The effect of zinc sulfate on prevention, incidence, and severity of mucositis in leukemia patients undergoing chemotherapy

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ABSTRACT

Purpose: This study aimed to evaluate the effect of zinc sulfate on the incidence and severity of mucositis in leukemia patients undergoing chemotherapy.

Methods: This was a randomized clinical trial and placebo-controlled, triple blinded study. This study was conducted on leukemia patients undergoing chemotherapy. The subjects were randomly allocated into an experimental (received 50 mg zinc sulfate capsules) and a control group (received placebo capsules). Zinc and placebo capsules were administered three times daily for 14 days from the first day of chemotherapy. Mucositis was measured by the oral mucositis index and World Health Organization mucositis scale on the 4th, 7th, and 14th days after chemotherapy. The data were analyzed using independent t-test, chi-square test, and Repeated Measures Analysis of Variance (RM-ANOVA).

Results: The results showed a significant difference between the two groups in terms of the incidence of mucositis, which was 2.1 times higher in the control group in comparison to the zinc sulfate group. The results of RM-ANOVA also indicated a significant difference between the two groups regarding the mean score of objective and subjective evaluation of mucositis during the three study periods (F = 7.83, p = .007 and F = 5.79, p = .01, respectively).

Conclusion: The results of this study indicated that zinc sulfate reduced the incidence and severity of mucositis in leukemia patients undergoing chemotherapy. As zinc sulfate prevented and relieved mucositis in leukemia patients under chemotherapy, using zinc sulfate is recommended in clinical setting. Yet, further studies are suggested to confirm these findings.

1. Introduction

Leukemia is a cancer of blood and blood cells involving an unregulated proliferation of leukocytes in the bone marrow (Hinkle and Cheever, 2014). The incidence of leukemia was reported to be 3.7 per 100 000 person-years in a city in Iran and 11.25 per 100 000 person-years in other countries, such as UK (Bhayat et al., 2009; Dastgiri et al., 2011). Overall, 8% of total cancer patients suffer from leukemia (Koohi et al., 2015).

To date, major advancements have occurred in management of cancer patients (Rastogi et al., 2011). Evidence has also shown that more aggressive regimens, such as chemotherapy, have improved locoregional tumor control and survival of cancer patients (Rastogi et al., 2011). However, these treatments lead to some problems, such as mucositis. Chemotherapy-induced mucositis, as an acute condition, usually occurs one week after chemotherapy (Sonis, 2009).

Additionally, the highest frequency of mucositis has been reported on the 10th day after chemotherapy (Martinez et al., 2014). However, it resolves during three weeks (Sonis, 2009). A previous study revealed that 81.3% and 90% of patients with cancer (Al Ibraheemi and Shamoun, 2016) and acute leukemia (Martinez et al., 2014) under chemotherapy suffered from mucositis. It should be noted that use of concomitant chemotherapy and/or targeted agents increased the risk for mucositis (Villa and Sonis, 2015).

Mucositis consists of four phases, including “initial inflammatory/vascular, epithelial breakdown, ulcerative/bacteriological and healing phases” (Sonis, 1998). In ulcerative phase of mucositis, some complications, such as pain (Sonis et al., 2004), dysphagia (Mercadante et al., 2015), and difficulties in eating, swallowing, and talking might occur (Scully et al., 2006). Therefore, patients have to receive painkillers and nutritional support (Jensen and Peterson, 2014). Other complications of mucositis are treatment discontinuation (Campos et al., 2014) and
weight loss (Elting et al., 2007). In addition, oral hygiene care, medical and healthcare appointments, and hospitalization might increase as a result of mucositis (Jensen and Peterson, 2014). In a study on malignant hematologic patients (acute leukemia and non-Hodgkin lymphoma), 21.9% of hospitalization episodes were related to mucositis (Martinez et al., 2014). Moreover, quality of life of cancer patients was significantly affected by mucositis. Cancer patients with mucositis experienced pain, physical limitations, and psychological discomfort (Martinez et al., 2014). Furthermore, inability to eat and drink and mouth pain limited the quality of life of leukemia patients with mucositis (Martinez et al., 2014).

