Original Article

Magnesium Supplementation May Not Be Protective against Carboplatin-Induced Nephrotoxicity But May Be Beneficial for Children Suffering Malignancies: A Randomized Clinical Trial

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Abstract

Background: Magnesium oxide may be effective in renal insufficiency prevention after carboplatin therapy. We have evaluated magnesium oxide impression on the serum creatinine (Cr) and blood urea nitrogen (BUN) levels plus glomerular filtration rate (GFR) in cancerous children.

Materials and Methods: A group of children with different cancers ($n = 18$) was treated with 250 mg/day magnesium oxide supplementation (MOS) and compared with a matched placebo-treated group ($n = 18$). After 2 weeks, carboplatin chemotherapy started. We compared serum Cr, BUN, and GFR values before and 3 and 7 days post intervention.

Results: Serum Cr and BUN were increased significantly 3 and 7 days after intervention in both the groups. Serum Cr and BUN were not statistically different between the MOS and placebo groups before the intervention and 3 or 7 days after carboplatin administration ($P > 0.05$). Three days after the intervention, the GFR reduced from 101.38 ± 14.67 to 90.11 ± 10.52 mL/min/1.73 m^2 in the MOS group. Furthermore, in the placebo group, 3 days after the intervention, the GFR was reduced from 97.5 ± 9.71 to 92.33 ± 10.61 mL/min/1.73 m^2. Further, in the MOS group, after 7 days of the intervention, the GFR was reduced to 84.11 ± 12.47 mL/min/1.73 m^2. In the placebo group, after 7 days of the intervention, the GFR was diminished to 85.38 ± 10.66 mL/min/1.73 m^2 ($P = 0.371$).

Conclusion: The current study suggests that magnesium supplementation does not prevent carboplatin-induced nephrotoxicity in children with malignancies. Anyway, we propose magnesium oxide supplementation for this group of pediatrics because magnesium is an essential element for cell and tissue growth, maintenance, and metabolism.

Keywords: Carboplatin, magnesium, pediatrics, renal insufficiency

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Introduction

Although malignancies in children are rare, it is estimated that 10,000–15,000 new cases in the first and the second decades of life are diagnosed or occurred. Before reaching adulthood, 1/600 children die due to such malignancies.[1-3] An estimation for the United States population proposed that among pediatrics, approximately 11% of deaths expected to be due to pediatric cancers were in 2020.[4] Chemotherapy has been beneficial in the treatment of these malignancies

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and enhancement of 5-year survival. Anyhow, chemotherapy is associated with various complications.[5,6]

Platinum complexes are used efficiently and frequently in approximately 50% of cases of chemotherapies. Today, three FDA-approved platinum formulations are used essentially: cisplatin, carboplatin, and oxaliplatin. Routinely, oncologists prescribe cisplatin or carboplatin for children's malignancies.[7,8] Notable side effects of platinum formulations include nephrotoxicity, ototoxicity, neurotoxicity, cardiotoxicity, hemotoxicity, hepatotoxicity, and enterotoxicity. Cisplatin is a drug choice for patients suffering from neuroblastoma and osteosarcoma or brain tumors. Because of cisplatin neurotoxicity and nephrotoxicity, its less toxic analog, the carboplatin, has been introduced.[8,9]

Nowadays, carboplatin is the first-line therapeutic option for pediatric malignancies. Carboplatin is applicable for patients suffering germ cell,[10] neuroectodermal, and weak glioma tumors.[11] It is also for the management of neuroblastoma,[12] malignant mesenchymal tumor,[13] and Wilms' tumor.[14] The albuminuria, increased renal circulation, decreased glomerular filtration rate (GFR), or disturbed tubular function can occur during and after platinum drug administration time. Chemotherapy-induced nephrotoxicity is reversible, but renal insufficiency or progressive chronic renal failure is probable. Chronic and severe renal failures exert diverse clinical outcomes. Anyway, halting the therapy or decreasing the therapeutic dose could result in risk remission or malignancy promotion.[9,15]

