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Effectiveness of additional therapy with vitamin D (5.000 IU) on reducing diabetic neuropathy pain

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ABSTRACT

Background and objectives. Diabetic neuropathy is microvascular complication of diabetes mellitus that attacks the peripheral nervous system and manifested as persistent electrocution pain. Patients with diabetic neuropathy are often found in conditions of vitamin D deficiency. Vitamin D has a neuroprotective effects that plays a role in increasing axonogenesis, preventing nerve degeneration, and is an anti-inflammatory agent that can reduce diabetic neuropathy pain. Determine the effectiveness of additional therapy with Vitamin D 5.000 IU on the reduction of diabetic neuropathy pain in patients with diabetes mellitus at Bethesda Hospital, Yogyakarta.

Materials and methods. This study is a Randomized Controlled Trial that has been completed. Data were taken from patients with diabetic neuropathy diagnosed by Diabetic Neuropathy Examination and Diabetic Neuropathy Symptoms at Bethesda Hospital, Yogyakarta. There were 34 subjects involved and divided into two groups: treatment group given symptomatic therapy with additional Vitamin D 5.000 IU and the control group receiving only symptomatical therapy. Furthermore, pain intensity development data using VAS at weeks 0, 4, and 8 were analyzed using non-parametric Mann Whitney test.

Results. Both groups experienced a decrease in pain intensity, but the treatment group which was given symptomatic therapy with additional vitamin D 5.000 IU was significantly better as seen from the difference between the VAS rate before and after therapy (p=0.010) (p<0.05).

Conclusions. Additional vitamin D 5.000 IU in diabetes mellitus patients with diabetic neuropathic pain can decrease pain intensity better compared to just receiving symptomatic therapy.

Keywords: diabetes mellitus, diabetic neuropathy, vitamin D

List of abbreviations

ACEIs – Angiotensin Converting Enzyme Inhibitors
AGE – Advance Glycation End-Products
ARBs – Angiotensin II Receptor Blockers
COX-2 – Cyclooxygenase-2
DNS – Diabetic Neuropathy Examination
DNS – Diabetic Neuropathy Symptoms
iNOS – inducible Nitric oxide synthase
IU – International Unit
M-CSF - Macrophage Colony-Stimulating Factor
NF-κB – Nuclear Factor Kappa B
NGF – Nerve Growth Factor
NO – Nitric Oxide
PGE2 – Prostaglandin E2
RAGE – Receptor Advance Glycation End-products
RCT – Randomized Controlled Trial
TNFα – Tumor Necrosis Factor Alpha
VAS – Visual Analogue Scale
15-PGDH – 15-prostaglandin dehydrogenase

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INTRODUCTION

Diabetes mellitus is a condition of hyperglycaemia due to the body's inability to produce the insulin hormone or insulin resistance occurs [1]. The International Diabetes Federation stated that in 2019, diabetes sufferers in the world reached 463 million people, while based on 2018 RISKESDAS data in Indonesia, the number of diabetes sufferers in Yogyakarta reached 15,540 people [1,2].

Diabetic neuropathy is a microvascular complication of diabetes mellitus that affects the peripheral nervous system with symptoms of continuous tingling, burning, prickling, or electric shock [3]. This pain can be found in 30-50% of diabetes mellitus patients [4].

Hyperglycaemia is associated with increased polyol pathway activity, where the affinity of the aldose reductase enzyme to glucose is higher, resulting in the accumulation of sorbitol and increased activity of the sorbitol dehydrogenase enzyme. The accumulation of sorbitol in nerves that cannot pass through the cell membrane, can increase the intracellular osmotic pressure and cause osmotic stress, thereby interfering with axonal transport and damaging the nervous structure. Hyperglycaemia also causes proteins to undergo non-enzymatic glycation, transforming them into AGE (advanced glycation end-products) and binding to their receptor, RAGE, triggering oxidative stress, increased proinflammatory cytokines activity, and NF-κB expression, leading to nerve dysfunction and diabetic neuropathy [4,5].

Vitamin D is neuroprotective which plays a role in increasing axonogenesis and preventing nerve degeneration [6]. Vitamin D also acts as an anti-inflammatory agent by inhibiting cytokine macrophage colony-stimulating factor (M-CSF), enzyme inducible nitric oxide synthase (iNOS), and decreasing NF-κB synthesis. Vitamin D deficiency conditions are associated with increased intensity of pain in diabetic neuropathy [7]. Pain intensity measurement can be done using visual analogue scale (VAS), which is a measure of a straight line with a length of 10 cm where the left end indicates no pain and the right end indicate the worst pain [8].

