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

Huikai Miao^a Rongzhen Li^a Dongni Chen^a Jia Hu^a Youfang Chen^a
Chunmei Xu^b Zhesheng Wen^a

^aDepartment of Thoracic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China; ^bDepartment of Endocrinology and Metabolism, Shandong Provincial Qianfoshan Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Keywords

Chemotherapy · Meta-analysis · Peripheral neuropathy · Vitamin E

Abstract

Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is a common symptom, but prophylactic measures cannot still be carried out effectively. In addition, the efficacy of vitamin E in preventing peripheral neurotoxicity caused by chemotherapy is inconclusive. Therefore, we collected the relevant randomized controlled trials (RCTs) and performed a meta-analysis to examine whether the vitamin E has a positive effect in CIPN. **Methods:** We searched PubMed, EMBASE, Cochrane, and other databases in December 2019 for eligible trials. Two reviewers conducted the analysis independently when studies were homogeneous enough. **Results:** Eight RCTs, involving 488 patients, were identified. Upon pooling these RCTs, patients who received vitamin E supplementation of 600 mg/day had a lower incidence of CIPN (risk ratio [RR] 0.31; 95% confidence interval [CI] 0.14–0.65; $p = 0.002$) than the placebo group. Vitamin E played a key role in decreasing the incidence of peripheral

neuropathy in the cisplatin chemotherapy group (RR 0.28; 95% CI 0.14–0.54; $p = 0.0001$). Moreover, vitamin E supplementation significantly decreased patients' sural amplitude after 3 rounds of chemotherapy (RR –2.66; 95% CI –5.09 to –0.24; $p = 0.03$) in contrast with that of placebo supplementation, while no significant difference was observed when patients were treated with vitamin E after 6 rounds of chemotherapy. In addition, the vitamin E-supplemented group had better improvement in the neurotoxicity score and lower incidence of reflexes and distal paraesthesias than the control group. **Conclusion:** Available data in this meta-analysis showed that vitamin E supplementation can confer modest improvement in the prevention of CIPN.

© 2021 S. Karger AG, Basel

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common adverse effects of chemotherapeutic agents, which confines the effects of chemotherapy largely. The incidence of this disabling pain reaches up to 68% in the short term when receiving che-

motherapy [1]. The severe pain of CIPN causes the loss of functional abilities and lower patients' quality of life. The additional financial burden and the waste of medical resources caused by CIPN also cannot be ignored [2].

However, the neuropathogenesis of CIPN is still unclear. Multifactorial pathological processes may be involved, including oxidative stress, apoptosis, immune response, and neuroinflammation [3]. Accumulating studies have indicated that the production of reactive oxygen species is a significant cause of peripheral neuropathy induced by chemotherapy [4], and many researchers have proposed that an antioxidant substance could provide effective protection against peripheral neuropathy [5]. Currently, there is no effective therapy demonstrated effective in the prevention of CIPN [6].

Vitamin E is regarded as a treatment for neuropathy and is useful for the alleviation of chemotherapy-related toxicities [7]. It has been shown that the plasma levels of vitamin E in patients who developed severe CIPN following cisplatin were significantly reduced [8], and vitamin E supplementation ameliorated neurotoxicity in animals receiving cisplatin by eliminating oxygen-free radicals [7]. Pace et al. [9, 10] suggested that vitamin E lower the incidence and severity of cisplatin- and paclitaxel-induced peripheral neurotoxicity. Similarly, Argyriou et al. [11] conducted a randomized controlled trial (RCT) and reported that vitamin E had a protective effect on chemotherapy-induced peripheral nerve damage. A recent study also found that vitamin E helped paclitaxel-induced neuropathy and improved sensory nervous system function [12]. However, the negative findings about the effect of vitamin E on CIPN were reported in some clinical trials [13–15]. Thus, whether vitamin E can improve or prevent CIPN is still controversial. Our study was aimed to summarize the currently available evidence, and conduct a meta-analysis to further study the effect of vitamin E on the prevention of CIPN, providing the convincing medical advice for clinicians to prevent CIPN.

