

Management of peripheral neuropathy symptoms with a fixed dose combination of high-dose vitamin B₁, B₆ and B₁₂: A 12-week prospective non-interventional study in Indonesia



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ABSTRACT

Background: Peripheral neuropathy is a common condition which can have a significant impact on quality of life. It occurs as a component of several common and rare diseases or can be idiopathic and can present with various symptoms. **Aims and Objectives:** This study is aimed at evaluating the effectiveness and safety of the fixed dose combination of vitamin B₁, B₆ and B₁₂ in mild to moderate peripheral neuropathy of various etiologies in the Indonesian population. **Materials and Methods:** This was a prospective, open label, multi-center, single arm observational study (Indonesian Clinical Trial Registry No: INA-KPAODYA). A total of 411 subjects with mild to moderate peripheral neuropathy of various etiologies, who met the eligibility criteria, were included in the study. A subject was considered to have "completed" the study if the study procedures, up to Visit 3 (one month of treatment) were accomplished. Procedural results and 12-week clinical outcomes are reported. **Results:** Treatment with combination of vitamin B₁, B₆ and B₁₂ in subjects with symptoms of PN showed significant improvement in overall Total Symptom Score (TSS), within 14 days. The treatment also successfully reduced individual components of TSS from baseline to Visit 5. A significant percentage reduction was also observed for all the Visual Analogue Scale (VAS) parameters at the end of 12 weeks, while the Quality of Life (QoL) scores increased from baseline to the end of treatment. **Conclusions:** The fixed dose combination of vitamin B₁, B₆ and B₁₂ was effective and well tolerated in subjects with mild to moderate peripheral neuropathy, of various etiologies.

Key words: Peripheral neuropathy, Vitamin B₁, B₆ and B₁₂, Tingling, Numbness, Prospective study, Vitamin deficiency, TSS, VAS, SF-8, QoL

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INTRODUCTION

Peripheral neuropathy (PN) is a clinical condition, wherein the peripheral nervous system is damaged.¹ Symptoms of PN can be diverse, patients often experience prickling, tingling, numbness, a reduced ability to feel pain or changes in temperature, a burning pain, and allodynia.²⁻⁵ The common causes of PN include systemic diseases like diabetes, environmental toxins, vitamin and nutritional deficiency, drug-induced traumatic injury, excessive consumption or alcohol abuse, immune system diseases or viral infection, hypothyroidism, genetic and idiopathic.⁵⁻⁹ Although the exact incidence of PN is not well documented, there is data showing a prevalence of 8.1% in general population at the age of 40-49.⁹ Early diagnosis and treatment are crucial to maintaining the quality of life (QoL) and avoid further progression of the disease and development of severe symptoms. When symptoms are severe or irreversible, PN can lead to deterioration of QoL.¹⁰

Various treatment options are available for the management of neuropathy.¹¹ Studies have shown effectiveness of Vitamin B, Alpha Lipoic Acid (ALA) and Acetyl L Carnitine in the management of mild to moderate PN^{9,12-16} and B Vitamins can also be used as co-treatment in advanced stages.¹⁷⁻¹⁹

Vitamin B (B₁, B₆, B₁₂) deficiencies, may lead to an impaired nervous system.²⁰ The three vitamins are complementary as they act via different modes of action.¹⁹ Thiamine diphosphate is the active form of vitamin B₁ and serves as a cofactor for several enzymes involved primarily in carbohydrate catabolism²¹ and may prevent microvascular complications in diabetes.²¹ Vitamin B₆ also is a coenzyme in many different metabolic reactions including transaminases and L-amino acid decarboxylases, which are crucial for the synthesis of neurotransmitters like dopamine, serotonin and γ aminobutyric-acid (GABA).²² Vitamin B₁₂ may improve the nerve regeneration and restores nerve function, decreases neurotoxic cytokines, and improves myelin structure.²¹

Fixed dose combination products of vitamin B₁, B₆ and B₁₂ were found to be effective, safe and well tolerated in the treatment of PN in earlier studies.^{13,14,23,24} The combination of vitamin B₁, B₆ and B₁₂ is commonly used in the clinical practice for decades to treat peripheral neuropathy, however, the level of published scientific evidence is not high but this treatment is seen as a well-established, experience-based treatment. Additionally, majority of the studies showing effectiveness of this combination, in treatment of PN, have been performed with diabetic patients not providing information on the effect in PN of any other etiology.²⁵ The objective of the present non-

interventional study was to evaluate the effectiveness and safety of commercially available fixed-dose combination of vitamin B₁ (100 mg), B₆ (100 mg) and B₁₂ (5000 mcg) once daily, in routine clinical practice in mild to moderate PN of various etiologies in addition to diabetes, in the Indonesian population.

