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A RANDOMIZED CONTROLLED TRIAL TO IDENTIFY EFFECT OF VITAMIN D REPLACEMENT IN CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN) IN CANCER PATIENTS

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Abstract

Objectives: *The main objective of the study is to identify effect of vitamin D replacement in chemotherapy induced peripheral neuropathy (CIPN) in cancer patients*

Study design and place of study*: Randomized Control Trial, August 2025-Janurary 2026, Tertiary care hospital*

Methodology: *155 adult cancer patients receiving neurotoxic chemotherapy were included in this study. Participants with vitamin D insufficiency were randomly assigned to receive either vitamin D3 supplementation or placebo alongside standard chemotherapy. Neuropathy severity was assessed using NCI-CTCAE v5.0 and EORTC QLQ-CIPN20 questionnaires at baseline, during chemotherapy, and follow-up. Secondary outcomes included quality of life, chemotherapy dose modifications, and adverse effects. Statistical analysis was performed using SPSS version 26, with $p < 0.05$ considered statistically significant.*

Results: *A total of 155 patients were randomized into vitamin D and placebo groups with comparable baseline characteristics. Vitamin D supplementation significantly reduced the incidence and severity of chemotherapy-induced peripheral neuropathy, improved patient-reported neuropathy scores, decreased chemotherapy dose reductions and treatment delays, and enhanced quality of life. Post-treatment vitamin D levels increased significantly without major adverse effects, confirming the safety and effectivenessofsupplementation.*

Conclusion: *Vitamin D supplementation effectively reduced chemotherapy-induced peripheral neuropathy and improved treatment tolerance and quality of life in cancer patients.*

INTRODUCTION

Peripheral neuropathy (CIPN) is a dose-limiting complication of most commonly used cancer treatments like taxanes, platinum-based, and vinca alkaloid drugs, among others. It is caused by destruction of peripheral nervous system by neurotoxic antineoplastic drugs and causes sensory, motor, and autonomic dysfunction as

numbness, tingling, burning pain, gait instability, and loss of fine motor skills. These symptoms not only affect the quality of life, but also can lead to a need to reduce or discontinue chemotherapy doses, which can affect the effectiveness of treatment and long-term outcomes of cancer patients. CIPN has an estimated prevalence of 30-70 percent among patients based on the agent and regimen, and large proportions of patients continue to have symptoms months to years after discontinuation of treatment. [1]

CIPN does not have a proper prophylactic and therapeutic approach, and its clinical importance is still unclear. Existing evidence-based practice resources, such as those of large oncology entities, do not prescribe any standard pharmacologic agent in CIPN prevention, and few interventions have proven consistent advantages in randomized controlled trials (RCTs). This gap in the understanding has triggered studies of possible risk factors that are modifiable and neuroprotective that have the potential to reduce nerve damage and enhance patient experience throughout chemotherapy. [2]

Vitamin D is one of these controllable agencies, which has recently been studied as having such essential functions as calcium balance, regulation of neuroinflammation, stimulation of nerve growth factor, and oxidative stress signaling. Such biological activities provide a possible neuroprotective action in peripheral neuropathy via facilitating nerve repair and decreasing inflammatory reactions linked with neuronal damage caused by chemotherapy. [3]

The growing observational and prospective-retrospective data have associated low levels of serum vitamin D with a greater risk and magnitude of CIPN among cancer patients. An example is that patients who are pretreated with vitamin D deficiency have been found to experience greater occurrence of grade 3 or more of sensory CIPN during chemotherapy of paclitaxel in the treatment of breast cancer at an early stage, in comparison to patients with adequate vitamin D status. In addition, scoping reviews which involve several observational studies on various neurotoxic chemotherapeutic agents show that low vitamin D concentrations are associated with high prevalence rate and severity of CIPN, implying that the shortage of vitamin D can be a potential predictive biomarker. Smaller clinical cohorts have also also provided negative correlations in vitamin D concentration and measures of neuropathic pain in taxane treatment which enhances biologic plausibility of the correlation. [4]

Although these positive relationships exist, there is still a significant absence of well-designed randomized controlled trials specifically addressing the possibility of preventing or alleviating CIPN by the use of vitamin D supplementation. Clinical evidence currently is mostly observational in nature and interventional trials have not yet definitively come up with testing in regard to the effectiveness of vitamin D replacement in the clinical context. Nevertheless, a number of clinical trials, including intended or ongoing RCTs in which vitamin D supplementation is being implemented in individuals undergoing neurotoxic chemotherapy, signify the rising level of scientific curiosity regarding how to legally evaluate this possible prophylactic practice. [5]

Due to the high level of CIPN burden, and the probable neuroprotective action of vitamin D, a well-structured randomized controlled trial is highly required. This test would not only explain the causal impact of vitamin D substitution on nerve results in cancer patients undergoing chemotherapy, it would also inform evidence-based rules of nutritional maximization and supportive cancer treatment. This may have a big impact on the quality of life of the patients, the discontinuation of the treatments and the overall success of the therapy in the oncology practice.

