Original Paper

Effect of Zinc Sulfate on Kidney Function in Cisplatin-Treated Cancer Patients

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Abstract

Background: cisplatin is a potent chemotherapeutic agent that is currently used in management of many and various types of tumors. Cisplatin causes dose-related nephrotoxicity that significantly affects kidney function and limits cisplatin use with maximum required dose and usefulness. This study was to assess the protective and ameliorativen effect of zinc sulfate on kidney function and nephrotoxicity caused by cisplatin in cancer patients.

Patients and methods: 41 patients were enrolled in the study and were randomized into two groups. Patients in group I (N=20) received cisplatin based regimen every 21 days for six consecutive cycles. Patients in group II (N=21) received zinc sulfate plus cisplatin based regimen during the six consecutive cycles of treatment. Serum urea, creatinine and magnesium levels were measured at base line and 21 days after 1, 2, 4 and 6 cycles of cisplatin based regimen. The glomerular filtration rate of patients was calculated according to updated version of the Modification of Diet in renal Diseases formula.

Results: In group I, cisplatin based regimen after 6 cycles of treatment caused significant ($P<0.05$) increment in serum urea and creatinine and significant ($P<0.05$) decline in The glomerular filtration rate and magnesium in comparison to base line levels. Serum urea and creatinine levels of group II were significantly ($P<0.05$) lower than that of group I while glomerular filtration rate and magnesium were significantly ($P<0.05$) higher than that of group I.

Conclusion: zinc sulfate significantly ameliorated nephrotoxicity and improving kidney function in cisplatin-treated patients.

Keywords: zinc sulfate, cisplatin, kidney function, nephrotoxicity.

Introduction

Cisplatin is an alkylating-like agent with potent antitumor efficacy that is widely used in treatment of various types of cancers[(1)]. Currently, cisplatin clinical use is complicated by the dose-dependent nephrotoxicity which can occure in form of acute kidney injury (AKI) in approximately 20-30% of patients[(2)]. Acute kidney injury accounts for increased morbidity and mortality [(3)] and thereby cisplatin dose should be decreased to avoid nephrotoxicity at the expense of maximum chemotherapeutic effectiveness.[(1,3)].

Although newer agents with relatively less toxicity and equal antitumor effectiveness have been introduced, cisplatin continues to be widely used in chemotherapy as first line antitumor agent[(4)]. Vigorous hydration with normal saline as the only available preventive measure cannot prevent severe and lifelong nephrotoxicity that can result from cisplatin use[(3,5,6)]. Typically, AKI mainly manifested as an increases in the serum creatinine and blood urea nitrogen

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concentrations begins several days after the dose of cisplatin[7]. The urine output is usually normal (non-oliguric) or even there is polyuria after cisplatin treatment[7]. Hypomagnesemia is common, even in the absence of a decline in the GFR [8,9].

The major mechanisms of acute kidney injury due to cisplatin are apoptosis and necrosis that occur through many pathways[1]. Cisplatin cause DNA damage response pathways by the alkylating action[1]. Cisplatin induces oxidative stress by induction of reactive oxygen species[10] with inactivation of anti-oxidant systems[11,12] and decreased intracellular ATP levels [13,14].

Reactive oxygen species induce an intense inflammatory response that further aggravate tubular cell injury[1] through activation of NF-kB leading to the renal overexpression of TNF-α[15] which in turn activate many chemokines and cytokines in the kidney[15,16]. Three apoptotic pathways have been concerned in cisplatin-induced epithelial cell death in kidney: the intrinsic (mitochondrial) pathway, the extrinsic pathway that is initiated through death receptors (TNFα receptors or Fas), and the endoplasmic reticulum stress pathway[1].

Zinc is essential trace element that is involved in cellular metabolism[17], numerous enzymes activity[18,19], immune function[19,20], wound healing[19], protein and DNA synthesis and cell division[21]. It has antioxidant and anti-inflammatory effects [22,23]. As the oxidative stress and inflammatory response play a major role in cisplatin-induced nephrotoxicity, zinc may have a preventive and/or ameliorative effect on kidney. In mice, Zinc sulfate had a reno-protective effect against cisplatin toxicity[24]. Studies on animal models with cisplatin induced renal injury using zinc gluconate or zinc histidine demonstrated ameliorative effect of zinc against cisplatin-induced toxicity[25-27].

