



Effect of Vitamin E on Oxaliplatin-induced Peripheral Neuropathy Prevention: A Randomized Controlled Trial

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ABSTRACT

Background: Peripheral neuropathy is one of the most important limitations of oxaliplatin base regimen, which is the standard for the treatment of colorectal cancer. Evidence has shown that Vitamin E may be protective in chemotherapy-induced peripheral neuropathy. The aim of this study is to evaluate the effect of Vitamin E administration on prevention of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer.

Methods: This was a prospective randomized, controlled clinical trial. Patients with colorectal cancer and scheduled to receive oxaliplatin-based regimens were enrolled in this study. Enrolled patients were randomized into two groups. The first group received Vitamin E at a dose of 400 mg daily and the second group observed, until after the sixth course of the oxaliplatin regimen. For oxaliplatin-induced peripheral neuropathy assessment, we used the symptom experience diary questionnaire that completed at baseline and after the sixth course of chemotherapy. Only patients with a score of zero at baseline were eligible for this study.

Results: Thirty-two patients were randomized to the Vitamin E group and 33 to the control group. There was no difference in the mean peripheral neuropathy score changes (after – before) between two groups, after sixth course of the oxaliplatin base regimen (mean difference [after – before] of Vitamin E group = 6.37 ± 2.85 , control group = 6.57 ± 2.94 ; $P = 0.78$). Peripheral neuropathy scores were significantly increased after intervention compared with a base line in each group ($P < 0.001$).

Conclusions: The results from this current trial demonstrate a lack of benefit for Vitamin E in preventing oxaliplatin-induced peripheral neuropathy.

Keywords: Colorectal neoplasms, oxaliplatin, peripheral nervous system diseases, Vitamin E

INTRODUCTION

Oxaliplatin is a third-generation organoplatinum with antineoplastic effect through production inter and intrastrand platinum DNA crosslinks and inhibition of DNA replication and transcription.^[1] This drug used for the treatment of colorectal cancer and other gastrointestinal malignancies and its common regime is folfox protocol.^[2]

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One of the most important limitations of oxaliplatin use is peripheral neuropathy that occurs in 85–95% of all patients.^[3] This complication may reduce dosage and duration of oxaliplatin administration, affects survival, and impairs patients' quality of life.^[4,5] The effects of oxaliplatin on nerves seem to depend on the chelation of calcium by oxalate, which may impair sodium influx and result in neuronal hyperexcitability.^[6-8] The most common acute neurological symptoms experienced by patients are cold sensitivity and tingling and numbness in the hands (85–55%), respectively.^[9] In the chronic phase, the most common symptoms include tingling, numbness, and aching or burning pain (29–13%)^[10] and these symptoms frequently remain persistent 2 years after treatment.^[11]

Chemotherapy-induced peripheral neuropathy (CIPN) pharmacological treatments, such as antidepressants and amifostine induce additional adverse effects and have limited efficacy.^[12] Therefore, significant interest in the preventative or neuroprotective investigation against CIPN seems reasonable. Recent studies have shown the potential use of several nutritional supplements such as, acetyl-lcarnitine, glutamine, alpha-lipoic acid, Vitamin E, Group B vitamins and several drugs such as amifostine, carbamazepine, oxcarbazepine, Ca/Mg infusion, glutathione, xaliproden, to prevent CIPN.^[13,14] However, clinical evidence for standard use and significant benefit of these agents is insufficient and sparse.^[15,16]

Vitamin E, the major lipid-soluble antioxidant in the body, protects the of membranes' integrity by inhibiting lipid peroxidation and has a central role in neurological structure and function maintenance.^[17] Peripheral neuropathy symptoms in Vitamin E deficiency syndromes appear to be similar to the signs and symptoms of CIPN.^[18] Previous studies have shown that Vitamin E may be protective in CIPN due to cisplatin and paclitaxel,^[19-21] but at present, evidence of a possible role of Vitamin E in protection from oxaliplatin-induced neuropathies unclear, may be due to heterogeneity of the studies.^[22,23]

Therefore, the aim of this study is evaluating the effect of Vitamin E administration on prevention of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer.

