RESEARCH ARTICLE

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Oral Vitamin B12 versus Placebo for the Prevention of Chemotherapy-Induced Peripheral Neuropathy in Gynecological Cancer Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Objective: To evaluate the efficacy of vitamin B12 (cyanocobalamin) in preventing chemotherapy-induced peripheral neuropathy (CIPN) in patients with gynecological cancer who are receiving neurotoxic chemotherapy. **Materials and Methods:** This randomized, double-blind, placebo-controlled study enrolled gynecological cancer patients undergoing chemotherapy at Rajavithi Hospital between January and September 2021. Patients were assigned in a 1:1 ratio to receive either vitamin B12 (500 micrograms) or a placebo, administered as two oral tablets twice daily from the start of chemotherapy until four weeks after completing six cycles. Primary endpoints included the incidence of CIPN, measured by the Patient Neurotoxicity Questionnaire (PNQ) score, and quality of life, assessed by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) at four time points: (i) before the first chemotherapy cycle, (ii) before the third cycle, (iii) before the sixth cycle, and (iv) four weeks after completion. Safety was evaluated by monitoring vitamin B12-related adverse events. **Results:** Forty patients were randomized into either the vitamin B12 group (n = 20) or the placebo group (n = 20). Chemotherapy regimens included taxane-based combinations with either carboplatin (87.5%) or cisplatin (12.5%). The incidence of CIPN (PNQ score ≥ 4) was significantly lower in the vitamin B12 group than in the placebo group (5% vs. 20%, p = 0.008; OR 0.21, 95% CI: 0.07–0.66). No significant differences in FACT/GOG-Ntx scores or adverse effects were observed (p > 0.05). **Conclusion:** This study highlights the significant effect of vitamin B12 in reducing the incidence of CIPN among gynecological cancer patients undergoing neurotoxic chemotherapy, with a favorable safety profile. Therefore, vitamin B12 may be recommended as a preventive measure for CIPN in this context.

Keywords: Vitamin B12- chemotherapy-induced peripheral neuropathy- neurotoxicity- chemotherapy

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is the second most common chemotherapy-related toxicity after hematologic toxicity. Neurotoxic chemotherapeutic regimens frequently used in gynecological cancer patients included platinum agents (e.g., carboplatin, cisplatin), taxanes (e.g., paclitaxel, docetaxel), and vinca alkaloids (e.g., vincristine) [1]. In addition to chemotherapy type, the risk of CIPN is related to cumulative dose, concomitant use of other neurotoxic agents (e.g., ethanol, lead, mercury, nitric oxide, botulinum toxin), and patient's characteristics, such as age, diabetes, vitamin deficiency, hypothyroidism, and infection [2].

The incidence of CIPN is approximately 30-50% among chemotherapy patients, reaching up to 70% in those treated with paclitaxel or oxaliplatin [3]. CIPN can develop at any time during chemotherapy and may continue to worsen for weeks or months after treatment ends, particularly with cisplatin. It typically affects the peripheral nervous system, presenting as a symmetric sensory neuropathy with symptoms such as numbness, loss of proprioceptive sense, tingling, burning, heat and cold hyperalgesia, or allodynia in a stocking-glove distribution (hands or feet). Paclitaxel and vincristine may also impact motor fibers, leading to motor neuropathy, while autonomic neuropathy, more common with vinca alkaloids, can cause orthostatic hypotension and severe constipation [4].

The exact mechanism of CIPN remains unclear and varies among chemotherapeutic agents. Theories suggest nerve damage may result from microtubule disruption (impairing axonal transport), oxidative stress, mitochondrial damage, neuronal apoptosis, myelin

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sheath damage, and neuroinflammation, ultimately leading to peripheral nerve degeneration or small fiber neuropathy [5]. In gynecological cancers, taxane agents exert antimitotic effects by disrupting microtubules and blocking mitochondrial energy supply in afferent neurons. Platinum agents, in contrast, damage the dorsal root ganglion, causing mitochondrial dysfunction and neuronal apoptosis. These disruptions affect sensory neurons (e.g., A-delta and C fibers), resulting in neuropathic pain characterized by hyperalgesia and allodynia [6].

CIPN presents in various symptom patterns and can significantly impair quality of life [7, 8]. For instance, patients with upper extremity involvement may struggle with tasks such as buttoning shirts, opening bottles, and writing, while those with lower extremity involvement may have difficulty standing, walking, climbing stairs, and driving. These limitations often lead to depression, anxiety, and frustration due to difficulties in daily activities. Furthermore, CIPN disrupts optimal cancer treatment, as affected patients may require dose reductions, treatment delay, or premature discontinuation of chemotherapy, potentially leading to disease progression and poorer survival outcomes.

Interesting in preventing CIPN has grown in recent years due to its significant burden. Effective prevention and treatment not only enhance physical functioning and quality of life but also directly improve survival by enabling patients to receive optimal chemotherapy. Various substances, including amifostine, glutathione, vitamin E, intravenous calcium or magnesium infusion, anticonvulsants, antidepressants, and selective serotonin reuptake inhibitors, have been studied as CIPN prophylactics. However, no studies have demonstrated strong clinical benefits from these interventions [2, 9]. Early detection of symptoms before they interfere with daily functioning currently appears to be the most effective approach.

