

Improvement of Quality of Life in Patients with Peripheral Neuropathy Treated with a Fixed Dose Combination of High-Dose Vitamin B1, B6 and B12: Results from a 12-week Prospective Non-interventional Study in Indonesia

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Abstract

Objective: The 12-week prospective, non-interventional study conducted in Indonesia aimed to evaluate the effectiveness and safety of a fixed combination of high-dose vitamin B1, B6 and B12 in subjects with peripheral neuropathy (PN) of various etiology. As PN is known to significantly impair patients' quality of life (QoL), special attention has been paid to this aspect and QoL data were collected as secondary outcome parameters over time.

Methods: The study enrolled subjects aged 18–65 years with mild or moderate PN of various etiologies. PN symptoms were measured by Total Symptom Score (TSS) and Visual Analogue Scale (VAS) at visit 1 (baseline), visit 2 (day 14), visit 3 (day 30), visit 4 (day 60), and visit 5 (day 90). At visits 1, 3, 4, and 5, the subjects also reported QoL data as assessed by the Short Form 8 (SF-8) Health Survey Questionnaire. Changes from baseline to other follow-up visits were calculated by exploratory analysis for TSS, VAS, and QoL scores.

Results: Data of 411 subjects with PN (104 diabetic, 44 carpal tunnel syndrome, 112 idiopathic, 25 other, and 126 with combinations of different causes) were available at baseline. Mean total TSS had improved by 62.9% at visit 5. Mean VAS reductions at visit 5 ranged from 57.8–89.6% for the evaluated symptoms numbness, burning, tingling, pain, and paresthesia. Symptom relief was associated with a significant improvement in QoL. This was evident in the total population by a significant increase of the physical component summary score (PCS) and the mental component summary score (MCS) at visit 5 compared to baseline (both $p < 0.0001$). In addition, all etiologic subgroups showed a significant progressive QoL improvement over time. Study results related to effectiveness have been published previously; the focus of this publication is on QoL improvement, assessed by one of the secondary parameters.

Conclusion: The study results suggest that the fixed dose combination of high-dose vitamin B1, B6 and B12 is effective to treat mild to moderate PN of various etiologies and is well tolerated. The improvements in PN positively affected the patients' QoL as reflected by the SF-8 scores.

Keywords: Quality of life; Peripheral neuropathy; Neurotropic B vitamins; Tingling; Numbness; PCS; MCS; TSS; VAS

Introduction

Peripheral neuropathy (PN) is a disease in which peripheral nerves are damaged. The symptoms can be very multifaceted and often include burning, stabbing or electric shock-like pain, numbness, tingling, allodynia, and other sensory but also motor or autonomic

symptoms, depending on which nerves are impaired. The underlying causes of PN are equally diverse; the most common etiology is diabetes, but alcohol abuse, B vitamin deficiencies, infections, entrapment disorders, environmental toxins, certain drugs, and other diseases and factors can also trigger the condition [1-3]. It is assumed that up to 50% of patients with diabetes suffer from PN [4,5]. While the prevalence of diabetes is strongly increasing globally, neuropathies due to nutritional deficiencies are most prevalent in low income countries [6]. Another frequent cause of PN is carpal tunnel syndrome, a form of median nerve neuropathy that affects 4–5% of the population [7]. However, in about 22% of cases, the underlying cause of PN remains unknown and the disease is considered idiopathic [1,3].

In the early stage of PN, patients may experience only mild and frequently disregarded signs that have at most a small impact on daily activities. For example, it may happen that the patient has difficulty turning a key in the lock, unfastening buttons, and opening bottles and jars [8]. As the disease progresses, symptoms tend to worsen and affect the patients increasingly on the physical but also on the mental level. Numerous publications have reported that PN significantly impairs the quality of life (QoL) [5,9-22]. However, a large proportion relates to the population of diabetics [5,11-14,17,20-22], and fewer pay attention to other etiologic subgroups [9,10,15,16,18]. Nevertheless, most of them show that patients with PN not only experience QoL impairments by reduced physical functioning but may also suffer more likely from depression, poorer sleep, and an impaired social life, particularly when PN progresses and the symptoms become painful [9-12,15-18,21]. The Short Form 8 (SF-8) Health Survey Questionnaire used in the present study is an 8-item short form providing a health-related QoL (HRQoL) profile. It is the latest version of the globally recognized Short Form Health Surveys that is characterized by a high test-retest reliability. The survey has shown to be sensitive to change and is therefore assumed to be appropriate for the assessment of QoL changes over time [23].