Investigations reported the dose-dependent cisplatin-induced nephrotoxicity among 30%–40% of recipients. The consequences of cisplatin toxicity include hypomagnesemia and reduced GFR because of excretion from the kidney and damages to the proximal tubule and ascending limb of Henle.[9,15] Cisplatin acts via DNA damaging and inducing oxidative stress, mitochondrial dysfunction, disrupting the protein synthesis, and co-working with tumor necrosis factor to damage the tumor cells.[16]

Magnesium is involved in more than 600 biochemical reactions in the human body.[17,18] Its supplementation enhances the heart and skeletal muscle performance,[19] prevents depression,[20] plays a role in type 2 diabetes control,[21] and has the blood pressure-lowering effect.[22] Carboplatin therapy could result in hypomagnesemia and reduced GFR with less severity than cisplatin. High-dose carboplatin therapy is associated with glomerular dysfunction and hypomagnesemia with 0%–25% frequency in pediatrics. These are in addition to sporadic renal failure. Rarely, carboplatin induces renal failure after high-dose chemotherapies in children receiving autologous germ cell grafts. Cisplatin and carboplatin are administered frequently for different types of malignancies in children. Notable adverse events of cisplatin include nephrotoxicity, reduced GFR, and hypomagnesemia. Anyway, carboplatin also harbors these complications but with lower frequency. Although hydration is a proper approach for remediation of nephrotoxicity, it is not sufficient in most cases.[23,24]

In rats, hypomagnesemia could cause dehydration and upregulation of organic cation transporter (rOCT2). Magnesium protects against cisplatin-induced acute kidney injury by preventing platinum accumulation.[25,26] Consequently, platinum accumulation and its related dehydration could promote acute kidney injury. There are several studies on the nephroprotective effects of magnesium in cisplatin-administered patients. Anyhow, a few studies exist about such carboplatin treatment in pediatrics. We aimed to evaluate the protective impact of magnesium therapy against carboplatin-induced nephrotoxicity based on clinical laboratory findings.

Materials and Methods

It is a randomized control trial on children with various malignancies referred to Amirkabir Hospital of Arak city, Markazi Province center, Iran. Oncologic management and monitoring are done based on the standard guidelines. Studied children with malignancy were under precise and routine visiting in oncology department during study time. As the type of cancers was variable, specific related standard guidelines, including chemotherapy and radiotherapy, were done for each malignancy. Researchers made follow-up for occurring any adverse event or exclusion criteria during the study period. Malignancies included germ cell tumor, neuroblastoma, primary neuroectodermal tumor, Ewing sarcoma, rhabdomyosarcoma, and ovary tumor [Table 1]. We have evaluated all patients under carboplatin treatment based on oncology team decisions and current therapeutic guidelines.

We have evaluated all patients under carboplatin treatment based on oncology team decisions and current therapeutic guidelines. We have categorized participants into MOS and placebo groups using a random number generation tool in Excel software (Microsoft Excel Worksheet; 2019; Microsoft Co., USA), where each group included 18 individuals. Briefly, after visiting with the oncology subspecialist, we allocated a unique number to each child. For this simple randomization, we run the random number generation using the RAND function in Excel software in another parallel column and sort the random numbers in ascending format. We considered the first 18 numbers as the placebo group and the other 18 numbers as the MOS group. After that, the name of patients for each allocated number was extracted and awarded to the interventional oncologist for prescribing coded drugs: the placebo or magnesium oxide. If any child exited the study, a newly diagnosed case was included as the replacement. We included patients with a definitive diagnosis of cancer in the study.