In clinical practices, some physicians prescribe oral vitamin B to treat peripheral neuropathy, including CIPN, due to its known benefits for the nervous system. Thus, we are interested in evaluating the effect of vitamin B in preventing CIPN. The reason is not only its clinical use but also because vitamin B has the advantages of being low cost, commonly available and less toxicity.

A recent study reported that vitamin B12 supplementation reduced CIPN severity and improved daily physical activity in breast cancer with CIPN and vitamin B12 deficiency [10]. Following this, the same researchers conducted a pilot, randomized, placebo-controlled trial on the efficacy of oral vitamin B for preventing and treating CIPN [11]. Although vitamin B was not superior to placebo, it showed benefits for sensory CIPN in lymphoma patients receiving R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin oncovin, and prednisolone) and in lung cancer patients treated with paclitaxel and carboplatin. Thus, the present study was developed to evaluate the effect of vitamin B12 (cyanocobalamin) in preventing CIPN among gynecological cancer patients receiving neurotoxic chemotherapy, including taxanes, platinum agents, and vinca alkaloids, to improve the quality of life and potentially enhance survival outcomes.

This study aimed to test the hypothesis that patients receiving oral vitamin B12 would experience lower CIPN incidence and improved quality of life compared to those receiving a placebo. Therefore, the objective was to compare CIPN incidence and quality of life between gynecological cancer patients undergoing neurotoxic chemotherapy in the oral vitamin B12 and placebo groups.

Materials and Methods

Study design and settings

This study was a randomized, double-blinded, placebo-controlled trial involving 40 gynecological cancer patients undergoing neurotoxic chemotherapeutic regimens at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand, from January 6 to September 30, 2021. The trial was registered prospectively with the Thai Clinical Trials Registry (TCTR ID 20210104003; URL: http://www.thaiclinicaltrials.org/show/TCTR20210104003) and approved by the Rajavithi Hospital institutional review board (IRB No.63205). No protocol amendments were made after the trial began. We planned to perform this study following the CONSORT 2010 guidelines [12].

Randomization, concealment, and blinding

An independent investigator generated the randomization sequence with web-based software (www.Randomization.com) using a block-of-four design and a 1:1 allocation ratio for vitamin B12 and placebo groups. Randomization numbers were stored in sequentially numbered, sealed-opaque envelopes. An independent pharmacist, uninvolved in the study, prepared and stored the vitamin B12 and placebo tablets. After eligible participants provided inform consent, a nurse assigned each a study identification number, which was given to the pharmacist, who then dispensed the appropriate tablets based on the randomization code. All participants, clinicians, outcome assessors (gynecologic oncology fellows and on duty at the one-day chemotherapy unit), and investigators remained blinded to treatment assignments throughout the study. Blinding was ensured by using vitamin B12 and placebo tablets identical in appearance, color, packaging, labeling, and instruction.

Participants

Chemotherapy-naïve patients aged 18-70 years with confirmed gynecological cancer (ovarian, endometrial, cervical, and vulvar), schedule for their first cycle of neurotoxic chemotherapy with at least one of the following: taxanes (i.e., paclitaxel or docetaxel), platinum derivatives (i.e., carboplatin or cisplatin), or vinca alkaloids (i.e., vincristine or vinblastine), and with planned treatment duration of at least three months, were recruited. Eligible criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0-1, a life expectancy of at least six months, and adequate bone marrow, kidney, and liver functions. Patients were required to be fluent in Thai and able to complete the Thai versions of the Patient Neurotoxicity Questionnaire

(PNQ) and the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) questionnaires. Exclusion criteria included hypersensitivity to vitamin B12, prior neurotoxic chemotherapy, pre-existing peripheral neuropathy (e.g., alcohol abuse, vitamin deficiency, diabetes, hypo- or hyperthyroidism, hereditary neuropathy, syphilis, or AIDS-Acquired Immunodeficiency Syndrome), current CIPN treatments, use of vitamins or supplements, pregnancy, breastfeeding, vegetarian diet, cognitive impairment or severe mental illness, difficulty swallowing pills, or a mean corpuscular volume of red blood cells over 100 fL (suggestive of B12 or folic deficiency). Moreover, signs and symptoms suggestive of vitamin B12 deficiency included paresthesia, numbness, impaired vibration or position sense, gait instability, glossitis, and pallor; patients exhibiting any of these features were also excluded from the study.

Interventions

The study drug consisted of an oral vitamin B12 tablet (500 micrograms (mcg)), and a matching starch-based placebo provided by a pharmaceutical company. The tablets were identical in size, shape, color, and packaging. Each amber zip-lock bag contained 112 tablets for a 28-day supply. The dosage was two tablets taken orally after meals, twice daily, starting on the first day of chemotherapy and continuing for four weeks after completing six cycles.

Outcome measurements

The primary outcome was the incidence of CIPN, defined as a PNQ score of 4 or higher. The secondary outcome included quality of life, assessed by FACT/GOG-Ntx score, as well as adverse effects of vitamin B12 (e.g., rash, hypersensitivity, nausea/vomiting, and diarrhea) and other chemotherapy-related toxicities (e.g., anemia, leukopenia, neutropenia, thrombocytopenia, renal and liver toxicity).

The PNQ is a validated, patient-reported questionnaire to assess the incidence and severity of CIPN. It includes two items on sensory and motor functions, graded from A to E, which reflect patients' subjective symptoms and their impact on daily activities (ADL). Grade A indicates no symptoms, while grade E represents the most severe symptoms [13]. This study's scores were interpreted as follows: A = 1, B = 2, C = 3, D = 4, and E = 5. CIPN was defined as a PNQ score of 4 or higher, as this level indicates symptoms impacting ADL.