MATERIALS AND METHODS

Subjects

This prospective, open-label, non-interventional (observational) single arm, multi-center study was conducted in Indonesian population at 8 centers. The study was performed in accordance with Declaration of Helsinki (1964) and received approval from the Independent Ethics Committee/Institutional Review Board/local regulatory; all subjects provided informed consent prior to their participation (Indonesian Clinical Trial Registry No: Neurobion Non-interventional (NENOIN) Study INA-KPA0DYA).

Subjects with PN of various etiologies, including Diabetes Mellitus, nutritional, alcoholic neuropathy, carpal tunnel syndrome, idiopathic and others, who were willing to provide signed informed consent were enrolled in the study. Subjects aged ≥ 18 years and ≤ 65 years and subjects with peripheral neuropathy diagnosed by using either a Michigan Neuropathy Screening Instrument (MNSI) score of ≥ 7 in Patient Administered Questionnaire and Health care Professional Score of ≥ 2.5 OR Toronto Clinical Neuropathy Score (TCNS) of ≥ 6 were included in the study.

Subjects with known, clinically significant cardiovascular, pulmonary, gastrointestinal, hematological, hepatic, renal or endocrine diseases (except diabetes mellitus) or those with history/sign/symptoms suggestive of genetic neuropathy or those who underwent any gastrointestinal surgery in the last 6 months before consent or with a plan for surgery during the study or those with any clinically significant or unstable medical or psychiatric condition that in the opinion of the Investigator would affect the subject's ability to participate in the study or those who were the participants in other clinical trials in last one month were excluded from the study.

Further, subjects with intake of vitamin B complex products for more than 1 week consecutively in the last 3 months before consent or those with known hypersensitivity to any component of Neurobion[®] Forte tablet and subjects with severe neuropathy [TCNS ≥ 12 or visual analogue scale (VAS) ≥ 7 for pain] who were on therapy with NSAIDs, gabapentin, pregabalin, or any other

anti-inflammatory drugs were excluded from the study. Subjects who were on any treatment like methotrexate which interferes with neuropathy or any other cytostatic drug treatment were excluded. Subjects with pregnancy, planning to become pregnant or breastfeeding were also excluded from the study.

Study Drug

The eligible subjects received the study drug (Vitamin B₁/Thiamine Mononitrate, 100 mg, Vitamin B₆/Pyridoxol Hydrochloride 100 mg and Vitamin B₁₂/Cyanocobalamin 5000 mcg marketed as Neurobion® Forte in Indonesia) orally once daily for 12 weeks. Subjects were followed up, post 14 days of treatment, and on a monthly basis for upto 3 months.

Outcome measures

Primary outcome measure

Total Symptom Score (TSS): TSS (stabbing pain, burning pain, paresthesia, and numbness) was scored by the physician or a trained nurse regarding their frequency and intensity.²⁴ Total Symptom Scores were recorded at baseline and at each study visit. Comparison of TSS for every visit was made with baseline scores which ranged from 0 (no symptoms) to a maximum of 14.64 points (all symptoms are severe and [almost] continuously present).

Secondary outcome measures

1. Visual Analogue Scale (VAS) score: Change in severity of each symptom of neuropathy (e.g. pain, burning, paresthesia, numbness, etc.) from baseline up to 3 months of treatment was recorded by the subject using a VAS ranging from 0-10 (0 indicating no symptoms and 10 worst possible symptoms).

2. Short Form-8 (SF-8) Health Survey Questionnaire (QoL): At baseline and at 4 weeks interval was recorded on Visits 1, 3, 4 and 5.²⁵

3. Evaluation of safety was based on the occurrence of any adverse event (AE) during the 12 week study period and was graded based on the severity, onset and the course of AE.

Statistical analysis

Any significant differences in change from baseline to other follow-up visits for variables such as TSS, QoL scores and VAS scores were assessed by exploratory analysis, using appropriate statistical tests which included Wilcoxon signed rank test, independent t-test, Cochran-Armitage Trend Chi-square test, etc. depending on the type and distribution of data. Mean percentage reduction from baseline, of overall TSS and individual symptom scores, of VAS score for each symptom, and QoL data were summarized. Univariate and multivariate logistic regression analysis was performed to

identify the factors contributing to the QoL [(physical component summary (PCS) and mental component summary (MCS), physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health scores]. Statistical analyses were made utilizing SAS Version 9.1.3 (NC, USA).

