

Assessment of systemic effects of ginger on salivation in patients with post-radiotherapy xerostomia

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Original Article

Abstract

BACKGROUND AND AIM: Our aim was to assess the clinical efficacy of ginger capsule (Zintoma herbal capsule) in the relief of symptoms in patients with post-radiotherapy xerostomia.

METHODS: This study was a randomized double-blind, parallel clinical trial of ginger usage in patients with post-radiotherapy xerostomia. Sixty-one subjects were selected from patients with xerostomia of Imam Khomeini Cancer Institute, Tehran, Iran. Subject-based dry mouth scores derived from 100 mm visual analogue scales (VAS) were recorded at baseline. Patients also completed a questionnaire on the first visit regarding the symptoms of xerostomia. The patients received ginger capsule (30 persons) or placebo (31 persons) three times daily over a 2-weeks period. At the end of day 14, dry mouth scores derived from VAS were recorded again and patients responded to the additional variables regarding dry mouth symptoms and quality of life issues. $P < 0.05$ was considered significant. Data were analyzed using SPSS.

RESULTS: The mean treatment effect on day 14 was 33.7 ± 20.9 mm in the ginger group and 23.6 ± 17.3 mm in the placebo group. The analysis indicated marginally significant improvement of xerostomia with ginger prescription ($P = 0.057$). At the end of intervention there was no significant difference between the two groups regarding improvement of quality of life or dry mouth symptoms.

CONCLUSION: It seems that ginger could be helpful in the treatment of xerostomia. Since ginger is considered a safe herbal medicine with only few and insignificant adverse/side effects further studies in larger group of patients are recommended to provide the effect of ginger on different complaints of xerostomia.

KEYWORDS: Ginger, Radiation, Xerostomia

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Saliva is the production of major and minor salivary glands dispersed in the oral cavity. The subjective report of oral dryness is termed xerostomia.¹

Several factors can cause xerostomia, but radiation therapy is one of the main causes. Radiation therapy of the head and neck region is used for treatment of primary and recurrent tumors in the upper aerodigestive

tract and squamous cell carcinoma (SCC) of oral cavity and sinuses, salivary gland tumors and nasopharynx carcinoma.² Radiotherapy is an effective treatment for head and neck cancer, but because traditional radiotherapy treatment fields frequently include the major salivary glands, xerostomia is a common late toxic effect of radiation therapy in patients with head and neck

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cancers.²⁻⁴ It has been proved that radiation exposure has its own side effects such as disordering the salivary function, microbial infections, tastelessness and osteoradionecrosis of the jaw.⁵

Treatment of salivary hypofunction and xerostomia is primarily palliative and can be accomplished by multiple approaches⁶ such as chewing gum,⁷ sugar free lozenges,^{8,9} salivary substitutes,¹⁰ Biotène products, Oral balance products,^{11,12} and toothpastes.¹³ Amifostine has been approved by the Food and Drug Administration (FDA) to relief the incidence and severity of radiation-induced xerostomia, but it requires parenteral administration, has potential side effects, and is not universally available.¹⁴ Electro-stimulation of tongue and palate, hyperbaric oxygen therapy and herbal medications are used by researchers to improve xerostomia.^{13,15}

It is important to have a wide variety of products that can help modify the xerostomia symptoms. These products should be convenient to use, safe, with minimal side effects, and tested for safety and efficacy in controlled clinical trials.⁷ The superior trait of saliva is its oral immunologic protection, therefore can never be replaced by any other synthetic substitute.¹⁶

Nowadays, there are various successful herbal drugs in clinical trials for alleviating xerostomia, Bakumondo-to, LongoVital, and linseed extract Salinum are examples of these drugs.¹⁵

Chamani et al. showed that salivation after injection of ginger extract was significantly higher than that of other herbal extracts and the negative control group in rats ($P < 0.010$).¹³ According to some research on herbal drugs, ginger has excellent chronological effect on post-synaptic M3 receptors.^{13,17} Extracts and fractions of ginger (*Zingiber officinale*) have been shown to protect against chemically-induced tissue damage. The radioprotective effect of ginger extract has also been confirmed.¹⁸⁻²³ Ginger is not only known as a safe herbal medicine but also as an anti-cancer, anti-clotting, and

anti-inflammatory agent that has analgesic activities.²⁴

In this study, we evaluated the effect of ginger on increasing salivation and improvement of quality of life and dry mouth symptoms in patients with post-radiotherapy xerostomia.

