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The Effect of Vitamin E on Cisplatin Induced Nephrotoxicity: A Clinical Trial Study

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Abstract

Background

Cisplatin is a common platinum based chemotherapy drug that is commonly used for the treatment of the solid tumors. It is believed that this drug has nephrotoxic effects due to its oxidative action. Therefore, it is believed antioxidant agents such as vitamin E can prevent this nephrotoxic effect; however, the human studies are not sufficient. We aimed to assess the effect of vitamin E against cisplatin induced nephrotoxicity.

Materials and Methods

In a randomized controlled trial, the patients were grouped into two control and target group. Both groups should receive cisplatin with a dose of 50 mg/m^2 as single dose or in 3 to 5 divided doses. The target group received 400 IU of vitamin E daily until two days after discontinuing cisplatin and the control group received only cisplatin. Patients' serum urea, creatinine, and Kidney injury molecule-1 (KIM-1) levels were measured and compared between the two study groups and in a before-after manner.

Results

Totally, 29 patients were grouped into 17 controls and 12 patients in target group. The KIM-1biomarker was statistically higher in control group at the end of study (p=0.040). When assessing the before-after results, KIM-1 biomarker showed a significant decrease (1.10±0.32 pg/mL to 0.71±0.09 pg/mL; p<0.05).

Conclusion

Based on the results, it seems vitamin E can help to protect kidney against cisplatin toxicity; however, further clinical trials are needed to support our findings.

Key Words: Cisplatin, Children, Nephrotoxicity, Vitamin E.

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1- INTRODUCTION

Cisplatin is a well-known antitumor agent with platinum base that is used very commonly in a range of cancers including ovary, testis, head and neck, bladder and lung cancers and also metastatic cancers such as mesothelioma, melanoma, prostate, and breast cancers (1, 2). The drug was first introduced in 1845, named Peyrone's chloride (3); however, it was in 1978 that the name cis-diamminedichloridoplatinum (II) or cisplatin was given to the drug compound (4). Variants of cisplatin including carboplatin, oxaliplatin, and satraplatin were further developed over time to overcome some shortcomings of the cisplatin (5). However, the limiting side effects have remained in this family of chemotherapy drugs. Toxicities such as neurotoxicity, ototoxicity, and nephrotoxicity are among these limiting side effects that have restricted the high dosage use of them (6). The most common reported side effect of cisplatin is its nephrotoxicity that brings acute kidney injury (AKI) in around one-third of the patients who received this drug (7).

Several underlying mechanisms are listed as the contributors of cisplatin nephrotoxicity. It has been found that cisplatin makes a cross-link with DNA and interferes with DNA synthesis process. It also initiates an inflammatory state (8). Besides the above mentioned mechanisms, the cornerstone of the cisplatin nephrotoxicity is the production of the reactive oxygen species (9). Moreover, cisplatin causes glutathione depletion and mitochondrial dysfunction that brings an imbalance in oxidant and antioxidant tissue balance status (10). It seems that all the above mentioned terminate into one conclusion, that is oxidative stress produces cisplatin nephrotoxicity and it seems providing antioxidant treatment can help to overcome this problem.

Vitamin E is a fat soluble antioxidant in the body that acts as a free radical scavenger (11). Vitamin E inhibits lipid peroxidation and protects tissue cells membranes (12). Its benefits in many disease conditions such as cardiovascular problems have been proven (13). It has been reported that patients who receive cisplatin have decreased levels of vitamin E (14); and thus studies have been conducted using vitamin E alone or in combination with other antioxidant factors to bring the oxidant-antioxidant balance and prevent the nephrotoxicity (15-18); however, most of these studies were conducted on animal models, few human studies are available (19). Thus, we aimed to assess the effect of vitamin E supplementation to protect cisplatin nephrotoxicity in a population of cancerous patients.

2- MATERIALS AND METHODS

2-1. Study design and population

This was a randomized-controlled study conducted in Hematology and Oncology department of Dr. Sheikh hospital (Mashhad University of Medical Sciences, Mashhad, Iran) between May 2018 and January 2019. Thirty cases that met inclusion criteria were chosen. Using simple random computer generated numbers; the patients were grouped into two groups. The first group (target group) consisted of 12 cases and the second group (control group) had 17 patients.

2-2. Drug administration

All the patients should receive 50 mg/m^2 of intravenous cisplatin in 3 to 5 divided doses. We tried to match the received doses of cisplatin in target and control groups, in order to adjust the confounding factors. The twelve patients in target group received a further 400 IU of vitamin E daily until two days after discontinuing cisplatin. However, the control group did not receive vitamin E. The administered

dosage of vitamin E was based on previous studies (19). The patients were recommended to take vitamin E tablets after lunch.

2-3. Inclusion and exclusion criteria

The included patients were among the hospitalized patients who were undergoing treatment for any type of cancer including testis, head and neck, cervix, lung, and germ cell tumors who received cisplatin. The patients should receive cisplatin as chemotherapy treatment, and should have no nephrology problem or renal failure. Furthermore, they should receive no other nephrotoxic drugs. If any other nephrotoxic drugs were added in the course of the cancer treatment or any kind of acute or chronic renal failure were occurred, patients were excluded from the study.