A sample size of 411 subjects was estimated by assuming a 50% improvement in clinical symptoms of PN as evaluated by TSS (baseline up to 3 months of treatment) and a precision of 5.5%, confidence interval 95%, level of significance 5% and a dropout rate of 20%. All statistical tests were two-tailed and performed with The Statistical Package for Social Science (SPSS Inc., Chicago, USA; version 15.0 for Windows).

RESULTS

Of 414 subjects screened, 411 subjects (297 females and 114 males) who met the eligibility criteria were enrolled in the study. The baseline characteristics of study subjects are shown in Table 1. A total of 399 subjects completed and 12 subjects discontinued the study. The mean age of the subjects was 50.9±8.25 years (22 to 65 years).

Total symptom score

The mean (±SD) TSS at baseline was 5.45 (±2.036) and 4.35 (±1.914) at Visit 2. The mean TSS change from baseline to Visit 2 (1.090±1.4097) was statistically significant

Table 1: Demographic characteristics

	N=411 (100%)	Min; Max
Etiologies		
Diabetic	104	
Carpal tunnel syndrome	44	
Idiopathic	112	
Other	25	
Combination*	126	
Gender, n (%)		
Male	114 (27.7)	
Female	297 (72.3)	
Age (years)		
Mean±SD	50.9±8.25	22; 65
Ethnicity, n (%)		
Javanese	151 (36.7)	
Sundanese	27 (6.6)	
Malay	33 (8.0)	
Madurese	0 (0.0)	
Batak	38 (9.2)	
Other	162 (39.4)	
Height (cm)		
Mean±SD	157.9±7.51	105; 180
Weight (kg)		
Mean±SD	62.5±10.86	34; 98
Body mass index (kg/m ²)		
Mean±SD	25.07±4.034	13.6; 49.9

Values represent the mean±standard deviation. *Combination included Diabetic & Nutritional or Diabetic & Carpel tunnel syndrome & Idiopathic etc

($p < 0.0001$). The mean (\pm SD) TSS at Visit 3, 4 and 5 were 3.551 (± 1.6919), 2.786 (± 1.4801) and 2.020 (± 1.2808) respectively. The mean (\pm SD) TSS change from baseline to Visit 2, 3, 4 and 5 ($p < 0.0001$) were 1.090 (± 1.4097), 1.892 (± 1.652), 2.677 (± 1.873) and 3.448 (± 2.066) respectively. A reduction of 62.9% in TSS from baseline to Visit 5 was observed during the study.

Figures 1 and 2 represent mean score and mean percentage reduction of the individual symptoms as well as overall total score assessed by TSS questionnaire, from baseline to Visit 5 respectively. As evident in Figure 1, significant reduction ($p < 0.0001$) in overall total score was observed within 14 days of treatment, the reduction was observed at all follow-up study visits.

Numbness

Overall, a 55.9 mean percentage reduction in numbness from baseline to Visit 5 was observed during the study. At each visit, the change from baseline value was statistically significant ($p < 0.0001$).

Stabbing pain

Overall, a 64.7 mean percentage reduction in stabbing pain from baseline to Visit 5 was observed during the study. At each visit, the change from baseline value was statistically significant ($p < 0.0001$).

Burning pain

Overall, 80.6 mean percentage reduction in burning pain from baseline to Visit 5 was observed during the study. At