Methods

Search Strategy

Search Methods for the Identification of Studies

Two independent reviewers completed a systematic search in PubMed, EMBASE, Cochrane databases, CNKI, Wanfang, and CHKD from the inception dates to December 31, 2019. All disagreements were resolved by discussion between the reviewers. The search was restricted to human subjects with the following keywords: chemotherapy, neuropathy or peripheral neuropathy or peripheral nerve toxicity or neurotoxicity or CIPN, and vitamin E or tocopherol. There were no language limitations.

Selection and Excluded Criteria

The titles and abstracts identified from the above databases were browsed independently by two reviewers. A consensus was reached by consultation. When no agreement was reached, a third reviewer was involved in the decision. The following studies were excluded (1) not RCTs (2) patients included in the trials without chemotherapy (3) trials without vitamin E supplement and placebo for comparison (4) study population with diabetes.

Data Extraction

Two reviewers collected and organized the following data from all included trials independently. Items included were first author name, publication year, country, number of total participants, cancer type, vitamin E prevention regimen, chemotherapy regimen, number of participants in each group, and outcomes. The characteristics of the included articles were summarized.

Methodological Quality and Risk of Bias

The methodological quality of RCTs was assessed by two researchers (M.H.K. and L.R.Z.) independently to avoid the risk of overestimation of the intervention effects. The specific assessment methods were based on Cochrane risk-of-bias criteria: (1) generation of the allocation sequence, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, and (6) selective reporting. Each was graded as low-risk, high-risk, or unclear risk.

Data Analysis

The main outcomes were the incidence of peripheral neuropathy (IPN) induced by chemotherapy, sural amplitude (SA), median amplitude (MA), and other evaluation parameters, including neurotoxicity score, the incidence of reflexes and distal paraesthesia (RDP). Review Manager (RevMan) version 5.3 was used for data processing. For dichotomous variables, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. For continuous variables, mean differences with 95% CIs were calculated. If there were no significant heterogeneities in the data of the different trials, the fixed-effects model was applied. Otherwise, we used the random-effects model [16]. Subgroup analyses by the dose of vitamin E (either 600 mg/day or 400 mg/day) and the type of chemotherapy regimen (either cisplatin or oxaliplatin) were performed to evaluate the efficacy of vitamin E in the prevention of CIPN. In addition, subgroup analysis of the number of chemotherapy cycles (either 3 or 6 cycles) was applied to assess the parameters of SA. The I^2 was calculated, which can be interpreted as the percentage of the variation between studies that is attributed to heterogeneity rather than chance. $I^2 = 0\%$ means no heterogeneity, $I^2 > 50\%$ indicates a high heterogeneity; and $I^2 = 100\%$ means that all variation derives from study heterogeneity. Sensitivity analyses were performed to exclude specific studies and to evaluate if any study could significantly influence the overall results. Publication bias was evaluated via Funnel plots made by RevMan5.3. The statistical significance was determined as $p < 0.05$.

Fig. 1. Flow diagram of the study selection process. RCT, randomized controlled trial; CIPN, chemotherapy-induced peripheral neuropathy.

Results

Search Results

A total of 514 references were identified in the initial search from the PubMed, EMBASE, Cochrane, CNKI, Wanfang, and CHKD databases. No references were gained from non-English databases, according to the excluded criteria. After getting rid of the duplicate references, 458 references were remained to be browsed. Due to the exclusion of studies with improper design, there were 40 references left to be assessed for full-text review. Finally, 8 references were considered for inclusion after excluding the other 32 references for other reasons. The entire search progress is described in Figure 1.

Study Characteristics

Among the final 8 references, 4 studies were conducted in Europe, 2 in Greece [11, 17] and 2 in Italy [9, 10] and for non-European studies, 2 studies were conducted

in Iran [12, 15], 1 in the USA [13] and 1 in Brazil [14]. The major characteristics of the included studies are summarized in Table 1. In all, 488 patients were included in the meta-analysis, and the number of participants in each arm ranged from 13 to 96. The experimental intervention was vitamin E supplementation as an adjuvant to cisplatin, paclitaxel, and other chemotherapies. In 4 trials, 210 patients received vitamin E treatment at a dose of 400 mg/day [10, 12, 14, 15], and in 3 trials, 251 patients received 600 mg/day vitamin E [11, 13, 17]. Furthermore, only in 1 trial, 27 patients received 300 mg/day vitamin E in the experimental group [9]. The durations of the treatment with vitamin E varied from initiation of chemotherapy to 3 months after the cessation of chemotherapy.

