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Does Vitamin E Mitigate Cisplatin-induced Nephrotoxicity in Cancer Patients: Results from a Randomized Placebo-Controlled Clinical Trial

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Abstract

Background: Cisplatin (CP) is a potent antineoplastic agent in the treatment of wide a range of cancers, but it is accompanied with nephrotoxicity, a major limiting side effect. The aim of the present study was to evaluate the possible protective effect of vitamin E in the prevention of CP-induced nephrotoxicity.

Method: In this randomized clinical trial, a total of 51 patients treated with CP chemotherapy were randomly assigned to receive vitamin E supplementation (400 Iu/ daily) (N=26) or placebo (N=25). Serum creatinine, glomerular filtration rate (GFR), and neutrophil gelatinase-associated lipocalin were measured prior to each chemotherapy cycle and one month after the cessation of the cycles.

Result: Compared to the baseline, a significant decrease was observed in the blood levels of neutrophil gelatinase-associated lipocalin and serum creatinine in the vitamin E group (P=0.001). GFR was not reduced in the vitamin E group (P=0.001), and vitamin E was generally tolerated well.

Conclusion: Our findings indicated that vitamin E exert protective effects against CP-induced nephrotoxicity, a finding which requires larger studies for confirmation.

Keywords: Cisplatin, Nephrotoxicity, Neutrophil gelatinase-associated lipocalin, Vitamin E

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Introduction

Cisplatin (CP) is a major chemotherapy agent that has significantly improved the treatment of many malignancies, including testicular, ovarian, breast, small-cell lung, and head and neck cancer.[1] CP binds to DNA, forming inter- and intra-strand cross-links, which results in defective DNA templates and an arrest of DNA synthesis and replication.[1-3] Drug resistance and considerable side effects are significant downsides that have mainly limited CP use in cancer therapy.[4] CP has been combined with other cancer drugs in order to overcome drug resistance.[4]

Major side-effects of CP are neurotoxicity, ototoxicity, nausea and vomiting, and nephrotoxicity;[5] nephrotoxicity occurs in about one-third of patients undergoing cisplatin treatment, manifesting as lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels.[6] CP specifically binds to renal cells and concentrates in the kidney, particularly in the proximal tube. Inflammation, oxidative stress injury, mitochondrial dysfunction and apoptosis are some of the proposed mechanisms of CP-induced renal injury, which entail tubular damage and tubular dysfunction with sodium, potassium, and magnesium wasting.[6-8] Most of the time, the changes are reversible. Volume expansion and saline diuresis remain the most clinically effective preventive strategies.[9] Regarding the underlying mechanism of nephrotoxicity, many approaches have been proposed for renoprotection such as inhibition of CP uptake by renal cell, inhibition of CP bioactivation through obstructing ɣ-glutamyltrans peptidase, blocking cell death pathways, inhibition of inflammatory responses and antioxidants to reduce oxidative stress.[9] Amifostine,[10] melatonin,[11] vitamin C and E,[12] allopurinol,[13] Ebselen,[13] and N-acetyl cysteine[14] are examples of drugs that reduce the oxidative stress injury induced by CP by scavenging free radicals and other mechanisms.[9] The results of clinical trials are inconclusive regarding the effect of antioxidants. For instance, a dietary supplement consisting of vitamin C, vitamin E and selenium has been tested in 48 Dutch cancer patients, where no significant difference was observed between the test and the placebo groups concerning the severity of CP-induced renal injury.[15]

Some animal and human studies have supported the role of vitamin E in CP toxicities (especially neurotoxicity). Pace et al.[16] showed that oral supplementation with vitamin E (30 mg/d before CP chemotherapy until three months after treatment suspension) reduced the incidence and severity of peripheral neurotoxicity. Nematbakhsh et al.[17] administered 1g/kg vitamin E in 32 Wistar rats for four days and treated them with CP (6 mg/kg), concluding that vitamin E, as prophylaxis, demonstrated certain nephroprotective effects in rats. Another study by Nematbakhsh et al. evaluated the role played by the gender of vitamin E in CP-induced nephrotoxicity. One group from each gender of Wistar rats was administered a single dose of CP (7 mg/kg; i.p), treated with vitamin E (1 g/kg/day) for seven days and compared with the same gender in the control group. The results showed that vitamin E might prevent CP-induced nephrotoxicity in male, yet it did not possibly induce such nephro-protectant effect in females.[18] Ajith et al.[19] showed that the coadministration of high doses (500 mg/kg) of vitamin E and C in mice, increased the activities of renal antioxidant enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. These antioxidants are partially effective in preventing the renal damage of CP. Other animal studies such as Appenorah et al. have confirmed the protective role of vitamin E in reducing nephrotoxicity,[20] showing that the co-administration of vitamin E and C (100mg/100g body weight) reduce the level of blood urea nitrogen (BUN) and lipid peroxidase in rats.