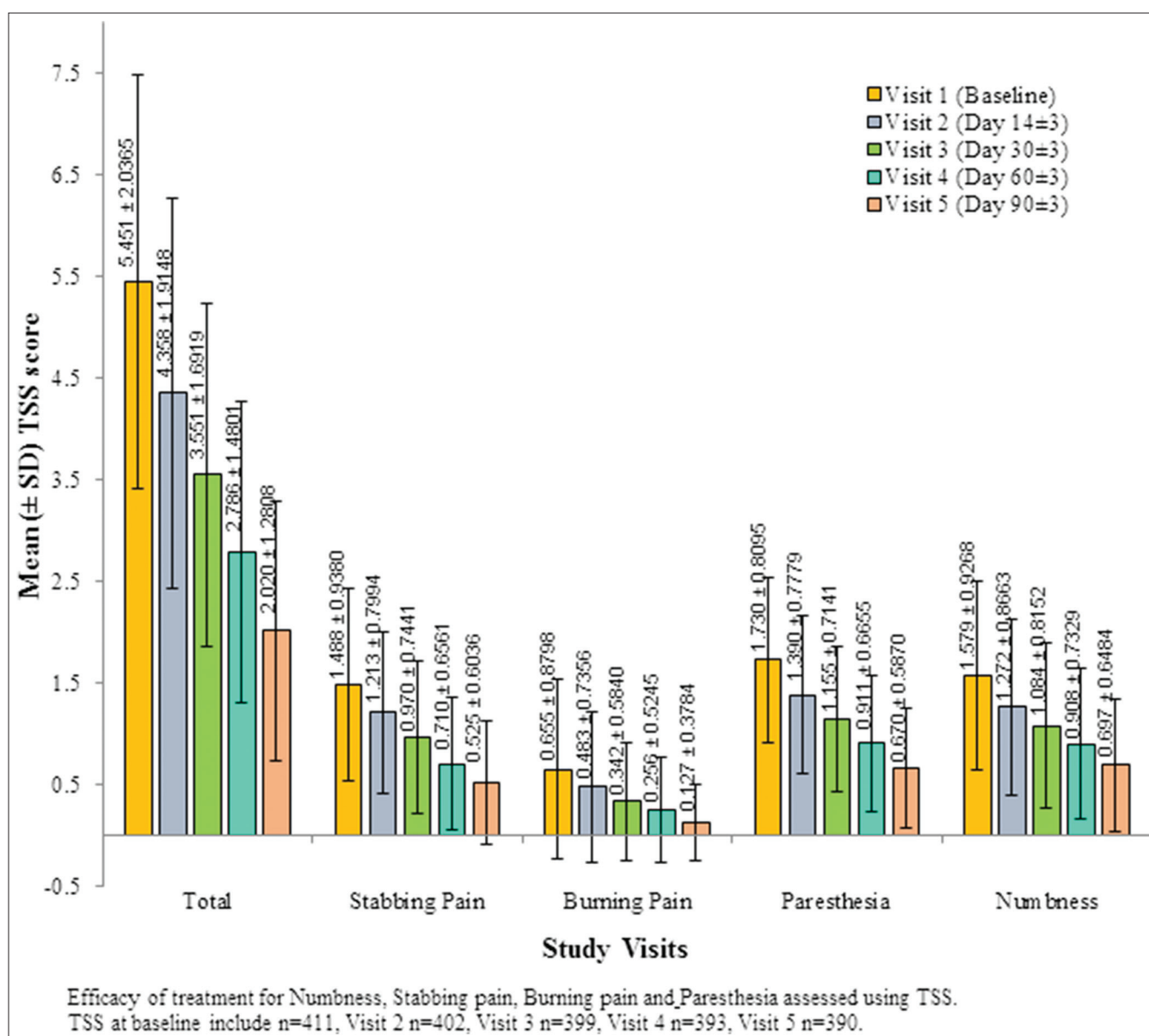


Figure 1: TSS – Total Symptom Score (TSS) and Individual Component Score across Study Visits