METHODS

Study design and participants

This study was a prospective randomized, controlled clinical trial (IRCT2015030621350N1), designed to evaluate the effects of Vitamin E consumption on oxaliplatin-induced peripheral neuropathy in a patient with colorectal cancer. This trial was conducted in

referral university hospital in Isfahan (Iran's third largest city, located in the center of Iran), Iran. The Medical Ethics Committee of Isfahan University of Medical Sciences has approved the study design, protocols and informed consent procedure (the ethical code was 293032).

Seventy patients with colorectal cancer were enrolled in this study through convenience sampling method. We included patients who were 18–75 years of age, diagnosed with colorectal cancer and scheduled to receive oxaliplatin-based regimens (oxaliplatin + 5-fluorouracil + leucovorin [FOLFOX4]; oxaliplatin: 85 mg/m² intravenous [IV] on day 1, 5-fluorouracil: 400 mg/m² IV bolus, followed by 600 mg/m² IV continuous infusion for 22 h on days 1 and 2, leucovorin: 200 mg/m² IV on days 1 and 2 as a 2-h infusion before 5-fluorouracil^[24]) and had more than 6 month life expectancy. The following general exclusion criteria were considered: Previous history of peripheral neuropathy or symptomatic peripheral neuropathy at entry into the study, received other chemotherapy regimens, currently receiving anticoagulants, platelet aggregation inhibitors, opioids, anticonvulsants, tricyclic antidepressants, and previous history of hemorrhagic stroke.

The sample size was calculated on the assumption, based on detection of two-third standard deviation difference in the main outcome (peripheral neuropathy score) that was observed in the study by Argyriou *et al.*,^[19,20] with $\alpha = 0.05$ and power = 80%. We considered 10% attrition rate and the final sample size was estimated 35 patients in each group.

As the flow diagram of patient recruitment was presented in Figure 1, 75 enrolled patients were randomized into Vitamin E group (35 patients) and control group (35 patients).

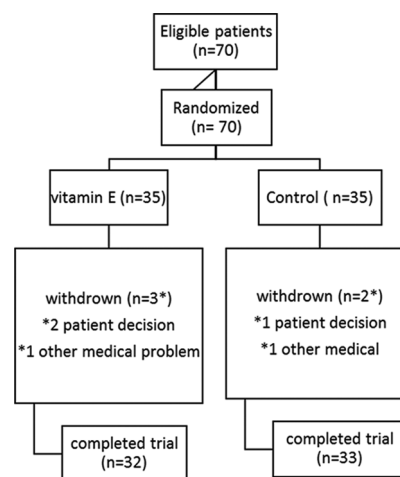


Figure 1: Flow diagram of participants through each stage of the study

Intervention and variable assessment

Enrolled patients were randomized into two groups, within 4 days of the beginning of the oxaliplatin treatment, through random allocation sequence (block size 25). The first group received Vitamin E (E-Vigel, Dena, Iran) at a dose of 400 mg daily and the second group observed, until after the sixth course of the oxaliplatin-based chemotherapy regimen. Because of the control group with no intervention we could not use blindness for participants and physicians.

For peripheral neuropathy assessment, we used the symptom experience diary questionnaire, that was developed by the NCCTG,^[25] asking patients to answer 7 specific symptom-related questions about any peripheral neuropathic symptoms on a 0–10 scale (0 being no symptoms and 10 being as bad as it can be). The total score was the sum of all questions scale (range: 0–70). Total score >0 were defined as peripheral neuropathy. In other studies, validity and reliability of Persian version of this questionnaire were assessed.^[26] This questionnaire was completed at baseline, prior to each chemotherapy treatment, and after the sixth course of chemotherapy completion. Only patients with a total score of zero at baseline were eligible for this study.

Statistical analyses

All statistical analysis was performed using SPSS version 20 (Release 2011, SPSS Inc., Chicago, IL, USA) for windows. Findings have shown as relative frequencies, mean, and standard deviation.

The differences of quantitative, normally distributed data in two groups (Vitamin E and control) were assessed by independent *t*-test. For data that was not normally distributed (diagnosed by Kolmogorov–Smirnov test) the Mann–Whitney U-test statistics were used. Chi-square tests were used for qualitative data to compare the two groups. For comparing the before and after intervention in each group paired *t*-test were used. All tests were two-sided, and $P < 0.05$ are considered as significant. The statistical approach was based on an intention to treat.

