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A Randomized, Placebo Controlled Trial of Oral Zinc for Chemotherapy-Related Taste and Smell Disorders

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Abstract

Abnormalities in taste and smell are commonly reported in patients receiving chemotherapy and may hinder appetite, dietary intake, nutritional well-being, and quality of life. Oral zinc has been used to treat taste and smell abnormalities in several altered physiologic states, including renal failure, liver disease, head trauma, and pregnancy, with varying results. The authors conducted a double-blinded, placebo-controlled randomized clinic trial over 3 months. Eligible patients were those taking chemotherapy that had alterations in taste and/or smell. The measurement of the primary end point, improvement in altered taste and smell, was made using a 0–100 scale (100

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describing no loss or distortion in taste and smell, and 0 describing the worst distortion or loss of taste and smell). Twenty-nine subjects were enrolled in each treatment group, of whom 31 were white, 26 African American, and 1 Native American. Forty-one patients were female. A wide range of cancer types was represented, with breast the most common (21 patients). The zinc dose was 220 mg orally twice daily (equivalent of 50 mg elemental zinc twice daily). There was no statistically significant improvement in loss or distortion of taste or smell with the addition of zinc. There was a trend toward improvement over time in all groups, except in the zinc group where there was a nonsignificant worsening in loss of smell over time. Zinc at standard doses did not provide significant benefit to taste or smell in patients receiving chemotherapy.

Keywords

cancer; chemotherapy; smell; taste; zinc

INTRODUCTION

Alterations in taste and smell are commonly reported in patients taking chemotherapy (1) and may hinder appetite, dietary intake, nutritional well-being, and quality of life (2). Taste and smell function is initially controlled by growth factors, which stimulate stem cells in both taste buds and olfactory epithelial cells (3). There are multiple growth factors that act in this manner, including trace metals (e.g., zinc, copper), hormones (e.g., thyroxine), vitamins (e.g., vitamins A, B12) adenylyl cyclase (3), and many others. Chemotherapy can cause loss of taste and smell acuity due to inhibition of any of the growth factors involved in these sensory functions and subsequently can cause distortions associated with this acuity loss. Zinc is one of these growth factors and is a component of the salivary enzyme carbonic anhydrase VI (3), which is one growth factor responsible for sensory stem cell stimulation (4). Patients with carbonic anhydrase VI deficiency uniformly exhibit either loss of taste and smell acuity and/or taste and smell distortion (4). Zinc treatment of these patients activates carbonic anhydrase VI synthesis and reverses these sensory findings (5). Chemotherapy can be associated with alterations in zinc metabolism and could potentially cause carbonic anhydrase VI deficiency in some patients. However, the complexity of chemotherapy could influence various aspects of these systems that are not zinc-related.

Oral zinc has been used to treat taste and smell dysfunction in several altered physiologic states, including renal failure, liver disease, head trauma, and pregnancy, with varying results. Very little has been written about the use of zinc in patients receiving chemotherapy. One report suggested prevention of taste dysfunction with zinc infusions during chemotherapy for lung cancer as evaluation by electrical taste thresholds using an electrogustometer (6). No placebo-controlled studies have been reported using zinc to mitigate some of the effects of chemotherapy on taste and smell abnormalities. In this study, patients with chemotherapy-induced taste and/or smell changes were randomized to receive zinc or placebo to determine whether taste and/or smell abnormalities would improve with oral zinc supplementation (Table 1).

METHODS

This was a double-blinded, placebo-controlled, randomized clinical trial. The Investigational Drug Pharmacy randomized subjects using sealed envelopes that were blinded to enrolling physicians. The trial was conducted from 2002 to 2005, and approved by the Virginia Commonwealth University (VCU) Institutional Review Board and the Massey Cancer Center Protocol Review and Monitoring System Committee.

The measurement of the primary end point, change in taste and smell, was made using a 0–100 scale (100 describing no loss or distortion in taste and smell, and 0 describing the worst distortion or loss of taste and smell). Prior to intervention and at 1, 2, and 3 months after initiating zinc versus placebo, each subject completed a survey measuring degree of taste and smell dysfunction. The primary end points of the study were the difference in number of units between each subject's baseline score, and his/her highest score on the 0–100 scale over the 3-month period.

Each subject was dispensed a 3-month supply of zinc sulfate or placebo from the investigational pharmacy. The zinc dose was 220 mg orally twice daily (equivalent of 50 mg elemental zinc twice daily), a dose that has been used in prior randomized trials (7). The zinc used was a standard dietary supplement that can be obtained without a prescription and was provided by three manufacturers: Upsher-Smith, Major, and United Research Labs. In a previous randomized trial, oral zinc was not found to cause adverse effects (7). The matching placebo capsules, from Spectrum, contained lactose monohydrate powder and looked identical to the zinc capsules. Patient compliance was monitored by monthly pill counts.

Patients 18 years old currently receiving, or who had received, chemotherapy as part of their cancer treatment at the VCU Oncology Clinics were asked if they have had any loss or change in their sense of taste or smell since starting chemotherapy. Those answering “yes” were invited to participate in the study. There were no limitations regarding gender, type of chemotherapy, or type of cancer.

