



Effect of Oral Magnesium Oxide Supplementation on Cisplatin-Induced Hypomagnesemia in Cancer Patients: A Randomized Controlled Trial

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Abstract

Background: Hypomagnesaemia is one of the main side effects of cisplatin-based chemotherapy regimens in cancer patients. The aim of the current investigation was to evaluate the effect of oral magnesium oxide (MgO) supplementation on cisplatin-induced hypomagnesemia.

Methods: This parallel-randomized controlled, open label trial was conducted in a hospital of Iran University of Medical Sciences in Tehran between December 2009 and May 2011. Participants were 69 adult patients with newly diagnosed non-leukemia neoplasms candidate for starting cisplatin-based chemotherapy. Oral MgO supplement according to cisplatin dose (500 mg MgO per 50 mg/m² of cisplatin) as 2-3 divided daily doses was started after completion of each chemotherapy cycle and continued to the next cycle for the intervention group. Patients in the control group did not receive any supplementation. Serum magnesium (Mg) was measured before each chemotherapy cycle. The main outcome was measuring serum Mg change and hypomagnesaemia rate during chemotherapy treatment.

Results: Sixty-two participants (31 intervention- 31 controls) enrolled into the study. Serum Mg levels showed significant difference between the two groups ($P=0.01$). There was a significant decrease in serum Mg of the control group ($P=0.001$). At the end of follow-up period prevalence of hypomagnesaemia in the intervention group was 10.7% versus 23.1% in the control group.

Conclusion: Continuously oral supplementation with MgO according to cisplatin dose (500 mg MgO per 50 mg/m² cisplatin) as 2-3 divided daily doses at rest days between chemotherapy cycles reduces the decline in serum Mg levels and also the prevalence of hypomagnesaemia in cancer patients.

Keywords: Cisplatin, Cancer, Hypomagnesaemia, Magnesium oxide, Magnesium

Introduction

Hypomagnesaemia is one of the well-known and common side effects of cisplatin that was first reported in cancer patients about three decades ago (1, 2). Magnesium (Mg) is the second most abundant intracellular cation in the human body. It is an essential co-factor for many enzymes involved in cellular metabolic pathways (3).

Although Mg homeostasis is regulated by intestinal absorption and renal excretion (4, 5), the kidney has the main role in the regulation of serum Mg concentration. Cisplatin as a part of some chemotherapy regimens causes renal tubular necrosis resulting in decreased tubular reabsorption of Mg (4-12).

Prevalence of cisplatin-induced hypomagnesaemia in these patients is between 29 to 100% (1, 7, 13-21). Incidence and severity of hypomagnesaemia depend on cumulative doses of cisplatin, chemotherapy cycles and periods of cisplatin administration (13, 16-18, 22-24). Mg deficiency can cause neurological-muscle disorders, electrocardiographic changes, mental disorders, electrolyte disturbances and even sudden death because of tetany or heart attack (14, 15, 19, 25-28).

The first Mg supplementation study in cancer patients receiving cisplatin-based regimen was done in 1982 (28). After that several interventional investigations in this area reported various results; positive effects (29-34), or no effects of oral or intravenous Mg supplementation (14, 17, 35). Although most studies have shown that supplementation with different doses of Mg salts could reduce or prevent hypomagnesaemia, but still there is no certain guideline; a guideline that clearly determines the best amount, type and duration of Mg salts supplementation according to cisplatin doses to attain optimum effect.

In Iran, we have only accessed to magnesium oxide (MgO) tablet for oral Mg supplementation to prevent or treatment of hypomagnesaemia therefore this study was designed to find out its effect on cisplatin-induced hypomagnesaemia in our patients. In this investigation, the effect of MgO according to cisplatin dose was evaluated on the cisplatin-induced hypomagnesaemia and serum Mg changes in cancer patients.

