A Randomized, Controlled Clinical Trial to Evaluate the Effects of Zinc Sulfate on Cancer Patients with Taste Alterations Caused by Head and Neck Irradiation

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BACKGROUND. In uncontrolled clinical trials, the administration of oral zinc sulfate has been reported both to prevent and correct taste abnormalities in cancer patients receiving external radiotherapy (ERT) to the head and neck region.

METHODS. Eighteen patients were randomized to receive either zinc sulfate tablets (a dose of 45 mg) or placebo tablets three times a day at the onset of subjective perception of taste alterations during the course of ERT and up to 1 month after ERT termination. Taste acuity was determined by measuring detection and recognition thresholds for four taste qualities. Intolerance of zinc sulfate or placebo administration was investigated, and the oral cavity was examined. All the evaluations were studied prior to, at weekly intervals during, and 1 month after ERT administration.

RESULTS. Taste acuity for one or more taste qualities was already impaired before ERT. During ERT treatment, taste alterations were experienced at least once for a minimum of 3 of the 8 measured thresholds by 100% of the patients, and 33.3 % of the patients became aware of some alteration within the first week of treatment. The patients treated with placebo experienced a greater worsening of taste acuity during ERT treatment compared with those treated with zinc sulfate. One month after ERT was terminated, the patients receiving zinc sulfate had a quicker recovery of taste acuity than those receiving placebo. Statistically significant differences between the two groups emerged for urea detection and sodium chloride recognition thresholds during ERT treatment and for sodium chloride, saccharose, and hydrogen chloride recognition thresholds after the termination of ERT treatment.

CONCLUSIONS. This pharmacologic therapy is effective and well tolerated; it could become a routine in clinical practice to improve the supportive care of patients with taste alterations resulting from head and neck cancer. ***Cancer*** **1998;82:1938–45.** © *1998 American Cancer Society.*

KEYWORDS: head and neck cancer, taste alterations, radiotherapy, zinc sulfate administration.

A reduction in taste sensitivity (hypogeusia), an absence of taste sensation (ageusia), or a distortion of normal taste (dysgeusia) often occurs in patients receiving external beam radiotherapy (ERT) for cancers of the head and neck region.[1–5] In patients with head and neck cancer as well as those with malignancies at other sites, abnormal taste acuity for one or more taste qualities are often present even before the beginning of ERT[2,4,5] or chemotherapy.[6,7]

During a course of curative radiotherapy of 60–70 gray (Gy) over 6–8 weeks, taste function becomes measurably impaired by the first

week of treatment for urea[4] and becomes worse during the second week of treatment.[4,8,9] The greatest degree of compromise is reached during the third and fourth weeks of treatment and lasts throughout the entire radiation cycle.[2,4,5,10] Taste loss is not observed until radiation doses of 20 Gy have been administered to the head and neck regions.[11,12] In 50% of the patients, taste loss is reported to be exponential up to an accumulated dose of 30 Gy and involves all 4 tastes (sweet, sour, bitter, and salty).[1,2] However, for taste thresholds, the bitter and salty qualities show the earliest and greatest impairment and the sweet quality the least.[4,8,13] A dose of 60 Gy causes a relative taste loss in over 90% of patients.[11]

A partial improvement of taste is generally observed between the 20th and the 60th day after termination of radiotherapy, whereas a full recovery is generally achieved within 4 months after treatment,[2–4,9,13]and other authors have reported an increase in taste thresholds 1 year or more after ERT.[4,8,14,15]

In animal studies, taste changes may result from direct pathologic effects of radiation on taste buds, namely, a reduction in the number of buds and the number of cells per bud and damage to the microvilli of the taste cells.[4,11,16,17]

According to different authors, zinc plays an important role in taste perception.[18–22] Zinc deficiency has been linked to a diminished sense of taste in rats;[23] in humans who were made zinc deficient experimentally;[22,24] and in subjects with diseases such as chronic renal failure,[25,26] alcoholic cirrhosis,[27,28] and regional enteritis.[29] Administration of zinc to some patients with hypogeusia has normalized serum and parotid zinc levels, taste perception, and taste bud anatomy.[20,22,25,26,30] In clinical trials involving patients with taste dysfunction resulting from cancer, chronic kidney disease, or other pathologies, reduced taste acuity has been reversed in some patients by means of zinc administration.[19,20,22,25,26,31,32] Several patients who presented with idiopathic hypogeusia, dysgeusia, hyposmia, and dysosmia were empirically treated with zinc sulfate orally, and within a short time their symptoms diminished and their hypogeusia improved.[18] In uncontrolled clinical studies, the administration of zinc has been reported to correct abnormalities of taste in cancer patients who had received ERT to the head and neck region over 1 year previously.[4] Other authors have not noted improvement in taste acuity with zinc administration in patients with taste and smell dysfunction secondary to a variety of etiologic factors.[3,32,33]

We carried out a double blind, randomized study of 18 cancer patients who underwent ERT for head and neck cancers, with the main aim of evaluating the effects of zinc sulfate administration versus placebo in the management of taste alterations caused by radiotherapy.

