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Evaluation of Intravenous Magnesium Supplementation as Prophylaxis for Cisplatin-induced Hypomagnesemia

Kazem Anvari, Mehdi Sielanian Toussi♦, Marjaneh Mirsadraee

Department of Radiotherapy and Oncology, Cancer Research Center, Omid Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

Abstract

Background: We assessed the effects of cisplatin-based chemotherapy, magnesium supplementation, probable contributory factors such as cisplatin cumulative dose and dose per cycle on serum magnesium levels.

Methods: In this prospective randomized study, serum magnesium levels of 59 newly diagnosed adult patients receiving cisplatin-based chemotherapy were studied. The patients were randomly allocated to receive magnesium supplementation at a dose of 5 g IV per cycle (n=31) or to a control group (n=28). Serum magnesium levels <1.8 mg/dL were considered to indicate hypomagnesemia.

Results: The decrease in mean magnesium levels with continuing chemotherapy courses was significant in both groups with a more prominent decrease in the control group. In courses 4 and 5, mean magnesium levels were significantly higher among those who received magnesium supplementation than in the control group.

Thirty patients (50.8%) had at least one incident of hypomagnesemia after beginning chemotherapy. All hypomagnesemia incidents were mild (mean 1.69, range; 1.52-1.79 mg/dL). Hypomagnesemia was more frequent in the control group (38.7% vs. 60.7%, *P*=0.09). Although age and sex had no significant effect on the incidence of hypomagnesemia, more hypomagnesemia incidents were observed in patients who received cisplatin in a single loading dose than in those who received the drug in divided doses for each cycle (71.4% % vs. 42.9%, *P*=0.056).

Conclusion: Magnesium supplementation at a dose of 5 g per cycle partially compensated for cisplatin- induced magnesium loss. Monitoring magnesium levels and magnesium supplementation is warranted, especially for those undergoing protracted courses of cisplatin-based chemotherapy. Patients who receive the drug in a single loading dose might be more prone to magnesium loss.

Keywords: Cisplatin, Magnesium, Hypomagnesemia, Magnesium supplementation

♦Corresponding Author:
Mehdi Sielanian Toussi, Department of Radiotherapy and Oncology, Cancer Research Center, Omid Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
Tel:/Fax: +98- 511-8461518
Email: silanianm@mums.ac.ir

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Table 1. Comparison of mean magnesium levels between chemotherapy courses 1 (baseline) and 5 in each group.

Groups	Course 1 (baseline)		Course 5		
	Number of tests	Mean Mg±1SD* (mg/dL)	Number of tests	Mean Mg±1SD (mg/dL)	T-test *P* value
Control	28	2.19±0.22	16	1.82±0.16	<0.001
Mg supplementation	31	2.19±0.32	16	1.96±0.28	0.072

* Standard deviation

Introduction

Cisplatin, a widely used antineoplastic agent, can cause hypomagnesemia because of renal tubular damage and urinary magnesium wasting.[1, 2] Cisplatin-induced hypomagnesemia has been reported in a significant percentage of patients.[3-6] Hypomagnesemia may be detected during treatment and can persist months or years after the end of therapy due to renal tubular inadequacy in magnesium reabsorbsion.[7-10]

The early clinical features of hypomagnesaemia include loss of appetite, nausea, vomiting and fatigue. These symptoms are often attributed to therapy for the underlying disease. As the decline in magnesium level continues, numbness, tingling, muscle cramps, seizures and cardiac arrhythmia may occur. Severe hypocalcemia and hypokalemia can develop after severe hypomagnesemia.[11] Most cases of chemotherapy-induced hypomagnesemia are mild and remain undiagnosed; however, severe clinical manifestations have been reported.[12-14]

The results of several controlled trials indicate that magnesium supplementation can reduce the incidence of hypomagnesemia in patients receiving cisplatin-based chemotherapy.[3, 5, 15] However, the dose of magnesium supplementation and the magnitude of its clinical benefit remain uncertain. The doses used for magnesium supplementation vary widely.[16] Magnesium is a predominantly intracellular element and less than 2% is present in the extracellular fluid compartment. As a result, magnesium wasting may occur despite the presence of normal plasma magnesium levels.[7, 17]

In this randomized controlled study, we assessed the incidence of hypomagnesemia and the prophylactic effect of magnesium supplementation at a fixed dose of 5 g in adult patients who received cisplatin-based chemotherapy in our department.

