A Randomized Double-Blind, Placebo-Controlled Trial of Zinc Sulfate Supplementation for Alleviation of Radiation-Induced Oral Mucositis and Pharyngitis in Head and Neck Cancer Patients

Duangjai Sangthawan MD*,
Temsak Phungrassami MD*, Wattana Sinkitjarurnchai MD**

** Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*
*** Department of Otorhinolaryngology Head and Neck Surgery, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand*

Objective: *To determine the efficacy of zinc sulfate supplementation in reducing of radiation-induced oral mucositis and pharyngitis in head and neck cancer patients.*
Material and Method: *One hundred forty four head and neck patients were enrolled in a randomized, double-blind, placebo-controlled trial. Patients who received radiation therapy alone or postoperative radiation therapy were eligible. Radiation therapy used conventional fractionation with 1.8 to 2.0 Gy per fraction, to total doses of 50 to 70 Gy over five to seven weeks. Drug and identically appearing placebo were self-administered 50 mg (10 cc) per meal, three times a day at mealtime. The zinc sulfate and placebo were administered beginning on the first day of radiation, and continued daily including weekends until radiation was completed. Patients were evaluated before radiation, weekly during radiation and at the first month after completion of radiation.*
Results: *The baseline characteristics of patients, tumor, and treatment were not significantly different between the two groups. There were no statistically significant differences between the two treatment groups in frequency of patients experiencing greater than or equal to grade 2 oral mucositis and pharyngitis at each week during radiation and at the first month after completion of radiation. Six patients (17%) in the zinc sulfate and ten patients (23%) in placebo group developed grade 3 oral mucositis, which was not significantly different. Twenty-two patients (32%) in the zinc sulfate and nineteen patients (27%) in the placebo group developed grade 3 pharyngitis, which was not significantly different. However, there was no observation of grade 4 oral mucositis and pharyngitis in either group. Nausea and vomiting were mostly of mild degree. Adverse events were not statistically significant different between the two groups.*
Conclusion: *It was concluded that zinc sulfate administered during head and neck radiation therapy produced no significant benefit in relieving radiation-induced oral mucositis and pharyngitis with acceptable side effects.*

Keywords: *Zinc sulfate, Oral mucositis, Pharyngitis, Radiation therapy, Head and neck cancer*

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Radiation mucositis is considered to be an inevitable and the most troubling but transient side effect of head and neck irradiation[1,2]. This radiation effect causes local discomfort and pain and this can cause eating and swallowing difficulties with nutritional problems as well as worsening the patient's quality of life[3,4]. Severe mucosal effects will necessitate hospitalization and may lead to interruption of radiotherapy, thereby potentially compromising local tumor control and survival[5-7]. At present, several interventions have been found to have some benefit in preventing or reducing the severity of mucositis associated with cancer treatment. Meta-analyses of 89 randomized clinical trials of interventions for the prevention of oral mucositis, included data for mucositis comprising 7,523 randomized patients[8,9]. Interventions evaluated were acyclovir, allopurinol mouthrinse, aloe vera, antibiotic pastille or paste,

Correspondence to:
Sangthawan D, Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand.
Phone: 074-451-502, 074-451-503, Fax: 074-429-927
E-mail: sduangja@medicine.psu.ac.th

benzydamine, betacarotene, calcium phosphate, chamomile, Chinese medicine, chlorhexidine, etoposide, folinic acid, glutamine, granulocyte/macrophage colony-stimulating factor (GM-CSF), histamine gel, honey, hydrolytic enzymes, ice chips, iseganan, keratinocyte GF, misonidazole, pentoxifylline, povidone, prednisone, prostaglandin, sucralfate, systemic antibiotic clarithromycin, and zinc sulfate. Interventions of which there was more than one trial in the meta-analysis finding a significant difference when compared with a placebo or no treatment were amifostine, Chinese medicine, hydrolytic enzymes, and ice chips. Other interventions showing some benefit in only one study were benzydamine, calcium phosphate, etoposide bolus, honey, iseganan, oral care, and zinc sulfate. It is hard to draw definitive conclusions regarding the use of these interventions or to provide evidence-based guidelines for the prevention of radiation mucositis. Additional study is required to identify safe and effective strategies to prevent ulcerative mucositis.

