

# The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity in cancer patients treated with cisplatin-based chemotherapy: A randomized, placebo-controlled study

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**BACKGROUND:** Cisplatin is a chemotherapeutic agent with a wide range of anticancer effects. Two main toxicities of this drug are nephrotoxicity and myelosuppression. These toxic effects are related to free radical damage, reduction in antioxidant levels and oxidant stress. **METHODS:** In this study, 22 patients received 400 IU vitamin E and 200 µg selenium daily and 24 patients received placebo. The primary outcome was nephrotoxicity and the secondary outcome was bone marrow suppression. Glomerular filtration rate (GFR) and complete blood count with differential (CBC/diff) including of white blood cell (WBC) count, hemoglobin (Hb), and platelet counts were determined at the start of chemotherapy and before each cycle as well as one month after cessation of chemotherapy in both groups. **RESULTS:** Significant differences in GFR were observed between the two groups after the third cycle and one month after the end of chemotherapy ( $p < 0.05$ ). WBC, Hb, and platelet counts showed significant differences between the study groups after the second and third cycles ( $p < 0.05$ ). While after one month WBC and platelet counts demonstrated significant differences ( $p < 0.05$ ), Hb changed insignificantly ( $p > 0.05$ ). **CONCLUSIONS:** According to our findings, vitamin E and selenium can be used to reduce cisplatin-induced nephrotoxicity and bone marrow suppression. **KEYWORDS:** Chemotherapy, Vitamin E, Selenium; Cisplatin, Nephrotoxicity, Myelosuppression, Glomerular Filtration Rate.

## BACKGROUND

Cisplatin, cis-diamminedichloroplatinum (II), is a platinum compound with the broadest range of clinical activity and the most substantial toxicity profile. Cisplatin-based therapy is curative in testicular cancer and is very active in gynecologic cancers, gastrointestinal malignancies, genitourinary cancers, head and neck cancers, lung cancer, and other malignant diseases.<sup>[1]</sup> Nephrotoxicity is one of the important dose limiting side effects since 20% of patients receiving high-dose cisplatin have severe renal dysfunction.<sup>[2]</sup> These toxic effects are related with free radical damage, reduction in antioxidant levels, and oxidant stress, which are induced by cisplatin.<sup>[3]</sup>

One of the interventions to reduce oxidative stress in renal failure patients is administration of antioxidants such as alpha-tocopherol. Another way to overcome the oxidative stress is to use substances such as erythropoietin and sodium selenite with an indirect effect on oxidative stress.<sup>[4,5]</sup> With no adverse effects on therapeutic outcome, some antioxidants, such as pineal hormone melatonin (MLT) and selenium, can even increase the efficacy of chemotherapy and reduce toxicity.<sup>[6-8]</sup>

Multiple animal studies support the hypothesis that vitamin E succinate (VES, alpha-tocopherol succinate) interferes with cisplatin-induced damage. These studies suggest that concurrent treatment with this supplement can be useful in protection against nephrotoxicity.<sup>[3,9-12]</sup> Ajith et al. designed a study to compare the effectiveness of single and multi doses of vitamin C (500 mg/kg), vitamin E (500 mg/kg), and vitamin C plus E (250 mg/kg each) in prevention of acute renal failure. They found that co-administration of single and multi doses of vitamins in mice caused a significant decline in glutathione level and protection from cisplatin-induced increased serum urea, creatinine levels, and renal malondialdehyde (MDA).<sup>[9]</sup> Another study showed vitamin E to be effective in preventing oxidative renal damage in mice.<sup>[12]</sup> Atasayar et al. found that aminoguanidine (an antioxidant agent) as well as vitamin C-E combination resulted in a lower incidence of nephrotoxicity in rats.<sup>[10]</sup> Another research addressed the role of ascorbic acid and alpha-tocopherol monoglucoside (TMG) in reducing cisplatin-induced higher plasma creatinine and urea levels and lipid peroxidation in mice. The authors

