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CLINICAL INVESTIGATION **Head and Neck**

ZINC SULFATE IN THE PREVENTION OF RADIATION-INDUCED OROPHARYNGEAL MUCOSITIS: A PROSPECTIVE, PLACEBO-CONTROLLED, RANDOMIZED STUDY

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Purpose: To determine the effect of oral zinc sulphate supplementation on radiation-induced oropharyngeal mucositis in patients with head-and-neck cancer.

Materials and Methods: Thirty patients with head-and-neck cancer were randomly assigned to receive either zinc sulfate or placebo. Primary tumors were localized in the larynx in 14 patients, in the nasopharynx in 4, in the oral cavity in 4, in a salivary gland in 1, in the maxillary sinus in 1, in neck nodes (lymphoma presenting primarily) in 3 and in neck metastases from an unknown primary in 3. In the placebo group, 3 patients were excluded; 1 patient died during treatment, 1 left the study, and 1 did not come to the 6 week control visit. The patients were treated with telecobalt radiotherapy at conventional fractionation (2 Gy/fraction, five fractions weekly, for 20–35 fractions within 4–7 weeks). The median radiation dose was 6400 cGy (4000–7000 cGy). Oral mucositis was assessed by two independent physicians, experts in radiation oncology, using the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring criteria.

Results: In the zinc sulfate group, Grade 3–4 mucositis was not detected in any patient; Grade 0 mucositis was detected in 2, and Grade 1 in 8, and Grade 2 in 5 patients. In the placebo group, Grade 2 mucositis was detected in 4 and Grade 3 in 8 patients. We observed that the degree of mucositis in the patients in the zinc sulfate group was significantly lower than that in the placebo group ($p < 0.05$). Confluent mucositis developed earlier in the placebo group than in the zinc sulfate group after the onset of treatment ($p < 0.05$) and started to improve sooner in the zinc sulfate group than in the placebo group ($p < 0.05$).

Conclusions: Zinc sulfate is beneficial in decreasing the severity of radiation-induced mucositis and oral discomfort. These results should be confirmed by additional evaluation in randomized studies with a larger number of patients.

Mucositis, Radiotherapy, Zinc sulfate, Head-and-neck cancer.

INTRODUCTION

In recent years, more head-and-neck cancer patients have been treated with radiotherapy (RT) Because most of them are surviving, an increasing need for oral care has resulted (1). A number of biochemical complications, such as damage to cellular DNA and membrane structures, and alterations in the immune system, arise as a result of radiation treatment (2).

In patients receiving RT for head-and-neck malignancies, oral mucositis is a frequent complication (3, 4), and it is the major dose-limiting side effect (5, 6). During conventional RT (2 Gy/d and 10 Gy/wk), a mucosal reaction starts in the second week (4, 7, 8). Oral mucositis is thought to be a complex biologic process involving direct damage to the divided cells of the oral epithelium, with depletion of the basal epithelium, modulated by the immune system, inflammatory process, and superinfection by oral bacterial flora (5). It is divided into four phases: the inflammatory phase, epithelial phase, ulcerative/bacteriologic phase, and healing phase (9–11).

Mucositis can be intensely painful, can have substantial effects such as by limiting food intake, and may be a potential portal for infection (12). Thus, mucositis may lead to delays in administration or dosage limitations in antineoplastic treatments, increased hospitalization, and increased cost (13). It may have an adverse effect on the radiocurability of cancer (14) and patient survival (5).

All patients develop some degree of oral mucositis, the severity of which is variable and is influenced by both patient- and treatment-related factors. It is estimated that approximately 60% of patients receiving standard RT and >90% of those receiving experimental modalities (i.e., combined chemotherapy and RT, altered fractionations) will develop severe oral mucositis (5).