RESULTS

A total of 70 patients were enrolled in this study. A consort diagram illustrates patient flow through each stage of the study [Figure 1]. Baseline characteristics of two groups are described in Table 1.

After sixth course of the oxaliplatin-based chemotherapy regimen, near all of patient had experienced peripheral neuropathy (100% Vitamin E group, 96% control group, $P = 0.8$) and peripheral neuropathy scores was significantly increase after intervention compared with baseline in each group ($P < 0.001$) [Table 2].

Table 1: Baseline patient characteristics in control and Vitamin E group

Factor	Vitamin E (n=32)	Control (n=33)	P
Mean age (SD)	56 (14.32)	58.93 (13.62)	0.40
Gender (%)			
Male	75 (n=24)	51.5 (n=17)	0.07
Female	25 (n=8)	48.5 (n=16)	

SD=Standard deviation

Table 2: Overall Incidence and peripheral neuropathy scores between groups

Factor	Vitamin E (n=32) (%)	Control (n=33) (%)	P
Incidence of peripheral neuropathy			
Before	0	0	1
After	32 (100)	32 (96)	0.8
P	<0.001	<0.001	
Mean peripheral neuropathy scores (SD)			
Before	0	0	1
After	6.37 (2.85)	6.57 (2.94)	0.78
P	<0.001	<0.001	

SD=Standard deviation

Mean difference (after – before) of peripheral neuropathy scores were not significantly different in two group (6.37 ± 2.85 [range: 2–13] for patients in Vitamin E group and 6.57 ± 2.94 [range: 0–14] for control group [$P = 0.78$]) [Table 2].

Assessment of mean difference (after – before) of peripheral neuropathy scores by age and sex groups separately in each group showed that peripheral neuropathy scores changes were not affected by age and sex.

DISCUSSION

Colorectal cancer is the third most common cancer in the world.^[27] Because of improvements in detection and management, survival has increased in colorectal cancer patients, and quality of life is an important factor for cancer survivors.^[27] Oxaliplatin, in combination with 5-fluorouracil, is now widely used in the treatment of colorectal cancer.^[28] Peripheral neuropathy is a major side effect of oxaliplatin that can affect the patient's quality of life.^[28]

Scientific evidence for investigating agents that could assist with chemotherapy-induced peripheral neuropathy prevention and treatment is limited, and there are no explicit recommendations that can be given for the prevention or treatment of this side effect.^[12,29]

The present study provides an experimental evidence of a possible role of Vitamin E in protection from

oxaliplatin-induced neuropathies in patients with colorectal cancer. In the current setting, we found that Vitamin E at a dose of 400 mg daily is not able to effectively protect from peripheral neuropathy in patients that exposure to six courses of chemotherapy with oxaliplatin. Although near all of both the Vitamin E and the control groups presented peripheral neuropathy symptoms, the overall patient-reported peripheral neuropathy scores between the two groups were not significantly different.

In agreement with our finding, Afonseca *et al.*^[23] failed to show any significant effect of Vitamin E with a dose of 400 mg daily in the peripheral neuropathy reduction, in patients treated with oxaliplatin. In Afonseca *et al.* study, eighteen patients with colorectal and gastric cancer who had been scheduled to receive oxaliplatin-based chemotherapy were randomized to the Vitamin E group and 16 to the placebo group, cumulative incidence of 83% with peripheral neuropathy was observed in the Vitamin E group, versus 68% in the placebo group ($P = 0.45$). Also, Kottschade *et al.*^[22] reported results similar to our findings, even with higher doses of Vitamin E (400 mg twice a day). Kottschade *et al.* was conducted in 189 patients undergoing therapy with neurotoxic chemotherapy, utilizing twice daily dosing of Vitamin E (400 mg)/placebo and reported, There was no difference in the incidence of peripheral neuropathy between the two arms (34% Vitamin E, 29% placebo; $P = 0.43$).^[22]

