Original Communication

Protective Effects of Vitamin E on Chemotherapy-Induced Peripheral Neuropathy: A Meta-Analysis of Randomized Controlled Trials

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Received: January 22, 2013; Accepted: August 26, 2013

Abstract: *Purpose:* This study aimed to investigate the neuroprotective effects of vitamin E for preventing chemotherapy-induced peripheral neuropathy (CIPN). *Methods:* A comprehensive search from 1973 through July 2011 identified randomized controlled trials (RCTs) that reported the preventive effects of vitamin E on CIPN. The relative risk (RR) of CIPN with vitamin E supplementation, compared with placebo, was assessed with the Bayesian random effect model and expressed as RR with a 95 % credible-interval (CrI). Bayesian outcome probabilities were calculated as the probability (P) of RR <1. *Results:* Five RCTs, involving 319 patients, were identified. Upon pooling these RCTs, vitamin E supplementation (300–600 mg/day) had a significant effect on CIPN prevention (RR 0.43; 95 % CrI 0.10–1.00, P=97.5 %). Subgroup analysis by chemotherapeutic agent type was only available for cisplatin and showed that vitamin E supplementation significantly reduced the incidence of CIPN (RR 0.26; 95 % CrI 0.06–0.89, P=98.1 %). Furthermore, there were no adverse effects caused by vitamin E supplementation in any of the RCTs. *Conclusion:* Available data included in this meta-analysis show that vitamin E supplementation might significantly prevent CIPN. Currently, however, the data are insufficient to confidently conclude the true value. Large-scale, rigorously designed RCTs are needed to confirm the role of vitamin E supplementation in CIPN prevention.

Key words: vitamin E, peripheral neuropathy, chemotherapy

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting adverse effect associated with several chemotherapeutic agents, negatively affects a patient's quality of life. The incidence of CIPN varies with the chemotherapeutic agent; CIPN can occur in 28 %–100 % of patients who receive cisplatin, in 57 %–83 % of those who receive paclitaxel, and in 85 %–95 % of those who receive oxaliplatin [1].

The initial symptoms of CIPN commonly include paresthesia (tingling) and dysesthesia in the toes and fingers, which eventually spreads proximally in a "glove-and-stocking" distribution [2]. These symptoms usually develop weeks to months after the initiation of chemotherapy and may continue and become irreversible, even when the cancer treatment is withdrawn [3]. After CIPN has developed, methods to reverse the neurological impairment are limited [4]. Although many pharmacological agents have been tested, currently there is no effective standard treatment for CIPN. Therefore, many preclinical and clinical trials over the past decade have focused on preventive treatments with neuroprotective agents [5]. Despite this effort, no agent has yet been demonstrated to have definitive neuroprotective activity, including the adrenocorticotropic hormone analogue Org 2766 [6–8], amifostine [9], and leukemia-inhibitory factor [6, 10, 11].

While the cause of CIPN is still poorly understood and the neuropathogenesis mechanisms of different chemotherapy agents appear to differ from each other, the evidence suggests that some adverse effects induced by certain chemotherapy agents are the result of free radicals, which are often called reactive oxygen species [12, 13]. Some animal studies have shown that antioxidant supplementation could play a beneficial role in protection against various chemotherapy-induced toxicities associated with oxidative stress [14–16].

Vitamin E is one of the most extensively studied antioxidants for the treatment of vitamin E deficiency-induced neuropathy and for the alleviation of chemotherapy-related toxicities. In one pilot study, plasma vitamin E levels in cancer patients who developed severe neuropathy after cisplatin treatment were significantly reduced, and in another group of patients, cisplatin was found to significantly reduce plasma vitamin E levels after 2 and 4 treatment cycles [17].

