Efficacy of Pilocarpine and Bromhexine in Improving Radiotherapy-induced Xerostomia

Farid Abbasi1 • Sareh Farhadi2* • Mostafa Esmaili3

1Associate Professor, Department of Oral Medicine, Faculty of Dentistry, Shahed University, Tehran, Iran
2Assistant Professor, Department of Oral and Maxillofacial Pathology, Faculty of Dentistry, Shahed University, Tehran, Iran
3Assistant Professor, Department of Oral Medicine, Faculty of Dentistry, Shahed University, Tehran, Iran
*Corresponding Author; E-mail: dr.sfarhadi@gmail.com

Received: 17 January 2012; Accepted: 6 March 2013

This article is available from: http://dentistry.tbzmed.ac.ir/joddd

© 2013 The Authors; Tabriz University of Medical Sciences
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background and aims. Xerostomia is one of the most common complications of head and neck radiotherapy. The aim of this study was to evaluate and compare the efficacy of pilocarpine and bromhexine in improving radiotherapy-induced xerostomia and its associated symptoms.

Materials and methods. In this single-blind, randomized crossover study, pilocarpine and bromhexine tablets were used by twenty-five patients suffered from xerostomia, with a medical history of head and neck radiotherapy. At step A, the patients were treated with pilocarpine for 2 weeks. In addition, they were asked to take bromhexine for 2 weeks with a one-week washout period. At step B, the inverse process was conducted (first bromhexine, then pilocarpine). Whole resting saliva was collected from patients before and after receiving each medication by precise measurements. Then, efficacy of the two drugs in the treatment of xerostomia and its related oral complications was evaluated using questionnaires by Dichotomous format. The results were statistically analyzed using t-student and Fisher’s exact and chi-squared tests. Statistical significance was set at P<0.05.

Results. The difference between saliva secretion rates before and after medications was not significant for bromhexine users at two steps of the study (P=0.35); however, it was significant for pilocarpine users (P=0.0001). Users of both drugs showed significant differences in improvement of xerostomia, chewing, swallowing, tasting and mouth burning.

Conclusion. Pilocarpine is probably more effective in improving xerostomia and its associated problems compared with bromhexine, although the use of the latter was also shown to ease some of the consequences of radiotherapy in the head and neck region.

Key words: Bromhexine, pilocarpine, radiotherapy, xerostomia.
Introduction

The importance of saliva in protecting the oral cavity becomes more apparent when malfunction of salivary glands results in xerostomia. The problems experienced by patients may include a persistent dry or burning sensation, eating difficulties, diminution in taste acuity, discomfort during speaking, mucosal infections, denture intolerance and bacterial sialadenitis. These symptoms reflect not only the mechanical function (moisture, irrigation and lubrication) of saliva, but also its buffering properties.

Nowadays, consumption of antidepressant drugs, radiotherapy of the head and neck region and some systemic diseases, such as diabetes mellitus, are some of the conditions that induce xerostomia. Radiotherapy is used for suppression of malignant cells but injury to normal cells can be inevitable. Most of the patients with a history of head and neck radiotherapy complain of some degrees of xerostomia due to presence of salivary glands in the radiation field. Hence, destruction of gnathic bone and oral mucosa might be notable. A reduction in salivary flow rate and decrease of its pH is paralleled with a change in saliva competence and shifting of oral microflora to cariogenic bacterial spices. Therefore, discomfort in chewing, swallowing, speech, sleep and also progressing of periodontal diseases and dental caries probably occur in the presence of xerostomia.

Studies have led to four therapeutic suggestions for xerostomia: preventive and symptomatic treatments, local and systemic stimulation. In relation to systemic medications, bromhexine is recognized as a diluting agent of mucous secretions in respiratory tract and pilocarpine is a parasympathomimetic medication acting as salivary and lacrimal secretion stimulator. Many studies have verified that pilocarpine can provide clinically significant symptomatic relief to patients suffering from radiotherapy-induced xerostomia and also in cases of Sjögren syndrome, but there are few studies about efficacy of bromhexine in these cases. Furthermore, we could not find any reports making comparisons between efficacy of pilocarpine and bromhexine in these conditions.

