutes can be used. These products are mainly based on carboxymethylcellulose (CMC) so these commercials...
are more viscous than saliva and do not stimulate visco-
elastic property of saliva. They also lack the immunological
protection of the saliva which is mainly due to lysozyme,
lactoferrin, lactoperoxidase, and immunoglobulins of the
natural saliva.7

BioXtra is a new generation of products to relief Xero-
stomia which includes hydroxyl-ethyl cellulose, xylitol,
glucose oxidase, lactoperoxidase, polyglyceryl methacrylate,
lactoferrin, lysozyme, monofluorophosphate, and other
component of natural saliva. It is introduced in several forms
such as spray, mouth wash, gel, toothpaste.8,9

Because of lacking study to compare the efficacy of two
forms of BioXtra (spray and mouthwash) on radiotherapy-
induced Xerostomia, we tried to achieve this goal.

MATERIALS AND METHODS

Our study was a randomized double blind clinical trial (ap-
proved by Ethics Committee of the Research Division of
Qazvin University of Medical sciences) and registered on
clinical trial. gov: Identifier number: NCT01195233) 20
patients (10 male, 10 female) who were previously subjected
to radiotherapy for head and neck cancer at Cancer Institute,
Imam Khomeini Hospital, were asked to participate in this
study. Coordinator explained the process to each patients
and informed consent were signed by them. All the patients
agreed to participate. This project was granted approval by
Ethics Committee.

Patients with subjective complaint of dry mouth since
radiotherapy (≥50Gy) for HNC encompassing bilateral
major salivary glands, atleast 6 months earlier were eligible
to participate. The age of our patients were 18 years or older.
They take nutritious orally (i.e. not parenterally or through
PEG tube). Patients with a history of cancer recurrence,
end stage malignancies, systemic disease that causes
xerostomia such as diabetes mellitus, sjogren syndrome
were excluded. Patients, who were taking any medications
with anticholinergic side effects such as antidepressants or
diuretics, were also excluded.

Using random allocation software, all eligible patients
allocated in two groups:

The first group was given BioXtra spray for 2 weeks fol-
lowed by 1 week wash-out period then, they used BioXtra
mouthwash for the next 2 weeks. The order of the interven-
tions was changed for the second group (the first 2 weeks,
BioXtra mouthwash and after the washout, BioXtra spray
was applied).

During the study, application of other products for the
treatment of xerostomia such as saliva substitutes or stimu-
lants was not allowed; although, patients could take sips of
water frequently. However, they were permitted to use other
mouth care systems such as antifungal treatment or topical
analgesic agents.

The clinician who visited the patients during the study
was different from the one who gave the intervention to the
patients. Data collectors and the one who analyzed the data
know the groups only as A or B and they did not know the
order of drug usage.

Involved patients were asked to fill out two forms of
questionnaire at first visit or day 0. They were also asked to
complete two other forms at the second visit (day 14) and
the third visit (day 35). Questionnaires which were used was
similar to shadad et al8 designed in two forms including VAS
and dichotomous scale (yes or no) as below:

**Questionnaire for the first day of treatment**

Variables recorded based on 100 mm VAS

| 1. To what extent your mouth is dry? (Extremes: 0 ‘not dry at all’, 100 = ‘worst imaginable dryness’). |
| 2. Do you have difficulty in swallowing because of your dry mouth? (Extremes: 0 = ‘no difficulties at all’, 100 = ‘very severe difficulties swallowing’). |
| 3. Do you have speech difficulty because of your dry mouth? (Extremes: 0 = ‘no difficulties at all’, 100 = ‘very severe difficulties with speech’). |
| 4. Do you have difficulty in chewing as a result of your dry mouth? (Extremes: 0 = ‘no difficulties at all’, 100 = ‘very severe difficulties in chewing’). |
| 5. Do you have a burning sensation in your mouth? (Extremes: 0 = ‘no burning at all’, 100 = ‘very severe burning mouth’). |
| 6. Is taste affected by your dry mouth? (Extremes: 0 = ‘not affected at all’, 100 = ‘very severe alteration of taste’). |