Hemati et al.[21] administered 400 Iu vitamin E and 200 mcg selenium to 22 patients treated with cisplatin and compared them with the placebo group, observing significant differences in glomerular filtration rate (GFR) between the two groups following the third cycle and one month after the end of the chemotherapy. None of the aforementioned studies evaluated the nephroprotective effect of vitamin E as monotherapy.

Several studies have suggested that tubular injury-based biomarkers could be more useful than traditional markers (such as serum creatinine) to predict and diagnose acute kidney injury.[22-26] One of these biomarkers is neutrophil gelatinase-associated lipocalin (NGAL). Serum NGAL is a highly sensitive, specific, and predictive early biomarker for kidney injury regarding a wide range of disease processes.[27] Moreover, serum NGAL levels have been reported to increase following drug-induced renal injury.[28, 29] We aimed at analyzing serially measured NGAL along with serum creatinine to evaluate the possible protective effects of vitamin E on CP-induced nephrotoxicity.

Methods

This study was designed as a prospective, randomized, double-blind, placebo controlled study performed from 2015 to 2017. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IUMS). Informed consent was obtained from all patients and the trial was registered at IRCT (Iranian registry of clinical trial) with the code number of IRCT201701011497N5.

CP-based chemotherapy candidates were randomized into two groups. Inclusion criteria were patients aged ≥18 years and having GFR≥60 mL/min. Exclusion criteria were comorbidities affecting renal function (such as diabetes mellitus, hypertension and past history of renal dysfunction), previous chemotherapy and treatment with other supplementation, use of nephrotoxic drugs such as NSAIDs, aminoglycosides, colistin, vancomycin, cyclosporine and tacrolimus, and liver disease (bilirubin >2mg/dl, AST/ALT >2.5 times the upper limit normal).

A research coordinator conducted the randomization and delivered the study drug. The participants and investigators were blinded to the treatment assignment. The list of random numbers was generated by a research coordinator. Eligible participants were randomly assigned 1:1 to either

