J Nephropharmacol. 2023; 12(1): e10533.

https://www.jnephropharmacology.com DOI: 10.34172/npj.2022.10533

Journal of Nephropharmacology

See the commentary by Momenzadeh (J Nephropharmacol. 2023;12(1):e10567)

The effect of oral zinc sulfate on prevention of chemotherapy-induced oral mucositis in breast cancer patients treated with adriamycin and cyclophosphamide; a double-blind randomized clinical trial

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ARTICLE INFO

Article Type:
Clinical Trial

Article History:
Received: 14 July 2022
Accepted: 23 August 2022
Published online: 22 November 2022

Keywords:
Breast cancer
Zinc sulfate
Oral mucositis
Chemotherapy

ABSTRACT

Introduction: One of the most important complications faced by cancer patients is chemotherapy-induced oral mucositis (CIOM). In addition, the role of orally used zinc sulfate in its prevention and treatment is still a controversial issue and the results in this regard have not been conclusive.
Objectives: Evaluation the effect of zinc sulfate supplement on prevention of CIOM in breast cancer patients treated with adriamycin and cyclophosphamide was the aim of this study.
Patients and Methods: The current double-blind randomized clinical trial was conducted on 87 patients with breast cancer. Consumption of two oral zinc sulfate tablets and two placebo tablets with food was prescribed in the case (44 patients) and control (43 patients) groups, respectively. During the 4 cycles of chemotherapy, the incidence and severity of CIOM, the onset time of mucositis from the start of chemotherapy, the severity of pain, and the severity of dry mouth were recorded. In addition, the patients' quality of life was recorded using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
Results: Findings revealed that the severity of CIOM in the first, second, and third sessions with the values of 1.22 ± 1.01, 1.18 ± 0.97 and 1.02 ± 0.79, respectively, was significantly lower in the case group than the control group with the values of 1.91 ± 0.89, 1.80 ± 0.92, and 1.67 ± 0.85, respectively ($P < 0.05$). In addition, the severity of pain and dry mouth in the first and second sessions of chemotherapy was significantly lower in the case group ($P < 0.05$). However, no significant difference was observed between the two groups in quality of life ($P > 0.05$).
Conclusion: Oral zinc sulfate had a significant role in reduction of the incidence and severity of CIOM, the severity of dry mouth, and the severity of pain in the initial sessions of chemotherapy. However, no significant difference was in postponing the incidence of CIOM and the quality of life of patients in the case group.
Trial Registration: This trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20150304021338N2; https://irct.ir/trial/51105, ethical code# IR.MUI.MED.REC.1399.277).

Implication for health policy/practice/research/medical education:
In a double-blind randomized clinical trial study, 87 patients with breast cancer that were divided into two groups. Patients in the control group received placebo tablets, and the case group received zinc sulfate tablets. The results of this study showed that oral zinc sulfate had a significant role in reducing the incidence and severity of mucositis, the severity of dry mouth, and the severity of pain in the initial sessions of chemotherapy.
Please cite this paper as: Roayaei M, Andalib Z, Akhavan A. The effect of oral zinc sulfate on prevention of chemotherapy-induced oral mucositis in breast cancer patients treated with adriamycin and cyclophosphamide; a double-blind randomized clinical trial. J Nephropharmacol. 2023;12(1):e10533. DOI: 10.34172/npj.2022.10533.

Introduction

Cancer is one of the major causes of disorders, mortality, and disability worldwide. Currently, due to the increasing prevalence of cancer, a large amount of efforts of the care systems are directed to this group of patients to reduce chemotherapy-induced complications and the burden of the disease imposed on these patients and improve the patients' quality of life (1). One of the most widely

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employed treatments in cancer is chemotherapy, which is one of the main treatment modalities for lung, breast, bladder, colorectal, cervix, ovary, and prostate cancers (2).