Methodological Quality

Overall, 5 trials (62.5%) had adequate sequence generation, 4 trials (50%) had adequate concealed allocation, and the outcomes of 4 trials (50%) were judged to be ad-

Table 1. Main characteristics of all studies included in the meta-analysis

First author	<i>n</i>	Country	Type of cancer	Intervention group	<i>n</i>	Contrast group	<i>n</i>	Chemotherapy	Outcomes
Pace et al. [9]	27	Italy	Lung, ovarian, rhinopharynx, urethral, gastric, testicular, esophageal, ethmoidal, and tongue	Vitamin E 300 mg/d	13	Placebo	14	Cisplatin	IPN, NS, SA, SSCV, MA, RDP
Argyriou et al. [11]	30	Greece	Lung, cervix, testicular, head and neck, and gastric	Vitamin E 600 mg/d	14	Placebo	16	Cisplatin	IPN, SA
Argyriou et al. [17]	32	Greece	Lung, breast, and ovarian	Vitamin E 600 mg/d	16	Placebo	16	Paclitaxel	IPN, SA
Pace et al. [10]	41	Italy	Lung, glioblastoma, endometrial, bladder, surreal gland, and carcinosarcoma	Vitamin E 400 mg/d	17	Placebo	24	Cisplatin	IPN, NS, SA, MA, RDP
Kottschade et al. [13]	189	America	Breast, lung, and other	Vitamin E 400 mg/d	96	Placebo	93	Paclitaxel, cisplatin, carboplatin, oxaliplatin	IPN
Afonseca et al. [14]	34	Brazil	Colorectal and gastric	Vitamin E 400 mg/d	18	Placebo	16	Oxaliplatin	IPN
Zeinab et al. [15]	65	Iran	Colorectal	Vitamin E 400 mg/d	32	Placebo	33	Oxaliplatin	IPN, NS
Gholamreza et al. [12]	70	Iran	Breast	Vitamin E 400 mg/d	35	Placebo	35	Paclitaxel	SA, SSCV

IPN, incidence of peripheral neuropathy; NTS, neurotoxicity score; SA, sural amplitude; SSCV, sural sensory conduction velocity; MA, median amplitude; RDP, reflexes and distal paraesthesia.

equately blinded. However, most of these studies (87.5%) did not have enough information about the risk of incomplete outcome data, and none of them mentioned selective reporting bias. The risk of bias is shown in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000515620.

Primary Outcomes

Incidence of Peripheral Neuropathy

The IPN was the primary outcome which directly reflected the occurrence of CIPN. Seven of the 8 studies were available to investigate the IPN, and the total number of participants was 206 and 212 for the vitamin E group and placebo group, respectively. The pooled results found a significantly lower IPN with vitamin E than placebo, while the high heterogeneity should not be ignored (RR 0.82; 95% CI 0.68–0.98; $p = 0.03$; $I^2 = 88\%$) (Fig. 2a). Considering that different doses of vitamin E and various chemotherapy regimens were used in different studies, we conducted the parallel subgroup analysis with the fixed-effects model. The subgroup analysis results revealed that no significant difference in the IPN in patients treated with vitamin E 600 mg/day compared with pla-

cebo, with high heterogeneity (RR 0.81; 95% CI 0.57–1.15; $p = 0.24$; $I^2 = 79\%$). Because of the apparent heterogeneity in the group receiving vitamin E 600 mg/day, we did a sensitivity analysis by excluding the study of Kottschade et al. [13] due to its low methodological quality. The sensitivity analysis suggested a significantly positive effect of vitamin E 600 mg/day on preventing CIPN as compared to placebo (RR 0.31; 95% CI 0.14–0.65; $p = 0.002$; $I^2 = 0\%$) (Fig. 2b). However, the vitamin E 400 mg/day group displayed no difference in the reduction of the IPN compared with the placebo group (RR 0.93; 95% CI 0.79–1.10; $p = 0.39$; $I^2 = 82\%$) (Fig. 2b). Besides, due to the study conducted by Pace et al. [9], the vitamin E 300 mg/day on the prevention of peripheral neuropathy might have significant clinical value.

