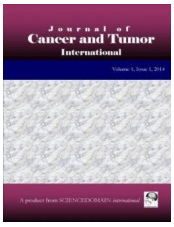

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Can Calcium and Magnesium Infusion before and after Oxaliplatin Administration Improves Its Neurotoxic Effect?

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Authors' contributions

This work was carried out in collaboration between both authors. Author MSZ designed the study, performed the statistical analysis, formulated methodology of the study, shared in patients follow up during period of treatment. Author HMHRE managed the analyses of the study, managed the literature searches and wrote the first draft and final version of the manuscript, wrote the protocol and got the IRB acceptance for the study from the committee of the faculty and she is the corresponding author. Both authors read and approved the final manuscript.

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ABSTRACT

Introduction: The oxaliplatin neurotoxicity is one of two distinct phases: an acute and a dose-limiting cumulative phase. Large doses of I.V Ca & Mg is given before and after oxaliplatin in FOLFOX protocol.
Aim: We aimed to evaluate the efficacy of Ca & Mg in improving or eliminating oxaliplatin-induced neurotoxicity.
Study Design: Randomized double controlled placebo study.
Place and Duration of Study: Clinical Oncology department at Mansoura university hospital, Egypt at the period from July 2014 up to December 2016 inclusive.
Methodology: In our study, 140 Patients with adenocarcinoma of the colon received 6 months of FOLFOX protocol. Patients were choiced to receive I.V calcium gluconate plus magnesium sulfate (1 g for both of them) in 100 mL of D5W for about 30 minutes immediately before and after each

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cycle of oxaliplatin (70 patients), or an identical looking placebo shortly before and after each cycle of oxaliplatin (70 patients) in a random manner. The primary end point was a comparison between neurotoxicity assessed by Common Terminology Criteria for Adverse Effects (CTCAE) version 4.0 in both groups.

Results: There was statistically significant difference as regard grade of neuralgia. Grade II neuralgia is higher in the study group II (45.7%) compared to (22.9%) in the study group I. There was statistically significant difference as regard grade of paresthesia. Grade II & III are higher in study group II (51.4%, 14.3%) compared to (30.0%, 4.3%) in study group I.

Conclusion: Ca and Mg administration with oxaliplatin have been well tolerated. Our results support the role of Ca & Mg in decreasing neurotoxicity associated with oxaliplatin.

Keywords: Colorectal cancer; neurotoxicity; oxaliplatin; Ca gluconate.

1. INTRODUCTION

Oxaliplatin is a member of widely accepted standard protocols for treatment of stage III and stage IV colorectal cancer (CRC). Also, it is now commonly used in the treatment of other malignancies including esophagogastric and pancreatic cancers [1].

Chemotherapy protocols that contain oxaliplatin are widely used and having a good effects with response rate as high as 53% and a quite low rate of side effects as nausea, vomiting and leucopenia. However, neurotoxic side effects restrict its use and cause patient irritability. The oxaliplatin causing neurotoxicity is one of two distinct phases: a transient, acute phase that can appear during or after administration of oxaliplatin with a short time and a dose-limiting cumulative sensory phase of neuropathy [2].

The neuropathy associated with oxaliplatin is different from the neuropathy that happens with cisplatin. The two agents will lead to a glove stocking neuropathy that increases with elevating the dose. But oxaliplatin is accompanied by an acute neuropathy in the form of muscle twitches, sensation of discomfort in the throat and intolerability to the coldness which is generally associated with each oxaliplatin dose [3]. The acute form occurs within short minutes of administration of oxaliplatin and is able to sustain for one to two days in the form of paresthesia and tingling. Sometimes, there is an unordinary sensation in the tongue or limb stiffness, and may be increased by cold exposure. The rate of acute form of neuropathy ranges from 81.5 up to 98% [4]. The sustained sensory chronic neuropathy appears as paresthesia and proprioceptive changes. They do not disappear in between cycles of chemotherapy. It happens in about 15% of patients after total doses of oxaliplatin ranges from 780-850 mg/m2 [2].