PATIENTS AND METHODS

The study was carried out at the Radiotherapy Department and the Pain Therapy and Palliative Care Division of the National Cancer Institute of Milan between March 1995 and December 1996. All patients who were beginning ERT treatment for head and neck cancer for the first time were asked to enter the study.

Exclusion criteria were as follows: 1) demolitive surgery of the tongue, palate, or oropharynx; 2) the presence of oral lesions, such as stomatitis, ulcers, necrosis, or candidiasis; 3) complete or full upper dentures; 4) elimination of the olfactory component of taste after laryngectomy; 5) concomitant administration of chemotherapy and or any other kind of drug affecting taste;[21] 6) lesions of cranial nerves V, VII, IX, or X; 7) damage to the nervous system after surgery or cerebral lesions; 8) metabolic alterations or disorders; 9) endocrine or neurologic diseases known to influence taste and/or smell sensitivity;[34] 10) local disease in the nose or ears; and 11) lack of cooperation on the part of patients.

Of 38 patients who were to begin receiving ERT, 22 patients were eligible, of whom 18 gave their informed consent to participate in the study.

Study Design

The 18 patients enrolled were randomized to receive either elemental zinc sulfate in 45-mg tablets or placebo tablets 3 times daily after meals, starting from the onset of subjective perception of taste alterations (hypogeusia or dysgeusia) and continuing through ERT until 1 month after ERT termination.

Patients were assigned to zinc treatment or placebo alternatively after the random selection to give to the first patient.

The zinc sulfate (zinco solfato, IDI Farmaceutici, Pomezia, Rome, Italy) and placebo were given in tablet form and were indistinguishable, so that neither the patients nor the physicians (evaluator and prescriber) were aware of the assignment. Blood samples to estimate zinc concentration were taken, and the results were archived by a third doctor so that the results would be unknown to the other two doctors.

All patients were informed about the necessity of regular hygiene of the oral cavity, and the same alcohol free mouthwash for oral cleansing was prescribed for everyone.

Patients were also advised not to use any other kinds of oral rinses, such as anaesthetic rinses or anti-

TABLE 1
Solute Concentration Used for Taste Detection and Recognition Scoring

Taste quality	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	Sature
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

Normal ranges have been reported previously.
Detection thresholds/recognition thresholds:

NaCl	(1–4/1–4)
Saccharose	(1–4/1–4)
HCl	(1–4/2–4)
Urea	(2–4/2–4)

fungal rinses. When necessary, the physician prescribed such oral rinses, and the patient who received the prescription was suspended from the trial.

Taste Acuity Evaluation

Taste acuity was determined for each patient by measuring detection and recognition thresholds, which were obtained by a standard three-stimulus drop technique for four taste qualities (salty, sweet, sour, and bitter). We report herein the methodology used in our study, which was previously described by Mossman and Henkin.[4] The technique involved introducing three drops in sequence into the oral cavity; two of these were water and one was a solute dissolved in water. The solutes were sodium chloride (NaCl, for salt), saccharose (for sweet), hydrogen chloride (HCl, for sour), and urea (for bitter). For each basic taste we used 11 odorless solutions at progressively increased concentrations (expressed in mmol/L), as described in Table 1. The detection and recognition thresholds for each taste quality were scored according to decreasing taste acuity on a scale of 1–11. The normative values we used were previously published by other authors[4,18,35](Table 1).

For threshold determination, the subject was required to taste each drop in the entire oral cavity and make two responses: 1) which of the three drops tasted different from the others, and 2) what the characteristic taste of the dissimilar drop was, i.e., whether the drop was salty, sweet, sour, or bitter. The lowest concentration of solute that the subject distinguished as being different from water was called the detection threshold. The lowest concentration of solute that the subject recognized as salty, sweet, sour, or bitter was called the recognition threshold.

Thresholds were determined for each taste quality before preceding to the next one. Taste acuity evaluations were performed prior to, at weekly intervals during, and 1 month after ERT in both groups under study.