Materials and Methods

Subjects

This study was performed between December 2009 and May 2011 in Oncology Ward of *Rasoul-e-Akram* Hospital of Iran University of Medical Sciences (IUMS), Tehran, Iran. Adult patients (≥ 16 y/o) could be participated in the study if they had newly diagnosed non-leukemia neoplasm and were scheduled for starting cisplatin-based chemotherapy regimens in six cycles, were not suffering from hypomagnesaemia, renal failure and alcoholism and were not using diuretics, aminoglycosides, cyclosporine, amphotericin B and Mg-

containing medicines and supplements. Exclusion criteria were death before the end of intervention or discontinuing intake of MgO supplement.

To detect the mean difference of MgO supplement with a standardized difference of moderate ($SD=0.5$) between two groups, considering type one error of 0.05 and power of 80%, we calculated 30 subjects per group. Considering loss of patients in follow-up period about 10%, 34 patients were determined for each group. Finally, 69 patients allocated to the intervention and the control groups with minimization method, because they needed to match according to cisplatin dose and number of cycles.

Study design

In this open-label parallel study, patients in the intervention group received oral MgO supplement (250 mg tablet-21Century Health Care, Inc., USA, equal to 150 mg Mg) according to Cisplatin dose: 500 mg MgO for each 50 mg/m² of cisplatin, as 2-3 divided daily doses after completion of each chemotherapy cycle continuing to the next cycle and also 2 or 3 wk after the final cycle. The control group did not receive any supplementation as placebo during treatment. The supplementation method was a combination design of Bodnar, Martin and Hodgkinson studies (13, 29, 36).

The study protocol was approved by the Ethics Committee of IUMS and the written informed consents were obtained from all participants of the study. This clinical trial was registered in Iranian Registry of Clinical Trials (IRCT) with registration code of: IRCT201112048299N1.

Biochemical measurements

Patients' biochemical indices were measured before starting each chemotherapy cycle using BT 3000 automated analyzer. UV method was used for determining serum Phosphorus (P) (mg/dl). Ion selection method was used for measuring serum Sodium (Na) (mEq/l) and Potassium (K) (mEq/l). Serum Mg (mg/dl), Calcium (Ca) (mg/dl) and Creatinine (Cr) (mg/dl) levels were measured by Xylidyl Blue, Arsenazo and Jaff methods, respectively.

According to our laboratory assessment, serum Mg concentration less than 1.8 mg/dl was considered as hypomagnesaemia state.

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL, USA) for windows, version 15. We used mean and standard deviation (SD) to describe continuous variables and number and percentage for describing categorical variables. Categorical variables were examined using Chi-square test. We used student *t*-test for comparing means between the two groups. To compare the mean difference of MgO supplement across the two groups during times, we used repeated measurement of analysis

of variance. All statistical tests were two-tailed, with a significance level of 0.05.

Results

Study population

Totally, 62 out of 69 participants completed the study; three patients withdrew from the study because of death, three participants withdrew due to changing their treatment place and one for inability to tolerate oral MgO due to intense nausea. Four patients reported grade1 (mild) diarrhea (36) just at the beginning of their supplementation. Demographic and clinical data of 62 patients are shown in Table 1.