**Questionnaire for the second and the third visits (day 14 and 35) of treatment**

Variables recorded based on 100 mm VAS

| 1. How effective was the product system at relieving your dry mouth? (Extremes: 0 = ‘not effective at all’, 100 = extremely effective’). |
| 2. How pleasant was the taste of the product? (Extremes: 0 = ‘not pleasant at all’, 100 = ‘extremely pleasant’). |
| 3. How pleasant did your mouth feel after using the product system? (Extremes: 0 = ‘not pleasant at all’, 100 = ‘extremely pleasant’). |
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Questionnaire for the second and the third visits (Day 14 and 35) of treatment period variables recorded based on Dichotomous scales (Yes or No)

1. Did the product make your dry mouth better? Yes No
2. Did the product make you chew easier? Yes No
3. Did the product make you swallow easier? Yes No
4. Did the product make you talk easier? Yes No
5. Did the product improve your sensation of taste? Yes No
6. Did the product improve the burning sensation? Yes No
7. Would you like to continue using this product? Yes No
8. Did you feel better after using this product? Yes No
9. Was the product easy to use? Yes No

We used SPSS vs 18.0 to analyze our data considering level of significance less than 0.05. Statistical analysis between two forms (spray and mouthwash) was done using Student t-test (for VAS scale) and exact fisher test (for dichotomous scale).

RESULTS

Our study was performed on 20 patients (10 males and 10 females). Table 1 shows VAS scores recorded for the first question. Mean VAS for each question at first day is reported.

<table>
<thead>
<tr>
<th>Question</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71.2</td>
<td>23.9</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>56.7</td>
<td>35.9</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>62.0</td>
<td>25.2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>64.5</td>
<td>31.5</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>41.2</td>
<td>34.2</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>61.0</td>
<td>36.1</td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Improvement in xerostomia regarding application of BioXtra spray and mouthwash after 14 days (VAS scales)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Spray Mean</th>
<th>SD</th>
<th>Mouthwash Mean</th>
<th>SD</th>
<th>Mean difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in oral dryness</td>
<td>33.1</td>
<td>21.3</td>
<td>35.7</td>
<td>29.4</td>
<td>2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Pleasant taste of product</td>
<td>41.5</td>
<td>30.5</td>
<td>43.0</td>
<td>30.8</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Pleasant feel after usage of product</td>
<td>39.4</td>
<td>28.9</td>
<td>39.2</td>
<td>31.7</td>
<td>0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Independent t-test, NS: No significant

Table 3: Improvement in xerostomia regarding application of BioXtra spray and mouthwash after 14 days (dichotomous scales)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Spray Yes</th>
<th>No</th>
<th>Mouthwash Yes</th>
<th>No</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in oral dryness</td>
<td>18</td>
<td>2</td>
<td>14</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement in chewing</td>
<td>13</td>
<td>7</td>
<td>12</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement in swallowing</td>
<td>14</td>
<td>6</td>
<td>12</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement in speech</td>
<td>17</td>
<td>3</td>
<td>15</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement in taste</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Improvement in burning sensation</td>
<td>14</td>
<td>6</td>
<td>12</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Tendency toward continuing treatment</td>
<td>17</td>
<td>3</td>
<td>17</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Feel better after usage</td>
<td>19</td>
<td>1</td>
<td>15</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Ease of application</td>
<td>19</td>
<td>1</td>
<td>17</td>
<td>3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Fisher exact test, NS: No significant

At the beginning of the study, all the patients (100%) were suffering from xerostomia. A total of 19 patients had dryness at night. Getting bad taste in mouth, effect of denture, avoiding speaking was observed in 16 (80%), 4 (20%) and 18 (90%) of the patients, respectively. Five patients (25%) used saliva substitute among them 4 patients (80%) found it useful.