As the progression of PN can be prevented or slowed down and some of the nerve alterations may even be reversible, an early diagnosis is crucial to prevent or reduce significant impairments of QoL [24]. The diagnosis of PN is usually based on history and bedside examination and can also take into account the results of screening tools, such as questionnaires and more or less advanced tests. The simplest clinical testing utilizes, for example, a piece of cotton wool or a cocktail stick [25-27]. Using these types of simple tools along with a proper medical history can provide sufficient insights for a fast and easy diagnostic procedure.

For the treatment of PN, various options are available, including preventive, non-pharmacological, and pharmacological approaches. Guideline-based treatments focusing on neuropathic pain [28] and aimed primarily at symptomatic relief are effective in reducing neuropathic pain symptoms but can be associated with significant side effects and do not contribute to the restoration of nerve health. These treatments mainly include antidepressants, anticonvulsants, and opioids [2,28,29]. In addition to guideline treatments, other pharmacological treatment options are available which can be used already in early to moderate stages of PN and are well tolerated. Additionally to symptom relief, they contribute to nerve health restoration. One of these options is neurotropic B vitamins (B1, B6 and B12) for which effectiveness in treating PN has been shown [30-34].

Although effective symptom relief is the most important parameter and is therefore investigated in most studies, improvement of QoL is a critical factor for patients and should be investigated as well.

The present non-interventional study aimed to evaluate the effectiveness and safety of a fixed-dose combination of high-dose vitamin B1 (100 mg), B6 (100 mg) and B12 (5 mg) in the routine treatment of patients with mild to moderate PN of various etiologies in Indonesia. While most studies on PN focus on diabetic PN, this study enrolled all patients with PN symptoms regardless of the cause of the disease. Detailed results on the effectiveness on the symptoms have already been published [35], while the present publication focuses on the secondary parameter QoL as assessed by the SF-8.

Methods

Subjects

The study enrolled subjects aged 18-65 years with mild or moderate PN of various etiologies, including diabetic, nutritional, alcoholic, carpal tunnel syndrome, idiopathic, and others. All subjects provided signed informed consent prior to study inclusion. PN was diagnosed by using either the Michigan Neuropathy Screening Instrument (MNSI) [36] or the Toronto Clinical Neuropathy Score (TCNS) [37]. Only subjects with MNSI scores ≥ 7 (subject administered questionnaire) and ≥ 2.5 (healthcare professional score) or a TCNS ≥ 6 were included.

Subjects were excluded from the study for the following reasons: known clinically significant cardiovascular, pulmonary, gastrointestinal, hematological, hepatic, renal or endocrine disease (except diabetes mellitus); history; signs or symptoms suggestive of genetic neuropathy; any gastrointestinal surgery in the last six months before consent; plan for surgery during the study; any clinically significant or unstable medical or psychiatric condition that in the opinion of the investigator would affect the subject's ability to participate; participation in other clinical trials in the last month; intake of vitamin B complex products for more than one consecutive week in the last three months before consent; known hypersensitivity to any component of the active pharmaceutical ingredients or excipients contained in the study treatment; severe neuropathy (TCNS ≥ 12 or Visual Analogue Scale (VAS) ≥ 7 for pain) treated with other medication such as gabapentin, pregabalin, or any other anti-inflammatory drugs; any treatment like methotrexate which interferes with neuropathy or any other cytostatic drug treatment; pregnancy, pregnancy plans or breastfeeding.