Table 1: Demographic and general characteristic of the patients in trial

Variables	Intervention group / (n=31)	Control group / (n=31)
Sex, n (%)		
Male	19 (61.3)	24 (77.4)
Female	12 (38.7)	7 (22.6)
Age (year) (mean±SD)	59.6±10.6	51.4±12.9
Cancer Type, n (%)		
Ampula of Vater carcinoma	0 (0)	1 (3.2)
Breast	2 (6.5)	0 (0)
CUP (Carcinoma of Unknown Primary)	2 (6.5)	0 (0)
Esophageal cancer	1(3.2)	4 (12.9)
Gastric cancer	14 (45.2)	10 (32.3)
Head and Neck cancer	1 (3.2)	2 (6.5)
Hepatocellular carcinoma	2 (6.5)	0 (0)
Lymphoma (NHL, HL)	1 (3.2)	2 (6.5)
Lung cancer (SCLC, NSCLC)	1 (3.2)	6 (19.4)
Melanoma	1 (3.2)	0 (0)
NET (Neuro Endocrine Tumor)	0 (0)	1(3.2)
Osteosarcoma	0 (0)	3 (9.7)
Ovarian cancer	6 (19.4)	1 (3.2)
Pleural Mesotelioma	0 (0)	1 (3.2)
Stage at diagnosis, n (%)		
II	1 (3.2)	5 (16.1)
III	18 (58.1)	12 (38.7)
IV	12 (38.7)	14 (45.2)
Magnesium Oxide dose, n (%)		
500 mg/day (equal to 300 mg Mg)	2 (6.5)	
1000 mg/day (equal to 600 mg Mg)	28 (90.3)	
1500 mg/day (equal to 900 mg Mg)	1 (3.2)	
Cumulative dose of cisplatin (mg/m²)	433.5±90.3	436.4±84.1
Treatment duration (month)	4.8±0.6	4.9±0.7
Cisplatin dose, n (%)		
≤ 50 mg/m ²	2 (6.5)	2
51-100 mg/m ²	28 (90.3)	28
>100 mg/m ²	1 (3.2)	1

There were no significant differences in age, sex, treatment duration and cisplatin cumulative doses between the two groups and also in baseline serum Mg and other biochemical indices.

Changes of serum Mg during chemotherapy

We found significant differences in serum Mg levels between the two groups during six chemotherapy cycles ($P=0.01$) (Table 2). In the control group decreasing Mg level during period were significant ($P=0.001$). We also compared mean differences of Mg levels between two groups in each cycle; the differences were significant from fifth cycle until the end of follow-up period ($P=0.001$, $P=0.002$ and $P=0.007$ respectively) (Fig. 1).

Hypomagnesaemia

Percentage of hypomagnesaemia during treatment in patients receiving six chemotherapy cycle protocol is shown in Fig. 2. In these patients, prevalence of hypomagnesaemia in the intervention group was 0% at base line (before the first cycle) and 10.7% at the end of the treatment cycle, whereas it increased from 0% to 23.1% in the control group. The most hypomagnesaemia rate belonged to cycle six and the peak of it was seen from cycle four to six. All hypomagnesaemia patients in both group had grade 1 hypomagnesaemia (37), except one patient in the control group who had grade 2 (37)

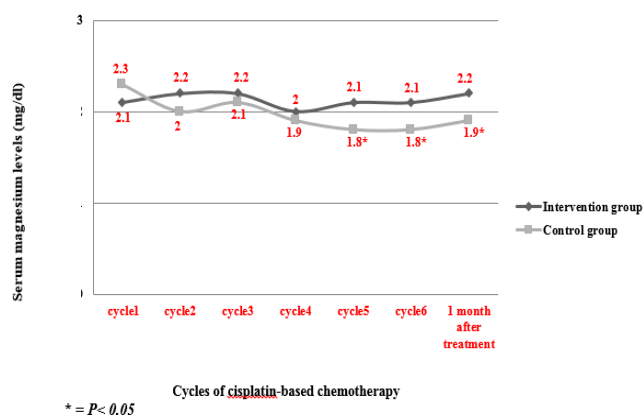


Fig. 1: Trend of serum magnesium levels (mean) during cycles of cisplatin-based chemotherapy in cancer patients

Other serum electrolytes changes

Serum K levels of patients showed significant differences between the two groups ($P=0.03$) (Table 2). In the control group there was a significant decrease of potassium level during periods ($P=0.02$). Other serum biochemical indices did not differ significantly between two groups.