Zinc, an essential nutrient, is the second most abundant trace element in the human body. The role of zinc in a wide range of cellular processes, including cell proliferation, reproduction, immune function, and defense against free radicals, has been well established[10-12]. Zinc supplementation strategies have been shown to be beneficial against oxidant damage and the progression of reactive oxygen species (ROS)-induced disease[13-16]. Ertekin's trial[17] suggested that the effect of zinc sulfate supplements was to scavenge rapidly superoxide radicals from the environment and accelerate the activity of erythrocyte Cu-Zn SOD enzyme. To date, there are limited trials that evaluate and show the benefit of zinc sulfate in reducing radiation-induced mucositis[18,19].

The objective of the present study was to evaluate if zinc sulfate supplementation during radiation therapy was effective in reducing of radiation-induced oral mucositis and pharyngitis.

Material and Method

Study design

The present study was designed as a randomized, double blind, placebo-controlled trial, in which patients were randomly assigned to receive either zinc sulfate or placebo during radiation therapy. The present study protocol and the informed consent disclosure were approved by the Research and Medical Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand. All participants who met the entrance criteria received a verbal and written explanation of the present study. Written informed consent was obtained from all subjects before randomization. A block of four-randomization procedure was undertaken to achieve a balanced assignment. The trial statistician generated the randomization sequence via a computerized random number generator. In order to conceal the allocation process, a pharmacy staff was responsible for keeping the randomization list and assigned participants to the trial group.

Patients' eligibility

The present study was conducted at the Radiation Oncology Division, Department of Radiology, Songklanagarind Hospital, between September 2006 and October 2007. Patients, who were older than 18 years, had histologically documented diagnosis of head and neck cancer, had a Kanofsky performance status at least 70 were eligible. Patients were ineligible if they were previously diagnosed with cancer, had other concomitant cancers, distant metastases or recurrent cancer, had undergone prior radiation therapy or chemotherapy, or had received drug containing zinc.

Radiation therapy

Radiation therapy was delivered to the patients either as radiation therapy (RT) alone or as postoperative radiation therapy. All patients were treated with Cobalt-60 or 6 MV photon machine. The standard arrangement consisted of two lateral parallel opposing fields or ipsilateral wedge-pair portals for the primary tumor and upper cervical lymph nodes and/or an anterior portal field for the lower cervical nodes and supraclavicular nodes. The daily fractionation was 1.8 to 2 Gy. A total dose of 50 to 70 Gy over 5 to 7 weeks was administered.

Zinc sulfate/placebo

The zinc sulfate and placebo were prepared as an oral syrup, identical in taste and consistency. The zinc sulfate consisted of an elemental zinc at a concentration of 5 mg per cc.

All syrup was manufactured by the Songklanagarind Hospital Pharmacy. Zinc sulfate and placebo were self-administered at 10 cc per meal, three times a day at meal times. The patients were instructed to take the syrup on the first day of radiation and to continue daily including weekends until the completion of radiation. Patients and investigators

were unaware of which treatment was administered. Compliance was monitored by weekly assessment of the patient record diary and the amount of syrup remaining in the bottle.

Concomitant medications

Xylocain viscous and analgesic medication (classified according to WHO analgesic ladder) was given whenever considered necessary. Antibiotics and antifungal agents were prescribed whenever infection was documented or suspected.

Outcomes

The primary end-point of the present study was to evaluate the frequency of development of greater than or equal to grade 2 oral mucositis and pharyngitis. The secondary end-points included evaluation of an oral and throat pain scores, an adverse effect of zinc sulfate, and treatment morbidities.

Clinical and laboratory assessments

All patients were evaluated before radiation, weekly during radiation, and at one month after completion of radiation. Clinical assessment was as follows, severity (grading) of oral mucositis and pharyngitis, oral and throat pain scores, need for analgesic drug, need for feeding tube, and unplanned hospitalization due to mucositis. Grading of oral mucositis and pharyngitis were assessed according to National Cancer Institute-Common Toxic Criteria (NCI-CTC) v.2[20]. The intensity of oral and throat pain were rated by the patients themselves using the visual analogue scale, with "no pain" at the left end being given a 0 score and "most pain imaginable" at the right end with a score of 10. Body weight was checked before radiation as a baseline and once a week. Placement of feeding tube was needed if patients had too much trouble in eating or swallowing, or if they lost more than 20% of their pretreatment weight.

The blood samples including hematology and chemistry, were obtained before treatment, at the fifth week during radiation, and at the first month after the completion of radiation therapy.