Based on this preliminary evidence, a few randomized controlled trials (RCTs) have been conducted to study the use of vitamin E in CIPN prevention. In these studies, the dosage range of vitamin E was 300–600 mg per day. The results, however, have been conflicting. Studies with small sample sizes and low methodological quality showed that vitamin E had a significant beneficial effect on CIPN prevention [18–21]. On the other hand, a large, double-blinded RCT conducted in 2010 did not find a significant beneficial effect of vitamin E on protection against CIPN [22].

A Cochrane review, published in 2011, evaluated the efficacy of several agents, including vitamin E, for preventing cisplatin-associated neurotoxicity [23]. However, this review included only two RCTs that studied vitamin E and noted that the data were insufficient to conclude that vitamin E has a preventive effect against cisplatin-induced peripheral neuropathy.

The current study investigated the neuroprotective effect of vitamin E on CIPN by conducting a meta-analysis of RCTs, including a recently published large, double-blinded RCT.

Methods

Search strategy

Databases, Medline (PubMed), the Excerpta Medica (EMBASE), and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, were searched for the following key words: chemotherapy or radiotherapy, neuropathy or peripheral neuropathy or peripheral nerve toxicity or neurotoxicity, and vitamin E or tocopherol. The bibliographies of relevant papers were also searched. There were no language limitations.

Selection criteria

Randomized controlled trials (RCTs) from 1973 until July 2011 that reported on the preventive effects of vitamin E on CIPN were included. The main outcome measure was the incidence of neurotoxicity. RCTs that evaluated the treatment effect rather than the preventive effect were excluded.

Study selection

Title, abstracts, and full articles of all relevant studies were independently evaluated by two authors (S.N. Eum and J.Y. Lee). Discrepancies between authors were settled by discussion. For articles with insufficient or missing data, the trial authors were contacted for clarification.

Data extraction

The following data were extracted from the final analysis RCTs: first author name, publication year, country, number of total participants, vitamin E prevention regimen, cancer type, relative risk (RR) of CIPN incidence with 95 % confidence interval (CI), and the ratio of the number of CIPN occurrences to the number of participants in each group. Furthermore, any adverse events related to vitamin E prevention were reviewed.

Quality assessment

The methodological quality of each trial was evaluated by two authors according to the Jadad scale [24]. Any discrepancies between the authors were resolved through discussion. This scale evaluates RCTs on the basis of five components: (1) description of randomization, (2) appropriate method for randomization, (3) description of double-blinding, (4) appropriate method for double-blinding, and (5) description of withdrawals and dropouts. Scores greater than 3 are considered high quality.

Main and subgroup analysis

The overall effects of vitamin E on CIPN prevention were estimated in each trial. The primary outcome measure was RR of CIPN incidence with vitamin E supplementation compared with no intervention or placebo. The effects of vitamin E when used with different types of chemotherapeutic agents were estimated in the subgroup analysis. Adverse events reported for each trial were evaluated as a secondary outcome measure.

Statistical analysis

The effects of vitamin E supplementation on the incidence of CIPN, compared with placebo, were assessed according to a hierarchical Bayesian random effects model. A Bayesian meta-analysis was performed according to the method used in a previous study by Salpeter *et al.* [25], in which non-informative prior distribution is applied while assuming that the numbers of observed CIPN in the vitamin E-supplemented and control groups are binomially distributed in each trial. For the non-informative prior, we chose an RR that is normally distributed with a mean of 0 and a wide variance (10^5 on the log scale) as a prior probability. We specified a uniform (0,2) prior probability for the standard deviation (SD) of the distribution that described between-study variance. Three parallel Markov-chain Monte Carlo (MCMC) chains were run for 300,000 iterations, sampling every 10 generations (by setting the "thin" option as 10). The resultant statistics were summarized after discarding 50,000 samplings as burn-in. The treatment effects were reported as both a median point estimation of RR with a 95 % associated credible interval (CrI), and a posterior probability (P) that the RR is greater than 1. Heterogeneity was presented as the SD between studies; a SD close to 0 indicates little heterogeneity, while an SD greater than 1 reflects substantial heterogeneity [26]. Since the results of Bayesian meta-analyses are known to be sensitive to the priors of between-study variance when the number of studies is small [27], we performed a sensitivity analysis by varying the prior distribution for the between-study standard deviation as follows: uniform distributions of the standard deviation were set to (0,4), (0,6), (0,8), and (0,10).