The FACT/GOG-Ntx score is a subscale used to measure health-related quality of life in cancer patients [14], focusing on symptoms and concerns related to CIPN. It includes 11 items assessing sensory (5 items), motor (3 items), and autonomic symptoms (3 items) [15], each scored on a 5-point Likert scale (0 = "not at all", 1 = "a little bit", 2 = "somewhat", 3= "quite a bit", and 4 = "very much"). Total scores range from 0 to 44, with higher scores indicating more severe CIPN and a greater impact on quality of life. We plan report mean or median scores for each group and compared them at each time point.

The PNQ and FACT/GOG-Ntx questionnaires were translated into Thai and approved by three independent neurologists to assess CIPN in this study. Item-to-item comparison with the original version, evaluated by Item-Objective Congruence (IOC), showed high validity (0.92), and Cronbach's alpha coefficient indicated high reliability (0.81).

All outcome measures, including efficacy and safety endpoints, were assessed at four-time points: (i) before the first chemotherapy cycle, (ii) before the third cycle, (iii) before the sixth cycle, and (iv) four weeks after the sixth cycle. Assessments were conducted by gynecologic oncology fellows on duty in the chemotherapy unit, who were not involved in this study.

Study procedure

After approval, eligible patients gave informed consent and were randomly assigned to either the vitamin B12 or placebo group (1:1). Baseline data, including clinicopathological characteristics, PNQ, and FACT/GOG-Ntx scores, were collected before the first chemotherapy cycle. Vitamin B12 (500 mcg) or placebo was administrated twice daily, from the first cycle until four weeks after the sixth. Follow-ups every 28 days included pill counts, with participants below 80% compliance excluded from analysis. PNQ and the FACT/GOG-Ntx scores were measured before the third and sixth cycles, and adverse events were recorded at the final visits four weeks after the sixth cycle.

Sample size calculation

The study sample size was calculated using a formula for two independent proportions (1:1 ratio), with a two-tailed alpha of 0.05 and 80% power [16]. Based on the average CIPN incidence with paclitaxel (60%) and the risk estimate from Schloss et al. [11] (OR 5.78; 95%CI 1.63, 20.5), we assumed CIPN incidence would be 60% in the placebo group and 12% in the vitamin B group. This calculation required at least 15 participants per group. Accounting for a 30% drop-out rate, the final estimated sample size was 20 per group, totaling 40 participants.

Statistical analysis

Statistical analysis was conducted using the Stata version 15.1 (Stata Corp, College Station, Texas, USA). All analyses adhered to the intention-to-treat principle, preserving the original randomization. Based on Shapiro-Wilk test results, baseline characteristics were summarized as frequency and percentage for categorical data and mean ± standard deviation or median and range for continuous data. Comparisons between groups were made using the student t-test or Wilcoxon rank-sum test for continuous variables and Chi-square or Fisher's exact test for categorical variables. A generalized linear mixed model (GLMM) was employed to assess treatment effects over time, adjusting for each time point. GLMM analyses included linear regression for normally distributed outcomes, quantile regression for non-normally distributed outcomes, and logistic regression for categorical outcomes. Statistical significance was set at p less than 0.05.

Results

Between January 6 and September 30, 2021, 43 gynecological cancer patients scheduled for their first cycle of taxanes, or platinum-based chemotherapy, were enrolled in the study (see Figure 1). Three patients were excluded before randomization due to loss of follow-up before starting the chemotherapy (n=1), death (n=1), and withdrawal from the trial (n=1). Consequently, 40 patients were randomly assigned to the vitamin B12 or the placebo groups, and all were included in the intention-to-treat analysis.

Baseline characteristics were similar between the vitamin B12 and placebo groups (Table 1). The mean age was 49.9 ± 10.7 years, with 55.0% post-menopausal. One-third of patients were overweight (BMI≥ 25 kg/m^2). Hypertension (32.5%) was the most common comorbidity, followed by dyslipidemia (17.5%), diabetes (15.0%), and venous thrombosis (7.5%). No diabetic patients showed signs of peripheral neuropathy before chemotherapy. Fifteen percent had a prior cancer history; however, those were chemotherapy naïve patients, and 4% had prior radiotherapy. Ovarian/fallopian tube cancer was the most common (50%), followed by endometrial cancer (27.5%), cervical cancer (15%), and synchronous cancers (7.5%). Early-stage cancer (45%), advanced-stage (40%), and recurrent cancer (15%) were presented. Most patients (87.5%) received the standard paclitaxel-carboplatin regimen for ovarian and endometrial cancers, while 12.5% received paclitaxel-cisplatin for cervical or vulva cancers.

At follow-up, nearly all patients had completed six chemotherapy cycles. One ovarian cancer patient in the placebo group developed CIPN during the third cycle of chemotherapy (paclitaxel and carboplatin). Her chemotherapy dose was reduced by 20% following standard CIPN management protocols, which involve dose reduction or cessation [2, 17]. Despite this, her CIPN worsened, and she completed only five cycles.

Mixed-effects model analysis of the PNQ score (sensory and motor) and the FACT/GOG-Ntx revealed a statistically significant difference between the vitamin B12 and placebo group ($p<0.05$), as shown in Table 2. Furthermore, significant differences were also observed at each time point, indicating notable time and treatment effects on CIPN development.