Patients and methods

Patients

A total of 41 cancer patients who had a confirmed diagnosis of a malignant solid tumor that needed cisplatin-based therapy in the oncology unit in al-sadar medical city in Al-Najaf Governorate were participated in the current study. Informed consents were obtained from all participants of the study. Demographic details were collected from participants. Clinical data for diagnosis and therapeutic regimen were obtained from case notes and treatment chart. The protocol of study was accepted by the Ethical Committees in Faculty of Medicine in Kufa University. Samples collection had started in October 2014 and continue until July 2015.

Inclusion criteria for patients included was age between 18 and 65 years. Exclusion criteria for patients were pregnancy or lactation, preexisting renal impairment, metastasis to the central nervous system, severe cardiopulmonary comorbidity, previous radiotherapy or chemotherapy, and hypersensitivity to cisplatin or other platinum derivatives.

Study treatment: Patients participated in this study were randomized into two groups: *Group I*: Patients (N=20) received 6 cycles of cisplatin based regimen at 21-days interval. *Group II*: Patients (N=21) received 6 cycles of cisplatin based regimen at 21-days interval plus zinc sulfate. cisplatin was manufactured by Bristol-Myers Squibb as 1 mg/mL (50 or 100 mg) Platinol-AQ intravenous Injection. Cisplatin dose was 75 mg/m^2 and combined with other chemotherapeutic agents which don't potentiate nephrotoxicity by cisplatin, such as gemcitabine docetaxel, 5-flourouracil and etoposide[28,29]. Oral 220 mg-zinc sulfate tablets (50 mg of elemental zinc) were administered twice daily for all patients in group II. zinc sulfate tablets were manufactured by Alhavi CO., Iran. Batch NO. 0100890.

Kidney function evaluation: Assessment of the nephrotoxic effect of Cisplatin was based on changes in levels of serum creatinine, urea and magnesium as the biomarkers of renal function. GFR was calculated from serum creatinine level. according to updated version of Modification of Diet in Renal Disease (MDRD). Three milliliters of blood were collected from participants in the present study before the 1st dose and 21 days after 1st, 2nd, 4th and 6th dose of chemotherapy. Serum was collected from each blood sample and frozen at -80 ˚C.

Serum creatinine concentration was measured by colorimetric assay kit from Cayman Chemical Co. (Catalog Number. 700460). Serum urea concentration was measured by Serum Urea Colorimetric Assay Kit (Catalog Number. 501094) from B*ioMerieux*, France. Serum magnesium concentration was measured Magnesium liquicolor (Catalog Number 10010) from HUMAN, Germany. Updated version of the MDRD formula was used to calculate GFR from the serum concentration of creatinine : GFR [ml / min / 1.73 m^2] = 175 × $Scr^{-1.154}$ ×$age^{-0.203}$ × 1.212 (if black) × 0.742 (if female) where Scr is serum creatinine[30].

Statistical Analysis : SPSS 16.0 for windows lnc was used for performing statistical analyses. Quantitative variables were expressed as mean ± SEM. Comparison between baseline value and value of either 1st, 2nd, 4th, or 6th cycle of same treatment group were done by paired-sample t-test. Chi- Square test or unpaired-sample t-test were used for the comparisons between the two study groups variables. In all tests, level of significance was P<0.05 unless another level was stated.

Results

Patients' characteristics

The comparison of patients characteristics data between the two randomization groups revealed insignificant (p>0.05) differences as shown in table (1).

Effect of treatment on serum creatinine levels: In group I, Cisplatin based regimen caused significant increment (P < 0.05) in serum creatinine (mg/dl) level after 2, 4 and 6 cycles when compared with that of baseline, as shown in figure (1).

Levels of serum creatinine (mg/dl) in group II patients that received Cisplatin based regimen plus zinc sulfate were significantly lower (P < 0.05) than that of the of group I after 4 and 6 cycles of treatment as shown in figure (1).