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A number of agents with different activation mechanisms have been used in the prevention and treatment of mucositis induced by anticancer therapies (15). These have been only supportive, consisting of measures to alleviate pain and provide adequate hydration and eliminate secondary infections (5). A number of locally, systemically applied agents and new, unproved agents have been investigated to prevent or treat mucositis. These include antibiotics, disinfectants (chlorhexidine, hydrogen peroxide, selective decontamination, multiagent topical mouth rinses), anti inflammatory agents (benzydamine, chamomila, glucocorticosteroids), cytokines (granulocyte-colony-stimulating factor, granulocyte macrophage colony-stimulating factor [GM-CSF], interleukin-II, transforming growth factor-β keratinocyte growth factor), mouth-coating agents (sucralfate), vitamins (vitamin A and E), prostaglandins (PGE-1, PGE-2), anticholinergic agents (propantheline), antioxidants (azelastine, β-carotene), antiviral agents (acyclovir), immunomodulatory agents (immunoglobulin, indomethacin, pentoxifylline), amino acids (glutamine), angiogenesis inhibitors (thalidomite), cytoprotectors (amifostine), hormones (melatonin), and other modalities (cryotherapy, soft laser) (9).

Unfortunately, at present, no widely accepted prophylaxis or effective treatment is available for mucositis, which has been of interest to scientists for 20 years (9, 16).

During the past 30 years, many researchers have demonstrated the critical role of zinc, a Group IIb metal, in diverse physiologic processes, such as growth and development, maintenance and priming of the immune system, and tissue repair (17). A number of studies have shown zinc to be the catalytic component of >300 enzymes (18–21), the structural constituent of many proteins, and the regulatory ion for the stability of proteins and in preventing free radical formation. Therefore, zinc is a pivotal element in ensuring the functioning of various tissues and organs, including the immune response (18, 21).

Physiologically bioavailable zinc has been identified as a nutrient essential for normal growth, sexual development, wound healing, fighting infections, sense of taste, night vision, healthy epithelial tissue, cell-mediated immunity, and other vital functions (22).

Studies have shown that in Turkey the daily dietary intake of zinc has been, in general, below the recommended daily allowance value (23–26), and a reduction has been demonstrated in the mean plasma and serum zinc levels of head-and-neck cancer patients compared with normal controls (27–30). Zinc deficiency has been also reported in patients with a number of malignancies (27, 31–34).

Abundant evidence has demonstrated the antioxidant role of zinc (22, 35–37). Two mechanisms have been elucidated: the protection of sulfhydryl groups against oxidation, and the inhibition of the production of reactive oxygens by transition metals (36, 37).

Zinc ions may induce the synthesis of metallothionein (MT), because sulfhydryl-rich proteins are protective against free radicals (36). MTs play pivotal roles in metal-related cell homeostasis because of their high affinity for metals, in particular zinc. Twenty cysteine amino acids are in reduced form and bind seven zinc atoms through mercaptide bonds forming metal thiolate clusters. Moreover, MTs are antioxidant agents because the zinc-sulphur cluster is sensitive to changes in the cellular redox state, and oxidizing sites induce the transfer of zinc from its binding sites in MTs to those of lower affinity in other proteins, as it occurs for superoxide dismutase activation. Thereby, the redox properties of MTs are crucial for their protective roles against the cytotoxic effect of reactive oxygen species, ionizing radiation, electrophilic anticancer drug and mutagens, and metals. MT is an excellent scavenger of the hydroxyl radical. Iron and copper ions catalyze the production of hydroxyl radicals from H_2O_2, and zinc is known to compete with both iron and copper for binding to cell membranes, thus decreasing the production of hydroxyl radicals (18, 19).

A major biochemical function of zinc includes the maintenance of membrane structure and function. Zinc also has a special role in skin and connective tissue metabolism and in wound healing (21, 22, 35, 36, 38). Zinc plays a part in the maintenance of epithelial and tissue integrity by promoting cell growth and suppressing apoptosis and by its underappreciated role as an antioxidant protecting against free radical damage during inflammatory responses. Thus, in the case of diarrhea, the multiple functions of zinc may help to maintain the integrity of the gut mucosa to reduce or prevent fluid loss (38).

