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Effect of Oral Zinc Sulphate in Prevention of Radiation Induced Oropharyngeal Mucositis During and After Radiotherapy in Patients with Head and Neck Cancers

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Abstract

Introduction: Mucositis is a disturbing side effect of radiotherapy treatment for head and neck cancer. To date, no effective modality for its prophylaxis and treatment has been found. We performed this study to evaluate the efficacy of oral zinc sulphate in delaying the onset of oral and pharyngeal mucositis and decreasing their severity.

Materials and Methods: A total of 58 patients who were treated for head and neck squamous cell carcinoma with radiotherapy or chemoradiotherapy were randomly assigned to receive oral zinc sulphate (220 mg) or an oral placebo 3 times a day during their radiotherapy course. Total radiation dose was 6000 cGy to 7000 cGy by conventional radiotherapy. Seventy nine percent of the patients also received concurrent chemotherapy. Oral and pharyngeal mucositis were scored according to an RTOG protocol.

Results: Time to onset of mucositis did not vary between the two groups. However, oral mucositis scores were less severe in the zinc group in weeks 4 to 6. The difference was statistically significant and the *P* values for weeks 4, 5 and 6 were 0.02, 0.007, and 0.012, respectively. Treatment interruptions in both groups were the same (four cases each) and all were due to dysphagia (pharyngeal mucositis).

Conclusion: Our results suggest that zinc is effective in reducing the severity of oral mucositis but not pharyngeal mucositis. Treatment interruptions were more frequently caused by pharyngeal mucositis which presented as dysphagia, rather than oral pain that was a manifestation of oral mucositis.

Keywords: Radiotherapy, Head and neck cancer, Oropharyngeal mucositis, Zinc sulphate

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Introduction

Mucositis is a disturbing side effect of radiotherapy for head and neck cancers. The term mucositis is generally used when erythema, inflammation and/or ulceration are present.[1-3] This adverse event occurs in 30-90% of patients receiving radiotherapy for head and neck cancers.[3,4] While undergoing radiation treatment, the onset of mucositis usually begins after a dose of 1500 cGy and reaches maximum intensity when a patient is irradiated to 3000 cGy.[5] Patients report mucositis as the worst side effect they experience.[6] It is debilitating, painful and sometimes dose limiting.[1,7] Mucositis related discomfort causes more than 10% of patients who undergo radiotherapy to have unplanned changes in their treatment schedules.[6] Treatment interruption and prolonged total radiation time resulting from treatment interruption decreases the chance of cure.[1,8] Clearly, this is undesirable for both the patient and physician. Another aspect is the economic burden which cannot be ignored. The need for a liquid diet, gastrostomy tube, prolonged treatment course and hospitalization may have a significant economic impact on the patient, hospital and insurance services.[7, 9-11]

Damaged tissues that are produced during radiotherapy could be an ideal environment for the growth of bacteria, viruses and fungal agents, which could lead to bacteremia and sepsis. This is especially important if concurrent chemotherapy is prescribed and myelosuppression occurs.[1,2,7]

The use of multiple agents has been studied, but no definite modality is known to be effective as a prophylaxis for mucositis. Many studies have evaluated the effectiveness of multiple agents, namely: acyclovir, allopurinol, aloe vera, antibiotic pastille, benzamidine, chlorhexidine, amifostine, Chinese medicines, hydrolytic enzymes, ice chips, anti-inflammatory drugs and honey, among others. A few of these agents have shown some degree of effectiveness in preventing mucositis but the results have not been conclusive.[1, 2, 6, 12,13]

Zinc sulphate seems to be one of the promising agents in mucositis prevention. In two studies, it was effective in reducing mucositis severity.[14,15] Given that zinc is an essential micronutrient in the body and that zinc deficiency among the population in Iran has been reported; a study of the effectiveness of zinc sulphate among Iranian patients is logical. The two above-mentioned studies on zinc sulphate have only researched oral mucositis, although pharyngeal mucositis can occur, too. Pharyngeal mucositis may be more important because it is not directly measured and the patient himself/herself reports its severity. It may be more of an indicator of a patient's wellness rather than oral mucositis. Therefore, the aim of this study is to evaluate the effectiveness of zinc sulphate in both oral and pharyngeal mucositis prophylaxis during a course of radiotherapy for our patient population.

