

Clinical evaluation of BIOXTRA in relieving signs and symptoms of dry mouth after head and neck radiotherapy of cancer patients at Seyed-al-Shohada Hospital, Isfahan, Iran

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Abstract

Background: Radiotherapy of head and neck cancers causes acute and chronic xerostomia and acute mucositis. Xerostomia increases risk of radiation caries and affects on oral comfort, fit of prostheses, speech, swallowing, and the growth of caries-producing organisms. Salivary flow rate can be measured by asking patients some questions. There are different types of commercial synthetic saliva such as BIOXTRA, but until now, no one can effectively relieve xerostomia. We tried to design a clinical research on BIOXTRA efficacy for treating xerostomia.

Materials and Methods: In this research, 58 patients with head and neck cancer (except salivary gland cancers) treated in Seyed-al-Shohada Hospital. The patients received at least 40-50 GY; and after 2 months of compilation treatment, they were evaluated by asking about having xerostomia. Before and after treatment with the BIOXTRA, the PH of the oral cavity, *candida albicans*, and lactobacillus counts measured and documented in laboratory. We used BIOXTRA for 2 weeks, 3 times daily, and then re-evaluated patients with some questions.

Results: The counts of *candida albicans* and lactobacilli statistically significant decreased.

Conclusion: Xerostomia for most patients improved clinically during the day and night while PH of the oral cavity increased.

Key Words: BIOXTRA, radiotherapy, xerostomia

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Received: 20.12.2011, Accepted: 16.05.2012

INTRODUCTION

Treatment end points for patients with malignant

disease have historically been reflected by objective tumor response, overall survival and/or disease-free survival. However, over the past three decades, with the introduction of multi-modality treatments and the increasing number of cancer survivors, has come the growing awareness and concern for the psychosocial needs of patients with cancer.^[1]

Head and neck cancers are 2.8% of all new cancer cases that almost 1/3rd of patients are women. Head and neck cancers have a fairly good chance to cure.

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.102976

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How to cite this article: Gookizadeh A, Emami H, Najafizadeh N, Roayaei M. Clinical evaluation of BIOXTRA in relieving signs and symptoms of dry mouth after head and neck radiotherapy of cancer patients at Seyed-al-Shohada Hospital, Isfahan, Iran. *Adv Biomed Res* 2012;1:72.

Because of certain head and neck anatomy, radiotherapy with or without chemotherapy of cancers is one of the main treatment modalities.^[2]

There is both acute and long-term sequel of radiation therapy for head and neck cancers, which occurs due to effects on normal tissues. Permanent xerostomia is the most prevalent late side effect of RT for H&N cancers, and is a major cause of reducing quality of life. An alteration in taste can also occur, and decrease in oral intake may also contribute to decrease saliva production. Temporary loss of saliva, which is significant after delivery of 10 Gy to salivary glands while administration of approximately 40 to 50 Gy, causes permanent loss of their functions.^[2,3]

Xerostomia is most marked when the amount of salivary mucous membranes moist is reduced by 50%.^[4,5]

Decreased saliva causes dry mouth, tingling, decreasing sense of taste, difficulty swallowing dry foods, teeth caries, gum disease, bad breath, oral health costs, discomfort when using dentures, and increasing opportunities infections such as *candida albicans*.^[6]

Patients asking many questions, can help identify and demonstrate reduce salivary gland function. A definitive answer to at least 1 of the following 4 questions can be indicated to reduce salivation.

- (1) Do you complain of dry mouth during the day or night?
- (2) Do you feel xerostomia in your mouth when you eat?
- (3) Do you use liquids for dry food ingestion?
- (4) Is it because of dry mouth you avoid talking to those around you?

Other methods include imaging techniques, and collecting saliva can also be used to measure it.^[4,5,7]

Autoimmune diseases such as Sjogren syndrome, HIV infection, and GVHD after bone marrow transplantation are other causes of xerostomia. Also, decreased saliva and immunoglobulin's abnormalities may be seen in people who have been used silicone breast implants.^[8]

Patients with renal failure who are on hemodialysis are also suffering from reduced salivary gland function.^[9]

Up to now, no effective treatment for dry mouth has been discovered.

Cholinergic drugs such as Pilocarpin can improve xerostomia, but they have many complications.^[10,11]

Patients should be instructed to drink adequate fluids, rinse, and gargle with a weak solution of salt and baking soda several times a day (½ teaspoon of salt and 1 teaspoon of baking soda added to 1 quart of water). This regimen can refresh the mouth, loosen thick, tenacious oral secretions, and alleviate mild mucositis pain.^[4-6]

Xerostomia often improves with time, but it is a long lasting and frequently permanent problem that adversely impacts quality of life. Commercially available salivary substitutes or artificial saliva (oral rinses containing hyetellose, hyprollose, or carmellose) relieve the discomfort of xerostomia by temporarily wetting the oral mucosa. Although they can provide temporary relief, especially prior to eating, many patients must take frequent sips of water to remain comfortable. In addition to being inconvenient, this can lead to secondary problems such as nocturia from late night fluid intake in men with prostatic hypertrophy and in men and women with small bladder capacity.^[12]

A commercially available oral moisturizer (Optimoist) produces significant benefit for patients with H&N cancers undergoing radiation therapy.

