The effect of zinc sulphate in the prevention of radiation induced oral mucositis in patents with head and neck cancer

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► ***Original article***

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ABSTRACT

Background: To investigate the effect of zinc sulphate for prophylaxis of radiation-induced oral mucositis in patients with head and neck cancer. ***Materials And Methods:*** In the department of Radiation Oncology, Ankara Numune Education and Research Hospital, 40 patients with head and neck cancer were selected randomly to receive either Zinco-C 25 mg, four tablets daily or control group who did not receive any drug. The patients were treated with Cobalt 60 teletherapy unit with conventional fractionation of 2 Gy/fraction. Oral mucositis were assessed by using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring criteria, before treatment, once a week during treatment and after treatment. Statistical analyses were performed using the SPSS for Windows software package. ***Results:*** In all patients, rates of grade 0, 1, 2, 3 mucositis were found 37.5%, 32.5%, 27.5% ve 2.5% respectively. Grade 0, 1, 2, 3 esophagitis were found 20%, 40%, 32.5%, 7.5%, respectively. Grade 4 mucositis and esophagitis were not detected in any patients. Between two groups, no relation was found between giving zinc and mucositis/esophagitis. Before radiotherapy, plasma zinc levels were lower in 20 patients (%50). In control group patients, post treatment serum zinc levels were significantly lower than zinc sulphate group (p=0.05). Incidence of mucositis and esophagitis was decreased when serum zinc levels were normal before and after treatment, though this was not statistically significant (p=0.476, p= 0.351 respectively). ***Conclusion:*** We found that zinc sulphate prophylaxis does not reduce incidence of mucositis and esophagitis. This may be due to before radiotherapy serum zinc levels in the patients who were given zinc were generally lower than control group. In other hand we showed that in control group patients, post treatment serum zinc levels were significantly lower than zinc sulphate group (p=0.05).

Keywords: *Mucositis, head and neck cancer, radiotherapy, zinc, prevention.*

INTRODUCTION

Head and neck cancers account for 4% of all cancers [(1)]. When treating these cancers with radiation therapy (RT) the most important problem is mucositis. Oral mucositis is thought to be a complex biological process that involves direct damage to the divided cells of the oral epithelium, along with depletion of the basal epithelium, which is modulated by the immune system, inflammatory processes, and super-infection, by oral bacterial flora. Mucositis can be painful and can cause substantial effects, such as by limiting food intake and altered taste, and may be a potential portal for infection. Mucositis can result in an interruption of RT during which time tumor cell regeneration can

occur. Moreover, as a result of mucositis oral food intake is reduced, which can lead to weight loss and deterioration in overall clinical condition [2-5].

Zinc is an antioxidant and an essential nutrient for normal growth; wound healing, response to infections, sense of taste, night vision, healthy epithelial tissue, tissue repair, cell-mediated immunity, and other vital functions [6-8]. The therapeutic role of zinc in acute infantile diarrhea, acrodermatitis enteropathica, prevention of blindness in patients with age-related macular degeneration, and treatment of the common cold has been reported [9].

We designed a prospective study to investigate the effect of zinc sulphate supplementation as prophylaxis of radiation-induced oral mucositis and esophagitis in head and neck cancer patients, who were treated with RT.

MATERIALS AND METHODS

Study design and patient characteristics

The study was conducted at Ankara Numune Education and Research Hospital, Department of Radiation Oncology and included 40 patients with head and neck cancer that were randomly assigned to the treatment group (4 Zinco-C 25-mg tablets daily) or the control group (no treatment). All the patients provided written informed consent to participate in the study. The study protocol was approved by The Turkish Ministry of Health Ethics Committee. Median age of the patients was 57 years (range: 41-74 years), and all had an RT field >33% of the buccal mucosa and were ECOG 0-2.

Radiation therapy

The patients were treated with conventional fractionation of 2 Gy. The treatment portals consisted of the primary tumor and the upper cervical lymph nodes, the lower cervical lymph nodes and supraclavicular lymph nodes. The median radiation dose in all the patients was 6440 cGy (range: 4600-7000 cGy) and the median dose in the treatment group was 6625 cGy (range: 6000-7000 cGy) versus 6316 cGy (range: 4600-7000 cGy) in the control group.

Clinical assessment and laboratory testing

Oral mucositis was assessed according to Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria before RT, once a week during RT and after RT. Complete blood count and biochemical tests were performed before RT, every week during RT, and the day after RT was completed. Serum zinc level measurement was performed at Refik Saydam Hıfzısıhha Center, Poison Research Department using an ICP-MS (inductively coupled plasma mass spectrometry) unit before RT and the day after RT was completed.