Despite the high incidence and serious and debilitating complications of mucositis, no preventive and treatable interventions are currently available. Although some Complementary and Alternative Medicines (CAM), such as Chinese herbal medicine, have been used to prevent and treat mucositis, their therapeutic outcomes are not approved (Meyer-Hamme et al., 2013). Moreover, it was shown in a systematic review that chlorhexidine was not effective in preventing the incidence of mucositis and decreasing its severity (Cardona et al., 2017). Some mucositis management strategies and other therapeutic modalities, including drugs such as amifostine, palifermin, benzylamine HCl, and pentoxifylline, low-level laser therapy, gene transfer interventions, and several organic products, have been also used in this regard (Villa and Sonis, 2015). However, the effects of these interventions have not been completely confirmed. In order to gain better treatment outcomes, some researchers preferred to use zinc sulfate.

Zinc is needed for multiple cellular activities, and the immune system is particularly dependent on adequate availability of this crucial trace element (Chandra and McBean, 1994). Moreover, zinc performs as an organelle stabilizer and a stabilizer of the structure of DNA, RNA, and ribosome. It is also a significant cofactor for DNA synthesis, an important factor for wound healing, and a necessary trace component for improving the immune system (Ertekin et al., 2004). However, how zinc affects mucositis is not completely clear (Kwon, 2016). Researchers have reported that zinc increased the gastrointestinal epithelial barrier function and consequently decreased cell death and detachment (Skrovanek et al., 2014). Zinc increased the overall survival of patients with advanced nasopharyngeal cancer (Lin et al., 2009). Surprisingly, some researchers believed that zinc sulfate might decline the intensity of mucositis in cancer patients under chemotherapy (Arbabi-kalati et al., 2012). In a study on pediatric cancer patients, Cheng et al. (2001) indicated that severity of chemotherapy-induced oral mucositis and the related pain was significantly reduced in zinc sulfate group (Cheng et al., 2001). Moreover, taste of the patients who had received zinc sulfate was recovered more quickly one month after radiotherapy (Ripamonti et al., 1998). On the other hand, some studies have reported that zinc sulfate was not effective in severity and incidence of mucositis. Mansouri et al. indicated that zinc sulfate could not prevent or decrease the severity and duration of mucositis in patients undergoing hematopoietic stem-cell transplantation (Mansouri et al., 2012). Additionally, Sangthawan et al. demonstrated no significant differences between zinc and control groups concerning the incidence of grade 2 oral mucositis and pharyngitis at every week during radiation and within the first month after completion of radiation (Sangthawan et al., 2013). However, the question remains whether zinc sulfate is effective in preventing mucositis in leukemia patients. Previous studies on mucositis have shown somehow contradictory results regarding the effect of zinc sulfate (Arbabi-kalati et al., 2012; Cheng et al., 2001; Ertekin et al., 2004; Mansouri et al., 2012; Mosalaei et al., 2010). Indeed, review of the literature revealed that a few studies have been performed on the effect of zinc sulfate on prevention of chemotherapy-induced mucositis (Arbabi-kalati et al., 2012; Mansouri et al., 2012; Mehdipour et al., 2011). Moreover, a limited number of studies have been focused on leukemia patients. It should be noted that mucositis has many complications that decrease leukemia patients’ quality of life (Martinez et al., 2014). On the other hand, zinc sulfate improved cancer patients’ survival and treatment rates (Lin et al., 2009). Considering the limited number of studies on leukemia patients’ mucositis and the valuable effect of zinc sulfate, this study aims to evaluate the effect of zinc sulfate on prevention, incidence, and severity of mucositis in leukemia patients under chemotherapy.

2. Methods

2.1. Hypothesis

In this study, the three following hypotheses were examined:

1) Zinc sulfate would prevent mucositis in leukemia patients under chemotherapy.
2) Mucositis in leukemia patients under chemotherapy would happen later in the zinc sulfate group in comparison to the control group.
3) Severity of mucositis in leukemia patients under chemotherapy would be milder in the experimental group in comparison to the control group on 4th, 7th, and 14th days of the study.

2.2. Design

In this randomized trial and placebo-controlled study, leukemia patients under chemotherapy were randomly assigned to receive either zinc sulfate or placebo. Therefore, it was a parallel study.