Materials and Methods

This prospective randomized clinical trial was conducted by the Cancer Research Center at the Oncology Department of Omid Hospital, which is affiliated with Mashhad University of Medical Sciences. Patients were enrolled if they were newly diagnosed cases with a life expectancy of more than 6 months and received cisplatin-based chemotherapy at Omid Hospital between November 2008 and February 2010. Exclusion criteria were a history of myocardial infarction, abnormal renal function (CrCl <60 mL/min) and age younger than 15.

The following data were collected: age, sex, diagnosis, chemotherapy regimen, cisplatin dose per cycle and cisplatin administration method in each cycle (divided dose over 3-5 days or single loading dose). Magnesium levels were measured before each treatment course, from course 1 (baseline) through course 5, using the Xylidyl blue method (Pars Azmoon kit, karaj, Iran). Magnesium levels less than 1.8 mg/dL were considered hypomagnesemia. The effects of four chemotherapy courses on serum magnesium level were evaluated. Patients were randomly selected to receive either magnesium supplementation during pretreatment hydration at a dose of 5 g, or to act as controls and receive no magnesium. Written consent was obtained from all participants. The project received approval from the Ethical Board, Deputy of Research, Mashhad University of Medical Sciences.

All patients, based on cisplatin dosage per day, were prehydrated with 1-3 L of 5% dextrose plus KCl 20 meq/L and NaCl 30 meq/L. The drug was diluted in normal saline containing 12.5 to 25 g of mannitol and infused at a rate of 1 mg/min. Patients were posthydrated with 1-2 L of the above solution. For patients who were supplemented with magnesium, the drug was

Table 2. Comparison of mean magnesium levels in different treatment courses between the two groups.

Chemo course	Mg supplementation		Control		
	n	Mean Mg ± 1 SD (mg/dL)	n	Mean Mg ± 1 SD (mg/dL)	T-test *P* value
Course 1, baseline*	31	2.14 ± 0.30	28	2.18 ± 0.31	0.58
Course 2	29	2.09 ± 0.25	28	2.06 ± 0.25	0.67
Course 3	30	2.05 ± 0.30	27	1.95 ± 0.24	0.16
Course 4	27	2.03 ± 0.25	23	1.87 ± 0.16	< 0.01
Course 5	16	1.97 ± 0.28	16	1.79 ± 0.16	0.03

* Magnesium levels prior to chemotherapy.

diluted in the prehydrating solution in a single day or in divided doses based on the cisplatin administration method. Magnesium was administered after the patient was examined for patellar reflex and breath rate of 16 breaths/min or more. The patients were monitored at 15 min intervals for signs and symptoms of magnesium intoxication, which included dizziness and depressed respiratory rate.

Statistical analysis

The data were analyzed statistically with SPSS version 11. Independent-sample t-tests were used to compare mean magnesium levels between groups, and intergroup variations in mean magnesium levels were assessed with paired-sample t-tests. Simple error bars were used to indicate the distribution of mean magnesium levels representing one standard deviation within consecutive treatment courses. The incidence of hypomagnesemia in different groups was compared with the chi-squared test. We considered a *P* value less than 0.05 as significant.

Results

A total of 59 patients (36 men, 23 women) with a median age of 59 years (range: 16-80) were evaluated. The median number of chemotherapy courses was five (range: 3-6) and the cisplatin dose per cycle was between 80 and 100 mg/m2. In 45 patients, the drug was given in divided doses, and in 14 patients it was given as a single-day dose. The magnesium supplementation and control groups consisted of 31 and 28 patients, respectively. We observed no case of magnesium intoxication in the supplementation group. There were no statistically significant differences in the distribution of variables in the magnesium supplementation and control group, including sex (male: 51.6% vs. 71.4%, *P*=0.12), age (<50; 48.4% vs. 51.8%, *P* value: 0.64) and cisplatin administration method (single loading dose: 29% vs. 17.9%, *P* value 0.31). Chemotherapy regimens included cisplatin +5-FU (n=34), cisplatin + doxorubicin (n=7), cisplatin + etoposide + bleomycine (n=9), cisplatin + etoposide (n=5) and the remaining 4 patients received other cisplatin-based regimens. Besides cisplatin, none of the other prescribed chemotherapeutic agents had known effects on serum magnesium levels. The recorded diagnoses were as follows: esophageal and gastric malignancies (n=27), germ cell malignancies (n=10), osteosarcoma (n=7), head and neck malignancies (n=6), bladder carcinoma (n=4), lung carcinoma (n=3) and other malignancies (n=2).