Similarly, subgroup analysis was conducted by grouping the type of chemotherapy in the fixed-effects model

Fig. 2. a Forest plots showing the relationship between the IPN and vitamin E. **b** Subgroup analysis of the IPN in different doses of vitamin E. **c** Subgroup analysis of the IPN in different types of chemotherapy. IPN, incidence of peripheral neuropathy; RR, risk ratio; CI, confidence interval.

(For figure see next page.)

Fig. 3. a Forest plots showing the relationship between the SA and vitamin E. **b** Subgroup analysis of the sural amplitude in different rounds of chemotherapy. **c** Forest plots showing the relationship between the MA and vitamin E. SA, sural amplitude; MA, median amplitude; CI, confidence interval.

(Fig. 2c). The combination of vitamin E and cisplatin group [9–11] displayed a significantly lower IPN with no heterogeneity than the combination of placebo and cisplatin group (RR 0.28; 95% CI 0.14–0.54; $p = 0.0001$; $I^2 =$

0%). However, for the combination of vitamin E and oxaliplatin group, the result showed that there was no difference in the IPN compared with the placebo group (RR 1.08; 95% CI 0.95–1.22; $p = 0.24$; $I^2 = 34\%$).

Fig. 4. **a** Forest plots showing the relationship between the neurotoxicity score and vitamin E. **b** Forest plots showing the relationship between the SSCV and vitamin E. **c** Forest plots showing the relationship between the RDP and vitamin E. RDP, reflexes and distal paraesthesia; SSCV, sural sensory conduction velocity; RR, risk ratio.

Sural Amplitude

SA is the action potential amplitude of the sural muscle, which is a reliable index for evaluating the condition of peripheral neuropathy. Five studies measured changes in SA before and after supplementation with vitamin E. We used the fixed-effects model to merge the mean difference values, and the pooled mean difference was 0.58 (95% CI -0.24 to 1.40; $p = 0.17$) with high heterogeneity ($I^2 = 72\%$) (Fig. 3a), which indicated that vitamin E did not improve SA compared to placebo. Thus, a subgroup analysis was conducted based on the number of chemo-

therapy cycles. Further analysis indicated that vitamin E could reduce the extent of SA in patients after 3 rounds of chemotherapy compared with the placebo group, but high heterogeneity still existed (mean difference = 1.06; 95% CI 0.14–1.98; $p = 0.02$; $I^2 = 82\%$) (Fig. 3b). Subsequently, we performed a sensitivity analysis after ruling out a study conducted by Shamsaei et al. [12], which included Asian instead of European in the study cohort. The sensitivity analysis demonstrated a significantly protective effect on SA with vitamin E after three rounds of chemotherapy compared with placebo (mean differ-

Fig. 5. Egger's plot of the IPN. SND, standard normal deviate; CI, confidence interval; IPN, incidence of peripheral neuropathy.

ence = -2.66 ; 95% CI -5.09 to -0.24 ; $p = 0.03$; $I^2 = 0\%$). Nonetheless, significant improvement in SA was not detected with vitamin E supplementation after 6 rounds of chemotherapy (mean difference = -1.28 ; 95% CI -3.11 to 0.54 ; $p = 0.17$; $I^2 = 40\%$) (Fig. 3b).

Median Amplitude

Similar to SA, MA is another indicator that reflects the severity of peripheral neuropathy. Two previous studies [9, 10] reported MA were available to measure the change in MA before and after the application of vitamin E. Compared to the participants treated with placebo, vitamin E was more effective in remission for MA with a pooled mean difference of -3.00 (95% CI -5.32 to -0.68 ; $p = 0.01$) with low heterogeneity ($I^2 = 0\%$) (Fig. 3c).

