

## EFFECTIVITY ANALYSIS OF NEUROPROTECTOR (VITAMIN B COMPLEX AND MECOBALAMIN) AS NEUROPATHIC PAIN SUPPORTIVE THERAPY IN ELDERLY WITH TYPE 2 DIABETES MELLITUS

MADE KRISNA ADI JAYA\*, NI MADE OKA DWICANDRA

Department of Clinical Pharmacy, Health Sciences Institute Medika Persada Bali, Denpasar, Bali, Indonesia.

Email: krisnaadijaya598@gmail.com

Received: 09 August 2017, Revised and Accepted: 12 September 2017

### ABSTRACT

**Objective:** Neuroprotector (Vitamin B complex or mecobalamin) is often used as a supportive neuropathic pain therapy. The effectiveness of this drug remains controversial, especially in geriatrics with Type 2 diabetic neuropathy pains. The aim of this study was to compare the diabetes neuropathic pain reduction in elderly with and without neuroprotective supplementation.

**Method:** The study was conducted by prospective cohort design. 132 agings were observed during 4 weeks at Neurology Polyclinic, Sanglah Public Hospital, Denpasar, Bali-Indonesia. Individuals undergoing the first-line neuropathic pain therapy who received neuroprotector supplementation were included in the exposure group (66 individuals), while those not receiving neuroprotective supplementations were included in the nonexposure group (66 individuals). The pain scores were measured by numeric rating scales instruments. The measured outcome was a decrease in diabetic neuropathic pain scores.

**Result:** Both groups showed reduce on pain scores statistically different compared to baseline pain score ( $p < 0.05$ ). The comparison head-to-head on neuroprotector supplementation group showed significantly greater to reduce the pain score compared to nonexposure group ( $p < 0.05$ ). The relative risk of pain score reduction more than 2 units was 1.37 (confidence interval [CI] 95%: 1.05-1.80) and the number need to treat was 5 (CI 95%: 3-28) compared to nonexposure group.

**Conclusion:** Individuals who are undergoing the first-line neuropathic pain therapy and getting Vitamin B complex or mecobalamin supplementation had decreased pain intensity better than without supplementation therapy.

**Keywords:** Effectivity, Vitamin B complex, Mecobalamin, Neuropathic pain, Elderly.

© 2017 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>) DOI: <http://dx.doi.org/10.22159/ajpcr.2017.v10i12.21845>

### INTRODUCTION

Diabetes mellitus (DM) is part of the chronic metabolic diseases that cause major neuropathy in the sufferer [1-3]. Neuropathy in DM is a disorder that occurs in the peripheral nervous system, due to DM. According to the Rochester study, the incidence of diabetic polyneuropathy in patients >60 years is greater than in other age groups (52%), so geriatrics need special attention [4-6].

Management of neuropathic pain and another neuropathy problem, commonly utilized tricyclic antidepressant such as amitriptyline and gamma-aminobutyric acid analog such as gabapentin and pregabalin as the first-line therapy [7,8]. Phenomenon in health facilities often found clinicians add supportive therapy in the form of neuroprotectors such as Vitamin B complex (contain Vitamin B1, B6, and B12) or mecobalamin (Vitamin B12). Based on preliminary studies conducted at Sanglah Denpasar General Hospital, 70-85% of geriatric patients with diabetic neuropathy pain get supplementation of Vitamin B complex or mecobalamin.

The use of neuroprotectors as a therapy supporting the pain of diabetic neuropathy is still controversial. A review by Jayabalan and Low, 2016, showed no evidence that the use of Vitamin B12 supplementation was associated with the improvement of clinical symptoms of diabetic neuropathy [9]. A randomized control trial study, in diabetic neuropathy patients, addition of methylcobalamin and alpha-lipoic acid showed significant improvement in the outcome of pain interference and sleep interference compared without the addition of methylcobalamin and alpha-lipoic acid [10,11]. There are no data related to the effectiveness of neuroprotectors in the local area.