Discussion

Cis-diamminedichloro-platinum (II) (CDDP, cisplatin) is an important cytotoxic agent that has been used as part of some chemotherapeutic regimens since 1973. Hypomagnesaemia has been one of the main side effects of cisplatin (1, 7, 8, 14-16, 19, 20, 22, 24, 38, 39). The aim of this clinical study was to assess the effects of oral magnesium oxide supplementation according to cisplatin dose on serum Mg changes and cisplatin-induced hypomagnesaemia in cancer patients.

Our study revealed the significant effect of oral magnesium oxide supplementation according to cisplatin dose (500 mg/day MgO per each 50 mg/m² dose of cisplatin (equal to 300-900 mg Mg)) on reducing the decline in serum magnesium levels after the six cycles of cisplatin-based chemotherapy. MgO consumption based on the schedule also resulted in lower prevalence of hypomagnesaemia in supplemented group than control group.

These results are similar to a study on epithelial ovarian cancer patients receiving Paclitaxel - cisplatin (75mg/m²) regimen every three week for six cycles: serum Mg in placebo group (n=21) was significantly lower than intervention group (n=20) who were supplemented prehydration with intravenous 5g magnesium sulfate (MgSo₄) (equal to 500 mg Mg) before each cycle of chemotherapy and 500 mg oral magnesium subcarbonate supplementation three times per day (equal to 370.5 mg Mg) between cycles of chemotherapy (36). Compared to Bodnar and et al. study (36), we prescribed higher Mg dose in the form of magnesium oxide whereas getting similar results without considering intravenous supplementation.

Table 2: Mean serum biochemical levels of two groups on 6 cycles of cisplatin chemotherapy

Variables	Intervention group (n=31)							Control group (n=31)							Within P-value	Between P-value
	Cycles of chemotherapy						One month after treatment	Cycles of chemotherapy						One month after treatment		
	1	2	3	4	5	6		1	2	3	4	5	6			
Serum Mg	2.1±0.3	2.2±0.4	2.2±0.4	2.0±0.3	2.1±0.3	2.1±0.4	2.2±0.4	2.3±0.3	2.0±0.3	2.1±0.4	1.9±0.3	1.8±0.3	1.8±0.3	1.9±0.3	0.000*	0.01**
Serum K	4.3±0.3	4.3±0.3	4.2±0.4	4.3±0.5	4.3±0.4	4.2±0.3	4.2±0.2	4.4±0.4	4.4±0.4	4.6±0.5	4.5±0.4	4.4±0.5	4.4±0.4	4.2±0.5	0.02*	0.03**
Serum Ca	8.8±0.6	8.8±0.6	8.8±0.7	8.8±0.6	8.9±0.8	8.5±0.7	8.7±0.6	8.8±0.9	8.9±0.8	8.8±0.6	8.7±0.6	8.9±0.6	8.9±0.6	8.6±0.7	0.02*	0.74
Serum Na	141.1±2.7	141.1±2.6	140.4±2.6	138.6±4.7	139.7±2.3	139.5±3.0	140.4±2.2	139.9±4.3	138.3±4.1	138.6±4.2	139.5±3.2	138.9±4.5	138.7±3.9	138.5±3.1	0.07	0.08
Serum P	3.2±0.8	3.2±0.7	3.0±0.9	3.1±0.9	3.2±0.5	3.3±0.6	3.4±0.6	3.1±0.6	3.5±0.8	3.6±0.8	3.6±0.9	3.6±0.7	3.3±0.9	3.4±0.8	0.21	0.06
Creatinine	1.1±0.2	1.1±0.2	1.1±0.3	1.1±0.2	1.2±0.2	1.1±0.2	1.1±0.2	1.0±0.3	1.1±0.3	1.1±0.3	1.0±0.2	1.1±0.2	1.0±0.3	1.1±0.3	0.26	0.25

†Data are presented as means ± standard deviation.

* Significant difference within groups ($P < 0.05$).