Materials and Methods

This phase III, double blind, placebo controlled, randomized clinical trial was conducted in our university based Radiotherapy Department. The protocol was also approved by the University Ethics Committee. Randomization was performed by using a random numbers table in a statistics textbook. Fifty-eight patients who were treated with either radiotherapy or chemoradiotherapy during June 2008 to June 2009 were entered in the study. The purpose of the study was described to each patient verbally and a signed written consent was taken.

Patients had histological proven diagnoses of squamous cell carcinoma of the head and neck. They also were in good performance status with a Karnofsky scale $\geqslant 70$ percentage. A Karnofsky performance status scale $\geqslant 70$ is used when the patient is able to do self care without assistance but is unable to do normal daily activities.16 Patients were administered radiotherapy or chemoradiotherapy with a curative intent. Planning target volume receiving at least 6000 cGy total radiation dose, with no less than one third of the oral cavity in the primary beam and delivering at least 4500 cGy to the cervical esophagus were the inclusion criteria.

Exclusion criteria were: patient's refusal, co-morbid disease (diabetes mellitus, hypertension,

systemic infection, active heart disease, etc.), poor oral hygiene [infection (viral, bacterial or fungal), active gingivitis or oral ulcer] and concurrent medications, with the exception of pain killers to relieve mucositis before or during treatment. Patients were randomly assigned to receive either zinc sulphate or placebo. Patients who stopped the treatment were withdrawn from the study, but contemporary treatment interruption due to mucositis was not the criteria for study withdrawal. Patients received zinc sulphate capsules (220 mg), three times a day, at 8 hour intervals, from day 1 until the end of treatment, including weekends.

Oral and pharyngeal mucositis were assessed weekly according to the Radiation Therapy Oncology Group (RTOG) scoring system by two radiation oncologists during treatment and at weeks 1 and 2 post-treatment.[17] Patients were treated with Co-60 gamma ray up to 6000-7000 cGy in 180-200 cGy fractions, 5 fractions per week through parallel-opposed lateral fields and an anterior field for the lower neck. Forty six (79.3%) patients received concurrent chemotherapy with weekly cisplatin, daily capecitabine or 5-fluorouracil (5-FU) and cisplatin during the first 3 days of the first week and during the first 3 days of the last week. General physical examination, complete blood count, BUN, Cr, and liver function tests were checked prior to the onset of treatment and before each chemotherapy course. Placebo capsules were identical in shape and color to zinc sulphate and were filled with starch. Patients received capsules from the 1st day of treatment until the last day. Any patient not receiving radiotherapy for more than 3 days was considered a treatment interruption. Patients were informed about brushing teeth daily and avoiding hot, cold, sour, or spicy foods during treatment.

In this study, the Mann-Whitney, Pearson chi-square and Fisher's exact tests were used. $P<0.05$ was considered significant.

Results

Tables 1 and 2 summarize the demographic characteristics for the patients and their treatment. Most patients were over the age of 60 (mean = 57.3 years, median = 60, range = 15-83 years) and male gender was predominant in both groups. The most prevalent primary site was the larynx, followed by the nasopharynx and tongue. Stages 3 and 4 were the predominant tumor stages. The treatment was done as adjuvant in the majority of patients. Chemoradiation was administered more than radiotherapy alone and most received cisplatin/5-FU as concurrent chemotherapy. No statistical differences in the development of oral and pharyngeal mucositis due to differences in these modalities: age, sex, disease, stage, treatment, and chemotherapy regimen were found.