Therefore, this study was designed to evaluate and compare the efficacy of pilocarpine and bromhexine in improving radiotherapy-induced xerostomia and its associated symptoms.

Materials and Methods

This single-blind, randomized crossover study evaluated twenty-five patients of Imam Reza Hospital of Kermanshah, Iran, who suffered from xerostomia and their medical history showed head and neck radiotherapy, corresponding to similar studies in this manner. All the patients were over 18 years of age and had been treated with more than 4500cGy of radiation dose in 6.5 weeks more than 6 months previously. Patients with recurrent cancer, diabetes mellitus, asthma, consumption of antidepressant drugs and sensitivity to pilocarpine and bromhexine were excluded from the study. After taking an informed consent, the study was planned in 2 steps of A and B in order to reduce experimental errors. At step A, the patients were advised to use 5-mg pilocarpine tablets (Mahya Daroo Co.) 4 times daily for 2 weeks. After 2 weeks, the patients were asked to stop taking the drug for one week in order to obliterate the pharmacologic effects of the drug (wash-out period). Then, they were asked to take 8-mg bromhexine tablets (Mucolin tablets, Tolidaroo Co.) 4 times daily for 2 weeks. The inverse process was conducted at step B (first bromhexine, then pilocarpine). The patients’ whole resting saliva was collected and measured precisely before and after every course of medication by two experts: one oral medicine specialist and one student of dentistry who was trained in this procedure. The resting saliva secretion was measured using spitting methods and levels of lower than 0.01 mL reflected dysfunction of salivary glands. The patients were not informed about the prescribed drugs as dictated by the single-blind research design.

Then, the patients answered the self-administered questionnaire, during the first visit (zero day) and fourteen days after taking the medication; this was repeated for another drug in the same manner. The questionnaire was designed by a specialist of oral medicine in relation to dichotomous scale, including 15 questions about xerostomia and its oral complications such as swallowing, speech, tasting problems and burning sensation.

Improvement of xerostomia and other oral complications was statistically analyzed by chi-squared and Fisher’s exact tests. Increase in saliva secretion, before and after medication, was analyzed by Student’s t-test. Statistical significance was defined at P<0.05.

Results

Tables 1 and 2 show the rate of saliva secretion at step A (first pilocarpine, then bromhexine) and B (first bromhexine, then pilocarpine), respectively, in four separate evaluations: before and after first
and bromhexine, have been used for some years and fortis, salivary stimulating drugs, such as pilocarpine xerostomia. In order to relieve these oral discom-

creases in saliva secretion after bromhexine adminis-
tration was limited in cases with complete sup-
pression of salivary gland function. On the other
hand, there are few scientific reports on bromhexine
increases saliva secretion, the practitioners have pre-
ferred to advise it rather than artificial saliva in these
situations; however, indication of pilocarpine pre-
scription was limited in cases with complete sup-
pression of salivary gland function. On the other
hand, there are few scientific reports on bromhexine

The present single-blind study generally showed
the superiority of Pilocarpine to Bromhexine in im-
proving radiotherapy-induced xerostomia but further
investigations are necessary to compare the long-
term efficacy of these two drugs. In addition, appli-
cation of quality of life questionnaire in 100-scale
ivaluation and before and after second evaluation.
Comparisons between the rate of secretion showed
no significant differences in bromhexine users
(P=0.35) but there were significant differences in
pilocarpine users (P=0.0001).

Furthermore, 28% and 100% of bromhexine and
pilocarpine users showed improvement of
xerostomia after fourteen days, respectively. Statis-
tical analysis showed significant differences in im-
provement of xerostomia for users of both medica-
tions (P=0.0001).

All the (100%) pilocarpine users and 14.3% of
bromhexine users demonstrated improvement of
chewing difficulties; similarly, 87.5% of pilocarpine
users and 25% of bromhexine users showed im-
provements in swallowing problems; 100% of pilo-
carpine users and 14.3% of bromhexine users, re-
ported relief of speech problems and 90.9% of pilo-
carpine users and 20.8% bromhexine users showed
improvements in tasting difficulties. Finally, 100%
of pilocarpine users and 66.7% of bromhexine users
demonstrated improvements in burning sensation.
All the differences mentioned were statistically sig-
nificant with P-values of 0.0001, 0.04, 0.005, 0.0001
and 0.004 for improvement in chewing, swallowing,
speech, tasting problems and burning sensation,
respectively.