2.3. Allocation

In this study, allocation concealment was used to prevent selection bias. To achieve this goal, the patients and individuals who enrolled them into the study were unaware of group allocations. The allocation concealment mechanism was performed in three steps; i.e., capsules form and appearance, randomization, and outcome measurements, by three individuals with no clinical involvement in the trail as follows:

First, zinc sulfate or placebo capsules were prepared in similar color, shape, and weight. The researcher’s assistant who was a faculty member of Shiraz University of Medical Sciences (SUMS). He allocated zinc sulfate or placebo capsules to A or B codes randomly. Then, he prepacked 42 capsules in similar bottles for each patient. He was the only person who knew the groups until the analysis was finished. Second, in order to achieve allocation concealment, a researcher’s assistant who was blind to the study groups performed the randomization. Third, the study outcomes were evaluated by a nurse who was blind to the study groups.

2.4. Randomization

Leukemia patients under chemotherapy were assigned to an experimental and a control group by block randomization with block sizes of two. In so doing, an online statistical randomization program was used to generate the randomization sequence. The randomization was performed by a researcher’s assistant who was not involved in the trial and was blind to the study groups. In this step, based on the allocation sequence, bottles A or B were sequentially numbered in opaque sealed envelopes. They were kept in a place with appropriate humidity and temperature. To enter the study, the researcher’s assistant gave the next numbered envelope to the patient.

2.5. Blinding

In this triple blind study, the researchers and participants were blind to zinc sulfate and placebo capsules. To achieve this aim, zinc sulfate and placebo capsules were completely similar in color, shape, and weight. The researcher’s assistant who collected the data and the statistician who analyzed the data were also blind to the study groups.
2.6. Settings

This study was conducted in two hematology-oncology wards in Nemazee Hospital affiliated to SUMS, Shiraz, Iran.

2.7. Sample size

In order to determine the study sample size and detect differences between the experimental and control groups, a pilot study was conducted to assess the effect of zinc sulfate on mucositis in leukemia patients undergoing chemotherapy. Based on the pilot study, the difference in proportion prevention between the experimental and control groups was 30% (first proportion = 60%, second proportion = 30%) in leukemia patients undergoing chemotherapy. Similar to this pilot study, the difference prevalence of mucositis in other previous studies on radiation-induced mucositis were 30.5% (Moslemi et al., 2014), 36.6% (Arbabi-kalati et al., 2012), and 76.67% (Ertekin et al., 2004). Therefore, based on the 30% difference in prevention which required a larger sample size, power of 80%, and α = 0.05, an 80-patient sample size was estimated. Then, the sample size was increased to 86 patients to allow dropping-out (43 patients in the experimental group and 43 in the control group).

2.8. Sample

The target population consisted of all adult leukemia patients treated with chemotherapy, such as 5-fluouracil, Cytarabine, Doxorubicin, Daunorubicin, Idarubicine, Bleomycin, Vincristine, Cyclophosphamide, Cisplatin, Methotrexate, Ifosfamide, Mitoxantrone, and Taxane.

The inclusion criteria of the study were being 18 years old or above, undergoing chemotherapy, being alert and oriented, being able to swallow capsules, and not showing mucositis symptoms such as ulcers, erythema, edema, pain, and dysphasia. It should be noted that the patients’ levels of alertness and orientation were evaluated by asking these four questions: who are you or who am I, where are you, what time is it, and what just happened.

On the other hand, the exclusion criteria of the study were having suffered from mouth ulcers and mucositis within the past 3 months, being under radiotherapy, pregnancy and lactation, having allergy to zinc, and suffering from systemic diseases such as diabetes, immune system deficiency, and other malignancies. In order to assess mucositis symptoms, the patients’ mouths were evaluated for thrush, mucositis, or wounds before the intervention. It should be mentioned that as the patients might have not received treatment for the wounds before the intervention. Therefore, both groups were homogeneous with respect to using the scale could range from 0 to 15. In this study, inter-rater reliability of the objective scales of mucositis was 0.89.