We have found that both oral and pharyngeal mucositis have increasing trends in weeks 1 to 7 during treatment and also greater mucositis severity in the control group. Oral and pharyngeal mucositis began at the end of week 2 (after 1800 - 2000 cGy) in both groups. At the end of the 2nd week, 31% of the zinc group developed oral mucositis; this number in the control group was 37%. This difference was not statistically significant and oral mucositis initiated simultaneously in both groups. In weeks 4, 5 and 6, the severity of oral mucositis was lower in the zinc group, which was statistically significant (P=0.02, 0.007 and 0.012 for weeks 4, 5 and 6) (Table 3). However, the severity of pharyngeal mucositis was not statistically different in the two groups. One grade 3 oral mucositis occurred in week 5 in the control group (compared to none in the zinc group). However, for grade 3 pharyngeal mucositis; the earliest occurrence was at the end of the 3rd week in the zinc group and 1 week later in the control group.

During the 2 weeks after treatment completion, a decrease in severity of both oral and pharyngeal mucositis was seen, however there was no significant difference between the groups.

The same number of treatment interruptions (4 cases, 13.7%) was observed in both groups. The breaks in treatment were due to dysphagia rather than oral problems. Our patients tolerated zinc sulphate well.

Table 1. Patients' demographic characteristics.

Patient's characteristics	Zinc group	Control	*P* value
Age			
≤60 (mean: 44.7years)	14 (48.3%)	15 (51.7%)	0.793
>60 (mean: 65.9years)	15 (51.7%)	14 (48.3%)	
Mean age (years)	58.1	56.5	
Median age (years)	60	58	
Gender			
Female	9 (31.0%)	9 (31.0%)	0.770
Male	20 (69.0%)	20 (69.0%)	
Disease			
Tongue	6 (20.7%)	6 (20.7%)	NA
Larynx	16 (55.2%)	10 (34.5%)	
Nasopharynx	4 (13.8%)	8 (27.6%)	
Oral cavity, except tongue	0 (0.0%)	2 (6.9%)	
Hypopharynx	2 (6.9%)	2 (6.9%)	
Unknown primary	0 (0.0%)	1 (3.4%)	
Stage			
Early stage (I,II)	6 (20.7%)	12 (41.4%)	0.089
Locally advanced (III-IV)	23 (79.3%)	17 (58.6%)	
Histology			
Well differentiated	10 (34.5%)	12 (41.4%)	0.237
Intermediately differentiated	13 (44.8%)	9 (31.0%)	
Poorly differentiated	6 (20.7%)	8 (27.6%)	

Discussion

Mucositis, which is a complication of radiotherapy for head and neck cancers, is reported as the worst side effect by patients receiving radiotherapy.[5,6] It may lead to treatment breaks in 11% of patients.[7] Studies have shown a prolongation of treatment time or 2-3 weeks rest during a course of radiotherapy decreases the chance of cure, especially in squamous cell carcinoma. This is due to cell repopulation during treatment.[8,18] In addition, mucositis may bring about reduced quality of life, economic burdens, or even hospitalizations.[9-11,19] Therefore, it is very important to find a treatment modality or modalities to prevent mucositis or lessen its prevalence and severity. In our study, we have evaluated the effect of zinc sulphate in both oral and pharyngeal mucositis and found it reduced the severity of oral mucositis during the second half of the course of treatment, but caused no change in pharyngeal severity.

Multiple agents have been used to prevent radiation-induced mucositis, but results have been controversial or even paradoxical. Sucralfate is a protective agent and has long been used for peptic ulcer disease. Carter [20] and Makkonen [21] tested sucralfate for preventing mucositis; but results were not satisfactory. However, Cengiz's study on this agent was promising.[22] Since bacterial or fungal colonization may play an inflammatory or ulcerative process, some investigators have studied antimicrobial and antiseptic agents. Symonds et al. studied PTA (Polymyxin E, Tobramycin and Amphotericin B) lozenges that were not effective.[23] El Seed[24] and Wipers[9] were not successful in preventing or treating mucositis by antimicrobial agents. Ferretti et al. tested chlorhexidine and this agent showed positive results.[25]

Amifostine is a radio-protective agent that protects DNA from damage by free radical agents. In a randomized study by Buntzel et al., amifostine was effective in preventing radiotherapy induced oral and pharyngeal mucositis.[26] However, Brizel et al. argued against routine use of amifostine. In their randomized trial, in order to evaluate the effect of amifostine on mucositis and xerostomia; nausea, vomiting and hypotension were seen more

Table 2. Patients' treatment characteristics.