Oncology team members did evaluations on the clinical signs and symptoms, tumor markers (alpha-fetoprotein or cancer antigen 125), immunocytochemistry, and fluorescence *in situ* hybridization test results for differential and definitive diagnosis. In addition, ultrasound, computed tomography scan, magnetic

Table 1: Demographic and general data of investigated individuals

Variable	Status	Groups	
		Magnesium supplemented (%)	Placebo (%)
Gender	Male	7 (38.89)	12 (66.67)
	Female	11 (6.1)	6 (33.33)
Carboplatin dose (mg/m^2)	400	2 (11.11)	5 (27.78)
	500	3 (16.67)	2 (11.11)
	560	10 (55.56)	11 (61.11)
	600	3 (16.67)	0
Types of malignancy	Germ cell tumor	5 (27.78)	4 (22.22)
	Neuroblastoma	4 (22.22)	6 (33.33)
	Primary neuroectodermal tumor	3 (16.67)	2 (11.11)
	Ewing sarcoma	2 (11.11)	2 (11.11)
	Rhabdomyosarcoma	3 (16.67)	4 (22.22)
	Ovary tumor	1 (5.56)	0
Malignancy involvement period (years), mean±SD		5.38±2.35	5.11±1.45

SD: Standard deviation

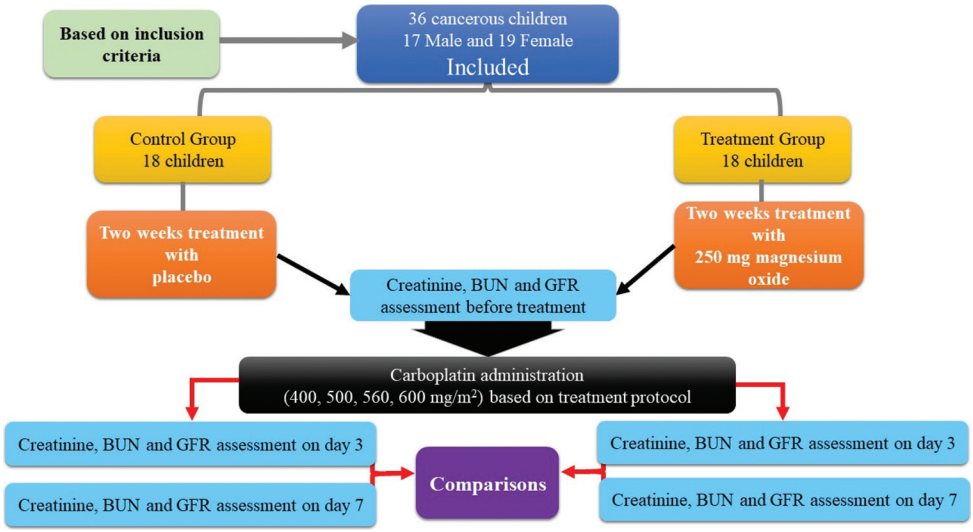

Figure 1: Study workflow diagram including selection, intervention, and comparison steps and assessed variables

resonance imaging, and positron emission tomography scan were the other diagnostic tools. Patients treated with different carboplatin doses based on the oncologist's prescription, including 400, 500, 560, or 600 mg/m^2 doses. Patients were included in or excluded from the study based on the defined criteria. Considered inclusion criteria were the age between 2 and 15 years, involvement with malignancy and hospitalization history in the oncology ward, treatment with carboplatin and not cisplatin, and no contraindication for magnesium reception. Exclusion criteria were GFR <30 mL/min or platinum drugs, nephrotoxic medications, antibiotics usage, and any history of hypersensitivity to carboplatin.

The MOS category received 250 mg/day magnesium oxide tablets (Jalinous Pharmaceutical Company, Iran) for 2 weeks before chemotherapy onset with carboplatin. The placebo group was treated with one tablet placebo (Jalinous Pharmaceutical Company, Iran) for 2 weeks before carboplatin reception. Serum creatinine (Cr), blood urea nitrogen (BUN) measurement, and GFR calculation were done before treatment and 3 and 7 days after intervention initiation for each patient in the mentioned groups. Serum BUN (Pars Azmoon, Iran) and Cr (Pars Azmoon, Iran) levels were assessed by an automated chemistry analyzer (BT 3000; Biotecnica Instruments S. p. A., Italy) and the clinical laboratory ward of the hospital. We calculated GFR values using the MDRD equation[27] online calculator developed by Dr. Andrew S. Levey (available on: https://www.mdcalc.com/mdrd-gfr-equation). Figure 1 depicts a brief scheme of the study workflow and investigated variables.