The study aims to determine the effectiveness of supplemental therapy with 5000 IU of vitamin D in reducing the pain of diabetic neuropathy in patients with diabetes mellitus at Bethesda Hospital in Yogyakarta, Indonesia.

MATERIALS AND METHODS

The study uses secondary data from the Randomized Controlled Trial research design that existed from February to April 2021. There are 34 subjects of diabetes mellitus patients with diabetic neuropathic pain at Bethesda Hospital, Yogyakarta. The sample count is calculated using openepi software with a sample of at least 14 people. The subjects were divided into 2 groups: the control group receiving only symptomatic therapy and the treatment group who received additional therapy of 5,000 IU of vitamin D. In this study, pain scale were assessed using the VAS before and after intervention in weeks 0, 4 and 8.

The criteria for inclusion in this study included (1) patient with type 2 diabetes mellitus with diabetic neuropathic pain who agreed to participate in the study, (2) patients who had been diagnosed with diabetic neuropathies based on Diabetic Neuropathy Examination (DNE) and Diabetic Neuropathy Symptoms (DNS), (3) patients who were over 18 years of age, while, the exclusion criteria include (1) patients who are allergic to vitamin D, (2) patients who had diseases or disorders in the liver and kidneys, (3) woman who were pregnant and lactating, (4) patients who stopped controlling in the middle of the course of the study, (5) patients who died before the end of the study.

Univariate analysis is done to find out the baseline characteristics of each subject. Bivariate analysis uses the chi-square test to determine the relationship between confounding variables and independent variables to dependent variable. The study also conducted a normality test to determine the distribution of data using the Shapiro-Wilk test and non-parametric Mann Whitney test using SPSS software to find out the relationship between intervention and decreased intensity of pain in diabetic neuropathy before and after therapy in both groups.

This research has been ethically validated by the Bethesda Hospital Yogyakarta research ethics commitee (No. 63/KEP-RSB/XII/21).

RESULTS AND DISCUSSION

The study was attended by 34 subjects, with 19 females (55.9%) over 15 males (44.1%). A cohort study by Abraham, A et al., (2018) stated that women suffer more from diabetic neuropathic pain with higher intensity of pain than men after measuring using VAS [9]. Singh, A et al., (2016) stated that estrogen is neuroprotective so that a decrease in estrogen levels in postmenopausal women can increase the risk of diabetic neuropathy [10]. In this study, the age ratio was 63.1471±9.03573 years, where diabetic neuropathy was discovered as the age increased due to the reduction in the body's ability to suppress free radicals that caused endothelial damage and resulted in diabetes neuropathy [11]. Long-term diabetes mellitus in both groups averaged 9.3382±7.58659 years with both dominant controlled diabetes. Nisar et al., (2015) stated that long duration of diabetes accompanied by poor glucose control leads to metabolic disorders, endothelial injury, and an increase in oxidative prod-

ucts and glycosylation end products [12]. Both groups were also dominated by subjects with vitamin D deficiency (70.6% vs 58.8%). Sari et al. (2020) stated that diabetic neuropathy was often associated with vitamin D deficiency because it was found that serum vitamin D levels were lower compared to those who did not have diabetic neuropathy [6]. Patients with diabetes who have hypertension are targeted to have blood pressure below 130/80 mmHg. Diabetes with hypertension can increase the risk of macrovascular and microvascular complications so antihypertensive drugs such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are needed [13]. According to the American Diabetes Association, patients with diabetes mellitus are given anti-platelet aspirin, especially to those with a history of atherosclerosis to reduce the risk of cardiovascular disease [14]. Administration of statin is recommended in patients with diabetes mellitus who have a history of cardiovascular disease [15]. While, vitamin B have a neuroprotective role in preventing the onset of diabetic neuropathic pain [16]. Analysis of standard therapy data comparison of the two groups obtained a p value >0.05, which means comparison of the therapy between the two equal groups. The subjects were diagnosed with diabetic neuropathy using DNE and DNS scoring. In the treatment group, obtained a DNE rate of 4.18 ± 0.951 and the control group had a DNE rate of 4.06 ± 0.899. Whereas the DNS rate of the treatment group was 2.24 ± 1.091 and the control group had a DNS rate of 2.35 ± 0.862. Both groups had no significant differences with p>0.05 [Table 1].