Treatment characteristics	Zinc group	Control	*P* value
Radiation dose			
≤50 Gy	0 (0.0%)	0 (0.0%)	0.792
50-60 Gy	14 (48.3%)	17 (58.6%)	
>60 Gy	15 (51.7%)	12 (41.4%)	
Mean	59.03 Gy	57.7 Gy	
Treatment modality			
Radiotherapy alone	0 (0.0%)	1 (3.4%)	NA
Chemoradiotherapy alone	3 (10.3%)	5 (17.2%)	
Surgery followed by radiotherapy	5 (17.2%)	6 (20.6%)	
Surgery followed by chemoradiotherapy	18 (62.1%)	17 (58.6%)	
Chemotherapy regimen			
No concurrent chemotherapy	5 (17.2%)	7 (24.1%)	0.517
With concurrent chemotherapy	24 (82.8%)	22 (75.9%)	

in the amifostine group which was statistically significant. The main reasons for stopping amifostine were nausea, vomiting and hypotension. Amifostine reduced both acute and chronic xerostomia, but mucositis was not decreased by this agent. Amifostine is expensive and the authors of that study debate its adverse effect on tumor radiosensitivity, although reduced tumor radiosensitivity due to amifostine was not demonstrated in their study.[27, 28]

Worthington et al. performed a review and concluded that amifostine provided minimal benefit by reducing only mild to moderate mucositis, while ice chips and Chinese medicine were effective at all levels. Hydrolytic enzymes reduced moderate and severe mucositis.zinc sulphate showed some benefit, but only one study was included in the review.[13]

Although many trials have been undertaken to solve or diminish this problem; thus far palliative rinses, barrier protectants, topical antimicrobials, ice and analgesics are the only available interventions.[5]

One agent that has yielded positive results in reducing radiation-induced mucositis is zinc.[14, 15] Zinc, an essential micronutrient, is a catalytic component in more than 300 enzymes such as carbonic anhydrase, alkaline phosphatase, and superoxide dismutase, among others.[16,29] This element is also an essential cofactor in various cellular processes such as DNA synthesis, RNA polymerase and reverse transcriptase, wound healing, growth and immunity (particularly cell-mediated immunity).[30, 31] The growth and reproductive effects of zinc are related to its influences on DNA synthesis, protein synthesis, and cell division.[32] In addition, zinc is an antioxidant which protects cell membranes against injury from free radicals.[33] Thymidine kinase and lactate dehydrogenase are synthesized inadequately during periods of zinc deficiency.[31] Its role in collagen synthesis and vitamin A metabolism is important and a zinc deficiency can lead to skin changes and disturbed retinal function.[29] Zinc is generally well tolerated in moderate doses although zinc toxicity (nausea, gastrointestinal irritation, acute renal tubular necrosis and interstitial nephritis) have been reported in cases when large doses (1-2 g) were ingested.[30]

Zinc has shown promising results when used in studies to reduce radiation side effects. Ripamonti et al., in a randomized controlled trial, evaluated the effect of zinc sulphate in taste preservation in patients who received radiotherapy for head and neck cancer. Significant differences were detected for urea and sodium chloride taste sensation during radiotherapy, and for sodium chloride, saccharose and hydrogen chloride after radiotherapy.[34]

Understanding how mucositis occurs may help to use more appropriate modalities for its prevention. Mucositis development is divided

Table 3. Oral mucositis in weeks 4 to 6.

Week	Mean (SD) in zinc group	Mean (SD) in control group	*P* value
4th week	0.724 (0.455)	1.071 (0.466)	0.02
5th week	0.724 (0.455)	1.142 (0.525)	0.007
6th week	0.862 (0.441)	1.250 (0.518)	0.012

into five phases: (1) initiation, (2) message generation, (3) signaling and amplification, (4) ulceration, and (5) healing. In the initiation phase, the main process is caused by radiation induced DNA damage via free oxygen radicals. In the next phase some transcription factors are activated, mainly NF-κB. Afterwards, activated transcription factors move to the nucleus and up regulate as many as 200 genes, including genes that code for pro-inflammatory cytokines and adhesion molecules. Then, effector proteins are produced and tissue injury increases. In the next phase (signaling and amplification), agents such as TNF-alpha are produced and injury increases. As a result of these cascades, ulcer(s) appear during the ulceration phase. Healing, the last phase is not well understood. Zinc is effective during the initiation and message generation phases.[2]