Study design and treatment

The study was conducted as a prospective, open-label, non-interventional (observational) single arm, multi-center study at eight centers in Indonesia. Eligible subjects received the study drug (vitamin B1/thiamine mononitrate 100 mg, vitamin B6/pyridoxol hydrochloride 100 mg and vitamin B12/cyanocobalamin 5 mg, marketed as Neurobion® Forte in Indonesia) orally once daily for 12 weeks. Subjects were followed up after 14 days of treatment and thereafter monthly for up to 90 days.

Ethical standards

The NENOIN (Neurobion Non-interventional) study (Indonesian Clinical Trial Registry No.: INA-KPA0DYA) was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and received approval from the local regulatory authority and Independent Ethics Committee/Institutional Review

Board. All subjects provided informed consent prior to their participation.

Outcome measures

Primary outcome measure: The Total Symptom Score (TSS; including stabbing pain, burning pain, paresthesia, and numbness) was administered by the physician (part of study team) and recorded at baseline and at each study visit up to 90 days of treatment. The TSS scale ranges from 0 (no symptoms) to 14.64 points (all symptoms severe and (almost) continuously present) [38]. In the following results section, TSS scores are given as means (\pm standard deviation (SD)).

Secondary outcome measures: Subjects recorded the severity of each evaluated symptom of neuropathy (numbness, burning, tingling, pain, and paresthesia) at baseline and at each study visit up to 90 days of treatment by using a VAS (range from 0-10; 0=no symptoms; 10=worst possible symptoms).

The SF-8TM Health Survey Questionnaire (4-week recall period) to assess QoL was administered at baseline (visit 1) and at visits 3 (day 30), 4 (day 60), and 5 (day 90). It includes the same eight health domains as the SF-36v2[®] Health Survey but uses only eight questions. Physical component summary scores (PCS; mainly including physical functioning, role physical, bodily pain, and general health) and mental component summary scores (MCS; mainly including vitality, social functioning, role emotional, and mental health) are calculated accordingly from the domains.

As for TSS, the VAS and the SF-8 PCS/MCS scores are also given as means (\pm SD) subsequently.

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 the AE.

Statistical analysis

For variables such as TSS, VAS, and QoL scores, any significant differences in change from baseline to other follow-up visits were calculated by exploratory analysis, using appropriate statistical tests including Wilcoxon signed rank test, independent t-test, Cochran-Armitage trend, chi-square test, etc. [39]. Mean percentage improvement of TSS, VAS, and QoL from baseline to other follow-up visits was calculated based on mean TSS, mean VAS, and mean SF-8 PCS and MCS scores. Factors associated with QoL were assessed by univariate and multivariate logistic regression analysis. All statistical analyses were performed using SAS Version 9.1.3 (NC, USA).

The sample size of 411 subjects was estimated based on the following assumptions: a 50% improvement from baseline up to 90 days of treatment in clinical symptoms of PN as evaluated by TSS, 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 accomplished with The Statistical Package for the Social Sciences (SPSS Inc., Chicago, USA; version 15.0 for Windows).

Results

Baseline characteristics

Baseline characteristics of the 411 subjects (297 females and 114 males) aged 22-65 years who met the eligibility criteria and were enrolled in the study have been published previously [35]. The etiology

of PN was diabetic in 104 subjects, carpal tunnel syndrome in 44, idiopathic in 112, other in 25, and a combination of different causes (e.g. diabetic+nutritional or diabetic+carpal tunnel syndrome +idiopathic) in 126 subjects.

PN symptoms as measured by Total Symptom Score (TSS) and Visual Analogue Scale (VAS)

TSS was scored at baseline (visit 1) as well as after 14 days (visit 2), 30 days (visit 3), 60 days (visit 4) and 90 days (visit 5). The mean total TSS (full analysis set; FAS) at baseline of 5.45 ± 2.04 improved progressively over time in the course of the treatment to 2.02 ± 1.28 at visit 5, which represents an improvement of 62.9%. Changes from the respective study visits to baseline were highly significant ($p < 0.0001$) at each visit. This was also true for the improvement of the individual symptoms in the FAS population [35] and improvements over time in all etiologic subgroups ($p < 0.0001$) [40].

