Original Article

Investigating the Effect of Zinc on the Prevention of Acute Peripheral Neuropathy in Cancer Patients Treated with Taxanes

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Abstract:

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a major complication of many chemotherapeutic agents, including taxanes. Here, we aimed to investigate the effect of zinc on CIPN. **Materials and Methods:** This is a double-blinded controlled clinical trial that was performed in 2020–2021 in Isfahan on 55 cancer patients. We collected the data regarding CIPN, its severity, presence of abnormal deep-tendon reflexes, paresthesia, restriction in daily activities, and restriction in self-care and pain. Patients were divided into two groups: Patients in the first group were treated with capsules of zinc sulfate 25 mg daily and the control group received placebo. The duration of treatments was 3 months. Patients were visited 6, 9, and 12 weeks after study initiation. **Results:** There was a statistically significant decrease in the frequency of CIPN in the intervention group (37.03% vs. 14.8%, $P < 0.001$). The evaluation of the severity of neuropathy and presence of abnormal deep-tendon reflexes also demonstrated significant decrease in the intervention group during the study ($P < 0.001$ for both), but no significant changes were observed in the placebo group ($P > 0.05$). The activity limitations and pain severity improved significantly both in the intervention and placebo groups ($P < 0.001$ for both groups and items). The intervention group, however, had significantly lower frequencies of activity limitation and lower pain severity within compared to the control group during the study ($P < 0.0\ 01$). **Conclusion:** Zinc supplement therapy resulted in reduced frequency and intensity of CIPN in patients undergoing chemotherapy with taxanes.

Keywords: *Zinc, Peripheral Nerve Disease, Taxanes, Neoplasms*

Introduction

Cancer is one of the leading causes of mortality among populations, especially with the increasing trend due to the changes in the lifestyle and environmental factors.[1] The incidence and mortality of 27 major cancers in the world were 14.1 million new cases and 8.2 million deaths in 2012.[2,3] The most common causes of cancer death were pulmonary, hepatic, and gastric cancers, respectively. Cancer statistics among Iranians also show that the number of cancers is more than 110 per 100,000 people.[4,5]

Chemotherapy is one of the most widely used treatments in cancer. Taxane-based chemotherapy is the conventional treatment for breast cancer and can significantly improve progression-free survival and overall survival of patients. Chemotherapy of treatments could also be associated with complications.[6,7] Recently, many efforts have been made to improve the quality of life (QOL) in patients treated with chemotherapy and reduce the complications.

Chemotherapy-induced peripheral neuropathy (CIPN) is a major complication of many chemotherapeutic agents, including platinum, taxanes, and vincristine.[8] The incidence of CIPN is 61% in the 1st month after chemotherapy, 60% in the first 3 months and 30% in 6 months or more.[9,10] The main mechanism responsible for causing neuropathy is not yet fully understood. The types of CIPN could depend on the total cumulative dose and type of drug. Susceptibility to CIPN is more common in patients with diabetes, alcoholism, or inherited neuropathy.[11,12]

Various studies have been conducted to prevent or reduce the severity of CIPN. Evidence suggests that intravenous calcium and magnesium therapy can help reduce oxaliplatin-induced CIPN without reducing response to treatment.[13,14] Vitamin E

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supplement therapy may also reduce CIPN and other factors including glutamine, glutathione, N-acetylcysteine, oxcarbazepine, and xaliproden have been considered.[15,16]

Zinc is an essential metal used to heal wounds and the use of zinc as an anti-inflammatory agent has been very common in different studies.[17] Zinc is also found in the spinal cord, in the dorsal root ganglia, and in the nociceptive nerves.[18]

Considering the lack of a human-focused clinical trial on the potential effect of zinc to prevent the onset and exacerbation of CIPN, and given attention to the inconsistency of the results of existing retrospective studies, conducting a clinical trial on this issue seemed necessary. As a result, here we aimed to investigate the effect of zinc on the management of CIPN in cancer patients treated with taxanes.

Materials and Methods

This is a double-blinded controlled clinical trial that was performed in 2020–2021 in hematology clinics affiliated to Isfahan University of Medical Sciences. The current study was conducted on cancer patients in need of chemotherapy (adjuvant and neoadjuvant or recurrence) by taxanes. The study protocol was approved by the Research Committee of Isfahan University of Medical Sciences and the Ethics committee has confirmed it (Ethics code: IR.MUI.MED. REC.1398.613, Iranian Registry of Clinical Trials (IRCT) code: IRCT20200422047166N1).

