The Efficacy of Vitamin B1, B6, and B12 Forte Therapy in Peripheral Neuropathy Patients

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Keywords:
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VAS

ABSTRACT

Background: Peripheral neuropathy can be caused by diabetes mellitus, nutritional deficiencies, entrapment or Carpal Tunnel Syndrome (CTS), and idiopathic.

Objective: To determine the therapeutic efficacy of Vitamin B1, B6, and B12 forte in relieving symptoms of peripheral neuropathy.

Methods: This was pre- and post-experimental study involving patients with moderate peripheral neuropathy (Toronto Clinical Neuropathy Score [TCNS] ≥6 and Michigan Neuropathy Screening Instrument [MNSI] ≥7) taken from outpatient neurological clinic of Dr. Kariadi Hospital, Semarang. The patient was prescribed vitamin B1 100 mg, B6 100 mg, and B12 5000 mcg once daily for 2 months. Evaluation of the numerical pain rating scale in the form of VAS and Total Symptom Score (TSS) was conducted at the first and second month. The VAS score difference test was conducted with the Wilcoxon test and TSS with the Post Hoc test and considered significant if p <0.05.

Results: There were 30 patients aged 18 - 65 years, consisted of 70% female and 30% male. The etiology of peripheral neuropathy was idiopathic (40%), CTS (26.7%), DM (23.3%), and HNP (10%). There were significant differences of the VAS scale and TSS at every evaluation.

Conclusion: Administration of VitB1, B6, and B12 forte relieved symptoms of moderate peripheral neuropathy with improvement of VAS and TSS scores.

1. Introduction

The definition of neuropathic pain according to the International Association for the Study of Pain (IASP) is pain triggered by a primary lesion or dysfunction of the nervous system and can be caused by compression or infiltration of the nerves depending on its location. It can be defined as an abnormal pain that occurs either as a result of lesions of the peripheral or central nervous system. The prevalence is approximately 1.5% of all population in the United States. Several diseases can manifest as neuropathic pain, such as trigeminal neuralgia, diabetic neuropathy, spinal cord injury, cancer, stroke, and degenerative neurological disease.1

According to Attal et al, the incidence of neuropathic pain was also found to be quite high in Europe, namely 7-8% of the general population.2 In Indonesia, based on the results of a multicenter outpatient study in 14 teaching hospitals conducted by the Pokdi Nyeri PERDOSI, there were 4,456 cases of pain, 9.5% were neuropathic pain. In 2012, the cases increased up to 21.8% based on the study in 13 hospital with more sensitive screening instruments.3 Most of subjects were men (62.1%) aged 40-60 years with low back pain, carpal tunnel syndrome, frozen shoulder, diabetic neuropathy, and brachialgia.4 Neuropathic pain will also affect the quality of life and sleep. Bartley, et al stated that severe and chronic neuropathic pain could increase the risk of anxiety, depression, and decreased quality of life. Choi, et al also reported that of all subjects with neuropathic pain, 67.3% experienced moderate to severe pain; 43.5% showed prolonged pain over two years; and 32.4% suffered from sleep disturbances due to pain, and 22.8% of patients were dissatisfied with the current management of pain.5

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Conclusion: Administration of VitB1, B6, and B12 forte relieved symptoms of moderate peripheral neuropathy with improvement of VAS and TSS scores.
Pain sensation is normally initiated by activity on afferent unmyelinated (C-) and thinly myelinated (Aδ-) nerves. These nociceptors will usually not be excited without external stimulation. However, when peripheral nerve lesions occur, these neurons may become abnormally sensitive and develop pathological spontaneous neurological activity.6

The spontaneous ectopic activity in damaged nerve cells also indicates an increase of m-RNA expression for voltage-gated sodium channels. This group of sodium channels at ectopic site is responsible for the low threshold of action potential and hyperactivity. This can cause sensitivity to stimuli. Thus, when there is a stimulus that normally does not cause pain, it can immediately cause excessive pain instead.6

Lesions in nerve cells will cause regeneration and the growth of neuromas in its proximal part. Abnormal excitation and discharge can appear in this neuroma. This can cause spontaneous abnormal pain in the neuropathic patient.1,6

After a nerve cell lesion occurs, the activated macrophage will enter the endoneural blood vessel into the nerve and release cytokines. This inflammatory mediator will induce ectopic activity on damaged nerve cells as well as nearby normal nerve cells. Patients with inflammatory neuropathies will experience very deep pain.6