Based on the background of the problem, further research is needed to relate the effective analysis of neuroprotector (Vitamin B complex and mecobalamin) as supportive therapy in the treatment of neuropathic pain in geriatric patients with Type 2 DM. The results of this study are expected to be used as evidence-based medicine for clinicians, to determine the best therapy for treating diabetic neuropathic pain patients, especially in the elderly patient group in Indonesia. The novelty of this study was to directly compare the effects of neural supplementation and comparison of head-to-head Vitamin B complex and mecobalamin in geriatric patients with diabetic neuropathic pain.

### METHODS

#### Subject

The population in this study was geriatrics, diagnosed with diabetic neuropathy, and had an initial numeric rating scales (NRS) pain score of at least 2 units. The data were taken at the outpatient neurology polyclinic of the Central Hospital of Sanglah in Denpasar-Bali. The inclusion criteria were defined as men and women aged  $\geq 60$  years, patients with DM Type 2 with controlled blood sugar levels, patients with a diagnosis of painful diabetic neuropathy, and patients on therapy with the first-line neuropathic pain medicine with and without neuroprotector admission. The exclusion criteria were defined as patients who were not willing to participate in the study, patients with a history of heart disease, kidney failure, and impaired liver function.

Sampling was carried out after obtaining the approval of a Sanglah Hospital research ethics committee with ethical clearance number 185/UN.14.2/R&D/2015 as well as informed consent from the patients. Patients will be included in the study if they are willing to be part of the

study. By completing the informed consent and signing it, the patient has consented to be part of this research. Research individuals will be divided into two groups, i.e., groups that get exposure and nonexposure. Exposure was neuroprotector supplementation (Vitamin B complex or mecobalamin).

#### Clinical assessment

The sampling technique was used for nonprobability consecutive sampling where researchers would take all individuals who were diagnosed with painful diabetic neuropathy in accordance with the inclusion and exclusion criteria up to the minimum number of individuals met. Using the formula of robustness analysis in a cohort study, the minimum sample to be observed to represent the population in each group were 66 individuals.

Baseline characteristics determined in this study were age, gender, risk factor of study individuals (e.g., hyperlipidemia, hypertension, smokers, and duration of diabetes), ongoing neuropathic pain therapy, and initial pain scores measured using NRS instruments. This characteristic is chosen by the equilibrium judgment that the individual is derived from equivalent characteristics. Outcome measurements were done by direct measurement method, in which individuals will be measured initial pain score before therapy and the final pain score after 4 weeks of therapy.

#### Clinical outcome

Clinical outcomes observed include the decrease in initial and final pain scores of each group (dependent sample) and comparison of reduced pain scores between groups (independent sample). Both outcomes will be analyzed using analytical analysis.

#### Statistical analysis

Statistical analysis was conducted on baseline characteristics and clinical outcome tests. Baseline characteristics were analyzed by nonparametric Mann-Whitney U (MWU) and Chi-square tests. Clinical outcomes were done by Wilcoxon sign rank test on dependent sample and MWU on independent sample. A Chi-square analysis was selected for the analysis of relationships among variables in this study. Probability values (p) of <0.05 were examined statistically significant for all analyses. All analysis was conducted using SPSS 17 for Windows software.

## RESULT AND DISCUSSION

### Subject recruitment

Within 4 months, a total of 144 diabetic neuropathy individuals were successfully collected. Eight individuals did not meet the study criteria and 136 individuals were enrolled in the study. The individual recruitment flow is shown in Fig. 1.

The individuals did not meet the criteria of the study, among others, were not willing to be involved in the study (two individuals), three individuals received advanced pain therapy (2<sup>nd</sup> and 3<sup>rd</sup> line), and three individuals had uncontrolled blood glucose level. In the observation period, in the exposure group, there were four individuals who had dropped out because of low adherence (<80%).

### Subjects characteristics

The demographics of the study individuals were determined by age, sex, risk factors, ongoing therapy, and initial pain scores, as showed in Table 1. Table 1 shows that the results of characteristic analysis both in neuroprotector groups (exposure) and usual care (nonexposure) were not significantly different. This means the individuals of the study in both groups were equal and would not affect the observed outcome of the study.