The inclusion criteria were confirmation of cancer by biopsy, being a candidate for chemotherapy using taxanes and signing the written informed consent to participate in this study. We should note that patients were selected based on the stage of the disease that required chemotherapy according to international protocols (American Society of Clinical Oncology, European Society for Medical Oncology and National Comprehensive Cancer Network). Patients with diabetes, neurological disorders, and neuropathies did not enter the study. The exclusion criteria were patient's death and patient's will to exit the study.

A total of 60 patients were selected from cancer patients who referred to Isfahan hematology clinics for chemotherapy and then randomly assigned to the intervention and control groups using even and odd blocks. Since the present study is a pilot study, we considered 30 people in each group.

At the beginning of the study, all patients were instructed on how to conduct the study and the informed consent forms were completed by the patients. Then the patients "demographic information, information about the type and stage of patients" cancer and chemotherapy dose and regimen, as well as information about the patient's neuropathic score at the beginning of the study were recorded.

We collected data regarding CIPN using a checklist. The presence of neuropathy was diagnosed by an expert neurologist, then the severity of neuropathy was examined and scored from 1 to 5 according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[19] Based on this criteria, Grade 1 was considered as asymptomatic: Loss of deep-tendon reflex and/or no paresthesia. Grade 2 was considered as symptomatic: Limitation of activity with tools-need for limited medical intervention. Grade 3 was considered as severe symptoms: Restrictions on daily activities and self-care. Grade 4 was life-threatening symptoms: Requires immediate medical intervention and Grade 5 was death.

The deep-tendon reflexes were examined dividing to normal or abnormal reflexes, presence of paresthesia, restriction in daily activities, and restriction in self-care were also checked. The pain of patients was also measured using the Visual Analog Scale that scores the pain from 0 (least pain) to 10 (most severe pain).

Afterward, the patients were randomized into two groups of intervention and placebo. In order to randomly select patients in the two groups, a number (from 1 to 152) was prepared for each patient. Blocking and stratification methods were used to randomly distribute patients based on their number in the intervention and placebo group. For this purpose, envelopes were given to patients randomly and patients received their medications based no their codes. It should be noted that the patient did not know the nature of their medication (drug or placebo) and the physician collecting the study information (internal medicine assistant) did not know the patient code (the study was double blind).

The first group received capsules of zinc sulfate 25 mg daily (recommended to take at least 1 h before or 2 h after meals) and the second group received placebo capsules exactly similar to the zinc capsules. Patients received their medication daily for 3 months. The patients were referred to the clinics every 3 weeks for 3 months (three follow-up sessions) and then examined and evaluated for CIPN every session.

The obtained data were entered into the Statistical Package for the Social Sciences (SPSS) (version 24, SPSS Inc., Chicago, Illinois, US). We used Independent t-test and repeated measure tests to compare the data between different time lines and also different groups. $P < 0.05$ was considered significance threshold.

Results

In the present study, 60 patients were recruited based on the criteria and were divided into two groups each containing 30 patients. Five patients were excluded due to their will ($N = 4$) and patients death ($N = 1$). Data of 55 patients were analyzed. The CONSORT flow chart of the patients is shown in Figure 1.

Initial analysis of demographic data showed that the study population consisted of 45 women (81.8%) and 10 men (18.2%), and the mean age of the patients was 52.20 ± 11.6 years ranging from 28 to 77 years. The mean dosage of the taxanes was 157.89 ± 19.82. Based on our data, there were no significant differences between two groups regarding age, weight, height, dosage of drugs and gender ($P > 0.05$). These data are indicated in Table 1.

We evaluated and compared the frequency of CIPN, its severity, abnormal deep-tendon reflexes, paresthesia, and other factors among patients. At the beginning of the study, there were no significant differences between two groups regarding the evaluated variables ($P > 0.05$) but during the study, we found that there was a significant decrease in the frequency of CIPN in the intervention group ($P < 0.001$). Evaluation of the severity of neuropathy and presence of abnormal deep-tendon reflexes also demonstrated significant decrease in the intervention group during the study ($P < 0.001$ for both), but no significant changes were observed in the placebo group ($P > 0.05$). We should also note that there were significant differences between intervention and control group within 6 weeks regarding CIPN and deep-tendon reflexes and 9 weeks regarding neuropathy severity.