All statistical analyses in this meta-analysis were performed with WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and the R Statistical Computing Program (http://www.R-project.org/).

Results

Study selection

A total of 421 studies were identified from three databases and relevant bibliographies. Figure 1 shows the process of study selection. After excluding 38 duplicate studies and 364 studies that did not satisfy the inclusion criteria, based on a title and abstract review, we reviewed the full texts of the remaining 19 studies. Among these, 14 studies were excluded for the following reasons: 13 were not RCTs, and one was excluded because its patients were thought to overlap with those of other studies. Finally, 5 RCTs were included in this meta-analysis [18–22].

Study characteristics and quality

The general characteristics of the 5 studies included in this meta-analysis are summarized in Table I. A total of 319 participants were analyzed: 163 participants were assigned to no intervention or placebo groups and 156 participants to vitamin E prevention groups. The age ranges were not reported in most studies.

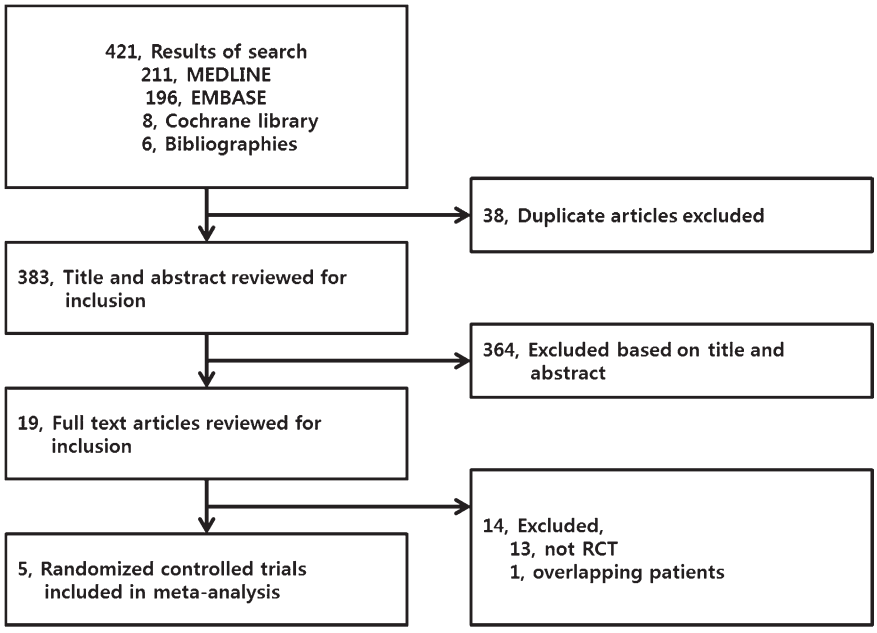

Figure 1: Flow diagram of study selection.

Gender distribution was reported in all studies except for Pace *et al.* [18], and 31.5 % of the total participants were male. The selected trials were published between 2003 and 2010. Two studies were conducted in Italy [18, 21], 2 in Greece [19, 20], and 1 in the United States [22]. Three of the 5 RCTs were open-label with blind assessment [18–20], and the others were double-blinded trials [21, 22]. The types of chemotherapy used included cisplatin-based therapy in 3 trials [18, 19, 21], paclitaxel-based therapy in 1 trial [20], and various chemotherapeutic regimens in 1 trial [22].

