



ORIGINAL ARTICLE

The Effect of Hydration Therapy with and without Magnesium Sulfate on Prevention of Cisplatin-Induced Nephrotoxicity

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ABSTRACT

Background: Cisplatin is an antineoplastic agent used to treat many malignancies; however, the main side effect of cisplatin is nephrotoxicity. The aim of this study was to evaluate the effect of hydration therapy with and without magnesium on prevention of cisplatin-induced nephrotoxicity.

Methods: This retrospective study was performed on 46 patients with malignancy who were candidate to receive cisplatin as their protocol for chemotherapy during years 2011-2016. Of these, 22 patients were treated with hydration and magnesium sulfate (1 gr magnesium sulfate 50% and 10 mEq potassium chloride 15% in 1000 ml normal saline before and after cisplatin administration) and 24 patients were treated with hydration alone. Cisplatin was administered in cycles every 21 days. Serum sodium, Potassium, creatinine (sCr) and creatinine clearance (CrCl) were assessed before each chemotherapy cycle and after the last course of chemotherapy.

Results: There was significant difference between two studied groups in post chemotherapy sCr and Potassium ($P < 0.05$); however, no significant difference was observed between two groups in serum magnesium and sodium levels ($P > 0.05$). In terms of sCr, as nephrotoxicity index, the absolute risk of nephrotoxicity in patients receiving hydration with magnesium was 19% more than the other group. The relative risk of nephrotoxicity in patients receiving hydration with magnesium was 4.4 fold more than another group.

Conclusion: Risk of cisplatin-induced nephrotoxicity in patients receiving hydration with magnesium sulfate was higher than group of patients not receiving magnesium besides hydration.

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Introduction

Cisplatin is an antineoplastic agent used to treat different kinds of malignancies such as testis, ovary, and mesothelioma.¹ The cytotoxic effects of cisplatin in tumor cells and other differentiated cells are caused by various mechanisms including direct cytotoxic effects of crosslinking in cellular DNA and induction of apoptosis by changes in protein kinase.² More than 50% of cisplatin is excreted through urine in the first day after cisplatin

administration.^{3,4} Consequently, the concentration of cisplatin in kidney cells is several folds higher than the other organs.³⁻⁵ In this way, cisplatin leads to the necrosis and apoptosis of proximal kidney cells, which also leads to reduced glomerular filtration and increased creatinine in the form of acute renal damage.⁵ Nephrotoxicity is a well-known and main side effect of cisplatin.^{1,6-8} It is reported in approximately one-third of patients treated with single-dose of cisplatin (50 mg/m²). In addition, 20-

40% of patients receiving high dose of cisplatin have had severe acute kidney damage.⁹ Older age, female gender, cigarette smoking and preexisting kidney disease have been associated with cisplatin-induced nephrotoxicity.^{1,9-11} Direct damage to the proximal tubule and thick ascending part of the loop of Henle leads to a defect in the tubular reabsorption process.¹² Hypomagnesaemia is the most important electrolyte imbalance caused by the defect in tubular reabsorption; reported in approximately 50% of patients receiving cisplatin.¹²⁻¹⁴ Furthermore, magnesium depletion due to diarrhea and anorexia alone exacerbates the damage to the renal cells besides the cisplatin-induced hypomagnesemia. The mechanisms proposed in this regard are related to the effect of magnesium on the active cisplatin transporter system,¹⁵ as well as its association with an organic cation transporter 2.¹⁶ Accordingly, development of measures to reduce cisplatin-induced nephrotoxicity and understanding the role of magnesium supplementation in cisplatin-induced nephrotoxicity would be of great necessity.

Despite a vast source of literature, there is not still any definitive opinion regarding the protective effect of magnesium sulfate on prevention of cisplatin-induced nephrotoxicity. Several studies have shown the beneficial effect of magnesium on alleviation of cisplatin-induced nephrotoxicity,^{5,17,18} whereas others have shown the contradictory results.^{19,20} Therefore, the aim of this study was to compare level of nephrotoxicity in patients receiving cisplatin and hydration therapy with and without magnesium as well as the effect of using magnesium supplements to reduce cisplatin-induced nephrotoxicity.