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## Original article

Hemati, et al.: Effects of vitamin E and selenium on cisplatin-induced nephrotoxicity suggested that ascorbic acid monoglucoside (AsAG) or TMG have implications to prevent drug-induced nephrotoxicity in humans.<sup>[11]</sup>

Interactions between selenium and platinum-containing chemotherapy agents have been extensively studied. With consumption of selenium in mice, the activity of cisplatin increased and its toxicity decreased.<sup>[8]</sup> Intraperitoneal injection of selenium and high doses of vitamin E could increase antioxidant concentrations in rats. Therefore these agents may have a protective property in cisplatin-induced neph-



male to female (M/F) ratio were  $25.8 \pm 4.6 \text{ kg/m}^2$  and 19/3, respectively. One patient with gastric cancer and two patients with cervical cancer were female. The control group suffered from bladder cancer (n = 6), gastric cancer (n = 5), head and neck cancer (n = 4), esophageal cancer (n = 3), lung cancer (n = 2), testicular cancer (n = 2), cervical cancer (n = 1), and malignant mesothelioma (n = 1). In this group, the youngest patient was 20 and the oldest was 71 years old (mean age:  $55 \pm 11$  years). BMI and M/F ratio were  $26.8 \pm 3.0 \text{ kg/m}^2$  and 20/4, respectively. One patient with gastric cancer, one patient with cervical cancer, one patient with head and neck cancer, and one patient with esophageal cancer were female. Table 1 shows the information of the participants. Independent t-test showed no significant differences in mean age and mean BMI between the two groups. Moreover, the study groups did not show significant differences in gender according to Fisher's exact test ( $p > 0.05$ ). Tumor types in each group are shown in table 2. There were no significant differences regarding tumor types and their numbers between the two groups. Table 3 summarizes the pathology, stages, and treatment of patients. Cisplatin dose in each cycle and total doses of cisplatin in two groups are presented in Table 4. If GFR value was between 30-60 ml/min, the cisplatin dose was reduced to half of the prior dose and if  $\text{GFR} < 30 \text{ ml/min}$ , cisplatin was not continued. Independent t-test showed no significant differences between the study groups regarding the mean cisplatin dose in one cycle and total cisplatin dose. Although the total cisplatin dose was modified in the control group because of GFR reduction in some patients, independent t-test showed no significant differences between the two groups ( $p > 0.05$ ). GFR values before each chemotherapy cycle and one month after the end of chemotherapy in the study groups are shown in Table 5 and Figure 1. Independent t-test showed no significant differences between the two groups in GFR scores before the first, second, and third chemotherapy cycles ( $p > 0.05$ ). However, the results showed significant differences in GFR values before the fourth cycle and one month after the end of chemotherapy between the two groups ( $p < 0.05$ ). Repeated measures ANOVA suggested significant differences in mean GFR values between chemotherapy cycles in each group ( $p < 0.001$ ). The results after the end of chemotherapy are compared in Table 6 and Figure 2. Although WBC count did not show significant differences before the first and second cycles ( $p > 0.05$ ), independent t-test indicated significant differences between the two groups before the third and fourth cycles and one month after the cessation of chemotherapy ( $p < 0.05$ ). According to repeated measures ANOVA, there were significant differences in mean WBC count between chemotherapy cycles in each group ( $p < 0.001$ ).

Blood Hb levels in the target and control groups before each chemotherapy cycle and one month after the end of chemotherapy are shown in Table 7 and Figure 3. Independent t-test did not reveal any significant differences in Hb levels before the first and second cycles and one month after the termination of chemotherapy ( $p > 0.05$ ). However, significant differences were present before the third and fourth cycles ( $p < 0.05$ ). Repeated measures ANOVA showed significant differences in blood Hb levels between chemotherapy cycles in each group ( $p < 0.001$ ).