By using both forms of BioXtra (spray and mouthwash), we observed improvement in xerostomia and its complications. Results of application of two systems after 14 days listed in Tables 2 and 3.

DISCUSSION

We showed that BioXtra products (spray and mouthwash), have significant effects on xerostomia related complications along with better acceptance among patients. Both products have the same effects on alleviating xerostomia complications. Their acceptance among patients is similar. These products have the most effect on improvement of oral dryness and speech with least on patients taste.

Xerostomia is considered as a major side-effect following radiotherapy in the field of head and neck. It can adversely affect patient’s quality of life. Oral functions such as ability to swallow, speaking can be violated. Susceptibility to dental caries and oral infections is common among these patients. As a result of impaired lubrication, low tolerance for dental prostheses can be observed. These symptoms can change food choices with subsequent malnutrition.

To reduce the severity of oral complications due to xerostomia, aggressive oral care before radiotherapy is recommended. Evaluation of oral health status by a dental team...
before starting radiotherapy is vital part. Special attention must be given to mucosal lesions, dental caries, periodontal problem and improper dentures.\(^1\)

Current management of xerostomia largely relies on the symptomatic treatment. Pharmacologic management include the use of fluoride agents for optimal oral hygiene, antimicrobials to prevent oral infection, saliva substitutes to overcome dryness, and dialogagic agents to stimulate the remaining salivary gland tissues for saliva production.\(^12,13\)

Saliva substitutes containing hydroxyethyl, hydroxypropyl, or CMC may be helpful by temporarily wetting the oral mucosa to overcome complications of xerostomia.\(^14\)

Jellema et al a study regarding use of a xanthan gum-based saliva substitutes, showed similar improvement with this salivary substitute and placebo (of similar composition, without xanthan gum). They concluded that this agent was no longer of benefit rather than other saliva substitutes.\(^15\)

BioXtra is a new generation of products to relief xerostomia which includes hydroxyl-ethyl cellulose, xylitol, glucose oxidase, lactoperoxidase, polyglyceryl methacrylate, lactoferrin, lysozyme, monofluorophosphate, and other component of natural saliva.\(^9\)

Shahdad et al\(^8\) in a double-blind, cross-over study compared the usefulness of the BioXtra system and bio-thene oral balance system for radiation induced xerostomia in twenty patients. The results showed that BioXtra system is significantly effective in reducing symptoms associated with radiotherapy induced xerostomia. Improvement of the symptoms such as oral dryness, problem in chewing, difficulty in speaking, and swallowing along with changes in taste are significant. Their results showed that the acceptance of the taste of BioXtra products (Tooth paste, mouthwash and gel) were better among patients.\(^8\)

Dixir et al\(^9\) in their study evaluated the effect of BioXtra system on 34 patients with radiotherapy induced xerostomia. At the beginning of their study, 19 patients suffer from severe xerostomia which was fallen to nine patients after treatment. Their results showed significant improvement with xerostomia related complications. Although, it was observed to have fewer effects on alleviating oral pain but its effect was significant. The mean VAS score was 59.8 at the beginning of treatment course which reduced to 36.4 at day 28 which was statistically significant (p < 0.001).\(^9\)

Gookizadeh et al\(^16\) in their study tried to design a clinical research on BioXtra efficacy for treating xerostomia in 58 patients with head and neck cancer (except salivary gland cancers). In comparison with results before treatment with BioXtra, xerostomia during the day and night and speech impairment was significantly lower after treatment, but xerostomia while eating and drinking water during a meal indicated no significant difference, because in this situation, we need more saliva flow, and BioXtra cannot improve xerostomia with different scores.\(^16\) Our results are in concordance with previous studies.

Studies on BioXtra system among patients with other cause of xerostomia and also evaluating the effect of BioXtra on bacterial colonization are recommended.

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REFERENCES