Table 3 presents the CIPN assessment between the two groups using GLMM analysis. The incidence of CIPN was 12.5%, with one patient (5%) in the vitamin B12 and four patients (20%) in the placebo group (Figure 2). The risk estimate (OR) indicated a significantly lower CIPN risk in the vitamin B12 group, showing a 79% reduction compared to placebo (OR 0.21, 95%CI 0.07, 0.66). After adjusting for age, cancer type, stage, and treatment modalities, vitamin B12 further reduced CIPN risk by 96% compared to placebo (OR 0.04, 95%CI 0.01, 0.29)

After adjusting for period effect and

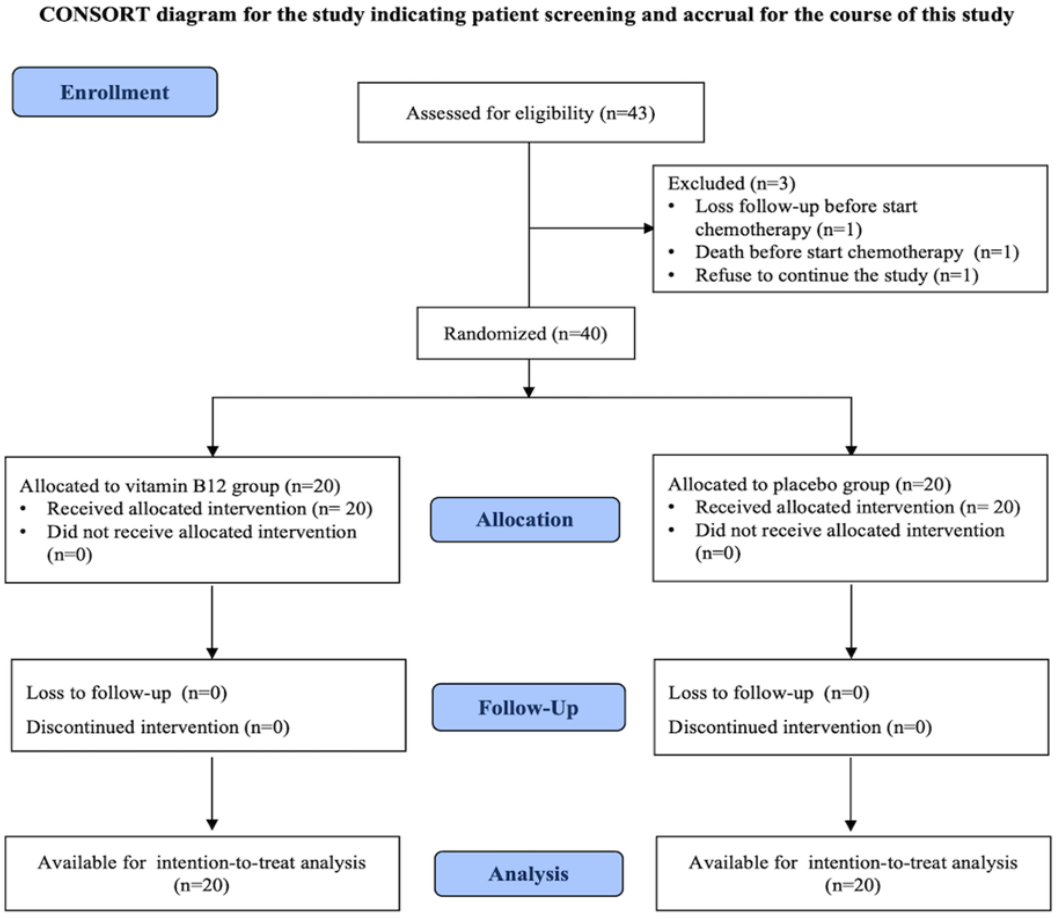

Figure 1. Participant Flow Diagram after Randomization to either Vitamin B12 or Placebo Group