Effect of treatment on serum urea levels

In group I, Cisplatin based regimen caused significant increment (P < 0.05) in serum urea (mg/dl) level after the sixth cycle when compared with that of baseline, as shown in figure (2). Levels of serum urea (mg/dl) in group II patients that received Cisplatin based regimen plus zinc sulfate was significantly lower (P < 0.05) than that of the of group I after the sixth cycle of treatment as shown in figure (2).

Effect of treatment on serum magnesium levels: In group I, Cisplatin based regimen caused significant decrement (P < 0.05) in serum magnesium (mg/dl) level after 1, 2, 4 and 6 cycles when compared with that of baseline, as shown in figure (3). Levels of serum magnesium (mg/dl) in group II patients that received Cisplatin based regimen plus zinc sulfate were significantly higher (P < 0.05) than of that of group I after 4 and 6 cycles of treatment as shown in figure (3).

Effect of treatment on GFR: In group I, Cisplatin based regimen caused significant decrement (P < 0.05) in GFR (ml/min) after 2, 4 and 6 cycles when compared with that of baseline, as shown in figure (4). GFR (ml/min) in group II patients that received Cisplatin based regimen plus zinc sulfate were significantly higher (P < 0.05) than of that of group I after 4 and 6 cycles of treatment as shown in figure (4).

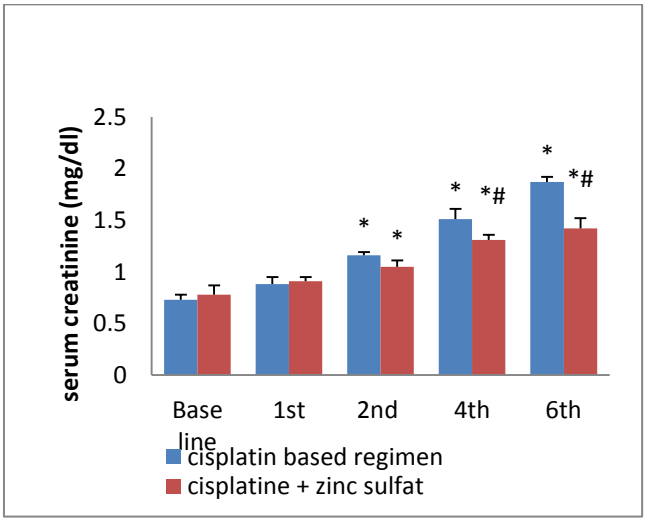
Discussion

Effects of cisplatin based regimen on study parameters

In the present study, cisplatin-based regimen caused significant decline in kidney function that elucidated by significant increment ($P < 0.05$) after 2 cycles and highly significant increment ($P < 0.01$) after 4 and 6 treatment cycles in serum creatinine levels when compared with that at baseline. Insignificant increment ($P > 0.05$) in serum urea level after 1, 2 and 4 cycles was resulted from treatment with cisplatin based regimen and significant increment ($P < 0.05$) was observed after the sixth cycle of treatment in comparison to base line level. These results are in good agreement with that shown by Arunkumar *et al* (2012)[31] where they observed significant ($P < 0.05$) serum creatinine levels increment and insignificant increment ($P > 0.05$) in BUN after 5 cycles of cisplatin treatment in comparison to base line level. Kumara et al (2014)[32] revealed that there is significant increment in serum creatinine level in patients after 2 and 4 cycle of cisplatin chemotherapy in comparison to base line levels. However, non-significant changes of serum urea after the 1st, 2nd, 4th cycle might be due to the poor sensitivity and specificity of serum urea[33,34] which is affected by many non-renal factors that affect generation of urea and elimination.[35]

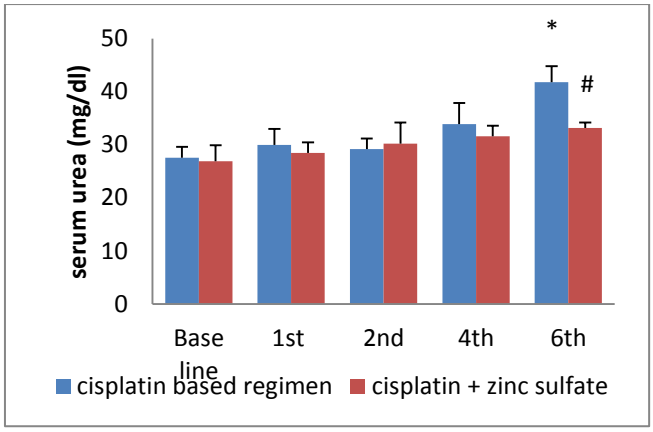
Table 1. Characteristics data for all included patients.