Large doses of I.V Ca & Mg is given before and after oxaliplatin in FOLFOX protocol. At the clinical settings; they represent the most used regimen for the prevention of FOLFOX neuropathy. The oxalate was released from the metabolism of oxaliplatin. This oxalate is chelating the Ca & Mg. They are involved in the function of ion channels in nerve membranes. So, Ca & Mg may eliminate or improve this induced neuropathy [5]. Unlike the acute form neurotoxicity, the cumulative toxicity of oxaliplatin appears to be due to direct toxic effect on the nerve itself [6].

The benefit was noticed for both the acute and chronic neuropathy, with no evident antagonistic effect on the antitumor effect of FOLFOX. Subsequently, a lot of oncologists used I.V Ca & Mg as a part of the pre-treatment medications for patients under FOLFOX protocol. Divalent cations had the power to change voltage-gated sodium channels. It is hypothesized that the acute neuropathy of oxaliplatin is related to calcium chelation caused by oxalate. Increasing the extracellular calcium has been found to increase the sodium channel closure. And, this leads to decrease the over excitability of the peripheral neurons which seen in the neuropathy caused by oxaliplatin. Magnesium supplementation has been studied in preventing hypomagnesemia caused by cisplatin [7,6].

1.1 Aim

In this prospective randomized double controlled placebo study, we aimed to evaluate the efficacy of Ca & Mg in improving or eliminating oxaliplatin-induced neurotoxicity.

2. PATIENTS AND METHODS

In our randomized double controlled placebo study, 140 Patients with adenocarcinoma of the colon who attended to clinical oncology & nuclear medicine department at Mansoura university hospital at the period from July 2014 up to December 2016 inclusive. The patients were treated with curative-intent resection. They were scheduled to receive 6 months (12 cycles) of FOLFOX protocol as adjuvant treatment (ie. oxaliplatin, leucovorin and fluorouracil, involving oxaliplatin 85 mg/m2) every 2 weeks.

The studied patients needed to have adequate hematological parameters, serum total bilirubin and serum creatinine to allow chemotherapy and normal levels of calcium and magnesium. Women at the age of childbearing period must have a negative pregnancy test. A central venous line was inserted before the beginning of chemotherapy protocol. Patients were excluded from the study if they had a pre-existing peripheral neuropathy of any grade or had received neurotoxic chemotherapy like oxaliplatin, cisplatin, taxanes or vinca alkaloids previously prior to existing treatment.

At the beginning of our study and before each 2-week cycle of chemotherapy; we performed a brief history, physical examination, and CBC for each patient. Neurotoxicity assessments were obtained in each setting. The primary neuropathy assessment was described by Common Terminology Criteria for Adverse Effects (CTCAE) version 4.0.

Questionnaires were obtained from the patients before each dose of FOLFOX to provide data regarding grades of peripheral motor neuropathy, peripheral sensory neuropathy, neuralgia, and paresthesia.

Patients were choiced to receive I.V calcium gluconate plus magnesium sulfate (1 g for both of them) in 100 mL of D5W for about 30 minutes immediately before and after each cycle of oxaliplatin (70 patients), or an identical looking placebo shortly before and after each cycle of oxaliplatin (70 patients) in a random manner. The normal level of serum Calcium (total) is 9-11 mg/dl and 1.8-3.6 mg/dl for serum level of Magnesium. Patients were classified by age (less than 50 years *vs.* 50 years and more) and gender. The primary end point was a comparison between neurotoxicity assessed by Common Terminology Criteria for Adverse Effects (CTCAE) version 4.0 in both groups.

2.1 Statistical Analysis

SPSS (version 21) were used to analyze data. The normality of data was tested with one-sample Kolmogorov-Smirnov test. Qualitative data were described by using number and percent. Chi-square was used to test association between categorical variables. Continuous variables were presented as mean ± SD (standard deviation). Student – test was used to compare means of 2 groups.