In week 0 and week 4, both groups have a p value =1.000 and 0.277, which means there was no significant difference (mean VAS 5.82vs5.69 and 3.39vs4.47). In week 8, both groups have a p value =0.033, meaning there is a significant differential (VAS ratio

TABLE 1. Baseline characteristic of subjects

	Symptomatic therapy + 5000 IU of vitamin D		Symptomatic therapy		p
	(n=17)	%	(n=17)	%	
Age Mean (year)	64.2941 ± 9.48528		62 ± 9.50174		0.468
Sex					0.490
Male	6	35.3	9	52.9	
Female	11	64.7	8	47.1	
Duration of diabetes mellitus Mean (year)	11.2059 ± 9.50174		7.4706 ± 4.58418		0.458
Marital status					0.223
Not married	0	0	2	11.8	
Married	14	82.4	14	82.4	
Divorced	3	17.6	1	5.9	
Educational background					0.072
Elementary school	1	5.9	1	5.9	
Junior high school	3	17.6	0	0	
Senior high school	9	52.9	5	29.4	
Associated's degree	2	11.8	2	11.8	
Bachelor degree	2	11.8	9	52.9	
Occupation					0.132
Businessman	1	5.9	2	11.8	
Private sector employee	3	17.6	1	5.9	
Unemployement	2	11.8	2	11.8	
Retired	4	23.5	9	52.9	
Housewife	6	35.3	1	5.9	
BUMN's employee	0	0	2	11.8	
Village head	1	5.9	0	0	
Type of health financing					0.286
BPJS	14	82.4	11	64.7	
Company insurance	0	0	2	11.8	
Independent costs	3	17.6	4	23.5	
Comorbid					
Hypertension					0.167
Yes	7	41.2	12	70.6	
No	10	58.8	5	29.4	
Cardiovascular disease					0.040
Yes	5	29.4	12	70.6	
No	12	70.6	5	29.4	