As a consequence of peripheral nociceptor hyperactivity, a dramatic secondary change occurs in the dorsal horn of the spinal cord. Lesions of the peripheral nerves will increase the excitation ability of multireceptors in spinal cord neurons (wide-dynamic-range neurons). This hyperexcitation is manifested by increased nerve cell activity in response to nocuous stimulation, expansion of the receptive neuronal field, and the spread of spinal hyperexcitation to other segments.6

Under normal circumstances, neurons in the dorsal horn will receive a strong inhibition from GABA (gamma-aminobutyric acid). In animal study, partial nerve injury will initiate apoptosis of GABA in the superficial portion of the neuron in the dorsal horn. This increases the pain stimulation a neuropathic patient will receive.

Pharmacotherapy that can be used to relieve neuropathic symptoms are anticonvulsants, antidepressants, and neurotropics agent, which include vitamins B1, B6, and B12. Neurotropic vitamins is meant to normalize nerve function by improving metabolic disorders by providing the required intake.5 Administration of vitamins B1 (100mg), B6 (100mg), and B12 (200mcg) has been shown to be effective in neuropathic symptoms.7 There was still a few data regarding vitamins B1, B6, and B12 as determinants factors of peripheral neuropathy symptoms reduction (pain, burning, tingling, and numbness), as well as the increasing incidence of peripheral neuropathy. Thus, we want to know more about the effects of vitamins B1, B6, and B12 to symptoms of peripheral neuropathy (pain, burning, tingling and numbness).

2. Methods

This was a prospective cohort experimental study with consecutive sampling method and a sample size of 30. It was conducted in the outpatient neurology clinic Dr. Kariadi Hospital, Semarang by using a pre and post-test design. Subjects diagnosed with peripheral neuropathy who met the inclusion criteria were given vitamins B1, B6, B1 vitamin B1 (100mg), B6 (100mg), B12 (5000mcg) for 2 months. Evaluation and measurement of the neuropathy degree were carried out on days 0, 30, and 60. The inclusion criteria were aged 19-64 years; willing to be the subjects; suffering from moderate peripheral neuropathy (MNSI Score ≥ 7) or TCNS ≥ 6; various etiologies, such as diabetes mellitus, nutritional, CTS, idiopathic, etc.) Meanwhile, the exclusion criteria were history of cardiovascular, respiratory, gastrointestinal, hematological, hepatic, renal or endocrine disease (except diabetes mellitus); received methotrexate therapy or other cytostatic drugs; hypersensitivity to Vit B1, B6, B12 forte; suspected of having inherited neuropathy; in pregnancy or breastfeeding; underwent gastrointestinal surgery at least 6 months before the study; had mental illness or in psychiatric therapy; had received NSAIDs, gabapentin, pregabalin, or other anti-inflammatory drugs due to severe neuropathy (TCNS ≥ 12, VAS ≥ 7); or had taken oral or parenteral Vit B complex (Vit B1 100-300mg, B6 50-600mcg, B12 200-5000mcg) for more than 1 week in the last 3 months before the study.

The method of diagnosis used the Michigan Neuropathy Screening Instrument (MNSI) and the Toronto Clinical Neuropathy Score (TCNS). The improvement of neuropathy symptoms was assessed at each visit using the VAS scale and Total Symptom Score (TSS) by assessing symptoms including pain intensity, burning, tingling, and numbness. The total symptoms score data was then compared at each visit to see if there were significant reductions in neuropathy symptoms after the use administration of vitamin B1, B6 and B12 therapy. The VAS score difference test was conducted with Wilcoxon test and TSS with the Post Hoc test, and considered to be significant if p <0.05.
3. Results

In this study (Table 1), it was found that the subjects were predominantly female (70%) and idiopathic etiology (40%) with a mean age of 52.9 years. The etiology of all the subjects consisted of carpal tunnel syndrome (26.7%), diabetes mellitus (23%), and hernia nucleus pulposus (10%), respectively. There were also patients with risk factors that could affect the outcome of the study, they were hypertension (60%), smoking (30%), alcohol (3.3%), and consumption of tea or coffee (100%).