Characteristics	Group I	Group II
Number of patients	20	21
Sex (male/female)	13/7	15/6
Age (yr) Mean ± SEM	52.6± 2.45	54.68±4.23
Weight (kg) Mean ± SEM	83.53± 2.91	80.46±3.64
Height (cm) Mean ± SEM	165.3±2.76	171.4±0.88
Body Surface Area (m^2) Mean ± SEM	1.70±3.55	1.72±4.42
No. of Hypertensive	3	2
No. of Diabetics	2	4
Agents received with cisplatin:	No.	No.
5-flourouracil + docetaxel	9	7
Etoposide	4	3
gemcitabine	3	5
5-flourouracil	4	6



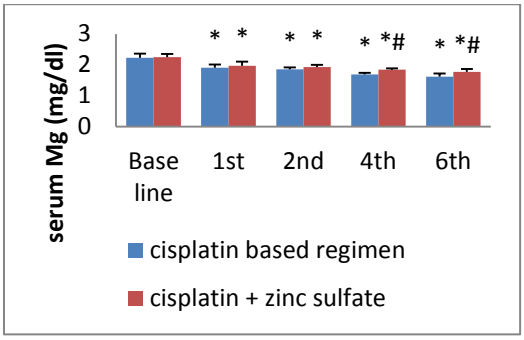
* P < 0.05 compared to baseline values of the same treatment group. # p<0.05 compared to group I at same cycle of treatment.

Figure 1. values of serum creatinine levels (Mean ± SEM) at baseline and after 1, 2, 4 and 6 cycles in group I (cisplatin based regimen, n=20) and group II (cisplatin + zinc sulfate, n= 21).



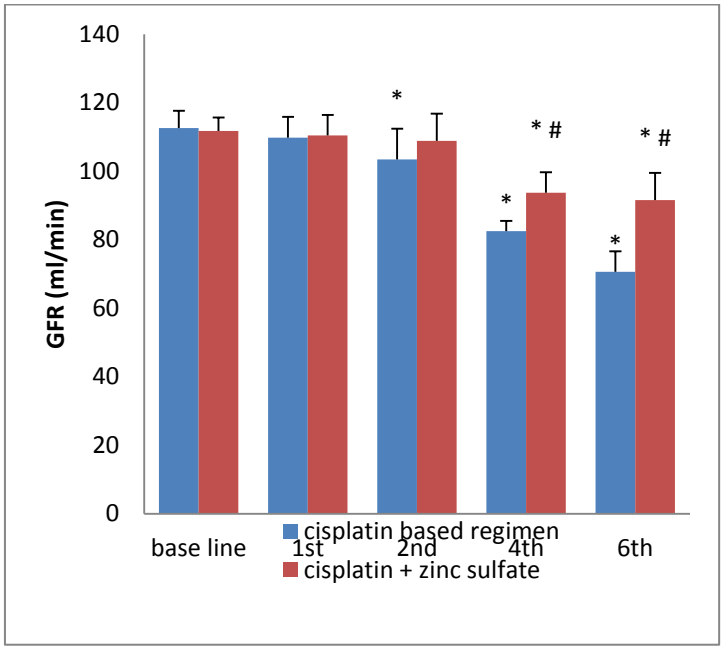
* P < 0.05 compared to baseline values of the same treatment group. # p<0.05 compared to group I.

Figure 2. values of serum urea levels (Mean ± SEM) at baseline and after 1, 2, 4 and 6 cycles in group I (cisplatin based regimen, n=20) and group II (cisplatin + zinc sulfate, n= 21).