Currently, there is no doubt that zinc is an essential trace element for the immune system (39). A slightly decreased zinc status may first influence the immune system, owing to an increased number of infections (19, 39). Several data support the view that the impact of zinc on immunocompetence is greater in cell-mediated immunity than in humoral (21). In particularly, chemotaxis by neutrophils and monocytes, thymic endocrine activity, antigen presentation by MHC class II molecules, natural killer activity, cytokine production, and TH1/TH2 balance are the immune functions affected the most by zinc, as well as TH3 cells (18, 19, 21, 39, 40).

Zinc is present in the cell nucleus, nucleolus, and chromosomes, and zinc stabilizes the structure of DNA, RNA, and ribosome. Numerous enzymes associated with DNA and RNA synthesis are also zinc metalloenzymes, including RNA polymerase, reverse transcriptases, and transcription factor IIIA (41). The chromosome breaks might be due to increased oxidative damage, perhaps owing to loss of activity of Cu/Zn superoxide dismutase or the DNA-repair enzyme containing zinc (20).

Zinc acts as a signalling substance akin to conventional neurotransmitters in normal physiology (42, 43).

The benefit of zinc supplementation has been clearly illustrated in several randomized controlled trials (44–53). Excess oral ingestion of zinc to the point of toxicity (100–300 mg/d) is rare. Zinc sulfate in amounts of 712 g/d can cause GI irritation and vomiting (54).

From all these investigations, we have determined that zinc acts as an antioxidant, an organelle stabilizer, and a

stabilizer of the structure of DNA, RNA, and ribosome and is an important cofactor for DNA synthesis, a vital component for wound healing, an essential trace element for the immune system, and an anti-inflammatory agent. Therefore, we decided to use zinc sulfate in the prevention of radiation-induced mucositis.

METHODS AND MATERIALS

Study design

This was a prospective, randomized, placebo-controlled study in which patients were randomly assigned to receive either zinc sulfate or placebo during RT.

Choice of patients

Thirty adult patients (>18 years of age) with histologically proven cancer of the head and neck (Karnofsky's performance status ≥70) who were to receive curative RT or chemoradiotherapy were eligible for the study. The criteria for exclusion were as follows: previous history of autoimmune or chronic inflammatory disease, RT and cytotoxic chemotherapy had previously been administered, use of medicine with the aim of mucositis prophylaxis, less than one-third of buccal mucosa was in the RT region, and patient refused entry.

Patient characteristics

Between May 2001 and May 2002, in the Department of Radiotherapy, Atatürk University, 30 patients (24 men and 6 women; median age 54 years, range 18–71) were selected randomly to receive either zinc sulfate or placebo capsules three times daily. The local ethics committee approved the study protocol before patients were entered. All patients provided written informed consent after receiving information about the study before treatment was assigned. Primary tumors were localized in the larynx in 14, in the nasopharynx in 4, in the oral cavity in 4, in a salivary gland in 1, in the maxillary sinus in 1, in neck nodes (lymphoma presenting primarily) in 3, and in neck metastases from an unknown primary in 3 patients. In the zinc sulfate group, 13 patients were men, and 2 were women (median age 53 years, range 36–69). Primary tumors were localized in the larynx in 6 patients, in the nasopharynx in 3, in the oral cavity in 3, in neck nodes (lymphoma presenting primarily) in 2, and neck metastases from an unknown primary in 1 patient. In the placebo group, 11 were men and 4 were women (median age 59 years, range 18–71). However, 3 patients were excluded; 1 patient died during treatment, 1 left the study, and 1 did not come to the 6 week control visit. Primary tumors were localized in the larynx in 5 patients, in the nasopharynx in 1, in the oral cavity in 1, in a salivary gland in 1, in the maxillary sinus in 1, in neck nodes (lymphoma presenting primarily) in 1, and neck metastases from an unknown primary in 2 patients (Table 1).