Mucositis was assessed by Oral Toxicity Scale of WHO. This instrument was designed based on objective (redness or erythema, and ulcer development) and subjective signs (ability to swallow, sensitivity of mucosa). Accordingly, mucosa was classified into four grades as follows: grade 0, no changes detected in oral cavity; grade I, oral soreness and erythema in mucosa, gums, tongue, or palate; grade II, erythema and ulcers, but solid diet tolerated; grade III, oral ulcers, only “pasty” food and liquid diet tolerated; and grade IV, ulcers, erythema, pain, inability to swallow liquids, oral alimentation impossible, and narcotics used for pain relief. The total score of this scale could range from 0 to 4. Oral Toxicity Scale of WHO has shown good validity. Additionally, correlation coefficients between this scale and mouth and throat soreness questionnaire ranged from 0.45 to 0.55 (Stiff et al., 2006). In our study, inter-rater reliability of the subjective scales of mucositis was 0.91. It should be noted that all assessments were performed by a single person.

2.10. Data collection

After getting permission from SUMS, the researcher (second author of this study) got access to the subjects. She introduced herself to the participants and explained the study objectives to them. It should be noted that before the study, all patients who met the inclusion criteria were trained about oral hygiene both verbally and in written. Oral hygiene was also emphasized at any stage of assessment. This included fluid intake, rinsing teeth with a soft toothbrush, and refraining from using alcohol, cigarettes, hot and cold fluids, and spicy and sour foods. All participants were also evaluated by objective mucositis scale prior to the study. Then, the patients with the score of zero in the objective mucositis scale and Oral Toxicity Scale of WHO were enrolled into the study. It should be noted that all subjects used chlorhexidine and nystatin oral solution at the beginning of chemotherapy. This initial treatment continued until neutrophil count was 1000 cells/mm³. Therefore, both groups were homogenous with respect to using chlorhexidine and nystatin mouthwashes. After all, the experimental group was treated with zinc sulfate and the control group with the placebo.

2.11. Intervention

Zinc sulfate and placebo capsules were prepared by a pharmacist in a similar form (codes A and B). The subjects were aware of the drugs administration and dosages. They were asked to contact the researchers or their assistant in case any adverse events occurred (nausea, vomiting, diarrhea, rash, etc (Skidmore-Roth, 2015)). The dosage of zinc sulfate was based on another study in which Zinco 220 capsules containing 50 mg zinc were used (Ertekin et al., 2004). After gaining the participants’ approval and providing them with explanation about the benefits and side effects of zinc sulfate capsules, 42 capsules (zinc sulfate or placebo) were given to the patients. Then, the patients in the experimental and control groups were asked to consume the capsules three times daily (9 a.m., 1 p.m., and 5 p.m.) for 14 days from the first day of chemotherapy.

2.12. Outcomes

The outcomes of this study were objective and subjective evaluation of mucositis, time of beginning of mucositis, and prevention of mucositis. The subjects were evaluated on 4th, 7th, and 14th days after chemotherapy by the researchers’ assistant who was blind to the experimental and control groups.

Generally, the pattern of mucositis after drug consumption was the
same as that on days 3–5 after the beginning of chemotherapy (Kooshyar et al., 2017). Then, it increased on days 7–10 or 7–14 (Chaveli-López and Bagán-Sebastián, 2016; Kostler et al., 2001). In several studies conducted on patients undergoing chemotherapy, mucositis was evaluated on days 3, 7, 10, and 14 (Cheng et al., 2001). Therefore, days 4, 7, and 14 were considered as evaluation times in the present study.

2.13. Ethical considerations

This study was registered in Iranian Registry of Clinical Trials (www.irct) with ID: IRCT2014010213690N2. It was also approved by the Ethic Committee of SUMS. Permission of the study was obtained from SUMS, Nemaze hospital, and hematology-oncology wards. Consent forms were also signed by the participants. The subjects were explained about the objectives and procedures of the study. In addition, they received information about the side effects of the study and drugs. They were also informed that they had the right to withdraw during the study. Moreover, a numerical code was used for patients’ anonymity.

2.14. Data analysis

In this study, administration of zinc sulfate was the independent variable, while objective and subjective scales of mucositis were the dependent variables. The data were analyzed using the SPSS statistical software, version 20. Data analysis was performed using descriptive and inferential statistical methods. Kolmogorov-Smirnov test showed that the data were normally distributed. Thus, difference between the two study groups regarding demographic characteristics was evaluated by independent t-test and Chi-square test. At baseline, the two groups were compared using independent t-test. Moreover, Repeated Measures Analysis of Variance (RM-ANOVA) was used to compare the two groups regarding mucositis at the four time periods. P < .05 was considered to be statistically significant.