VAS scores were collected at the same times as TSS and improved for all evaluated symptoms significantly from baseline to each visit ($p < 0.0001$). Mean VAS reductions from baseline to visit 5 were 57.8% for numbness, 63.5% for burning, 65.2% for tingling, 69.1% for pain, and 89.6% for paresthesia [35].

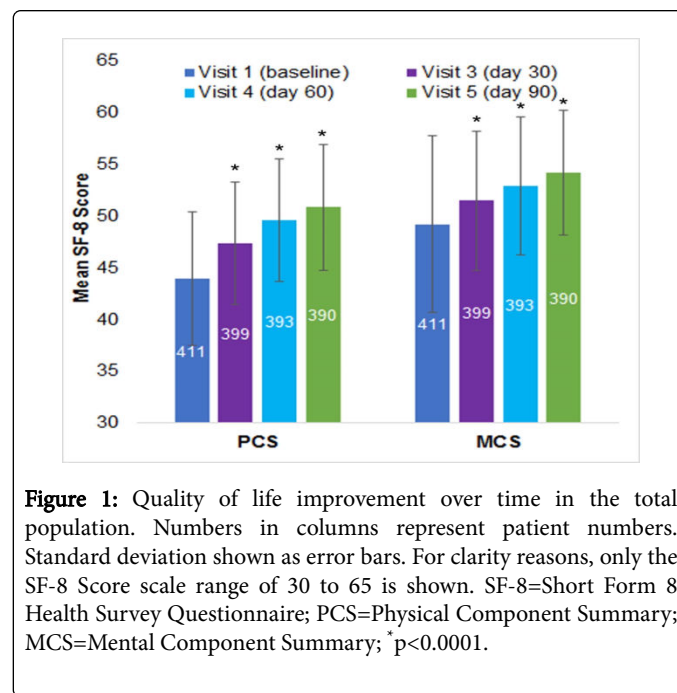


Figure 1: Quality of life improvement over time in the total population. Numbers in columns represent patient numbers. Standard deviation shown as error bars. For clarity reasons, only the SF-8 Score scale range of 30 to 65 is shown. SF-8=Short Form 8 Health Survey Questionnaire; PCS=Physical Component Summary; MCS=Mental Component Summary; * $p < 0.0001$.

Quality of life as measured by SF-8

Total population: Of the 411 total included subjects at baseline, QoL was assessed by the administration of the SF-8 questionnaire in 399 subjects at visit 3, in 393 subjects at visit 4 and in 390 subjects at visit 5.

A significant improvement was observed in PCS scores from baseline to visit 5 (Figure 1). The mean PCS score increased from 43.97 ± 6.47 at baseline to 47.35 ± 5.93 at visit 3, 49.64 ± 5.93 at visit 4, and 50.85 ± 6.08 at visit 5, with all changes being statistically significant ($p < 0.0001$). On average, the PCS score improved by 15.7% from baseline to visit 5.

Likewise, MCS scores increased in a similar way during the course of the study (Figure 1). As for PCS, changes between the respective study visit and baseline were highly significant in all cases ($p < 0.0001$). With a mean score of 49.23 ± 8.54 at baseline and scores of 51.48 ± 6.73 at visit 3, 52.92 ± 6.66 at visit 4, and 54.19 ± 6.06 at visit 5, MCS improved in comparison with PCS to a lesser extent by 10.1% from baseline to visit 5.

Etiologic subgroups

At baseline, subjects with diabetic neuropathy ($n=104$) had a mean PCS score of 44.14 ± 6.52 which improved to 50.30 ± 6.36 at visit 5 ($p < 0.0001$). The mean MCS score also increased significantly from 49.20 ± 9.19 at baseline to 53.01 ± 6.36 at visit 5 (Figure 2; $p < 0.05$).