Methods

This study was a randomized double-blind, parallel clinical trial of ginger usage in patients with post-radiotherapy xerostomia. This proposal had been evaluated by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (code K/87/103). The participants read and signed an official consent form. Sixty-one subjects were selected from patients with xerostomia from the Imam Khomeini Cancer Institute, Tehran, Iran. Registration ID of IRCT was IRCT138807012227N2.

In this research, the patients were minimum 18 years old with a history of radiotherapy treatment for neck cancer who had major and minor salivary glands disorders and experienced symptoms such as dry mouth when taking foods orally.

Exclusion criteria included any treatment for cancer in the last three months, patients who had not received the determined radiotherapy course completely, those who were pregnant, smokers, diabetics, those with recurrences of cancer or terminal cancer, Sjogren's syndrome, cancer of the salivary glands and other causes of xerostomia and those taking anticoagulant medication or nifedipine.²⁵

A pharmacognosist prepared drug packages in the same type with two different codes, A and B (patients and examiner were blinded to the packages' ingredients), which consisted of starch capsule and Zintoma herbal capsule. Participants were randomly allocated by random digit numbering in two groups, received the package one by one until the sample size was completed. Patients of the experimental group (30 persons) were given the ginger capsule (Goldaru Company, Zintoma herbal capsule, Iran) three times

daily and patients of the control group (31 persons) received placebo three times daily over a 2-week period. Starch was used as placebo (Figure 1).

Participants who signed the consent form were obligated not to use any other products or medicine for treatment of dry mouth, but were permitted to use frequent small sips of water or any other mouth care products for the relief of dry mouth as needed (e.g. topical analgesics, topical antiseptics, and antifungal treatments).

To determine the presence of xerostomia in the study population, each patient was evaluated using the Fox questionnaire.²⁶ In this way the patients were enrolled by their scores derived from 100 mm visual analogue scales (VAS) registered on day 0 and 14 of a 2-weeks period. We categorized the patients into two groups according to their pre-intervention (baseline) VAS score: a. patients with significant xerostomia ($x > 63.3$ mm) and b. patients with non-significant

xerostomia ($x < 63.3$ mm).

The patients received ginger capsule or placebo three times daily over a 2-weeks period. At the end of day 14, dry mouth scores derived from VAS were recorded again. The mean dry mouth VAS score on day 14 was considered as mean treatment effect in each group.²⁵

Patients also completed a questionnaire including continuous variables on the first visit regarding the symptoms of xerostomia such as speech, chewing and swallowing difficulties, bad taste and burning sensation. At the end of day 14, patients responded to the additional dichotomous variables regarding dry mouth symptoms and quality of life issues (Table 1).

The Student's t-test and chi-square test were used to compare initial group differences for continuous and categorical dates, respectively. To compare the xerostomia score, two-way analysis of variance (ANOVA) was used²⁷ with