### Vitamin B complex and mecobalamin effectivity analysis

The results of the observations showed the group of patients undergoing neuropathic pain treatment with neuroprotective addition (exposure group) and without neuroprotective addition (nonexposure group), both group (dependent sample) had significant neuropathic pain relief compared to baseline ( $p < 0.05$ ). However, when compared to head-to-head between the exposure group and nonexposure group (independent sample), it was seen that the exposure group was better in reducing the pain score than nonexposure significantly ( $p < 0.05$ ) as shown in Table 2. Individuals in the exposure group can be classified into two subgroups, the group receiving the Vitamin B complex (Vitamins B1, B6, and B12) and mecobalamin (Vitamin B12). The two subgroups were carried out with nonparametric analysis to determine whether there are differences in effectiveness. The results are presented in Table 3.

In Table 3, it was shown that both Vitamin B complex and mecobalamin had no significant effect difference in decreasing pain score ( $p > 0.05$ ).

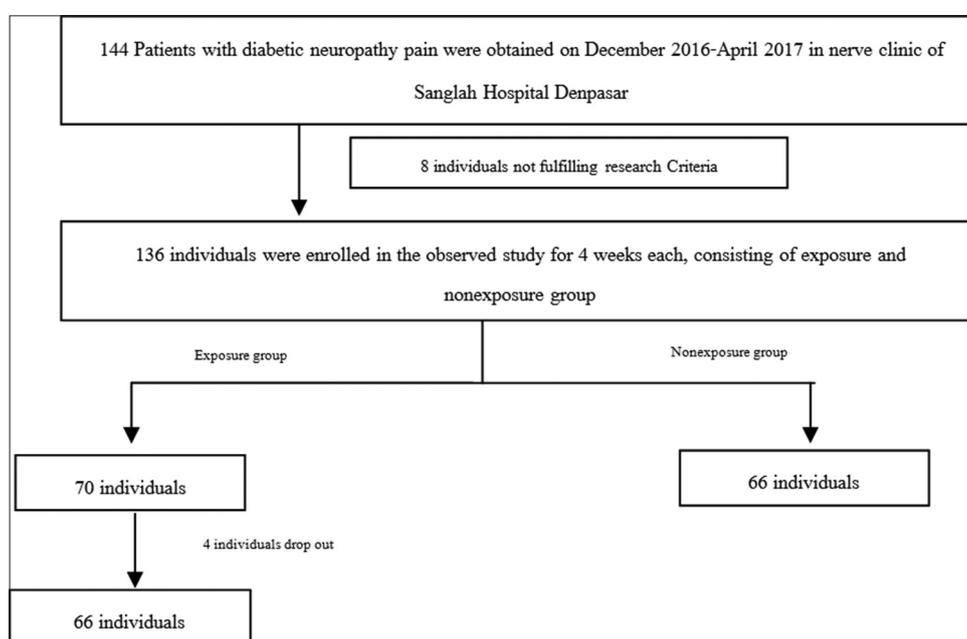


Fig. 1: Recruitment flow of research individuals, sample size 132 individuals

Table 1: Baseline characteristic

Baseline characteristics	Exposure group	Nonexposure group	p	Analysis
Age (year)	63.36±4.42	63.45±4.08	0.970 NS	MWU
Sex				
Male (n=66 [%])	37 (56.06)	39 (59.09)	0.725 NS	Chi-S
Female (n=66 [%])	29 (43.94)	27 (40.91)		
Risk factor				
Hyperlipidemia (n=66 [%])				
Yes	39 (59.09)	31 (46.97)	0.163 NS	Chi-S
No	27 (40.91)	35 (53.03)		
Hypertension (n=66 [%])				
Yes	31 (46.97)	33 (50)	0.728 NS	Chi-S
No	35 (53.03)	33 (50)		
Smoking (n=66 [%])				
Yes	16 (24.24)	21 (31.82)	0.241 NS	Chi-S
No	50 (75.76)	45 (68.18)		
Diabetes duration (n=66 [%]) (years)				
<5	35 (53.03)	29 (43.94)	0.296 NS	Chi-S
>5	31 (46.97)	37 (56.06)		
Neuropathic pain therapy				
Amitriptyline (25 mg OD) (n=66 [%])	34 (51.52)	30 (45.45)	0.486 NS	Chi-S
Gabapentin (100 mg TID) (n=66 [%])	32 (48.48)	36 (54.54)		
Baseline pain scores (unit)	3.59±0.99	3.29±1.02	0.850 NS	MWU