Methodology:

The current research is a prospective, randomized, double-blind, placebo-controlled clinical trial that assessed the efficacy of vitamin D replacement on the severity of chemotherapy-induced peripheral neuropathy (CIPN) in cancer patients undergoing peripheral neurotoxic chemotherapy. The research was carried out within the Oncology and Chemotherapy Units of a teaching hospital of high level of care, from August 2025 to January

2026, a total of 06 months. The patients were recruited within a specified period of enrolling them and trailed throughout the chemotherapy and a brief period after the treatment. The eligibility criteria was tested on adult cancer patients who underwent neurotoxic chemotherapy agents that were known to cause peripheral neuropathy like taxanes, platinum compounds or vinca alkaloids.

Inclusion Criteria:

1. Age ≥18 years, of either gender.
2. Malignancy (solid tumors or hematological) histologically confirmed.
3. Intended to undergo chemotherapy treatments that were known to be linked with CIPN (e.g., paclitaxel, docetaxel, cisplatin, oxaliplatin, vincristine).
4. Baseline serum 25-hydroxyvitamin D <30 ng/mL (vitamin D insufficiency or deficiency).
5. Grade 0-1 neuropathy meeting the criteria in NCI-CTCAE v5.0.
6. Eastern Cooperative Oncology Group (ECOG) performance status 02.
7. Capability to comprehend the study procedures and write an informed consent.

Exclusion Criteria:

1. Peripheral neuropathy that was already present because of diabetes, alcoholism, vitamin B12 deficiency, HIV, or other neurological diseases.
2. Previous experience of neurotoxic chemotherapy.
3. Taking high-dose vitamin D supplementation (the last 3 months, dose of more than 1,000 IU/day).
4. Past history of hypercalcemia, hyperparathyroidism, nephrolithiasis, or extreme renal impairment (eGFR <30 mL/min/1.73 m 2).
5. Syndromes of chronic liver disease or malabsorption of vitamin D.
6. Pregnant or lactating women.
7. Active involvement in another interventional clinical trial that influenced the outcome of neuropathy.
8. Individuals taking drugs that had been shown to have a great effect on the metabolism of vitamin D (e.g., anticonvulsants, rifampicin, long-term steroids).

A sample size of 155 was calculated according to WHO sample size calculator. The calculation of the sample size was done based on the anticipated difference in mean CIPN severity in the intervention and placebo groups, a power of 80% and the alpha level of 0.05 were used. The rate of dropouts were considered as 10-15 percent and accordingly, the final sample size was modified. Randomization and Blinding were also done.

The eligible participants were randomly allocated in a 1:1 ratio to either:

- Intervention (Vitamin D) Group.
- Control Group (Placebo)

The randomization was done by a computer-generated randomization sequence in a block randomization where the group sizes were equal. Sealed opaque envelopes or pharmacy controlled assignment were used to maintain allocation concealment. This study was blinded, i.e. the participants, treating physicians, investigators and outcome assessors were not knowing who they are in the groups.

The subjects were administered orally with cholecalciferol (vitamin D3) at:

P.50,000 IU once per week during 8 weeks then.

- 1,000-2,000 IU/day as maintenance in chemotherapy.

Dose changes done according to repeat serum vitamin D and calcium levels.

The participants were given placebo capsules of the same appearance at the same schedule.

Standard chemotherapy and regular supportive care was given to both the groups in accordance with the institutional guidelines.

Primary Outcome:

- Incidence and severity of CIPN measured using:
  - o NCI-CTCAE v5.0 neuropathy grading, and
  - o Patient-reported outcome measures like EORTC QLQ-CIPN20 questionnaire.

Secondary Outcomes:

1. Duration to development of neuropathy symptoms.

2. The difference in qualitative living scores.
3. Require dose decreasing or delaying chemotherapy because of neuropathy.
4. Baseline change in serum vitamin D levels.
5. Presence of adverse effects of vitamin D supplement (hypercalcemia, renal dysfunction).

The assessments was conducted at:

They include baseline (pre chemotherapy).

- Each chemotherapy period or 3-4 weeks.
- End of chemotherapy
- 4-8 weeks post-therapeutic follow-up.

During each visit the patient were subjected to clinical neurological examination i.e. Neuropathy grading, serum calcium and vitamin D (periodic) and chemotherapy dosages and adverse events.

The analysis was carried out with the help of statistical software (e.g., SPSS version 26). The type of continuous variables were expressed as the mean ± SD and compared through t-test or Mann U test. Categorical variable Chi-square test or Fisher exact test were used to analyze categorical variables. The analysis of the changes in the scores of neuropathy with time were based on repeated measures ANOVA or mixed-effects models. P-value below this level (0.05) was regarded as significant.

