



The Effect of Orally-Administered Zinc in the Prevention of Chemotherapy-Induced Oral Mucositis in Patients with Acute Myeloid Leukemia

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Abstract

Background: Oral mucositis is a frequent yet serious adverse event associated with chemotherapy in acute myeloid leukemia. Although a wide spectrum of drugs has been tested for prophylaxis of oral mucositis, few of them are satisfactory. There is currently substantial clinical interest in zinc (Zn) as an antioxidant and a protective agent against chemotherapy-related normal tissue injury. Therefore, in the present study, we investigated whether zinc prevents oral mucositis associated with chemotherapy in patients with AML.

Methods: A total of 140 patients with AML were randomly selected and divided into two groups where the case groups received zinc sulfate 220 mg orally and the control groups received placebos 3 times a day during their chemotherapy course. Data were analyzed by SPSS version 15 software. Mann-Whitney U test was used to evaluate mucositis, and pain intensity.

Results: The incidence rates of mucositis were all markedly lower in oral zinc sulfate group than in control ($P = 0.004$).

Conclusions: Zinc is available for preventing the complications of oral mucositis, and thus for improving patient quality of life.

Keywords: Mucositis, Leukemia, Zinc Sulfate

1. Background

Oral mucositis (OM) is a common dose-limiting complication in patients receiving systemic anticancer chemotherapy or local irradiation for tumors in the head and neck area. With prevalence between 10% and 100%, depending on the cytotoxic regimen and patient-associated variables, this morbid condition represents a significant problem in oncology (1).

Oral mucositis can be painful, significantly affect nutritional intake, mouth care and quality of life, and have a significant economic impact (2, 3).

Several agents have been tested to reduce the severity of, or prevent mucositis. Current treatments for oral mucositis in the clinics settings are local anesthetics, paliferin, glutamine, caphsol mouth rinse, amifostine and antimicrobial agents (4, 5).

Zinc (Zn) is an essential intracellular mineral of "exceptional biologic and public health importance" with important enzymatic cofactor activities for cell membrane sta-

bility, DNA and RNA structure. At the cellular level, zinc is critical for cell survival, affecting signal transduction, transcription, and replication. Zinc thus plays an essential role in growth, immune function, proteoglycan synthesis, antioxidant defense, formation of collagen and a critical component in the healing wound. Zinc ability to retard oxidative processes has long been recognized. Many studies have reported that Zn plasma levels may negatively affect wound healing significantly (6, 7).

Acute myeloid leukemia (AML) is a cancer of the myeloid line of blood cells, characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is treated initially with chemotherapy aimed at inducing a remission. Patients may go on to receive additional chemotherapy or a hematopoietic stem cell transplant (8).

This article outlines the role of zinc on the oral mucosa status in patients with acute myeloid leukemia (AML) during antineoplastic therapy.

2. Methods

This clinical trial was a double-blind, randomized, placebo controlled study. Subjects were selected from patients who referred to the oncology department at Tabriz Shahid Ghazi Tabatabaai hospital, Tabriz, Iran. All patients were enrolled between April and September, 2013.

Inclusion criteria included: i) Patients undergoing chemotherapy with AML, and ii) chemotherapy treatment by a regimen with the same mucositis probability.

Exclusion criteria included: i) prior chemotherapy or treatment with any chemotherapy agent, ii) any malignancy within the last 5 years, iii) infection, iv) any oral ulcers and mucositis developed before starting chemotherapy, and v) known allergy to oral zinc-containing or multi-vitamin medications.

The present study was carried out on one hundred and forty patients with acute myelogenous (or myeloid) leukemia (AML) (18 -71 years of age) were randomly divided into two groups: the first group received zinc-supplement orally; 220 mg zinc sulfate capsules 3 times daily (Alhavi Co., Tehran, Iran) and the second group or the control group were given placebo capsules during their chemotherapy course.

The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences, and all patients gave written, informed consent. IRCT registration number is: IRCT2013042312510N2.

Patients were followed up 2 weeks after the treatment commenced (week 2) and at the end of treatment (week 4). Patients who dropped out before completing treatment were asked to complete all outcome measures on exiting the trial.

Oral mucositis was graded from 0 to 4, using World Health Organization (WHO) criteria and was diagnosed from 1 to 4, as seen in [Table 1](#).

Table 1. World Health Organization (WHO) Criteria of Oral Mucositis

Description	Grade
Normal moisture	1
Scant saliva	2
Absence of moisture, sticky, viscous saliva	3
Absence of moisture, coated mucosa	4

The degree of pain was evaluated based on a visual analog scale, where zero indicates no pain and ten is the most severe pain that can be endured. Patients showed the degrees of their pain by a ruler. Patients were requested to choose a number from 1 to 10 that expressed their pain intensity.

The results were analyzed by SPSS version 15 software. The independent samples t-test was used to evaluate mucositis recovery time. Mann-Whitney U test evaluated mucositis, and pain intensity. The Friedman test was used to evaluate the effect of time. P was considered significant at the 0.005 level for the Mann-Whitney U test.