The vitamin E dosage regimens used in each trial were as follows: 300 mg daily [18], 300 mg twice-daily [19, 20, 22], and 400 mg daily [21] during chemotherapy; these regimens continued for 1 [22] or 3 months [18–21] after the suspension of chemotherapy. In all studies, CIPN was assessed by two neurologists although different methods were used in each study; CIPN assessment for each study is shown in Table I. The evaluators in all but one study were blinded to the vitamin E treatment status [18]. Follow-ups were performed after the third and sixth chemotherapy courses and after end of vitamin E treatment [18–20], or after the third chemotherapy course and 1 month after vitamin E treatment [21], or prior to each chemotherapy course and at 1 and 6 months after chemotherapy completion [22].

In the assessment of methodological quality in accordance with the Jadad scale [24], only 2 studies [21, 22] among the included studies received a score greater than 3 (Table II).

Effects of vitamin E for the prevention of CIPN

A hierarchical random-effects Bayesian meta-analysis of pooled data from the 5 RCTs showed that the RR of CIPN with vitamin E supplementation, compared with that of placebo, was 0.43 (95 % CrI, 0.10–1.00), and the posterior probability of a benefit to CIPN reduction by vitamin E supplementation (an RR < 1) was 97.5 % (Figure 2). The estimate of the between-study standard deviation on a log-RR scale was 0.76, indicating moderate heterogeneity among the studies.

It is known that the prior distribution of between-study variance is crucial for statistical inferences in small studies [27], so we assessed the sensitivity to the choice of prior distribution. When using a prior distribution with a large between-study standard deviation [i.e., uniform (0,10)], we found that the posterior probability of benefit exceeded 95 %, even though the CrI for the overall RR included 1 (RR = 0.42; 95 % CrI, 0.10–1.21; P = 0.96), indicating significant beneficial effects of vitamin E supplementation.

Publication bias was not assessed because all three statistical tests that are commonly recommended for systematic reviews have low sensitivity for the detection of publication bias if there are 10 or fewer studies [28–30].

Table I: Characteristics of randomized controlled trials included in the meta-analysis.

Ref.	Study/Year	Regimen	Assessment of CIPN	N[a]	Type of chemotherapy and dosage	Type of cancer	RR (95 % CI)	No. CIPN / no. participants	
								Vitamin E group	Control group
18	Pace, 2003	Vitamin E 300 mg daily vs. control; before chemotherapy and continued for 3 months after the suspension of chemotherapy	Electrophysiological evaluation: standardized history for detection of neuropathic symptoms, pinprick and vibratory sensations, strength, and deep tendon reflexes Clinical evaluation: Modified Neurological Symptom Score	27	Cisplatin-based regimen/ cumulative median dose 420 mg/m^2 (treatment & placebo)	Lung (15), Ovarian (3), Nasopharynx (2), Urethral (2), Gastric (1), Testicular (1), Esophageal (1), Ethmoid (1), Tongue (1)	0.36 (0.15–0.83)	4/13	12/14
19	Argyriou, 2006	Vitamin E 300 mg BID vs. control; during chemotherapy and continued for 3 months after the suspension of chemotherapy	Electrophysiological evaluation: motor conduction of ulnar and peroneal nerves, and sensory conduction of ulnar, sural, and superficial peroneal nerves Clinical evaluation: Neurological Symptom Score and Neurological Disability Score	30	Cisplatin-based regimen/ mean dose per course 120.6 mg vs. 121.9 mg, six courses of treatment	Lung (SCLC,15), Cervical (6), Testicular (4), Head & neck (5), Gastric (5)	2.5 (1.16–5.47) [b]	3/14	11/16
20	Argyriou, 2006	Vitamin E 300 mg BID vs. control; during chemotherapy and continued for 3 months after the suspension of chemotherapy	Electrophysiological evaluation: motor conduction of ulnar and peroneal nerves, and sensory conduction of ulnar, sural, and superficial peroneal nerves Clinical evaluation: Neurological Symptom Score and Neurological Disability Score	32	Paclitaxel-based regimen/ cumulative mean dose 332.8 mg vs. 328.1 mg	Lung (NSCLC,10), Breast (19), Ovarian (8)	0.3 (0.1–09)	3/16	10/16
21	Pace, 2010	Vitamin E 400 mg daily vs. placebo; before chemotherapy and continued for 3 months after the suspension of chemotherapy	Electrophysiological evaluation: standardized history for detection of neuropathic symptoms, pinprick and vibratory sensations, strength, and deep tendon reflexes Clinical evaluation: Total Neuropathy Score	41	Cisplatin-based regimen/ cumulative dose >300 mg/m^2	Lung (26), Glioblastoma (9), Endometrial (5), Bladder (1), Adrenal gland (1), Carcinosarcoma (1)	0.14 (0.02–1.00)	1/17	10/24