Chemotherapy, like other treatments, has complications such as vomiting, nausea, hair loss, fatigue, sleep disorders, mouth ulcers, oral mucositis, ovarian failure, hyperuricemia, neuropathy, cardiomyopathy, hemorrhagic cystitis, and renal dysfunction (3). Since renal dysfunction is associated with decreased renal clearance of drugs, it can lead to the incidence and severity of complications in patients using anticancer drugs. In this regard, adriamycin-induced renal injury impairs the function of endothelial progenitor cells and causes chronic and progressive glomerular changes that lead to terminal renal failure. In addition, some other studies have also reported renal dysfunction as a possible risk factor for severe oral mucositis; However, they considered confounding factors such as oral microflora or genetic factors may be effective on this relationship and the detailed mechanism related to renal dysfunction and oral mucositis remains unknown (4).

On the other hand, oral mucositis is one of the serious complications in patients undergoing radiotherapy or chemotherapy. A research indicates that 40% of cancer patients undergoing chemotherapy or bone-marrow transplantation suffer from oral mucositis (5). Oral mucositis causes debilitating and painful inflammation of the mouth and can lead to the opioid use (6). Due to the patients' inability to use oral nutrition, they are forced to take advantage of enteral or intravenous feeding systems. Severe mucositis can affect the patients' treatment plan and may result in the discontinuation of the treatment in some cases (7,8).

Mucositis is often treated with chlorhexidine, sodium carbonate, saline mouthwashes, and local anesthetics such as diphenhydramine, promethazine mixed with milk of *magnesia* and can additionally be controlled using taste masking compositions such as sucralfate, anti-inflammatory substances such as chamomile extract (*Matricaria recutita*), topical steroids, and sufficient water consumption. However, none of these can completely cure mucositis (7,9-13).

Furthermore, some studies have investigated the zinc effects on wound healing and health of epithelial tissue that revealed that zinc sulfate supplementation causes rapid healing of leg and stomach ulcers. Moreover, these studies have mentioned that zinc sulfate supplementation has a greater effect on patients having sufficient serum zinc levels (14). Several studies have been conducted to evaluate the role of oral zinc sulfate in the treatment of chemotherapy-induced oral mucositis (CIOM). These studies showed it has the potential to reduce the CIOM the incidence and its severity (14,15). In contrast, some other studies have not considered the zinc administration to be significant in preventing and delaying the incidence of mucositis (16). The review of literature indicates that the results regarding the effect of zinc are contradictory, and its effect on patients' xerostomia, pain, and quality of life has received less attention.

Objectives

The present study has eliminated the possible confounding effects of the type and dosage of the chemotherapy drug and investigated the effect of oral zinc sulfate on the prevention of CIOM in breast cancer patients treated with adriamycin and cyclophosphamide.

Patients and Methods

Study design

This randomized double-blind clinical trial was conducted on all women with breast cancer in need of chemotherapy (adjuvant, neoadjuvant, or recurrence) that referred to Seyed-al-Shohda hospital in Isfahan during 2021-2022.

The sample size of 92 patients (46 individuals in each group) was selected with 95% confidence level and 80% test power; regarding the results of previous studies (15) the incidence of mucositis in two groups with and without the zinc administration was equal to 0.3 and 0.07, respectively.

The criteria for entering the study included having breast cancer confirmed by biopsy, being a candidate for receiving chemotherapy containing adriamycin and cyclophosphamide, not having oral mucositis before the study, and having a normal serum zinc level.

It should be noted that as the selection criteria attended to patients' stage of the disease, performance status, and previous treatments, patients whose stage of the disease required chemotherapy according to international protocols [American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN)] were selected to participate in this study.

In addition, in case of patient's lack of cooperation or their death during the study, the sample was excluded from the study.

The patients' serum zinc level was checked, and they were included in the study in case of the normal serum zinc level. At the beginning of the study, their basic and clinical information including age, gender, height, weight, body mass index (BMI), type of chemotherapy drug, dose of chemotherapy drug, incidence and severity of mucositis, pain, and dry mouth were recorded. Using random allocation software, the patients were then divided into two groups.