Methods

This retrospective study was performed on 46 patients who were candidates to receive cisplatin-based chemotherapy according to the underlying malignancy during years 2011-2016, referring to “Alzahra” and “Seyedolshohada” hospitals of Isfahan, Iran. 22 out of 46 patients received hydration along with magnesium sulfate (group 1), whereas 24 patients just received hydration (group 2). Inclusion criteria were age range of 15-75 years old and glomerular filtration rate (GFR) of more than 75 ml/min/1.73m². Patients who were receiving non-steroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides were not included in the study. It should be noted that in the second group, if serum magnesium level was less than 1.8 mg/dL, magnesium was injected as much as 1 g of magnesium sulfate.

Cisplatin and Hydration Protocol

Dose of cisplatin and chemotherapy protocols were scheduled depending on the tumor type and the condition of the patient (calculated according to the body surface area). The mean dose of cisplatin administered was 50-100 mg/m² which was administered as a 2-hour intravenous infusion in 500 ml of normal saline. Courses of cisplatin were administered every three weeks.

Group 1 received 1000 ml normal saline containing 10 mEq potassium chloride 15% and 1g magnesium sulfate 50% during 2 hours before and after administration of

cisplatin. Another group (group 2) received 1000 ml normal saline plus 10 mEq potassium chloride 15% alone (without magnesium sulfate).

Biochemical Parameters Measurement

Various biochemical tests, including serum creatinine, magnesium, sodium and potassium were measured the day before each chemotherapy course and after the last course of chemotherapy. Glomerular filtration rate (GFR) was calculated according the cockcroft-gault formula:

$$GFR = \frac{140 - age(years) * weight(kg)}{72 * cr(\frac{mmol}{l})}$$

Nephrotoxicity was defined as an increase of serum creatinine by 0.5 mg/dl or more above the baseline and reduction of GFR by 50% or more during each course of chemotherapy, respectively.

Statistical Analysis

Data were analyzed using SPSS version 19.0. Paired T-test was used to determine the difference between parameters before each course of chemotherapy and after the last course. P value<0.05 was considered statistically significant.

Results

Of the 46 patients who were treated with cisplatin during the study period, 24 patients (52.2%) were male. The mean age of the patients in group 1 was 16.7±50 years, whereas in group 2, it was 16.6±44 years (P>0.05).

As shown in Table 1, there was a significant difference between the two studied groups in post chemotherapy serum creatinine and Potassium levels (P<0.05); however, no significant difference was observed between the two groups in magnesium and sodium (P>0.05). Mean value of GFR in both groups were close to the marginal level. However, GFR was reduced by 50% in patients who had increased serum creatinine by more than 0.5 mg/dL.

There was a significant difference in post-treatment potassium levels in both groups; however, both groups received the same protocol regarding the potassium. There was not found any significant difference for magnesium and sodium between two groups. Changes of serum creatinine and GFR levels as “nephrotoxicity index” are shown respectively in Figures 1 and 2.