Table 1. Patient characteristics

Variable	Zinc sulfate group	Placebo group
Gender (*n*)		
Male	13	8
Female	2	4
Age (y)		
Range	36–69	18–71
Median	53	59
Tumor site (*n*)		
Larynx	6	5
Nasopharynx	3	1
Oral cavity	3	1
Primary lymphoma in neck ganglion	2	1
Primary unknown, neck metastases	1	2
Salivary glands		1
Maxillary sinus		1
Surgery before radiotherapy (*n*)		
Yes	11	8
No	4	4
Concurrent chemoradiotherapy (*n*)		
Yes	3	3
No	12	9
Radiotherapy dose (cGy)		
Range	4000–7000	4000–6800
Median	6600	6200

Oral hygiene and clinical and laboratory evaluations

Before treatment, each patient was informed about oral hygiene during RT. The rules to be obeyed during RT were given orally, in writing and, throughout treatment, they were given by means of controls, i.e., at every mucositical examination we reminded our patients to obey oral hygiene rules. These regulations were as follows: to drink water, to brush the teeth with a soft brush after each meal and with mouth jellies including fluoride, to avoid alcoholic drinks, to not smoke cigarettes, to not drink liquids that were too hot or too cold, to not eat excessive spiced or sour foods, and to not eat hard foods.

All the patients were examined by an experienced dentist before RT, and necessary interventions and suggestions were made. RT was not launched until exact improvement could be obtained.

Oral mucositis was assessed by two independent radiation oncology doctors using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring criteria before treatment, once a week during treatment, after treatment, and 6 weeks after treatment. The break time of treatment was noted. The exact blood count, liver and renal functions tests, biochemical tests, and measurement of body weight were done before treatment, every week during RT, the first day after RT, and 6 weeks after treatment.

Radiotherapy

Twenty-two patients had undergone surgery before RT, and 8 patients were treated with RT only. The patients were

treated with telecobalt RT (Picker C-9) at 80 cm SSD using conventional fractionation of 2 Gy/fraction, five fractions weekly for 20–35 fractions within 4–7 weeks. According to tumor stage, localization, and histologic type, the treatment portals consisted of two lateral parallel opposing fields for the primary tumor and upper cervical lymph nodes and/or an anterior portal field for the lower cervical lymph nodes and supraclavicular lymph nodes. Immobilization with a thermoplastic mask was established for all patients, and individual lead protective blocks were used. During RT, the indication for treatment interruption owing to mucositis was determined independently by two doctors working in the radiation oncology clinic.

The median radiation dose was 6400 cGy (range 4000–7000). In the zinc sulfate group, the median radiation dose was 6600 cGy (range 4000–7000), and in the placebo group, it was 6200 cGy (range 4000–6800). Three patients in the zinc sulfate group and three in the placebo group were administered concomitant chemoradiotherapy (Table 1).

Drug therapy

Zinc sulfate (containing 50 mg zinc; Zinco 220 capsule, Berko Ilaç Istanbul) and placebo capsules were administered randomly to the patients included in the study. The placebos were empty capsules bought from the same medicine firm to be identical to the zinc sulfate capsules. The patients were instructed to take the capsules three times daily at 8-hour intervals. The patients began taking the medicine the first day of RT. The patients continued taking the capsules during RT and for 6 weeks after treatment, including weekends and other times when interruption of RT was necessary. In addition to the capsules, local anesthetic solutions and analgesic agents were given to patients developing pain from mucositis.

Statistical analysis

In this study, we planned to evaluate the duration, severity, and onset of oropharyngeal mucositis according to the dose of RT in 27 patients chosen randomly. After the necessary data had been collected, statistical analysis was done using the Statistical Package for Social Sciences, version 10.0. The Mann-Whitney *U* test and Fisher's exact chi-square test were used to compare the mean values of the data between the zinc sulfate and placebo groups. To make measurement analysis of more than two, the Friedman variation analysis was used. $p < 0.05$ was accepted as statistically significant.