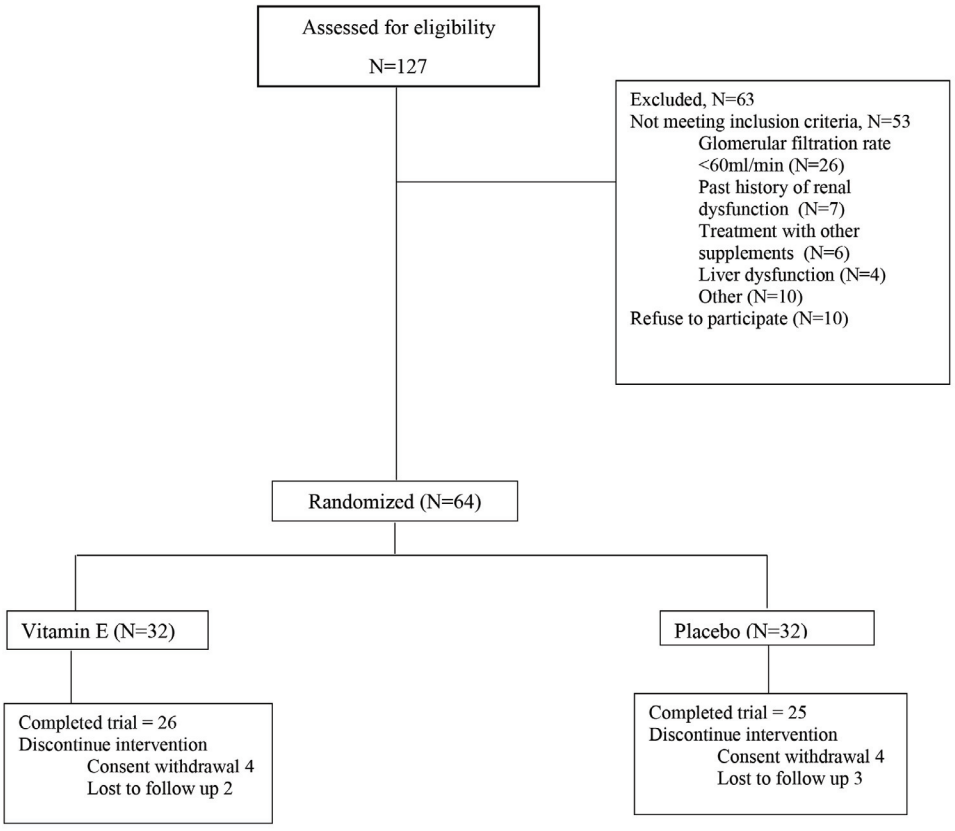


Figure 1. The trial implementation profile according to the consolidated standard of reporting trials.

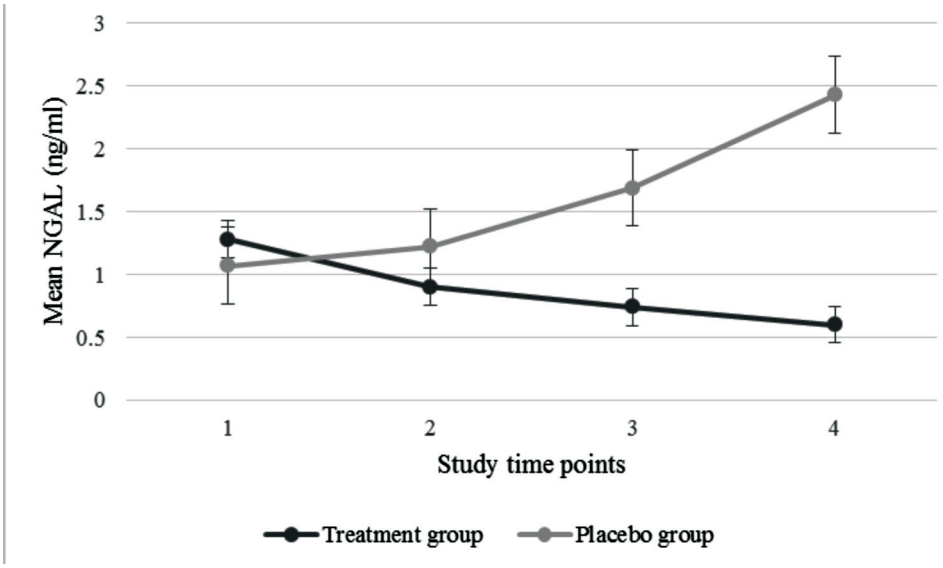
Table 1. Characteristics of patients

	Treatment group (N=26)	Placebo group (N=25)	*P* value
Age (years) (mean±SD; range)	49.5±8.9 (32-64)	50.9±16.6 (19-77)	0.71
Male/female	16/10	13/12	0.62
Tumor types			
Gastric cancer	12(46.2%)	8 (32%)	
Lung cancer	6 (23.1%)	5 (20%)	
Ovarian cancer	4 (15.4%)	1 (4%)	
Breast cancer	2 (7.7%)	2 (8%)	
Hodgkin lymphoma	1 (3.8%)	3 (12%)	0.38*
Bladder cancer	1 (3.85)	-	
Cervical cancer	-	1 (4%)	
Head and neck cancer	-	2 (8%)	
Thymic carcinoma	-	1 (4%)	
Malignant mesothelioma	-	2 (8%)	
Total dose of cisplatin (mg/m^2) (mean±SD)	332.3±66.2	320.7±59.1	0.51

*There were no significant differences regarding tumor types and their numbers between the two groups.

treatment or placebo group in accordance with the predefined randomization list with a block size of four.