Discussion

Radiotherapy of head and neck may result in a de-
crease in salivary pH and its rate of secretion. There-
fore, any discomfort of chewing, swallowing, speech and sleep may occur in the presence of
xerostomia. In order to relieve these oral discom-
forts, salivary stimulating drugs, such as pilocarpine and bromhexine, have been used for some years and

Discussion

Radiotherapy of head and neck may result in a de-
crease in salivary pH and its rate of secretion. There-
fore, any discomfort of chewing, swallowing, speech and sleep may occur in the presence of
xerostomia. In order to relieve these oral discom-
forts, salivary stimulating drugs, such as pilocarpine and bromhexine, have been used for some years and

their efficacy has been verified in some experimental
studies. In the present study, improvement of xerostomia was shown using both medications. Chitapanarux et al17 and Ram et al,20 in line with this study, reported that pilocarpine has obvious palliative effects on xerostomia and sleep of patients. Previous studies21-23 have shown that pilocarpine has a great ability to prevent radiotherapy-induced xerostomia. Haddad et al24 showed the preventive effect of both drugs and Wu et al25 reported that pilocarpine can improve xerostomia induced by Sjögren syndrome. Although, some researchers have reported that pilocarpine in-
increases saliva secretion,26,27 Warde et al, contrary to the results of the present study, reported no signifi-
cant differences in recovery from xerostomia and quality of life between pilocarpine and placebo users.28 It seems that use of VAS scale in their study and different frequencies of drug administration can explain this lack of difference.

Notable effects of pilocarpine have been confirmed
in improving radiotherapy-induced xerostomia,10-12,24
Sjögren syndrome29 and immune dysfunction condi-
tions.30 Given the efficacy of this medication in in-
creasing saliva secretion, the practitioners have pre-
ferred to advise it rather than artificial saliva in these
situations; however, indication of pilocarpine pre-
scription was limited in cases with complete sup-
pression of salivary gland function. On the other
hand, there are few scientific reports on bromhexine
with definite results. However, Avisar et al32 and Frost-larsen et al33 showed improvement of
xerostomia with administration of bromhexine in
cases of Sjögren syndrome.

The present study showed significant differences
in all the signs and symptoms of radiotherapy-
induced xerostomia using both medications, though
pilocarpine showed a more effective role compared
with bromhexine. Previous studies34-36 have shown
significant increases in saliva secretion following
pilocarpine administration. Frost-larsen et al13 in
line with the present study, reported significant in-
creases in saliva secretion after bromhexine admini-
stration but Misawa et al37 could not find any signifi-
cant differences. Different etiologies of xerostomia
in these studies can probably explain the situation.

Table 1. Mean and SD of saliva secretion at step A
(first pilocarpine, then bromhexine) before and after
first and second evaluations

<table>
<thead>
<tr>
<th>Time of evaluation</th>
<th>Rate of secretion (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before first evaluation</td>
<td>0.08±0.02</td>
</tr>
<tr>
<td>After first evaluation</td>
<td>0.69±0.27</td>
</tr>
<tr>
<td>Before second evaluation</td>
<td>0.08±0.02</td>
</tr>
<tr>
<td>After second evaluation</td>
<td>0.11±0.06</td>
</tr>
</tbody>
</table>

Table 2. Mean and SD of saliva secretion at step B
(first bromhexine, then pilocarpine) before and after
first and second evaluations

<table>
<thead>
<tr>
<th>Time of evaluation</th>
<th>Rate of secretion (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before first evaluation</td>
<td>0.08±0.02</td>
</tr>
<tr>
<td>After first evaluation</td>
<td>0.09±0.01</td>
</tr>
<tr>
<td>Before second evaluation</td>
<td>0.08±0.02</td>
</tr>
<tr>
<td>After second evaluation</td>
<td>0.61±0.23</td>
</tr>
</tbody>
</table>
VAS might be a more precise evaluation of the situation.

**Conclusion**

Pilocarpine is probably more effective in improving xerostomia and its associated problems compared with bromhexine, although the use of the latter was also shown to remove some consequences of radiotherapy in the head and neck region.

**References**