Table 1. Baseline Clinical Characteristics of Participants in Two Groups

Characteristics	Total (n = 40)	B12 group (n = 20)	Placebo group (n = 20)	p-value
Age (year), mean ± SD	49.9 ± 10.7	50.6 ± 8.5	49.3 ± 12.6	0.704[c]
BMI (kg/m^2), mean ± SD	23.8 ± 5.7	23.3 ± 7.1	24.3 ± 4.1	0.586[c]
Underlying disease, n (%)	19 (47.5)	10 (50.0)	11 (55.0)	0.752[a]
Hypertension, n (%)	13 (32.5)	6 (30.0)	7 (35.0)	0.736[a]
Diabetes, n (%)	6 (15.0)	1 (5.0)	5 (25.0)	0.182[b]
Dyslipidemia, n (%)	7 (17.5)	3 (15.0)	4 (20.0)	1.000[b]
DVT/PE, n (%)	3 (7.5)	1 (5.0)	2 (10.0)	1.000[b]
Others+, n (%)	7 (17.5)	3 (15.0)	4 (20.0)	1.000[b]
Previous history of cancer, n (%)	6 (15.0)	2 (10.0)	4 (20.0)	0.661[b]
Previous treatment of cancer, n (%)	7 (17.5)	3 (15.0)	4 (20.0)	1.000[b]
Surgery	3 (7.5)	1 (5.0)	2 (10.0)	
Radiotherapy	4 (10.0)	2 (10.0)	2 (10.0)	
Type of current cancer, n (%)				0.161[b]
Ovarian/Fallopian tube cancer	20 (50.0)	11 (55.0)	9 (45.0)	
Endometrial cancer	11 (27.5)	3 (15.0)	8 (40.0)	
Cervical cancer	6 (15.0)	3 (15.0)	3 (15.0)	
Synchronous cancer++	3 (7.5)	3 (15.0)	0 (0.0)	
FIGO stage of cancer, n (%)				0.764[b]
Early (I-II)	18 (45.0)	10 (50.0)	8 (40.0)	
Advanced (III-IV)	16 (40.0)	8 (40.0)	8 (40.0)	
Recurrence	6 (15.0)	2 (10.0)	4 (20.0)	
Treatment modalities, n (%)				0.901[b]
Chemotherapy alone	6 (15.0)	3 (15.0)	3 (15.0)	
Chemotherapy with surgery	24 (60.0)	13 (65.0)	11 (55.0)	
Chemotherapy with radiotherapy	1 (2.50)	0 (0.0)	1 (5.0)	
Chemotherapy with surgery with radiotherapy	9 (22.5)	4 (20.0)	5 (25.0)	
Chemotherapeutic agents, n (%)				1.000 [b]
Paclitaxel and carboplatin	35 (87.5)	18 (90.0)	17 (85.0)	
Paclitaxel and cisplatin	5 (12.5)	2 (10.0)	3 (15.0)	
ECOG performance status, n (%)				1.000[a]
0	20 (50.0)	10 (50.0)	10 (50.0)	
1	20 (50.0)	10 (50.0)	10 (50.0)	
Smoking, n (%)				1.000 [b]
No	39 (97.5)	20 (100.0)	19 (95.0)	
Yes	1 (2.5)	0 (0.0)	1 (2.5)	
Caffeine consumption, n (%)				0.451[b]
No	31 (77.50)	17 (85.0)	14 (70.0)	
Yes	9 (22.50)	3 (15.0)	6 (30.0)	

+ Others underlying diseases includes hepatitis B infection, gout, myocardial infarction, and HIV infection; ++ synchronous ovarian and endometrial cancer; [a]p-value from Chi-square test; [b]p-value from Fischer's exact test; [c]p-value from student t-test; Abbreviation: DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; kg, kilograms; n, number; NA, not available; m, meters; PE, pulmonary embolism

treatment-period interaction, no significant differences were found between the vitamin B12 and placebo group for PNQ (including PNQ sensory and PNQ motor) and FACT/GOG-Ntx (p≥0.05). However, a significant period effect was observed, as PNQ scores decreased in the third cycle compared to the first (median difference -0.25; 95%CI, -0.45, -0.06, p=0.012) and the sixth cycle compared to the first (median difference -0.25; 95%CI, -0.45, -0.06, p=0.012). Similarly, PNQ sensory scores significantly declined in the third cycle compared to the first (median difference -0.28; 95%CI, -0.48, -0.09, p=0.005) and the sixth cycle compared to the first (median difference -0.30; 95%CI, -0.49, -0.10, p=0.003).

Table 4 shows no serious adverse events (e.g.,

Table 2. Statistics for Primary and Secondary Outcomes

Outcomes	Placebo versus vitamin B12		Difference in time		Placebo versus vitamin B12 over 4-time points	
Scores	T score	P score	T score	P score	T score	P score
Primary outcome						
PNQ	4.87	<0.001*	5.72	<0.001*	5.63	<0.001*
PNQ sensory	5.17	<0.001*	6.35	<0.001*	6.27	<0.001*
PNQ motor	2.88	0.004*	3.02	0.002*	3.03	0.002*
Secondary outcome						
FACT/GOG-Ntx	3.2	0.001*	3.3	0.001*	3.4	0.001*

Notes: The analysis incorporated the comparison of subjects in each arm who experienced CIPN compared to those who did not using a mixed effects model. *Significant p-value <0.05; Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy, FACT/GOG-Ntx, the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; km, kilometers; PNQ, patient neurotoxicity questionnaire

Table 3. Chemotherapy-Induced Peripheral Neuropathy Assessment Compared among Two Groups