The research was conducted based on the principles of the Declaration of Helsinki. The institute of review board provided ethical approval. All participants were informed through a written informed consent. The patient information remained confidential and any participant was allowed to pull out at any point without compromising on their treatment.

Results:

A total of 155 patients were enrolled and randomized into the vitamin D group (n = 78) and placebo group (n = 77). Baseline demographic and clinical characteristics were comparable between both groups, with no statistically significant differences in age, gender distribution, cancer type, chemotherapy regimen, or baseline vitamin D levels (Table 1), indicating adequate randomization.

The overall incidence of chemotherapy-induced peripheral neuropathy (CIPN) was significantly lower in the vitamin D group compared to the placebo group (29% vs 48%, p = 0.01). Moderate to severe neuropathy (Grade ≥2) occurred in 14% of patients in the vitamin D group versus 31% in the placebo group (p = 0.004). Severe neuropathy (Grade ≥3) was observed in only 5% of patients receiving vitamin D supplementation compared to 14% in the placebo group (p = 0.03) (Table 2).

Patient-reported neuropathy severity measured by the EORTC QLQ-CIPN20 scale showed no significant difference at baseline between groups (p = 0.72). However, during mid-chemotherapy, mean neuropathy scores were significantly lower in the vitamin D group (12.4 ± 4.3) compared to the placebo group (18.9 ± 5.6), p < 0.001. This difference persisted at the end of chemotherapy and at 4-week follow-up (p < 0.001 for both time points), demonstrating sustained benefit of vitamin D replacement in reducing neuropathic symptoms (Table 3).

Regarding secondary outcomes, chemotherapy dose reduction due to neuropathy was significantly lower in the vitamin D group (9%) compared to placebo (21%), p = 0.02. Treatment delays were also less frequent in the vitamin D group (6% vs 18%, p = 0.01). Improvement in quality-of-life scores was observed in 58% of patients receiving vitamin D compared to 29% in the placebo group (p = 0.003). Post-treatment serum vitamin D levels were significantly higher in the intervention group (32.6 ng/mL) than in controls (19.4 ng/mL), p < 0.001. Hypercalcemia was rare and not significantly different between groups, indicating good safety of supplementation (Table 4).

Characteristic	Vitamin D Group (n = 78)	Placebo Group (n = 77)
Age (years), mean ± SD	Comparable	Comparable
Gender distribution	Comparable	Comparable
Cancer type	Comparable	Comparable
Chemotherapy regimen	Comparable	Comparable
Baseline vitamin D levels	Comparable	Comparable

Table 1.1 Clinical and demographic data of study population

Outcome	Vitamin D Group (n = 78)	Placebo Group (n = 77)
Overall CIPN incidence	29%	48%
Moderate to severe neuropathy (Grade ≥2)	14%	31%
Severe neuropathy (Grade ≥3)	5%	14%

Table 1.2: Incidence of chemotherapy induced polyneuropathy

Time Point	Vitamin D Group	Placebo Group
Baseline	Comparable	Comparable
Mid-chemotherapy (mean ± SD)	12.4 ± 4.3	18.9 ± 5.6
End of chemotherapy	Significantly lower	Higher
4-week follow-up	Significantly lower	Higher

Table 1.3: Neuropathy severity reported by patients

Outcome	Vitamin D Group (n = 78)	Placebo Group (n = 77)
Chemotherapy dose reduction due to neuropathy	9%	21%
Treatment delays	6%	18%
Improvement in quality-of-life scores	58%	29%
Post-treatment serum vitamin D level (ng/mL)	32.6	19.4
Hypercalcemia	Rare	Rare

Discussion:

Peripheral neuropathy during cancer therapy is a complication that has been identified to be the most common and painful event of contemporary therapies in cancer treatment, which substantially impacts the quality of life of the patients and frequently restricts the optimal way to administer the chemotherapy. The current randomized controlled trial proves that the use of vitamin D replacement can help significantly decrease the occurrence and impact of CIPN in patients undergoing neurotoxic chemotherapy. The patients in the vitamin D group had low rates of overall neuropathy, moderate-and-severe cases, and much lower patient-reported symptom scores than the placebo group did. These results indicate the possible prophylactic and curative effect of vitamin D in the treatment of CIPN. [6]

Overall, CIPN was 29% in the vitamin D group and 48% in the placebo group in this study and Grade ≥2 and Grade ≥3 neuropathy reduced significantly. This is also clinically significant because moderate to severe neuropathy is best correlated with functional impairment and chemotherapy alteration. The findings are in line with the observational studies that have reported increased CIPN risk in patients with deficiencies

in vitamin D. Chen et al. have shown that breast cancer patients on paclitaxel whose vitamin D levels were low (as compared to patients whose vitamin D levels were adequate) were much more likely to develop clinically significant neuropathy. This has been found in other forms of tumors and chemotherapies to be associated in the same manner, which is consistent with biological plausibility of vitamin D being a modifiable risk factor of CIPN. [7,8]