Ethical statement

All patients were under standard therapeutic regimens based on the approved guidelines prescribed by oncology subspecialists. There were no interventions except those prescribed by the specialist for each patient. There were no patients with magnesium formulation contraindication, and if it was potential, the patient became excluded from the

study. All patients and the parents were free to be included or excluded from the study without any obligation message or discussion. All guardants were informed about carboplatin complications and probable magnesium effects throughout the study time. After that, they certified their conformity and consent by signing the consent form. This study is confirmed by the research deputy of Arak University of Medical Sciences and the medical research ethics committee with registration No. IR.ARAKMU.REC.1398.086 and clinical trial code: IRCT20190619043948N1.

Statistical analysis

We used SPSS version 20 software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, version 20.0. Armonk, NY, USA: IBM Corp.) for statistical analysis. Mean ± standard deviation (SD) was compared with independent samples *t*-test to evaluate the probable effect of magnesium therapy on renal insufficiency or reduced function prevention.

Results

The mean ± SD of age was 7.5 ± 3.12 years in MOS and 7.61 ± 3.74 years in the placebo category (P = 0.924) [Table 1]. Table 1 contains the demographic, drug doses, type of malignancy, and cancer involvement period data of the study participants. There were 17 daughters and 19 sons with somewhat similar age limits. The most frequently used carboplatin dose was 560 mg/m^2. Seven (38.89%) and 12 (66.67%) sons were present in the MOS and the placebo groups, respectively. There was no meaningful association between the age, gender, type of malignancy, Cr, or BUN level, and GFR with a duration of malignancy involvement with carboplatin dosage ($P > 0.05$; data not shown). Most patients in both the groups were received 560 mg/m^2 carboplatin doses, and there was no meaningful difference between both the groups when comparing the malignancy involvement period ($P = 0.681$).

In the MOS group, the mean ± SD of serum Cr levels before treatment and 3 and 7 days after intervention was equal to 0.63 ± 0.13, 0.73 ± 0.11, and 0.79 ± 0.11, respectively ($P = 0.000$). In the placebo group, the mean ± SD of serum Cr levels before and 3 and 7 days after intervention were equal to 0.67 ± 0.12, 0.75 ± 0.1, and 0.81 ± 0.12, respectively (P = 0.000). Serum Cr levels were increased significantly after 3- or 7-days after treatment in both placebo and MOS than before the intervention. However, there was not any considerable difference between the MOS and placebo groups before intervention ($P = 0.631$), 3-days ($P = 0.463$), or 7-days ($P = 0.441$) after intervention carboplatin administration initiation [Figure 2].

In the MOS group, the mean ± SD of serum BUN levels before treatment, 3 days after intervention, and 7 days after intervention was equal to 20.38 ± 2.52, 20.88 ± 2.65, and 22.5 ± 2.7, respectively (P = 0.000). In the placebo group, the mean ± SD of serum BUN levels before treatment, 3 days after intervention, and 7 days after intervention was equal to 19.38 ± 3.68, 21 ± 3.54, and 23.77 ± 4.59, respectively (P = 0.000). Serum BUN levels were increased significantly after 3- or 7-day treatment onset, albeit these levels were not meaningfully different between placebo and intervention categories (P = 0.394 for comparison before treatment, P = 0.974 for BUN 3 days after intervention, and P = 0.434 for BUN after 7 days after chemotherapy) [Figure 3].