Secondary Outcomes

The secondary outcomes in the meta-analysis were the neurotoxicity score, sural sensory conduction velocity (SSCV), and the incidence of RDP. A composite neurotoxicity score was calculated for each patient in three included studies [9, 10, 15], according to the severity of neuropathic symptoms and electrophysiologic changes [18]. Analysis showed that vitamin E significantly decreased the neurotoxicity score and displayed moderate heterogeneity (mean difference = -1.47 ; 95% CI -2.45 to -0.49 ; $p = 0.003$; $I^2 = 67\%$) (Fig. 4a). Then, we carried out a sensitivity analysis by excluding the study conducted by Salehi et al. [15], as it had a different chemotherapy regimen. The results found a significantly improved effect on the neurotoxicity score with vitamin E compared to placebo (mean difference = -2.65 ; 95% CI -4.01 to -1.29 ; $p =$

0.0001 ; $I^2 = 0\%$) (Fig. 4a). The SSCV is the action potential conduction velocity of the sural muscle in electromyography. The pooled results presented that there was no significant difference in the vitamin E group compared with the placebo group (mean difference = -0.39 ; 95% CI -1.82 to 1.03 ; $p = 0.59$; $I^2 = 52\%$) (Fig. 4b). RDP reflected the physiological status of limb muscles. The pooled result revealed that vitamin E played a significant role in the lower incidence of RDP than placebo (mean difference = 0.50 ; 95% CI 0.29 – 0.87 ; $p = 0.01$; $I^2 = 8\%$) (Fig. 4c).

Publication Bias

The Egger's plot based on the IPN is shown in Figure 5. The result showed that no obvious reporting bias was observed ($p = 0.408$).

Discussion

Results of this meta-analysis showed that vitamin E supplementation can confer modest improvement in the prevention of CIPN. Patients who received vitamin E supplementation of 600 mg/day had a significantly lower incidence of CIPN than the placebo group. Vitamin E played a key role in reducing the IPN in the cisplatin chemotherapy group.

Peripheral neuropathy is one of the most debilitating toxicities in cancer patients receiving chemotherapy [19]. The incidence of CIPN varies with different antineoplastic agents, namely 28–100% of patients who receive cisplatin [20] and 57–83% of patients who receive paclitaxel [21]. In addition to chemotherapy regimens, the incidence of CIPN was often related to the therapeutic dose [22]. Severe acute CIPN required chemotherapy dose reduction or cessation, leading to the progression of cancer and eventually a poor prognosis in patients [23].

Many pharmacological agents, such as glutathione [24], calcium, and magnesium infusions [25], and venlafaxine [26] have been studied for the treatment of CIPN. The effect of vitamin E on the improvement of CIPN is still controversial. The results of the animal study proved the positive effect of vitamin E, which urged more researchers to seek its validity in clinical trials [5, 27]. A previous review made by Bove et al. [28] concluded that the severity of peripheral neuropathy varies inversely with the level of vitamin E. The vitamin E deficiency caused by chemotherapy made the nervous system more vulnerable to damage. A review, published in 2011, included 2 RCTs that contained vitamin E supplementation and proved the preventative effect of vitamin E against

CIPN [22]. However, only 2 RCT studies seem not reaching a convincing conclusion. In another published meta-analysis, which included 5 available RCTs, the positive neuroprotective effects of vitamin E were confirmed. In addition, the study concluded that vitamin E supplementation could attenuate the development of CIPN [29]. Whereas, Huang's meta-analysis included 6 RCTs and failed to demonstrate a statistically significant effect of vitamin E on the incidence of CIPN [30].