Mean±SD, n=132, NS: Not significant, n: Number of individual, MWU: Mann-Whitney U analysis, Chi-S: Chi-square analysis, OD: Once daily, TID: 3 times a day. SD: Standard deviation

Table 2: Effectivity of neuroprotector as supportive neuropathic pain therapy

Research group	Variable	Baseline (unit)	Final (unit)	Decrease pain score (unit)	p value (dependent sample)*	p value (independent sample)**
Exposure (Vitamin B complex or mecobalamin addition) (n=66)	Mean pain score	3.59	0.67	-2.9	<0.001 Sig.	0.041 Sig.
	SD	0.99	0.81	0.18		
Nonexposure (usual care) (n=66)	Mean pain score	3.29	0.62	-2.67	<0.001 Sig.	
	SD	1.02	0.84	0.18		

Mean±SD, n=132, \*: Wilcoxon sign rank test, \*\*: Mann-Whitney U test; Sig: Significant; n: Number of individual, SD: Standard deviation

Table 3: Subgroup analysis of the efficacy Vitamin B complex versus mecobalamin

Subgroup of exposure group	Dose	Decrease of pain score		p value
		>2 (unit) (%)	2 (unit) (%)	
Vitamin B complex (n=37)	1 tablet OD (Vit. B1 50 mg; B6 100 mg; B12 100 mcg)	26 (70.27)	11 (29.73)	0.613 NS
Mecobalamin (n=29)	500 mcg OD	22 (75.86)	7 (24.4)	

n=66, n: Number of individual, NS: Not significant, OD: Once daily, Vit: Vitamin

This suggests that both Vitamin B complex and mecobalamin both have a better effect in reducing the diabetic neuropathic pain score than without the administration of neuroprotective agents.

Based on the results obtained, it can be determined the value of relative risk (RR) and number need to treat (NNT) individual to exposure group and nonexposure, with the result shown in Table 4.

RR values show that individuals in the exposure group experienced a decrease in pain intensity >2 units, 1.37 times greater than nonexposure group, whereas an NNT score of 5.08, meaning that every five individuals given neuroprotective supplementation would get one good effect to decrease of diabetic neuropathic pain.

The results of research obtained similar to an open-label prospective study that showed 24 weeks of neuroprotective treatment in patients with DM with polyneuropathy showing healing at tingling (p<0.03), upper limb symptoms (p<0.003), ataxia (p<0.004), and signs of impaired position (p<0.009) sense, vibration sense (p<0.0001), pinprick sensation (p<0.004), and knee reflex (p<0.004) improved

from baseline [10]. Systematic review studies conducted in neuropathy patients with DM treated with combination agents (Vitamin B complex with cyanocobalamin) and single methylcobalamin suggests a symptomatic relief increase compared to electrophysiologic therapy [12].

Supplementation of Vitamin B complex or mecobalamin may be useful in patients with neuropathy to overcome the deficiency that occurs. One of the mechanisms suspected of contributing to the treatment of neuropathic pain is that neuroprotectors can act as direct and crucial donors from methyl groups to myelin sheaths that isolate axons and in DNA metabolism for nerve regeneration [10,13]. In Vitamin B12 deficiency, hypomethylation occurs in the central nervous system. Inhibition of B12-dependent enzyme methionine synthase results in a decrease in the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine [14]. Deficiencies in the SAM component interfere with the methylation reaction in the myelin sheath. Methylation of homocysteine into methionine requires the presence of Vitamin B12 [15]. The elderly population is generally deficient in Vitamin B12; so, it needs the intake of vitamins from outside the

Table 4: RR value and NNT individuals

Research group	Decrease of pain score		RR (CI 95%)	NNT (CI 95%)
	>2 (unit) (%)	2 (unit) (%)		
Exposure (n=66)	48 (72.73)	18 (27.27)	1.37 (1.05-1.80)	5.08 (3-28)
Nonexposure (n=66)	35 (53.03)	31 (46.97)		

n=132, n: Number of individual, RR: Relative risk, NNT: Number need to treat, CI 95%: Confidence interval 95%

body [16]. Based on the results of research that has been done, the provision of neuroprotector supplementation may be considered to be given to geriatric with Type 2 diabetes neuropathy pain to be able to support the treatment of neuropathic pain given by the physician.