3. Results

The data were collected from March to June 2014. The subjects were followed for 14 days after beginning of chemotherapy. Flow chart of the leukemia patients during the study has been illustrated in Fig. 1. At the first stage, eligibility assessment, 101 leukemia patients were evaluated and 15 patients were excluded. At the second stage, allocation, the remaining 86 patients were randomized into experimental and control groups. At the third step, follow-up, all 86 patients continued the study on the 4th day. However, two leukemia patients in the zinc sulfate and control groups were excluded due to death (n = 1) and no reason (n = 1) on the 7th day of the study. On the 14th day also, seven patients in the intervention group and eight ones in the control group were dropped from the study. At the fourth step, analysis, the data of the participants were analyzed on 4th, 7th, and 14th days (Fig. 1).

Since zinc sulfate might have some side effects, the subjects were assessed for any complications, harms, and unintended effects during the study. The researchers had decided to stop the trial in case of occurrence of any negative events that might be related to the supplement and placebo capsules. However, based on the reports of the researchers, participants, and researchers’ assistants, the study had no serious and considerable side effects or adverse events.

3.1. Demographic and clinical characteristics

The mean age of the patients was 39.17 (SD = 17.07) years in the experimental group and 33.80 (SD = 13.73) years in the control group. The majority of the patients in both experimental and control groups were male. In addition, 25 leukemia patients (73.5%) in the experimental group and 28 ones (70.0%) in the control group were married. Besides, 28 patients (77.8% in the experimental group and 73.4% in the control group) had secondary and high school education. Moreover, most patients in both experimental and control groups (58.3% and 59.0%, respectively) were diagnosed with acute myeloid leukemia. Furthermore, the mean number of previous chemotherapy cycles was 5.72 (SD = 1.36) and 5.05 (SD = 2.18) in the experimental and control groups, respectively. The majority of subjects in the experimental (75%) and control (81.8%) groups used Cytarabine + Fludarabine and Cytarabine + (Daunorubicin or Idarubicine or Doxorubicin). The results revealed that both groups were homogenous concerning all demographic (age, gender, education level, and marital status) and clinical (diagnosis, number of previous chemotherapy cycles, chemotherapy regimens, and chemotherapy agents dosage) characteristics (Table 2).

3.2. Prevention of mucositis

During the 14 days of the study, 27 subjects in the experimental group (75.00%) and 17 ones in the control group (47.22%) did not have the signs and symptoms of mucositis. The results of Chi-square test showed a significant difference between the experimental and control groups regarding the prevention of mucositis ($\chi^2 = 5.84, p = .01$). Therefore, the hypothesis that zinc sulfate would partially prevent mucositis in leukemia patients under chemotherapy was confirmed.

3.3. Incidence of mucositis

The findings of this study indicated a significant difference between the two groups regarding the incidence of mucositis. During the 14 days of the study, 9 patients (25.00%) in the experimental group and 19 ones (54.28%) in the control group showed mucositis. Thus, the incidence of mucositis was 2.1 times higher in the control group in comparison to the zinc sulfate group.

3.4. Onset of mucositis

The results of this study showed that onset of mucositis occurred on days 5.83 (SD = 3.37) and 4.58 (SD = 2.47) in the experimental and control groups, respectively. Although mucositis had started earlier in
the control group than in the experimental group, the results of independent t-test indicated no significant difference between the two groups regarding the onset of mucositis (t = -.95, p = .34). Therefore, the second hypothesis that mucositis would occur later in leukemia patients in the zinc sulfate group in comparison to those in the control group was not confirmed.