Statistical analysis

Statistical analysis was performed using the SPSS 15.0 statistical package software (SPSS Inc, Chicago, Illinois). The Mann Whitney U test was used to compare mean data values between the groups. Statistical significance was set at $p \leq 0.05$.

RESULTS

The characteristics of the patients in both groups were presented in table 1. Pathological diagnoses of the patients were presented in the table 2. Before RT, plasma zinc levels were low in 20 patients (50%).

Post-treatment serum zinc levels were significantly lower in the control group than in the treatment group ($p = 0.05$, figures 1-3).

Grade 0, 1, 2, and 3 mucositis were observed in 37.5%, 32.5%, 27.5%, and 2.5% of the patients, respectively. Grade 4 mucositis was not noted in any of the patients. When compared two groups for the development of mucositis, there was no relationship between zinc replacement and mucositis ($p = 0.159$, table 3).

Among the patients with low pre-treatment serum zinc levels, grade 1 mucositis was observed in 6 patients, grade 2 in 7 patients, and grade 3 in 1 patient. Among the patients with normal pre-treatment serum zinc levels, grade 1

Table 1. Patient characteristics.

	Treatment group (n = 16)	Control group (n = 24)
Gender		
Male	15	24
Female	1	0
Age (years)	42-74 (median:56)	41-73 (median: 58)
Tumor Locaion		
Laryngeal	13	22
Gingiva	0	1
Malignancy of un-known origin	1	0
Floor of the mouth	0	1
Nasopharyngeal	2	0
Surgery before radiotherapy		
Yes	7	17
No	9	7
Concurrent chemo-therapy	10	10

Table 2. Histopathological diagnoses of the patients.

Tumor site	Histopathology
Larynx	Squamous cell carcinoma (n = 35)
Gingiva	Squamous cell carcinoma (n = 1)
Malignancy of unknown origin	Squamous cell carcinoma (n = 1)
Floor of the mouth	Adenoid cystic carcinoma (n = 1)
Nasopharyngeal	Non-keratinizing (n = 1), Undifferentiated carcinoma (n = 1)

and 2 mucositis were observed in 7 and 4 patients, respectively, and grade 3 mucositis was not noted in any of the patients. Likewise, among the patients with low

post-treatment serum zinc levels, grade 1 and 2 mucositis was noted in 8 and 6 patients, respectively; in those with normal post-treatment serum zinc levels grade 1 mucositis was noted in 5 patients, grade 2 in 5 patients, and grade 3 in 1 patient (table 4). These results show that the incidence of mucositis was lower in the patients with normal serum zinc levels before and after RT, though that was not statistically significant (p = 0.476).

Among the patients with low pre-treatment serum zinc levels, grade 1 mucositis was observed in 6 patients, grade 2 in 7 patients, and grade 3 in 1 patient. Among the patients with normal pre-treatment serum zinc levels, grade 1

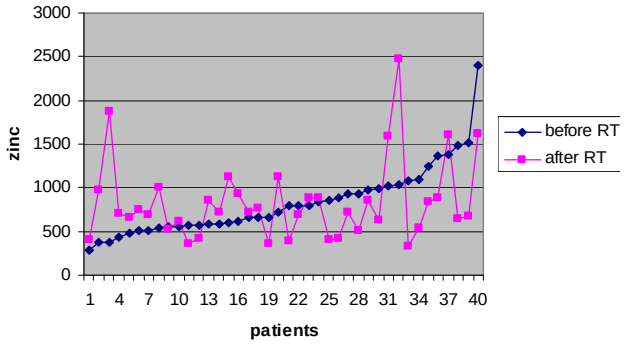

Figure 1. Alterations in serum zinc levels in all the patients.

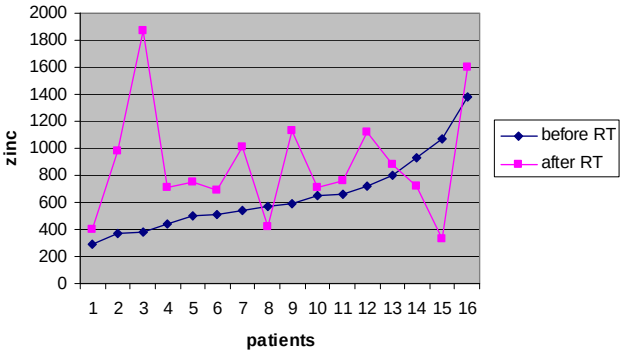

Figure 2. Alterations in serum zinc levels in the treatment group.

