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Original Article

SCN9A and SCN10A Polymorphism and Therapeutic Effectiveness of Lidocaine Local Anesthetic Injection in Subjects with Diabetic Neuropathy Pain

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ABSTRACT

Background: Diabetic neuropathy pain (DNP) is one of the complications experienced by more than half of the diabetic population. Treatment using lidocaine injection is one of the effective ways to manage pain in patients with DNP. Pain therapy using lidocaine locally targets the SCN9A and SCN10A genes, which encode the sodium receptors Nav1.7 and Nav1.8. The effect of lidocaine inhibits these sodium channels to reduce pain transmission. **Purpose**: This study aims to analyze the effect of polymorphism of genes encoding Nav1.7 and Nav1.8 on the effectiveness of lidocaine local injection therapy in patients with DNP. **Methods**: This study was an analytic observational study with a cross-sectional approach. A total of 63 people with DNP were genotyped for the SCN9A rs 6746030 gene and the SCN10A rs12632942 gene using Real-Time PCR/qPCR and DNA sequencing. **Result**: The results showed that 91.2% and 70.6% of the population who experienced decreased pain had the GA mutant allele in the SCN9A rs6746030 gene and the AG mutant allele in the SCN10A rs12632942 gene. The results showed a significant association of Nav1.7 and Nav1.8 gene polymorphisms with the effectiveness of lidocaine local anesthetic injection therapy in diabetic neuropathy pain patients ($p < 0.05$). **Conclusion**: This study shows that there was an association between Nav1.7 and Nav1.8 gene polymorphisms and the effectiveness of lidocaine local anesthetic injection therapy in patients with DNP. Lidocaine injection therapy that targets the Nav1.7 and Nav1.8 sodium channels involving the SCN9A and SCN10A genes can be a therapeutic alternative for patients with DNP.

Keywords: Diabetes, Diabetic neuropathy pain, Nav1.7, Nav1.8, polymorphism.

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INTRODUCTION

A metabolic condition called diabetes mellitus is dangerous to everyone's health. As to Saeedi et al. (2019), the International Diabetes Federation has estimated that 9.3% of the population, or 463 million people, had diabetes in 2019.[1] This number is expected to increase to 10.2% by 2030 and 10.9% by 2045. Diabetes mellitus is linked to nervous system abnormalities, macrovascular, and microvascular problems. According to Viigimaa et al. (2019), macrovascular consequences include peripheral arterial disease, cerebrovascular disease, and coronary heart disease. Nephropathy, retinopathy, neuropathy, and diabetic microangiopathy are examples of microvascular consequences.[2] Many diabetics are said to suffer from diabetic neuropathic pain (DNP), a complication.[3]

Diabetic neuropathy is nerve damage due to high blood sugar levels, characterized by numbness, burning, and prickling, especially in the toes, soles, and lower limbs. This condition becomes very disruptive to the daily activities of the sufferer which can lead to a decrease in quality of life.[4,5] Diabetic neuropathy pain results from damage to pain-carrying pathways, with symptoms of hyperalgesia, allodynia, and spontaneous pain.[6]

Management of diabetic neuropathy pain is still difficult, although efforts have been made to produce more effective and rational therapeutic approaches.[5] First-line recommendations for diabetic neuropathy pain therapy include tricyclic antidepressants, gabapentin, pregabalin, and topical lidocaine.[7] Diabetic neuropathy pain therapy using lidocaine injection is currently being practiced. Diabetic neuropathy pain therapy using lidocaine local anesthetic injection is currently being carried out, lidocaine is injected at the pain point, which is a hyperirritable point/place located in the muscle or fascia structure close to the damaged nerve.[8] According to research by Seah et al. (2017), parenteral lidocaine administration is safe and effective in controlling neuropathic pain, and subcutaneous lidocaine infusion is also effective in some cancer patients and is well tolerated.[9] Studies using subcutaneous lidocaine infusion show effectiveness at a rate of 100-160 mg/hour. In this study, lidocaine appeared effective in some patients characterized by a decrease in pain scores, a reduction in morphine oral equivalent (MOE) dose, subjective assessment, and minimal side effects of lidocaine were also reported.

