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Study the Effect of Serum Magnesium Level on Chemotherapy Induced Peripheral Neuropathy

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Abstract

Introduction: Magnesium, the second most abundant intracellular cation in the body, required for cellular energy metabolism and has an important role in membrane stabilization, nerve conduction, ion transport, and calcium channel activity. Manifestation of magnesium deficiency includes numbness, tingling, muscle contractions and cramps, seizures (sudden changes in behaviors caused by excessive electrical activity in the brain), personality changes, abnormal heart rhythms, and coronary spasms can occur.

Materials and Method: The patient's history and clinical examination were recorded followed by prechemotherapy baseline serum magnesium level using validated analyzer (Cobas Integra 400 plus) in biochemistry lab using the same serum which was separated from patient's drawn venous blood on which serum creatinine was routinely performed avoiding the need to draw extra blood for this test. After determining the serum Magnesium result, treating nurse gave MgSO4 (50% - 01mg/2ml) and KCL (15% - 1.5 mg/10ml) to the patient as a premedication to avoid the side effects resulting from chemotherapy.

Result and Discussion: The data from the study did not yield significant result to support the effect of Magnesium on CIPN but the gradual decrease in the mean serum magnesium level does warrant further exploration on large population to review hypomagnesemic symptom. In this study baseline value for male and female were Mean ± SEM, 2.046 ± 0.008350 (N=20) and 2.038 ± 0.004787 N=12 respectively with P value of 0.4903. Furthermore premagnesium level for 2nd cycle Mean ± SEM= 1.970 ± 0.007255 N=20 (male) and 1.980 ± 0.01285 N=12 (female) ,3rd cycle Mean ± SEM= 1.929 ± 0.009383 N=20 (male) and 1.921 ± 0.008657 N=12 (female), 4th cycle Mean ± SEM= 1.891 ± 0.009907 N=20 (male)and 1.888 ± 0.02229 N=12 (female), 5th cycle Mean ± SEM= 1.836 ± 0.01080 N=20 (male) and 1.873 ± 0.05166 N=11 (female), and 6th cycle Mean ± SEM= 1.828 ± 0.04453 N=9 (male) and 1.833 ± 0.08750 N=4 (female) and the P value for 2nd, 3rd, 4th,5th, and 6th cycle were 0.4688, 0.5848, 0.9200, 0.3658, and 0.9581 respectively.

Above results show that the pre-magnesium level for 2nd , 3rd , 4th, cycle for both sex group were nearly same but before 5th cycle mean serum magnesium level in males were lower compared to their female counterpart.

Conclusion: In conclusion, Taxanes and Vinca alkaloids have an effect on serum magnesium level but in combination with platinum compounds there was a further decrease in the magnesium level so the combination therapy using multiple compounds and its effect on serum level requires further exploration. Due to limited patient population, there was no significant data to support the effect on magnesium level. Moreover, clinical examination is not an effective method for evaluation for CIPN. So there is stringent need to evaluate the effect of serum Magnesium level in larger cancer population. NCS (Nerve conduction study) will need to be carried out for CIPN assessment to give the precise result.

Keywords: Serum Magnesium; Platinum's Compounds; Taxanes Compounds; Vinca Alkaloids; CIPN; Neuropathy; Hypomagnesemia; Hypocalcaemia;

NCS Cancer and Serum magnesium

Magnesium, the second most abundant intracellular cation in the body, plays an important role in numerous enzymatic reactions. Thus, maintenance of adequate intracellular magnesium levels is essential for normal physiological and metabolic processes [1]. Symptoms and signs may occur when plasma levels drop below the normal range (0.7 - 0.94 mmol/L). However, it is important to note, that as magnesium is largely intracellular, a body deficit may still be present with a normal plasma concentration, although this is rare. The symptoms and signs can be variable, and may be attributed to the underlying malignancy or treatment [2]. The normal body magnesium content is around 1000 mmol or 22•66 g, of which 50–60% is in the bone. Extracellular magnesium accounts for only 1% or so of total body magnesium (TBMg). The normal serum magnesium concentration or [Mg2+] ranges between 0•75 and 0•95mmol/L (1•7–2•2 Mg/dL, 1•5–1•9 meq/L) [3].

A study published in the year 2000 found that almost half of cancer patients admitted to the intensive care unit (ICU) had low magnesium levels. Magnesium deficiency may have contributed to their disease, but it may in fact also be due to their cancer treatment [4]. (Table 1)

Total body magnesium: 20–28 g (modified according to Shils, 1997) [5].