At the start of the chemotherapy treatment, all the necessary explanations were orally provided to the patients, who were informed about the course of the treatment and the purpose of the study during a visit about one week before the start of the treatment. The patients were given a clinical examination of the mouth to ensure that they do not have any oral complications such as mucositis before the start of chemotherapy. Then,

the consumption of two oral zinc sulfate tablets (Al-Hawi Company) and two placebo tablets (Al-Hawi Company) with food was prescribed in the case and control groups, respectively.

During four cycles of chemotherapy, patients were visited every three weeks by a trained radio-oncology assistant. The incidence of mucositis, the grade of mucositis, the time of the onset of mucositis from the start of chemotherapy, the severity of pain and, and the severity of dry mouth were recorded.

The patients' pain was determined based on the visual analogue scale (VAS) from 0 (no pain) to 10 (pain as bad as it could possibly be). The severity of dry mouth was recorded by the Late Effects on Normal Tissues-Subjective, Objective Management and Analytic (LENT-SOMA) scale based on the score 1 (normal moisture), 2 (scant saliva), 3 (absence of moisture, sticky, and viscous saliva), and 4 (absence of moisture, coated mucosa) (17).

The severity of mucositis was measured based on the criteria prepared by the World Health Organization (WHO) (18) and Spijkervet criteria (19). Based on the Spijkervet criteria, the symptoms of mucositis were examined in 8 spots of the mouth. Each of the color change, erythema, pseudo-membrane formation, and ulceration was given one point, which were then added up for each patient.

In addition, the EORTC QLQ-C30 questionnaire was used to evaluate the patients' quality of life before the start of chemotherapy and in the last follow-up session. Considering the validity and reliability the previous studies have been confirmed the Persian version of this questionnaire for cancer patients (20). In this study, only the overall score obtained from 30 items of this questionnaire was considered.

Statistical analysis

Finally, the collected data was analyzed with SPSS software (version 26) and presented as means ± standard deviation (SD) or frequency (%). Normal distribution of data has been confirmed by the results of the Kolmogorov-Smirnov test, thereby an independent samples *t* test, chi-square test, and ANOVA repeated measures were applied to compare the mean of quantitative data, the frequency distribution of qualitative data, and the trend of changes in the severity of pain, mucositis, and dry mouth over time, respectively. The significance level was considered less than 0.05 in all analyses.

Results

In the current study, out of 92 women with breast cancer, two patients in the case group and three of the control group were excluded because of not continue the follow-up duration or not taking zinc regularly as prescribed (Figure 1).

The case and control groups included 44 patients with the mean age of 48.98 ± 9.65 years and 43 patients with the mean age of 47.91 ± 9.13 years, respectively. In terms of height, no significant difference observed in weight, age, BMI, adriamycin dose, and cyclophosphamide dose ($P > 0.05$; Table 1).

The incidence of CIOM in the case group was 38.6% in the first session, 36.4% in the second session, 25% in the third and fourth session of chemotherapy while in the control group it was 74.4% in the first session, 69.8% in the second session, 74.4% in the third session, and 46.5% in the fourth session of chemotherapy. The incidence of CIOM in the case group was significantly lower in the first, second, and third sessions ($P < 0.05$). In addition, the severity of CIOM in the first, second, and third sessions was significantly lower in the case group (1.22 ± 1.01, 1.18 ± 0.97 and 1.02 ± 0.79, respectively) than the control group (1.91 ± 0.89, 1.80 ± 0.92, and 1.67 ± 0.85, respectively) ($P < 0.05$; Table 2, Figure 2).

In addition, the severity of pain in the first and second sessions of chemotherapy in the case group with the means of 2.00 ± 3.44 and 1.91 ± 3.27 was significantly lower than that of the control group with the means of 3.59 ± 3.98 and 3.64 ± 4.01, respectively ($P < 0.05$). Additionally, in the case group the severity of dry mouth was significantly lower in all chemotherapy sessions ($P < 0.05$) such that during 4 chemotherapy sessions, the severity of dry mouth was significantly decreased in the case group over time. In addition, the patients' quality of life in the case group increased significantly after the last chemotherapy session with the mean of 51.64 ± 11.32 as compared to the first session with the mean of 50.45 ± 10.25 ($P = 0.011$); but quality of life had no significant change in the control group ($P = 0.552$; Table 3).