The treatment group received one pearl tablet containing 400 Iu vitamin E daily. Following randomization, the participants took either vitamin E (treatment group) or placebo (control group) tablet. The drugs were prescribed one day before the initiation of chemotherapy and continued along chemotherapy cycles until three weeks after the end of the treatment. The vitamin E and placebo pearl were provided by Zahravi pharmaceutical company (Tabriz, Iran). The tablet shapes and packaging of the placebo were identical



*Study time point: Before each chemotherapy cycle and one month after the cessation of the cycles.

Figure 2. Mean changes of neutrophil gelatinase-associated lipocalin (NGAL) in study time points regarding the treatment and placebo groups which were significantly higher in the placebo group.

Table 2. Urine neutrophil gelatinase-associated lipocalin (NGAL) levels at the initiation and during the four courses of cisplatin administration

NGAL (ng/ml)	Treatment group (N=26) mean±SD	Placebo group (N=25) mean±SD	*P*-value *
NGAL 1(baseline)	1.28±0.95	1.07±0.85	-
NGAL 2	20.9±0.71	1.22±1.18	0.002
NGAL 3	0.74±0.44	1.69±1.39	<0.001
NGAL 4	0.6±0.34	2.43±2.19	<0.001

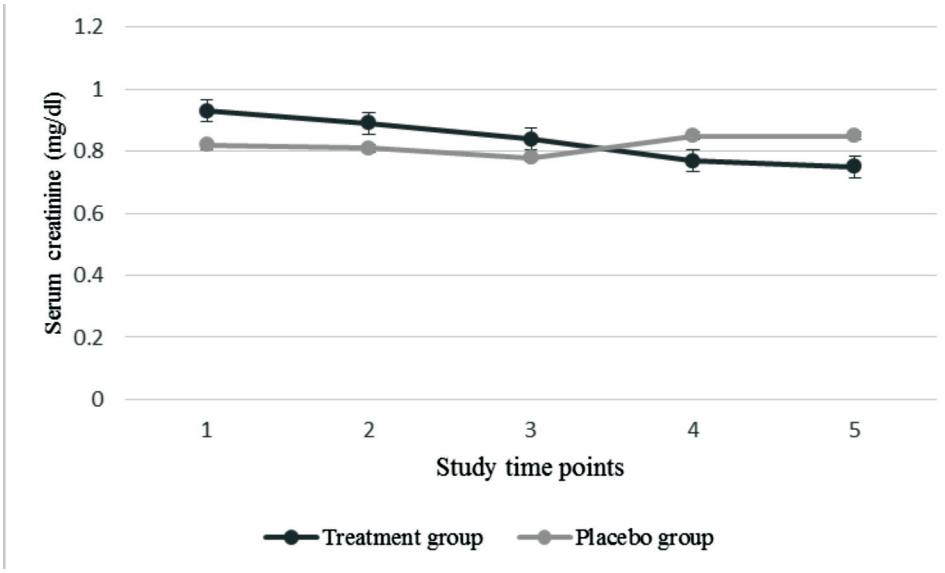
* The results are based on ANCOVA.

to those of vitamin E pills. Investigators evaluated drug compliance by counting the pills and participants with less than 80% compliance were removed from the study. A hydration protocol was applied to both groups. CP was mixed with 1 liter of normal saline plus 20 meq potassium chloride (KCl) and 1g of magnesium sulfate over three hours and 500 mL normal saline were used over two hours for all patients to reduce CP nephrotoxicity.

CP was administered intravenously on days 1 of each chemotherapy cycle for four cycles every 21 days. We tried to select the most uniform chemotherapy regimens to match the study groups. Therefore, patients undergoing another treatment beside the protocol were not enrolled in the study. The dose range of cisplatin was 50-75mg/m^2.

For NGAL analysis, venous blood samples were taken at study time points. Blood samples were spun at 1500*g for 10 minutes and stored at -80°C until analysis. NGAL was analyzed using commercially available enzyme-linked immunosorbent assay kit (Biovendor, Vienna, Austria). NGAL was measured prior to each chemotherapy cycle for four cycles.

The primary outcome included changes in NGAL and serum creatinine and the estimated GFR was compared with the baseline values in each cycle following CP treatment for four cycles. Blood urea nitrogen (BUN), sodium, potassium, magnesium, complete blood count with differentials (CBC/diff), serum creatinine, and GFR were determined prior to each chemotherapy cycle and one month after the cessation of the cycles. As an estimation of creatinine clearance, GFR was calculated using MDRD (Modification



*Study time point: Before each chemotherapy cycle and one month after the cessation of the cycles.