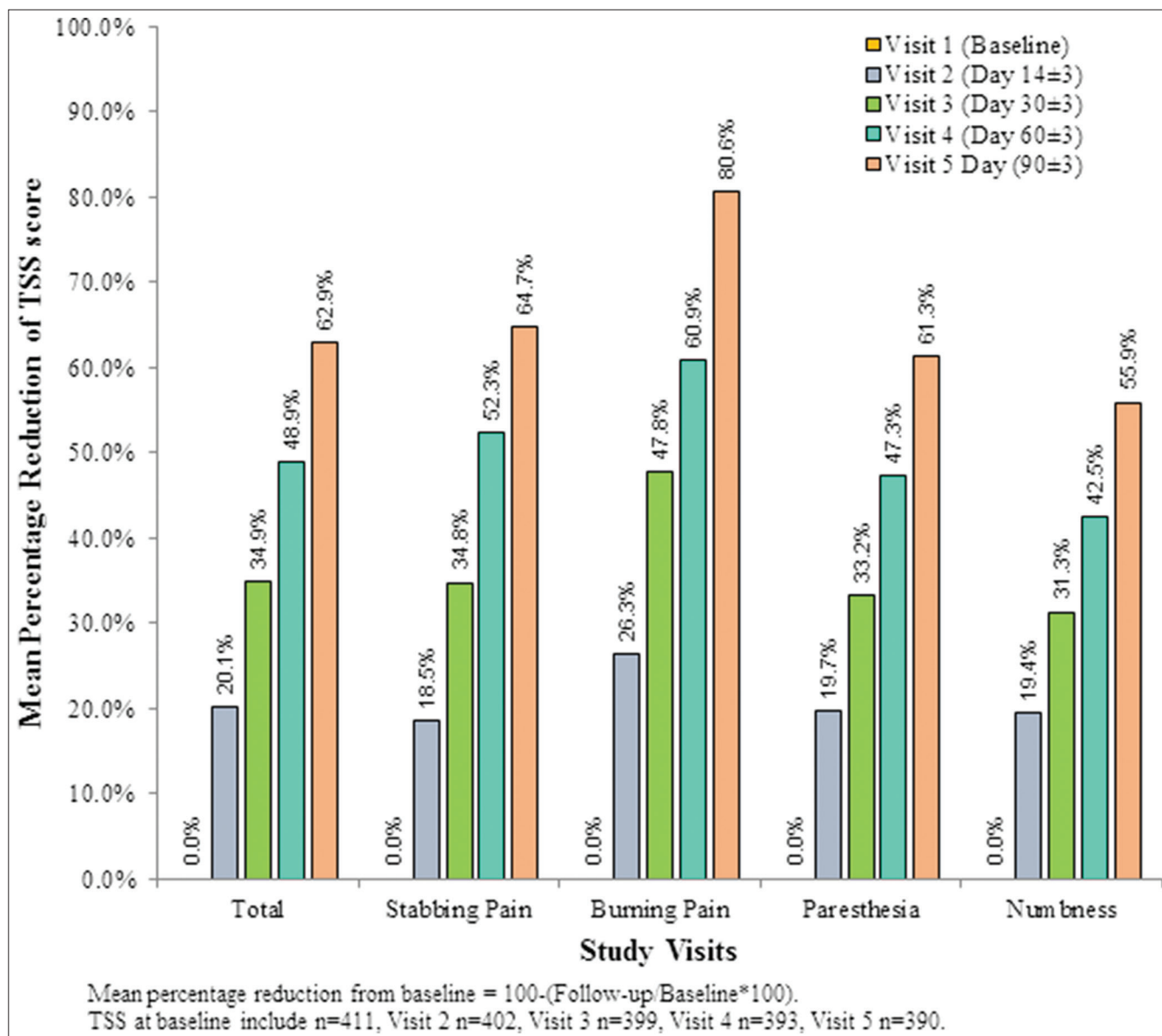


Figure 2: Mean Percentage Reduction of Total Symptom Score (TSS) and Individual Component Score across Study Visits

each visit, the change from baseline value was statistically significant ($p < 0.0001$).

Paresthesia

Overall, a 61.3 mean percentage reduction in paresthesia from baseline to Visit 5 was observed during the study. At each visit, the change from baseline value was statistically significant ($p < 0.0001$).

Visual analogue scale

The mean (\pm SD) score and the mean percentage reduction from baseline to Visit 5 in VAS for numbness, burning pain, tingling, pain, and paresthesia, is presented in Figure 3 and Figure 4, respectively.

Numbness

A reduction in mean (\pm SD) VAS score for numbness was observed from baseline, 4.24 (\pm 1.380) to Visit 5, 1.79 (\pm 1.012) which was statistically ($p < 0.0001$) significant. A 57.8 mean percentage reduction in VAS for numbness from baseline to Visit 5 was observed during the study.

Burning

A reduction in mean (\pm SD) VAS score by total for burning was observed from baseline, 4.11 (\pm 1.499) to Visit 5, 1.50 (\pm 1.402) which was statistically ($p < 0.0001$) significant. A 63.5 mean percentage reduction in VAS for burning from baseline to Visit 5 was observed during the study.