MATERIALS AND METHODS

This study was a clinical randomized controlled trial (from 2008 to 2009), conducted in Radiation Oncology Department of Seyed-al-Shohada Hospital, Isfahan University of Medical Sciences, on some head and neck cancer patients, with no age and sex limitation that received at least 4000 cGY RT with parallel opposed field and daily fraction of 180 cGY.

Ethical approval was obtained from the local research ethics committee in school of medicine before recruitment. The study was performed in accordance with published guidelines and is reported in accordance with the CONSORT statement. Except salivary gland cancer, head and neck cancer patients were eligible for an enrolment. They received radiotherapy and went away at least 2 months from their treatment, but they would be excluded if they had diseases associated with xerostomia (such as autoimmune disease, connective tissue disease, etc.), used drugs which xerostomia is one of their side effects, and had a past history of radiotherapy in head and neck cancer region.

The main objective was to evaluate whether Bioxtra gel would improve radiation-induced xerostomia,

lactobacillus colony count, *candida albicans* in the saliva cultures and oral cavity PH.

55 patients were defined as eligible patients. Written informed consent was recorded from subjects who agreed to participate.

The primary end-point was xerostomia, which was measured at the end of 2 weeks after finishing therapy. *Candida albicans*, lactobacillus colony count, and oral cavity PH measured as secondary end-points at the end of treatment for increasing power coefficient of xerostomia.

At the first day of treatment, xerostomia and saliva stream evaluated by some questions such as whether patients had complained of xerostomia during days or nights, felt xerostomia while eating, drank water for swallowing dry food and if avoided talking to people because of xerostomia. One absolute positive answer to at least one of these questions presents decreased saliva. Then, we used a special table for scoring in order from 0 to 1. Then, we tried to find the mean score of the patients and analyzed with Chi-square test.

The other options evaluated are basic PH with PH strip, basic lactobacillus colony count and *candida albicans* of the mouth in special cultures in laboratory. Then, patients were recommended to drink water when they need to and use ice chips to wet their mouth. Chewing gum, using lemon, avoidance of hot or cold and peppery food was also recommended.

Patients received 2 Bioxtra gel for 2 weeks (1 spoon, 3 times a day). They went for assessment of xerostomia, swallowing, and oral cavity examined for infections and teeth condition. After 2 weeks, xerostomia evaluated again by the same questions, and oral cavity PH, lactobacillus colony count and *candida albicans* checked in laboratory.

Qualitative results such as xerostomia were compared by using Chi-square test and quantitative results such as oral cavity PH, lactobacillus colony count and *candida albicans* used t-test.

RESULTS

Between 2008 and 2009, 55 head and neck cancer patients were evaluated for xerostomia. The average age of the patients was 54.9 +15.5 years (range: 19-82). 32 (58.2%) patients were males, and 23 (41.8%) were females. There was no significant difference between the mean ages of these 2 groups ($P = 0.86$).

In the evaluation of xerostomia before treatment with

the Bioxtra gel, their most common symptom was xerostomia during the days and nights. The mean xerostomia score was 4.25 + 1.6.

For assessing the difference between male and female patients, Mann-Whitney test was used that indicated no significant difference between two sexes ($P = 0.48$). Also, in accordance to variance analysis, there was no association between xerostomia and age ($P = 0.13$).

In comparison with results before treatment, results of xerostomia evaluation after treatment are shown in Figure 1.

In accordance to Wilkoxon test on these data, the mean of xerostomia score was significantly lower after treatment ($P = 0.004$). In accordance to Mac nemar test, xerostomia during the day and night and speech impairment has significant difference, but xerostomia while eating and drinking water during a meal indicate no significant difference ($P = 0.004$ with SD = 1.67 before treatment and 1.19 after treatment).

Comparing mean and standard deviation of xerostomia before and after treatment is shown in Table 1.