Figure 3. Mean changes of serum creatinine in study time points regarding the treatment and placebo groups, which were significantly higher in the placebo group.

Table 3. Variations of serum creatinine (SrCr) and glomerular filtration rate (GFR) levels before each chemotherapy cycle and one month after the end of chemotherapy

	Treatment group (N=26) mean±SD	Placebo group (N=25) mean±SD	*P* value*
Serum creatinine (mg/dL)			
SrCr 1(baseline)	0.93±0.1	0.82±0.1	-
SrCr 2	0.89±0.1	0.81±0.1	0.46
SrCr 3	0.84±0.1	0.78±0.2	0.94
SrCr 4	0.77±0.1	0.85±0.2	0.005
SrCr 5 **	0.75±0.1	0.85±0.2	0.002
GFR (mL/min)			-
GFR 1(baseline)	82.8±13	96.2±20.6	-
GFR 2	86.7±15.8	97.4±20.3	0.53
GFR 3	94.4±17.4	103.4±27.8	0.93
GFR 4	106.1±22	90.7±24.5	0.001
GFR 5 **	107.6±18	93.3±24.6	0.001

*The results are based on ANCOVA; **One month after the end of chemotherapy

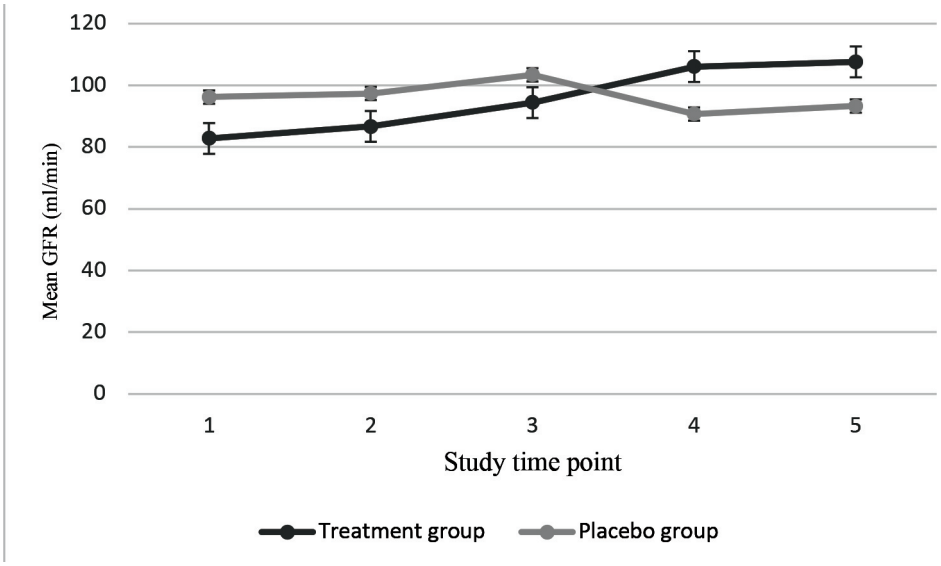
of Diet in Renal Disease) formula.[30]

All adverse events (mostly gastrointestinal) were recorded and followed up during the study period.

A previous study by Hemati et al. showed that vitamin E was able to reduce GFR by 10mL/min from baseline to one month after the cessation of the chemotherapy cycles with a standard deviation of 14. A clinically important difference of 10, as compared with the active drug, is considered to be acceptable. Assuming an alpha 0.05 and a power of 0.80, with a drop-out rate of 10%, we estimated a sample size of 32 patients in each arm of the study.

Statistical analysis

The baseline characteristics and laboratory data were presented as the means and standard deviations (SD) for continuous variables and as frequencies and percentages for categorical variables. To calculate the parameters, independent t-test, analysis of covariance (ANCOVA) and Fisher's exact test were employed. A value of $P \leq 0.05$ was considered as statistically significant.



*Study time point: Before each chemotherapy cycle and one month after the cessation of the cycles.

