ORIGINAL ARTICLE

Protective Effect of Forced Hydration with Isotonic Saline, Potassium Chloride and Magnesium Sulfate on Cisplatin Nephrotoxicity: An Initial Evaluation

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Abstract

Background: Nephrotoxicity is one of the major side-effects of cisplatin that has been seen in about 20% of treated patients. The aim of this study was to assess the effectiveness of a forced hydration protocol comprised of isotonic saline, potassium chloride (KCl) and magnesium sulfate ($MgSO_4$) on prevention of cisplatin nephrotoxicity.
Methods: This cross sectional prospective study was performed on cancer patients treated in Shafa Hospital, Ahvaz, Iran from November 2009 to March 2010. The patients were under at least 50 mg/m^2 cisplatin. All patients received 1000 mL isotonic saline plus 20 mEq of KCl and 2 g of $MgSO_4$ during 2-3 hours before, and 500 mL of the same solution over the two hours after administration of cisplatin. The prescribed dose of the solution was to the extent facilitating a urine flow of at least 100 mL/h for two hours prior to chemotherapy and 2 hours post-chemotherapy. Cisplatin nephrotoxicity was defined as an increase in the SCr equal or over 0.5 mg/dL during the 5 day follow-up post-chemotherapy.
Results: A total of 76 patients (48 men and 28 women with mean (SD) age of 51.0 (17.6) years) were studied. Mean cumulative cisplatin dose was 86.7 (43.1) mg/m^2. Hypokalemia and hypomagnesemia were not observed in any patient. Cisplatin nephrotoxicity (increase of creatinine) was developed in 5 patients (6.6%). The mean dose of cisplatin in patients with and without nephrotoxicity was 83 and 86.97 mg respectively which showed no significant difference between them (P = 0.8).
Conclusion: The new protocol was able to decrease the rate of cisplatin nephrotoxicity from about 20% to 6.6%. Further case control studies with larger sample sizes are recommended to evaluate the effectiveness of this protocol.

Keywords: Cisplatin; Chemotherapy; Forced Fluid Therapy; Nephrotoxicity

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INTRODUCTION

Cisplatin is a potent and a major antineoplastic medication which is used in the treatment of patients with solid cancers such as head and neck, esophagus, bladder, womb neck, metastatic breast, testis, ovarian and non-small cell lung cancer (1-4).

Kidneys accumulate cisplatin through peritubular uptake and retain it to a greater degree than other organs and they are its principal excretory organs. In addition, cisplatin is a potent cellular toxin which causes renal tubular dysfunction, and thus decreases the glomerular filtration rate (GFR) leading to acute and chronic renal impairments (5-7). In spite of these known side effects, it is still one of the main medications in chemotherapy due to its powerful anti-tumoral effects (2,4,8).

Cisplatin-induced nephrotoxicity has been reported to occur in about 18-25.2% of Iranian cancer patients including patients treated in our center in Ahvaz (9,10).

Different strategies have been offered to prevent or diminish nephrotoxicity of this medication (11,12). The aim of this study was to evaluate the effectiveness of a forced hydration protocol comprised of isotonic saline fluid, magnesium sulfate ($MgSo_4$) and potassium chloride (KCl) on prevention of cisplatin nephrotoxicity.

METHODS

Study design and patients

This cross sectional prospective study was performed between November 2009 and March 2010 on patients under chemotherapy in Shafa Hospital, Ahvaz, Iran. The study was approved by the ethical committee of the Nephrology Research Center, affiliated to Ahvaz Jundishapur University of Medical Sciences.

From all patients; demographic features, history of previous diseases and medications, type of cancer, dose of

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prescribed cisplatin, vital signs, and laboratory findings including serum creatinine (SCr) and blood urea nitrogen (BUN) were collected and entered into a predesigned checklist.

Patients receiving cisplatin equal or over 50 mg/m^2 as part of their chemotherapy diet were included in the study. Patients with the following characteristics were excluded from the study:

1. Patients who refused follow-up visits.
2. Patients who had used non-steroidal anti-inflammatory drugs, aminoglycoside, radiocontrast, angiotensin-converting-enzyme inhibitors such as captopril and enalapril and angiotensin receptor blockers such as losartan in the two weeks prior to cisplatin therapy.
3. Patients with SCr over 1.4 mg/dL in men and 1.2 mg/dL in women before receiving cisplatin.
4. Patients with abnormal vital signs prior to or during 5 days after receiving cisplatin, i.e. blood pressure less than 90/60 mmHg, pulse rate more than 100 beats/ minute, respiratory rate more than 25 breaths/minute, and body temperature more than 37.2°C in the morning or 37.7°C in the afternoon.
5. Patients who did not tolerate receiving the serum due to underlying diseases such as heart failure.
6. Patients with hyperkalemia, (serum potassium over 5.5 mEq/L) before chemotherapy.