RESULTS

In the placebo group, 3 patients were excluded from analysis: 1 patient who died during treatment, 1 who withdrew from the study, and 1 who did not attend the 6-week control visit after treatment. The total evaluation was done for 27 patients.

Mucositis developed in 13 of 15 patients in the zinc sulfate group, but did not develop in 2 patients. Grade 1 mucositis was found in 8 patients and Grade 2 in 5 patients. Mucositis Grade 3 and 4 did not develop in any of the zinc sulfate group of patients. The dose of RT for the patients in whom mucositis developed in the zinc sulfate group was 3600 cGy (range 2400–4400).

Varying degrees of mucositis developed in the 12 patients in the placebo group: Grade 2 mucositis in 4 patients and Grade 3 in 8 patients. Grade 4 mucositis did not occur in any of the placebo group. The median RT dose was 2000 cGy (range 1800–2800).

In the analysis carried out between the zinc and placebo groups, a statistically significant difference was found in the week mucositis developed, in the severity of mucositis, and in the RT dose at which mucositis developed (Table 2).

In the first clinical evaluation 6 weeks after treatment, mucositis was found in only one of the patients in the zinc sulfate group compared with 10 patients in the placebo group. The distinction between the two groups was statistically significant (Fisher's exact chi-square test 16.2, $p < 0.01$; Table 3).

The mucositis began to appear in the second week at 1800 cGy. At the start of the third week and in the middle of the fourth week, it peaked and then began to lower. After 2400 cGy, the difference in the mucositis scores between the zinc and placebo groups was statistically significant and continued to be until 6 weeks after treatment.

No RT was interrupted or terminated because of mucositis. Nonsteroidal anti-inflammatory and analgesic medication was administered to 1 patient with Grade 2 mucositis in the zinc group and 4 patients with Grade 2 mucositis in the placebo group. No statistically significant difference was found between the two groups in the measurement of body

Table 2. Correlation between mucositis starting week and severity

Group	Start of mucositis (wk)	Severity of mucositis (Grade)	RT dose at which mucositis developed (cGy)
Zinc sulfate ($n = 15$)	3 (0–5)	1 (0–2)	3600 (2400–4400)
Placebo ($n = 12$)	2 (2–3)	3 (2–3)	2000 (1800–2800)
Both ($n = 27$)	3 (0–5)	2 (0–3)	2800 (1800–4400)
p	$p < 0.05$	$p < 0.05$	$p < 0.01$

Abbreviation: RT = radiotherapy.
Numbers in parentheses are the range.

Table 3. Mucositis situation 6 weeks after radiotherapy

Group	Presence (n)	Absent (n)	Total (n)
Zinc sulfate	1 (6.7)	14 (93.3)	15 (100)
Placebo	10 (83.3)	2 (16.7)	12 (100)
Total	11 (40.7)	16 (59.3)	27 (100)

Fisher Exact χ^2 test 16.2, $p < 0.01$.
Numbers in parentheses are percentages.

weight carried out weekly. When both groups were evaluated individually, weight loss increased as the week of RT advanced (Friedman chi-square test 40.42 $p < 0.001$). Although the difference in body weight measured before RT and the first day after RT was statistically significant, this distinction disappeared between the baseline and 6-week post-RT measurement. RTOG Grade 3 vomiting and nausea developed in 3 patients in the zinc sulfate group. No pathologic findings were detected in the exact blood count, liver function tests, kidney function tests, and biochemical tests made weekly.

DISCUSSION

During conventional RT (2 Gy/d and 10 Gy/wk), the mucosal reaction starts in the second week. The reaction progresses to focal mucositis by Week 3, and confluent forms are seen from the end of the third week of RT (4, 7, 8).