Table 1. Patients' basic and clinical characteristics in the two groups

Characteristics	Zinc group (n=44)	Control group (n=43)	*P* value
Age (y)	48.98±9.65	47.91±9.13	0.597
Weight (kg)	67.50±4.52	67.00±3.62	0.500
Height (cm)	163.59±2.31	164.67±1.55	0.061
BMI (kg/m²)	25.21±1.38	24.70±1.24	0.077
Adriamycin dose (mg/m²)	103.50±4.62	103.02±4.65	0.633
Cyclophosphamide dose (mg/m²)	1035.00±46.23	1030.23±46.47	0.634

Data are shown as mean ± SD.

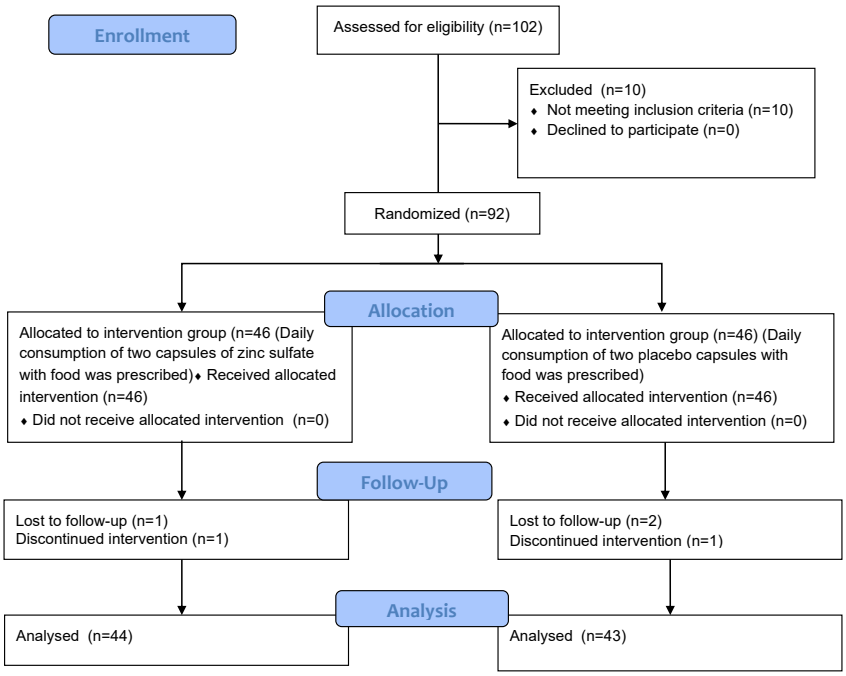

Figure 1. Consort flowchart of patients.

Discussion

Mucositis has been reported as one of the worst complications of chemotherapy in patients undergoing radiotherapy such that it may lead to the discontinuation of treatment in 11% of patients (16). According to the results of previous studies, CIOM in non-keratinized mucosa usually starts in the first and second weeks of chemotherapy and subsides in the third or fourth week after chemotherapy (21). In addition, mucositis may reduce the quality of life, increase economic burden, or even lead to patients' hospitalization. Therefore, it is very crucial to specify supplemental treatments to prevent mucositis or reduce its prevalence and severity. Consequently, the current study purposed to evaluate the impact of oral zinc sulfate on oral mucositis and suggested the administration of zinc caused a significant decrease in its incidence and severity in the first to third sessions of chemotherapy in the case group. Moreover, the time interval from the start of chemotherapy to the incidence of oral mucositis was non-significantly longer in the case group.

