Original Article

Polymorphism of Gene OPRM A118G and COMT G158A and Pain Sensitivity of the Minangkabau Ethnic, Indonesia

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Abstract

Background: Opioid is considered analgesic that has been used for thousands of years because of their effectiveness in treating pain during surgery. The opioid receptor encoded by the OPRM1 gene has several variants, including 118 A>G (adenine to guanine) that lead to different pain sensitivity. Other factors that also contribute to pain sensitivity are endogen opioids which are encoded by the COMT gene, which commonly has 168 G>A (guanine to adenine) polymorphism. This study aims to analyze the association between OPRM1 A118G and COMT G158A gene polymorphisms with pain sensitivity in the Minangkabau ethnic group.

Materials and Methods: This cross-sectional study took samples by consecutive sampling from 60 Minangkabau dan 30 non-Minangkabau patients that undergo general anesthesia in Dr. M Djamil Hospital and Andalas University Hospital, Padang, West Sumatra, Indonesia from early November 2021 until the end of January 2022. The association between OPRM1 A118G and COMT G158A gene polymorphisms with ethnicity and pain sensitivity was analyzed by Kruskal Wallis and Chi-square formulas respectively.

Results: We found there were no significant differences between OPRM1 A118G and COMT G158A gene polymorphisms in Minangkabau and non-Minangkabau ethnics (p=0.36 and p=0.53 respectively). The Difference between pain sensitivity before and after surgery in OPRM1 A118G and COMT G158 gene polymorphisms are not significant in Minangkabau ethnic (p>0.05).

Conclusion: OPRM1 A118G and COMT G158A gene polymorphisms had no significant association with pain sensitivity in Minangkabau ethnic.

Keywords: Gene polymorphism, OPRM1 A118G, COMT G158A, pain sensitivity, general anesthesia, fentanyl, Minangkabau ethnic

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Please cite this article as: Indra B, Lipoeto NI, Tjong DH, Rahman S. Polymorphism of Gene OPRM A118G and COMT G158A and Pain Sensitivity of the Minangkabau Ethnic, Indonesia. J Cell Mol Anesth. 2023;8(2):73-83. DOI: https://doi.org/10.22037/jcma.v8i2.39484

Introduction

Pain is an unpleasant sensory and emotional experience that is associated with, or similar to that associated with actual or potential tissue damage. (1) The mechanism of pain is influenced by many factors such as race, ethnicity, gender, social conditions, and individual experiences of pain (2). Research shows that genes play a very important role in determining pain sensitivity, susceptibility to chronic pain, and response to postoperative pain (3). The G allele in the gene is associated with decreased pain sensitivity in non-Hispanic whites, but on the other hand, in Hispanics and African Americans, it tends to increase pain sensitivity (4). The Malays have a lower degree of pain than the Chinese and Indians, while the Indians are reported to have a higher degree of pain than the Malays and Chinese (5).

Opioids are analgesics that have been used for thousands of years and are effective in treating pain. The opioid receptor encoded by the OPRM1 gene, has several variants, including 118 A>G (adenine to guanine) (6). OPRM1 118A>G is the most common variant of OPRM1, which is the focus of genetic research related to opioid response. The substitution of A to G at position 118 (118 A>G) in exon 1 lead to differences in opioid sensitivity, analgesic requirements, and postoperative variation in pain sensitivity (7).

In the human body, there are also natural or endogenous opioids that play a role in the pain response. One of the endogenous opioids is endorphins which are the most potent endogenous opioids and are found in the central and peripheral nervous systems. The A118G polymorphism can alter the binding affinity of endorphins and their potential cellular activity (6).

Opioid and catecholaminergic systems may influence each other. The enzyme Catechol-O-methyltransferase (COMT) functions for the breakdown of biologically active catecholamines such as dopamine, adrenaline, and noradrenaline (8). This substance is involved in various physiological processes, including pain modulation. Several polymorphisms have been identified in the COMT gene. The most studied variant is G158A, where the substitution of the G to A nucleotide at codon 158 results in an amino acid change from valine to methionine (9). Patients with the G to A polymorphism showed higher pain perception than the homozygote allele (10).