Treatment and follow ups

All patients received 1000 mL isotonic saline plus 20 mEq of KCl and 2 g of $MgSO_4$ during 2-3 hours before, and 500 mL of the same solution over the two hours after administration of cisplatin. The prescribed dose of the solution was to the extent providing a urine flow of at least 100 mL/h for two hours prior to chemotherapy and 2 hours post-chemotherapy. A day before chemotherapy and then 5 consecutive days after receiving cisplatin, blood samples were taken and analyzed for BUN and SCr with commercial kits. Cisplatin nephrotoxicity was defined as an increase in the SCr equal or over 0.5 mg/dL during 5 days post-chemotherapy.

Statistical analysis

Statistical package for social sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Chi-square test was performed to evaluate the correlation of variables. Statistical significance was assessed at the less than 0.05 probability level in all analyses.

RESULTS

Demographic

Eighty-seven patients were enrolled in this study; which of them, 11 patients were excluded. In the remaining 76 patients, 48 were men (63.2%) and 28 were women (36.8%) with a mean (SD) age of 51.0 (17.6) years. Most patients aged 50 to 60 years (Figure 1). There was no significant difference between mean age of men and women (P = 0.67).

Cisplatin dosage and outcome of treatment

Most patients (60%) had gastric cancer (Table 1). The mean (SD, min-max) cumulative dose of cisplatin administered was 86.7 (43.1, 50-200) mg/m^2. Most patients