** Significant difference between groups ($P < 0.05$).

Mg: Magnesium (mg/dl); K: Potassium (mEq/l); Ca: Calcium (mg/dl); Na: Sodium (mEq/l); P: Phosphorous (mg/dl).

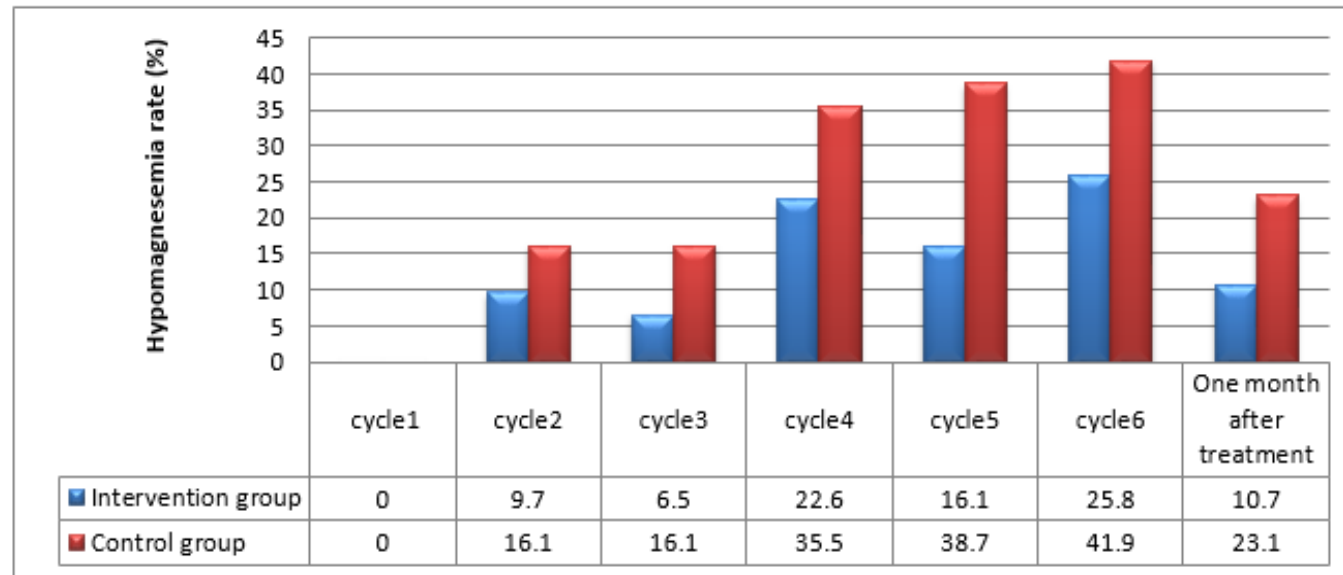


Fig. 2: Percentage of hypomagnesaemia during cycles of cisplatin-based chemotherapy in cancer patients

Another randomized study on two groups of head and neck cancer patients receiving 100 mg/m² cisplatin every three to four wk and 10 mEq (5 mmol) oral magnesium aspartate hydrochloride (MgAH) three times per day (equal to 365.1 mg Mg) continuously (n=13), or 5 mmol three times per day intermittently at the time of decreasing serum Mg level (≤ 1.4 mg/dl) (n=10), showed no statistically significant difference between two groups but by the cycle 3 all patients in the control group needed Mg supplementation (17).

The number of cycles and cumulative doses of cisplatin were reported as the major contributing factors for the severity of hypomagnesaemia (9, 14-17, 20, 29, 40). We found the significance differences after the fourth cycle whereas Martin and colleagues (29) demonstrated significantly higher serum Mg levels in both oral and intravenous Mg supplemented cancer patients from the second cycle or from the third cycle respectively than their control group. Although he suggested that most patients who received cumulative doses of cisplatin more than 400 mg/m² will developed some degree of hypomagnesaemia, in our study hypomagnesemia occurred after first cycle whereas most cumulative doses of cisplatin more than 400 mg/m² belonged to fifth and sixth cycles where there were the higher rates of hypomagnesaemia in control group.