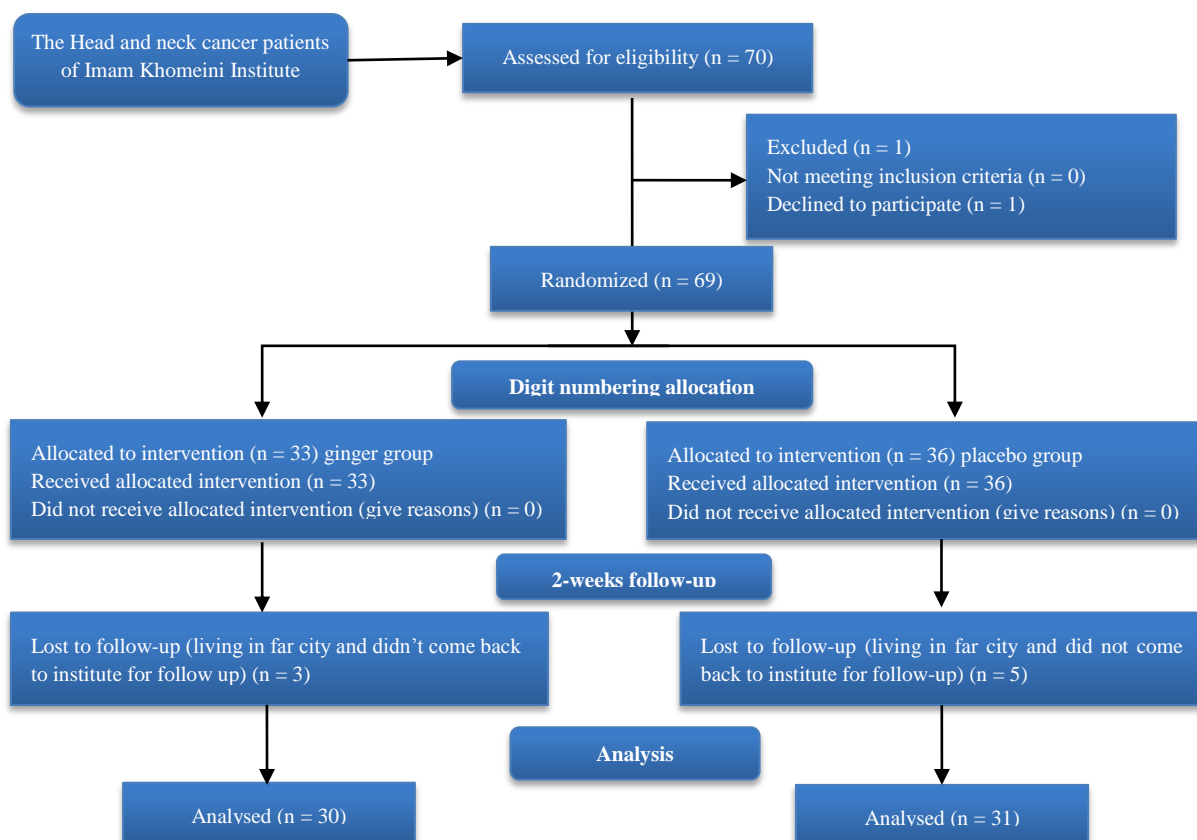


Figure 1. Flow diagram of the study

Table 1. Patient questionnaire completed on day 0 and day 14*

How dry is your mouth? (0 = not dry at all, 100 = worst imaginable dryness)
Do you have difficulty chewing because of your dry mouth? (0 = no difficulties at all, 100 = very severe difficulties with chewing)
Do you have difficulty swallowing because of your dry mouth? (0 = no difficulties at all, 100 = very severe difficulties swallowing)
Is speech difficult because of your dry mouth? (0 = no difficulties at all, 100 = very severe difficulties with speech)
Is taste affected by your dry mouth? (0 = not affected at all, 100 = very severe alteration of taste)
Do you have a burning sensation in your mouth? (0 = no burning at all, 100 = very severe burning mouth)
Did the drug make your dry mouth better? Yes/No
Was the drug most useful in the night? Yes/No
Did the drug stop you waking in the night? Yes/No
Did the drug improve your sensation of taste? Yes/No
If you wear denture, did the drug help with the retention of the denture? Yes/No
Did you meet people more than you used to? Yes/No
Did you speak to people more than you used to? Yes/No
Did you get out of the house more than you used to? Yes/No
Did the drug make chewing easier? Yes/No
Did the drug make swallowing easier? Yes/No
Did the drug make talking easier? Yes/No
If you have a burning mouth, did the product improve the burning sensation? Yes/No
Did the drug make your dry mouth better? (0 = not dry at all, 100 = worst imaginable dryness)

*Questions 1-6 were asked on day 0, and questions 7-18 were mentioned on day 14

treatment as one factor and the category of baseline xerostomia severity as the other.

$P < 0.05$ was considered significant. Data were analyzed using SPSS software (version 17, SPSS Inc., Chicago, IL, USA).

Results

Sixty-one patients participated in this study. After breaking the prescribed drug code, it was determined that 30 patients used ginger (Zintoma herbal capsule) and 31 patients used the placebo.

The patients in both groups were compared together in different characteristics, such as age, sex and elapsed mean time after last radiotherapy. There was no significant difference between them (Table 2).

Because exact categorization between the

two groups for radiotherapy dose, the site and type of cancer was not possible, there was no estimation for type and site of cancer between both groups.

Using the VAS patients were questioned about xerostomia before ginger or placebo prescription. The mean treatment effect on day 14 (considering the categorization of patients in two groups with significant and non-significant xerostomia) was 33.7 ± 20.9 mm VAS score in the ginger group and 23.6 ± 17.3 mm VAS score in the placebo group (Figure 2).

The two-way ANOVA test indicated marginally significant improvement of xerostomia with ginger prescription ($P = 0.057$). Meanwhile, there was no interaction between the ginger group and significant xerostomia ($P = 0.930$).