Figure 4. Mean changes of glomerular filtration rate (GFR) in study time points concerning the treatment and placebo groups, which were significantly higher in the treatment group.

Table 4. Variations of serum magnesium (Mg) and potassium (K) levels before each chemotherapy cycle and one month after the end of chemotherapy

	Treatment group (N=26) mean±SD	Placebo group (N=25) mean±SD	*P* value*
Serum magnesium (mg/dL)			
Mg 1(baseline)	1.9±0.15	1.9±0.15	-
Mg 2	2.1±0.21	1.9±0.19	0.46
Mg 3	2.1±0.19	1.9±0.17	0.03
Mg 4	2.1±0.26	2.1±0.25	0.61
Mg 5**	2.2±0.35	2.1±0.33	0.63
Serum potassium (Meq/l)			-
K 1(baseline)	4.1±0.29	4.1±0.45	-
K 2	4.1±0.42	4.2±0.44	0.94
K 3	4.1±0.22	4.1±0.41	0.98
K 4	4.1±0.36	4.2±0.35	0.51
K 5**	4.1±0.33	4.2±0.43	0.51

*The results are based on ANCOVA; **One month after the end of chemotherapy

All analyses were performed using SPSS statistics software V23.0 (SPSS Inc.; Chicago, IL, USA).

Results

Between January 2015 and September 2017, 51 patients were enrolled in this study. More than 130 eligible cancer patients were visited and 51 were randomly assigned to the study.

Figure 1 reports the trial implementation profile according to the consolidated standard of the reporting trials. Of the 127 cancer patients assessed for eligibility, 64 were randomly assigned (32 patients in each group) with a ratio of 1:1. 26 patients in vitamin E and 25 patients in placebo group completed the four cycles of study protocol. Reasons for interrupting treatment are reported in figure 1.

Table 1 shows the patient demographic and disease characteristics at the baseline. There was no difference between the groups regarding any of the factors and characteristics, the mean dose of CP administration, and tumor types and their numbers (P=0.38).

As illustrated in figure 2 and table 2, serum levels of NGAL were significantly higher in the placebo group during the four cycles of CP administration. According to ANCOVA, there were significant differences in mean serum NGAL levels between the two groups compared to the baseline levels.

Table 3 shows serum creatinine and GFR values during the four courses determined prior to each chemotherapy cycle and one month after the cessation of CP administration cycles (Figures 3 and 4). Independent t-test and ANCOVA showed significant differences between the two groups in terms of serum creatinine and GFR values before the first, second, and fourth chemotherapy cycles and one month after the cessation of the cycles (P<0.05). However, the results showed no significant differences between the two groups regarding serum creatinine and GFR values in the third cycle of chemotherapy (P>0.05).

Blood magnesium (Mg) and potassium (K) levels are shown in table 4. The Independent t-test and ANCOVA did not reveal significant differences in Mg and K levels during the study period. However, prior to the third cycle, significant differences (P=0.03) were observed between the two groups as far as Mg serum levels are concerned.

Vitamin E and placebo were well-tolerated, and no adverse effect relevant to vitamin E administration was reported by the participants.

Discussion

In this randomized, double-blind, placebo-controlled study, it was observed that vitamin E 400 Iu once daily supplementation for four cycles of CP administration showed a significant reduction in the serum levels of NGAL (as a renal injury biomarker) compared with baseline levels

and placebo arm. Moreover, GFR values, in contrast to serum creatinine levels, were not reduced in the vitamin E group. However, it is to be noted that the small sample size renders it difficult to establish a strong relationship between the uses of vitamin E as nephroprotective agent in patients receiving CP.