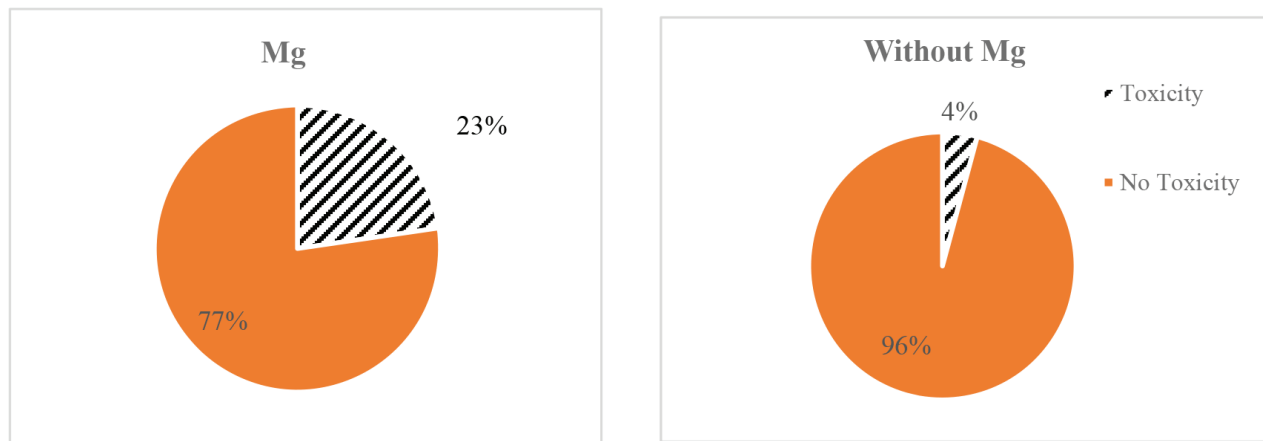
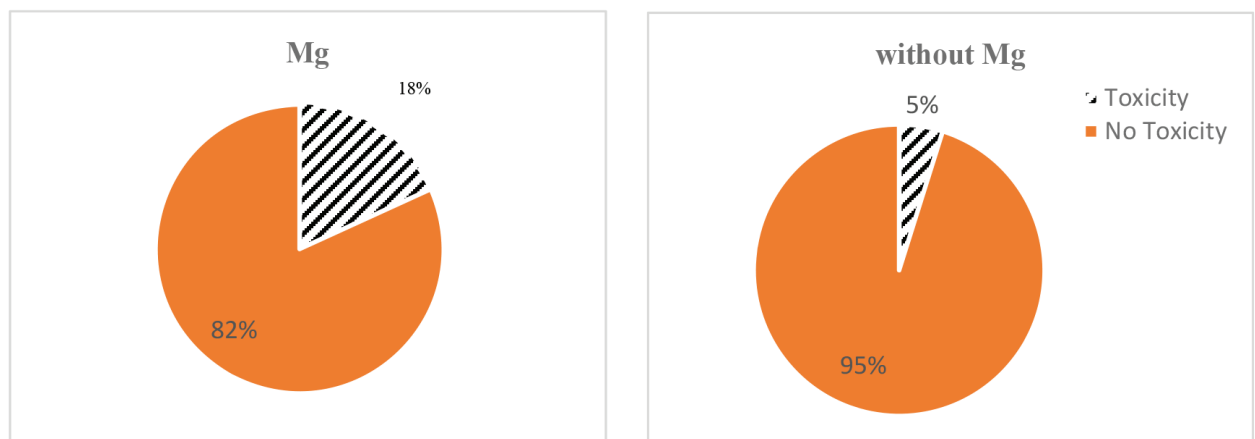
As shown in Figure 1, the absolute risk increase (ARI) and relative risk increase (RRI) for nephrotoxicity (according to the mentioned definition) was 19% and 4.4 times, respectively. This means that the absolute risk and relative risk of nephrotoxicity in group 1 patients receiving hydration along with magnesium sulfate was 19% and 4.4 fold, respectively more than the other group. Moreover, number need to harm (NNH) was 5; means that one in 5 patient who received magnesium sulfate developed nephrotoxicity.

Considering GFR reduction (by 50%) also as a nephrotoxicity index based upon our definition, 4 out of 22 patients in group 1 (18.2%) and 1 out of 24 patients (4.8%)

Table 1: Biochemical parameters and GFR in patients receiving cisplatin and hydration with and without magnesium sulfate

Variables	Hydration therapy with Magnesium sulfate N=22	Hydration therapy without Magnesium sulfate N=24	P value
GFR (Pre chemotherapy)	90.5±17.8	94.67±21.4	0.21
GFR (post chemotherapy)	80.1±33	98.9±27.16	0.06
Cr (Pre chemotherapy)	0.89±0.17	0.81±0.13	0.06
Cr (post chemotherapy)	1.1±0.48	0.83±0.16	0.01
K (Pre chemotherapy)	3.8±1.1	3.9±1.2	0.8
K (post chemotherapy)	4.3±0.5	3.1±1.4	0.001
Mg (Pre chemotherapy)	2.02±0.27	1.97±0.12	0.39
Mg (post chemotherapy)	2.03±0.39	2.1±0.24	0.22
Na (Pre chemotherapy)	137±3.5	138±3	0.5
Na (post chemotherapy)	138±4.4	137±4.2	0.5