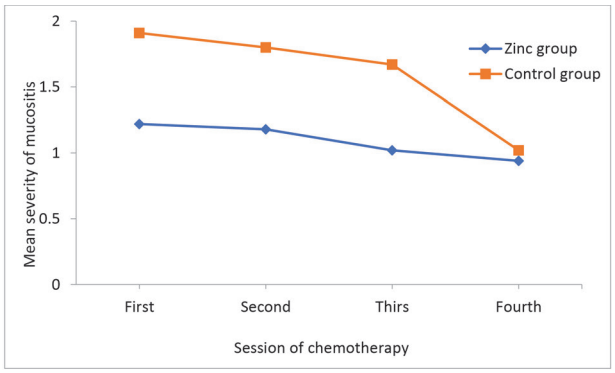

Figure 2. Linear diagram of the mean severity of chemotherapy-induced oral mucositis in the two groups.

It is thought that oral mucositis is caused by a complex biological process that includes direct damage of oral epithelium cells during division, decrease of epithelium basal layer cells, a weakness in regulating the immune system of the body, an increase in the intensity of inflammatory processes, and an increase in infection with oral flora (22). At present, it seems that not only zinc causes to increase the re-epithelialization but also reduces tissue inflammation and bacterial activity by inducing rapid wound healing.

Zinc controls the immune system and T lymphocytes. A decrease in the serum zinc level leads to lymphopenia and a decrease in cellular and humoral immunity. Further the protective and therapeutic effect of oral zinc sulfate is considered for treating oral injuries and the healing of mucosal and tongue wounds (14). Some researchers have studied the effect of zinc sulfate on radiotherapy- and CIOM. For example, according to the study by Ertekin et al, grades 3 and 4 mucositis were not observed in any patients in the zinc sulfate group. In general, the severity of mucositis in the zinc sulfate group was significantly lower. Furthermore, they suggested that there was a significant incidence of mucositis in the placebo group earlier than the zinc sulfate group (23). Although the results of their study were in line with present study, the difference in the time of the onset of mucositis was not significant in our study.

Table 2. The incidence of chemotherapy-induced oral mucositis in the two groups

Chemotherapy-induced oral mucositis	Zinc group (n=44)	Control group (n=43)	*P* value
Incidence of oral mucositis			
1st session of chemotherapy	17 (38.6%)	32 (74.4%)	0.005*
2nd session of chemotherapy	16 (36.4%)	30 (69.8%)	0.032*
3rd session of chemotherapy	11 (25%)	32 (74.4%)	0.010*
4th session of chemotherapy	11 (25%)	20 (46.5%)	0.238*
Severity of mucositis			
1st session of chemotherapy	1.22±1.01	1.91±0.89	0.022**
2nd session of chemotherapy	1.18±0.97	1.80±0.92	0.041**
3rd session of chemotherapy	1.02±0.79	1.67±0.85	0.037**
4th session of chemotherapy	0.94±0.51	1.02±0.87	0.748**
Within group *P* value***	<0.001	<0.001	
Mucositis onset time from the start of the chemotherapy	4.00±2.03	3.94±1.71	0.920**

Data are shown n(%) or mean ± SD.
* Significance level obtained from chi-square test to compare the frequency distribution of mucositis between the two groups.
** Significance level obtained from the independent samples *t* test to compare the mean severity of mucositis between the two groups.
*** The significance level obtained from the repeated measures ANOVA to compare the changes in the severity of mucositis in each of the two groups.

Table 3. The patients' severity of pain, dry mouth, and quality of life in the two groups

Outcomes	Zinc group (n=44)	Control group (n=43)	*P* value*
Pain			
1st session of chemotherapy	2.00±3.44	3.59±3.98	0.048
2nd session of chemotherapy	1.91±3.27	3.64±4.01	0.030
3rd session of chemotherapy	1.67±3.40	3.18±4.09	0.065
4th session of chemotherapy	1.77±3.50	3.09±3.99	0.105
P value**	<0.001	<0.001	
Severity of dry mouth			
1st session of chemotherapy	1.37±0.69	1.73±0.87	0.039
2nd session of chemotherapy	1.30±0.64	1.77±0.80	0.003
3rd session of chemotherapy	1.29±0.68	1.59±0.79	0.037
4th session of chemotherapy	1.25±0.54	1.54±0.79	0.048
Within group *P* value**	0.024	0.088	
Quality of life			
1st session of chemotherapy	50.45±10.25	53.51±10.68	0.182
4th session of chemotherapy	51.64±11.32	53.68±12.23	0.425
P value**	0.011	0.552	

Data are shown as mean ± SD.
*Significance level obtained from the independent samples *t* test to compare the mean severity of mucositis between the two groups.
**Significance level obtained from the repeated measures ANOVA to compare changes in the severity of mucositis in each of the two groups.