Table 1: Distribution and Concentrations of Magnesium in a Healthy Adult

Percent Distribution	Concentration
Bone	(60–65%) 0.5% of bone ash
Muscle	(27%) 6–10 mmol/kg wet weight
Other cells	(6–7%) 6–10 mmol/kg wet weight
Extracellular	(<1%)
Erythrocytes	2.5 mmol/l
Serum 55% free 13% complexes with citrate, phosphate, etc. 32% bound, primarily to albumin	0.7–1.1 mol/l
Mononuclear blood cells	2.3–3.5 mmol/cell
Cerebrospinal fluid 55% free 45% complexed	1.25 mmol/l
Sweat Secretions	0.3 mmol/l (in hot environment) 0.3–0.7 mmol/l

Magnesium and Anticancer drugs

Cisplatin, a platinum-based chemotherapy drug used to treat various types of cancer, can cause a number of serious side effects, including magnesium deficiency in up to 90% of patients. The results of a 2008 study indicate that prophylactic (preventive) magnesium supplementation can prevent these side effects and decrease the severity of cisplatin-induced kidney damage without interfering with the anticancer effect of the drug. In fact, among cisplatin-treated cancer patients, those given magnesium had significantly slower disease progression and longer survival times, when compared with patients given a placebo. The four-year survival rate was 63% in the magnesium group and 36% in the placebo group [6]. Carboplatin, an analogue of cisplatin, causes less nephrotoxicity, and only 10% of patients treated with carboplatin develop hypomagnesemia [7].

Taxanes have become key drugs in the treatment of several malignancies as the antitumor activity of paclitaxel and docetaxel was established in the early 1990s. A major problem in the clinical use of these drugs, particularly paclitaxel, has been the development of sensory neuropathy [8]. Numbness and tingling of the extremities, loss of deep tendon reflexes, and distal muscle weakness are the most frequent neurotoxicities. Bothersome sensory changes usually reverse over time. Loss of motor function is a more serious side effect that requires drug discontinuation and a search for contributing factors [9].

Peripheral neuropathy and anticancer drugs

Platinum's compounds(Cisplatin, Carboplatin, Oxaliplatin)

Cisplatin-induced neurotoxicity is cumulative, and symptoms are detected only after considerable toxicity has occurred. The severity of the symptoms is related to the total cisplatin dose and may be dose limiting in some patients [10]. The features of sensory peripheral neuropathy are consistent across studies and suggest damage to large myelinated sensory fibers, taking the form of progressive symmetrical sensory neuropathy, with initial paresthesias and more severe sensory ataxia [11]. Neurotoxicity is also infrequent and peripheral neuropathy and ototoxicity are seen. Carboplatin produces more myelosuppression than cisplatin and thrombocytopenia is the dose-limiting toxicity [12]. Oxaliplatin's dose-limiting toxicity is related to peripheral nerve function and ultimately the development of peripheral neuropathy [13].

Taxanes and anticancer drugs: (Paclitaxel, Docetaxel)

Study that assessed the cellular changes that occur after administration of paclitaxel in rats, suggested that the paclitaxel-induced peripheral neuropathy (PIPN) is characterized by injury of sensory neurons and their supporting cells in the peripheral nervous system, macrophage activation in both the DRG and peripheral nerve and microglial activation within the spinal cord. Paclitaxel may also interfere with axonal transport, thus affecting the ganglion soma cells at least at the functional level [14].

Vinca alkaloids: (Vincristine, Vinblastine)

Vincristine induced neurotoxicity is caused by interference with microtubule function resulting in blockage of axonal transport and thus in axonal degeneration. Demyelization and muscle damage are probably secondary to axonal degeneration and denervation, respectively. Vincristine associated neuropathy is reversible unless the degeneration process has reached the perikaryon. Regeneration requires nerve sprouting. Growth factors (as insulin-like growth factor I) are released by denervated muscles. After absorption by the distal axonal end, growth factors will be transported to the nucleus, resulting in nerve sprouting and regeneration. Neuronal microtubules have a function in nerve sprouting. It is probable that vincristine interferes with the process of regeneration [15].

Peripheral neuropathy

"Peripheral neuropathy is defined as dysfunction of peripheral neurons (motor, sensory, and autonomic), resulting in signs and symptoms (sensory) of paresthesia, dysesthesia, hypoesthesia, hyperesthesia, loss of proprioception, loss of touch and temperature discrimination, areflexia, and pain and/or (motor) weakness" [16].