Peres et al.[31] evaluated the role of NGAL in monitoring the renal function in patients with head and neck cancer receiving CP. 50 patients were treated with three sessions of CP. Blood and urine were collected 24 hours prior to CP, 24 hours following infusion, 48 hours after each application, and 35 days after the end of the treatment. The results showed that 78% of patients developed acute kidney injury and the NGAL levels increased more rapidly and remained high at the end of the treatment. The NGAL levels correlated with serum creatinine and GFR in demonstrating renal injury. NGAL responses against AKI are very fast. In our study, NGAL serum levels were significantly reduced after vitamin E administration. On the other hand, the NGAL levels increased significantly in the placebo arm. Although we observed a similar pattern in the serum creatinine and GFR values, it seems that NGAL serum level is a more sensitive marker affected dramatically after vitamin E administration. Karademir et al.[32] investigated the potential nephro-protective effect of theophylline in 60 patients (30 in each arm) planned to receive CP. As the endpoint, they measured urinary NGAL and serum creatinine, with results showing that urine NGAL levels were significantly high after two hours of CP administration. However, high NGAL levels were also detected in the group not receiving theophylline. The GFR values decreased significantly in both arms within time (P= 0.006), and no significant difference was observed between the groups. The authors concluded that urine NGAL level is a superior biomarker compared to serum creatinine regarding the detection of early AKI and theophylline has insignificant nephroprotective effects. Administration of vitamin E significantly reduced the serum levels of NGAL in our patients. On the other hand, the GFR values did not increase in patients receiving vitamin E. Nonetheless, the exact mechanism of CP-induced nephrotoxicity is not exactly known and several studies have suggested that nephrotoxicity is induced by lipid peroxidation and free radicals. Vitamin E acts as a free radical scavenger against oxidative stress. Reduction in renal injury biomarkers (NGAL and serum creatinine) verifies the potential role of vitamin E in protection against CP-induced nephrotoxicity.

Naziroglu et al.[33] investigated the preventive effect of selenium and high dose vitamin E (1000mg/kg) administration on CP-induced nephrotoxicity in rats. Levels of oxidative injury markers such as malondialdehide, glutathione peroxidase, catalase, urea, and creatinine were significantly reduced in the treatment groups. The authors suggested that the combination of Se-vitamin E might play a role in the prevention of CP-induced nephrotoxicity. As we mentioned before, Hemati et al.[21] showed that a combination of selenium and vitamin E reduced CP-induced nephrotoxicity in cancer patients. In this study, the clinical criteria of RIFLE (risk, injury, failure, loss, and end-stage kidney disease) were used as the endpoint of the study and GFR values significantly increased following vitamin-Se administration for three cycles. It seems that the longer duration of antioxidant administration, even before the initiation of chemotherapy, is more effective in the reduction of renal injury induced by CP.

There are few human studies on this subject and the results of the available studies are controversial. Furthermore, most of these studies employ combinations of antioxidants to prevent CP-induced nephrotoxicity. Weijl et al.[15] supplemented patients with 400 mg vitamin E, 100 mcg Se and 1000 mg vitamin C. They did not observe a significant reduction in renal and bone marrow damages. 64% of the intervention group and 26% of the placebo group were non-compliant due to gastrointestinal problems. The authors suggested that the lack of compliance might have been an important reason for failure to prevent the oxidative damage caused by

chemotherapy.

Hu et al.[34] investigated the effects of selenium (400 mcg/day) on the toxicity of CP, where renal and bone marrow damage was significantly reduced in the patients who received selenium.

On the contrary, some other studies have indicated that vitamin E is not a nephroprotectant against CP-induced nephrotoxicity in the presence of female sex hormone estrogen.[35, 36] The male to female ratio was equal in the present study without any significant differences; therefore, we were not able to address the effect of gender difference, hence the necessity of larger studies for confirmation.

The nephroprotective effect of vitamin E has been evaluated for other nephrotoxic drugs such as vancomycin and cyclosporine. A recent review by Elyasi et al.[37] showed that vitamin E was able to prevent vancomycin nephrotoxicity in animal models. Parra Cid et al.[38] showed the promising effects of antioxidants such as vitamin E in neutralizing cyclosporin nephrotoxicity.

Although the reported results are interesting, they should be interpreted with caution due to the limited number of patients and the dosing regimen of vitamin E.

In conclusion, because cancer and chemotherapy can cause much pain and adverse effects in patients, introduction of modalities that could at least reduce the side-effects of chemotherapy might have a great influence on the patients' quality of life. Although a study with a larger number of patients is needed to confirm the protective role of vitamin E, we propose this vitamin as a safe and effective antioxidant in reducing the oxidative toxicity of CP. Meanwhile, the routine usage of an agent that protects kidneys against CP will allow for the use of CP, which is an effective drug in repeated courses without any decrease in higher doses.

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Conflict of Interest

None declared.

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