Diabetic neuropathy pain therapy with lidocaine locally acts on sodium receptors Nav 1.7 and Nav1.8 in the dorsal root ganglion nervous system. Lidocaine sensitively inhibits the action of sodium receptors Nav 1.7 and Nav1.8 so that pain stimuli are not forwarded in the somatosensory pathway.[6,10,11] Apart from inhibiting sensory impulses, lidocaine binding to sodium receptors (Nav 1.7) and (Nav1.8) can also reduce the local inflammatory process.[12,13] The important role of Nav1.7 and Nav1.8 on pain has been proven by genetic studies in humans. There are three pain syndromes that are linked to mutations of SCN9A, the gene that codes for Nav1.7:

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idiopathic peripheral nerve fiber neuropathy, intense paroxysmal pain, and hereditary erythromelalgia. Furthermore, osteoarthritis, sciatica, amputation pain, lumbar dissection, and pancreatitis are further illnesses linked to prevalent SCN9A variations and their associated pain. According to genetic research, the common variant of rs6746030 in SCN9A is linked to pain perception.[14]

Small fiber neuropathy can result from mutations in the SCN9A and SCN10A genes, which separately account for roughly 28.6 and 5% of cases.[15] Pain signals are transmitted by nociceptors, which are equipped with SCN9A and SCN10A genes, respectively, which dictate the synthesis of alpha subunits for NaV1.7 and NaV1.8 sodium channels, respectively.[16] These mutations result in abnormally open sodium channels, which increase the transmission of pain signals and make the person more sensitive to stimuli by enabling sodium ions to flow into the nociceptors excessively.[17]

The lack of research analyzing the effect of polymorphism of genes encoding Nav1.7 and Nav1.8 on the effectiveness of lidocaine local injection therapy in patients with diabetic neuropathic pain so this study was conducted. This study is to determine the variants and analyze the effect of SCN9A gene polymorphism and SCN10A gene on the effectiveness of lidocaine local anesthetic injection therapy in diabetic neuropathy pain patients.

MATERIALS AND METHODS

Study design

This study was an analytical observational study with a cross-sectional approach by observing or measuring data on independent variables and dependent variables at the same time. This study has received approval from the health research ethics committee of the Faculty of Medicine, Wijaya Kusuma University with number 69/SLE/FK/UWKS/2021.

Participants

The sampling technique used total sampling, and the 63 samples size was made up of 14 males and 48 women. The following conditions had to be met in order for a patient to be included in this study: they had to be over eighteen years old, have type 2 diabetes mellitus for at least three years, have inferior extremity pain (cruris region), have received injection therapy of lidocaine local anesthetic, and be willing to sign an informed consent form. Individuals with type 2 diabetes who were already taking medication for additional comorbidities, had a lidocaine allergy, had impaired liver function, or had coronary heart disease were not included.

Variable

The variables used to analyze the characteristics of respondents in this study were age, gender, duration of diabetes, duration of DNP, fasting blood glucose (FBG), random blood glucose (RBG), 2-hour postprandial blood sugar (2-h PPBS), hemoglobin A1c (HbA1c), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), blood pressure, pain scale, SCN9A gene polymorphism rs 6746030, SCN10A gene polymorphism rs12632942.

Pain scale measurements were made using the Visual Analog Scale (VAS) with a value range of 0 - 10 measured before and 3 days after lidocaine injection with a dose of 0.1 - 0.3 ml subcutaneously at the pain location, i.e., lower extremity irritable points obtained from medical records. The measurement results of FBG, RBG, 2-h PPBS, HbA1c, LDL, HDL, TC, TG, and blood pressure were categorized into normal and abnormal. Categorized as normal if FBG <100 mg/dL, random blood sugar <200 mg/dL, 2-h postprandial blood sugar <140 mg/dL, HbA1c <48 mmol/mol, LDL <130 mg/dL, HDL >40 mg/dL (male) and >50 mg/dL (female), total cholesterol <200 mg/dL, triglycerides <150 mg/dL (John, 2012). Meanwhile, blood pressure results were normal when systolic blood pressure <140 mmHg and diastolic pressure <90 mmHg.

Genotyping

The variation of SCN9A rs 6746030 gene polymorphism and SCN10A rs12632942 gene polymorphism was analyzed through 3 cc venous blood collection. After DNA isolation, polymorphism was examined by Real-Time PCR/qPCR (Roche High Pure PCR Template Preparation Kit). Furthermore, the rhAmp SNPs genotyping method was carried out with the LightCycler® system (Roche 480II) to determine SNPs. The primers used in this study to determine variations in the SCN9A gene (rs6476030) and the SCN10A gene (12632942) are presented in Table 1. Amplification using real-time PCR with the following steps: 950C for 10 minutes, followed by 40 cycles consisting of 950C denaturation for 10 seconds, 600C annealing for 30 seconds, and 680C extension for 20 seconds. Genotyping of the SCN9A gene was classified into two groups: wild type (GG) and mutant (GA/AA), genotyping of the SCN10A gene was also classified into two groups: wild (AA) and mutant (AG/GG).