3. Results

As shown in [Table 2](#), there were no significant differences in gender and age between the two groups and distribution of them were the same in both groups ($P > 0.05$).

Table 2. Patients' Demographics (N = 70)

Variables	Case	Control
Gender, No. (%)		
Female	25 (35.7)	29 (41)
Male	45 (64.3)	41 (59)
Age	12.6 ± 46.3	49.4 ± 11

In the zinc sulfate group, Grades 0 and 1 mucositis were detected in 51.4% and 34.3% patients and 92.9% and 27.5 patients in the control group after the second week of zinc administration. As shown in [Table 1](#), the response rate was not significantly different between the control and Zn groups ($P > 0.05$) ([Table 3](#)).

The results of the present study indicated that the frequency of severe mucositis (grade 3 - 4) was significantly lower in case group (1.4%) than in control group (7.2%) at the end of the 4th week of treatment ($P = 0.004$) ([Table 4](#)).

This study showed that there was no statistically significant difference in patient pain intensity between the two treatment groups after two weeks. We found that zinc supplementation was not associated with decreased pain intensity. In contrast, the use of placebo for the relief of oral pain was significantly larger in control group than in Zn group at the end of the 4th week of treatment ($P = 0.03$). The analytical results of this study for degree of pain is presented below ([Table 5](#)).

4. Discussion

We investigated whether zinc sulfate could improve the symptoms of oral mucositis among patients with AML and in this study our findings supported the use of zinc sulfate as a symptomatic treatment for oral mucositis. There was a statistically significant difference in clinical and cure rate between the two treatment groups. Zinc sulfate seems to be one of the promising agents in mucositis prevention.

Table 3. Oral Mucositis Grades in Both Groups of Patients (N = 70)

Mucositis	Case				Control			
	Week 2		Week 4		Week 2		Week 4	
	No.	%	No.	%	No.	%	No.	%
Grade 0	36	51.4	65	92.9	32	46.4	49	71
Grade 1	24	34.3	4	5.7	19	27.5	15	21.7
Grade 2	8	11.4	1	1.4	8	11.4	5	7.2
Grade 3	2	2.9	0	0	9	13	0	0
Grade 4	0	0	0	0	1	1.4	0	0

Table 4. Effect of Zn on the Incidence of Oral Mucositis and Pain in Patients with Leukemia Who Received Chemotherapy

Experimental Groups	No.	Mean of the Incidence of Oral Mucositis	
		Weeks 2	Weeks 4
Control group	70	1.1 ± 0.96	0.6 ± 0.36
Zinc sulfate group	70	0.66 ± 0.9	0.3 ± 0.08

Table 5. Mean Pain Intensity in Both Groups of Patients

Pain (VSA)	Mean	P Value
Week 2	-0.25	0.8
Week 4	-2.1	0.03

In the two studies, it was effective in reducing mucositis severity. This is in accordance with the findings of Ertekin et al. in 2004 (9) and Watanabe et al. in 2010 (10).

Ertekin et al. reviewed the incidence of radiation-induced oral mucositis in head and neck cancer patients and showed that the rate is over 80% (9).

Watanabe et al. carried out a clinical trial comparing the effects of Zn supplementation and azulene (control) on the incidence of oral mucositis and they concluded that Zn supplementation could be highly effective in reducing it (10).

We reported here that systemic oral intake of zinc sulfate was effective for prevention of oral mucositis associated with chemotherapy in patients with AML.

Arbabi-kalati et al. showed that although the use of zinc sulfate did not decrease the incidence of mucositis in patients, it improved the intensity of oral mucositis and xerostomia (11).

In that study patients were selected according to chemotherapy regiment prescribed, not their disease. It seems that the type of disease may affect the effectiveness

of zinc.

However, Mehdipour et al. found that the use of topical zinc sulfate in treated groups decreased the severity of chemotherapy induced oral mucositis in patients with AML (12).

Pain from radiochemotherapy therapy-induced mucositis is a significant clinical problem for patients with head and neck cancer (13).

In the present study, zinc had no role in pain relief (P = 0.03). Our findings corroborate those reported by Arbabi-kalati et al. reporting that prophylactic using zinc sulfate did not decrease pain intensity (11). However Watanabe et al. had shown that the pain intensity markedly was lower in zinc group than in control (10). It seems that a high dose of zinc has no effect on pain intensity.

The result of the present study may be due to the role of zinc in protein and collagen synthesis and in tissue growth and epithelization (14, 15).

In this study we investigated the role of zinc on the oral mucosa status in patients with AML during antineoplastic treatment.

In summary, we found that Zn supplementation was associated with a decrease in overall oral mucositis among leukemic patients, whereas multivitamin had no significant effects on any of these or other outcomes. However, more research is needed to identify the site of zinc to relieve the pain. Wound healing is a complicated process that involves various cell types and structural proteins.

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Footnotes

Authors' Contribution: Narges Gholizadeh and Hadi Chavashi designed the study and were the supervisors. Masomeh Mehdipour, Soran Kahani and Maryam-Sadat Sadrzadeh-Afshar participated in doing the experiments. All authors read and approved the final manuscript.

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