Table I: Continued

Ref.	Study/Year	Regimen	Assessment of CIPN	N[a]	Type of chemotherapy and dosage	Type of cancer	RR (95 % CI)	No. CIPN / no. participants	
								Vitamin E group	Control group
22	Kottschade, 2010	Vitamin E 300 mg BID vs. placebo; during chemotherapy and continued for 1 month after the suspension of chemotherapy	Peripheral neuropathy utilizing the sensory neuropathy item from the CTCAE v. 3.0 criteria; Symptom experience diary	189	Taxane (109), cisplatin (8), carboplatin (2), oxaliplatin (50), combination (20)/ Dosage not stated.	Breast (115), Lung (5), Other (69)	Not stated[c]	34 % (33/96)[d]	29 % (27/93)

RR, relative risk; CI, confidence interval; BID, twice a day; CIPN, chemotherapy-induced peripheral neuropathy; SCLC, small cell lung carcinoma; NSCLC, non–small cell lung carcinoma; CTCAE, common terminology criteria for adverse events
[a]Number of participants who completed each trial. [b]RR was calculated inversely in this study. The RR was 0.31(0.11–0.9) when recalculated in the same way as the other studies. [c]RR was not stated in this study. The RR was calculated to be 1.18 (0.78–1.8) through an analysis of data about the incidence of CIPN in each group. [d]The number of CIPN in each group was not stated in this study. These numbers were calculated by means of a reverse estimation of the percentage in each group.

Table II: Methodological quality of the trials evaluated by the Jadad Scale [24].

Ref.	Study/Year	Jadad Scale					
		Description of randomization	Appropriate method for randomization	Description of double-blind	Appropriate method for double-blinding	Description of withdrawals and dropouts	Total Score
18	Pace, 2003	1	0	0	0	1	2
19	Argyriou, 2006	1	1	0	0	1	3
20	Argyriou, 2006	1	1	0	0	1	3
21	Pace, 2010	1	1	1	1	1	5
22	Kottschade, 2010	1	1	1	1	1	5

Jadad scale evaluates RCTs on the basis of 5 components: (1) description of randomization, (2) appropriate method for randomization, (3) description of double-blinding, (4) appropriate method for double-blinding, and (5) description of withdrawals and dropouts. Scores greater than 3 are considered high quality.