Platelet counts in the target and control groups before  
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#### Cancer type

##### Bladder cancer

##### Gastric cancer Esophageal cancer

##### Head and neck cancer

##### Lung cancer

##### Testicular cancer

##### Cervical cancer Thymic carcinoma

##### Malignant mesothelioma

#### Pathology

##### TCC

##### Adenocarcinoma

##### SCC/ Adenocarcinoma

##### Vocal cord carcinoma (SCC) (n = 2)

##### Supraglottic carcinoma (SCC) (n = 1)

##### Adenoid cystic carcinoma of parotid (n = 1)

##### SCC of maxillary sinus (n = 1) SCC of tongue (n = 1) NSCLC (n = 2) NSCLC (n = 2) NSGCT

##### NSGCT NSGCT NSGCT SCC SCC

##### Epithelial type

#### Stage

##### T3, T4, N+

##### M+ I-IIA

##### T3

##### T3

##### T3

##### T3 T3 IV T2b N0 M1a S3 (IIIC)

##### M1b S2 (IIIC) N3 S2 (IIc) N3 S2 (IIc) IVB T2N0M0 (I)

##### T4N1

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#### Table 1. Characteristics of patients

Age (years) (mean  $\pm$  SD; range) Male/female

Body mass index ( $\text{kg/m}^2$ )

NS: Not Significant SD: Standard deviation

#### Table 2. Tumor types

##### Tumor types

Bladder cancer Gastric cancer Esophageal cancer Head and neck cancer Lung cancer Testicular cancer Cervical cancer Thymic carcinoma  
Malignant mesothelioma

**Table 3. Pathology, stages, and treatments in the studied patients**

**Target (n = 22)**

53.0 ± 13.0 (18-72) 19/3 (86.4%/13.6%) 25.8 ± 4.6

**Target (n = 22)**

**Control (n = 24)**

55.0 ± 11.0 (20-71) 20/4 (83.3%/16.7%) 26.8 ± 3.0

**Control (n = 24)**

6 5 3 4 2 2 1 - 1

**Treatment**

CT for 4 cycles followed by CRT

CT

Esophagectomy followed by adjuvant CT

Total laryngectomy + PORT

Supraglottic laryngectomy + PORT

Surgery + PORT

Surgery + PORT Surgery + PORT + CT CT Surgery + adjuvant CT CT

CT then palliative RT Surgery+ PORT+ CT

RT and CT

**P-value**

0.648 (NS) 0.550 (NS) 0.360 (NS)

**Chemotherapy regimen**

GC

DCF Cisplatin-Paclitaxel

DCF DCF DCF DCF

Cisplatin-Paclitaxel Cisplatin-Paclitaxel Cisplatin-Paclitaxel BEP

Cisplatin-Paclitaxel EP

Doxorubicin -cisplatin

TCC: Transitional cell carcinoma; SCC: Squamous cell carcinoma; NSCLC: Non-small cell lung carcinoma; CT: Chemotherapy; CRT:

chemo- radiation; RT: Radiation therapy; PORT: Postoperative radiation therapy; G: Gemcitabine; C: Cisplatin; D: Docetaxel; BEP,

Bleomycin, etopo- side, cisplatin; EP: Etoposide, cisplatin

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6 4 3 2 2 2 1 -

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**Table 4. Cisplatin dosage**

**Cisplatin dose/cycle (mg/m<sup>2</sup>) (Mean ± SD)**

**Total dose of cisplatin (mg/m<sup>2</sup>) (Mean ± SD)**

**Target (n = 22)**

**Control (n = 24)**

**p**

0.956

0.387

76 ± 8 (mg/m<sup>2</sup>) No. of patients

76 ± 7 (mg/m<sup>2</sup>) No. of patients

Dose/cycle

Dose/cycle

60 1 60 1

75 19 75 21 100 2 100 2

306 ± 32

296 ± 43

Total dose Total dose (mg/m<sup>2</sup>) No. of patients (mg/m<sup>2</sup>)

240 1 187 300 19 224 400 2 262

240 300 400

No. of patients

1 1 1 1 18 2

**Table 5. Glomerular filtration rate (GFR) in the target and control groups before each chemotherapy cycle and one month after the end of chemotherapy**