Other Variables Assessed

Contemporaneously with the above-mentioned taste evaluations, we collected blood samples for zinc quantification. By means of a Likert scale (''no,'' ''a little,'' ''much,'' and ''very much''), the following symptoms were assessed: anorexia, dry mouth, pain, nausea, vomiting, and dysphagia. At the same time, we examined the oral cavity to evaluate the presence or absence of stomatitis, ulcers, candidiasis, and necrosis, and the weight of the patient was also taken.

The patient was also asked to report any unwanted symptoms or discomfort related to our prescribed drug (zinc sulfate or placebo).

The following data were collected for each patient: gender, age, type and site of tumor, tobacco and/or alcohol use (before, during, and after treatment), total ERT dose and fractioning, radiation fields, type and duration of ERT, and whether the patient had previously received chemotherapy.

Statistical Analysis

The Wilcoxon–Mann–Whitney two-tailed rank sum exact test was used to compare the following clinical characteristics of the two groups of patients (receiving zinc sulfate or placebo): side effects of ERT (candidiasis, dry mouth, dysgeusia, pain, nausea, vomiting, and dysphagia), measured as the maximum worsening with respect to basal time; total dose of ERT; age; percentage of weight loss at the end of ERT and 1 month after ERT; and zinc blood concentration at basal evaluation and at the onset of zinc sulfate or placebo treatment. Fisher's two-tailed exact test was used to compare the two groups with regard to gender, previous

chemotherapy treatment, and smoking and/or alcohol use.

The assessment was divided into two periods: during ERT and after ERT. For the ''during ERT'' period, the data were summarized by calculating, for each taste quality and for both detection and recognition thresholds, the area under the curve (AUC) of the differences found in each assessment and basal time evaluation[36] starting from the administration of zinc or placebo, and then standardizing by the duration in days of the assessment period (excluding the periods when the assessment was not performed). This summary measure could be interpreted as the mean daily variation with respect to basal time. For the ''after ERT'' period, the differences from the time of basal assessment to 1 month after ERT was calculated for each taste quality (detection/recognition thresholds).

For both kinds of syntheses (AUCs and final differences), the negative scores indicated an improvement and the positive scores a worsening; thus, the higher the score, the greater the worsening. These two different synthesis variables were considered response variables in evaluating the efficacy of zinc sulfate treatment versus placebo.

A description of the taste variables was given in terms of the median for the basal evaluation, for the AUC of the treatment period, and for the posttreatment difference by group of treatment.

The Wilcoxon–Mann–Whitney rank sum one-tailed exact test was used to compare the placebo group with the zinc sulfate group regarding the two response variables for each of the four tastes.

Patients with missing data on one variable were excluded from the analysis involving that variable. A P value of <0.05 was considered significant.

RESULTS

The patients' characteristics are described in Table 2. The tests carried out showed that there was no statistically significant difference between the two groups when the clinical and demographic variables were taken into consideration. Throughout the trial period, the use of alcohol and tobacco had not changed with the respect to values determined prior to treatment. All the patients had low serum zinc levels prior to ERT, as compared with the range for laboratory norms. All the patients were treated with daily fractions of 180–200 cGy lasting from 5 to 9 weeks, for a total dose of 45–70 Gy. The radiation fields were the same for all patients, and the tongue was always included.

Patient 11 stopped receiving ERT at the fourth week due to acute oral cavity toxicity (World Health Organization Grade 4); thus, an assessment at 1 month after ERT termination was not made.

None of the other patients developed oral cavity lesions during ERT. 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.

Before receiving ERT, 15 patients (88.9%) had already experienced a reduction in taste acuity in at least 1 of the detection or recognition thresholds for at least 1 of the 4 taste qualities, whereas 66.7% of the patients had 4 taste qualities compromised (in both detection and recognition thresholds).

Figure 1 shows the median thresholds of the four taste variables at the time of basal evaluation of the two treatment groups. It may be observed that, prior to ERT, although the detection thresholds of the placebo group were slightly higher than those of the zinc sulfate group, they were within normal limits (Table 1), with the exception of urea, which was slightly elevated compared with the norm. The median recognition thresholds for NaCl, urea, and HCl were higher than the norm for both groups, whereas the median recognition threshold for saccharose was within normal limits. We tested the hypothesis of differences between the two groups regarding these variables and found no significant differences.