2.1.1 The level of significance

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value).The results were considered:

- When the probability of error is more than 5%, so it is non-significant ($p > 0.05$).
- When the probability of error is less than 5%, so it is significant ($p \leq 0.05$).
- When the probability of error is less than 0.1%, so it is highly significant ($p \leq 0.001$).

The results are more significant when the smaller p- value is obtained.

3. RESULTS

Two arm, placebo-controlled, randomized, blind, parallel group design was used. One hundred and forty patients started FOLFOX therapy between July 2014 till December 2016 was enrolled in the present study and divided into two groups: the study group and the placebo one; each of them has 70 patients per each. Our data shows that the two study groups were matched regarding sex and age; (50%) were males and (50%) were females for both groups, while age for study group I is 48.30 (8.38) and for study group II is 48.95 (8.12) with no statistically significant difference (*P- value >0.05*) as we show in Table 1.

As regard toxicity; there is no statistically significant difference (*P-value >0.05*) regarding grade of sensory neuropathy and grade of motor neuropathy. However it is not statistically significant; grade II& III sensory neuropathy are higher in the study group II (31.4%, 7.1%) compared to (18.6%, 4.3%) in the study group I. Also, grade II & III motor neuropathy is higher in the study group II (30.0%, 7.1%) compared to (20.0%, 5.7%) in the group I as we mention in the Table 1.

On the other hand, there is statistically significant difference (*P-value <0.05*) as regard grade of neuralgia. Grade II neuralgia is higher in the

study group II (45.7%) compared to (22.9%) in the study group I (OR=2.9). In addition, there is statistically significant difference as regard grade of paresthesia. Grade II & III are higher in study group II (51.4%, 14.3%) compared to (30.0%, 4.3%) in study group I (OR =3.3, 6.4) respectively as we describe in Table 1 and Figs. 1 and 2.

Table 1. Distribution of patient's sex, age and grades of neurotoxicity

Items	Study group I n=70		Placebo group II n=70		χ^2 (*P value*)	OR (95%CI)
	No	%	No	%		
Sex						
Male	35	50.0	35	50.0	-	-
Female	35	50.0	35	50.0		
Age / years						
Mean (SD)	48.30 (8.38)		48.95 (8.12)		t=0.471	0.638
Min-Max	33-63		33-61			
G of Sensory neuropathy						
1	54	77.1	43	61.4	-	r (1)
2	13	18.6	22	31.4	3.5 (0.06)	2.1 (0.96-4.7)
3	3	4.3	5	7.1	0.98(0.32)	2.09 (0.47-9.2)
G of Motor neuropathy						
1	52	74.3	44	62.9	-	r (1)
2	14	20.0	21	30.0	2.1 (0.15)	1.8 (0.8-3.9)
3	4	5.7	5	7.1	0.31(0.57)	1.5 (0.4-5.9)
G of Neuralgia						
1	51	72.9	35	50.0	-	r (1)
2	16	22.9	32	45.7	8.3 ***(0.004)***	2.9 (1.4-6.1)
3	3	4.3	3	4.3	0.2 (0.65)	1.5 (0.3-7.6)
G of Paresthesia						
1	46	65.7	24	34.3	-	r (1)
2	21	30.0	36	51.4	10.5 ***(0.001)***	3.3 (1.6-6.8)
3	3	4.3	10	14.3	8.2 ***(0.004)***	6.4 (1.4-3.5)