**GFR (ml/min)**

**Target (n = 22)**

**Control (n = 24)**

116 ± 13 108 ± 16 97 ± 21 88 ± 23 84 ± 23 < 0.001

**p\***

0.353 (NS) 0.985 (NS) 0.425 (NS) 0.048 0.049

GFR 1 GFR 2 GFR 3 GFR 4 GFR 1 p\*\* NS: Not significant \* Independent t-test \*\* Repeated measures analysis of variance

mmonth

112 ± 17 108 ± 17 102 ± 16 98 ± 17 94 ± 14 < 0.001

**Figure 1. Mean changes of glomerular filtration rate (GFR) during and one month after chemotherapy in the target and control groups**

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**Table 6. White blood cell (WBC) count in the target and control groups before each chemotherapy cycle and 1 month after the end of chemotherapy**

**WWBC (10<sup>9</sup> cells/l)**

**Target (n = 22)**

WBC 1 WBC 2 WBC 3 WBC 4 WBC 1 p\*\* NS: Not significant \* Independent t-test \*\* Repeated measures analysis of variance

Control (n = 24)

7.6 ± 1.3 7.3 ± 1.2 5.9 ± 1.5 4.2 ± 1.7 5.6 ± 1.5 < 0.001

p\*

0.771 (NS) 0.652 (NS) 0.007 < 0.001 0.001

**Figure 2. Changes in white blood cell (WBC) count during and one month after chemotherapy in the target and control groups**

**Table 7. Blood hemoglobin (Hb) in the target and control groups before each chemotherapy cycle and 1 month after the end of chemotherapy**

Hb (mmol/l)

month

7.5 ± 0.8 7.4 ± 0.8 7.1 ± 1.0 6.6 ± 0.9 6.9 ± 0.6 < 0.001

Target (n = 22)

Hb 1 Hb 2 Hb 3 Hb 4 Hb 1 p\*\* NS: Not significant \* Independent t-test \*\* Repeated measures analysis of variance

Control (n = 24)

12.8 ± 1.2 12.1 ± 1.4 10.3 ± 1.4 9.8 ± 1.5 11.6 ± 1.2 < 0.001

p\*

0.135 (NS) 0.493 (NS) 0.035 0.012 0.739 (NS)

month

12.2 ± 1.2 11.8 ± 1.5 11.2 ± 1.3 10.8 ± 1.1 11.5 ± 1.2 < 0.001

**Table 8. Platelet (Plt) count in the target and control groups before each chemotherapy cycle and 1 month after the end of chemotherapy**

Plt (10<sup>9</sup>cells/l)

Plt 1 Plt 2 Plt 3 Plt 4 Plt 1 p\*\* NS: Not significant \* Independent t-test \*\* Repeated measures analysis of variance

Target (n = 22)

338±86 324±79 286±78 220±79 284±77 < 0.001

Control (n = 24)

331±85 304±90 217±90 122±54 121±56 < 0.001

p\*

0.775 (NS) 0.436 (NS) 0.008 < 0.001 < 0.001

month

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**Figure 3. Hemoglobin (Hb) changes during and one month after chemotherapy in the target and control groups**

**Figure 4. Platelet (Plt) changes during and one month after chemotherapy in the target and control groups**

each chemotherapy cycle and one month after the end of chemotherapy are presented in Table 8 and Figure 4. Independent t-test was not suggestive of significant differences regarding platelet count before the first and second cycles ( $p > 0.05$ ). This test demonstrated significant differences before the third and fourth cycles and one month after the course of chemotherapy ( $p < 0.05$ ). Repeated measures ANOVA showed significant differences in platelet count between chemotherapy cycles in each group ( $p < 0.001$ ).

## DISCUSSION

The role of vitamin E and selenium in protecting against cisplatin nephrotoxicity and bone marrow suppression was investigated in this study. The main limitation of this research was applying different cisplatin-based chemotherapy regimens with variable doses in patients. Therefore, it was difficult to match the studied groups. Moreover, although we had recommended all patients not to use any drugs without our consultation, some patients may have used nephrotoxic drugs without informing us. In addition, the antioxidant values of dietary regimens were different among the patients that may confound the results.