Cr: Serum creatinine, GFR: Glomerular filtration rate, K: Potassium, Mg: Magnesium, Na: Sodium

**Figure 1:** The frequency of nephrotoxicity in two groups with regard to serum creatinine as nephrotoxicity index.**Figure 2:** The frequency of nephrotoxicity in two groups with regard to glomerular filtration rate as nephrotoxicity index.

in group 2 developed nephrotoxicity, so that ARI, RRI and NNH was 14%, 3.5 and 7, respectively. Indeed, one out of 7 patients treated with hydration and magnesium was affected by kidney damage. Taking into account the results of both indexes of nephrotoxicity in this study, one in every 5-7 patients who received magnesium sulfate along with hydration developed acute kidney damage.

Discussion

Nephrotoxicity is a major well known side effect of platinum compounds such as cisplatin.^{7,8} There are

numerous studies showing the beneficial effects of magnesium sulfate on reduction of cisplatin-induced nephrotoxicity;^{5,17,18} however, they did not show a definitive role about the mechanism and protective effect of magnesium sulfate in preventing cisplatin-induced nephropathy.

In a study conducted by Yoshida et al. on cancer patients, loading with magnesium sulfate before cisplatin administration significantly reduced its nephrotoxicity.⁵ Martin et al. studied 41 patients in three groups (without any magnesium supplements, intravenous magnesium

and oral magnesium supplementation) and indicated that number of patients with nephrotoxicity induced by cisplatin was decreased in recipients of sulfate magnesium either oral or intravenous.¹⁸ Similarly, Hirea et al., compared serum creatinine changes in two groups of patients receiving cisplatin with and without magnesium sulfate and observed that supplementation with magnesium could be efficacious in preventing cisplatin-induced nephrotoxicity.¹⁷ On the other hand, studies on wistar rat have shown that magnesium sulfate supplements did not reduce cisplatin-induced nephrotoxicity. Ashrafi et al., studied 29 rats in 3 groups who received 20, 80, and 200 mg/kg magnesium sulfate, and the fourth group who received only normal saline. They found that low doses of magnesium supplementation could not prevent the occurrence of nephrotoxicity.¹⁹ Soltani et al., evaluated the effect of magnesium on cisplatin-induced nephrotoxicity in normal and streptozosin-induced diabetic rats. The results showed that magnesium supplements had no protective effect on cisplatin- nephrotoxicity in diabetic and non-diabetic rats.²⁰ In our study, the absolute and relative risk of nephrotoxicity in the group of patients receiving hydration and magnesium sulfate together was higher than the group with hydration alone, and thus no protective role for magnesium was defined.

Meanwhile, the concentration of potassium in group 1 was significantly reduced. This could be due to the reduced intake of potassium, gastrointestinal side effects of cisplatin and also due to the electrolyte imbalance caused by cisplatin-induced nephrotoxicity. Hypokalemia as a well-known and common side effect of cisplatin is reported in a number of studies (21-23).

The main goal of this study was to investigate nephrotoxicity induced by cisplatin with and without magnesium hydration. Although, this study did not show the preventive effect of magnesium on cisplatin-induced nephrotoxicity, there are some animal studies that have similar results to our results.

The comparison of mean values of GFR after treatment did not show any significant difference between the two groups which was probably due to small number of patients. This means that the group of patients with unchanged GFR (a drop of less than 50% in GFR) have compensated mean values of GFR, despite the presence of reduced GFR in group of patients who showed the "nephrotoxicity index" according to the definition provided in this study.

The mechanisms proposed for the transfer of cisplatin in kidney tubules, including active cisplatin transport system, as well as the re-absorption of cisplatin by an organic cationic transporter 2 (OCT2) (up regulation of OCT2 in Mg-deficient diet) have not been described clearly.⁴

Conclusion

According to the results of this study, risk of nephrotoxicity in patients receiving cisplatin along with hydration and magnesium sulfate was more than patients who received hydration alone. Therefore the protective role of magnesium sulfate could not be proved and further

studies with larger population are recommended to better clarify these effects

Conflict of Interest: None declared.

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