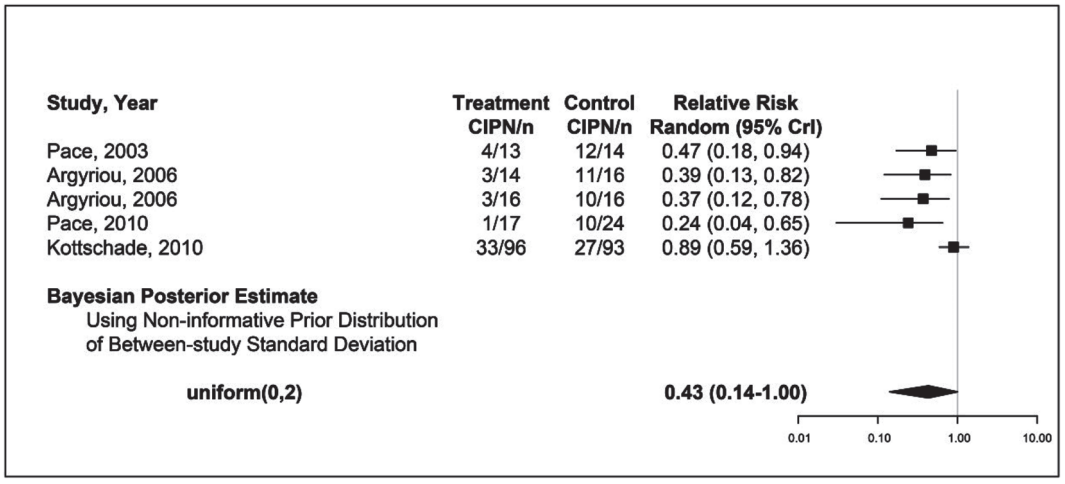

Figure 2: Preventive effects of vitamin E on chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients: a random-effects Bayesian meta-analysis.
CIPN, chemotherapy-induced peripheral neuropathy; CrI, credible interval. A black square denotes the point estimate, and the size of the square indicates the weight of the study. The vertical straight line denotes the null effect [relative risk (RR) = 1]. A horizontal line denotes the 95 % credible interval (CrI) for an individual study. The black diamond corresponds to the summary CrI.

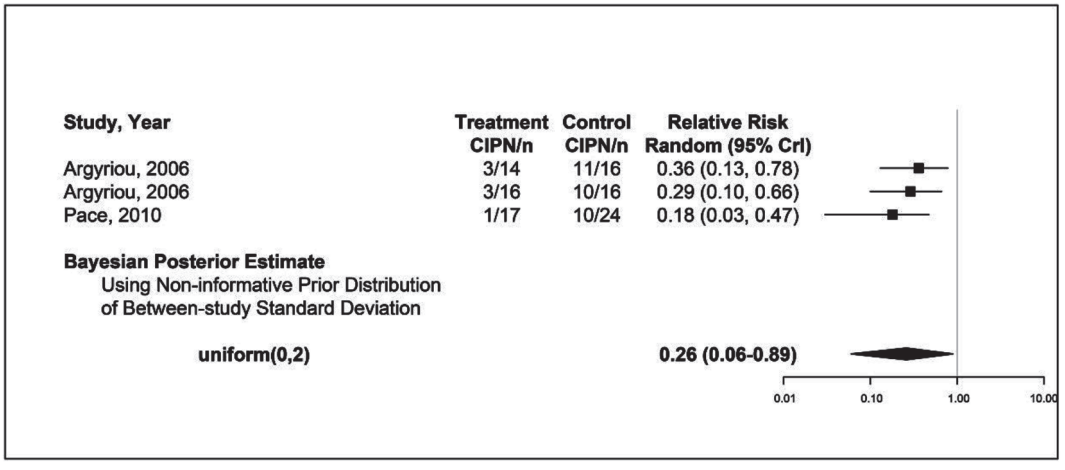

Figure 3: Preventive effects of vitamin E on cisplatin-induced peripheral neuropathy: subgroup analysis of three randomized controlled trials (RCTs).
CIPN, chemotherapy-induced peripheral neuropathy; CrI, credible interval. A black square denotes the point estimate, and the size of the square indicates the weight of the study. The vertical straight line denotes the null effect (relative risk (RR) = 1). A horizontal line denotes the 95 % credible interval (CrI) for an individual study. The black diamond corresponds to the summary CrI.

Subgroup analyses by type of the chemotherapeutic agent

Subgroup analysis according to the type of chemotherapeutic agent was only available for cisplatin. The result of a random-effect Bayesian analysis of the 3 RCTs that included cisplatin-based therapy [18, 19, 21] showed that vitamin E supplementation significantly reduced the incidence of CIPN (RR 0.26; 95 % CrI, 0.06–0.89; P = 0.981) (Figure 3). We also performed a sensitivity test for the subgroup analysis by varying the prior distribution of the between-study standard deviation. We considered that a uniform distribution of the standard deviation in the range (0,4) was large enough to assume a non-informative prior for subgroup analysis because the standard deviation from all 5 RCTs was estimated to be less than 1 (0.76–0.82). In the sensitivity test, we again obtained a high posterior probability of benefit (P≥0.95), although the CrI of the RR included 1 (the most conservative RR = 0.26; 95 % CrI, 0.03–1.68; P = 0.95).