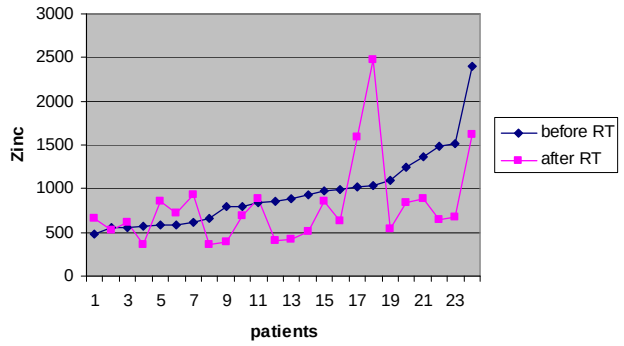

Figure 3. Alterations in serum zinc levels in the control group.

and 2 mucositis were observed in 7 and 4 patients, respectively, and grade 3 mucositis was not noted in any of the patients.

Likewise, among the patients with low post-treatment serum zinc levels, grade 1 and 2 mucositis was noted in 8 and 6 patients, respectively; in those with normal post-treatment serum zinc levels grade 1 mucositis was noted in 5 patients, grade 2 in 5 patients, and grade 3 in 1 patient (table 4). These results show that the incidence of mucositis was lower in the patients with normal

serum zinc levels before and after RT, though that was not statistically significant (p = 0.476).

Esophagitis was also evaluated in the patients. Grade 0, 1, 2, and 3 esophagitis was observed in 20%, 40%, 32.5%, and 7.5% of the patients, respectively. Grade 4 esophagitis was not noted in any of the patients. A statistical relationship between the administration of zinc and esophagitis was not noted (p = 0.596, table 5).

As such, in the mucositis and serum zinc level relationship, the incidence of esophagitis was lower in the patients with normal serum zinc levels before and after RT, but that was not statistically significant (P = 0.351, table 6).

Table 3. Zinc-mucositis relationship.

		Grade of mucositis				*Total*
		0	**1**	**2**	**3**	
Control	**Count**	12	7	5	0	*24*
	Expected	9	7.8	6.6	.6	
	Std. Residual	1.0	-.3	-.6	-.8	
Zinc +	**Count**	3	6	6	1	*16*
	Expected	6	5.2	4.4	.4	
	Std. Residual	*-1.2*	*.4*	*.8*	*.9*	

n=40	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.175	3	.159
Likelihood Ratio	5.726	3	.126

Table 4. The incidence of mucositis according to zinc levels before and after RT.

	Grade of mucositis					*Total*
	0	**1**	**2**	**3**	**4**	
Before RT: Low Zn	6	6	7	1	0	*20*
Normal Zn	9	7	4	0	0	*20*
After RT: Low Zn	7	8	6	0	0	*22*
Normal Zn	8	5	5	1	0	*18*
Total	***15***	***13***	***11***	***1***		***40***

n = 40	Value	df	Asymp. Sig. (2-sided)
Pearson's chi-square	2.495(a)	3	.476
Likelihood ratio	2.896	3	.408

Table 5. Zinc-esophagitis relationship.

		Grade of esophagitis				*Total*
		0	**1**	**2**	**3**	
Control	**Count**	6	10	6	2	*24*
	Expected	4.8	9.6	7.8	1.8	
	Std. residual	.5	.1	–.6	.1	
Zinc +	**Count**	2	6	7	1	*16*
	Expected	3.2	6.4	5.2	1.2	
	Std. residual	*–.7*	*–.2*	*.8*	*–.2*	

Table 6. The incidence of esophagitis according to zinc levels before and after RT.

	Grade of esophagitis					*Total*
	0	**1**	**2**	**3**	**4**	
Before RT: Low Zn	2	9	8	1	0	*20*
Normal Zn	6	7	5	2	0	*20*
After RT: Low Zn	4	9	8	1	0	*22*
Normal Zn	4	7	5	2	0	*18*
Total	***8***	***16***	***13***	***3***	***0***	***40***

n = 40	Value	df	Asymp. Sig. (2-sided)
Pearson's chi-square	3.276 (a)	3	.351
Likelihood ratio	3.382	3	.336

DISCUSSION

We found that the prophylactic administration of zinc sulphate did not reduce the incidence of mucositis or esophagitis in head and neck cancer patients treated with RT compared to controls. This may have been due to the fact that pre-radiotherapy serum zinc levels in the patients given zinc were generally lower than those in the control group (641 mg L^{-1} and 951 mg L^{-1}, respectively). High pre-treatment and post-treatment zinc levels were associated with a reduction in the incidence of mucositis and esophagitis, though this was not statistically significant due to the small number of patients. On the other hand, the present study shows that post-treatment serum zinc levels in the control group were significantly lower than those in the treatment group (p = 0.05).