3.5. Severity of mucositis

The results of this study revealed that the mean scores of objective and subjective evaluation of mucositis were lower in the experimental group in comparison to the control group on 4th, 7th, and 14th days of the study (Table 3 and Figs. 2 and 3). Therefore, the third hypothesis that severity of mucositis was milder in the experimental group compared to the control group on 4th, 7th, and 14th days of the study was approved. Moreover, according to Table 3, the results of RM-ANOVA indicated a significant difference between the two groups regarding the mean score of objective evaluation of mucositis during the three study periods (4th, 7th, and 14th days after beginning of chemotherapy) (F = 7.83, p = .007). The results of RM-ANOVA also showed a significant difference between the two groups concerning the mean score of subjective evaluation of mucositis during the three study periods (F = 5.79, p = .01).

4. Discussion

The results of this study showed that zinc sulfate partially prevented mucositis in the leukemia patients undergoing chemotherapy. Additionally, the number of patients who did not show the signs and symptoms of mucositis was significantly higher in zinc sulfate group
incidence of mucositis in the leukemia patients under chemotherapy. Ertekin et al. (2004) reported that six weeks after treatment, one patient in the zinc sulfate group and 10 patients in the control group had mucositis and the incidence rate of mucositis was 10 times higher in the control group in comparison to the zinc sulfate group (Ertekin et al., 2004). Additionally, Cheng et al. (2001) indicated that oral care protocol reduced the incidence of ulcerative mucositis by 38% in children (Cheng et al., 2001). Researchers have demonstrated that zinc deficiency led to impairment of immune defense, promotion of neoplasia, and enchantment of susceptibility to viral infections (Haase et al., 2008). Therefore, the higher incidence rate of mucositis in the control group might be related to zinc deficiency.

Although the current study results revealed no significant difference between the two groups regarding the onset of mucositis, it started (75%) in comparison to the control group (47.22%). Although some studies have been conducted on zinc sulfate and prevention of mucositis, some information regarding prevention of mucositis is missed (Arbabi-kalati et al., 2012; Mansouri et al., 2012; Moslemi et al., 2014). In the current study, prevention of mucositis was seen in 60% of the patients in the zinc sulfate group and 29.5% of those in the control group. Generally, zinc plays an essential role in improving the immune system, developing T cells (Fraker and King, 2004), and relieving viral warts (Al-Gurairi et al., 2002). Therefore, by increasing immune system activities, zinc sulfate prevents mucositis as an infectious disease.

The results showed that during the 14 days of the study, 25.00% and 54.28% of the leukemia patients undergoing chemotherapy experienced mucositis in the experimental and control groups, respectively. Therefore, mucositis was 2.1 times more common in the control group compared to the zinc sulfate group. Thus, zinc sulfate reduced the

* AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphoid leukemia.

1 Cytarabine + Fludarabine.

2 Cytarabine + (Daunorubicin or Idarubicine or Doxorubicin).

3 Vinristine + (Daunorubicin or Doxorubicin).

4 Vinristine + Cyclophosphamide or Cytarabine) + (Daunorubicin or Fludarabine or Cyclophosphamide).

5 Cytarabine + (Vinristine or Cisplatin or Idarubicine).

6 Cytarabine + (Fludarabine or Cyclophosphamide or Cisplatin) + (Idarubicine or Daunorubicin).

7 Cyclophosphamide + (Vinristine or Cisplatin or Cytarabine).

a mg/m².

### Table 3

The results of objective and subjective evaluations of mucositis in the experimental and control groups on 4th, 7th, and 14th days after onset of chemotherapy.

<table>
<thead>
<tr>
<th>Objective evaluation of mucositis</th>
<th>Days</th>
<th>RM-ANOVA * between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4th</td>
<td>7th</td>
</tr>
<tr>
<td>Mucositis (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>0.54</td>
<td>0.58</td>
</tr>
<tr>
<td>Control</td>
<td>0.54</td>
<td>0.73</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>2.17</td>
<td>1.4</td>
</tr>
<tr>
<td>Control</td>
<td>2.03</td>
<td>2.09</td>
</tr>
<tr>
<td>Subjective</td>
<td></td>
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<tr>
<td>Mucositis (SD)</td>
<td></td>
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</tbody>
</table>
| Experimental                      | 0.31 | 1.07 | 1.61 | F = 7.83, p = .007*
| Control                           | 1.91 | 3.05 | 3.70 |
| Mean (SD)                         |      |      |      |     |
| Experimental                      | 3.10 | 3.92 | 4.2  | (SD = 1.90) (SD = 3.92) (SD = 4.2)
| Control                           | 2.17 | 3.10 | 3.70 |