Mean ± SD of GFR was equal 101.38 ± 14.67 mL/min/1.73 m^2 in the MOS group and 97.5 ± 9.71 mL/min/1.73 m^2 in the placebo group before intervention (P = 0.177). Three days after intervention initiation, GFR mean ± SD reduced significantly to 90.11 ± 10.52 mL/min/1.73 m^2 in the MOS group (magnesium oxide reception) and 92.33 ± 10.61 mL/min/1.73 m^2 in placebo group (P = 0.266 for comparison of the MOS and placebo groups). After 7 days post intervention, the GFR was reduced to 84.11 ± 12.47 mL/min/1.73 m^2 in the MOS group and 85.38 ± 10.66 mL/min/1.73 m^2 in the placebo group (P = 0.371 for comparison of the MOS and placebo groups) [Figure 4].

Discussion

We have seen that magnesium supplementation in children with cancer cannot prevent carboplatin-induced nephrotoxicity. The average cancer involvement duration was similar in both the placebo and MOS groups. Mean serum Cr, BUN, and GFR were not significantly different between the placebo and MOS groups. However, differences existed between the groups in three measurement steps. It seems the magnesium oxide administration did not exert a considerable effect on the mitigation of carboplatin-induced renal insufficiency. Increased serum Cr and BUN level with decreased GFR, concomitantly, is representative of renal toxicity in both the MOS and placebo groups, which is not eliminated by magnesium oxide or placebo. Besides, in the magnesium oxide group, there was an 11.11% and 17.03% decrease in

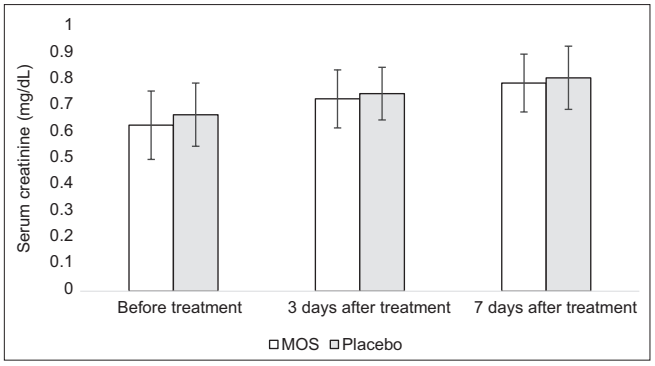

Figure 2: Mean ± standard deviation of serum creatinine concentration before treatment and 3-or 7-days after treatment in the placebo and MOS groups. There was a significant difference between before and 3 and 7 days after treatment in the MOS (P = 0.000) and placebo (P = 0.001) groups. However, there was not any difference between the placebo and MOS groups when compared together before intervention (P = 0.631), 3 days (P = 0.463), or 7 days (P = 0.441) after intervention onset (carboplatin reception)

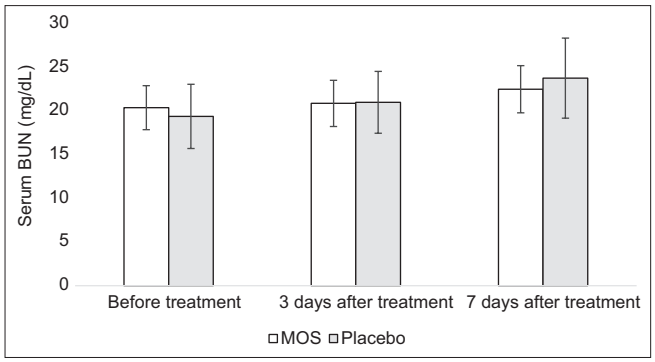

Figure 3: Mean ± standard deviation of serum blood urea nitrogen concentration before treatment and 3 or 7 days after treatment in the placebo and MOS groups. There was a significant difference among before and 3 and 7 days after treatment in the MOS ($P = 0.000$) and placebo ($P = 0.000$) groups. However, there was not any difference between the placebo and MOS groups when compared together before intervention ($P = 0.394$), 3 days ($P = 0.974$), or 7 days ($P = 0.434$) after intervention onset (carboplatin reception)