Table 2. Comparison of baseline characteristics between the two groups

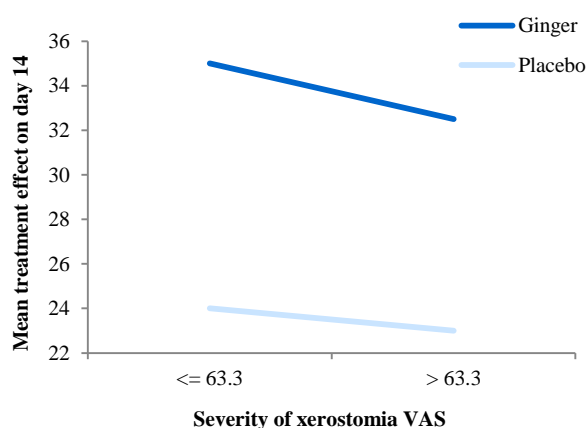
Characteristic	Ginger	Placebo	P
Sex			
Male [n (%)]	22 (73.3)	24 (77.4)	0.711
Female [n (%)]	8 (26.7)	7 (22.6)	
Age (year) (mean \pm SD)	51.5 \pm 18.4	54.4 \pm 15.6	0.506
Time elapsed after last radiotherapy (month) (mean \pm SD)	25.3 \pm 24.4	24.1 \pm 57.3	0.915
Systemic disease [n (%)]			
Yes	11 (36.7)	9 (29.0)	0.525
No	19 (63.3)	22 (71.0)	

SD: Standard deviation

Table 3. Comparison of dry mouth symptoms measured by visual analogue scales (VAS) score between the two groups before intervention

Symptom	Ginger	Placebo	P
	mean \pm SD	mean \pm SD	
Difficulty chewing	41.03 \pm 27.70	51.48 \pm 31.30	0.173
Difficulty swallowing	49.80 \pm 26.40	48.02 \pm 32.60	0.816
Speech difficulty	40.75 \pm 27.01	39.52 \pm 23.85	0.851
Affecting taste ability	24.73 \pm 25.80	37.27 \pm 32.90	0.104
Burning sensation in the mouth	18.62 \pm 21.02	22.89 \pm 23.76	0.461

SD: Standard deviation

**Figure 2.** This figure shows that xerostomia has improved in the ginger group (with significant and non-significant xerostomia), when compared to the placebo group
VAS: Visual analogue scales

The severity of major symptoms of xerostomia (difficulty with chewing, swallowing and speech, affecting taste ability, and burning sensation in the mouth)

were compared between both groups and there was no significant difference. The findings indicated that both groups were the same before the intervention (Table 3). Patients were questioned about the effect of treatment on their quality of life and improvement of dry mouth symptoms on day 14 (end of intervention) (Table 1). The questions were yes/no type. The chi-square test showed that there was no significant differences between the two groups regarding improvement of dry mouth symptoms (including speech, chewing and deglutition difficulties and burning sensation) and quality of life issues such as dry mouth throughout the day, dry mouth throughout the night, awakening in the night due to dry mouth, affecting taste ability, decreased denture retention, meeting less people, speaking less to people, and going out less than before (Table 4).

Table 4. The effect of treatment on improvement of dry mouth symptoms and quality of life

Item	Response	Ginger			Placebo			P
		Yes [n (%)]	No [n (%)]	Total [n (%)]	Yes [n (%)]	No [n (%)]	Total [n (%)]	
Did the drug make chewing easier?		18 (60.0)	12 (40.0)	30 (100)	10 (40.0)	15 (60.0)	25 (100)	0.140
Did the drug make swallowing easier?		18 (60.0)	12 (40.0)	30 (100)	11 (44.0)	14 (56.0)	25 (100)	0.237
Did the drug make talking easier?		17 (56.7)	13 (43.3)	30 (100)	10 (40.0)	15 (60.0)	25 (100)	0.218
If you have a burning mouth, did the product improve the burning sensation?		8 (26.7)	22 (73.3)	30 (100)	3 (12.0)	22 (88.0)	25 (100)	0.176
Did the drug make your dry mouth better?		23 (82.1)	5 (17.9)	28 (100)	18 (62.1)	11 (37.9)	29 (100)	0.092
Did the drug most useful in the night?		14 (56.0)	11 (44.0)	25 (100)	12 (46.2)	14 (53.8)	26 (100)	0.482
Did the drug stop you waking in the night?		8 (44.4)	10 (55.6)	18 (100)	9 (39.1)	14 (60.9)	23 (100)	0.732
Did the drug improve your sensation of taste?		2 (22.2)	7 (77.8)	9 (100)	5 (50.0)	5 (50.0)	10 (100)	0.210
If you wear denture, did the drug help with the retention of the denture?		4 (28.6)	10 (71.4)	14 (100)	5 (38.5)	8 (61.5)	13 (100)	0.586
Did you meet people more than you used to?		5 (38.5)	8 (61.5)	13 (100)	5 (35.7)	9 (64.3)	14 (100)	0.883
Did you speak to people more than you used to?		3 (27.3)	8 (72.7)	11 (44.0)	5 (41.7)	7 (58.3)	12 (40.0)	0.469
Did you get out of the house more than you used to?		2 (50.0)	2 (50.0)	4 (28.6)	2 (25.0)	6 (75.0)	8 (61.5)	0.386

However, concerning one question (dry mouth throughout the day) 82% of patients in the ginger group and 62% of patients in the placebo group felt improvement and this difference was marginally significant ($P < 0.100$).