A total of 277 magnesium measurements were obtained. A gradual decline in mean magnesium levels in most successive chemotherapy courses was noted in both the control and magnesium supplementation groups. However, the decrease in mean magnesium levels was greater in the control group (Figure 1). In the magnesium supplementation group, mean magnesium level in course 5 (after receiving four chemotherapy courses) was lower than at baseline, although the difference was not statistically significant. In the control group, there was a significant difference in mean magnesium levels between baseline and course five (Table 1).

Mean magnesium levels in the magnesium supplementation and the control groups were

Table 3. The incidence of hypomagnesemia at any time after prescribing cisplatin-based chemotherapy in the study groups.

Group	Total number	Cases with hypomagnesemia n (%)	Chi-squared *P* value
Magnesium supply			
Yes	31	12 (38.7)	
No	28	17 (60.7)	0.09
Sex			
Male	36	18 (50.0)	
Female	23	11 (47.8)	0.87
Age			
<50	30	15 (50.0)	
⩾50	29	14 (48.2)	0.69
Cisplatin administration			
Divided dose	45	19 (42.9)	
Single day	14	10 (71.4)	0.056

compared for each treatment course (Table 2). There was no significant difference in mean magnesium level between the two groups for chemotherapy courses 1 (baseline) through 3. However, the difference became significant in courses 4 and 5. This finding emphasized a greater decrease in the mean magnesium level in the control group as chemotherapy progressed.

Before cisplatin-based chemotherapy, the incidence of hypomagnesemia in the control and magnesium supplementation groups was 2 out of 28 (7.1%) and 5 out of 31 (16.1%), respectively. The incidence of hypomagnesemia in the two groups at any time after starting chemotherapy is presented in Table 3. Overall, 29 (49.1%) patients had hypomagnesemia. The degree of hypomagnesemia was mild in all cases (mean 1.69, range: 1.52-1.79 mg/dL). Only six patients (10.1%), two from the magnesium supplementation group and four from the control group, had magnesium levels less than 1.6 mg/dL at any time after chemotherapy. Although, more patients in the control group had at least one hypomagnesemia incident, the difference between groups did not reach a statistical significance (Table 3). Among patients receiving cisplatin in a single-loaded dose (including all five cases in the control group), hypomagnesaemia was more frequent than among patients who were given this drug in divided doses (Table 3).

Discussion

We found a gradual decline in the mean magnesium levels as cisplatin-based chemotherapy progressed in both the magnesium supplementation and control groups, with a greater decrease in the latter group. In accordance with other studies,[4, 18] this finding confirms the inverse correlation between cumulative cisplatin doses and magnesium levels. In previous studies, the reported incidence of cisplatin-induced hypomagnesemia varied between 40% and 90%.[2-5, 15] As in our patients, in most other trials, hypomagnesemia was mild and clinically asymptomatic. However, many early hypomagnesemia-related symptoms such as fatigue, irritability and loss of appetite are nonspecific, so the problem can remain undiagnosed.[4, 5,19]

Magnesium is mainly an intracellular cation of which less than 2% is located in extracellular fluid. About 60% of the total body magnesium content is present in bones, with approximately 38% in muscles and other soft tissues.[7] Therefore, serum magnesium level is not a reliable indicator of total body magnesium stores. In other words, magnesium loss may occur without a significant change in serum magnesium level. It might be a better approach to evaluate the magnitude of magnesium loss by measuring magnesium levels in bone or muscle before and after cisplatin-based chemotherapy. In a study by Lajer of patients receiving cisplatin-based chemotherapy, a 15% decline in muscle magnesium and a 10% reduction

in muscle potassium (K) were found. Depletion in muscle K accompanied by magnesium loss can contribute to muscle fatigue in these patients. In that study, plasma magnesium and plasma K levels were not reliable predictors of muscle magnesium and muscle potassium levels, respectively.[20]

Although it was not statistically significant, the incidence of hypomagnesemia was considerably higher in patients who received cisplatin as single-loaded doses than in patients who received divided doses in each cycle. This is a finding that should be validated by further studies.