This study aims to analyze the correlation between OPRM1 A118G and COMT G158A gene polymorphisms with pain sensitivity in the Minangkabau ethnic group to develop the concept of pain management so that it can provide optimal management of pain management in the Minangkabau ethnic group.

Methods

Ethical consideration: The trial was approved by the Ethical Committee, Faculty of Medicine of Andalas University (574/UN/16.2/KEP-FK/2021).

Patients: This cross-sectional study included patients by consecutive sampling method from all general anesthetic patients in Dr. M Djamil Hospital and Andalas University Hospital, Padang, West Sumatra, Indonesia. The patient must be opioid-free and have no psychiatric, neurologic, or chronic pain issues with a range of age between 16-65 years old.

We collected data from early November 2021 until the end of January 2022 and got 90 patients that suit the criteria. All patients signed informed consent for taking the blood and NRS checked before and after surgery. Patients received the same fentanyl range of dosage (3-5 mcg/kg) when induction state and the same postoperative analgesia.

Data and sample-collecting procedures: The patient's history was collected through Medical records and direct dialogue with patients. We assessed pain intensity using the NRS score before the surgical procedure and excluded if the NRS score was higher than 3. We collected 2 mL of blood just after induction of the anesthetic procedure. Post-surgical NRS score is assessed after patients wake in Post-Anesthesia Care Unit (PACU).

Measurement of DNA in patients: Isolation of genetic materials was done in Andalas University Biomedical Laboratory and measured using *Pure Link Genomic DNA Mini Kit (Invitrogen, Carlsbad, CA,*

USA). DNA isolation was carried out according to a kit procedure consisting of a sample preparation stage, a cell lysis stage, a DNA binding stage, a washing stage, and a DNA elution stage. *Genotyping* of OPRM1 A118G and COMT G158A. gen carried out by the *polymerase chain reaction* (PCR) method and then sequencing using the *QIAamp MinElute Virus Spin Kit* (Qiagen, Hilden, Malaysia).

Statistics: We used SPSS Statistics 26 application to analyze all of the data. The correlation between OPRM1 A118G and COMT G158A gene polymorphisms with pain sensitivity and ethnicity using Krusskall Wallis and Chi-square formulas respectively.

Results

Demographic and clinical characteristics data based on sex, age, comorbidities, and the American Society of Anesthesiologists (ASA) are shown in Table 1. The table showed that women were the most common patients in the Minangkabau and non-Minangkabau ethnic groups, 66.7% and 60%, respectively.

Meanwhile, the highest age group in the Minangkabau ethnic group was 46-55 years and 56-65 years (26.7%) and in the non-Minangkabau group, the highest age was in the range of 56-65 years (30%).

The most comorbid in both groups were hypertension (13.3%) and (16.7%). The dominant ASA in Minangkabau and non-Minangkabau ethnicity is ASA 2 (88.3%) and (93.3%).

The major surgical procedure in the Minangkabau Ethnic is Laparoscopy (25%) while in the non-Minangkabau Ethnic is Laparotomy (33.3%). A parametric test revealed there were no significant variations of gender, age, comorbidities, and ASA values between Minangkabau and non-Minangkabau ethnics (P>0.05) (Table 1).

The association between ethnicity and OPRM1 A118G gene polymorphism is shown in table 2. There was a tendency for the Minangkabau ethnic group to have a higher percentage of mutations than the non-Minangkabau ethnic group. The association between both of ethnic with polymorphism OPRM A118G rs1799971 showed not statistically significant (P=0.36).