A standard questionnaire used to assess taste abnormalities was used, as in similar studies (8). A sample size of 50 was calculated to yield 85% power to detect a difference of >20 units (on the 0–100 scale) of improvement between the control and zinc groups (at 5% significance level). A repeated measures analysis of variance using proc mixed function in SAS (SAS, Cary, NC) was used to appropriately adjust for person-to-person variability.

RESULTS

Twenty-nine subjects were enrolled in each treatment group of whom 31 were white, 26 African American, and 1 was Native American. Forty-one patients were female. A wide range of cancer types was represented, with breast the most common (21 patients). Only seven patients currently smoked. Twenty-six patients used multiple vitamins and 14 patients were receiving or had received radiation therapy, including 2 to the head and neck.

Fifteen patients did not complete the study. Reasons for discontinuation included death (non-study related) (4), cancer treatment discontinued (4), toxicity (diarrhea, abdominal pain, cramps, diaphoresis) (2), pill burden (2), family member asked the patient to withdraw consent (1), and no reason given (2).

In the two study groups there was no statistically significant difference in loss of smell, distortion of smell, loss of taste, or distortion of taste. There was a trend toward improvement over time in all groups (Figures 1 and 2), except in the zinc group where there was a nonsignificant worsening in loss of smell over time.

Taste and smell changes were highly correlated ($P < .0001$). Types of chemotherapy were analyzed, with no significant findings, although this was confounded by the fact that many of the patients were given combination chemotherapy.

DISCUSSION AND CONCLUSIONS

This pilot study of zinc versus placebo for chemotherapy-related taste and smell changes revealed no significant difference between the use of oral zinc supplement and placebo. This is consistent with the failure of similar doses of zinc to prevent head and neck chemotherapy taste alterations compared to placebo (9). However, this conclusion is tempered because time appeared to be a major factor, with improvement in all symptoms with placebo or zinc, except for loss of smell. Interestingly, sense of smell diminished over time with the zinc supplement. This parallels one small randomized trial in which zinc helped minimally during treatment but was associated with earlier recovery after radiation (10)

There were several limitations to this study. One was that formal taste and smell testing were not performed. This may have limited assessment of sensory changes; however, patient report is considered the gold standard in clinical care. Also, patients received multiple other medications and had other factors such as mucositis and oral infections that may have influenced taste, as well as emotional factors. There was no way to evaluate the effect of individual chemotherapeutic agents as most were used in combination. The small sample size may have obscured very small changes in smell and taste.

There are also strengths to the study. We used patient-reported outcomes of taste and smell, which we believed to be reliable and valid, based upon our clinical experience with these patients. The zinc dose, 50 mg twice daily, was chosen based on doses used successfully in other entities for taste changes, but may have not been a strong enough dose to effect a change. Therefore, although the study was carefully done, it has probably not answered all the questions regarding zinc's place in the treatment of chemotherapy-induced taste and smell changes. Indeed, zinc treatment has been shown to be beneficial mainly in patients with zinc deficiency (5) which may not be a metabolic factor among these patients.

Loss of taste and smell affect quality of life, particularly in patients with cancer on chemotherapy. It is a symptom that is often eclipsed by others such as pain, nausea, and fatigue. It affects appetite, nutritional status, and enjoyment of life. Based on this study, however, zinc would not be a treatment of choice. Until we are able to identify another therapy, it appears that the best approach to alterations in taste and smell includes practical

measures such as keeping the mouth clean and choosing appealing foods, as well as tincture of time.

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FIGURE 1.
Loss of taste over time.

FIGURE 2.
Loss of smell over time.

TABLE 1

Comparison of age, gender, tobacco use, cancer type, and chemotherapy

Demographic	Zinc treatment group	Placebo group
Female 41	n = 20	n = 21
Mean Age: 53	55.2	50.86
Tobacco Use: 25	12	13
Cancer Type		
Acute Leukemia 2	0	2
Bladder 2	1	1
Breast 25	12	13
Cervix 1	0	1
Colon 3	1	2
Lung 10	4	6
Melanoma 1	0	1
Non Hodgkins Lymphoma 4	2	2
Pancreas 2	1	1
Prostate 5	4	1
Sarcoma 3	2	1
Chemotherapy (many patients received more than one medication)		
Actinomycin-D 1	0	1
Adriamycin 21	8	13
Bevacizumab 1	0	1
Capecitabine 1	1	0
Carboplatin 7	5	2
Cisplatin 5	3	2
Cyclophosphamide 21	8	13
Cytarabine 2	0	2
Docetaxel 7	6	1
Etoposide 5	3	2
5-Fluorouracil 4	2	2
Gemcitabine 5	3	2
Idarubicin 1	0	1
Ifosfamide 1	1	0
Interleukin-2 1	0	1
Irinotecan 1	1	0
Mitoxantrone 1	0	1
Navelbine 2	2	0
Oxaliplatin 1	1	0
Paclitaxel 10	5	5
Rituxumab 3	2	1
Trastuzumab 2	2	0
Vincristine 5	2	3