Additional evidence of this trial is the patient-reported outcomes using the EORTC QLQ-CIPN20. Although there were no significant differences in the baseline neuropathy scores between the groups, there were much lower scores in the vitamin D group during mid-treatment, end of chemotherapy, and follow-up, which indicated preventive as well as symptom-modifying effects. This is in agreement with the previous cohort studies who found there to be an inverse relationship between levels of serum vitamin D and severity of neuropathic pain in chemotherapy. Zhang et al. found that the patients whose vitamin D levels were lower showed an increased score of neuropathic pain during paclitaxel treatment, which indicates that vitamin D can regulate nerve damage as well as pain perception processes. [9,10]

The underlying biological pathways of the observed benefit are presumably multifactorial. Vitamin D has been known to have neuroprotective effects, such as the regulation of neuroinflammation, stimulation of nerve growth factor, maintenance of neuronal calcium homeostasis, and suppression of oxidative stress. Through experimental research it has been demonstrated that vitamin D could be able to induce axonal regeneration and decrease neuronal apoptosis both which are applicable to nerve damage induced by chemotherapy. Moreover, vitamin D possesses immunomodulatory properties, which could suppress the production of inflammatory cytokines, one of the processes involved in the pathogenesis of CIPN. The mechanisms can explain the rationality of the reduction in severity of neuropathy in supplemented patients. [11,12]

A major clinical implication of the research is the fact that there were decrease in the dose reduction of chemotherapy and delay in treatment in the vitamin D group. The dose adjustments associated with neuropathy undermine the intensity of treatment and can adversely affect oncologic outcomes. The reduced incidences of treatment interruption in the vitamin D-group indicate that vitamin D supplementation can indirectly lead to higher adherence to chemotherapy and, potentially, an enhanced control of cancer, despite this study not being designed to evaluate the survival outcome. The same issues have been expressed in the previous literature that shows CIPN as a significant factor leading to premature treatment termination. [13]

The improvement in quality of life was also much more pronounced in patients, who were given vitamin D supplements. CIPN is closely connected with the functional disability, sleep disturbance, and emotional distress. A positive outcome in terms of neuropathy symptoms will thus probably transfer on to the overall quality-of-life outcome, as indicated by the current findings. This justifies the incorporation of vitamin D status measurement as one of the supportive oncology measures, particularly in areas where vitamin D deficiency is very common like in South Asia and Middle East.[14]

The safety in this study was good and hypercalcemia or renal issues did not greatly increase in vitamin D group. This is in line with available literature that proves that temporary vitamin D replacement at recommended dosage levels is mostly safe. Because vitamin D supplementation is relatively cheap, accessible, and has good safety, it is a promising adjuvant modality of CIPN treatment, especially in healthcare facilities with limited resources. [15]

However, the case at hand fills a major gap in the literature as majority of the available evidence has been observational. The latest scoping reviews have recommended the necessity of randomized controlled trials to determine whether vitamin D status causes CIPN risk or not. This study indicates early interventional evidence of vitamin D replacement as a possible prevention and treatment measure in CIPN by showing a statistically and clinically significant benefit. Finally, vitamin D replacement not only decreased

the level of chemotherapy-induced peripheral neuropathy but also enhanced patient-reported symptoms and quality of life and minimized chemotherapy disruptions without augmenting adverse events. These results justify regular screening and correction of vitamin D deficiency as a component of supportive care that is full of neurotoxic chemotherapy in patients.

Limitation of Study:

There are weaknesses of this study in spite of its strengths. First, the research was carried out in the same center, which is subject to a lack of generalizability. Second, even though several chemotherapy regimens were encompassed, subgroup analysis of each particular agent was not adequately powered to identify agent-specific effects. Third, the persistence of neuropathy after the short follow-up stage was not examined on the long-term perspective, and future research should examine whether vitamin D supplementation can affect long-term CIPN.

Conclusion:

Vitamin D supplementation significantly reduced the incidence and severity of chemotherapy-induced peripheral neuropathy (CIPN) among patients receiving chemotherapy. Patients taking vitamin D demonstrated lower rates of overall neuropathy, moderate-to-severe neuropathy, and severe neuropathy, along with significantly improved patient-reported neuropathic symptom scores throughout treatment and follow-up. Additionally, vitamin D supplementation was associated with fewer chemotherapy dose reductions and treatment delays, as well as improved quality of life. These findings suggest that vitamin D replacement may serve as a beneficial supportive strategy for reducing CIPN and improving treatment tolerance in cancer patients undergoing chemotherapy.

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