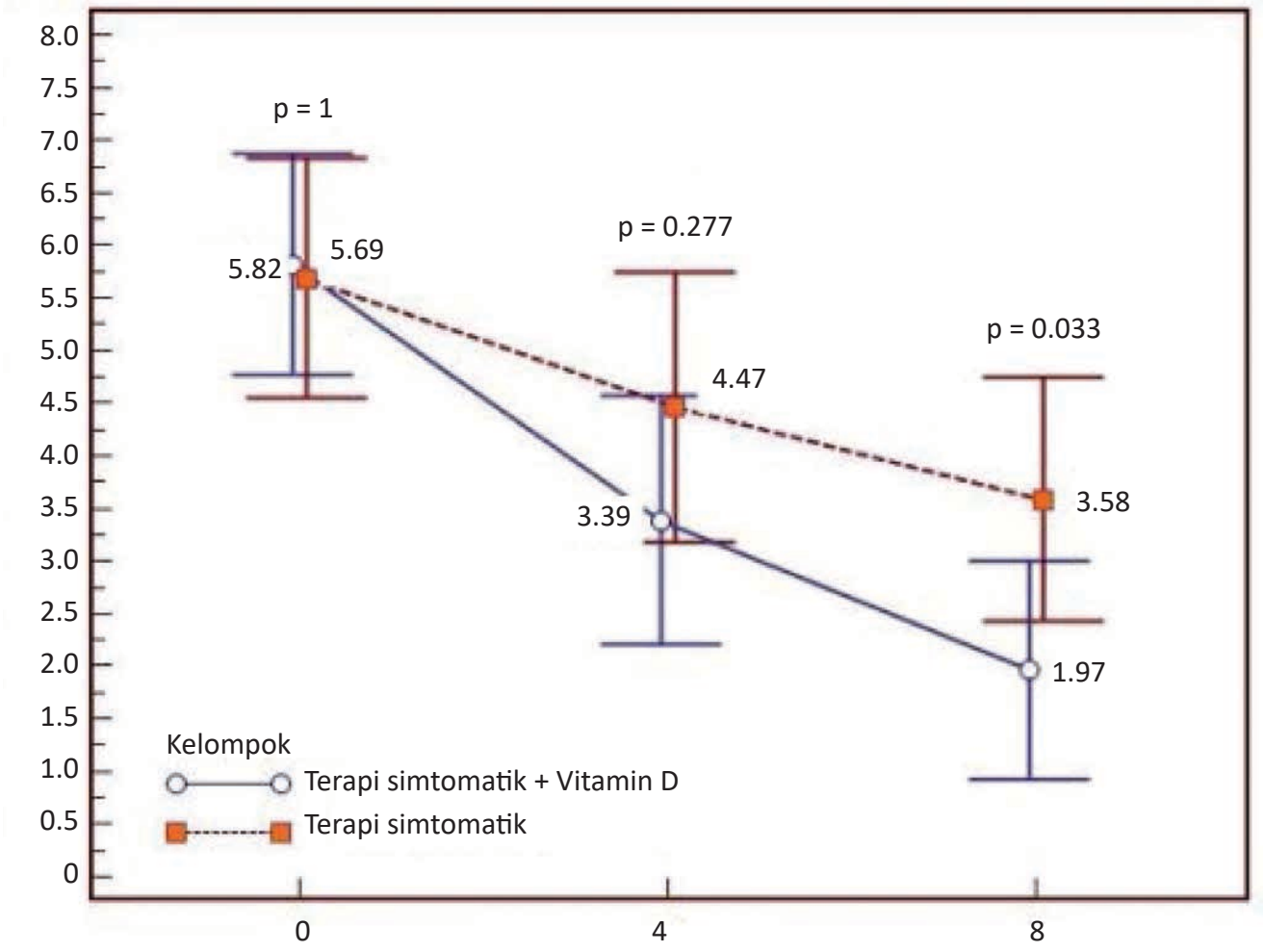

FIGURE 1. Graphic rate shows a comparison of the pain intensity ratios between the two groups measured with VAS from before therapy (week 0), week 4 and week 8 after therapy

1.97vs3.58). The difference between both groups at pre-therapy with week 8 was 3.8471vs2.1059 (p = 0.010). The decrease in the scale of diabetic neuropathy pain in the treatment group was significantly better than in the control group [Figure 1].

Neither the treatment group nor the control group obtained subjects who experienced side effects of the drug (Table 2).

Vitamin D is a neurotrophic hormone that has neuroprotective effects by increasing axonogenesis and preventing nerve degeneration. Diabetic neuropathy is often associated with a decrease in nerve growth factor (NGF) in the nerves, whereas vitamin D can enhance the NGF synthesis that plays a role in neural development. Vitamin D also plays a role in inhibiting COX-2 by stimulating 15-prostaglandin dehydrogenase (15-PGDH). The 15-PGDH enzyme will degrade prostaglandins and inhibit prostaglandin-E2 receptors. When prostaglandins are not inhibited, it can mediate neuropathic pain in the bone marrow during PGE2 depolarizes. Vitamin D suppresses proinflammatory cytokines such as TNFα and M-CSF in astrocytes and microglia. Vitamin D also inhibits the iNOS enzyme that produces NO (a

TABLE 2. Tables of side effects

Side effects	Symptomathic therapy + 5000 IU of vitamin D	Symptomatic therapy	%
Yes	0	0	0
No	34	34	100

neurotransmitters in the nociceptive pathway that cause central sensitization) so that it can reduce pain and nerve damage. Vitamin D also reduces the function of neutrophils that produce cytokines and NO when tissue damage occurs because the more neutrophils, the worse the progression of diabetic neuropathy [13].

The limitation in this study is to use secondary data of completed RCT research so that researchers cannot know the research process. Besides, this study's observation time is limited to eight weeks.

CONCLUSION

Supplemental vitamin D therapy of 5,000 IU in patients with diabetes mellitus with diabetic neuropathic pain can decrease the intensity of pain more

sharply compared to simply receiving symptomatic therapy without additional therapy.

Conflict of interest: None

Authors contributions

The studies of additional 5000 IU of vitamin D on reducing neuropathic pain in patient with diabetes mellitus, conceptualization, NAS, RTP, and S; methodology, RTP; software, NAS; validation, NAS, RTP, S; formal analysis, NAS, RTP; investigation, RTP; resources, RTP; data curation, NAS.; writing—original draft preparation, NAS; writing—review and editing, NAS; visualization, NAS; supervision, RTP, S; project administration, RTP, S; funding acquisition, RTP. All authors have read and agreed to the published version of the manuscript.

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