ORIGINAL ARTICLE

Preventive effects of zinc sulfate on taste alterations in patients under irradiation for head and neck cancers: A randomized placebo-controlled trial

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Background: Taste abnormalities are common among cancer patients after starting radiotherapy or chemotherapy. Considering the role of zinc and reports on its beneficial effects in taste perception, we evaluated the preventive effects of zinc sulfate on radiation-induced taste alterations. **Materials and Methods:** In a randomized, placebo-controlled trial, adult patients with head and neck cancers who were on schedule for radiotherapy, with or without chemotherapy, were allocated to receive zinc sulfate (50 mg, three times a day) or placebo; started with beginning of radiotherapy and continued for one month later. Taste acuity was determined by measuring detection and recognition thresholds for four taste qualities at baseline, at the end of radiotherapy, and a month later using the Henkin method. **Results:** Thirty-five patients (mean age = 59.2 ± 16.5, 60% male) completed the trial. The two groups were similar at baseline. After radiotherapy, and one month later, there was a significant increase in taste perception threshold for bitter, salty, sweet, and sour tastes in the placebo group ($P = 0.001$). In those who received zinc, there was only slight increase in threshold for perception of the salty taste ($P = 0.046$). No relevant side effects due to zinc sulfate were reported. **Conclusion:** Zinc supplementation in head/neck cancer patients under radiotherapy can prevent radiation-induced taste alterations. Further studies with longer follow-ups and with different doses of zinc supplementation are warranted in this regard.

Key words: Cancer, dysgeusia, radiotherapy, taste loss, taste perception, zinc sulfate

INTRODUCTION

Head and neck cancers account for about 3% of all cancers, and have a fairly good chance of healing.[1] Because of certain head and neck anatomy, radiotherapy with or without chemotherapy is one of the main treatment that significantly increased the survival of patients.[2] However, besides its anti-tumor effects, radiation causes damage in normal tissues located in the radiation portals. Although the exact mechanism is not yet known, a reduction in taste sensitivity (hypogeusia), an absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia) often occurs in cancer patients.[3] Chemotherapy and radiotherapy can result in taste disturbances by destroying taste receptor cells and affecting neural activities. However, in some patients, abnormal taste acuity for one or more taste qualities are even present before the beginning of radiotherapy or chemotherapy.[3] Taste abnormalities in cancer patients can decrease appetite and dietary intake, lead to malnutrition and weight loss,[4,5] and decrease quality of life and even survival.[3] Therefore, reversing the taste perception in cancer patients during their treatments is valuable.

According to several reports, zinc plays an important role in taste perception, and zinc deficiency is responsible (in some cases partially) for taste perception abnormalities in otherwise healthy persons,[6] various diseases,[7] and also in drug-induced taste disorders.[8] Zinc is a cofactor of alkaline phosphatase activity which is the most abundant enzyme in the membrane of taste bud. The main effects of zinc deficiency are the changes in the number and size of taste buds and structural changes in taste buds cells as well as decrease in related nerve sensitivity.[9,10]

Zinc supplementation has been shown to be effective in the treatment of taste and smell abnormalities observed among patients with taste disorders.[11] Even in healthy persons, zinc supplementation increased the recognition threshold for salty taste.[12,13] Few reports are also available from clinical trials on the effects of zinc supplementation on taste perception in cancer patients. Beneficial effects of polaprezinc (zinc L-carnosine)[14] and zinc infusion during chemotherapy[15] on taste disturbance in patients with head and neck cancer and lung cancer patients have been reported. However, a large clinical trial found not statistically significant effect of zinc sulfate therapy on

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the median interval to taste alterations under radiotherapy,[16] and another recent study found no significant benefit for zinc therapy with standard doses to taste or smell in cancer patients under chemotherap y.[17]

There is a lack of data and controversial results on the effects of zinc supplementation in prevention/treatment of taste alterations in cancer patients. With regards to the importance of appropriate management of taste abnormalities among cancer patients, we conducted a randomized double-blind placebo-controlled trial to evaluate the preventive effects of zinc sulfate on radiation-induced taste alterations in patients under irradiation for head and neck cancer.

MATERIALS AND METHODS

Patients and settings

This randomized, double-blinded, placebo-controlled trial was conducted between 2009 and 2010 in radiation-oncology department of Seyed-al-Shohada Hospital in Isfahan (Iran). Consecutive adult patients with head and neck cancers who were on schedule for radiotherapy with at least 2000 cGy to >30% of oral cavity, with or without chemotherapy, were considered as eligible patients. Those with oral candidiasis or other oral lesions (e.g., stomatitis, necrosis, and ulcers), cranial nerve injuries, and metabolic/endocrine disorders that may have effects on taste perception were not included. Ethical approval was obtained from the Ethical Committee of the Isfahan University of Medical Sciences and informed consent was obtained from all patients at recruitment.