In our study, in the placebo group, the median RT dose at the onset of mucositis was 2000 cGy (range 1800–2800). This result is comparable with that in the literature. The RT dose at the onset of mucositis in the zinc sulfate group was 3600 cGy (range 2400–4400). Mucositis began to appear in the second week at 1800 cGy. At the start of the third week and in the middle of fourth, it peaked and than began to lower. After 2400 cGy, the difference in the mucositis scores between the zinc and placebo groups was statistically significant and continued to be until 6 weeks after treatment (Table 2). No statistically significant differences in the RT dose were detected between the two groups.

No data are available about the use of zinc sulfate for oropharyngeal mucositis in the literature. However, agents with similar biologic activities (antioxidants maintainers of epithelial and tissue integrity, stabilizers of membrane structure and function, anti-inflammatory agents that enhance immunity, and wound-healing agents) have been used in the prevention or treatment of mucositis.

Ediz *et al.* (55), in their prospective, randomized, double-blind, placebo-controlled study, determined that the complications of mucositis in the sucralfate group in the first week were lower than in the placebo group. This distinction continued throughout the first month after treatment and was absent after the first month after treatment. They did not find any difference between the groups in the the number of days treatment was interrupted because of mucositis. Their findings demonstrated that sucralfate was effective in the prevention and treatment of oral mucositis in head-and-neck cancer patients, was administered easily, without serious side effects, and would be preferred because of its low cost. Cengiz *et al.* (56), in their prospective, randomized, double-blind placebo-controlled study, observed that varying grades of mucositis developed in all patients with head-and-neck cancer from RT. In the patients in the sucralfate group, they reported significantly lower grades of mucositis than in the placebo group ($p < 0.05$). In conclusion, Cengiz *et al.* reported that sucralfate mouth washing would be useful in the reduction of the intensity of oral mucositis due to RT, did not have serious side effects, was administered easily, and would be inexpensive, because it would be used routinely in the patients receiving RT to the head and neck. Carter *et al.* (57) in patients with advanced head-and-neck cancer who had undergone RT. They compared sucralfate and placebo stratified patients according to fractionation, use of concurrent chemotherapy, Karnofsky performance status, age, and pretreatment presence of a feeding gastrostomy tube. They found no differences between the groups in direct comparison. They found that Grade 3 mucositis was more common in the patients receiving concomitant chemotherapy ($p = 0.05$) or b.i.d. fractionation ($p = 0.04$) or with poor Karnofsky performance status ($p = 0.02$). The interval to healing was not associated with any of the pretreatment or treatment-related factors. Sucralfate did not result in any additional toxicity. They concluded that prophylactic treatment with the sucralfate during high-dose head-and-neck RT did not decrease the incidence of acute treatment side effects and that other modalities should be investigated.

Labar *et al.* (58), in their study carried out on 60 patients with bone marrow transplantation, reported that the incidence of severe oral mucositis was similar for both groups. They stated that 55% of patients receiving prostaglandin and 52% in patients receiving placebo did not develop mucositis. They found no differences in the duration of severe mucositis between the two groups (chi-square 0.95, p = not significant). Thus, prostaglandin was also not effective for the prophylaxis of oral mucositis.

The U.S. Food and Drug Administration has approved the use of amifostine as a cytoprotector for cisplatin chemotherapy and for radiation-induced xerostomia (59). Trog *et al.* (60), in a study of daily concurrent amifostine for patients with head-and-neck cancer receiving chemoradiotherapy, found that the degree of chemoradiotherapy-induced oral mucositis was significantly lower at all 10-Gy increments ($p < 0.05$), except at ≥ 60 Gy ($p > 0.05$). They found no statistically significant difference in toxicity (blood pressure, serum calcium, potassium, hematologic parameters, emesis, nausea or body weight loss) and concluded that amifositine given before each RT fraction for 6 weeks was tolerated well and reduced oral mocositis depending on the treatment.