Statistical Analysis

Data were analyzed using the SPSS 21 application using descriptive, normality, and relationship tests. Descriptive tests were conducted to describe the frequency of categorical data and to determine the mean ± standard deviation (SD). The relationship test of this study used Chi-square using the likelihood ratio value with a significance value of $p < 0.05$.

RESULTS

Table 2 data on the characteristics of respondents with a total sample of 63 people including 14 men and 48 women, the average age was 64.94 ± 8.67 years and had diabetes for 8.05 ± 4.97 years. The results of blood tests for glycemic control, lipid profile, and blood pressure show that more than half of the subject population has abnormal glycemic control, lipid profile, and blood pressure.

The results of analysis using Real-Time PCR/qPCR and sequencing SCN9A gene rs6746030 showed that the total population who received lidocaine injection mostly had the GA mutant genotype (56.5%), and did not experience decreased pain had the AA mutant allele (78.6%).

Table 1. SCN9A gene and SCN10A gene primers.

Protein/SNP	Oligonucleotides	Sequence (50' -30')	Concentration in PCR, microM
rs6746030		SCN9A	
	Forward	GTTCAACAATCTTG-TAGCAGGT	0.3
	Reverse	GTTGAGGGAGTATCA-CAGAAAG	0.3
	Probe G	6-FAM CC1TCC1G1T1A-C1ACAA BHQ1	0.1
	Probe A	HEX AACCTC1C1A1TA-CACAACC BHQ1	0.1
rs12632942		SCN10A	
	Forward G	GCGGGCAGGGCG-GCGGGGGCGCTCAG-GATTTCCTCAGGAT-GTG	1.1
	Forward A	CTCAGGATTTCCT-CAGGATCAA	0.2
	Reverse	GTGGACGACA-CAAGCTCCTCTG	0.3

The population that experienced decreased pain had the GA mutant allele (91.2%), did not experience decreased pain had the GA mutant allele (14.3%), and the GG mutant allele (7.1%) after lidocaine injection. Chi-square test results showed a significant association between Nav1.7 gene polymorphism (SCN9A rs6746030) with the effectiveness of lidocaine local anesthetic injection therapy in diabetic neuropathy pain patients (p = 0.000).

The results of Real-Time PCR/qPCR and sequencing of the SCN10A rs12632942 gene showed that the total population who received lidocaine injection mostly had the mutant AG genotype (56.5%), and experienced decreased pain had the mutant GG allele (29.4%). The total population who experienced decreased pain had the mutant allele (70.6%), who did not experience decreased pain had the mutant AG allele (39.3%) and the wild AA allele (35.7%). Chi-square test results showed a significant association between the polymorphism of the gene encoding Nav1.8 (SCN10A rs12632942) with the effectiveness of lidocaine local anesthetic injection therapy in diabetic neuropathy pain patients (p = 0.000).

The result that sequencing was not required for the entire SCN10A rs12632942 gene was because the relevant or significant mutation

Table 2. Respondent Characteristics.

Variable	Mean ± SD	n (%)
Age (year old)	64.94 ± 8.67	
Diabetes duration (years)	8.05 ± 4.97	
FBG (mg/dL)		
Normal	184.97 ± 95.620	20 (32.3)
Abnormal		42 (67.7)
RBG (mg/dL)		
Normal	265.50 ± 114.54	25 (40.3)
Abnormal		37 (59.7)
2h-PPBG (mg/dL)		
Normal	193.92 ± 94.74	26 (41.9)
Abnormal		36 (58.1)
HbA1c (mmol/mol)		
Normal	68.40 ± 37.10	14 (22.6)
Abnormal		48 (77.4)
LDL (mg/dL)		
Normal	154.92 ± 24.99	16 (25.8)
Abnormal		46 (74.2)
HDL (mg/dL)		
Normal	37.82 ± 7.68	9 (14.5)
Abnormal		53 (85.5)
TC (mg/dL)		
Normal	249.26 ± 41.68	5 (8.1)
Abnormal		57 (91.9)
Blood pressure (mmHg)	136.26 ± 30.53 / 80.35 ± 13.21	
Normal		18 (29)
Abnormal		44 (71)
TG (mg/dL)		
Normal	184.92 ± 50.47	6 (9.7)
Abnormal		56 (90.3)

Note: FBG (fasting blood glucose); RBG (random blood glucose); 2- h PPBS (2 hours postprandial blood sugar); HbA1c (hemoglobin A1c); LDL (low-density lipoprotein); HDL (high-density lipoprotein); TC (total cholesterol); TG (triglycerides).