Having considered the moment of subjective worsening of taste acuity reported by the patient to be the moment to start zinc sulfate or placebo treatment, we observed that after 1 week of ERT, 55% of the placebo group versus 11% of the zinc sulfate group had already begun their respective prescribed treatment. During the second week of ERT, taste alteration awareness rose to 77% for the placebo group and 66% for the zinc sulfate group, and then to 100% at the fourth week for both groups.

During ERT, taste alterations occurred at least once for a minimum of 3 of the 8 measured thresholds in 100% of the patients under study, and 33.3% of them became aware of some alteration within the first week of treatment.

Figure 2 shows that the median values, relative to AUC, of the differences from the time of basal assessment were higher for the placebo group than for the zinc sulfate group for both the detection thresholds and the recognition thresholds of all four taste variables (with the exception of the NaCl detection threshold, which was the same for both groups). This shows that, during ERT, the worsening of taste acuity in the placebo group was greater than in the zinc sulfate group.

The same trend was observed regarding the results of the final differences 1 month after ERT (Fig. 3). Patients in the zinc sulfate group had quicker recovery of taste acuity than the those in the placebo group

TABLE 2
Characteristics of Patients

	Zinc sulfate		Placebo		Total	
Characteristics	**No.**	**%**	**No.**	**%**	**No.**	**%**
Gender						
Male	6	67	8	89	14	78
Female	3	33	1	11	4	22
Age (yrs)						
Mean (SD)	55.5 (14.39)		60.3 (11.3)		57.9 (12.81)	
Primary tumor						
Maxillae sarcoma	1		1		2	
Rhinopharynx	2		1		3	
Tonsil	1		1		2	
Tongue	1		3		4	
Hypopharynx	1		1		2	
Non-Hodgkin's lymphoma	1		0		1	
Oropharynx	2		1		3	
Salivary gland	0		1		1	
Previous chemotherapy						
Yes	1	11	1	11	2	11
Cigarettes						
Yes	3	33	2	22	5	27
Alcohol						
Yes	4	44	4	44	8	44
ERT						
LINAC	6		5		11	
Cobalt-60	3		4		7	
Total mean ERT dose (SD)	63.5 (9.8)		61.1 (8.8)		62.3 (9.13)	
ERT duration (wks) (SD)	7.6 (1.22)		7.11 (1.3)		7.38 (1.28)	
Mean basal blood zinc concentration (μg/%) (SD)	78.8 (9.96)		78.1 (14.5)		78.5 (12.2)	
Mean blood zinc concentration at the beginning of zinc sulfate–placebo treatment (μg/%) (SD)	73.3 (9.0)		75.7 (12.4)		74.5 (10.6)	
% of weight loss at end of ERT	6.49 (4.58)		3.8 (1.8)		5.14 (3.6)	
% of weight loss 1 mo after ERT (SD)	6.14 (4; 4)		4.39 (1.7)		5.27 (3.38)	

SD: standard deviation; ERT: external radiotherapy; LINAC: linear accelerator 6 MV.

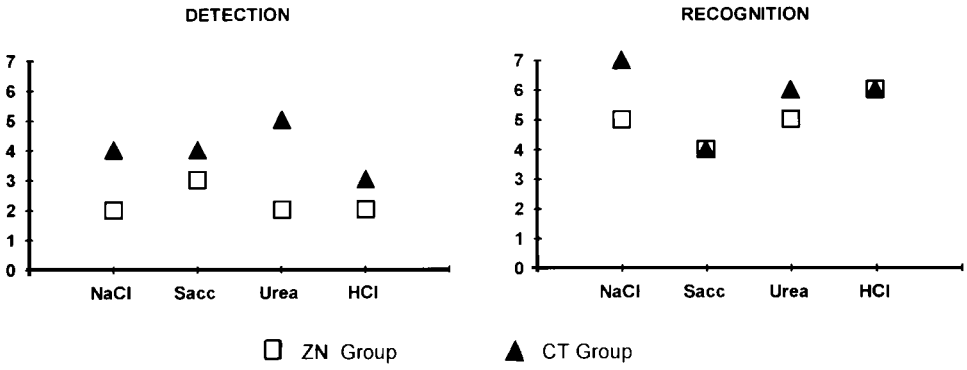

FIGURE 1. Median detection and recognition thresholds at basal evaluation (before external radiotherapy) are shown by treatment group. ZN: zinc sulfate; CT: placebo.