However, other studies demonstrate a significantly decreased incidence of peripheral neuropathy in the patients who received Vitamin E versus the control group.^[19,20,30] Argyriou *et al.*^[19] study was conducted in 30 patients scheduled to receive six courses of cisplatin-based regimens and randomly allocated to Vitamin E (daily dose of 600 mg/day) and control groups. This study shows the incidence of peripheral neuropathy differed significantly between groups, occurring in 21.4% of patients assigned to the Vitamin E supplementation group and in 68.5% of controls.^[19]

The discrepancies in these studies are may be due to differences in the patient characteristics, sample size, Vitamin E dose, type of chemotherapeutic agents such that most of the effective studies is relation to prevention of cisplatin-induced peripheral neuropathy.^[19,30]

Another finding of our study is that peripheral neuropathy scores changes were not affected by age and sex. Several studies reports that some of the risk factors associated with the development of CIPN include aging, diabetes, smoking, and reduced creatinine clearance.^[31-33]

Finally, may be further studies with larger sample size are needed to clarify the smaller effect of Vitamin E consumption on oxaliplatin-induced peripheral neuropathy prevention.

CONCLUSIONS

The results from this current trial demonstrate a lack of benefit for Vitamin E in preventing oxaliplatin-induced peripheral neuropathy.

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REFERENCES

1. Stockwell S. ONLINE FIRST: Metastatic Colorectal Cancer: Oxaliplatin-Based Therapy Shown to Improve Outcomes. *Oncology Times*; 2015.
2. DeVita VT, Lawrence TS, Rosenberg SA. *Cancer: Principles and Practice of Oncology-Advances in Oncology*: Wolters Kluwer/Lippincott Williams and Wilkins Health; 2010.
3. Gamelin E, Gamelin L, Bossi L, Quasthoff S, editors. *Clinical aspects and molecular basis of oxaliplatin neurotoxicity: Current management and development of preventive measures*. *Seminars in Oncology*. Elsevier; 2002.
4. Hartmann JT, Lipp HP. Toxicity of platinum compounds. *Expert Opin Pharmacother* 2003;4:889-901.
5. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: Clinical signs and optimal management. *Drugs* 2003;63:1549-63.
6. Saif MW, Reardon J. Management of oxaliplatin-induced peripheral neuropathy. *Ther Clin Risk Manag* 2005;1:249-58.
7. Park SB, Goldstein D, Lin CS, Krishnan AV, Friedlander ML, Kiernan MC. Acute abnormalities of sensory nerve function associated with oxaliplatin-induced neurotoxicity. *J Clin Oncol* 2009;27:1243-9.
8. Gamelin L, Capitain O, Morel A, Dumont A, Traore S, Anne le B, *et al.* Predictive factors of oxaliplatin neurotoxicity: The involvement of the oxalate outcome pathway. *Clin Cancer Res* 2007;13:6359-68.
9. Tofthagen C, McAllister RD, McMillan SC. Peripheral neuropathy in patients with colorectal cancer receiving oxaliplatin. *Clin J Oncol Nurs* 2011;15:182-8.
10. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-induced neuropathy and its association with quality of life among 2- to 11-year colorectal cancer survivors: Results from the population-based PROFILES registry. *J Clin Oncol* 2013;31:2699-707.
11. Pietrangeli A, Leandri M, Terzoli E, Jandolo B, Garufi C. Persistence of high-dose oxaliplatin-induced neuropathy at long-term follow-up. *Eur Neurol* 2006;56:13-6.
12. Schloss JM, Colosimo M, Airey C, Masci PP, Linnane AW, Vitetta L. Nutraceuticals and chemotherapy induced peripheral neuropathy (CIPN): A systematic review. *Clin Nutr* 2013;32:888-93.
13. Pachman DR, Barton DL, Watson JC, Loprinzi CL. Chemotherapy-induced peripheral neuropathy: Prevention and treatment. *Clin Pharmacol Ther* 2011;90:377-87.
14. Gutiérrez-Gutiérrez G, Sereno M, Miralles A, Casado-Sáenz E, Gutiérrez-Rivas E. Chemotherapy-induced peripheral neuropathy: Clinical features, diagnosis, prevention and treatment strategies. *Clin Transl Oncol* 2010;12:81-91.
15. Beijers AJ, Jongen JL, Vreugdenhil G. Chemotherapy-induced neurotoxicity: The value of neuroprotective strategies. *Neth J Med* 2012;70:18-25.
16. Trivedi MS, Hershman DL, Crew KD. Management of chemotherapy-induced peripheral neuropathy. *Am J Hematol Oncol* 2015;11:6.
17. Tiwari V, Kuhad A, Chopra K. Neuroprotective effect of vitamin E isoforms against chronic alcohol-induced peripheral neurotoxicity: Possible involvement of oxidative-nitroductive stress. *Phytother Res* 2012;26:1738-45.
18. Pace A, Giannarelli D, Galì E, Savarese A, Carpano S, Della Giulia M, *et al.* Vitamin E neuroprotection for cisplatin neuropathy: A randomized, placebo-controlled trial. *Neurology* 2010;74:762-6.
19. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, *et al.* A randomized controlled trial evaluating the efficacy and safety of vitamin E supplementation for protection against cisplatin-induced peripheral neuropathy: Final results. *Support Care Cancer* 2006;14:1134-40.
20. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, *et al.* Preventing paclitaxel-induced peripheral neuropathy: A phase II trial of vitamin E supplementation. *J Pain Symptom Manage* 2006;32:237-44.