Absorption and bioavailability of magnesium salts are other subjects; organic forms of Mg, especially Mg gluconate, are better sources of Mg than inorganic salts (41). A randomized trial on testicular cancer patients receiving 100 mg/m² (3 weekly) (four cycles of treatment) cisplatin showed that patients supplemented with intravenous 40 mmol MgSo₄ (equal to 986 mg Mg) following cisplatin administration and 10 mmol oral magnesium citrate three times per day (equal to 2166 mg Mg) on rest days (n=8) had significant higher serum magnesium concentrations than the unsupplemented group (n=9) (31). Their higher Mg supplementation dose or more bioavailability of magnesium citrate than magnesium oxide may be the cause of significant higher serum magnesium concentration in their intervention group.

Martin and colleagues (29) concluded that 12 mmol of intravenous MgSo₄ (equal to 295 mg Mg) in prehydration state or 21.45 mmol of oral daily magnesium pidolate (equal to 511 mg Mg) for 20 days were effective in hypomagnesaemia prevention for 100 mg/m² cisplatin dose. Incidence of hypomagnesaemia (serum Mg <1.76 mg/dl) after the fourth cycle of cisplatin in their intravenous magnesium arm and oral magnesium arm were 33% and 44% respectively while it was 90% in unsupplemented patients. In comparison, the prevalence of hypomagnesaemia at the fifth cycle of our trial that is equivalent to their forth cycle was 16.1% and 38.7% in the intervention and control groups respectively.

In a study, hypomagnesaemia was reported in 20% of patients receiving continuous oral MgAH (Moderate hypomagnesaemia <1.4 mg/dl) and in 30% of patients receiving intermittently oral MgAH (17).

Increasing urinary losses of Mg due to the effect of cisplatin on Mg reabsorption segments and tubular necrosis has been suggested as a main cause of cisplatin-induced hypomagnesemia (1, 3, 7-9, 14, 15, 20, 24, 34, 42). Severe diarrhea, low dietary magnesium intake and intestinal malabsorption may also potentiate hypomagnesaemia in these patients (43-45). Mg supplementation had beneficial effect on preventing renal tubular damage in cancer patients receiving cisplatin. In a study (36), serum creatinine levels during chemotherapy showed significant difference between supplemented and placebo groups. In the supplemented group, there was no significant difference in serum creatinine levels during treatment whereas in the placebo group it increased significantly during chemotherapy cycles (36). Serum creatinine levels showed no significant differences between the two groups of our patients receiving six-cycle chemotherapy protocol. In another investigation, serum creatinine levels showed no significant changes between groups receiving four cycles of treatment (31).

To the best of our knowledge, this clinical trial was the first study investigating the effect of MgO supplementation on cisplatin-induced hypomagnesaemia according to cisplatin dose in our coun-

try. Some of the limitations of the present study were no assessing of clinical manifestation of hypomagnesaemia and no measuring ability regarding amounts of dietary magnesium intakes and urinary magnesium excretions of patients that should be consider in future similar investigations.

Conclusion

Continuously oral supplementation with magnesium oxide as 2-3 divided daily doses according to cisplatin dose (500 mg MgO per 50 mg/m² cisplatin) starting after completion of each chemotherapy cycle and continued to the next cycle (at rest days between chemotherapy cycles) reduces the decline in serum Mg levels and also the prevalence of hypomagnesaemia in cancer patients.

Future clinical trials should be designed for better understanding of the efficacy and optimum level of other magnesium salts with different bioavailability as oral supplementation (according to cisplatin dose) on hypomagnesaemia rate in patients under different chemotherapy cycles. More investigations are needed to establish a useful guideline for Mg supplementation in patients receiving cisplatin-based chemotherapy.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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