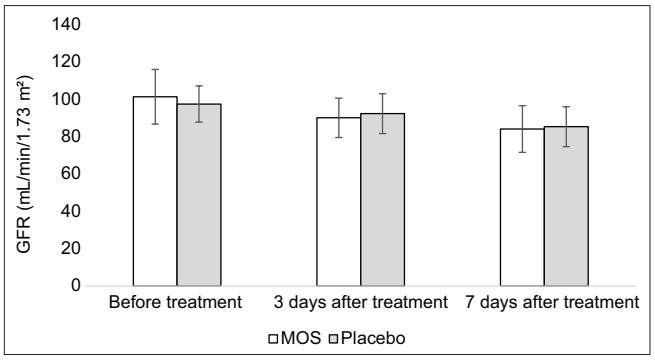

Figure 4: Mean ± standard deviation of glomerular filtration rate before and 3 or 7 days after treatment in the placebo and MOS groups. There was a significant difference among before and 3 and 7 days after treatment in the MOS ($P = 0.000$) and placebo ($P = 0.002$) groups. However, there was not any difference between the placebo and MOS groups when compared together before intervention ($P = 0.177$), 3 days ($P = 0.266$), or 7 days ($P = 0.371$) after intervention onset (carboplatin reception)

GFR on days 3 and 7 post intervention, respectively. However, in the placebo-treated group, there was a 5.3% (day 3) and 7.52% (day 7) decrease in GFR. It is contrary to reports about the efficacy of magnesium oxide in the prevention of carboplatin or cisplatin toxicity. Matsui *et al*. have shown that magnesium-treated children significantly experienced lower serum Cr levels after each chemotherapy course than placebo patients.[28] This finding did not confirm our study because we have seen that magnesium therapy is ineffective in serum Cr increment prevention. Furthermore, Kimura *et al*. have evaluated patients with head-and-neck cancer receiving cisplatin and magnesium supplementation in addition to hydration. They have treated the patients with magnesium supplementation for 4 years or 3 years plus hydration but held them one year without hydration. They have mentioned that this therapeutic regimen prevents renal insufficiency induced by cisplatin therapy.[29] Yamaguchi *et al*. have shown that short hydration plus magnesium supplementation prevents cisplatin renal toxicity when Cr clearance is upper than 70 mL/min.[30] This finding is contrary to our result. The leading cause of such discrepancy could be the treatment course. Yamaguchi *et al*.'s research team used a >50 mg/m^2 cisplatin regimen without magnesium supplementation but a high-volume hydration regimen. However, for the other two years, they used magnesium supplementation with a short hydration regimen.[30] However, we have supplemented our patients with magnesium only for 2 weeks. Therefore, the course of treatment has been too long in Kimura or Yamaguchi *et al*.'s research, but it was too short in our study.

Anyhow, Matsui *et al*. have evaluated 37 patients under 158 chemotherapy courses with cisplatin, from which 92 sessions were concomitant with magnesium oxide reception. In our study, 18 patients received only 14 doses of magnesium oxide. Kimura *et al*. and Yamaguchi *et al*.'s studies[29,30] were on adults and old patients, whereas we have evaluated pediatrics as Matsui *et al*.'s investigation.[28] In addition, the mentioned studies surveyed the effect of magnesium supplementation on kidney function after cisplatin therapy, whereas we have explored the carboplatin drug.

We hypothesized that cisplatin or carboplatin nephrotoxicity could result in hypomagnesemia. On the other hand, magnesium therapy may probably protect against renal damage.[29] However, our results imply that magnesium oxide supplementation before carboplatin administration may prevent nephrotoxicity. Confirmation or rejection of such evidence is too complicated because of population heterogeneity, the type of cancers, gender differences, and low sample size affecting the finding of slight differences where the variations are considerable. In addition, other complicating factors included different doses of carboplatin, shortage of magnesium supplementation course, inability to control nutritional regimen/habits that may result in the intervention with absorption, distribution, and metabolism of the drug, genetic polymorphisms, construct of the studied population, quality of the administered drug, and pediatric population limitations. Although the mentioned causes may be controllable, special considerations exist that are related to ethical and moral issues.