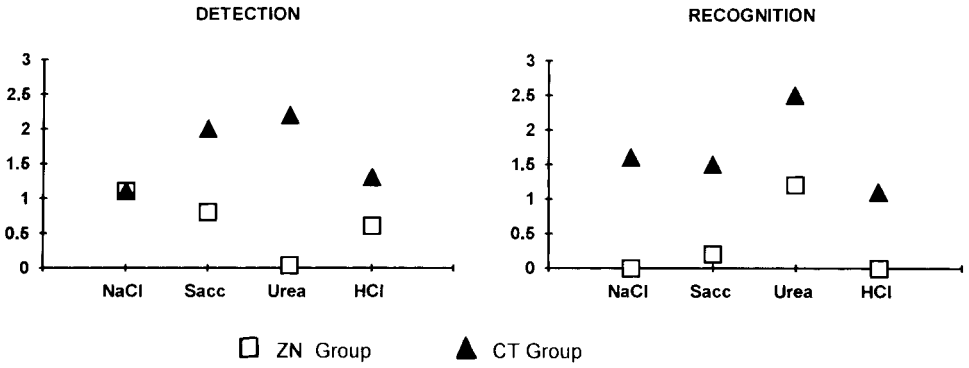

FIGURE 2. Median areas under the curves (AUCs) are shown for detection and recognition thresholds during external radiotherapy by treatment group. The negative scores indicate an improvement and the positive scores a worsening. ZN: zinc sulfate; CT: placebo.

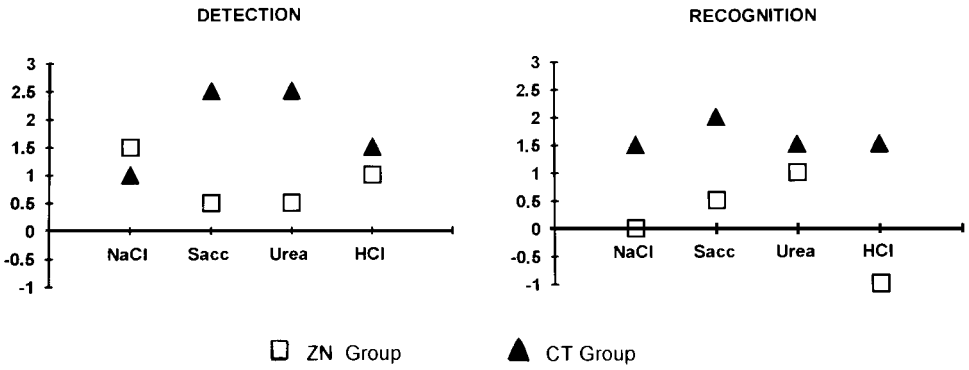

FIGURE 3. Median differences in detection and recognition thresholds, from the time of basal evaluation to 1 month after the end of external radiotherapy, are shown by treatment group. The negative scores indicate an improvement and the positive scores a worsening. ZN: zinc sulfate; CT: placebo.

(with the exception of the NaCl detection threshold), up to total recovery of taste acuity with respect to basal time and the NaCl recognition threshold, and even an improvement in the HCl recognition threshold.

Table 3 shows the results of the analyses carried out to test the differences in taste acuity loss between the two groups. Statistically significant results emerged in urea detection and NaCl recognition thresholds during ERT as well as in NaCl, saccharose, and HCl recognition thresholds at the end of ERT.

There was no statistically significant difference in weight loss between the two groups either at the end of ERT or 1 month after ERT.

No relevant gastrointestinal side effects due to zinc sulfate or placebo treatment were reported by the patients; thus, no patient required suspension of treatment.

DISCUSSION

In results that agreed with the literature,[2,4,5] we found that taste acuity was already impaired for one or more taste qualities before ERT in 88.9% and 66.7% of patients with head and neck cancers, respectively, and that 100% of them experienced taste alterations during ERT administered to those sites. In our study, at the time of basal assessment, the placebo group already showed a more compromised taste acuity compared with the zinc sulfate group, although this difference was not statistically significant. However, this compromise had no bearing on the results, considering that the analysis took into account the difference from the time of basal assessment for each evaluation.

Both our data and other data in the literature[4] suggest that patients who experience hypogeusia or dysgeusia before ERT is begun are subjectively unaware of any taste alteration, probably because changes in taste acuity occur gradually. It appears that after ERT is begun there is probably a more rapid worsening in taste acuity; thus, patients become aware of it.