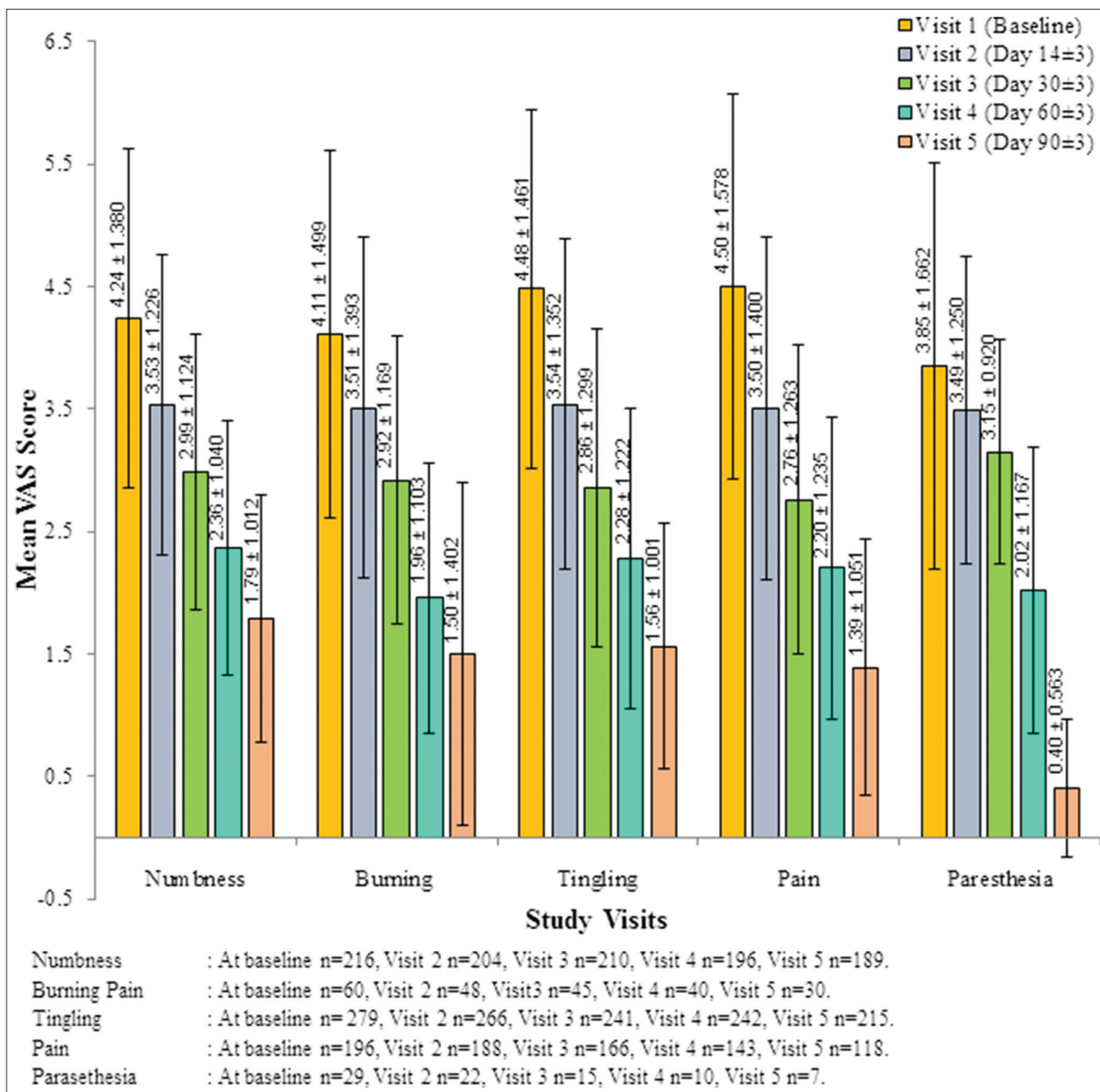


Figure 3: Visual Analogue Scale (VAS) Score for Peripheral Neuropathy Symptoms across Study Visits

Tingling

A reduction in mean (±SD) VAS score by total for tingling was observed from baseline, 4.48 (±1.461) to Visit 5, 1.56 (±1.001) which was statistically (p<0.0001) significant. A 65.2 mean percentage reduction in VAS for tingling from baseline to Visit 5 was observed during the study.

Pain

A reduction in mean (±SD) VAS score by total for pain was observed from baseline, 4.50 (±1.578) to Visit 5, 1.39

(±1.051) which was statistically (p<0.0001) significant. A 69.1 mean percentage reduction in VAS from baseline to Visit 5 was observed during the study.

Paresthesia

A reduction in mean (±SD) VAS score by total for paresthesia was observed from baseline, 3.85 (±1.662) to Visit 5, 0.40 (±0.563). An 89.6 mean percentage reduction in VAS for paresthesia from baseline to Visit 5 was observed during the study.