Subjects with carpal tunnel syndrome ($n=44$) showed a mean PCS score of 46.03 ± 6.97 at baseline. At visit 5, the PCS score had increased to 51.67 ± 7.96 ($p < 0.05$). Similarly, the mean MCS score improved in this subgroup from 49.32 ± 7.14 at baseline to 55.15 ± 5.66 at visit 5 (Figure 2; $p < 0.0001$).

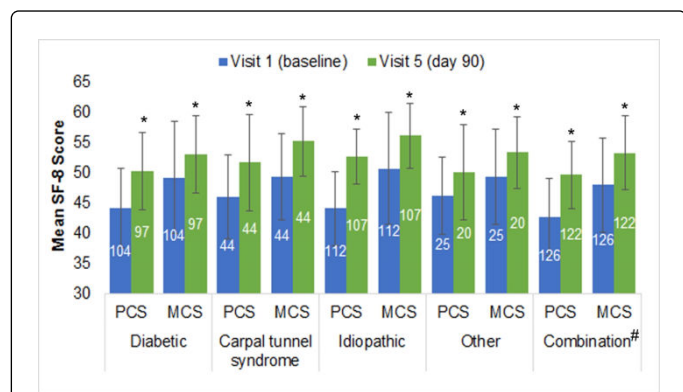


Figure 2: Quality of life improvement from baseline to study end in different etiologic subgroups. Numbers in columns represent patient numbers. Standard deviation shown as error bars. For clarity reasons, only the SF-8 Score scale range of 30 to 65 is shown. SF-8=Short Form 8 Health Survey Questionnaire; PCS=Physical Component Summary; MCS=Mental Component Summary; #neuropathy due to combinations of different etiologies; * $p < 0.05$.

Patients with idiopathic neuropathy ($n=112$) presented at baseline with a mean PCS score of 44.06 ± 6.05 . They had an improved mean PCS score of 52.58 ± 4.56 at visit 5 ($p < 0.0001$). Furthermore, the mean MCS score was 50.66 ± 9.30 at baseline and improved to 56.10 ± 5.40 at visit 5 in this subgroup (Figure 2; $p < 0.0001$).

Beyond that, patients with other types of neuropathy ($n=25$) and patients with more than one cause of neuropathy (combination; $n=126$) showed similar improvements. Mean PCS scores were 46.16 ± 6.44 (other) and 42.58 ± 6.38 (combination) at baseline and 50.07 ± 7.92 (other; $p < 0.05$) and 49.60 ± 5.59 (combination; $p < 0.0001$) at visit 5. In these subgroups, mean MCS scores amounted to 49.26 ± 7.87 (other) and 47.93 ± 7.74 (combination) at baseline and 53.31 ± 5.91 (other; $p < 0.05$) and 53.25 ± 6.15 (combination; $p < 0.0001$) at visit 5 (Figure 2).

QoL by severity of neuropathy at baseline

In principle, only patients with mild or moderate neuropathy were enrolled. However, on the first visit (baseline), 12 patients achieved results suggesting severe neuropathy which were not reported at inclusion. Accordingly, QoL data from baseline were reported from 196 subjects with mild neuropathy, 201 subjects with moderate neuropathy and 12 subjects with severe neuropathy. At visits 3, 4, and 5, data were available from 190, 186, and 184 patients with mild neuropathy, from 196, 195, and 194 patients with moderate neuropathy, and from each 11 patients with severe neuropathy.

Subjects with mild neuropathy had a mean PCS score of 45.20 ± 6.37 at baseline which increased to 51.50 ± 6.18 at visit 5. Similarly, subjects with moderate neuropathy started with a mean PCS score of 43.10 ± 6.30 and reached a mean PCS score of 50.08 ± 6.00 at visit 5. In contrast, the mean PCS score of subjects with severe neuropathy was somewhat lower with 39.92 ± 6.71 at baseline but sharply improved to 53.64 ± 3.79 (Figure 3; $p < 0.0001$ for all changes).