There are two published studies that researched the effect of zinc on radiation-induced mucositis. The first study was conducted by Ertekin et al. in a prospective randomized trial. There were 27 patients in their study, 15 in the zinc group and 12 in the control group whose ages ranged from 18 to 71 years. Primary tumor sites were the larynx, oral cavity, nasopharynx, lymphoma, unknown primary or metastasis, salivary glands and nasal sinuses. In the zinc group, mucositis started on average one week later (3rd week versus 2nd week in the control group). In the zinc group, no grade 3 or 4 mucositis occurred compared to three cases of grade 3 mucositis in the control group. The RTOG scoring criteria were used although only oral mucositis was evaluated. No interruption in the radiotherapy course was seen in either group. Mucositis (oral) initiation was delayed when zinc was used.[14]

In the other study, Lin et al. evaluated the effect of zinc on radiation induced mucositis prevention in head and neck cancer patients in a larger randomized placebo controlled trial. Ninety-seven patients were studied (49 in the zinc group and 48 in the placebo group). Primary disease sites were oral cavity, paranasal sinuses, parotid gland, malignancy of unknown origin, oropharynx, nasopharynx and hypopharynx. Patients had different stages of the disease (stages 1 to 4) and all were older than 18 years. Serum zinc levels were checked for all patients and a wide range was detected in both groups. Oral mucositis was evaluated according to the RTOG scoring system. When radiotherapy alone was prescribed, a significant difference was seen in mucositis severity between the two groups. Grades 2 and 3 oral mucositis occurred sooner in the control group. These benefits were only seen in the radiotherapy treated patients, but not for chemoradiotherapy. No known side effects related to zinc were detected in this study. Treatment interruption was not statistically different in the 2 groups; 24.5% in the zinc group and 32.6% in the control group. Patients were also evaluated for the effect of zinc on dermatitis and the results indicated a benefit in the zinc group.[15]

As previously mentioned, mucositis is a devastating side effect. This study has been performed to find a way to help reducing this side effect for patients who receive radiotherapy to the head and neck. In agreement with Lin's and Ertekin's studies, we also found that oral mucositis severity was less in cases who received zinc. In both groups of our patients, oral and pharyngeal mucositis occurred simultaneously (at the end of the 2nd week). This finding is not consistent with Lin's and Ertekin's studies in which zinc delayed mucositis initiation. In Ertekin's study, zinc led to a one week delay in oral mucositis initiation. This may be due to patient selection. Their study included more variable diseases, including lymphoma and salivary gland

tumors. Radiation treatment fields for lymphoma and salivary gland tumors are somewhat different from squamous cell carcinomas such as the tongue, larynx, nasopharynx, oral cavity and hypopharynx, which were the main primary sites in our study.[14] Pharyngeal mucositis showed no change in either group. Neither of the above-mentioned studies on zinc evaluated pharyngeal mucositis. The 13.7% occurrence of treatment interruptions in our study was lower than Lin's investigation but higher than Ertekin's. It must be emphasized that treatment interruptions were due to problems with eating rather than oral cavity pain. Consequently, pharyngeal mucositis may be more representative of patient well- being rather than physician's evaluation of one or a few symptoms. Our study was not large enough to evaluate the chemotherapy regimen, stage and primary site effects on mucositis.

Understanding which patient is at risk for mucositis development is important to identify and help patients who are at greater risk. Some criteria have been proposed including age, gender, nutritional status, oral microflora, inflammation and salivary function; but the two factors that we studied (age and sex) showed no relationship. This may, however, be due to the size of our study. In addition, a genetics study may provide more answers.[5]

Our results suggest that zinc is effective in reducing the severity of oral mucositis but not pharyngeal mucositis. Treatment interruptions were due more to pharyngeal mucositis which presented as dysphagia, rather than oral pain that was manifested as oral mucositis.

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