Further evaluations showed no significant changes in paresthesia and self-care limitations in both groups over time ($P > 0.05$ for both items) and no significant differences could be observed between two groups ($P > 0.05$ for both items). On the other hand, the activity limitations and pain severity improved significantly both in the intervention and placebo groups ($P < 0.001$ for both groups and items). The intervention group, however, had significantly lower frequencies of activity limitation and lower pain severity within compared to the control group during the study ($P < 0.001$). These data are summarized in Table 2.

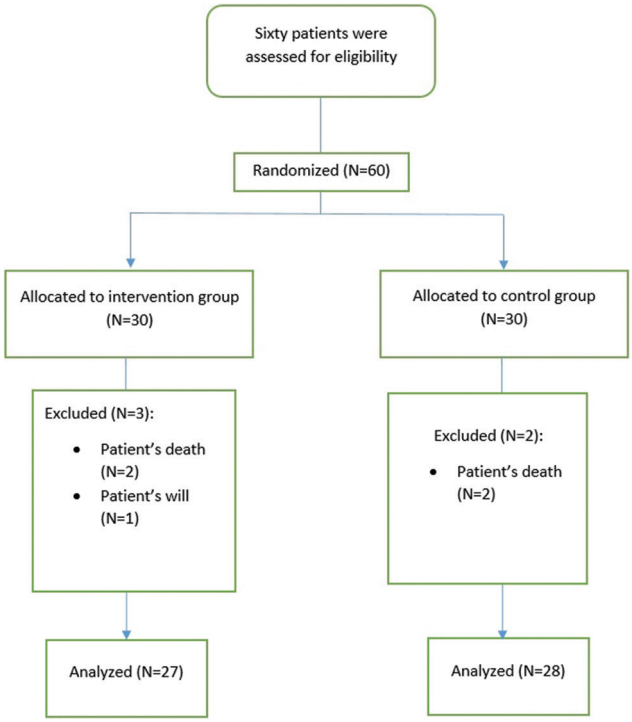

Figure 1: The CONSORT flow chart of the patients

Table 1: Evaluation of demographic data of the patients

Variable	Intervention (*n*=27)	Control (*n*=28)	*P*
Age	54.43±11.93	51±11.77	0.267
Weight	66.13±7.63	65.47±7.74	0.873
Dose	197±94.21	177±81.82	0.37
Height	161.30±8.3	161.83±5.7	0.77
Sex, *n* (%)			
Male	3 (11.1)	4 (14.2)	0.23
Female	24 (88.9)	24 (85.8)	

Discussion

The present study evaluated the use of zinc supplements in preventing and reducing the severity of CIPN in patients undergoing chemotherapy with taxanes. Based on our data, 37% of the study population had CIPN and this rate decreased to 14.8% at the end of the study in patients receiving zinc. We also found significantly decreased CIPN severity in the intervention group. Based on our data, significant differences were observed between groups within 6 and 9 weeks after the study initiation. Our data demonstrated significant improvements in the frequency of abnormal reflexes, activity limitation and pain in cases that received zinc and the control group had only improvements in activity limitation and pain within the study period, but the levels of activity limitation and pain were significantly lower in the intervention group as compared to controls. These data show the effectiveness of zinc supplement therapy in patients with CIPN. It should be noted that the pain severity and activity limitations also significantly improved during the study period in the controls but treatments with zinc resulted in more significant results.

CIPN could affect more than 50% of patients treated with commonly used classes of chemotherapy drugs and has significant decreasing effects on the QOL of patients.[20] As a result, there have been previous studies on the effectiveness of different agents in patients undergoing chemotherapy and possibility of CIPN. In 2018, a study was conducted by Luo *et al*. on the effects of zinc on CIPN. It was indicated that zinc could have significant effects on the CIPN and CIPN-induced pain through functions of transient receptor potential V1. It was discussed that administration of zinc in patients undergoing chemotherapy might reduce the frequency and severity of disease among them.[21] Another study was conducted by Lee and others in 2017 in Korea. This study evaluated the mechanisms of chemotherapy-induced hippocampal neurogenesis and

Table 2: Comparison of the frequency of chemotherapy-induced peripheral neuropathy, its severity, abnormal deep tendon reflexes, paresthesia, activity and self-care limitation, and pain severity between two groups