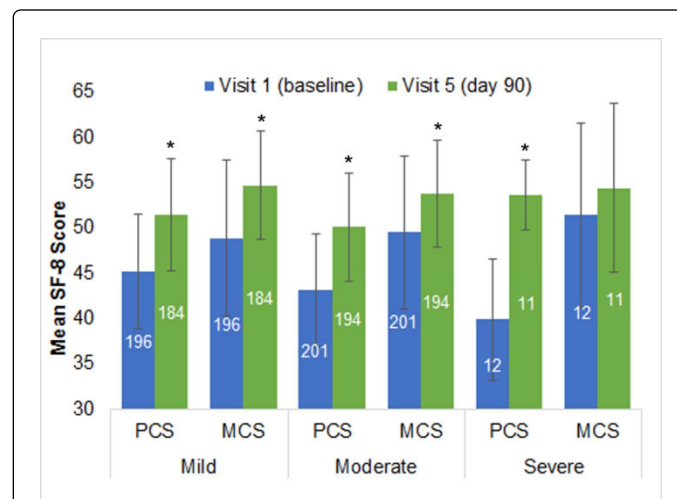


Figure 3: Quality of life improvement from baseline to study end in different severity subgroups. Numbers in columns represent patient numbers. Standard deviation shown as error bars. For clarity reasons, only the SF-8 Score scale range of 30 to 65 is shown. SF-8=Short Form 8 Health Survey Questionnaire; PCS=Physical Component Summary; MCS=Mental Component Summary; * $p < 0.0001$.

In terms of MCS, the mean scores of the subgroups were quite similar at baseline (mild: 48.90 ± 8.57 ; moderate: 49.49 ± 8.45 ; severe: 51.45 ± 10.12); however, a trend is visible for a lower impact in cases with more severe symptoms at visit 5 (mild: 54.69 ± 5.95 ; moderate: 53.76 ± 5.91 ; severe: 54.43 ± 9.29 ; Figure 3). Within subgroup changes from baseline were statistically significant for mild and moderate neuropathy ($p < 0.0001$) but differences within the subgroup of severe neuropathy and across the subgroups were not.

Safety

Only 14 (3.4%) of the 411 enrolled subjects experienced at least one AE during the study period. Of those, one subject had one serious AE (in-patient hospitalization or prolongation of existing hospitalization) which was assessed as not treatment-related. Three subjects had at least one treatment-related AE (two with gastrointestinal disorders, one

with skin and subcutaneous tissue disorders) and three at least one AE that led to study termination [35].

Discussion

Our study evaluated the effectiveness and safety of a fixed combination of high-dose vitamin B1, B6 and B12 in the treatment of mild to moderate PN of different etiologies. The results suggest that the study drug was highly effective in reducing the symptoms of PN in all subgroups [35,40]. Mean TSS improved progressively over time from baseline to visit 5 (day 90) by 62.9%, which favors long term treatment. In line with this finding, mean VAS reductions from baseline to visit 5 were 57.8% for numbness, 63.5% for burning, 65.2% for tingling, 69.1% for pain, and 89.6% for paresthesia. In addition, it was found that the patients' QoL improved in a similar way progressively over time; that is, the mean PCS and MCS scores increased significantly from baseline to visit 5 in the FAS population. The study included only patients who did not take analgesic or antineuropathic medications such as gabapentin, pregabalin, or anti-inflammatory drugs, and any use of these medications during the study period was reported. Since only two patients took such drugs during the study period, we conclude that the observed improvements were actually due to the study medication. We also exclude that the strong effects in our study may be solely due to a placebo effect because the effects were comparably strong and constantly improving over time in all etiologic subgroups and all observed symptoms and were evaluated by two different symptom scales (TSS and VAS). Further, the sample size of 411 patients strongly contributed to the validity of the study results. Beyond this, placebo effects on neuropathy symptoms such as pain are usually significantly less pronounced in placebo-controlled studies of comparable duration that evaluated similar B vitamin treatments in PN [31,41,42]. We also assume that the effects were not due to spontaneous recovery as PN is mostly chronic by nature, the symptoms tend to persist, and spontaneous improvements are uncommon in most neuropathies such as diabetic neuropathy [29,43].