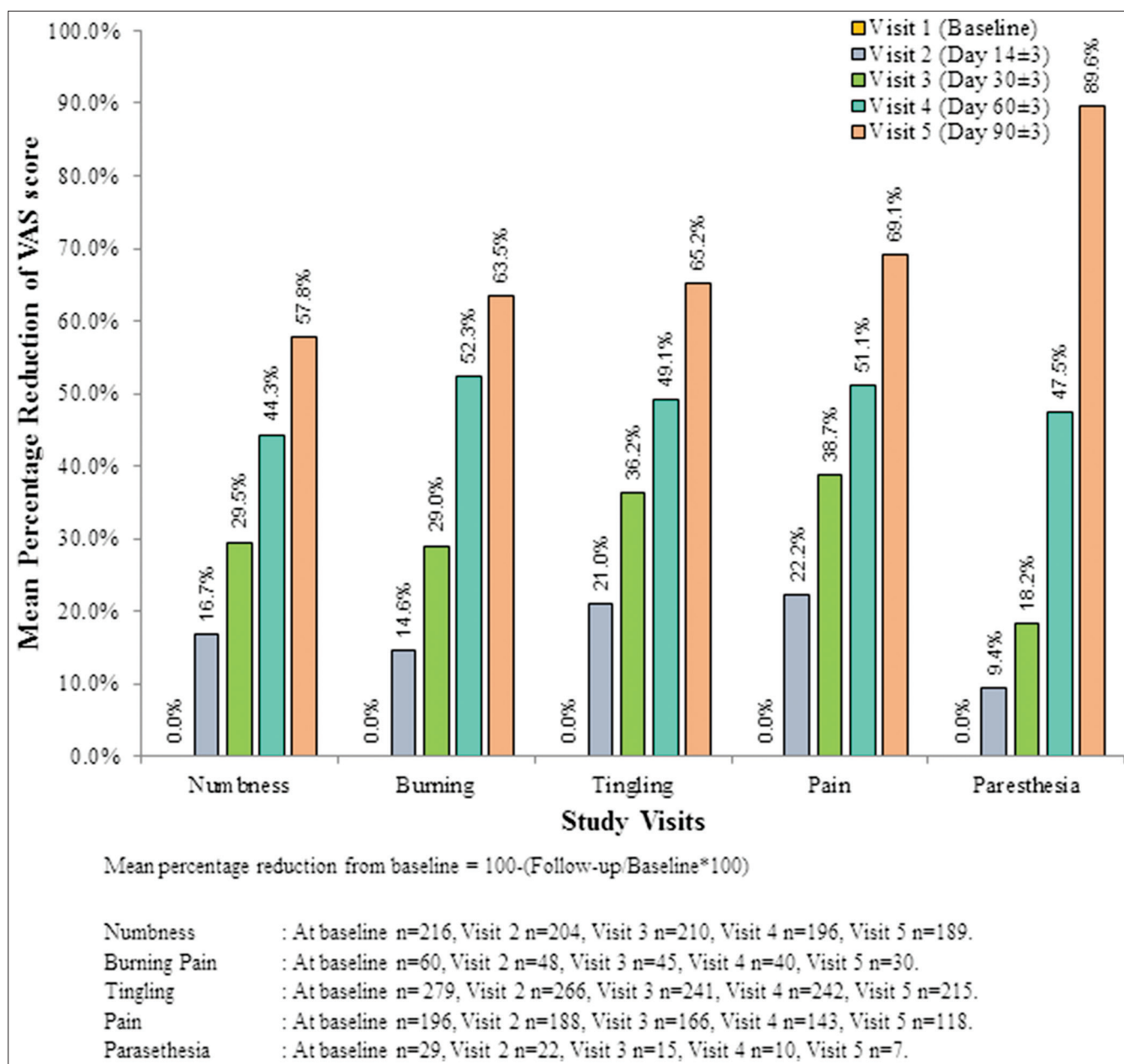


Figure 4: Mean Percentage Reduction of Visual Analogue Scale (VAS) Score Peripheral Neuropathy Symptoms across Study Visits

Quality of life

Significant improvement in QoL domains (PCS and MCS) as well as eight subdomains was observed from baseline to Visit 5. The mean PCS scores at baseline and Visit 5 were 43.965 ± 6.4726 and 50.847 ± 6.0778 respectively. The mean MCS scores at baseline and Visit 5 were 49.226 ± 8.5435 and 54.190 ± 6.0594 respectively. The improvement in QoL was consistent across all etiologies of PN.