* RM-ANOVA, repeated measures analysis of variance.
earlier in the control group than in the experimental group. Another study also indicated that mucositis developed earlier in the control group compared to the zinc sulfate group (Ertekin et al., 2004). Similarly, Mosalaei et al. showed no significant difference between head and neck cancer patients regarding the time of onset of radiation-induced oropharyngeal mucositis (Mosalaei et al., 2010). However, Lin et al. revealed that head and neck cancer patients in the control group developed grade 2 mucositis and dermatitis earlier than those in the zinc sulfate group (Lin et al., 2006). Differences in the results might be attributed to differences among subjects, diseases, interventions, and measurements.

During the present study days, severity of mucositis was milder in the zinc sulfate group in comparison to the placebo group, which is consistent with the findings obtained by Lin et al. (2006). Mehdipour et al. also conducted a study on leukemia patients under chemotherapy and showed that 10 mg zinc sulfate mouthwash (0.2%) reduced the severity of mucositis (Mehdipour et al., 2011). Correspondingly, researchers have reported a lower degree of radiation-induced oropharyngeal mucositis in head and neck cancer patients in the zinc sulfate group compared to those in the control group (Ertekin et al., 2004; Mosalaei et al., 2010; Moslemi et al., 2014). Therefore, zinc sulfate could relieve mucositis and dermatitis to some extent (Lin et al., 2006). Furthermore, researchers believed that delayed wound healing and skin lesions occurred as a result of zinc deficiency. On the other hand, zinc sulfate maintained epithelial and tissue integrity by promoting cell growth, suppressing apoptosis, and functioning as an antioxidant protecting against free radical damage throughout inflammatory reactions (Childers et al., 1993). Zinc also enhanced re-epithelization in the process of wound strengthening (Thompson and Fuhrman, 2005). Therefore, increase of zinc in serum both heals mucositis and reduces its severity.

4.1. Limitations

The present study had some limitations the first of which being inclusion of participants with different types and stages of leukemia receiving various types and doses of chemotherapeutic agents. Therefore, other studies are suggested to be performed on patients with one type of leukemia; e.g. acute myeloid leukemia, receiving similar chemotherapeutic agents. The second study limitation was that the two groups were not matched regarding chemotherapeutic agents (although randomization matched the groups in this regard). The third limitation was the short study period. Zinc was used for 14 days and mucositis was evaluated simultaneously. Thus, a longer period (e.g. 1–6 months) is recommended for mucositis evaluation in future studies. The fourth study limitation was selection of patients from two hematology-oncology wards in local hospitals in a megacity in Iran. Consequently, the findings might not be generalized to all leukemia patients around the world. The fifth study limitation was examination of the effect of zinc sulfate on mucositis in patients receiving chemotherapy. Hence, further studies are recommended to assess the effect of this supplement on other mucosal and gastrointestinal disorders (nausea, vomiting, and diarrhea). The effect of zinc sulfate is also suggested to be compared to other medications, such as mouthwashes.

4.2. Implications for practice

Based on the sample size, this was a feasibility study and provided evidence on the effect of zinc sulfate on mucositis in the leukemia patients under chemotherapy. Moreover, the implication of the study for clinical practice is that zinc sulfate was safe and cost-effective in leukemia patients and could be easily used at the beginning of chemotherapy. Using zinc sulfate accompanied with standard care of mucositis not only had no complications, but also prevented and decreased the severity of mucositis in leukemia patients. Consequently, it has several benefits if administered at a dose of 50 mg three times a day for 14 days. Since mucositis is a common problem in leukemia patients under chemotherapy and zinc sulfate can play a preventive role in this regard, the advantages of this supplement are recommended to be illuminated to healthcare workers as well as leukemia patients.

5. Conclusion

This study indicated that zinc sulfate partially prevented and decreased the incidence of mucositis in leukemia patients under chemotherapy. Moreover, objective and subjective scores of mucositis were lower in the zinc sulfate group compared to the control group. Yet, further researches are recommended for evidence-based practice.

Conflicts of interest

There were no conflicts of interest reported.

Ethical approval

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (88-4914).

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