Bensadoun *et al.* (61), in a randomized, multicenter, double-blind trial to evaluate the low-energy He/Ne laser (LEL) in the prevention of acute radiation-induced stomatitis, found that Grade 3 mucositis occurred with a frequency of 35.2% without LEL and 7.6% with LEL ($p < 0.01$) and that the frequency of "severe pain" (Grade 3) was 23.8% without LEL, falling to 1.9% with LEL ($p < 0.05$). They reported that LEL therapy was capable of reducing the severity and duration of oral mucositis associated with RT and that there was a tremendous potential for using LEL in combined treatment protocols using concomitant chemotherapy and RT. Cowen *et al.* (62) evaluated the efficiency of the helium-neon laser in the prevention of oral

mucositis induced by high-dose chemoradiotherapy before autologous bone marrow transplantation. They found that the cumulative oral mucositis score and occurrence and duration of Grade 3 oral mucositis were significantly reduced among laser-treated patients ($p = 0.04$ and $p = 0.01$, respectively). The improvement (from d + 2 to d + 7) in a daily mucositis index in the laser-treated patients was also statistically significant ($p < 0.05$). They reported that helium-neon laser treatment was well tolerated, feasible in all cases, and reduced high-dose chemoradiotherapy-induced oral mucositis.

Wagner *et al.* (63), in a pilot study in which they cured 32 patients with adjuvant RT after surgery (60 Gy in 30-dose fractions), reported that mucositis development became less in the patients given recombinant human (rh) GM-CSF compared with a control group during RT. The relief of pain was significantly improved statistically in the patients given rhGM-CSF ($p = 0.011$) compared with the control group. Because rhGM-CSF was tolerated well, they reported that the effectiveness should be investigated in a prospective controlled study. Sprinzl *et al.* (64) performed a prospective, randomized, open parallel-group, single-center study in 35 patients with Stage III and IV carcinoma of the head and neck. They reported that the statistical analysis concerning the degree of oral mucositis, perception of pain, incidence of secondary infections, and change in hematologic parameters revealed no superiority for GM-CSF compared with conventional mouthwash. As a result, faced with the tremendous costs of the regular use of a recombinant cytokine, they ended the clinical trial after 35 patients. Fung and Ferrill (65) analyzed published data assessing the use of GM-CSF to treat or prevent oral mucositis in a meta-analysis. They noted that a limited number of publications had reported that GM-CSF improved mucositis. They observed that a well-designed double-blind randomized study was needed to evaluate the reliability and effectiveness of this agent in the prevention or treatment of RT-induced oral mucositis.

Epstein *et al.* (66) evaluated 0.15% benzydamine oral wash in the prevention and treatment of the pain, erythema, and ulceration, along with radiation-induced oral mucositis. They reported that during conventional RT, regimens up to cumulative doses of 5000 cGy in the benzydamine group ($n = 69$) significantly ($p = 0.006$) reduced the erythema and ulceration by approximately 30% compared with that in the placebo group ($n = 76$); >33% of the benzydamine group remained ulcer free compared with 18% of the placebo group ($p = 0.037$). Also, benzydamine significantly delayed the use of systemic analgesics compared with placebo ($p < 0.05$). Benzydamine was not effective in subjects ($n = 20$) receiving accelerated RT doses (≥220 cGy/d). Early discontinuation because of adverse events occurred in 6% of benzydamine subjects and 5% of placebo subjects. They reported that benzydamine oral washing was tolerated well and was reliable for oral mucositis prophylactic treatment.