Following drug consumption, some patients reported some side effects. In the ginger group, 1 patient had constipation, 2 patients had vertigo, and 2 had dyspepsia. In the placebo group, 2 patients had headache and 2 patients had dyspepsia. Because the side effects were few, it was probable that other elements caused these problems, rather than ginger or placebo consumption.

Before the study was done, patients inquired about the use of saliva substitute or other products to decrease dry mouth. No one reported using artificial saliva. Four patients (6.5%) were using BioXtra gel. These patients agreed to discontinue using BioXtra gel in order to join the study.

Discussion

Some researchers conducted on the ginger plant have indicated parasympathomimetic effect.^{13,17,28} In researches conducted by Ghayur and Gilani, ginger was shown to have spasmolytic effect through blocking calcium channels²⁷ and was involved in activation of postsynaptic muscarinic M3 receptors in the stomach of rats.¹⁷ Chamani et al. discovered that ginger derivate was effective in increasing saliva of rats.¹³

The result of the recent study indicates that dry mouth improvement in patients who used ginger was marginally more significant than in patients in the placebo group. The statistical analysis showed that there was no significant difference in severity of symptoms of xerostomia between two groups and both groups of patients were similar in age, gender and time elapsed after last radiotherapy. This issue indicates that not only the two groups before the study were completely identical, but also it insists on the power of intervention and true randomly chosen sampling.

In this study, the improvement of xerostomia after ginger usage was marginally significant ($P = 0.057$). To achieve the best reliable results, the patients were divided into two groups with significant and non-significant xerostomia. The improvement of dry mouth was assessed based on this categorization. If this division was not done and all of the patients who had significant and non-significant xerostomia in the ginger or placebo group were assessed together, the results of the comparison between control and study groups were completely significant by the t-test ($P = 0.044$). In this study focus was placed on the two-way ANOVA test, to attain the most reliable results ($P = 0.057$).

Because the decrease in xerostomia through ginger usage was marginally significant as compared to the placebo, it is proposed that in future researches, more attention should be placed to increase sample size to gain the best absolute results.

Despite the improvement of xerostomia there was no meaningful difference between two groups regarding improvement of dry mouth symptoms and quality of life issues on day 14. It is probable that non-significant results were related to the small sample size and the psychological effect of the placebo.

It is not deniable that the range of radiation side effects depends on several factors such as scope, dose and volume of radiation actors rather than the ordinary performance of the salivary gland.²⁹ By consulting the radiotherapist-oncologist, there was no chance to differentiate the patients based on these factors, so it is probable that such factors in small sample could have biased the research results.

The radiotherapist-oncologist advised the patients to use water and liquids, to have good oral hygiene, and to use nystatin and chlorhexidine mouthwashes, and fluconazole during treatment. This advice about liquid consumption could have some effects on dry mouth. We had no remedy to omit this confounder factor, because it is necessary to

advise patients to use water and liquid based on moral rules.

For evaluation of severity of xerostomia and the treatment effect, dry mouth scores derived from VAS were recorded on days 0 and 14 in this study.

The best treatment for decreased salivation is protection. Advances in technology in the field of therapeutic radiation spares a portion of the major salivary glands from destruction.^{7,12} Great efforts were also made to develop radioprotective medications to decrease side effects of radiotherapy. By systemic application of amifostine, salivary gland function could be improved after therapy.²⁹

One reliable alternative to treat radiotherapy-induced hyposalivation is stem cell replacement. The recent identification of stem and progenitor cell populations will aid with future research, but a better understanding of cell turnover in salivary glands is still needed.³⁰

However, some patients who are going under radiotherapy are still suffering from the complications of xerostomia and more studies are needed to find new solutions for this problem.

Limitations

There was some limitation in our study such as different culture and language barrier

(participants spoke Turkish, Kurdish, etc.) that made some difficulties in answering the examiner's question, and low number of patients for treatment follow-up because of living distant from the institute which made sample size small to review. So, further studies in larger group of patients are recommended to provide the effect of ginger on various complaints of xerostomia.

Conclusion

This study showed that ginger decreased the severity of dry mouth in patients with post-radiation xerostomia, but it did not improve dry mouth symptoms or patients' quality of life. Conducting more research on this plant in the future, with attention to special characteristics (low cost, availability, safety) is advised.

Conflict of Interests

Authors have no conflict of interest.

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