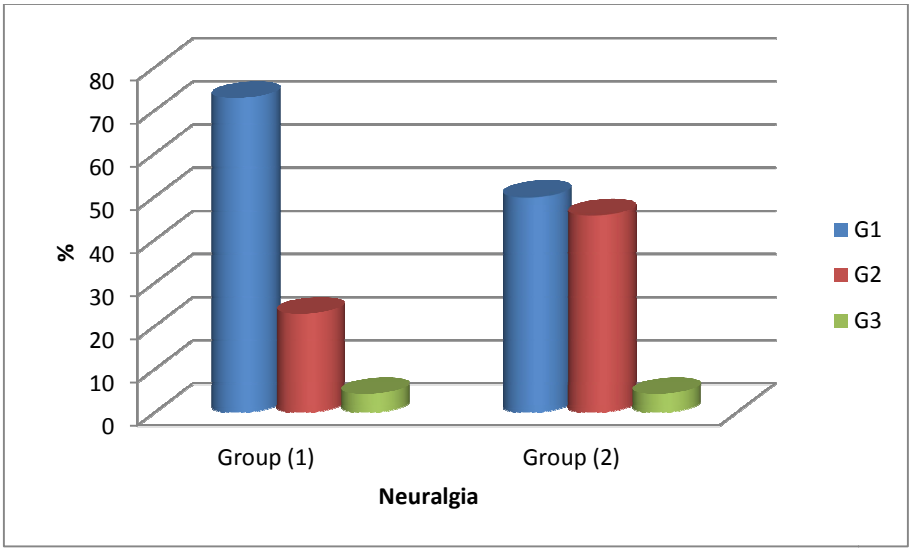

Fig. 1. Distribution of the grade of neuralgia in both groups

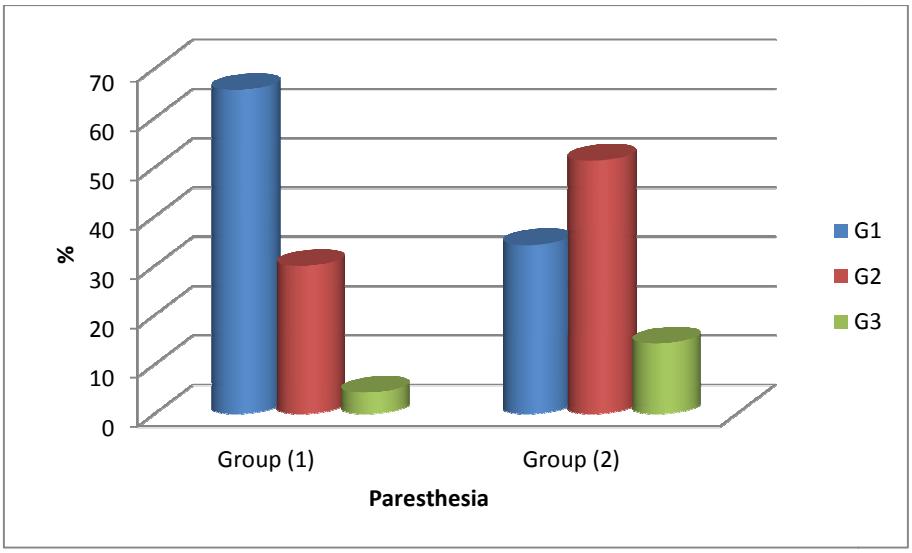

Fig. 2. Distribution of the grade of paresthesia in both groups

4. DISCUSSION

The question of the usage of Ca and Mg as a neuroprotectant for oxaliplatin is difficult to be definitively answered. Many studies are necessary to obtain the answer of this debate.

There have been 3 published retrospective trials for the utility of Ca & Mg as a neuroprotectant against oxaliplatin neurotoxic effect. Gamelin et al. studied [7]. 161 patient in a retrospective cohort trial and they reported positive results as compared with our study results. Knijn et al. [8] studied 732 patients entered in a clinical study randomly with Xeloda, oxaliplatin, and bevacizumab versus Xeloda, oxaliplatin, and cetuximab, with the use of Ca & Mg. The retrospective analysis, for 551 patients who received Ca and Mg during their initial treatment cycle, there was a slightly lower incidence of any physician-judged neurotoxicity (85% *vs.* 92%, respectively; *P_0.02*) and physician-judged grade 2 neurotoxicity (40% vs. 45%; *P_0.22*), in patients received Ca and Mg versus the patients who did not take Ca and Mg in association with their cycles (181 patients). In another retrospective study [9], ninety patients receiving FOLFOX protocol also administrated Gosha-Inki gan, a traditional Japanese herbal compound, Ca & Mg alone, Ca & Mg plus Gosha-Inki gan, or neither agent. No benefit was gained for Ca & Mg in this study which is contrary to our study results. The difference of Kono and his colleagues results (2011) from our results may be due to the use of this herbal compound that gives no benefit to the Ca & Mg and may even eliminate there beneficial effect in treatment of neurotoxicity.