Chemotherapy induced peripheral neuropathy

A number of factors influence the incidence of CIPN (Chemotherapy-induced peripheral neuropathy) in patients receiving neurotoxic chemotherapy, including patient age, dose intensity, cumulative dose, therapy duration, co-administration of other neurotoxic chemotherapy agents, and pre-existing conditions such as diabetes and alcohol abuse [17].

Electromyography (EMG) is painful, disturbing for the patients and it gives only a non-quantitative assessment of motor units' activity damage in the rare cases where motor impairment is severe and, therefore, already easily evaluable

clinically. Semi-quantitative assessment of sensory threshold or of muscle strength has also occasionally been proposed, but standardization of the instruments and of the methods to be used has never been achieved. Therefore, CIPN assessment should be based on effective and reliable clinical methods. Usually, objective assessment of neuropathic signs is performed with bedside clinical examinations (e.g. search for sensory and motor abnormalities, deep tendon reflex changes, orthostatic hypotension and constipation) [18].

Manifestation of CIPN

The symptoms or signs of CIPN depend mostly on which nerves are involved. The most common symptoms are: Pain (may be there all the time or come and go, like shooting or stabbing pain),Burning, Tingling ("pins and needles" feeling),Loss of feeling (can be numbness or just less ability to sense pressure, touch, heat, or cold), Trouble using your fingers to pick up or hold things; dropping things, Balance problems, Trouble with tripping or stumbling while walking, Pressure or temperature (mostly cold) may hurt more than usual, Shrinking muscles, Muscle weakness, Trouble swallowing, Constipation, Trouble passing urine, Blood pressure changes, Decreased or no reflexes. CIPN can cause severe pain and can affect your ability to do things like walk, write, button your shirt, or pick up a coin. If it gets very bad it can cause more serious problems like changes in your heart rate and blood pressure, trouble breathing, paralysis, or organ failure [19].

Methodology

Study Setting and Designs

This Prospective Cross Sectional study was designed to study the effect of serum magnesium level on chemotherapy induced peripheral neuropathy. The protocol was approved by the Human Research Ethical Committee (HREC) of Pramukh swami Medical College, Shree Krishna Hospital, Karamsad.

Data entry format (Proforma)

Proforma containing 7 pages information regarding patient was designed. First two pages of Proforma contains the details about some personal information e.g. name, age, sex, contact no, social history, personal habits, relevant dates etc. third page contains information regarding the patients general condition e.g. physical status, RS, CVS, etc. fourth and fifth page contains the information regarding the clinical evaluation data of the patient e.g. sensory examination, motor examination, reflexes, Romberg's sign, etc. sixth page contains serum magnesium level data of each patient before the next chemotherapy cycle was given as per the schedule. Seventh page contains information about chemotherapy drugs and their dose for each and every cycle as per the BSA by treating physician.

Selection of patients

1. Patients taking chemotherapy the following drugs in the Oncology department, MSPCC, SKH, Karamsad. a) Vinca alkaloids b) Taxanes c) Platinum's
2. All age groups were included in this study DM, Chronic alcoholism, Known cause of neuropathy, other cause of neuropathy, Spinal cord compression, History of systemic diseases (SLE, HIV.) all mentioned patient were excluded from this study.

Drugs selected for the study

Patients were prescribed Platinum's, Taxanes, and Vinca alkaloids group of drugs as per the BSA calculation by treating physician.

Method for data collection

Patients meeting the inclusion and exclusion criteria were recruited from the oncology department at Shree Krishna hospital, Karamsad. The patient's history and clinical examination were recorded. Then prechemotherapy baseline serum magnesium level were collected using validated analyzer (Cobas Integra 400 plus) in biochemistry lab by using the same serum which was separated from patient's drawn venous blood on which serum creatinine was routinely performed. So there was no need to draw extra blood from the patient for this test. After determining the serum Magnesium result, treating nurse gave $MgSO_4$ (50% means 01mg/2ml) and KCL (15% means 1.5 mg/10ml) to the patient as a premedication treatment to avoid the side effect which resulted from chemotherapy. $MgSO_4$ & KCL was given to those patients who receive platinum compounds (Cisplatin, Carboplatin, and Oxaliplatin) alone and in combination with other chemotherapy drug. Then the patient received chemotherapy as per treating clinician's plan/discretion. At every cycle patient's serum magnesium level was done prior to the initiation of chemotherapy. History and detailed clinical examination including neurological assessment as detailed in the Proforma were carried out by the treating physician to rule out the CIPN and carried out during these visits. NCS was done only if clinically indicated.