### Renal Toxicity

We used the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease) including three graded levels of injury (risk, injury, and failure) based on ei-

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ther the magnitude of elevation in serum creatinine or reduction in GFR values. The RIFLE classifications are as follows: - Risk: 1.5-fold increase in serum creatinine or 25% reduction in GFR

- Injury: Twofold increase in serum creatinine or 50% reduction in GFR - Failure: Threefold increase in serum creatinine or 75% reduction in GFR.<sup>[18]</sup>

If GFR decreased for 30-60 ml/min, the dose of cisplatin dose was halved. Chemotherapy was not continued if GFR was under 30 ml/min.<sup>[19]</sup> In the placebo group, GFR of three patients decreased by 40, 41, and 47%. These patients were placed in the injury category. GFR varied from a primary value of 115 ml/min to 57 ml/min in the fourth cycle (57% reduction) in one patient and cisplatin dose was hence halved (37 mg/m<sup>2</sup>, total dose 262 mg/m<sup>2</sup>). In a patient, GFR reduced from 96 ml/min to 57 ml/min and 48 ml/min in the third and fourth cycles, respectively (55% reduction). Therefore, 37 mg/m<sup>2</sup> of cisplatin was administered in these courses (total dose 224 mg/m<sup>2</sup>). In another patient, GFR changed from 98 ml/min to 53 ml/min and 25 ml/min in the third and fourth cycles, respectively (74% reduction). Dose limitation was hence performed in the third cycle. This patient was not treated longer since his GFR was under 30 ml/min at the beginning of the fourth cycle (total dose 187 mg/m<sup>2</sup>). These three patients were included in the failure category. Overall, renal dysfunction was observed in 25% of the placebo group whereas it occurred only in 9% of the target group. In the target group, two patients were allocated to the injury category. GFR of these patients decreased from primary values of 146 and 104 to 102 and 72, respectively (30% and 31% reductions). Dose limitation was not carried out for these patients.

The mean GFR values in all cycles were calculated in the two groups. In the beginning of the first, second, and third cycles, the values did not show significant differences between the two groups ( $p > 0.05$ ). However, the results showed significant

differences between the two groups after three cycles ( $98 \pm 17$  vs.  $88 \pm 23$  ml/min;  $p = 0.048$ ) and one month after the end of chemotherapy ( $94 \pm 14$  vs.  $84 \pm 23$  ml/min;  $p = 0.049$ ). Therefore, nephrotoxicity was lower in the target group after the third cycle and one month after the chemotherapy. Moreover, there were significant differences in mean GFR values between chemotherapy cycles in each group ( $p < 0.001$ ).

duced by cisplatin-based chemotherapy. Perhaps administration of these supplements from almost two months before starting chemotherapy could increase their nephroprotective effects. However, this subject needs further research.

#### Bone Marrow Suppression

CBC/diff was measured before starting chemotherapy cycles in all patients. WBC count of the target and control groups at the beginning of chemotherapy ( $7.5 \pm 0.8$  vs.  $7.6 \pm 1.3$ ;  $p = 0.771$ ) and before the second cycle ( $7.5 \pm 0.8$  vs.  $7.6 \pm 1.3$ ;  $p = 0.771$ ) did not show significant differences.

There were significant differences in WBC count between the target and control groups before the third ( $7.1 \pm 1.0$  vs.  $5.9 \pm 1.5$ ;  $p = 0.007$ ) and fourth ( $6.6 \pm 0.9$  vs.  $4.2 \pm 1.7$ ;  $p < 0.001$ ) cycles and one month after the end of chemotherapy ( $6.9 \pm 0.6$  vs.  $5.6 \pm 1.5$ ;  $p = 0.001$ ). As a result, co-administration of selenium and vitamin E is effective in reducing leucopenia induced by cisplatin-based chemotherapy. This effect was apparent from the third course.

Hb in the target and control groups did not show significant differences before the first ( $12.2 \pm 1.2$  vs.  $12.8 \pm 1.2$ ;  $p = 0.135$ ) and second ( $11.8 \pm 1.5$  vs.  $12.1 \pm 1.4$ ;  $p = 0.493$ ) cycles and one month after chemotherapy ( $11.5 \pm 1.2$  vs.  $11.6 \pm 1.2$ ;  $p = 0.739$ ).