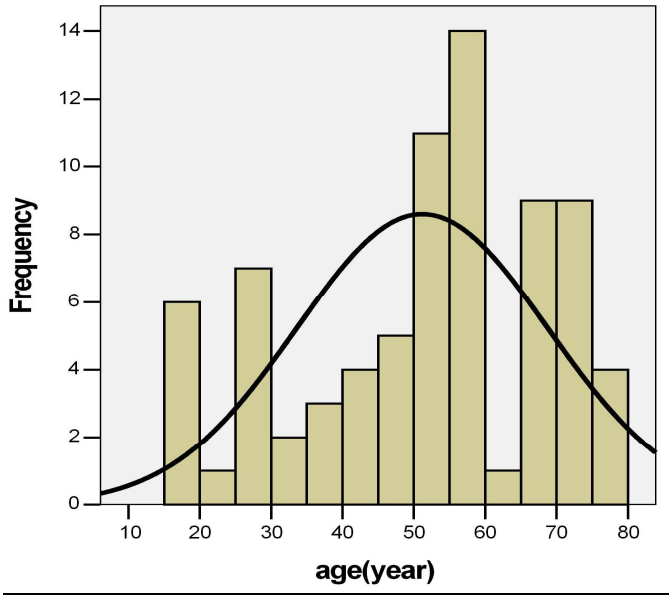

Figure 1. Age distribution of patients

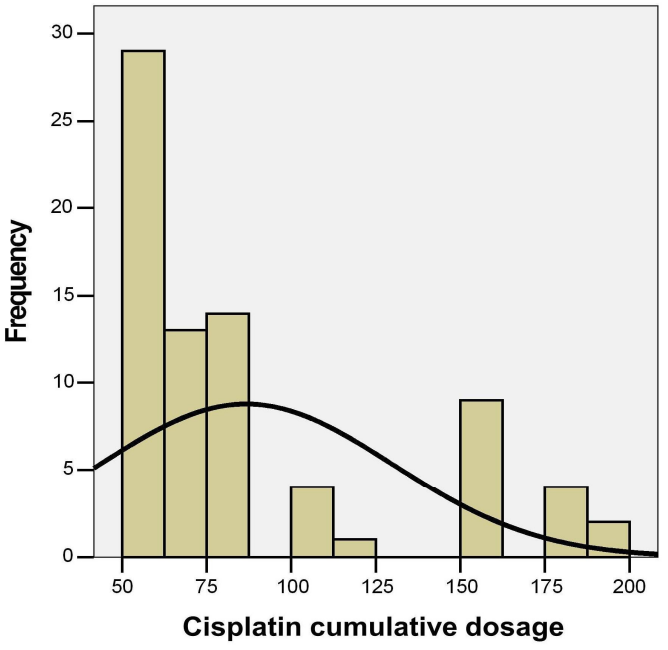

Figure 2. Distribution of cisplatin cumulative dose

(73.7%) received 50 to 99 mg/m^2 cisplatin (Figure 2). The mean (SD) courses of chemotherapy with cisplatin were 3.43 (3.31). Hypokalemia and hypomagnesemia were not observed in any patient. Cisplatin nephrotoxicity (increase of creatinine) was developed in 5 patients (6.6%). The mean dose of cisplatin in patients with and without nephrotoxicity was 83 and 86.97 mg respectively which showed no significant difference between them (P = 0.8).

Table 1. Distribution of type of malignancies among patients

Malignancy	No. (%)
Gastric Cancer	46 (60.6)
Non-Hodgkin's lymphoma	6 (7.9)
Hodgkin 's disease	5 (6.6)
Germ cell tumor	5 (6.6)
Liver metastatic cancer	4 (5.3)
Nasopharyngeal Adenocarcinoma	2 (2.6)
Breast Cancer	2 (2.6)
Osteosarcoma	2 (2.6)
Ewing's sarcoma	2 (2.6)
Carcinoid Tumor	1 (1.3)
Esophageal cancer	1 (1.3)
Total	76 (100)

DISCUSSION

Nephrotoxicity has been shown as a frequent major side-effect of the cisplatin which manifests with hypomagnesemia, hypocalcemia, hypokalemia, proteinuria and acute decline in the GFR or even chronic renal dysfunction (9,10,13-16). Several mechanisms have been proposed for renal dysfunction following exposure to cisplatin including tubular epithelium cell toxicity, vasoconstriction in the renal microvasculature, oxidative stress and robust inflammatory response (17). In most cases, renal dysfunction due to cisplatin is irreversible and thus more efforts for prevention of nephrotoxic effects of the drug seems mandatory (13).

Although the prophylactic effect of some of medications such as N-acetylcysteine, theophylline, and glycine on cisplatin nephrotoxicity have been investigated in many studies, they have been shown to be moderately promising (11-13,18). The frequency of cisplatin nephrotoxicity in Iranian patients is about 18-25.2%. In the present study, we showed that vigorous administration of intravenous saline with KCl and $MgSO_4$ which is capable of producing a urine output of at least 100 mL/h, can remarkably lower the risk of nephrotoxicity to 6.6%. Ozlos et al. similarly revealed the positive effect of extensive hydration on prevention of renal toxicities due to cisplatin (19). To prevent hypokalemia and hypomagnesemia which are two well-known renal side-effects of cisplatin, KCl and $MgSO_4$ were added to our protocol and this appeared to be helpful. Moreover, forced hydration has been revealed to be effective on prevention of hematological toxicities of cisplatin (20).

In this study, no association between different doses of cisplatin and development of nephrotoxicity was found. However, this association was previously demonstrated in some studies (21,22). Reece et al. ascertained that with more than 400 ng/mL peak plasma concentration of free platinum, decreased creatinine clearance can be seen by the fourth course of therapy in greater than 30 percent of patients (21). Hartman et al. similarly showed significant decrease in GFR of the patients receiving cisplatin at doses higher than 50 mg/m^2 (20). These findings suggest an important role of cumulative dose of the drug on inducing renal failure.

LIMITATIONS

The value of the study findings can be constrained by following factors. There was no control group in this study to compare the results of the new protocol with them. However, as the rate of nephrotoxicity prior to administration of the new protocol according to local statistics was shown to be about 20%, the reduction in percentage of nephrotoxicity is remarkable. Nevertheless, a further study with a control group is recommended. In addition, the frequency of cisplatin nephrotoxicity was low and therefore analysis of the effect of different doses of cisplatin on inducing renal failure was not possible.

CONCLUSION

Forced hydration along with potassium chloride and magnesium sulfate may decrease the risk of cisplatin nephrotoxicity. Case control studies with larger sample sizes are recommended to evaluate the effectiveness of this protocol.

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Conflict of interest: None to be declared

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