To evaluate patients' satisfaction of xerostomia treatment with Bioxtra gel, willing to continue using Bioxtra gel for the quality of life improvement, its taste satisfaction, and the feeling of xerostomia improvement were assessed. 39 patients (70.9%) were willing to continue taking it, 50 patients (90.9%) were

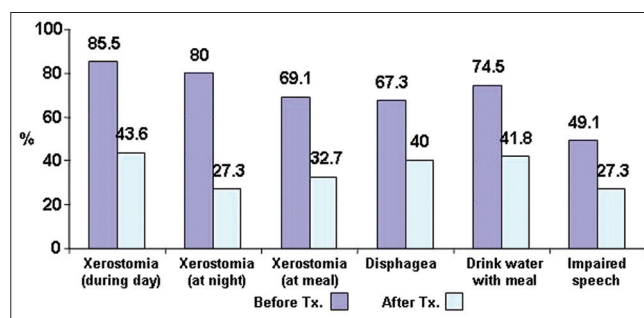


Figure 1: Frequency of xerostomia before and after treatment

Table 1: Comparing mean and standard deviation of xerostomia before and after treatment

Variable	Time				P
	Before treatment		After treatment		
	Number	%	Number	%	
Xerostomia during a day	47	85.5	24	52.7	0.001>
Xerostomia at night	44	80	15	27.3	0.001>
Xerostomia while eating	38	69.1	22	40	0.43
Drink water during a meal	41	74.5	23	41.8	0.59
Speech impairment	27	49.1	8	14.5	0.001

satisfied with its taste, and xerostomia of 32 patients (58.2%) were improved.

The mean PH was $5.42 + 0.66$ before treatment and $5.18 + 0.65$ after treatment. In accordance to T-paired test, the PH of the mouth before and after the treatment indicates significant difference ($P = 0.033$).

The mean colony counts of *candida albicans* was $81515 + 23733$ before treatment and $70303 + 27668$ after treatment. In accordance to T-paired test, the number of colony counts of *candida albicans* indicates significant difference ($P = 0.044$).

The mean colony counts of lactobacillus was $8975 + 23695$ before treatment and 84750 ± 25719 after treatment, but in accordance to T-paired test, the number of colony counts of lactobacillus indicates no significant difference ($P = 0.23$).

DISCUSSION

The present study indicates a significant superiority of Bioxtra gel for xerostomia during the day and a speech, but it doesn't indicate significant effect in swallowing xerostomia because in this situation, we need more saliva flow, and Bioxtra cannot improve xerostomia with different scores.

If Bioxtra gel used for 2 weeks, resulted significant improvement in xerostomia, Shahdad *et al.* indicated in a study. The effects of Bioxtra and Bioten are evaluated in this study and showed that Bioxtra significantly improves xerostomia more than Bioten.^[10]

Piet Dirix *et al.* in 2006 demonstrated that the use of Bioxtra gel after 4 weeks in head and neck cancer patients significantly decreased the xerostomia. In this study, mean of xerostomia, according to the VAS, was 59.8; and after the treatment, it became 36.4. As a result, the use of Bioxtra gel significantly improved the radiotherapy complications, especially xerostomia.^[9]

In this study, Bioxtra gel increased the PH. Naturally. Decrease in oral cavity PH is one of the complications of xerostomia that causes chemical effects on oral cavity tissues and teeth, proliferation of organisms such as lactobacillus and candida that induced severe teeth caries and other side effects.

In a series of 24 patients, whole unstimulated salivary flow rate improved from 0.12 to 0.24 mL/min after 2 weeks of therapy. Candida colonization decreased in 43%, and swallowing objectively improved in 75% of subjects.^[13] According to Dirix P *et al.* in 2007, 77% of patients improved after treatment with 32% had

an excellent response. After treatment with Bioxtra, quality of life significantly increased than placebo and anyone had complications, although further studies of this drug use are considered essential.^[14]

Shahdad *et al.*, in double-blind randomized cross trial, evaluated effect of Bioxtra and Bioten on radiation-induced xerostomia. In this study, patients were randomly received Bioten for 2 weeks, they had a week break, and again, they received Bioxtra for 2 weeks or vice versa. After assessment the results, both drugs were effective, but the improvement in xerostomia and speech with Bioxtra was more than with Bioten.^[15]

This gel could decrease lactobacillus counts and significantly decreased candida counts.^[10]

Although these results can be advised to patients, more trials addressing this issue with this drug and the other kind of drugs need to be undertaken.

Due to high cost and lack of insurance, those drug combinations require long term treatment and have daily application. If the cost is reduced and the drug exposure is available, the patients' quality of life will be improved.

Considering that there is still no cure for the relief of xerostomia caused by radiotherapy proven, as recommended routine, controlling is performed for xerostomia and compared with other drugs with different mechanisms.

Considering that xerostomia has undesirable effects on patients' quality of life and available treatment has a temporary effect, using more advanced methods of radiotherapy to prevent or to reduce these complications is recommended.

CONCLUSIONS

The present results show that Bioxtra gel is effective in decreasing radiation-induced xerostomia, and treatment may be considered as the favorable therapy in head and neck cancer patients who received radiotherapy and have xerostomia.

ACKNOWLEDGMENTS

This study was supported by a grant from Isfahan University of Medical Science.

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Source of Support: Isfahan University of Medical Science, **Conflict of Interest:** None declared.