Adverse effects of zinc sulfate

Safety was assessed on the basis of incidence of drug-related adverse events and clinical laboratory abnormalities. The severity of adverse events was categorized as mild (spontaneous symptomatic relief), moderate (need drug for symptomatic relief), and severe degree (need to stop all treatment).

Statistical analysis

Statistical analysis was done using STATA v.7. Intention-to-treat analysis was carried out. Categorical and continuous data were presented as frequency with percentage, mean and SD, respectively. The changes in pain scores were calculated for each patient by subtracting the scores during and after radiation from the score prior to radiation. A t-test was performed to compare continuous data between the two groups, Chi-square or Fisher's exact tests were performed to compare categorical data. Statistical significance was accepted at a p-value <0.05.

Results

Of the 144 patients randomized to protocol, 139 received the complete treatment. In the placebo groups, one died during the course of radiation, one denied radiation therapy, and one left the study due to personal reason. Two of zinc sulfate group patients died during the course of radiation. The causes of death in both groups were from other underlying diseases.

The baseline characteristics of patients, disease, treatment and laboratories are shown in Table1, Table 2, and Table 3. The majority of patients were male with a mean age of 62 years (SD 13) and 60 years (SD 12) in the zinc sulfate and placebo group, respectively.

Most patients in both treatment groups had locally advanced stage (stage III-IV). The total cumulative dose of radiation therapy were 6,650 (SD 1,021) and 6,683 (SD 688) in the zinc sulfate and placebo group, respectively. None of the characteristics differed significantly between the two treatment groups.

Oral mucositis and pharyngitis

In the second week, the patients in both treatment groups began to experience greater than or equal to grade 2 oral mucositis and pharyngitis. The number of patients experiencing these complications in both groups increased with time during treatment and reached the maximum frequency at week 4 and week 5 in the placebo group and zinc sulfate group, respectively for oral mucositis and at week 6 and week 5 in the placebo group and zinc sulfate group, respectively for pharyngitis (Fig. 1, 2). There were no statistically significant differences in frequency of patients experiencing greater than or equal to grade 2 oral mucositis and pharyngitis for every week between the two groups. Six patients (17%) and ten patients (23%) in zinc sulfate and placebo group developed grade 3 oral mucositis, which was not significantly

Table 1. Baseline patient and tumor characteristics

Characteristics	Zinc sulfate (n = 72)	Placebo (n = 72)
Age (year)	62 (13)	60 (12)
Gender		
Male	65 (90%)	60 (83%)
Female	7 (10%)	12 (17%)
Karnofsky performance status		
90-100	65 (90%)	67 (93%)
70-80	7 (10%)	5 (7%)
Tumor site		
Oral cavity	6 (8%)	18 (25%)
Oropharynx	21 (29%)	16 (22%)
Nasopharynx	1 (1%)	3 (4%)
Larynx	22 (31%)	16 (22%)
Hypopharynx	13 (18%)	9 (13%)
Major salivary gland	2 (3%)	6 (9%)
Nasal and paranasal sinus	2 (3%)	1 (1%)
Unknown primary site	5 (7%)	3 (4%)
Staging		
I-II	29 (40%)	26 (36%)
III-IV	66 (53%)	73 (60%)
Unknown primary site	5 (7%)	3 (4%)
Histology		
Squamous cell carcinoma	67 (93%)	64 (89%)
Non-squamous cell carcinoma	5 (7%)	8 (11%)
Smoking (yes)	59 (82%)	58 (81%)
Alcohol (yes)	52 (72%)	56 (78%)
Body weight (kilogram)	54 (9)	53 (11)

The values are expressed in frequency (%) and mean (SD).

Table 2. Radiation treatment characteristics

	Zinc sulfate (n = 72)	Placebo (n = 72)
Modality		
RT alone	56 (78%)	53 (74%)
Postoperative RT	16 (22%)	19 (26%)
Machine		
Linac	66 (92%)	69 (96%)
Cobalt-60	6 (8%)	3 (4%)
Mean overall treatment time (days)	52 (9)	52 (7)
Mean total radiation dose (cGy)	6,650 (1,021)	6,683 (688)

RT = radiation therapy
The values are expressed in frequency (%) and mean (SD).

different (p = 0.54). Twenty-two patients (32%) and nineteen patients (28%) in the zinc sulfate and placebo group developed grade 3 pharyngitis, which was not significantly different (p = 0.84). There was no observation of grade 4 oral mucositis and pharyngitis in either group.