It is well known that PN severely limits the patients' QoL. However, fewer studies examined the influence of treatment on both symptoms and QoL, allowing conclusions to be drawn about the direct relationship. For example, O'Connor listed in a review from 2009 the effects of pharmacological treatments like antidepressants on QoL. Several of the included studies had shown an efficacy of the substances to reduce pain and to improve different aspects of QoL, including physical and mental functioning [16]. Our results are also consistent with some other studies which followed up patients after successful non-pharmacological intervention and monitored QoL. For example, Slangen et al. investigated patients suffering from painful diabetic PN (P-DPN) after spinal cord stimulation and showed that QoL strongly increased over two years as the pain intensity decreased [44]. Furthermore, Powell et al. found in a randomized controlled trial (RCT) that phototherapeutic restoration of sensation in the lower extremities of senior diabetic patients with PN did not only reduce their fear of falling and the number of falls but also diminished pain and markedly improved QoL [45]. Similar results were obtained by Atroshi and colleagues who investigated patients with carpal tunnel syndrome before and after surgery and measured symptoms, disability, and HRQoL. They found that some QoL components improved simultaneously with the decrease in symptoms and the increase in functionality [9]. In contrast to that, Macare van Maurik et al. did not find a correlation between VAS and QoL in subjects with P-DPN after surgical nerve decompression followed up over 12 months [46].

Our results also show that the effectiveness of the treatment and its positive effects on QoL were independent of the etiology of PN. This is important to emphasize since in many patients no cause of PN can be found, leading to uncertainty on the part of the treating physician, so in many cases patients remain untreated or under-treated. Thus, our findings suggest that even patients with unclear etiology can benefit from treatment with high-dose vitamin B1, B6 and B12. That neuropathic pain interferes with patient functioning regardless of the cause of PN was already pointed out by Jensen et al. in a large-scale review that included the results of 52 studies. In general, the data suggested similar associations between pain severity and QoL in six different neuropathic conditions [15].

Furthermore, it is important to identify and diagnose the disease early and to start treatment at an early to moderately advanced stage to avoid disease progression, the development of more severe symptoms, or even neuropathic pain, which will significantly impact the patient's QoL. Early diagnosis and treatment still remain a barrier in many countries due to factors like low disease awareness on both sides (patients and health care professionals), knowledge on diagnostic tools, access to specialists in some countries, and others [6].

In addition, our results indicate that PN severity might have an impact on QoL, especially as far as the physical component is concerned. In our study, the mean PCS score was higher in patients with mild PN at baseline than in patients with moderate or severe PN. However, the subgroup with severe PN benefited the most from the treatment in terms of the PCS score increase, but the sample was quite small and the differences between the subgroups were not significant. Since Currie et al. demonstrated a clear association between severity of DPN symptoms and QoL in a large-scale study [13], it could be interesting to further investigate this aspect in a broader study with high-dose B vitamins.

The measurement of QoL is one of the strengths of this study. In addition, unlike many other studies on B vitamin treatment of PN, our study not only focused on the positive symptoms of PN (pain) but also evaluated negative symptoms such as numbness. The study is limited by its non-interventional, uncontrolled design although the sample size was sufficient and the effectiveness on symptoms and QoL was successfully proven in the observational setting, showing statistically and clinically relevant results. Assessment of the QoL could be limited by a potential bias because patients self-report in the SF-8. It could also be helpful to carry out a follow-up study as an RCT and extend the duration of the study, particularly because effects on QoL could be even more pronounced at later times. However, a placebo arm must be approved by the respective ethics committee as this treatment is well documented [47].

Conclusion

The results suggest that the fixed dose combination of high-dose vitamin B1, B6 and B12 is effective to treat mild to moderate PN of various etiologies and is well tolerated. Furthermore, the improvements in PN positively affect the patients' QoL as reflected by the SF-8.

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Conflict of Interest

The authors do not have any conflicts of interest to declare.

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