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Protective effect of selenium on cisplatin induced nephrotoxicity: A double-blind controlled randomized clinical trial

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ABSTRACT

Background: Renal injury is common following cisplatin infusion. Some agents have been used to attenuate cisplatin nephrotoxicity. However, except hydration, none of them has been proved to be effective.

Objective: In this study selenium as an antioxidant supplement was tested on cisplatin induced renal injury.

Patients and Methods: 122 cancerous patients (85 male and 37 female; age range of 14 to 82 years old) were enrolled to receive chemotherapy regimens consisting cisplatin. They were allocated into two groups using a random number list . Investigators, patients and analyzers all, were blinded in allocation by using sealed opaque envelopes. Intervention group received a single 400 mcg selenium tablet and patients in control group took a placebo tablet which was similar with selenium preparation in color, weight, shape and taste. Primary end points were an increase in plasma creatinine above 1.5 mg/dl in men and 1.4mg/dl in women, or increase of plasma creatinine more than 50% from baseline or urine flow rate less than 0.5 ml/kg/h. Creatinine level was measured initially and on the 5th day after cisplatin therapy.

Results: There was no difference in cumulative dose of cisplatin between the groups (p=0.54). There were not evidences of acute renal failure (ARF) in cases. While, among placebo group, 7 patients had criteria of acute kidney injury.

Conclusions: selenium could probably prevent cisplatin-induced acute kidney injury, when it is added to hydration therapy in cancerous patients.

Original Article

Implication for health policy/practice/research/medical education:
Renal injury is common following cisplatin infusion. Selenium could probably prevent cisplatin-induced acute renal failure when it is added to hydration in cancerous patients.

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1. Background

Renal involvement is common after cisplatin injection (up to 30%-50% of the cases) and is dose dependent. Renal involvement most often occurs in the second week of treatment (1-3). Renal damage has a wide spectrum of presentations such as hematuria, proteinuria, glucosuria, hypomagnesemia and most notably acute kidney injury (3).

Cisplatin is a potent toxin for cells. It enters into cells, gets hydrolyzed and then binds to DNA chain leading to cellular toxicity. Cisplatin accumulates largely in kidneys more than any other tissues and this explains the high susceptibility of kidneys to cisplatin. Renal microvasculature constriction immediately after cisplatin exposure in turn potentiates kidney injury. Many other mechanisms contribute in cisplatin nephrotoxicity including; an increase in inflammatory and activated oxygen and binding to glutathione in renal tubular cells (1-3).

Up to now, some methods have been applied to prevent or attenuate cisplatin nephrotoxicity including; saline infusion, osmotic diuresis, low dose and slow rate of cisplatin injection and co-administration of magnesium sulphate or hydroxide, amifostin, thiosulfate, N-acetyl cysteine, theophylline and glycine (4-12). Except for saline infusion, none of these methods has been proved to be effective (5,6,13). Selenium is an effective agent on glutathione peroxidases enzyme system that protects intracellular structures from oxidative stresses. Moreover, as being a moiety of thioreduxin reductase, it maintains antioxidant activity of vitamin C. As well, it supports vitamin E function for limitation of lipid oxidation (9-13).

HU YJ et al. performed a clinical trial on 41 patients. Forty one patients participated and received 400 mcg for 4 days before and after cisplatin infusion. They showed that, selenium prevented renal injury (14). In another clinical trial on 48 participants, Weijl et al. administered selenium, vitamin E and C versus placebo 1 week prior, till 3 weeks post cisplatin injection. They demonstrated that, there was not any difference in glomerular filtration rate between two groups (16).

2. Objectives

Few studies regarding the effects of selenium for prevention of cisplatin nephrotoxicity have been published (14-18). Therefore, we conducted this trial to evaluate the effects of selenium on cisplatin nephrotoxicity.

3. Patients and Methods

3.1. Patients

In this double-blind randomized controlled trial, 122 patients were enrolled (85 male and 37 female; age range of 14 to 82 years old). All adult cancerous patients candidate for chemotherapy, including cisplatin, entered the study. They all provided a written informed consent. Patients' baseline characteristic data were obtained including age, sex, type of cancer, dose, type of other co- administering chemotherapeutic agents and also previous chemotherapy regimens, first day urea, creatinine and CBC. Participants were allocated into two groups using a random number list. Investigators, patients and analyzers all were blinded in allocation by using sealed opaque envelopes. Intervention group received a single 400 mcg selenium tablet and patients in control group took a placebo tablet the day before chemotherapy which was similar in color, weight, shape and taste. Mean dose of cisplatin was 203.72 mg in both groups. The data were collected by a physician unaware of investigation. Exclusion criteria were plasma creatinine level above 1.5 and 1.4 mg/dl in men and women, respectively. Taking

nephrotoxic agents such as aminoglycosides and non-steroidal anti-inflammatory drugs within previous two weeks, taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers, presence of any infection, pancytopenia, hypotension and loss to follow up were the exclusion criteria. Primary end points were composed of increase in plasma creatinine above 1.5 mg/dl and 1.4 mg/dl in men and women, respectively or increase of plasma creatinine more than 50% from baseline or urine flow rate less than 0.5 ml/kg/h after cisplatin infusion. Initially, all patients' demographic and medical information were recorded consisting; age, gender, occupation, medications, previous chemotherapy agents and their doses, frequency of chemotherapy courses, physical exam and laboratory data. A blood sample was obtained for blood urea nitrogen (BUN), creatinine, uric acid, FBS, calcium, phosphorous, magnesium and CBC analysis. Patients were requested to empty their bladder at the time of chemotherapy initiation and measure their urine output during the next 6 hours by a scaled glass. Serum creatinine and BUN tests were repeated on the 5th day. All participants received either selenium 400 mcg or placebo the day before chemotherapy. It should be noted that all cases received 3 litres of saline and 40 mg intravenous furosemide during the first day.