However, there were significant differences before the third ( $11.2 \pm 1.3$  vs.  $10.3 \pm 1.4$ ;  $p = 0.035$ ) and fourth ( $10.8 \pm 1.1$  vs.  $9.8 \pm 1.5$ ;  $p = 0.012$ ) cycles between two groups. Data analysis indicated that chemotherapy-induced anemia could be clearly reduced by these micronutrient supplementations. The protective effect was noticeable from the third course just like the results of WBC. It is ambiguous for us why while WBC and platelet counts were obviously higher in the target group compared to the control group after one month, Hb values were not.

There were no significant differences in platelet count between the target and control groups before the first ( $338 \pm 86$  vs.  $331 \pm 85$ ;  $p = 0.775$ ) and second ( $324 \pm 79$  vs.  $304 \pm 90$ ;  $p = 0.436$ ) cycles. However, platelet counts indicated significant differences between the two groups before the third ( $286 \pm 78$  vs.  $217 \pm 90$ ;  $p = 0.008$ ) and fourth ( $220 \pm 79$  vs.  $122 \pm 54$ ;  $p < 0.001$ ) cycles and one month after chemotherapy ( $284 \pm 77$  vs.  $121 \pm 56$ ;  $p < 0.001$ ). It can be concluded that selenium and vitamin E may reduce cisplatin-induced thrombocytopenia.

Based on the results of this study, vitamin E and selenium could reduce bone marrow suppression.

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Our results suggest that co-administration of selenium and vitamin E is effective in reducing renal injury in- S56 Journal of Research in Medical Sciences | March 2012 Special Issue (1) |

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To the best of our knowledge, there have been few studies about this subject in humans and the results of the available studies are controversial. Hu et al. investigated the effects of selenium on the toxicity of cisplatin. Selenium was administered 4000 µg/day from four days before until four days after chemotherapy. WBC counts were higher in patients who received selenium. Administration of granulocyte stimulating factor and blood infusion were lower in these patients. Nephrotoxicity, evaluated by urine enzymes, was also significantly less in the patients who received selenium. The effects of selenium intake on the therapeutic activity of cisplatin was not discussed by the researchers.<sup>[20]</sup>

A randomized, double-blind, placebo-controlled study by Weijl et al. showed that patients who were supplemented with 400 mg vitamin E (as dl- $\alpha$ -tocopherol acetate), 100 µg selenium, and 1000 mg vitamin C did not have a significant reduction in renal and bone marrow damage. In this study, 64% of the intervention group and 26% of the placebo group were non-compliant because of gastrointestinal problems caused by the consumed beverage in the intervention group. The authors suggested that the lack of compliance may have been an important reason for failure to prevent the oxidative damage caused by chemotherapy. They proposed that a higher daily dose or longer period of supplementation and accumulation of other antioxidants can lead to prevent organ damages by free radicals.<sup>[3]</sup>

Other agents that have been investigated to reduce cisplatin nephrotoxicity are amifostine,<sup>[21,22]</sup> N-acetylcysteine (NAC),<sup>[23,24]</sup> cimetidine,<sup>[25,26]</sup> sulfa-containing amino acid,<sup>[27]</sup> procainamide,<sup>[28,29]</sup> allopurinol,<sup>[30]</sup> interleukin 10 (IL-10),<sup>[31]</sup> salicylates,<sup>[32,33]</sup> L-arginine,<sup>[34]</sup> and fibrates.<sup>[35]</sup>

Our study showed that antioxidant agents such as vitamin E and selenium are effective in reducing oxidative toxicity of cisplatin. We suggest designing a study with a larger number of patients to compare all of the promising protective agents with each other and placebo.

We believe that using a nephroprotective agent, like the routinely administered mesna, with cisplatin-based chemotherapy regimens, might protect from cystitis in chemotherapy with ifosfamide [e.g. in mesna, doxorubicin, ifosfamide, dacarbazine (MAID) regimen].

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