Intervention

Regarding the radiation therapy protocol, patients were treated with opposite fields that included the primary tumor and lymph nodes in the upper neck area, with daily 180 to 200 cGy fractions, 5 times a week; the total dose was 6000 to 7000 cGy within a period of 5 to 9 weeks. Based on a random table list generated by random allocation software, patients were allocated to receive zinc sulfate capsules (Alhavi Co., Tehran, Iran) 50 mg, three times a day, after meals or the same placebo. Medication was started with beginning of radiotherapy and continued one month after completion of irradiation. For assuring blindness of the patient and attending physician, coded zinc capsules and placebos were given to the patients by pharmacy operators without the knowledge of the patient group.

Assessments

As the primary outcome measure, taste acuity was determined by measuring detection and recognition thresholds for four taste qualities at baseline, at the end of radiotherapy, and a month later. Taste acuity was evaluated according to the 3-drop method introduced by Henkin which has been used with previous similar studies.[18,19] For this evaluation, solutions providing the four main tastes; sweet, salty, sour, and bitter, respectively, were prepared by sucrose, salt, hydrochloric acid, and urea. Eleven ascending concentrations were prepared for each solution as described in Table 1 in sealed bottles. Each time, the patient was asked to evacuate his/her sputum before the test, try desired solution, wash his/her mouth with distilled water, and then try another solution. In each test, three drops were poured in the patient's mouth, the two of them were water and another drop was from solution of the taste. Understanding and identifying the threshold for each taste was according to the loss of taste from 1 to 11 titrations. In each test, the patient answered two questions: (1) which of the three drops of a different taste? (2) what are the different types of drop? sweet, salt, sour, or bitter? The lowest concentration, by which the patient could identify difference from the water, was considered as the detection threshold. The lowest concentration of the patient as it tastes sweet, salt, sour, or bitter to detect, identify thresholds are considered. All patients were also visited with the attending physician weekly during radiotherapy and one month after completion of radiation therapy for correct use of the medication and possible side effects.

Statistical analysis

Data were analyzed by the SPSS software for windows version 16.0. Data are shown as mean ± SD, number (percent) or median [IQR] with regard to kind of variables. Qualitative parameters were compared between and within groups using the Chi-square/Mann-Whitney tests and Wilcoxon test, respectively. Quantitative parameters were compared between groups using independent *t*-Test. Taste threshold was considered as an ordinal variable. Statistical significance was accepted at $P < 0.05$.

RESULTS

During the study period, 35 patients (mean age = 59.2 ± 16.5, 60% male) with head/neck cancer entered the study and were randomized into the intervention (n = 20) and placebo (n = 15) groups. The two groups were similar

Table 1: Ascending concentrations of the four tastes solutions (reference 18)

Solution	1	2	3	4	5	6	7	8	9	10	11
NaCl (mmol/l)	6	12	30	60	90	150	300	500	800	1000	3000
Saccharose (mmol/l)	6	12	30	60	90	150	300	500	800	1000	Saturate
HCl (mmol/l)	0.5	0.8	3	6	15	30	60	90	150	300	500
Urea (mmol/l)	60	90	120	150	300	500	800	1000	2000	5000	8000

with regards to demographic and clinical [Table 2]. All the patients were treated with daily fractions of 180 to 200 cGy lasting from 5 to 9 weeks, for a total dose of 6 000 to 7000 cGy. The radiation fields were the same for all patients, and the tongue was always included.

The two groups were similar in baseline taste perception threshold for the four tastes. At the end of radiation therapy, there was a significant increase in taste perception threshold for bitter (5 to 6, $P = 0.003$), salty (4 to 5, $P = 0.002$), sweet (3 to 5, $P = 0.002$), and sour (4 to 5, $P = 0.002$) tastes in the placebo group. In patients who received zinc, taste perception threshold did not change significantly at the end of radiation, except the sour taste perception (4 to 5, $P = 0.038$) [Table 3]. One month after completion of radiotherapy, taste perception threshold was increased in the placebo group for all four tastes ($P = 0.001$). In those who received zinc, there was only slight increase in threshold for perception of the salty taste ($P = 0.046$) [Table 3]. Further analysis of data showed no association between age, gender, smoking history, cancer grade, or radiation dose with changes in four tastes perception thresholds after radiation therapy ($P > 0.05$). No relevant side effects due to zinc sulfate or placebo treatment were reported by patients, and no patient required suspension of treatment. None of the patients developed oral cavity lesions during radiotherapy. Throughout the whole period of the trial, no patient used anesthetic and/or antifungal rinses or mouthwashes for oral cleansing that were different from the one prescribed.