21. Leonetti C, Biroccio A, Gabellini C, Scarsella M, Maresca V, Flori E, et al. Alpha-tocopherol protects against cisplatin-induced toxicity without interfering with antitumor efficacy. *Int J Cancer* 2003;104:243-50.
22. Kottschade LA, Sloan JA, Mazurczak MA, Johnson DB, Murphy BP, Rowland KM, et al. The use of vitamin E for the prevention of chemotherapy-induced peripheral neuropathy: Results of a randomized phase III clinical trial. *Support Care Cancer* 2011;19:1769-77.
23. Afonseca SO, Cruz FM, Cubero Dde I, Lera AT, Schindler F, Okawara M, et al. Vitamin E for prevention of oxaliplatin-induced peripheral neuropathy: A pilot randomized clinical trial. *Sao Paulo Med J* 2013;131:35-8.
24. Manzullo EF, Anderson RW. Physicians' cancer chemotherapy drug manual 2001. *Ann Intern Med* 2002;136:340.
25. Sloan JA, Berk L, Roscoe J, Fisch MJ, Shaw EG, Wyatt G, et al. Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. *J Clin Oncol* 2007;25:5070-7.
26. Ayuri S, Aldavood M, Roham S. A survey of prevalence of colorectal chemotherapy side effects. *J Mashhad Med Sch* 2014;57:822-8.
27. Wu CC, Hsu TW, Chang CM, Yu CH, Lee CC. Age-adjusted Charlson comorbidity index scores as predictor of survival in colorectal cancer patients who underwent surgical resection and chemoradiation. *Medicine (Baltimore)* 2015;94:e431.
28. Yamamoto T, Hyakudomi R, Sugimoto S, Tokuka A, Sato Y, Nagai S, et al. A Multicenter Cohort Study for XELOX (Capecitabine, Leucovorin plus Oxaliplatin) therapy as first-line treatment in elderly patients with unresectable colorectal cancer. *J Cancer Ther* 2015;6:153.
29. Block KI, Koch AC, Mead MN, Toth PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic toxicity: A systematic review of the evidence from randomized controlled trials. *Int J Cancer* 2008;123:1227-39.
30. Pace A, Savarese A, Picardo M, Maresca V, Pacetti U, Del Monte G, et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. *J Clin Oncol* 2003;21:927-31.
31. Cavaletti G, Bogliun G, Marzorati L, Zincone A, Piatti M, Colombo N, et al. Early predictors of peripheral neurotoxicity in cisplatin and paclitaxel combination chemotherapy. *Ann Oncol* 2004;15:1439-42.
32. Dimopoulos MA, Mateos MV, Richardson PG, Schlag R, Khuageva NK, Shpilberg O, et al. Risk factors for, and reversibility of, peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: Subanalysis of the phase 3 VISTA study. *Eur J Haematol* 2011;86:23-31.
33. Kawakami K, Tunoda T, Takiguchi T, Shibata K, Ohtani T, Kizu J, et al. Factors exacerbating peripheral neuropathy induced by paclitaxel plus carboplatin in non-small cell lung cancer. *Oncol Res* 2012;20:179-85.

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