Adverse effects

Three of the 5 RCTs [19, 20, 22] evaluated adverse effects related to vitamin E during chemotherapy, and all 3 studies reported that there were no adverse effects caused by vitamin E supplementation.

Discussion

The antioxidant vitamin E is known to protect cells and tissues from the oxidative damage and associated side effects induced by cytotoxic drugs [31]. An animal study showed that supplementation with antioxidants, including vitamin E, could prevent doxorubicin-induced cardiomyopathy as well as cisplatin-induced renal and chromosomal damage without weakening their anti-tumor activity [32].

Moreover, the safety of vitamin E supplementation with chemotherapy has also been tested in several studies. According to a report that reviewed 6 studies of the effects of antioxidants on cancer therapy, 3 studies showed that antioxidant supplementation had no effect on survival, 2 studies demonstrated a beneficial effect on survival, and 1 study reported that supplementation increased the short-term but not long-term survival [33]. In addition, both *in vivo* [34] and clinical studies [18] have shown that vitamin E supplementation does not influence the antitumor activities of chemotherapeutic agents.

In the current study, a Bayesian meta-analysis synthesized the available 5 RCTs in order to evaluate the neuroprotective effects of vitamin E on CIPN. The posterior probability that vitamin E supplementation provided a benefit with regard to reduced CIPN incidence is greater than 95 %. The subgroup analysis also showed that there was a significant preventive effect of vitamin E supplementation against cisplatin-induced peripheral neuropathy (probability of benefit, ≥95 %). This result corresponds with the CIPN mechanisms that were recently proposed in both *in vitro* and *in vivo* studies [1]. Although the exact mechanisms of neuropathy associated with each class of chemotherapy drugs remain to be fully elucidated, studies suggest that the depletion of vitamin E caused by cisplatin renders neural tissues more susceptible to free radicals [35]. The study showed that plasma concentrations of antioxidants, including vitamin E, decreased in response to cisplatin infusion and returned to baseline levels just before the next chemotherapy cycle. The reduction in plasma vitamin E concentration is not caused by other factors, such as a diminished intake of vitamin E or increased renal loss. This decrease in plasma vitamin E is thought to be caused by oxidative stress-induced antioxidant consumption [13].

Furthermore, the clinical manifestations of cisplatin-induced peripheral neuropathy are similar to those of vitamin E deficiency-induced peripheral neuropathy, and pathological studies have shown that the dorsal-root ganglia neurons are a prime target for both vitamin E deficiency and cisplatin [36]. There is evidence that cisplatin-induced large fiber sensory neuropathy is dose-related and often becomes evident after a cumulative cisplatin dose of at least 300–350 mg/m^2 [23]. The 3 RCTs that reported positive results all evaluated vitamin E efficacy in patients whose cumulative cisplatin dosages exceeded 300 mg/m^2. However, the other 2 studies did not report the cumulative doses of platinum compounds and taxanes.

Taxanes have been suggested to cause dose-dependent distal axonal sensorimotor polyneuropathy, which is related to alterations in axonal transport because of inhibited tubulin polymerization [37]. Although there is no clear evidence for a possible neuroprotective role of vitamin E or other antioxidants in taxane-induced neurotoxicity, a few clinical trials discovered the effect of vitamin E on the prevention of taxane-induced peripheral neuropathy [20, 22]. The first trial to report a positive result suggested that the indirect beneficial effects of vitamin E on cell body secondary structural damage or metabolic dysfunction would improve the function of the entire sensory system [20]. For other chemotherapeutic agents, however, there is no evidence to show a connection between free radicals and CIPN. In the case of acute oxaliplatin neurotoxicity, some studies have indicated that the mechanism might be related to calcium chelation by oxalate and not to free radicals [1]. Due to the unclear causal relationship between free radicals and neurotoxicity, vitamin E may be less effective in CIPNs, compared to cisplatin-induced peripheral neuropathy.