Patient's data analysis

1. Sex group of the patients: Figure 5.1 shows sex categorization of the patients enrolled in the study. In the present study total 32 patients were enrolled, out of them 12 (37.5%) female patients & 20 (62.5%) male patients. (Figure A)
2. Age group of the patients: In present study all enrolled patients were divided into age groups: 0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80 ang 81-90 years.

Total 4 (12.5%) patients (means 1 patient of each range of age) were found in the age group of 11 to 20, 21 to 30, 71 to 80 and 81 to 90 years. Total 2 (6.25%) patients were found in the range of 0 to 10 year age. Total 4 (12.5 %) patients were found in the age group of 31 to 40 years. Total 7 (21.87%) patients were found in the age group of 41 to 50 years. Total 5 (15.62%) patients were found in the age group of 51 to 60 years. And Total 10 (31.25%) patients were found in the age group of 61 to 70 years. (Figure B)

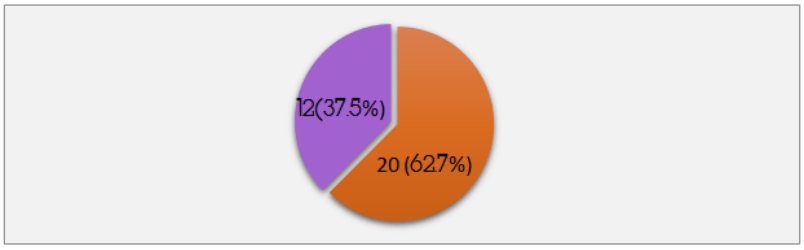

Figure A: Sex Group Classification – Male Vs Female

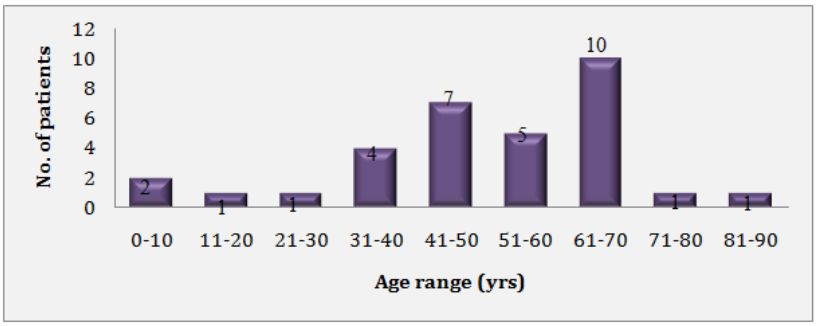

Figure B: Age Group Distribution

Smoking habits

Out of 32 patients 18 (56 %) patients were found to be smoker/gutkha chewing. And rest of 14 (44 %) patients were found to be non smoker/gutka chewing habbit. (Figure C)

Drug category distribution

Out of total 32 patients 14 (44%) patients have received platinum compounds(Cisplatin, Oxaliplatin, Carboplatin alone or in combination with other cytotoxic drugs). 14 (44%) patients have taken Taxanes(Paclitaxel, Docetaxel alone or in combination with other cytotoxic drugs) and rest of 4 (12%) patients have taken Vinca alkaloids (Vincristine, Vinblastine alone or in combination with other cytotoxic drugs). (Figure D)