Table 3. Sequencing Analysis Results of SCN9A rs6746030 and SCN10A rs12632942 Genes.

Genotype/ alleles	Total Subjects n (%)	Pain Change		p-value
		Decreased n (%)	Unchanged n (%)	
SCN9A rs 6746030				0.000*
AA (mutant)	22 (35.5)	0 (0)	22 (78.6)	
GA (mutant)	35 (56.5)	31 (91.2)	4 (14.3)	
GG (wild)	5 (8.1)	3 (8.8)	2 (7.1)	
SCN10A rs 12632942				0.000*
GG (mutant)	17 (27.4)	10 (29.4)	7 (25)	
AG (mutant)	35 (56.5)	24 (70.6)	11 (39.3)	
AA (wild)	10 (16.1)	0 (0)	10 (35.7)	

* Significant based on Chi-square - Likelihood Ratio analysis (p < 0.05).

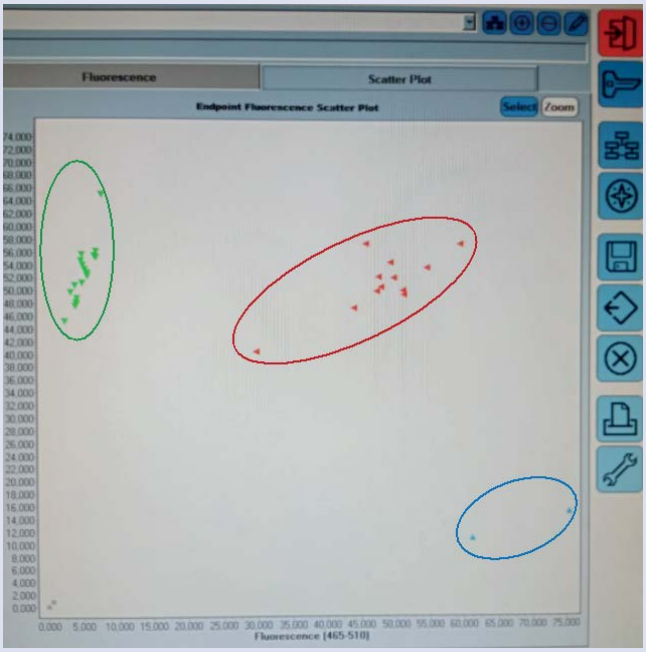

Figure 1. RhAmp SNPs genotyping results of SCN9A (rs 6746030). Green color and blue colors showed homozygote allele. Red color showed heterozygote allele.

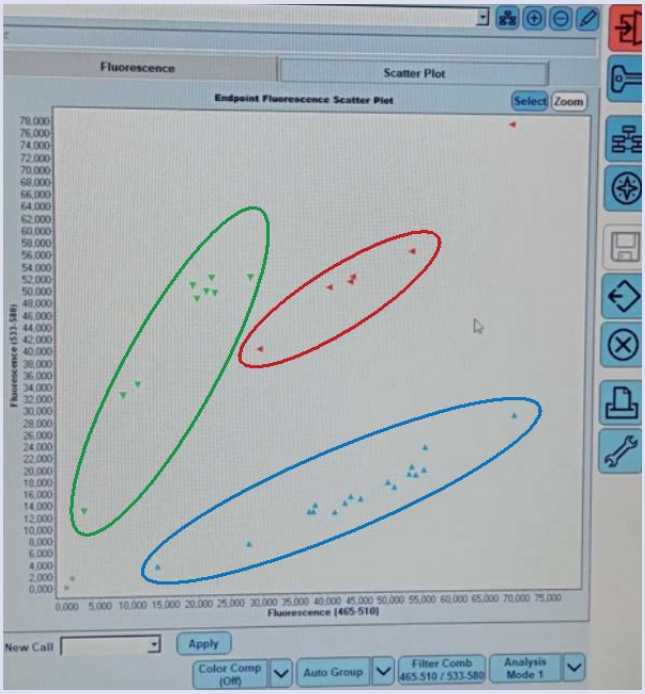

Figure 2. RhAmp SNPs genotyping results of SCN10A (rs12632942). Green color showed heterozygote allele. Red and blue colors showed homozygote allele.

that had occurred in the SCN9A rs6746030 gene was already known. Thus, the important information needed has already been found, and additional sequencing was no longer necessary.