Safety

Of 411 subjects enrolled in the study, 14 subjects (3.4%) experienced at least one AE during the study period. One subject reported one serious AE (in-patient hospitalization

or prolongation of existing hospitalization), three subjects had at least one treatment-related AE and three subjects had at least one AE leading to study termination. Of the 3 subjects with atleast (one treatment-related AE, 2 were with gastrointestinal disorders which included dyspepsia and nausea, and skin and subcutaneous tissue disorders (diabetic foot) in one subject.

DISCUSSION

The current non-interventional study investigated effectiveness and safety of the study drug in the management of mild to moderate PN. The treatment was

associated with a significant improvement in TSS, VAS for associated symptoms of PN and QoL as measured by SF-8 questionnaire. Earlier studies have shown the effectiveness of Vitamin B₁ either singly or in combination with Vitamin B₆ and B₁₂ mainly in subjects with diabetic neuropathy or alcoholic neuropathy.^{14,23,25} The current study however investigated and showed the effectiveness of the study drug across a broad range of etiologies.

A direct relation was observed between reduction of TSS and treatment duration from baseline to three months. A statistically and clinically significant reduction in overall TSS score and scores for individual components was observed as early as within 14 days of treatment with the study drug. We investigated several time points (30, 60, 90 days) and observed further significant improvement in scores at each visit [(stabbing pain (64.7%), burning pain (80.6%), paresthesia (61.3%) and numbness (55.9%) ($p < 0.0001$)]. With continued therapy, scores continued to improve up to the end of the study. This linear improvement in symptom score from baseline visit suggests the critical role of the study drug in alleviating the symptoms. It also suggests and supports the use of continued therapy for the management of symptoms of PN. Consistent symptom improvement has been considered as the most important goal of neuropathy management from a patient's perspective.²⁷ Moreover, the observed 1-point decrease in TSS over 5 visits suggests that at least one mild symptom was cured or one "moderate" symptom could be categorized as changed in severity to "mild" in fixed-dose treated patients in this study. At the end of the study period, the overall TSS score reduced by >50%. A reduction in TSS by 30% or ≥ 2 points is considered clinically relevant.²⁸

A study involving treatment with ALA in subjects with diabetic neuropathy (600 mg, 1200 mg, and 1800 mg) was associated with a significant reduction in TSS and its individual components such as stabbing pain and burning pain. Even at higher doses, no significant change was observed in scores for paresthesia and numbness.²⁵ In the current study, we observed improvement in all the four symptoms. Improvement in VAS score for the individual parameters corroborated with the observations of the TSS lending further credence to the effectiveness of the combination. Treatment with the study drug was also associated with a significant improvement in QoL parameters of both PCS and MCS.

The beneficial results observed in this study are in accordance with previous studies which demonstrated the efficacy of B vitamins in treating PN.^{17,29,30} These beneficial effects of combination therapy can be attributed to different modes of action of B Vitamins however the precise mode of action is not well understood some possible

explanations can be found in the literature. Cobalamin has been shown to improve neuropathy symptoms by neutralizing superoxide and peroxy-nitrite and restoring normal glutathione levels. Pyridoxal has been reported to prevent formation of advanced glycation end products (AGEs) thereby reducing microvascular disease.³¹ Thiamine diphosphate also has a role in preventing microvascular complications in diabetes.²¹ In safety analysis of the study, one subject had serious AE was assessed as not related to the study medication. Three subjects had at least one treatment-related AE and there were 3 study drug related discontinuations. Overall the study drug was well tolerated.

The limitation of this study is the non-interventional, one arm study design, not blinded or controlled by placebo. However, the sample size is high and the results are clearly proving the effectiveness. In a follow-up study, the duration can be longer to investigate the effect of the treatment after three months, considering the chronic disease condition and QoL of the patient.

In conclusion, the fixed dose combination of vitamin B₁, B₆ and B₁₂ is effective and well-tolerated in subjects with mild to moderate PN of various etiologies.

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Authors Contribution:

MH-Concept and design of the study, statistically analyzed and interpreted, reviewed the literature, manuscript preparation and critical revision of the manuscript; **NK**-Concept, collected data and helped in preparing first draft of manuscript; **RP**- Concept, collected data and review of literature and helped in preparing first draft of manuscript; **DT**-Concept, collected data and helped in preparing first draft of manuscript; **MB**-Concept, collected data and helped in preparing first draft of manuscript; **HH**-Concept, collected data and helped in preparing first draft of manuscript; **PP**-Concept, collected data and helped in preparing first draft of manuscript; **AF**-Concept, collected data and helped in preparing first draft of manuscript; **ADW**- Concept, collected data and helped in preparing first draft of manuscript.

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