Conclusion

The effect of magnesium supplementation to compensate for cisplatin-induced magnesium loss has been validated in different studies. Although most incidences of hypomagnesemia were mild and their clinical significance has not been clearly elucidated, the decrease in mean magnesium levels reflects total body magnesium loss and might contribute to some subtle symptoms such as fatigue. In our study, although magnesium supplementation at a dose of 5 g per cycle partially compensated for cisplatin-induced magnesium loss, the decline in magnesium levels as chemotherapy progressed was still evident. This finding may suggest the need for an even higher dose of magnesium supplementation for complete compensation.

Given the safety of magnesium administration, it seems reasonable to consider magnesium supplementation in patients who receive cisplatin-based chemotherapy, particularly for those receiving protracted chemotherapy courses. This study suggests that patients who receive cisplatin as a single-loaded dose in each cycle might be more prone to magnesium loss.

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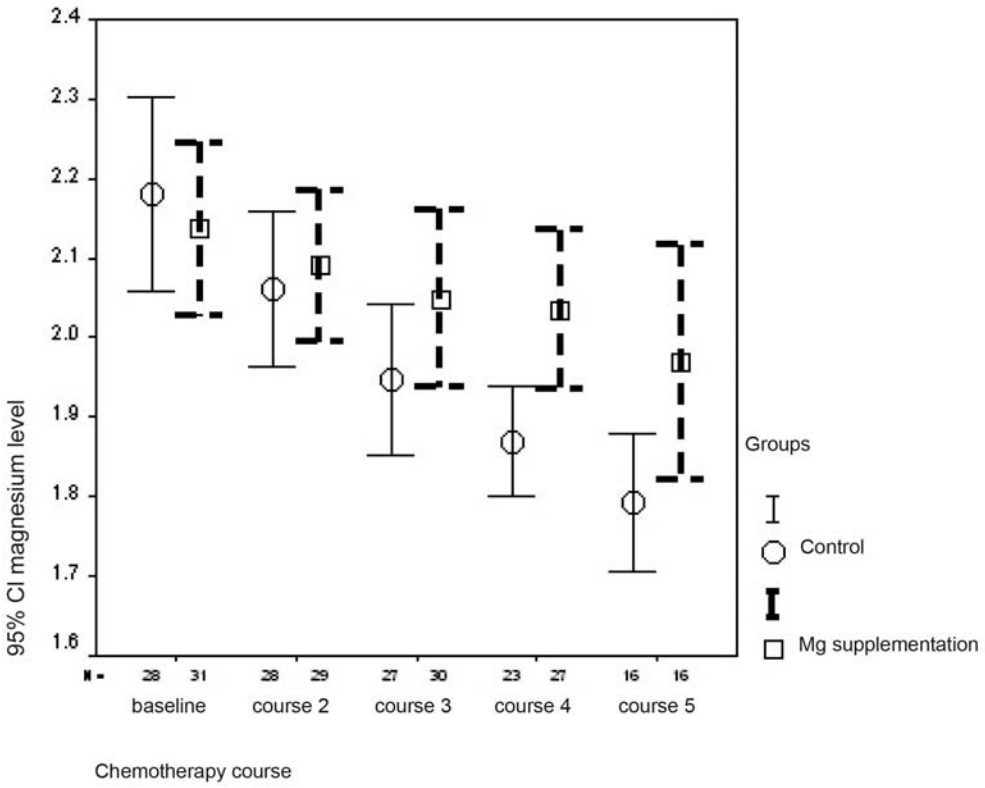

Figure 1. Mean magnesium levels before each chemotherapy course in the control and magnesium supplementation groups.

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