The mean radiation doses in developing of greater than or equal to grade 2 oral mucositis were 3,771 cGy (SD 989) and 3,675 cGy (SD 1,040) in the zinc sulfate and placebo group, respectively (p = 0.96). The mean doses in developing of greater than or equal to grade 2 pharyngitis were 3,530 cGy (SD 939) and

Table 3. Baseline laboratory characteristics

	Zinc sulfate (n = 72)	Placebo (n = 72)
Serum zinc (mg/L)	0.64 (0.13)	0.69 (0.16)
Serum albumin (g %)	4.26 (0.38)	4.28 (0.39)
Serum total protein (g %)	7.49 (0.60)	7.64 (0.53)
Serum hemoglobin (mg %)	12.62 (1.91)	12.34 (1.60)

The values are expressed in mean (SD).

3,525 cGy (SD 1,219) in the zinc sulfate and placebo group, respectively (p = 0.59).

Oral pain and throat pain

The mean scores of oral pain at baseline were 0.47 (SD 1.56) and 0.31 (SD 0.91) in placebo and zinc sulfate group, respectively (p = 0.51). The mean scores of throat pain at baseline was 0.17 (SD 0.75) and 0.36 (SD 1.21) in the placebo and zinc sulfate group, respectively ($p<0.05$). The mean differences of oral pain scores between baseline and each week began to increase from the first week of radiation therapy and reached a maximum at week 4 and week 5 in placebo and zinc sulfate group, respectively (Fig. 3). The mean differences of oral pain scores was lower in the zinc sulfate group, however, no significant differences were detected (p = 0.77). The mean differences of throat pain scores between baseline and each week began to increase from the first week of radiation therapy and reached a maximum difference at week 5 and week 6 in placebo and zinc sulfate group, respectively (Fig. 4). The mean difference of throat pain was also lower in the zinc sulfate group.

However, there was no statistically significant differences between the two treatment groups (p = 0.47).

Analgesic medication

Twenty patients (28%) in the zinc sulfate group and Twenty-two patients (30.5%) in the placebo

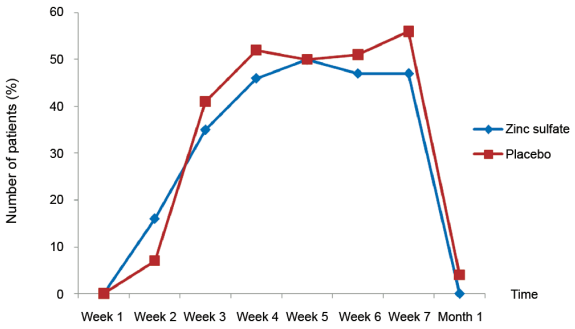

Fig. 1 Frequency of greater than or equal to grade 2 oral mucositis between zinc sulfate group and placebo group.

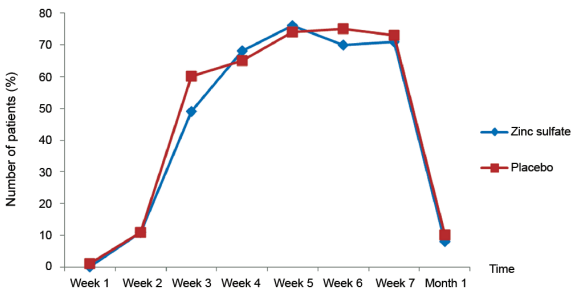

Fig. 2 Frequency of greater than or equal to grade 2 pharyngitis between zinc sulfate group and placebo group.

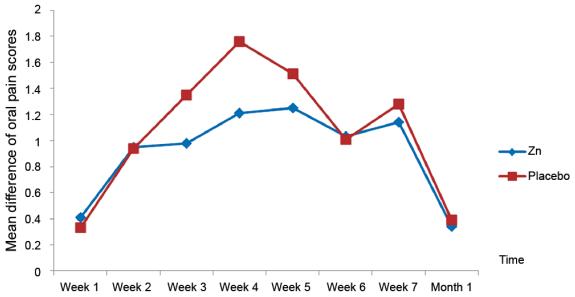

Fig. 3 Mean differences of oral pain scores.