Outcome	Total (n=40)	Vitamin B12 group (n=20)	Placebo group (n=20)	Period effect MD/OR (95%CI)	p-value†
Incidence of CIPN, n (%)	5 (12.5)	1 (5)	4 (20)	0.21 (0.07, 0.66)	0.008*
PNQ, mean ± SD					
Before chemotherapy	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	Ref.	
3rd cycle of chemotherapy	3.6 ± 1.3	3.3 ± 1.3	3.9 ± 1.4	-0.25 (-0.45, -0.06)	0.012*
6th cycle of chemotherapy	3.6 ± 1.6	3.3 ± 1.4	3.9 ± 1.8	-0.25 (-0.45, -0.06)	0.012*
4 weeks after completion of chemotherapy	2.7 ± 0.6	2.7 ± 0.6	2.7 ± 0.5	-0.28 (-0.35, 0.09)	0.296
Treatment effect, MD (95%CI)		-0.15 (-0.33, 0.03)	Ref.		
p-value		0.104	-		
PNQ sensory, mean ± SD					
Before chemotherapy	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	Ref.	
3rd cycle of chemotherapy	2.1 ± 0.9	1.9 ± 0.9	2.3 ± 0.9	-0.28 (-0.48, -0.09)	0.005*
6th cycle of chemotherapy	2.2 ± 0.9	2.0 ± 0.8	2.3 ± 0.9	-0.30 (-0.49, -0.10)	0.003*
4 weeks after completion of chemotherapy	1.7 ± 0.5	1.6 ± 0.5	1.8 ± 0.6	-0.16 (-0.35, 0.02)	0.08
Treatment effect, MD (95%CI)		-0.15 (-0.33, 0.03)	Ref.		
p-value		0.098	-		
PNQ motor, mean ± SD					
Before chemotherapy,	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	Ref.	
3rd cycle of chemotherapy, median (min-max)	1.5 (1.0-4.0)	1 (1.0-2.0)	1.5 (1.0-4.0)	-0.10 (-0.30, 0.11)	0.349
6th cycle of chemotherapy, median (min-max)	1.0 (1.0-5.0)	1.0 (1.0-4.0)	1.0 (1.0-5.0)	-0.08 (-0.28, 0.12)	0.417
4 weeks after completion of chemotherapy	1.1 ± 0.2	1.1 ± 0.3	1.0 ± 0.0	-0.001 (-0.20, 0.19)	1
Treatment effect, MD (95%CI)		-0.15 (-0.34, 0.04)	Ref.		
p-value		0.129	-		
FACT/GOG-Ntx, median (min-max)					
Before chemotherapy	0.0 (0.0-3.0)	0.0 (0.0-2.0)	0.0 (0.0-3.0)	Ref.	
3rd cycle of chemotherapy	4.0 (0.0-19.0)	3.5 (0.0-19.0)	5.0 (0.0-14.0)	-0.13 (-0.33, 0.08)	0.22
6th cycle of chemotherapy	4.5 (0.0-29.0)	8.5 (0.0-19.0)	6.0 (0.0-29.0)	-0.36 (-0.49, 0.05)	0.14
4 weeks after completion of chemotherapy	2.0 (0.0-7.0)	1.5 (0.0-7.0)	2.0 (0.0-7.0)	-0.05 (-0.24, 0.15)	0.636
Treatment effect, MD (95%CI)		-0.14 (-0.34, 0.05)	Ref.		
p-value		0.14	-		

Notes: CIPN occurrence is diagnosed as PNQ sensory score ≥ 4 points or PNQ motor score ≥ 4 points; †p-value from generalized linear mixed model analysis (GLMM), *Significant p-value <0.05; Abbreviations: CI, confidence interval, CIPN, chemotherapy-induced peripheral neuropathy, FACT/GOG-Ntx, the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; MD, median difference; OR, Odd ratios; PNQ, patient neurotoxicity questionnaire

anaphylactic shock or rash) were observed in patients receiving vitamin B12. Five patients (12.5%) developed hypersensitivity during the first chemotherapy cycle, with similar rates in both groups (15% in the vitamin B12 group and 10% in the placebo group), likely due to paclitaxel administration. There were also no statistically significant differences between the groups in the other chemotherapy-related toxicities, such as nausea/vomiting, anemia,

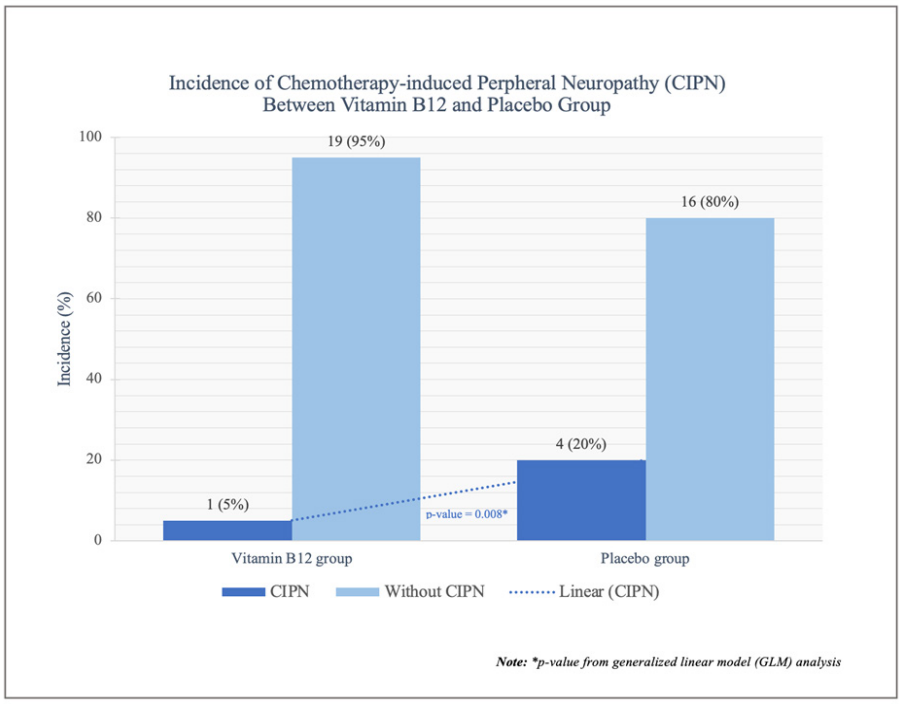

Figure 2. Comparison in Incidence of Chemotherapy-induced Peripheral Neuropathy Between Vitamin B12 Group and Placebo Group