Variables	Pre	6 weeks, *n* (%)	9 weeks, *n* (%)	12 weeks, *n* (%)	*P*1	*P*2	*P*3
Neuropathy							
Intervention	10 (37.0)	8 (29.6)	6 (22.2)	4 (14.8)	0.00	0.00	0.00
Placebo	10 (35.7)	10 (35.7)	9 (32.1)	9 (32.1)	0.81	0.74	0.73
*P*4	0.45	0.00	0.00	0.00			
Neuropathy severity							
Intervention	3.56±1.20	3.04±1.77	2.92±1.80	2.13±1.05	0.00	0.00	0.00
Placebo	3.46±1.33	3.32±1.60	3.31±1.71	3.12±1.22	0.07	0.06	0.84
*P*4	0.66	0.74	0.02	0.00			
Abnormal reflexes							
Intervention	8 (29.6)	6 (22.2)	4 (14.8)	3 (11.1)	0.00	0.00	0.00
Placebo	8 (28.5)	8 (28.5)	8 (28.5)	7 (25.0)	0.45	0.84	0.65
*P*4	0.38	0.00	0.00	0.00			
Paresthesia							
Intervention	5 (18.5)	5 (18.5)	4 (14.8)	4 (14.8)	0.89	0.86	0.9
Placebo	5 (17.8)	5 (17.8)	5 (17.8)	4 (14.2)	0.84	0.89	0.87
*P*4	1	1	0.87	0.74			
Activity limitation							
Intervention	12 (44.4)	10 (37.0)	8 (29.6)	6 (22.2)	0.00	0.00	0.00
Placebo	13 (46.4)	12 (42.8)	10 (35.7)	8 (28.5)	0.00	0.00	0.00
*P*4	0.92	0.00	0.00	0.00			
Self-care limitation							
Intervention	6 (22.2)	6 (22.2)	6 (22.2)	5 (18.5)	0.74	0.21	0.08
Placebo	6 (21.4)	6 (21.4)	5 (17.8)	5 (17.8)	0.64	0.82	0.97
*P*4	0.96	0.92	0.45	0.54			
Pain (10-0)							
Intervention	6.22±2.51	5.72±2.17	3.97±1.52	1.87±0.88	0.00	0.00	0.00
Placebo	6.52±2.33	6.41±2.55	6.10±2.97	4.77±1.53	0.00	0.00	0.00
*P*4	0.189	0.00	0.00	0.00			

declared that through disruption of vesicular zinc stores in hippocampal mossy fiber terminals, chemotherapy may impinge upon one or more of the sequential stages involved in the maturation of new neurons derived via adult neurogenesis.[22] These data could show the importance of zinc in the neural complications of chemotherapy.

It has also been demonstrated that zinc deficiency could impair hippocampal neurogenesis and neuronal differentiation.[23] These data emphasize the critical roles of zinc in neural and also cognitive functions. Jordan *et al*. evaluated the CIPN and the roles of agents in its prevention and managements. They mentioned that the treatment of CIPN could be conducted by dose reduction or discontinuation of causative chemotherapy, but there is still no proven and definite agent to prevent this complication.[24] Another study was conducted in 2018 by Sommer and others. It was stated that 30%–40% of patients undergoing chemotherapy could suffer from CIPN and supportive care should be performed to reduce the severity of CIPN.[25] These data are somehow in line with the findings of our study showing the importance and prevalence of CIPN among patients undergoing chemotherapy. The important point of our study was that we used zinc supplement therapy for patients and reported significant reduction in frequency and severity of CIPN and associated symptoms.

So far, only few studies have investigated the effects of zinc in neuropathies and to the best of our knowledge, this is the first clinical trial in the English literature that investigates these effects. The limitations of our study included restricted study population and not investigating the preventive effects of zinc supplement therapies among patients. We also were not able to rule out confounding factors such as dosage of chemotherapy drugs and the correlations between the mentioned factors. However, we believe that treatments with zinc could have significant therapeutic results on CIPN and further investigations on larger populations should be conducted.

Conclusion

Zinc supplement therapy resulted in reduced frequency and intensity of CIPN in patients undergoing chemotherapy with taxanes. These data support the use of zinc in the treatment of CIPN, but we believe that further studies on larger populations might be required.

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Conflicts of interest

There are no conflicts of interest.

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