Two letters to the editor from the authors of previous studies that supported vitamin E as a preventative of CIPN have criticized the methodology of the Kottschade *et al.* study [38, 39]. In their letters to the editor, the authors commented that the negative results might be explained by the inclusion of many different types of chemotherapy with different mechanisms of action to induce neuropathy; specifically, more than 80 % of the patients enrolled in this trial were treated with taxanes or oxaliplatin. In their reply, the authors of the Kottschade *et al.* study agreed that there was no evidence to show that vitamin E might be helpful for oxaliplatin-induced neuropathy, but stated that they had designed their study to include the more

common types of chemotherapy and thus conduct a broad-spectrum test of the efficacy of vitamin E on CIPN. They also pointed out that the same methodological problems might apply to the previous clinical trial [40, 41].

The dosing and vitamin E prevention regimens were not identical in the extracted RCTs. In 2 of the 5 trials, the prevention group received 300 mg of vitamin E twice daily during chemotherapy and continued this regimen for 3 months after suspension of chemotherapy [19, 20]. In one trial, the prevention group received 300 mg of vitamin E twice daily during chemotherapy and continued this regimen for only 1 month after the suspension of chemotherapy [22]. In the other 2 trials, the participants received 300 or 400 mg daily of vitamin E before chemotherapy and continued this regimen for 3 months after suspension of chemotherapy [18,21]. Nevertheless, 4 studies with different dosing regimens showed significant protective effects of vitamin E [18–21].

No adverse effects from vitamin E supplementation were reported by any of the reviewed studies. The recommended dietary allowance (RDA) for vitamin E is 15 mg for people aged 14 years and older [42]. Vitamin E deficiency is rare, but severe deficiency can cause peripheral neuropathy, ataxia, skeletal myopathy, and impairment of immune responses [43]. In contrast, although this is controversial, some evidence suggests that the regular use of high-dose vitamin E might increase the risk of all-cause mortality [44, 45] and that long-term vitamin E supplementation can increase the risk of hemorrhagic stroke [46]. Based on those findings, the European Food Safety Authority has set the tolerable upper intake level for adults at 300 mg per day [47]. However, the most recent meta-analysis concluded that vitamin E supplementation appears to have no effect on all-cause mortality, regardless of the dosage [48].

Although there are some concerns about the long-term use of high-dose vitamin E, the duration of its use for preventing CIPN is only during chemotherapy and the following 3 months, and studies have not found any adverse effects from such a short-term use of vitamin E. In patients with vitamin K deficiency or those who take aspirin, however, caution is necessary with regard to the use of high-dose vitamin E supplementation.

There are several limitations of this study. First, only 5 RCTs with small sample sizes were available for the analysis. Second, only 2 RCTs were of high methodological quality, according to the Jadad scale [24], and both were double-blind trials. Third, because there are still no validated evaluation tools for CIPN and assessments of CIPN are subjective in nature [1], the incidence assessment could have varied among the studies. Finally, a subgroup analysis was conducted only on the cisplatin group, due to the limited data availability. We attempted to contact the author of one of the RCTs for a subgroup analysis of the paclitaxel group [22], but received no response.

In summary, the available data included in the current meta-analysis show that vitamin E supplementation might be able to significantly prevent or treat CIPN. However, one cannot confidently conclude its true value against the chemotherapy-associated neurotoxicity unless large and rigorously designed RCTs are conducted to investigate the neuroprotective effects of vitamin E supplementation against the neurotoxicity caused by various chemotherapeutic agents.

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