Two prospective double-blind published trials. The CONCEPT trial did not show any significant advantage which is against our results, but the N04C7 trials suggested benefit for Ca & Mg as we demonstrated in our patients [3]. In another double-blinded, placebo-controlled clinical study which had 3 study arms, with about thirty patients in each study arm; the patients received Ca, Mg, and glutathione, or placebo. There were no significant differences statistically in the neurotoxic effect happened among the study groups [10]. This may be due to the small number of patients in each study group.

Nikcevich et al. [11] performed a randomized controlled trial that studied the effect of Ca and Mg on neuropathy in stage II or III colon cancer patients treated with FOLFOX as adjuvant settings. Their study was also stopped after the release of the interim results of the CONCEPT study.

Also, Chay and his colleagues reported in 2010 that their study was stopped early based on the first negative results of the CONCEPT trial. Median follow up was 8.7 months. Overall 22 out of 27 patients developed neuropathy. Arm A showed a rate of 77% of subjective neuropathy & Arm B showed 86% (P = 0.6). There was no statistical significant difference in neuropathy between both arms, during or at the end of

treatment. Median score of objective neuropathy was 6 in Arm A & 0 in Arm B (*P = 0.02*) [12]. The studies which closed early due to the results of the CONCEPT may be if continue their work; they can show a positive statistically significant findings compared to our data.

Gamelin and his colleagues reported in 2008 another study suggesting that Ca & Mg was beneficial. This report discussed preliminary data from the NEUROXA trial involving fifty two patients suffering from metastatic colorectal cancer; 50% of patients received Ca & Mg and 50% did not. They noticed a difference in the incidence of grade 3 neurotoxicity between the two study groups (5% *vs.* 24%; P-0.001) [13].

Also, Gobran published in 2013 findings supporting that the reduction in neurotoxicity in patients receiving Ca and Mg with oxaliplatin infusions was statistically significant. The study was performed from July 2008 to February 2011. They studied 30 patients in arm 1 who received calcium/ magnesium and another 30 patients in the placebo arm. All the patients received regimen containing oxaliplatin as adjuvant treatment. They used the NCI-CTCAE version 3.0 criteria for neuropathy assessment. Results concluded that 23.3% of patients receiving Ca and Mg developed neuropathy by the completion of therapy, vs. 46.6% in the placebo arm, a statistically significant difference [14]. This was comparable with our results as the study group developed sensory neuropathy in about 22.9% (GII, GIII), vs. 38.5% (GII, GIII) in placebo arm but it is not statistically significant. Also, motor neuropathy was 25.7% in study group vs. 37.1% in the placebo arm but also with no significance statistically. As regard neuralgia in our study, the placebo group showed 45.7% of patients, vs. 22.9% in the study group I and it shows good significance statistically. The results of this study were comparable with us despite the usage of different assessment scale for toxicity (NCI-CTCAE version 3.0 Vs. (CTCAE) version 4.0 in our study).

During the last few years, many studies suggest that, with regional changes worldwide, many oncologists have been using Ca & Mg in their routine work and this is clear from many studies mentioned previously. Our results support this issue which currently notes that Ca & Mg can be used for the prevention of neuropathy caused by oxaliplatin or to decrease its degree.

5. CONCLUSION

We use Ca and Mg with oxaliplatin protocol as premedication in our study. Our study results support the role of Ca & Mg administration in decreasing neurotoxicity associated with oxaliplatin. Further studies will be needed to adjust the optimal dose, repetation, and infusion time. Also, these studies will be helpful to determine the role of these administrations in oxaliplatin causing neuropathy.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study has the approval of the IRB committee of the Faculty of Medicine (MFM-IRB), Mansoura University, Egypt. The code number is R/17.05.66.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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