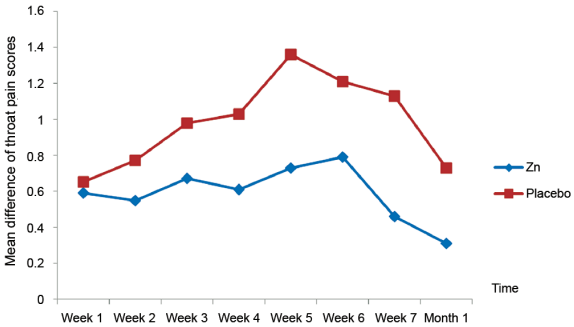

Fig. 4 Mean differences of throat pain scores.

Table 4. Treatment Morbidity

	Zinc sulfate	Placebo	p-value
Mean difference of body weight*	-3.17 (3.46)	-3.70 (3.79)	0.48
Weight loss (% of baseline)			
<5%	30 (42%)	24 (33%)	0.82
5-<10%	24 (33%)	26 (36%)	
10-<20%	17 (24%)	20 (28%)	
≥20%	1 (1%)	2 (3%)	
Unplanned hospitalization due to RT-induced mucositis	5 (7%)	3 (4%)	0.65
Nasogastric tube insertion	10 (14%)	9 (13%)	0.76
Intravenous fluid need	25 (35%)	25 (35%)	0.90

* Difference of body weight was the body weight (kilogram) of last week of radiation minus body weight before radiation therapy.
The values are expressed in frequency (%) and mean (SD).
RT = radiation therapy

group experienced step II analgesia. Forty-two patients (58%) in the zinc sulfate group and forty-one patients (57%) in the placebo group experienced step III analgesia. The frequency of using analgesic medication were not significantly different between groups (p = 0.71).

Treatment morbidity

The mean baseline body weight was 54 kg (SD 9) in the zinc sulfate group and 53 kg (SD 11) in the placebo group. The body weight in both groups decreased during the course of radiation therapy. At the last week of radiation, the mean body weight loss compared with baseline was 3.17 kg (SD 3.46) in the zinc sulfate group and 3.70 kg (SD 3.79) in the placebo group, but no statistically significant difference was noted between the groups. Need for unplanned hospitalization due to radiation-induced fatigue, nasogastric tube insertion, and intravenous fluid were not significantly different between two groups (Table 4).

Adverse event of zinc sulfate

Nausea and vomiting were mostly of mild degree. Only one patient in the zinc sulfate group developed a moderate severity of nausea and vomiting, which could be relieved by supportive treatment. Abdominal pain, diarrhea, fever, lethargy did not occur in either treatment groups. There was no detection of anemia or neutropenia in the zinc sulfate group.

Discussion

Although the eligibility criteria, radiotherapy protocols and dose of zinc sulfate supplementation in the current study were consistent with the previous trials[18,19], but the results did not support the benefit of zinc sulfate supplementation during radiation therapy.

Neither oral mucositis nor pharyngitis differed significantly between the two treatment groups. To date, there were only two trials that studied the effect of zinc sulfate for relieving mucositis in head and neck patients receiving radiation therapy and these trials significantly showed the benefit in relieving mucositis. The first one reported by Ertekin et al[18], showed that the zinc sulfate supplementation improved the oral mucositis and pharyngitis.

Thirty patients with head and neck cancer were randomly assigned to receive either zinc sulfate or placebo. They 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 the second trial was reported by Lin et al[19], studied 100 patients in a double blind randomized trial and found that patients in the control group developed grade 2 mucositis and dermatitis earlier than patients in the zinc sulfate group. There was also a significant difference in the development of grade 3 mucositis and dermatitis between the two groups. Patients in the zinc sulfate group were found to have milder mucositis and dermatitis.

The present study showed that zinc sulfate did not delay the starting of greater than or equal to grade 2 oral mucositis and pharyngitis as well as did not decrease frequency, severity of mucositis and treatment morbidities. The important limitation of the current trial was that the optimal dose of zinc sulfate

supplementation for relieving mucositis was still unknown. The authors chose to use of 150 mg per day of zinc sulfate, which was about 10 times higher than RDA, according to the benefit of zinc sulfate supplementation found in Ertekin et al's trial[18]. Recommended Daily Allowance (RDA) for zinc in adults is about 12-15 mg per day[21]. Nevertheless, patients did not experience the benefit of zinc sulfate. In terms of toxicity, the present study did not show any severe toxicities, although, the manifestations of over toxicity will occur with long-term exposure to as little as 100 to 300 mg of zinc per day (6 to 20 times the RDA)[22,23]. In summary, the benefit of zinc sulfate on relieving mucositis was still controversial. Therefore, the further study is needed and should consider not only the optimal dose of zinc sulfate supplementation but also the use of combined zinc sulfate with other interventions.