Table 4. Adverse Events in This Study

Parameters	Total (n = 40)	B12 group (n = 20)	Placebo group (n = 20)	p-value
Rash, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Hypersensitivity, n (%)	5 (12.5)	3 (15.0)	2 (10.0)	0.605[b]
Anaphylactic shock, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Nausea/Vomiting, n (%)	7 (17.5)	3 (15.0)	4 (20.0)	0.661[b]
Anemia, n (%)	33 (82.5)	15 (75.0)	18 (90.0)	0.370[a]
Leukopenia, n (%)	19 (47.5)	10 (50.0)	9 (45.0)	0.944[a]
Neutropenia, n (%)	24 (60.0)	10 (50.0)	14 (70.0)	0.124[a]
Thrombocytopenia, n (%)	7 (17.5)	3 (15.0)	4 (20.0)	1.000[b]
Renal toxicity, n (%)	5 (12.5)	2 (10.0)	3 (15.0)	1.000[b]
Liver toxicity, n (%)	8 (20.0)	5 (25.0)	3 (15.0)	0.695[b]

Notes: [a]p-value from Chi-square test; [b]p-value from Fisher's exact test; *Statistically significance p-value < 0.05; Abbreviation: NA, not available

leukopenia, neutropenia, thrombocytopenia, renal toxicity, and liver toxicity. By the study's end, no participants discontinued vitamin B12, placebo, or withdrawal due to unacceptable adverse events.

Discussion

Systemic chemotherapy is essential in treating gynecological cancers to improve survival and reduce recurrence risk. Commonly used agents include platinum compounds (carboplatin, cisplatin), sometimes combined with taxanes, antimetabolite, or anthracyclines, depending on cancer type, stage, and patient comorbidities. However, a frequent side effect, particularly paclitaxel and carboplatin combinations, is peripheral numbness in the limbs, affecting 58.6% of gynecological cancer patients [18]. Thus, effective strategies are needed to manage CIPN in affected patients.

CIPN can significantly impact daily functioning and quality of life, often causing psychological distress and limiting daily activities when severe [7, 8]. Additionally, CIPN is linked to poorer survival outcomes, as patients may not receive optimal cancer treatment if neurotoxic chemotherapy agents are reduced or discontinued due to CIPN [2, 17]. Therefore, the best approach is to identify at-risk patients and implement preventive measures before symptoms develop.

Various strategies, including pharmaceutical agents, supplements, and complementary or alternative medicine (CAM), such as magnet therapy, herbal remedies, acupuncture, and chiropractic manipulation, have been widely studied for CIPN prevention and treatment [2, 19]. However, these approaches are largely ineffective, particularly for sensory CIPN, as they do not promote

neuroprotection or neuroregeneration.

Oral vitamin B complex is a commonly used option for CIPN management in routine clinical practice. A pilot cross-over randomized trial [20] investigated the effects of the selective serotonin reuptake inhibitor (duloxetine) and vitamin B12 in patients with CIPN. While duloxetine significantly improved pain and numbness, it also caused more harm and had drug interactions, such as with warfarin. The study also noted a trend of improvement in pain and numbness with vitamin B12 administration [20]. Recently, a randomized trial comparing vitamin B complex, and placebo found no significant reduction in CIPN with vitamin B complex over placebo. However, vitamin B12 appeared beneficial in patients with vitamin B12 deficiency [11]. This led us to design a trial to evaluate the effect of vitamin B12 in preventing CIPN in gynecological cancer patients.

Vitamin B12 (cobalamin) supports nerve regeneration by promoting nerve cell survival, remyelination, and maintenance of myelin sheaths [21, 22]. This function is often impaired in CIPN patients. Accordingly, vitamin B12 can improve nerve function and even provide a complete cure for nerve function, especially physiologic sensory nerve conduction velocity, which could still be achieved in CIPN patients.

The standard guideline for treating vitamin B12 deficiency recommends 1,000 mcg of intramuscularly (IM) hydroxocobalamin three times weekly for two weeks, followed by maintenance every three months for life [23]. However, IM injections are time-consuming for patients and caregivers and increase healthcare costs. A Cochrane review concluded that 2,000 mcg of oral vitamin B12 (cyanocobalamin) daily, or 1,000 mcg daily, then weekly and monthly, may be as effective as IM administration for short-term neurological improvement in vitamin B12 deficient patients [24]. Moreover, a budget analysis also showed annual savings of $14.2 million from switching to oral vitamin B supplements [25]. Thus, our study administered 500 mcg of vitamin B12, with two tablets taken twice daily after meals in the intervention group.

We selected patients at risk for CIPN based on established risk factors, including chemotherapy regimen and underlying medical conditions. Previous studies indicate that CIPN incidence is approximately 60% with paclitaxel or cisplatin, typically occurring within the first month of treatment [3, 11]. Therefore, we included patients with ovarian/fallopian tube cancers, endometrial cancer, cervical cancer, and vulvar cancer conditions often treated with neurotoxic regimens to ensure a substantial number of CIPN cases. Despite all patients receiving paclitaxel-based regimens, CIPN incidence in our study was only 12.5%, which is lower than the previous reports [3, 11]. The possible reason may be reliance on subjective patient-reported outcomes, which may underestimate CIPN occurrences. However, almost all CIPN cases in our study emerged by the third chemotherapy cycle, suggesting that preventive strategies should ideally start at the first or second cycle.