This study has limitations, where the individuals involved in the study had baseline pain scores ranging only in the 2-5 unit range, which was incorporated into the mild-to-moderate pain category. The baseline pain score was unable to measure the effectiveness in severe degrees.

### CONCLUSION

Neuroprotectors (Vitamin B complex or mecobalamin) administration can reduce the intensity of diabetic neuropathy pain better than without administration in geriatrics that were running the first-line therapy of diabetic neuropathy pain.

### ACKNOWLEDGMENTS

We thank the entire medical and paramedical staff in Sanglah Public Hospitals Center for the support in the implementation of research. We also thank to Sanglah Hospital ethics committee on research permits were granted, and the research team in the Department of Clinical Pharmacy, Health Sciences Institute Medika Persada Bali for all of the support.

### REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27(5):1047-53.
2. Rasolabadi M, Khaledi S, Ardalan M, Kalhor MM, Penjvini S, Gharib A. Diabetes research in Iran: A scientometric analysis of publications output. *Acta Inform Med* 2015;23(3):160-4.
3. Han C, Whiting D, Guariguata L, Brown A, Dahlquist G, Dodd S, *et al.* IDF Diabetes Atlas. *Int Diabet Fed* 2013;???:14-25.
4. Tesfeye S. Epidemiologi and etiology of diabetic peripheral neuropathies. *Adv Stud Med* 2004;4:1014-21.
5. Keban SA, Najuah N, Abdillah S. The role of pharmacists in evaluating and intervening the patients with diabetic neuropathy. *Asian J Pharm Clin Res* 2017;10:127-31.
6. Moradi M, Mousavi S. Drug use evaluation of diabetes mellitus in non-hospitalized patients. *Int J Pharm Pharm Sci* 2016;8:337-41.
7. Javed S, Petropoulos IN, Alam U, Malik RA. Treatment of painful diabetic neuropathy. *Ther Adv Chronic Dis* 2015;6(1):15-28.
8. Wagle L, Thomas AA, Shrestha S. Drug utilisation study of stroke and other patients admitted to general ward of neurology unit at quaternary care private hospital. *Int J Curr Pharm Res* 2017;9:23-8.
9. Jayabalan B, Low LL. Vitamin B supplementation for diabetic peripheral neuropathy. *Singapore Med J* 2016;57(2):55-9.
10. Dominguez JC. A prospective open label 24-week trial of methylcobalamin in the treatment of diabetic polyneuropathy. *J Diabet Mel* 2012;02:408-12.
11. Vasudevan D, Naik MM, Mukaddam QI. Efficacy and safety of methylcobalamin, alpha lipoic acid and pregabalin combination versus pregabalin monotherapy in improving pain and nerve conduction velocity in Type 2 diabetes associated impaired peripheral neuropathic condition. *Ann Indian Acad Neurol* 2014;17:19-24.
12. Sun Y, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: Systematic review of clinical controlled trials. *Acta Neurol Taiwan* 2005;14(2):48-54.
13. Thakur S, Srivastava N. An update on neuropathic pain models. *Int J Pharm Pharm Sci* 2016;8:11-6.
14. Weir DG, Scott JM. The biochemical basis of the neuropathy in cobalamin deficiency. *Baillieres Clin Haematol* 1995;8(3):479-97.
15. Metz J. Pathogenesis of cobalamin neuropathy: Deficiency of nervous system S-adenosylmethionine? *Nutr Rev* 1993;51(1):12-5.
16. Arora H, Srivastava N, Bala K. Prevalence of vitamin D/B12 deficiency among urban populations complaining pain of lower limb and generalize weakness. *Asian J Pharm Clin Res* 2016;9:261-3.