Conclusion

Zinc sulfate administered during head and neck radiation produced no significant benefit in relieving radiation-induced oral mucositis and pharyngitis. However, it has an acceptable side effects.

Potential conflicts of interest

None.

References

1. Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003; 66: 253-62.
2. Spijkervet FK, van Saene HK, Panders AK, Vermey A, Mehta DM. Scoring irradiation mucositis in head and neck cancer patients. J Oral Pathol Med 1989; 18: 167-71.
3. Kam AY, McMillan AS, Pow EH, Leung KC, Luk HW. A preliminary report on patient acceptance of a novel intra-oral lubricating device for the management of radiotherapy-related xerostomia. Clin Oral Investig 2005; 9: 148-53.
4. Rose-Ped AM, Bellm LA, Epstein JB, Trotti A, Gwede C, Fuchs HJ. Complications of radiation therapy for head and neck cancers. The patient's perspective. Cancer Nurs 2002; 25: 461-9.
5. Elting LS, Cooksley C, Chambers M, Cantor SB, Manzullo E, Rubenstein EB. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer 2003; 98: 1531-9.
6. Lockhart PB. Oral complications of radiotherapy. In: Peterson D, Elias J, Sonis ST, editors. Head and neck management of the cancer patient. Boston: Martinus Nijhoff; 1986: 429-49.
7. Motallebnejad M, Akram S, Moghadamnia A, Moulana Z, Omidi S. The effect of topical application of pure honey on radiation-induced mucositis: a randomized clinical trial. J Contemp Dent Pract 2008; 9: 40-7.
8. Clarkson JE, Worthington HV, Eden OB. Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 2007; (2): CD001973.
9. Worthington HV, Clarkson JE, Eden OB. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 2007; (4): CD000978.
10. Brown KH, Rivera JA, Bhutta Z, Gibson RS, King JC, Lonnerdal B, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document #1. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull 2004; 25 (1 Suppl 2): S99-203.
11. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. Am J Clin Nutr 1998; 68 (2 Suppl): 447S-63S.
12. Fischer WC, Black RE. Zinc and the risk for infectious disease. Annu Rev Nutr 2004; 24: 255-75.
13. Garofalo JA, Erlandson E, Strong EW, Lesser M, Gerold F, Spiro R, et al. Serum zinc, serum copper, and the Cu/Zn ratio in patients with epidermoid cancers of the head and neck. J Surg Oncol 1980; 15: 381-6.
14. Westin T, Ahlbom E, Johansson E, Sandstrom B, Karlberg I, Edstrom S. Circulating levels of selenium and zinc in relation to nutritional status in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 1989; 115: 1079-82.
15. Silverman S Jr, Thompson JS. Serum zinc and copper in oral/oropharyngeal carcinoma. A study of seventy-five patients. Oral Surg Oral Med Oral Pathol 1984; 57: 34-6.
16. Meftah S, Prasad AS, Lee DY, Brewer GJ. Ecto 5' nucleotidase (5'NT) as a sensitive indicator of human zinc deficiency. J Lab Clin Med 1991; 118: 309-16.
17. Ertekin MV, Koc M, Karslioglu I, Sezen O, Taysi S, Bakan N. The effects of oral zinc sulphate

during radiotherapy on anti-oxidant enzyme activities in patients with head and neck cancer: a prospective, randomised, placebo-controlled study. Int J Clin Pract 2004; 58: 662-8.
18. Ertekin MV, Koc M, Karslioglu I, Sezen O. Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: a prospective, placebo-controlled, randomized study. Int J Radiat Oncol Biol Phys 2004; 58: 167-74.
19. Lin LC, Que J, Lin LK, Lin FC. Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. Int J Radiat Oncol Biol Phys 2006; 65: 745-50.
20. Trotti A, Byhardt R, Stetz J, Gwede C, Corn B, Fu K, et al. Common toxicity criteria: version 2.0. an improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 2000; 47: 13-47.
21. National Research Council. Recommened dietary allowances. 10th ed. Washington, D.C.: National Academy Press; 1989.
22. Percival SS. Neutropenia caused by copper deficiency: possible mechanisms of action. Nutr Rev 1995; 53: 59-66.
23. Kelly EJ, Quaife CJ, Froelick GJ, Palmiter RD. Metallothionein I and II protect against zinc deficiency and zinc toxicity in mice. J Nutr 1996; 126: 1782-90.