3.2. Ethical issues

Ethical issues committee of Ahvaz Jundishapur University of Medical Sciences approved this study.

3.3. Statistical analysis

To estimate sample size, we applied formula of comparing ratios in case of p_1=0.15, p_2=0, α=0.05 and β=0.20. We found p1 and p_2 values in our pilot study on 40 patients. We used independent-t and Chi-square tests to compare changes between two groups. Data were analyzed by SPSS (version 17) software and statistical significance was inferred at a p value< 0.05.

4. Results

Eleven (8%) patients (out of 133), were lost to follow up, therefore, excluded from the study (6 cases from treatment and 5 from placebo groups). Therefore, we analyzed 122 participants' data. Demographic characteristics are depicted in table 1. Distribution of frequency of cisplatin cumulative dose is summarized in table 2. Amongst neoplasms, gastric cancer was the most common (31% in selenium and 44.2% in placebo groups). Distribution of malignancies among patients is illustrated in table 3. There were not any differences in age, sex, presence of diabetes, hypertension, previous exposure to cisplatin and the number of chemotherapy courses between the two groups (p>0.5). There was no difference in terms of cumulative dose of cisplatin between the groups (p=0.54). Furthermore, comparing the mean single dose of cisplatin showed no difference (p=0.14).

Acute kidney failure occurred in seven patients in control group (61 patients [11.5%]), while, none of the patients were involved in selenium group (p =0.013).

5. Discussion

Cisplatin is an effective agent in a large spectrum of malignancies. Tubular dysfunction presenting with acute renal failure partially limits its use. Appropriate hydration decreases the rate of nephrotoxicity down from 50% to 10%. Meanwhile, benefits of other protective agents or methods are questionable (19,20).

In this trial, we observed 7 cases of cisplatin nephrotoxicity in the control group and none in

Table 1. Baseline characteristics of patients

	Selenium (N=61)	Placebo (N=61)
Age	44.77 Y	46.37 Y
Sex Female	18	19
Male	43	42
Creatinine	0.80 mg/dL	0.83mg/dL
Diabetes	2 (3.2%)	1(2.6%)
Hypertension	4(6.5%)	4(6.5%)
Cumulative dose of Cisplatin/mg <50	7 (11.5%)	3 (4.9%)
51-100	21 (34.4%)	17 (27.9%)
101-200	13 (21.3%)	17 (27.9%)
201-300	12 (19.7%)	11 (18%)
>300	8 (13.1%)	13 (21.3%)

Table 2. Distribution of frequency of cumulative dose of cisplatin

Cumulative dose of cisplatin (mg/d)	**selenium**		**placebo**		**total**	
	7	11.5%	3	4.9%	10	8.2%
50≤	21	34.4%	17	27.9%	38	31.1%
51-100	13	21.3%	17	27.9%	30	24.6%
101-200	12	19.7%	11	18%	23	18.9%
201-300	8	13.1%	13	21.3%	21	17.2%
≥301	61	100%	61	100%	122	100%

Table 3. Distribution of malignancies among patients

Malignancy type	**Selenium**	**Placebo**
Gastric cancer	19	27
Non-Hodgkin lymphoma	6	3
Hodgkin disease	6	3
Nasopharynx adenocarcinoma	2	1
Metastatic liver cancer	4	4
Germ cell tumor	2	6
Carcinoid tumor	0	1
Breast cancer	3	2
Osteosarcoma	2	3
Ewing sarcoma	1	3
Esophageal cancer	0	1
Thymic cancer	3	1
Lung cancer	8	3
Mandibular SCC	2	1
Ovarian CA	2	1
Bladder CA	1	0
Thyroid CA	0	1

the selenium group (p=0.013). In concordance with our results, Hu YJ et al. observed similar results in 41 cases. They demonstrated that, urinary enzymes after chemotherapy were lower in those who received 400 μg of selenium for 4 days (14). They didn't compare GFR or cre-

atinine in their groups, however lower aforementioned enzymes indicated less renal tubular damage. In comparison, their study had smaller sample size. In another study in Japan, Fujieda et al. conducted a trial on 30 rats. Half of the rats received selenium, and to the other half of the rats, a selenium free diet was delivered. They found no pathologic damage on kidney biopsy in selenium group (15). This result was in agreement with our study.

6. Limitations of the study

We had a single measurement of creatinine on the 5th day of chemotherapy. Therefore, it seems that we might have lost some cases with later mild acute renal failure.

7. Conclusions

It seems that selenium could probably prevent or attenuate cisplatin-induced acute renal failure when it is added to massive hydration in cancerous patients without any additional side effect.

Authors' contributions

AG, BO and AP designed the study. AP and BO wrote some parts of the paper. AG completed the final draft.

Conflict of interest

The authors declared no competing interests.

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