In contrast, a meta-analysis study reviewed previous studies and reported that although studies have shown the positive effect of zinc sulfate on mucositis after radiotherapy, no protection against mucositis was observed after chemotherapy (24).

Besides, a meta-analysis study by Tian et al showed that oral zinc sulfate was not associated with a delay in the onset of CIOM, a reduction in complications, or an improvement in the quality of life (16). In this meta-analysis, a specific regimen of chemotherapy was not considered; however, the type and dosage of chemotherapy drugs were standardized in two groups in our study to control the possible effect of these confounding factors on the results.

In addition, at all follow-up times in our study, the severity of dry mouth was less significantly in the case group. It seems that considering the decrease in the severity of mucositis and dry mouth in the case group receiving zinc, severity of pain was lower and the maximum difference was reported in the first and second sessions of chemotherapy.

In fact, it has been reported in the previous studies that the mucositis-induced pain leads to problems in swallowing and normal functions of the oral cavity. These problems along with xerostomia increase the risk of opportunistic infections (21). In addition, pain in the oral cavity and problems with eating can be the main reasons for discontinuing treatment. Therefore, it seems that paying attention to the patients' pain along with controlling the incidence of oral mucositis is of particular

importance. In contrast to the results of the current study, some other studies have not found the administration of oral zinc sulfate to be effective in reduction of oral pain severity (16). In contrast, similar to the current study, another meta-analysis showed that the administration of zinc could control the reducing the loss of taste, dry mouth, and oral pain in cancer patients. However, it had no effect on these patients' weight, quality of life, fatigue, and survival (24).

In this regard, although oral zinc sulfate could increase the quality of life of case patients through the reduction of severity and incidence of CIOM as well as dry mouth and pain but this increase was not significant in the present study.

Two review studies did not find a significant effect of zinc on the quality of life of cancer patients (16, 24).

It should not be ignored the role of confounding factors such as the type and dose of chemotherapy drug while evaluating the inclusion criteria can be one of the strengths of the present study. In addition, the simultaneous evaluation of the incidence and severity of mucositis, dry mouth, pain, and quality of life can be regarded as the other strong point of this study. In general, it is suggested to do further studies with a more comprehensive investigation of the effects of oral zinc sulfate on BC patients, the chemotherapy-induced complications, management of the progress of the disease, patient survival, and the complications of zinc consumption in a longer-term period.

Conclusion

The significant role of oral zinc in the incidence and severity reduction of CIOM as well as the dry mouth and pain severity in the initial sessions of chemotherapy has been shown in the current study. However, no significant difference in postponing the incidence of CIOM and the patients' quality of life was seen in the case group as compared with the control group.

Limitations of the study

The non-investigation of the effect of zinc on tumor growth and patient survival can be one of the weaknesses of this study.

Authors' contribution

Conceptualization, methodology, validation, supervision, funding acquisition: MR; Formal analysis, resources, data curation, writing—original draft preparation: ZA; Investigation, writing—review and editing, visualization, project administration: AA

Conflicts of interest

The authors declare that they have no competing interests.

Ethical Issues

The research was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (IR.MUI.MED.REC.1399.277). Accordingly, written informed consent was taken from all participants before any intervention. This study was part of radiation oncology residential thesis of Zeynab Andalib at this university. The trial protocol was approved in the Iranian registry of clinical trial (#IRCT20150304021338N2; https://irct.ir/trial/51105). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This work was supported by deputy research and technology of Isfahan University of Medical Sciences (Grant No. 399156).

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