Gaughran *et al*. in 2020 have reported that mild hypomagnesemia is frequent in carboplatin chemotherapy. They have mentioned that mild hypomagnesemia is frequent in chemotherapy with carboplatin. Gaughran *et al.* suggested that does hypomagnesemia play a role in carboplatin treatment complication manifestations.[24] We have seen that short-term magnesium supplementation cannot protect kidneys significantly against malfunction. In our work, serum Cr and BUN levels were slightly lower in the MOS group than in the placebo group. This finding is promising for magnesium supplementation for longer times in patients under carboplatin chemotherapy. Although there are various studies from the 19th century, researchers believe that further surveys are necessary to find out the facts of hypomagnesemia

and platinum-containing formulations. However, other studies confirm our findings or conclusion about the mild changes or inefficient effects of magnesium therapy as prophylaxis for nephrotoxicity prevention. Skinner *et al*. have shown that GFR was decreased weekly or moderately after 10 years of cisplatin or carboplatin therapy in children that confirms our finding. They concluded that induced toxicity due to the platinum drugs did not change after 10 years of treatment.[31] Stöhr *et al*. have reported that carboplatin and cisplatin nephrotoxicity is mild in sarcoma patients.[32] Collectively, nephrotoxicity due to the chemotherapy with platinum-containing formulations seems to be not progressive. The inefficiency of prophylactic magnesium therapy could be due to the shortness of the treatment period that was only one course in our study. However, long-term therapeutic sessions may exert efficient and sensible results in children under platinum-formulated drugs.

Magnesium is involved in energy metabolism, Na+/K + pump and calcium channel or RNA/DNA polymerase enzyme activity, and cell membrane stability. Therefore, in addition to an antioxidant property, it is probable that magnesium supplementation helps organ function and prevents cisplatin/carboplatin accumulation due to renal tubular transporter dysfunction.[7,15,16,26] Disturbances of essential trace elements and overloaded toxic elements in renal insufficiency could be notable and considerable in the Iranian population based on our previous experiences;[33] this experience shows that magnesium is reduced significantly in end-stage renal disease patients. Therefore, we think renal insufficiency may complicate trace element status in long-term therapeutic regimens. Renal function changes are insensible in children if we have a brief revise on Cr and BUN data. In turn, renal function quality affects trace element metabolism as the kidney excrete or reabsorbs them. Hence, magnesium supplementation, even not to be preventive of carboplatin-induced nephrotoxicity, may be beneficial in keeping body contents of magnesium in normal ranges and probably be safe in the long term.

Unfortunately, we do not have precise information about the status of essential or toxic trace elements in the healthy or not healthy Iranians to propose policies for managing therapeutic regimens. The current study, at least, taught us that magnesium therapy could not be too beneficial for the prevention of carboplatin-induced nephrotoxicity in cancerous children. However, remembering magnesium's role in the growth and metabolic pathways, magnesium oxide supplementation for patients under nephrotoxic therapeutic regimens, such as cancerous patients, could be beneficial.

Conclusion

The current study shows that magnesium supplementation did not prevent carboplatin-induced nephrotoxicity in cancerous children. Anyhow, we propose magnesium oxide supplementation for such patients because magnesium is an essential element for cell and tissue growth, maintenance, and metabolism. The authors suggest a multicenter study to clarify the effect of magnesium supplementation on kidney function of Iranian pediatrics suffering from cancer and needing carboplatin therapy.

Study limitations

The sample size and limitation to do a study on the children population due to psychological and parents sensations were our challenges in this research. We did this study on all available children who passed the inclusion criteria based on the denied status by the oncological team.

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Conflicts of interest

There are no conflicts of interest.

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