DISCUSSION

The findings demonstrated a statistically significant correlation between the efficacy of lidocaine local anesthetic injection therapy in patients with diabetic neuropathy pain and the polymorphisms of the Nav1.7 (SCN9A rs6746030) and Nav1.8 (SCN10A rs12632942) genes. Previous research has demonstrated the expression of sodium channels Nav1.7 and Nav1.8 in the peripheral nervous system and their potential involvement in neuropathic pain.[18] Research carried out in 2015 by Q. Li *et al.* revealed a correlation between the severity of neuropathic pain and SCN9A variations. A function in pain and nociception is played by the SCN9A gene, which codes for the sodium channel Nav1.7.[14] Particularly, Nav1.7 is expressed in sympathetic ganglion neurons, trigeminal ganglia, and dorsal root ganglia, which are responsible for stimulating pain-sensitizing receptors.[17]

The sodium channel-encoding SCN10A gene is present in nerve cells known as nociceptors, which are involved in the transmission of pain signals. The peripheral nervous system, which links the spinal cord and central nervous system to cells to sense touch, smell, temperature, and pain, includes nociceptors. The primary function of nociceptors is to transmit pain signals. The dorsal root ganglion region of the spinal cord contains the nociceptor core, sometimes referred to as the cell body.[19]

SCN9A gene mutations are known to cause decreased or no pain, while a small change in one amino acid in the SCN9A gene protein sequence/structure (gain-of-function) causes the Nav1.7 channel to be easily activated, contributing to three pain syndromes: inherited erythromelalgia, extreme paroxysmal pain, and idiopathic peripheral nerve fiber neuropathy.[19,20] Meanwhile, SCN10A gene mutations have been reported in 5% of cases of small fiber neuropathy, characterized by severe pain attacks and decreased ability to distinguish hot and cold sensations. The SCN10A rs12632942 gene is a pain-related polymorphism variant with genetic variation in the form of heterozygous mutant type (AG allele) or homozygous wild type (AA allele).[21] The SCN10A gene mutation causes a simple protein synthesis inhibition change in the alpha subunit of the Nav1.8 sodium channel. This causes the sodium channel to open more easily than usual, there is an increase in sodium ion exchange through the sodium channel which causes an action potential to arise at the nociceptor. This causes an increase in the transmission of pain signals so that a person becomes more sensitive to the sensation of pain. Small nerve fibers that continuously receive pain signals from nociceptors will eventually undergo a process of axonal degeneration.[21,22]

DNA alterations can occur due to exposure to carcinogens from the internal and external environment as well as medication. The main events that cause changes or mutations in these nucleotides are referred to as single nucleotide polymorphisms (SNPs). Polymorphisms can occur in the genes encoding Nav1.7 and Nav1.8, namely the SCN9A gene and the SCN10A gene, which are the target of lidocaine.[6] Changes that occur in these genes cause changes in the activity of sodium channels Nav1.7 and Nav1.8.[17] DNP therapy using lidocaine local anesthetic injection targeting sodium channels Nav1.7 and Nav 1.8 is not effective in reducing DNP if there are mutant-type polymorphisms in the SCN9A rs6746030 and SCN10A rs12632942 genes, otherwise if there are wild type polymorphisms in the SCN9A rs6746030 and SCN10A rs12632942 genes, local lidocaine injection is effective in reducing DNP. The SCN9A gene has a mutant allele AA while the wild allele is GG. In the SCN10A gene, the mutant allele is GG while the wild allele is AA.[23] This study showed that there were some samples with the SCN9A gene with the GA mutant allele that did not experience decreased pain. Future studies will require sequencing of the entire SCN9A gene due to the presence of the same chromosome which may allow for mutations in different nucleotides or other chromosomal mutations that have an association with pain incidence.

CONCLUSION

This study shows that there was an association between Nav1.7 and Nav1.8 gene polymorphisms and the effectiveness of lidocaine local anesthetic injection therapy in diabetic neuropathy pain patients. Lidocaine injection therapy that targets the Nav1.7 and Nav1.8 sodium channels involving the SCN9A and SCN10A genes can be a therapeutic alternative for patients with DNP. In chronic conditions and mutant type polymorphisms in the SCN9A rs6746030 and SCN10A rs12632942 genes cause lidocaine injection therapy to be less effective, so further studies need to be carried out to find new analgesics that can target sodium channel subunits that have undergone polymorphism changes.

ETHICS APPROVAL

This study has received approval from the health research ethics committee of the Faculty of Medicine, Wijaya Kusuma University with number 69/SLE/FK/UWKS/2021.

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COMPETING INTERESTS

All the authors declare that there are no conflicts of interest.

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UNDERLYING DATA

Derived data supporting the findings of this study are available from the corresponding author on request.

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