Lefebvre and Domenge (67), in a randomized study, compared the safety and efficacy of fluconazole suspension and amphotericin B suspension in patients with head-and-neck cancer who had candidiasis during treatment with chemotherapy and/or RT. A total of 123 assessable patients were given 50 mg fluconazole once daily and 120 were given 0.5 g amphotericin B three times daily for 7–14 days, depending on the clinical response. A positive culture result was obtained in 121 (46%) of 264 patients; *Candida albicans* was the most common. At the end of treatment, fluconazole and amphotericin B were equivalent (90% confidence interval −10.7 to +14.9) in terms of clinical cure and improvement, but the rate of mycologic cure was higher for fluconazole (48%) than for amphotericin B (35%). The incidence of adverse events was 39% for fluconazole and 44% for amphotericin B. They reported that fluconazole suspension appeared effective and safe. El-Sayed *et al.* (68) carried out a study to assess the toxicity and microbiologic efficacy of an economically viable antimicrobial lozenge in the treatment of patients receiving RT for head-and-neck cancer. Seventeen patients scheduled to receive radical or postoperative RT were provided with bacitracin, clotrimazole, and gentamicin lozenges (one lozenge dissolved in the mouth four times daily from Day 1 of RT until completion). They reported that the bacitracin, clotrimazole, and gentamicin lozenges were effective in the reduction of gram-negative flora and in the achievement of elimination of candida in most patients microbiologically. In addition, to evaluate the clinical efficacy of these lozenges, they emphasized that Phase III studies were needed.

Ripamonti *et al.* (50), in their study about the effect of zinc sulfate on taste alterations, evaluated acute oral cavity toxicity and reported that treatment needed to be discontinued in 11 of 18 patients at the fourth week because of acute oral toxicity. No oral cavity lesions were found in the other patients.

Sutherland and Browman (5) reviewed 59 studies to determine suitable criteria to describe, classify, and evaluate the agents used to treat oral mucositis prophylaxis in patients receiving RT for head-and-neck cancer. Of the 59 studies, 42 were not included in the classification schema because they did not meet the study's meta-analysis criteria: The 15 studies used in the meta-analysis were as follows: 5 sucralfate, 2 chlorohexidin, 1 prostaglandin-β1, 1 β-carotene, 1 hydrogen peroxide rinse, 2 antibacterial lozange, 1 low energy He/Ne laser, 1 benzydamine mouth rinse, and 1 povidone-iodine rinse study. Overall, when the grade of mucositis was evaluated by clinicians, severe oral mucositis had a lower incidence by 36% (odds ratio 0.64; 95% confidence interval 0.46–0.88). Subgroup analysis suggested that only the narrow-spectrum antibacterial lozenges were effective (odds ratio 0.45; 95% confidence interval 0.23–0.86); however, the power of the statistical data in the other classes may have been insufficient to detect differences. When the outcome was assessed by patients, no statistically significant difference was seen in the outcome between the treatment and control groups (odds ratio 0.79; 95% confidence interval 0.56–1.12). They reported that interventions chosen on a sound biologic basis to prevent severe oral

mucositis were effective. In particular, when oral mucositis was assessed by clinicians, narrow-spectrum antibiotic lozenges appeared to be beneficial.

In our placebo-controlled study, we found that oral zinc sulfate significantly delayed the starting week and reduced the severity of radiotherapy-induced oropharyngeal mucositis. The RT dose at which mucositis developed was greater in the zinc sulfate group than in the placebo group (Table 2). These results confirm that oral zinc sulfate supplementation during RT has similar effects to agents previously shown to have beneficial effects. Additionally, when we examined radiation-induced oropharyngeal mucositis 6 weeks after RT, we found mucositis in 1 of 15 patients in the zinc sulfate group and in 10 of 12 patients in the placebo group. This result proves that mucosal healing occurs earlier in the zinc sulfate group than in the placebo group (Table 3).

Excess oral ingestion of zinc to the point of toxicity (100–300 mg/d) is rare. Zinc sulfate in amounts of 2 g/d or more can cause GI irritation and vomiting (54). In our study, we used 150 mg/d of zinc sulfate. RTOG Grade 3 vomiting and nausea from zinc sulfate developed in 1 patient. This result was comparable with those in the literature.

CONCLUSION

Zinc sulfate is beneficial in decreasing the severity of radiation-induced oropharyngeal mucositis and oral discomfort. It is inexpensive and easy to administer, with no serious side effects. These results warrant further evaluation in a randomized study with a larger number of patients.

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