In our study, we collected all the newest published RCTs and tried to make a higher evidence-based quality analysis. Our primary outcomes included the IPN, which directly reflected the occurrence of CIPN in cancer patients after chemotherapy [31]. According to our analysis, vitamin E supplementation provided a significant reduction in the IPN in the cisplatin group, which was consistent with the meta-analysis by Eum et al. [29]. They found a significant preventive effect of vitamin E on CIPN with a probability of benefit greater than 95%. In the meta-analysis worked by Huang et al. [30] in 2016, 353 patients of 6 articles were involved in the study. They failed to report a statistically significant effect of vitamin E supplementation on the incidence of CIPN. The possible reason which accounted for the result was explored. We realized that Huang et al. [30] have searched the database from their inception to December 31, 2013. However, 2 more newly developed RCTs (Salehi et al. [15] and Shamsaei et al. [12]) were involved in the present study. Salehi et al. [15] reported that there was no difference in the mean peripheral neuropathy score changes between vitamin E and control groups. Nevertheless, Shamsaei et al. [12] reported that the delta amplitude of sural nerve was significantly lower among patients taking vitamin E supplements. Due to the various inclusions of studies, the discrepancy between 2 meta-analyses appears. Furthermore, the results that preventive effect of vitamin E supplementation on cisplatin was associated with neurotoxicity in Huang's report were consistent with our findings, which showed that the beneficial effect of vitamin E on the prevention of cisplatin-associated neurotoxicity.

The exact mechanisms of neuropathy associated with various chemotherapy drugs remains to be fully elucidated. Researchers tended to assume that cisplatin-induced neuropathy was dose-related, and the symptom manifested after an accumulative cisplatin dose [22]. Bove et al. [28] reported that the plasma concentrations of vitamin E fluctuated over the process of cisplatin treatment and returned to a favourable level, which suggested that vitamin E exhaustion after cisplatin treatment had a potential association with the occurrence of peripheral neuropathy.

However, our results demonstrated that vitamin E did not play a role in reducing the IPN in the paclitaxel group. Although paclitaxel has been confirmed to cause dose-dependent distal axonal sensorimotor polyneuropathy, both of the RCTs [12, 17] in our meta-analysis revealed that no remarkable difference was found between the vitamin E and placebo groups after treatment with paclitaxel. More high-quality RCTs are needed to investigate the influence of vitamin E on the peripheral neuropathy induced by paclitaxel.

Furthermore, in our study, only 600 mg/day vitamin E for 3 months presented significantly protective effects on the prevention of CIPN. It is worth noting that the dose and regimen of vitamin E were distinguished from existing studies. A study showed that an overdose of vitamin E could be harmful and increase the risk of overall mortality [32, 33]. However, other studies have argued that vitamin E supplementation did not have an effect on all-cause mortality, regardless of the dosage [34]. No adverse effects on vitamin E supplementation were reported by any of the reviewed studies. The use of vitamin E 600 mg/day for 3 months did not cause any adverse effects in our study. Generally, the regimen of vitamin E 600 mg/day for 3 months might be preferred for the prevention of CIPN.

The evaluation methodology of CIPN not only involves symptoms of pain and paralysis but also changes in electromyography [35]. In the meta-analysis, other outcomes measured by electromyography were also analysed. We found that vitamin E provided improvement of SA for patients who finished 3 cycles of chemotherapy, while there was no significant effect on SA for patients who finished the 6 entire cycles of chemotherapy. The original target of medical treatment is to cure cancer or delay progression of the disease, but current attention is focused more on the long-term influence for patients. Our study showed that vitamin E supplementation was not enough to improve the SA of patients who finished the 6 entire cycles of chemotherapy. To thoroughly evaluate the effect of vitamin E on the improvement of CIPN, we also conducted a meta-analysis to assess other indicators reflecting the severity of peripheral neuropathy, including MA, neurotoxicity score, SSCV, reflexes, and distal paraesthesias. Vitamin E played a key role in the improvement of MA, neurotoxicity score, RDP, and all evidence proved the efficacy of vitamin E in the prevention of CIPN was reliable. Furthermore, the nutrition status could also influence the side effect symptom in chemotherapy patients. Malnutrition is a prognostic factor for poor clinical outcome and severe side effect during chemoradiotherapy [36]. Many indicators could be used

to assess the nutrition status in cancer patients. The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF), NRS2002 scores, and PG-SGA score could be used for descriptive nutrition screening [37] and are useful prognostic factors for patients after chemoradiotherapy [38, 39]. However, none of the 8 studies included in our analysis involved the nutrition status as an outcome indicator, which might be a meaningful covariate in the analysis. The nutrition status should be paid more attention in the future RCT studies to provide more meaningful message for the physicians.