การศึกษา randomized double blind, placebo-controlled ของการให้ซิงค์ซัลเฟตระหว่างการฉายรังสีในผู้ป่วยมะเร็งระบบ หู คอ จมูก เพื่อลดอาการอักเสบของเยื่อบุช่องปาก ลำคอ

ดวงใจ แสงถวัลย์, เต็มศักดิ์ พึ่งรัศมี, วัฒนา สินกิจเจริญชัย

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของการให้ซิงค์ซัลเฟตระหว่างการฉายรังสีในผู้ป่วยมะเร็งระบบ หู คอ จมูก ในแง่การลดอาการอักเสบของเยื่อบุช่องปาก ลำคอ*

วัสดุและวิธีการ: *ทำการศึกษาแบบ randomized double blind, placebo-controlled ในผู้ป่วยมะเร็งระบบ หู คอ จมูกจำนวน 144 ราย ผู้ป่วยได้รับการฉายรังสีเพียงวิธีเดียวหรือได้รับการฉายรังสีหลังการผ่าตัด ปริมาณรังสี 1.8-2 Gy ปริมาณรังสีรวม 50-70 Gy ในระยะเวลา 5-7 สัปดาห์ และได้รับซิงค์ซัลเฟต หรือ placebo ครั้งละ 50 มิลลิกรัม (10 ซีซี) วันละ 3 ครั้ง รับประทานตั้งแต่วันแรกของการฉายรังสีรวมทั้งวันหยุดจนถึงวันที่ครบการฉายรังสี ผู้ป่วยได้รับการประเมินก่อนการฉายรังสีเป็นพื้นฐาน สัปดาห์ละ 1 ครั้ง ระหว่างการฉายรังสี และ 1 เดือนหลังครบฉายรังสี*

ผลการศึกษา: *ลักษณะทั่วไปของผู้ป่วย ลักษณะโรค เทคนิคการฉายรังสี ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ระหว่างผู้ป่วยกลุ่มที่ได้รับและไม่ได้รับซิงค์ซัลเฟตระหว่างการฉายรังสี ผลการประเมินอาการอักเสบของช่องปาก ลำคอ ที่มีระดับมากกว่าหรือเท่ากับ grade 2 ขึ้นไป พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วยทั้ง 2 กลุ่ม ระหว่างการฉายรังสีแต่ละสัปดาห์และหลังครบฉายรังสี 1 เดือน สำหรับผลการประเมินอาการอักเสบของช่องปาก ลำคอ grade 3 พบผู้ป่วย 6 ราย (ร้อยละ 17) ในกลุ่มซิงค์ซัลเฟต และผู้ป่วย 10 ราย (ร้อยละ 23) ในกลุ่ม placebo มีอาการอักเสบของช่องปาก grade 3 และพบผู้ป่วย 22 ราย (ร้อยละ 32) ในกลุ่มซิงค์ซัลเฟต และผู้ป่วย 19 ราย (ร้อยละ 27) ในกลุ่ม placebo มีอาการอักเสบลำคอ grade 3 โดยไม่พบความแตกต่างกันอย่างมีนัยสำคัญระหว่างผู้ป่วยทั้ง 2 กลุ่ม อย่างไรก็ตามไม่พบอาการอักเสบของช่องปาก ลำคอ grade 4 ทั้งกลุ่มซิงค์ซัลเฟตและ placebo อาการข้างเคียงที่พบคืออาการคลื่นไส้ อาเจียน ซึ่งมีความรุนแรงระดับเล็กน้อย และไม่พบความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วยทั้ง 2 กลุ่ม*

สรุป: *การให้ซิงค์ซัลเฟตระหว่างการฉายรังสีในผู้ป่วยมะเร็งระบบ หู คอ จมูก ไม่ลดอาการอักเสบของเยื่อบุช่องปาก ลำคอ อย่างมีนัยสำคัญทางสถิติและผลข้างเคียงของซิงค์ซัลเฟตอยู่ในระดับปลอดภัย*