RT-related zinc deficiency has been reported in numerous studies. In particular, in head and cancer patients pre-treatment blood zinc levels were significantly lower. Abdulla et al reported that zinc levels in plasma and whole blood in 13 patients with squamous cell carcinoma of the head and neck were significantly lower, and that the copper:zinc ratio in plasma was significantly higher, as compared to healthy controls [10]. The plasma zinc level was significantly lower in patients that did not respond to therapy and

died within 12 months than in those that responded to therapy and were in remission within 12-15 months. Among the patients that responded to therapy and were alive after 12-15 months, the level of zinc in plasma and whole blood, and the copper:zinc ratio were normal. The researchers suggested that plasma zinc and the copper: zinc ratio might be of value as potential screening and prognostic tests in patients with head and neck cancer [10].

Büntzel *et al.* studied 100 untreated patients with head and neck cancer in whom the serum concentration of selenium, copper, zinc, and ferrum was measured [11]. Of the patients, 66% of the patients had a low serum concentration of selenium, and 33% had low zinc and iron levels. Copper was elevated in 30% of the patients.[11] In Silverman and Thompson's study 75 patients with oral/oropharyngeal carcinoma were assessed for the relationship between serum zinc and copper levels, radiation-induced taste loss, and tumor status [12]. There were no significant differences between pre-treatment and post-treatment serum mineral levels in the cancer patients and 21 healthy controls. Among the 30 patients that did not experience spontaneous post-radiation taste recovery and were administered zinc sulphate, 11 reported an improvement in taste. Serum zinc levels rose markedly in the patients with taste improvement [12]. Ripamonti *et al.* reported that among their head and neck cancer patients, 1 month after external RT was terminated those that received zinc sulphate had earlier recovery of taste acuity than those that received a placebo [13].

The relatively low frequency of urinary tract infections in men may be due, in part, to the very high microbicidal zinc concentration in semen. Moreover, the effect of zinc on the common cold may be due to increased zinc concentration in the nasal mucosa, which may alter the conformation of the binding site between ICAM1 and the virus [14, 15]. According to Prasad *et al.*, zinc deficiency resulted in an imbalance of TH1 and TH2 functions. Zinc deficiency was associated with increases in tumor size, overall stage of cancer, and unplanned hospitalizations [16].

Ertekin *et al.* studied 30 patients with head and neck cancer that were randomly assigned to receive zinc sulphate or a placebo during RT [17].Grade 3-4 mucositis was not noted in the zinc sulphate group, but grade 0 mucositis was observed in 2 patients, grade 1 in 8 patients, and grade 2 in 5 patients. In the placebo group grade 2 mucositis was noted in 4 patients and grade 3 was noted in 8 patients. The degree of mucositis in the zinc sulphate group was significantly lower than in the placebo group ($P < 0.05$). Confluent mucositis developed earlier in the placebo group than in the zinc sulphate group after the onset of treatment and began to improve sooner in the zinc sulphate group than in the placebo group. Post-treatment serum zinc levels were significantly lower than pre-treatment levels in the control group [17].

Lin *et al.* conducted a study in Taiwan to determine if zinc supplementation could accelerate the healing of mucositis and dermatitis after RT [18]. Patients in the control group developed grade 2 mucositis and dermatitis sooner than patients in the experimental group. There was also a significant difference in the development of grade 3 mucositis and dermatitis between the 2 groups. Post-treatment serum zinc levels in the control group were significantly lower than those in the experimental group ($p = 0.02$) [18].

This study has some limitations. First, it has not double-blinded design and we could not use placebo. So, these limitations, of course, might lead some bias. Secondly, our study included small sample size, particularly in subgroups. Another important point is that there were more patients underwent surgery in control group than that of interventional group and this may be implicated overall results between two groups.

In conclusion, we found that zinc sulphate prophylaxis does not reduce incidence of mucositis and esophagitis in head and neck patients who were treated with RT. However, it appears that zinc supplementation maintains the plasma zinc level in these patients. The prophylactic efficacy of zinc administration could be proved by further prospective larger studies. Prophylactic administration of zinc can

be routinely used to increase the efficacy of RT and to decrease the likelihood that RT will be interrupted.

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