There are some limitations in our analysis should not be ignored. Firstly, only 8 RCTs were included in the analysis. The methodological quality of the RCTs involved was not satisfactory, and only 2 RCTs were of high methodological quality. Secondly, varied cancer populations across the studies influenced the consistency of the research. In addition, clinical outcomes, such as the disease response, adverse effects, and conditions of prognosis, were not reported clearly, impeding further analyses due to the insufficient data.

Conclusion

Vitamin E might contribute to prevent CIPN from patients underwent neurotoxic chemotherapy. The vitamin E supplement as the standard of care for prevention of

CIPN is moderately recommended in our study. More high-quality trials with standardized reporting of clinical outcomes about peripheral neuropathy are needed to explore the exact role of vitamin E in the prevention of CIPN.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

No authors report any conflict of interest.

Funding Sources

This work was supported by the National Natural Science Foundation of China (81871986).

Author Contributions

Huikai Miao and Rongzhen Li conceived and designed the study. Dongni Chen, Jia Hu, and Youfang Chen performed the analysis, prepared the figures and tables, and wrote the main manuscript. Chunmei Xu and Zhesheng Wen were involved in critically revising the manuscript. All the authors read and approved the final manuscript.

References

- Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain*. 2014 Dec; 155(12):2461–70.
- Pike CT, Birnbaum HG, Muehlenbein CE, Pohl GM, Natale RB. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. *Chemother Res Pract*. 2012; 2012:913848.
- Starobova H, Vetter I. Pathophysiology of chemotherapy-induced peripheral neuropathy. *Front Mol Neurosci*. 2017 May 31;10:174.
- Ladas EJ, Jacobson JS, Kennedy DD, Teel K, Fleischauer A, Kelly KM. Antioxidants and cancer therapy: a systematic review. *J Clin Oncol*. 2004 Feb 1;22(3):517–28.
- Appenroth D, Fröb S, Kersten L, Splinter FK, Winnefeld K. Protective effects of vitamin E and C on cisplatin nephrotoxicity in developing rats. *Arch Toxicol*. 1997;71(11):677–83.
- Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American society of clinical oncology clinical practice guideline. *J Clin Oncol*. 2014 Jun 20;32(18):1941–67.
- Granados-Principal S, Quiles JL, Ramirez-Tortosa CL, Sanchez-Rovira P, Ramirez-Tortosa MC. New advances in molecular mechanisms and the prevention of adriamycin toxicity by antioxidant nutrients. *Food Chem Toxicol*. 2010 Jun;48(6):1425–38.
- Kalkanis JG, Whitworth C, Rybak LP. Vitamin E reduces cisplatin ototoxicity. *Laryngoscope*. 2004 Mar;114(3):538–42.
- 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 Mar 1;21(5):927–31.
- Pace A, Giannarelli D, Galiè E, Savarese A, Carpano S, Della Giulia M, et al. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. *Neurology*. 2010 Mar 2;74(9):762–6.
- Argyriou AA, Chroni E, Koutras A, Ionomou 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 Nov;14(11):1134–40.
- Shamsaei G, Ahmadzadeh A, Mehraban N. The vitamin E preventive effect on taxol-induced neuropathy among patients with breast cancer: a randomized clinical trial. *Jundishapur J Nat Pharm Prod*. 2017;12(4):e65027.
- 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 Nov;19(11):1769–77.