The main finding of this study was a significantly lower incidence of CIPN in the vitamin B12 group compared to the placebo group (5% vs 20%, respectively, p=0.008). Also, the risk estimates showed that the patients taking vitamin B12 had a 79% lower risk of CIPN than those on placebo (OR 0.21, 95%CI 0.07, 0.66). This result aligns with a previous study, where patients in the placebo group had approximately six times higher odds of having CIPN than those in the vitamin B group (OR 5.78; 95%CI 1.63, 20.5) [11]. Similar findings may be due to both studies primarily involving female patients receiving taxane-based chemotherapy (approximately 70%) and using the PNQ score to diagnose CIPN.

Regarding the quality of life, we observed an increasing trend in FACT/GOG-Ntx scores during later chemotherapy cycles. This supported previous evidence that CIPN develops in a time- and dose-dependent manner [26, 27]. However, there was no significant difference in FACT/GOG-Ntx between the vitamin B12 and placebo groups. Although this questionnaire is validated by the neurologist and considered reliable, it remains a subjective tool reliant on the patient's self-reporting. Therefore, a more objective assessment tool for CIPN is needed better to evaluate the effect of vitamin B12 in this context.

This study has several strengths. First, it employed a rigorous, well-designed methodology with a randomized controlled trial including a placebo arm, along with participants, clinicians, outcome assessors, and investigators blinding. The balanced baseline characteristics between the two groups suggested effective randomization, thus minimizing the selection bias and confounding factors. Second, the use of the PNQ score and FACT/GOC-Ntx (Thai version) provided simple, easy, valid, and reliable tools for CIPN assessment. Third, an intensive monitoring protocol ensured the absence of serious adverse events from vitamin B12, confirming its safety and tolerability. Lastly, weekly phone reminders maintained high adherence, with a nearly 100% compliance rate, and all patients in this study had a complete follow-up.

Nevertheless, several limitations should be noted in the present study. The small sample size limits the generalizability of our findings, and while the study had adequate power to assess vitamin B12's effects on CIPN, larger randomized trials are needed to confirm other results. Additionally, our CIPN assessments relied on patient-reported outcomes (PNQ score and FACT/GOG-Ntx), which may introduce information or subjective bias. Future research should consider combining subjective and objective assessments, such as total neuropathy score (TNS), neurological examination, nerve conduction studies, or skin biopsy, despite their higher additional costs and need for specialized expertise. Furthermore, this study was limited by a short duration of treatment and follow-up period, with vitamin B12 administered only up to one month after the sixth chemotherapy cycle. CIPN may persist for longer periods due to unclear mechanisms, future study should consider extending treatment and follow-up period to 6 months or even a year after the completion of chemotherapy. Additionally, the study population was also heterogeneous; while we focused on gynecological cancer patients receiving taxanes and platinum combinations, CIPN's mechanism varied across chemotherapeutic regimens. Identifying which regimens

benefit most from vitamin B12 would be valuable for targeted interventions.

Recommendation for future research

To confirm the efficacy of vitamin B12 supplementation in preventing CIPN, future investigations should include larger, multicenter randomized controlled trials with adequate sample sizes to enhance generalizability and statistical precision. These studies should integrate both patient-reported outcomes and objective neuropathy assessments such as nerve conduction studies, neurological examinations, or TNS and enroll more homogeneous patient populations or apply stratified and adjusted analyses to reduce clinical heterogeneity. Extended longitudinal follow-up is also essential to capture delayed-onset and persistent CIPN beyond the early post-chemotherapy period. In addition, routine measurement of baseline and post-treatment vitamin B12 levels would help identify subclinical deficiency and clarify causal pathways. Collectively, these methodological refinements will strengthen both internal and external validity and provide more definitive evidence regarding the role of vitamin B12 in CIPN prevention.

In conclusion, the present study suggests that oral vitamin B12 may reduce the incidence of CIPN in gynecological cancer patients undergoing neurotoxic chemotherapy, supporting its potential as a preventive measure for CIPN in this clinical setting. However, due to certain limitations, this conclusion remains tentative. Larger randomized clinical trials with improved CIPN diagnostic tools and specific chemotherapeutic regimens are necessary to confirm vitamin B12's efficacy before recommending its use in CIPN management guidelines.

Author Contribution Statement

Putsarat Insin: Conceptualization; Resources; Supervision; Investigation; Formal analysis; Writing–original draft; Writing–review and editing. Trinya Chaiwongsa: Conceptualization; Data curation; Resources; Investigation; Writing–original draft. Nisa Prueksaritanond: Data curation; Resources; Investigation; Writing–review and editing. All authors have reviewed, edited, and approved the final version of this manuscript.

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If any scientific Body approved it/ if it is part of an approved student thesis

This study has not been approved by any additional scientific body beyond the institutional ethics committee, and it is not part of an approved student thesis.

How the ethical issue was handled (name the ethical committee that approved the research)

This trial was approved by the Rajavithi Hospital institutional review board (IRB No.63205).

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Availability of data (if applicable to your research)

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Was the study registered in any registration dataset (for clinical trials, guidelines, meta-analysis)

The trial was registered prospectively with the Thai Clinical Trials Registry (TCTR ID 20210104003; URL: http://www.thaiclinicaltrials.org/show/TCTR20210104003).

Any conflict of interest

The authors declared no conflicts of interest and confirmed that no sponsorship was received from vitamin B12 manufacturers.

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