Table 2: Demographic and clinical characteristics of patients

Clinical characteristics	Placebo	Zinc	*P*
Age (year)	56.1±15.6	61.6±17.2	0.343*
Female/Male	8 (53)/7 (46)	6 (3)/14 (70)	0.148**
Radiation dose (cGY)	62.9±3.9	63.2±3.3	0.831*
Cancer Grade			
II	9 (60)	9 (45)	0.458**
III	5 (33)	9 (45)	
IV	1 (6.7)	2 (10)	
Treatment			
Radiotherapy	12 (80)	15 (75)	0.378**
Chemoradiation	2 (13.3)	5 (25)	
Chemotherapy	1 (6.7)	0	
Smoking history	6 (40)	5 (25)	0.281**

Data are presented as mean±SD or number (%); *Independent *t*-test; **Chi-square Test

DISCUSSION

Taste abnormalities are common, but often underestimated and unrecognized, among cancer patients. From the cancer patients' point of view, however, they are major daily concerns and studies showed that these abnormalities can affect the daily quality of life, lead to malnutrition, and even decrease the survival.[3] Regarding the role of zinc in taste perception, we investigated if zinc supplementation can prevent taste alterations in head/neck cancer patients under radiotherapy. Our results showed that zinc supplementation (150 mg/day) during radiotherapy and continuing for one month later can prevent or at least decrease the effects of radiotherapy on taste perception for all of bitter, salty, sweet, and sour tastes. Unfortunately, we did not follow our patients for longer than one month and weather the beneficial effects of zinc on taste perception continue in long term needs further evaluations.

Few trials are available on the effects of zinc therapy on taste alteration among cancer patients. In a randomized clinical trial by Ripamonti *et al*. on a small number of head/neck cancer patients, treatment with zinc sulfate (45 mg, three times a day) during radiation and a month later resulted in lesser worsening of taste acuity during radiotherapy and quicker recovery of taste acuity one month later than those receiving placebo.[18] In another randomized trial by Watanabe and colleagues, polaprezinc (zinc L-carnosine) reduced the incidence of mucositis, pain, xerostomia (highly related to taste alteration), and taste disturbance in head/neck cancer patients under radiochemotherapy while it has effect on tumor response rate.[14] A phase III clinical trial on a large sample of head/neck cancer patients under radiotherapy reported the median interval to taste alterations as 2.3 *vs*. 1.6 weeks by zinc sulfate (45 mg orally three times daily) compared to placebo.[16] Besides these trials on oral zinc therapy, Yamagata *et al*. evaluated the effect of zinc including infusion on taste alteration in patients with lung cancer. Authors found increased taste thresholds in patients who had a low serum zinc concentration even before receiving chemotherapy, and prevention of further taste alteration by zinc therapy.[15] In contrast to these trials, a recent published randomized study by Lyckholm on patients under chemotherapy that had alterations in taste and/or smell found no improvement

Table 3: Median (IQR) threshold of taste perception for four tastes solutions

Tastes solutions	Placebo			*P**	Zinc			*P**
	Baseline	End of RT	Follow-up		Baseline	End of RT	Follow-up	
Bitter	5 (4-5)	6 (5-6)	7 (6-7)	0.001	4 (3.25-5)	4.5 (4-6)	5 (4-5.75)	0.077
Salty	4 (3-5)	5 (5-6)	7 (5-8)	0.001	4 (3-5)	5 (4-5.75)	4.5 (4-5)	0.046
Sweet	3 (3-4)	5 (4-6)	6 (5-7)	0.001	4 (3-5)	4 (3.25-5.75)	4.5 (3-5)	0.258
Sour	4 (4-5)	5 (5-6)	7 (6-8)	0.001	4 (4-4.75)	5 (4-5)	4 (4-5)	0.091

Data are presented as median (IQR) of the solution number; RT=Radiation therapy; *Wilcoxon test comparing baseline to follow-up data

in loss or distortion of taste/smell with 50 mg elemental zinc twice daily.[17] However, patients in this study were those with wide range of cancers and with already taste/smell alterations, and also in this study taste evaluation was based on a 0-100 scale that might not be as precise as methods of measuring taste threshold.

There are some limitations to our study. The sample size of our study was relatively small and included only head/neck cancer patients while taste alterations also occur in other type of cancers. More importantly, the follow-up was not long enough to show long-term effects and safety of zinc therapy. Also, we only measured changes in taste perception and if zinc therapy have had a real impact on dietary behavior of the patients, which is the final outcome, is not clear.

CONCLUSIONS

The present study results showed that a short course of supplementation with zinc sulfate in head and neck cancer patients under radiotherapy can prevent radiation-induced taste alterations. Accordingly, zinc therapy in cancer patients may prevent the detrimental effects of taste alteration on dietary behaviors and quality of life of cancer patients. Because long-term and excessive consumption of zinc may have a negative impact on the immune system in cancer patients, zinc supplementation should be used cautiously by cancer patients and further studies with longer follow-ups and with different doses of zinc supplementation are needed in this regard.

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