- 14 Afonseca SO, Cruz FM, Cubero DI, 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(1):35–8.
- 15 Salehi Z, Roayaei M. Effect of vitamin E on oxaliplatin-induced peripheral neuropathy prevention: a randomized controlled trial. *Int J Prev Med*. 2015 Nov 2;6:104.
- 16 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986 Sep; 7(3):177–88.
- 17 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 Sep;32(3):237–44.
- 18 Chaudhry V, Rowinsky EK, Sartorius SE, Donehower RC, Cornblath DR. Peripheral neuropathy from taxol and cisplatin combination chemotherapy: clinical and electrophysiological studies. *Ann Neurol*. 1994 Mar;35(3):304–11.
- 19 Cioroiu C, Weimer LH. Update on chemotherapy-induced peripheral neuropathy. *Curr Neurol Neurosci Rep*. 2017 Jun;17(6):47.
- 20 Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents. *Curr Opin Neurol*. 2007 Dec;20(6):719–25.
- 21 Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst*. 2008 Mar;13(1):27–46.
- 22 Albers JW, Chaudhry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. *Cochrane Database Syst Rev*. 2011 Feb 16(2):CD005228.
- 23 Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Support Care Cancer*. 2014 Aug;22(8):2261–9.
- 24 Cascinu S, Catalano V, Cordella L, Labianca R, Giordani P, Baldelli AM, et al. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol*. 2002 Aug 15;20(16):3478–83.
- 25 Gamelin L, Boisdron-Celle M, Delva R, Guérin-Meyer V, Ifrah N, Morel A, et al. Prevention of oxaliplatin-related neurotoxicity by calcium and magnesium infusions: a retrospective study of 161 patients receiving oxaliplatin combined with 5-Fluorouracil and leucovorin for advanced colorectal cancer. *Clin Cancer Res*. 2004 Jun 15;10(12 Pt 1):4055–61.
- 26 Durand JP, Alexandre J, Guillemin L, Goldwasser F. Clinical activity of venlafaxine and topiramate against oxaliplatin-induced disabling permanent neuropathy. *Anticancer Drugs*. 2005 Jun;16(5):587–91.
- 27 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 Mar 20;104(2):243–50.
- 28 Bove L, Picardo M, Maresca V, Jandolo B, Pace A. A pilot study on the relation between cisplatin neuropathy and vitamin E. *J Exp Clin Cancer Res*. 2001 Jun;20(2):277–80.
- 29 Eum S, Choi HD, Chang MJ, Choi HC, Ko YJ, Ahn JS, et al. Protective effects of vitamin E on chemotherapy-induced peripheral neuropathy: a meta-analysis of randomized controlled trials. *Int J Vitam Nutr Res*. 2013;83(2):101–11.
- 30 Huang H, He M, Liu L, Huang L. Vitamin E does not decrease the incidence of chemotherapy-induced peripheral neuropathy: a meta-analysis. *Contemp Oncol*. 2016;20(3):237–41.
- 31 Cavaletti G, Alberti P, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. *Lancet Oncol*. 2011 Nov;12(12):1151–61.
- 32 Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005 Jan 4;142(1):37–46.
- 33 Schürks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. *BMJ*. 2010 Nov 4;341:c5702.
- 34 Abner EL, Schmitt FA, Mendiondo MS, Marcum JL, Kryscio RJ. Vitamin E and all-cause mortality: a meta-analysis. *Curr Aging Sci*. 2011 Jul;4(2):158–70.
- 35 Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: a comprehensive survey. *Cancer Treat Rev*. 2014 Aug;40(7):872–82.
- 36 de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio)therapy: current evidence and guidance for design of future trials. *Ann Oncol*. 2018 May 1;29(5):1141–53.
- 37 Abbott J, Teleni L, McKavanagh D, Watson J, McCarthy AL, Isenring E. Patient-generated subjective global assessment short form (PG-SGA SF) is a valid screening tool in chemotherapy outpatients. *Support Care Cancer*. 2016 Sep;24(9):3883–7.
- 38 Wang J, Yu B, Ye Y, Shen J, Ding N, Tang H, et al. Predictive value of nutritional risk screening 2002 and prognostic nutritional index for esophageal cancer patients undergoing definitive radiochemotherapy. *Nutr Cancer*. 2018 Aug–Sep;70(6):879–85.
- 39 Gallois C, Artru P, Lièvre A, Auclin E, Lecomte T, Locher C, et al. Evaluation of two nutritional scores' association with systemic treatment toxicity and survival in metastatic colorectal cancer: an AGEO prospective multicentre study. *Eur J Cancer*. 2019 Sep;119:35–43.