2-4. Data gathering

In case of data gathering, patients demographic (such as age), and baseline data (such as Treatment duration, Treatment dosage, Na, K, Ca, and Mg) were recorded. Serum urea and creatinine were checked and glomerular filtration rate (GFR) was calculated at the baseline. Furthermore, kidney injury molecule-1 (KIM-1) urine level was also measured. Serum urea, creatinine, GFR, and KIM-1 urine level measurement were repeated at the end of study, and compared with the baseline.

2-5. Ethical consideration

In case of ethical points, all the patients' records were kept confidential. This study was conducted according to the Helsinki declaration. The patients were provided with written consent and the protocol of the study was approved by Ethics Committee of Mashhad University of Medical Sciences (ID-code: IR.MUMS.fm.REC.1395.652). This study is also registered in the Iranian Clinical Trial website (IRCT 20111024007892N8).

2-6. Data Analyses

The extracted data were recorded in Excel sheets and then entered in SPSS software version 18.0. Central and dispersion indicators including mean, median, and standard deviation (SD) were measured. The normality of the data was assessed using Kolmogorov-Smirnov test. According to the normality of the data, the indicators were compared using appropriate tests. Independent sample t-test or its non-parametric partner, Mann-Whitney test were used in order to compare the groups. Furthermore, we used paired t-test or Wilcoxon signed rank test to compare the data in a before-after manner.

3- RESULTS

Finally, 29 cisplatin treated patients were enrolled in the study and were grouped into 12 patients in target group and 17 controls. The mean age of the patients was 6±3.00 years that showed no difference between the two groups. The mean serum levels of urea before was 23.81±7.33 mg/dL with 23.70±6.44 mg/dL and 23.91±8.28 mg/dL in target and control groups, respectively; that showed no difference between the two groups. Also, target and control groups had a mean creatinine level of 0.55±0.14 mg/dL with 0.55±0.12 mg/dL and 0.55±0.15 mg/dL in target and control groups, respectively; that showed no difference between the two groups. Furthermore, the sodium, calcium, potassium, and magnesium mean serum levels were equal between the two groups. However, KIM-1 level was higher in target group (1.10±0.32 pg/mL vs. 0.73±0.20 pg/mL). **Table.1** shows the characteristics of the included targets and controls. **Table.2** shows the comparison of the urea, creatinine, and KIM between the two groups before and after the study. The KIM-1 level was significantly higher in control group after cisplatin administration (1±1.00 pg/mL vs. 0±0.09 pg/mL;

p=0.021). The serum level of urea and creatinine showed no difference between two groups before and after. In case of comparing serum parameter before and after the study; results showed a significant decrease in KIM-1 marker in target group (1.10±0.32 pg/mL to 0.71±0.09 pg/mL; p<0.05). **Table.3** shows details of the above mentioned results in target group.

Table-1: Baseline characteristics of the control and target groups.

Parameter	Control group, n=17 Mean± SD	Target group, n=12 Mean± SD
Age (year)	6±3.00	6.08±3.00
Urea before (mg/dL)	23.91±8.28	23.70±6.44
Creatinine before (mg/dL)	0.55±0.15	0.55±0.12
Na (mg/dL)	139±3.00	139±4.03
Ca (mg/dL)	9.47±0.33	9.61±0.30
K (meq/L)	4.26±0.58	4.34±0.51
Mg (meq/L)	2.00±0.15	1.96±0.14
KIM-1 before (pg/mL)	0.73±0.20	1.10±0.32

SD: Standard deviation; KIM: Kidney injury molecule; Control group: Cisplatin treated group; Target group: Cisplatin plus vitamin E treated group.

Table-2: Comparison of the serum urea, creatinine level, and KIM between the two study groups.

Parameter	Control group, n=17	Target group, n=12	P- value (Mann-Whitney)
Urea before (mg/dL)	23.91±8.28	23.70±6.44	0.195
Urea after (mg/dL)	24.42±5.85	19.37±8.08	0.947
Creatinine before (mg/dL)	0.55±0.15	0.55±0.12	0.894
Creatinine after (mg/dL)	0.54±0.07	0.50±0.09	0.356
KIM before (pg/mL)	0.73±0.20	1.10±0.32	0.004
KIM after (pg/mL)	0.97±0.35	0.71±0.09	0.040

KIM: Kidney injury molecule; Control group: Cisplatin treated group; Target group: Cisplatin plus vitamin E treated group.

Table-3: Comparing urea, creatinine, and KIM-1 levels before and after vitamin E administration in target group.

Parameter	Before	After	P- value
Urea (mg/dL)	23.70±6.44	19.37±8.08	0.05<
Creatinine (mg/dL)	0.55±0.12	0.50±0.12	0.05<
KIM-1 (pg/mL)	1.10±0.32	0.71±0.09	<0.05

KIM-1: kidney injury molecule.