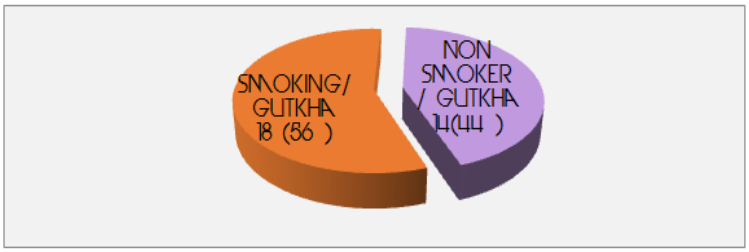

Figure C: Tobacco Consumption Distribution

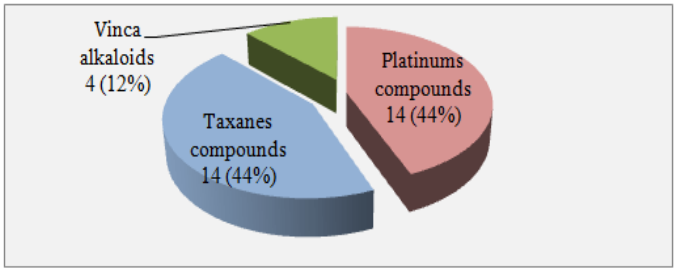

Figure D: Drug Category Distribution

Serum Mg++ Vs Chemotherapy cycle

At Baseline all patients (n=32) at the time of enrollment had mean serum magnesiun level of 2.04 mg/dl. Before the second cycle serum magnesium level for all the patients dropped down to 1.97 mg/dl followed by a further decrease prior to the third cycle at 1.92 mg/dl. Later, out of the total study population of 32, only 29 (90.62%), 28 (87.50%), 13(40.62%) patients took the fourth, fifth and sixth chemotherapy cycle respectively supporting the trend of decreasing serum magnesium level at 1.88, 1.84, 1.82 mg/dl respectively. (Figure E)

The below graphed data extracted using the Prism Graphpad Version 5.0 does not demonstrate any statistically significant change but does point us to gradual decrease in the mean serum magnesium level suggesting that there is a need to study this trend on larger cancer population to determine the chemotherapautic agents effect leading to hypomagnesemic symptom. (Figure F)

Only 2 (6.25%) out of 32 patients experienced peripheral neuropathy. Both the patients serum magnesium level were in the normal range when diagnosed with peripheral neuropathy. (Figure G)

The baseline serum Magnesium value for male and female were Mean ± SEM were 2.046 ± 0.008350 N=20 and 2.038 ± 0.004787 N=12 that is almost same for both the sex group with P value of 0.4903. Furthermore premagnesium level for 2nd cycle Mean ± SEM= 1.970 ± 0.007255 N=20 (male) and 1.980 ± 0.01285 N=12 (female) ,3rd cycle Mean ± SEM= 1.929 ± 0.009383 N=20 (male) and 1.921 ± 0.008657 N=12 (female), 4th cycle Mean ± SEM= 1.891 ± 0.009907 N=20 (male)and 1.888 ± 0.02229 N=12 (female), 5th cycle Mean ± SEM= 1.836 ± 0.01080 N=20 (male) and 1.873 ± 0.05166 N=11 (female), and 6th cycle Mean ± SEM= 1.828 ± 0.04453 N=9 (male) and 1.833 ± 0.08750 N=4 (female) and there P value for 2nd, 3rd, 4th,5th, and 6th cycle were found to be 0.4688, 0.5848, 0.9200, 0.3658, and 0.9581 respectively.

So above result shows that pre magnesium level for 2nd , 3rd , 4th, cycle for both sex group were nearly same but before 5th cycle male mean serum magnesium level were lower compared to their female counterparts. Since no additional patient were given the sixth cycle so the pre magnesium data for sixth cycle were similar in both the sex group.