Table 1. Characteristics of the subjects with peripheral neuropathy

| Variable          | F  | %    | Mean ± SD | Median (Range) |
|-------------------|----|------|-----------|----------------|
| Sex               |    |      |           |                |
| Male              | 9  | 30   |           |                |
| Female            | 21 | 70   |           |                |
| Age               | 52.9 ± 5.79 | 55 (36 – 61) |
| Etiology          |     |      |           |                |
| DM                | 7  | 23.3 |           |                |
| HNP               | 3  | 10   |           |                |
| CTS               | 8  | 26.7 |           |                |
| Idiopathic        | 12 | 40   |           |                |
| Subjective MNSI   |    |      | 7.90 ± 1.09 | 8 (6 – 10)     |
| Objective MNSI    |    |      | 1.20 ± 6.66 | 1 (0 – 3)      |
| TCNS              |    |      | 7.83 ± 1.05 | 8 (6 – 11)     |
| Hypertension      | 18 | 60   |           |                |
| Smoking           | 9  | 30   |           |                |
| Alcohol consumption | 1 | 3.3  |           |                |
| Tea and coffee consumption | 30 | 100 |            |                |

Table 2 showed that there were significant differences in the mean VAS and TSS score of all subjects with peripheral neuropathy of various etiologies who received B1, B6, B12 forte therapy, both from monitoring at the first month compared to the time of diagnosis (p <0.05), the second month compared to the first month (p <0.05), as well as the second month compared to the start of the study (p <0.05).

Table 2. The differences of VAS and TSS score among visits

| Variable | Mean ± SD (Range) | P   | P value between visits |
|----------|-------------------|-----|------------------------|
| VAS      |                   |     | 1 – 2 | 2 – 3 | 1 – 3 |
| VAS 1    | 3.75 ± 0.58 (3.1 – 4.8) | 0.00*| 0.00*  | 0.00*  | 0.00*  |
| VAS 2    | 2.71 ± 0.48 (2.1 – 3.6) | 0.00*| 0.00*  | 0.00*  | 0.00*  |
| VAS 3    | 5.57 ± 0.98 (5.65 – 7.98) | 0.00*| 0.00*  | 0.00*  | 0.00*  |
| TSS      |                   |     | 1 – 2 | 2 – 3 | 1 – 3 |
| TSS 1    | 7.37 ± 1.18 (5.65 – 10.3) | 0.00*| 0.00*  | 0.00*  | 0.00*  |
| TSS 2    | 5.57 ± 0.98 (4.00 – 7.98) | 0.00*| 0.00*  | 0.00*  | 0.00*  |
| TSS 3    | 3.87 ± 1.04 (2.33 – 5.65) | 0.00*| 0.00*  | 0.00*  | 0.00*  |

Note: * Significant; ¥ Friedman; ¥ Wilcoxon; ¥ Repeated Anova; ‡ Post Hoc

Table 3 showed an improvement in VAS score both for patients who have risk factors or not.

Table 3. The effects of risk factors to VAS score among visits

| Variable          | P value of VAS between visits 1 – 2 | 2 – 3 | 1 – 3 |
|-------------------|-------------------------------------|-------|-------|
| Hypertension      | P = 0.137‡                         | 0.829‡| 0.120†|
| Smoking           | P = 0.958§                         | 0.088‡| 0.649‡|
| Alcohol consumption | P = 0.643‡                        | 0.141‡| 0.384‡|

Note: ‡ t-test; † Mann Whitney
Table 4 showed that there was an improvement in the TSS score and significant differences of TTS in subjects who had a risk factor of smoking. In subjects with hypertension, there was a significant difference at the first visit compared to after receiving Vit B1, B6, B12 Forte for 2 months.

Table 4. The effects of risk factors to TSS among visits

| Variable     | P value of TSS between visits | P value of TSS between visits |
|--------------|-------------------------------|-------------------------------|
|              | 1 - 2                         | 2 - 3                         | 1 - 3                         |
| Hypertension | 0.202                       | 0.098†                       | 0.020*‡                      |
| Smoking      | 0.024*§                      | 0.005*†                      | 0.000*§                      |
| Alcohol      | 0.415                         | 1.000†                       | 0.418†                       |

Note: * Significant; † t-test; § Mann Whitney; ‡ Spearman’s; ¶ Kruskal Wallis; ¤ ANOVA

Figure 1. The effect of risk factors to VAS score among visits

Figure 2. The effect of risk factors to TTS among visits

4. Discussion

The hypothesis in this study was administration of vitamins B1, B6 and B12 Forte had an effect on reducing the symptom score of VAS or TSS in patients with peripheral neuropathy. TTS was chosen because we could directly observe 4 symptoms at once in neuropathic patients.