* P < 0.05 compared to baseline values of the same treatment group. # p<0.05 compared to group I.

Figure 3. values of serum magnesium levels (Mean ± SEM) at baseline and after 1, 2, 4 and 6 cycles in group I (cisplatin based regimen, n=20) and group II (cisplatin + zinc sulfate, n= 21).



* P < 0.05 compared to baseline values of the same treatment group. # p<0.05 compared to group I.

Figure 4. values of GFR (mean ± SEM) at baseline and after 1, 2, 4 and 6 cycles in group I (cisplatin based regimen, n=20) and group II (cisplatin + zinc sulfate, n= 21).

In the current study, serum magnesium level were significantly ($p<0.05$) lower than baseline levels after 1, 2, 4 and 6 cycles of cisplatin based regimen and these result are supported with results revealed by Arunkumar *et al* (2012)[31] where significant decrement ($p<0.05$) in serum magnesium level after 5 cycles of cisplatin based regimen was noted. Bodnar *et al* (2008)[36] observed significant decrement ($p<0.01$) in serum magnesium level after 1, 2, 3, 4, 5 and 6 cycles of cisplatin administration. Direct injury to magnesium reabsorption mechanism in the ascending limp of loop of Henle and the distal tubule by cisplatin is a possible mechanism behind cisplatin induced hypomagnesaemia[37].

Cisplatin based regimen caused significant decreasing ($p<0.05$) after 2 cycles and highly significant decreasing ($p<0.01$) in MDRD-GFR after 4 and 6 cycles in comparison to base line level. These results are reliable as they compared with that revealed by Bodnar *et al* (2008)[36] where they recorded significant decrease in GFR estimated from MDRD formula after 1, 3, 4, 5 and 6 cycles of treatment with cisplatin in patients with ovarian cancer.

Failure in reabsorption of sodium chloride due to cisplatin leads to increased sodium chloride delivery to the macula densa and then increased renal vascular resistance secondary to tubular-glomerular feedback and renal blood flow decrease within 3 hours after cisplatin infusion[38]. The changes in renal blood flow probably lead to the significant decline in GFR and then the significant elevation in serum kidney function parameters levels in the present study.[38]

Effects of cisplatin based regimen + zinc sulfate on study parameters

After 4 and 6 cycles of the present study, zinc sulfate addition to cisplatin treatment in patients of group II caused significant ($P < 0.05$) lowering of serum creatinine level in comparison to that of cisplatin based regimen treated group. In addition, zinc sulfate caused significant ($P<0.05$) lowering of serum urea in comparison to increased level of cisplatin based regimen treated group after 6 cycles of treatment. In accordance to our knowledge, there is no similar study on cancer patients but on experimental level, Satoh *et al* (2000)[24] reported that in mice zinc sulfate caused significant improvement on kidney function test (BUN and serum creatinine) against cisplatin-induced renal toxicity.
After 4 and 6 cycles of treatment in the present study, serum magnesium level and GFR estimated by MDRD formula of zinc sulfate-treated group was significantly higher ($P<0.05$) than that of cisplatin only treated group.

The results from the present study indicated that there is significant improvement in kidney function caused by addition of zinc sulfate to cisplatin based regimen in patients of group II and the protective effect is more prominent after 4 and 6 cycles of treatment when nephrotoxicity due to cisplatin in group I become more cumulative and intensive. According to our knowledge, there is no previous similar study that assess the effect of zinc sulfate on kidney function in patient with cisplatin-induced nephrotoxicity that support these results but results shown by Parham *et al* (2008)[39] showed protective effect of Zinc supplementation on kidney function in microalbuminuric type 2 diabetic patients. The antioxidant[40] and antiapoptotic[41] properties of zinc might play a role in protection from cisplatin-induced nephrotoxicity noticed in this study as are the major mechanisms responsible for it. This reno-protective effect noticed as preserving serum magnesium level and GFR and thereby maintaining serum creatinine and urea levels from being abnormally elevated.

Conclusion

The results from the this study showed that there is a significant protective effect caused by addition of zinc sulfate to cisplatin based regimen in patients of group II

Conflict of interest statement

None declared.

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