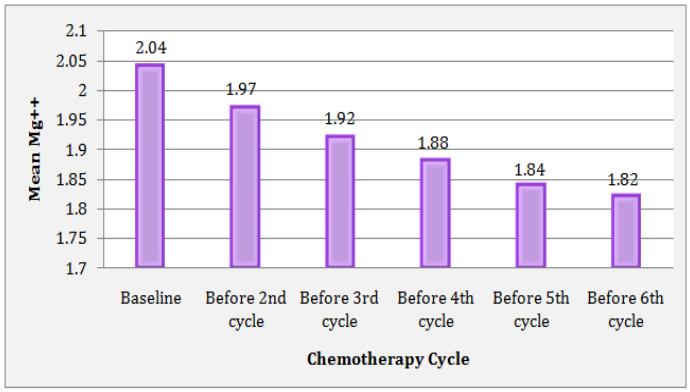

Figure E: Serum Mg++ Vs Chemotherapy Cycle

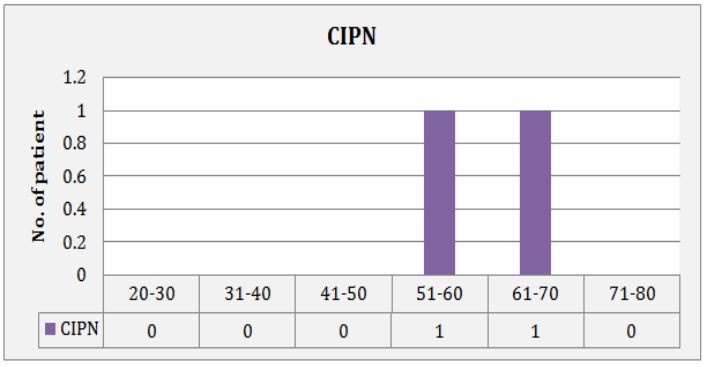

Figure F: No. of Patients Vs CIPN

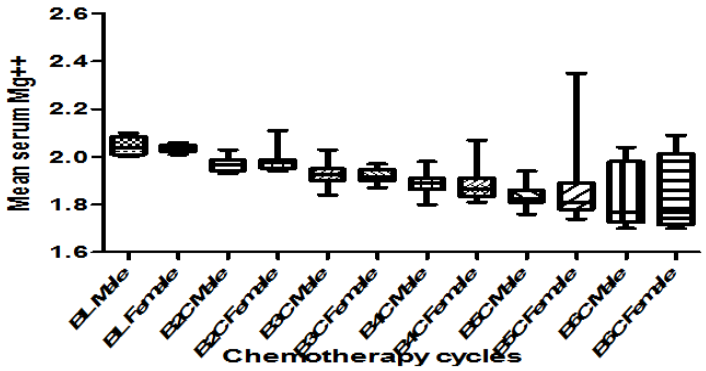

Figure G: Statistical Data of Mean Serum Mg++ Vs Chemotherapy Cycles

Conclusion

A noteworthy finding is the lack of studies focusing on the effects of low magnesium level in patients receiving chemotherapy. Neuropathic symptoms and its assessment in the patients receiving the chemotherapy is the need especially considering the current approach of symptomatic management that we adopt to mitigate the risks associated with chemotherapeutic agents.

Hypomagnesaemia during Treatment: The incidence of hypomagnesaemia reported here was 43%, which is relatively low compared with most other studies (incidence 29-100%). However, the number of evaluable cycles in this study was one less than the actual number of cycles of chemotherapy given, and the drop in magnesium levels increases with each cycle. Therefore, the results presented here underestimate the total effect of cisplatin. The degree of hypomagnesaemia is unpredictable. A same regimen can be given to a number of patients for the same number of cycles and although some patients will have a significant fall in their magnesium level, other patients will not be affected at all. To be able to judge how clinically important any drop in magnesium levels is would be helpful in guiding the treatment of the patient. This is an area worthy of investigation, although difficult due to the symptoms being non-specific and attributable to the underlying malignancy or the treatment.

Magnesium Supplementation to Prevent Hypomagnesaemia: Serum magnesium levels should be routinely assessed whenever electrolyte determinations are ordered in patients who are receiving cisplatin. The first study of magnesium supplements was not conducted until 1982 and the first randomized study was in 1986. Since then, many investigators have suggested that routine magnesium supplements should become part of cisplatin-containing regimens which complements the published studies explaining as to why the supplementation significantly reduces hypomagnesaemia and in sufficient doses can completely ameliorate hypomagnesaemia [2].

In this study premagnesium level for 2nd cycle Mean ± SEM= 1.970 ± 0.007255 N=20 (male) and 1.980 ± 0.01285 N=12 (female) ,3rd cycle Mean ± SEM= 1.929 ± 0.009383 N=20 (male) and 1.921 ± 0.008657 N=12 (female), 4th cycle Mean ± SEM= 1.891 ± 0.009907 N=20 (male)and 1.888 ± 0.02229 N=12 (female), 5th cycle Mean ± SEM= 1.836 ± 0.01080 N=20 (male) and 1.873 ± 0.05166 N=11 (female), and 6th cycle Mean ± SEM= 1.828 ± 0.04453 N=9 (male) and 1.833 ± 0.08750 N=4 (female).

In this study when Paclitaxel and docetaxel were given in combination with cisplatin patient's serum magnesium level gradually fell down but not to level where we could label it as causing hypomagnesaemic conditions. During the clinical examination it was observed that all the patient's had normal sensory, motor, and reflexes. In Conclusion, there is a strong need to understand the CIPN on larger population using more advanced technique such as Nerve conduction study in alliance with the clinical examination. The Current study with limited patient volume only indicates that supplemental magnesium is beneficial in patients receiving chemotherapy but the extent to which the effect ameliorate needs further exploration on larger population.

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