The total number of patients in this study was 30 patients with 21 female (70%) and 9 male (30%). This was similar to Katulanda et al. which stated that the prevalence of patients suffering from diabetic neuropathy in developing countries was predominantly female. This is also consistent with other studies on the epidemiology of neuropathic pain by Fillingim et al. and Bartley et al. They found that sensitivity to pain occurred more frequently in female than male. This could be the result of many factors, including biopsychosocial, hormones, and pain coping. Meanwhile, the mean age of the subjects in this study was 52 years. It was similar to a study by Perhimpunan Dokter Spesialis Saraf Indonesia which was conducted on 5,000 patients in hospitals in Jakarta, Surabaya, and Medan, which reported that 81% of neuropathy attacked patients who were 40 years old and older. Lautenbacher et al. and Wandner et al. indicated that old age patients had a higher pain sensitivity than younger. These studies also stated that the perception of pain or discomfort showed less consistent results in the younger age patients.

Smoking is a modifiable risk factor for diabetic neuropathy. According to the Center for Disease Control and Prevention (CDC), smoking will increase nerve damage in diabetic patients causing complications of peripheral neuropathy with symptoms of numbness, pain, lack of coordination, and weakness in hands and feet. Tesfaye et al. stated that the incidence of diabetic neuropathy was multifactorial related to metabolic disorders, oxidative stress, and growth factor deficiency. Wiggan et al. also reported that high triglyceride was the only clinical parameter correlated with the loss of nerve fiber density in diabetic neuropathy patients. This was because therapy was meant to control blood lipid level and administration of vitamin combination for 2 weeks helped in decreasing the total symptom score. Theoretically, hypertension and high blood sugar can accelerate microvascular and macrovascular complications that lead to nerve fiber damage and causing neuropathic symptoms. This is in line with this study, which showed that there was a significant relationship between the difference of TSS among visits and smoking as risk factor. Meanwhile, there was no statistically significant association between the risk factors of smoking, hypertension, and alcohol consumption with the VAS difference among visits although there was an improvement in the VAS score.

This study did not measure the patient’s blood sugar levels. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the best way to prevent and improve neuropathy was by controlling blood sugar levels within normal limits because it helped maintain nerve fibers.
All samples in this study were given combination therapy of vitamins B1 (100 mg), B6 (100 mg), and B12 (5000 mcg) forte once a day. In general, there were no serious side effects from the administration of this vitamin. Three of the 30 samples had reactions to vitamin B therapy, including nausea and vomiting. Vitamin B12 plays a role in the metabolism of fatty acids which are useful in repairing nerve myelin fibers. The role of vitamin B1 is to initiate nerve impulses from coenzymes and B6 is involved in the synthesis of neurotransmitters so that both of them can improve neuropathy. 

This study showed that there was a decrease in TSS after giving combination therapy of vitamins B1, B6 and B12 either after 30 days or 60 days. This was in accordance with the Farvid et al. They conducted a study with administration of B1 (10 mg), B2 (10 mg), B6 (10 mg), biotin (200 mg), B12 (10 mg) and folic acid (1 mg) supplementation and assessed by Michigan Neuropathy Screening Instrument (MNSI). It obtained a significant decrease of MNSI score from 3.96 to 1.00 (p = 0.01). A significant result was also found by Rizvi et al., a combination of vitamins B1 (100mg), B6 (100mg), and B12 (200mcg) was effective in 177 (57%) of 310 patients with diabetic peripheral neuropathy.

5. Conclusion
The administration of vitamins B1, B6 and B12 forte therapy has been shown to have an effect on the clinical outcome of patients with peripheral neuropathy with various etiologies. However, further research is still needed to assess other risk factors such as dyslipidemia, blood sugar levels, etc., comparing between etiologies, and the magnitude of the effect based on existing risk factors.

Ethical Approval
The ethical approval for this study was issued by the Health Research Ethics Committee of Medical Faculty Diponegoro University /EC/FK.UNDIP-RSDK/04 Feb/2016

Conflicts of Interest
There is no conflict of interest.

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All financial resources are borne by the researcher and sponsor.

Author Contributions
The conceptualization, writing preparation, validation, formal analysis, investigation, and data curation of this study was supported by Dodik Tugasworo. While, methodology, writing, and reviewing was supported by Maria Belladonna.

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