4- DISCUSSION

We conducted a study on a human population of children who underwent cisplatin treatment. We found that the cases who received vitamin E with a dose of 400 IU daily had significantly lower KIM-1 biomarker compared to the control group, although it was significantly higher in the target group at the baseline. Furthermore, it was shown that KIM-1 level significantly decreased after vitamin E administration. This demonstrates that not only does vitamin E administration show a superiority in protecting the kidney against cisplatin toxicity compared to the control group, but it also lowers KIM-1 as a kidney injury molecule with changes over time. Cisplatin is a chemotherapy drug with a dose-dependent effect that can be used alone or as an adjuvant with other chemotherapy drugs, especially in the treatment of the solid tumors. However, as the dose of the drug increases, its nephrotoxic effect also increases. Many attempts toward designing a new platinum

based chemotherapy drug ended in drugs with lower potency and lower nephrotoxicity. Therefore, due to its high potency, cisplatin is still used in the chemotherapy of many cancers (20). Studies believe that oxidant-antioxidant imbalance is the major cause of kidney injury in cisplatin chemotherapy. It is shown that the production of malondialdehyde and nitrogen oxide (NOx), and the activity of myeloperoxidase (MPO) can be increased due to the administration of the cisplatin. The chemotherapy with this drug also leads to the further expression of Inducible nitric oxide synthase (iNOS), and Endothelial nitric oxide synthase (eNOS) proteins in glomerular and tubular cells which further increases oxidative stress (21-23). Although several studies reported protective effects of vitamin E in cisplatin nephrotoxicity (15-18), to the best of our known search results it is assessed in only a few human trials until now (19).

Darwish et al. studied the effect of 75 mg/kg vitamin E supplementation for 14 days along with 6 mg/kg cisplatin administration as a single dose on 30 male white albino rats. Their assessments showed a reduction in lipid peroxidation and depletion in antioxidant molecules such as glutathione, catalase, and superoxide dismutase. Furthermore, vitamin E lowers inflammatory factors including NOx production and MPO activity (15). Moreover, it is believed that vitamin E lowers iNOS protein and enhances eNOS protein expression (24, 25). Also, vitamin E can reduce the accumulation of platinum in the kidney through forming a water-soluble complex. It is confirmed that vitamin E can protect the body against heavy metal toxicity (26-29). Abdel-Daim conducted another study to evaluate the effect of 100 mg/kg daily vitamin E with or without 100 mg/kg daily ceftriaxone for 10 days on the administration of cisplatin with a dose of 5 mg/kg daily for 6 days on 56 male albino rats. The results showed that vitamin E alone or in combination with ceftriaxone can ameliorate the antioxidant levels in rats' kidney and blood. It can also lower nitric oxide, malondialdehyde, and tumor necrosis factor alpha (TNF-α) concentrations (30). Azzi et al. reported that vitamin E reduces production of NO in epithelial cells and superoxide radicals in neutrophils through protein kinase C inhibition (31). Actually, vitamin E has anti-inflammatory effects along with antioxidant effects (31, 32). It has also been asserted that vitamin E exerts all these effects without interfering with the chemotherapy effects of cisplatin (33).

Aksoy et al. studied the effect of two antioxidant materials including selenium and vitamin E on cisplatin nephrotoxicity. They selected 40 female Wistar rats and divided them into five groups including control group, target group, selenium alone, vitamin E alone and the combination of vitamin E and selenium. The administered dosage of vitamin E was 1000 mg/kg. They concluded that vitamin E alone or in combination with selenium can ameliorate histopathologic changes due to cisplatin nephropathy (18). All the above mentioned studies (15, 18, 30, 31), had a finding in line with our study; however, they were conducted on animal models. Therefore, this empowers our study because it was among the few human studies of its field. We assessed KIM marker which is a novel indicator of kidney injury, and this further strengthened our study. However, our study was limited with some points, as we could not make the two groups very similar in case of the administered dose of cisplatin. Besides, our trial was limited with a restricted number of patients and further study with larger samples is needed. Hemati et al. conducted a randomized placebo-controlled study to assess the effect of 400 IU vitamin E and 200 µg selenium daily

(target) compared to placebo in patients (control) who received cisplatin chemotherapy. The target group consisted of 22 patients and the control group had 24 patients. Their results showed that the glomerular filtration rate, white blood cell count, platelet count, and hemoglobin were significantly higher in target group. They concluded that vitamin E and selenium combination reduces nephrotoxicity and bone marrow suppression of cisplatin (19).

5- CONCLUSION

This was among the few human studies in case of using vitamin E in order to ameliorate cisplatin nephrotoxicity. We found that vitamin E could lower KIM-1 as a kidney injury molecule. Thus, it seems that vitamin E protects kidneys against cisplatin induced nephrotoxicity; however, due to the low sample size of this study, further studies are needed to complete the result of this study.

6- CONFLICT OF INTEREST: None.

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