Studies of Henkin et al.[18,20,37] have shown that heavy metals, such as zinc, are involved in the physiology of taste function. Although the specific role of zinc in the control of taste or smell is unknown, it is functionally involved at several levels of cellular organization. At the receptor level, in the taste bud, zinc is a cofactor in alkaline phosphatase, the most abundant enzyme isolated from the taste bud membrane.[38] The cells of the taste buds have microvilli that are in direct communication with the oral cavity through an apical pore. A protein (gatekeeper) regulates the diameter and permeability of the pore

TABLE 3
Analysis of Significance of the Differences in Taste Loss Between the Zinc Sulfate Group and the Placebo Group

	P values[a]	
	During ERT (18 patients)	After ERT (17 patients)
NaCl[b]	0.362	0.0441
Saccharose[b]	0.092	0.082
Urea[b]	0.015[d]	0.053
HCl[b]	0.092	0.117
NaCl[c]	0.001[d]	0.0241[d]
Saccharose[c]	0.060	0.019[d]
Urea[c]	0.055	0.192
HCl[c]	0.085	0.028[d]

ERT: external radiotherapy.
[a] *P* values were determined by the Kruskal–Wallis exact test.
[b] Detection threshold.
[c] Recognition threshold.
[d] Values were statistically significant.

and its membrane, which in turn control the quantity of stimuli that pass through the pore per unit of time. Conformational changes in these protein molecules are controlled by the equilibrium of metals; consequently, a deficiency of some metals, zinc in particular, is reported to be associated with hypogeusia.[22,39–41]

The results of our study regarding the efficacy of zinc sulfate in preventing and/or reducing the intensity of ERT-induced taste alterations are in agreement with the results obtained in other uncontrolled and controlled clinical trials.[18–20,22,25,26,31–33]

Henkin[3] studied several patients who developed hypogeusia after ERT of different intensities was administered to several organs. The patients treated with 25 mg of oral zinc sulfate 4 times daily had partial or complete recovery of their taste acuity. Other patients who were prophylactically treated with zinc ion before ERT was begun developed less severe hypogeusia than did those who underwent ERT without zinc treatment.

Henkin et al.[37] and Schechter et al.[42] described a single blind trial in which the patients who failed to respond to placebo experienced significant improvement of their hypogeusia during zinc therapy. In a sample of these patients, withdrawal of zinc after hypogeusia improvement was followed by a worsening of hypogeusia and a reduction of serum zinc concentration toward lower, pretreatment levels.

In a randomized double blind clinical trial of 19 patients who underwent ERT for head and neck cancer, Silverman et al.[33] found that the daily administration of 72 mg of elemental zinc did not preserve or enhance taste (evaluated both subjectively and by the Elgustometer) at the end of treatment; however, a rapid improvement of taste perception was observed in 64% of patients treated with zinc as opposed to only 22% of the placebo group. No positive correlation was observed between weight maintenance and taste. Dysgeusia was not related to serum zinc levels or elgustometer readings even when these patients had low serum zinc levels prior to ERT as compared with the range of laboratory norms. Other authors have demonstrated associations between taste alterations and low serum zinc levels.[3,43]

In our study, there was no statistically significant difference in weight loss between the zinc sulfate group and the placebo group either at the time of ERT termination or 1 month after ERT. However, 6.5% of the patients in the zinc sulfate group lost weight, compared with only 3.8% of the patients in the placebo group. There did not appear to be any relation between the worsening of taste acuity and weight loss; this was in agreement with the results of Silverman et al.[33] but in disagreement with the results of Bolze et al.[10]

Our study was performed on a small sample group, the size of which was restricted for two reasons. First, the study required the commitment of both doctors and patients, and the frequent, rigorous objective assessments of taste acuity required substantial time. Furthermore, the strict exclusion criteria made the enrollment of patients very difficult.

If the sample had been larger, the power of the test to detect statistically significant differences between the two groups would have been improved. It should be pointed out that the data were analyzed in a proper way, providing the exact t-values that were specifically devised to evaluate small sample data, as opposed to asymptotic ones, which are valid only with larger numbers of patients.

As we found that zinc sulfate administration slowed down the worsening and accelerated the improvement of taste acuity in a clinically and statistically relevant way for some of the taste qualities (Figs. 2, 3 and Table 3), it is our opinion that zinc sulfate is a useful treatment; in addition, patients tolerate this treatment well.

Thus, a more careful evaluation of the subjective perception of taste alterations before, during, and after ERT by patients head and neck cancers should be carried out with immediate zinc sulfate administration. This clinical practice could become routine and improve supportive care, reducing the complications of specific oncologic therapies and consequently reducing patients' discomfort.

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