The association between OPRM1 polymorphism (rs1799971) and pain sensitivity in Minangkabau can be seen in Table 3. We used Kruskal Wallis analysis due to abnormal data distribution. Table 3 showed no significant difference between the OPRM1 genotype group in pain sensitivity before surgery, after surgery, and ΔNRS (NRS after surgery-NRS before surgery) in Minangkabau ethnic group (P=0.44, P=0.45, P=0.57, respectively).

The association between ethnicity and COMT G158A polymorphism by Chi-Square analysis showed in table 4. We found that COMT G158A gene polymorphism is not influenced by ethnicity (P=0.53).

The association between COMT polymorphism (rs4680) and pain sensitivity in Minangkabau can be seen in Table 5. We used Kruskal Wallis analysis due to abnormal data distribution. Table 5 showed no significant difference between COMT genotype groups in pain sensitivity before surgery, after surgery, and ΔNRS (NRS after surgery-NRS before surgery) in Minangkabau ethnic group (P=0.31, P=0.77, P=0.65 respectively).

Discussion

In this study, the percentage of women was higher than men in the Minangkabau (2:1 sequentially) and non-Minangkabau (3:2 sequentially) ethnic groups. The same composition was also found in a study conducted in San Antonio, USA which took samples with a minimum age of 18 years consisting of 62 samples (53: 9 ratio of women and men). (11) Because gender differences are associated with pain sensitivity, it is necessary to compare the genotypic distribution of the two sexes. The Chi-square is useful for ascertaining whether gender differences in distribution do not differentiate the distribution of the OPRM1 and COMT gene polymorphisms. There was no significant correlation between gender and gene polymorphisms OPRM1 and COMT in Minangkabau and non-Minangkabau ethnic groups (Minangkabau: OPRM1 p=0,343; COMT p=0,657) (Non-Minangkabau: OPRM1 p=0,719; COMT p=0,424).

Table 1: Demographic Data

Characteristic	Minangkabau n (%)	Non-Minangkabau n (%)	p
Gender			
Male	20 (33.3)	12 (40)	0.53
Female	40 (66.7)	18 (60)	
Ages (years), Mean±SD	43.45 ± 14.99	45.1 ± 14	
16-25	10 (16.7)	4 (13.3)	
26-35	8 (13.3)	5 (16.7)	0.97
36-45	10 (16.7)	4 (13.3)	
46-55	16 (26.7)	8 (26.7)	
56-65	16 (26.7)	9 (30)	
ASA Physical Status			
1	1 (1.7)	0	0.66
2	53 (88.3)	28 (93.3)	
3	6 (10)	2 (6.7)	
Comorbid			
Hypertension	8 (13.3)	5 (16.7)	
Type 2 Diabetes	4 (6.7)	2 (6.7)	0.71
Obesity	1 (1.7)	2 (6.7)	
Asthma	1 (1.7)	0	
Surgical Procedures			
Laparoscopy	21 (35)	7 (23.3)	
Laparotomy	15 (25)	10 (33.3)	
ORIF	3 (5)	3 (10)	
Tumor Removal	18 (30)	6 (20)	
Stabilization Decompression	3 (5)	2 (6.7)	
Tympanomastoidectomy	0 (0)	2 (6.7)	

ASA: *American Society of Anesthesiologists*, ORIF: *Open Resection Internal Fixation*

Table 2: Association of Sample Characteristics with OPRM1 A118G Gene Polymorphism

Characteristics	***Wild Type* (AA) (median (min-max))**	***Heterozygous mutant* (AG) (median (min-max))**	***Homozygous mutant* (GG) (median (min-max))**	**p**
Age (years)	49.5 (17-61)	46 (16 -65)	48 (17-65)	0.80
Gender (M/F)	22 (8/14)	25(7/18)	43 (17/26)	0.62
BMI (Kg/m^2)	23.03 (16-33)	21.87 (14-36)	22.76 (18-34)	0.21
Total dose of Fentanyl (mg)	200 (100-450)	200 (100-500)	200 (100-400)	0, 67

Min: Minimum value, Max: Maximum value BMI: *Body Mass Index*, Pre: Before surgery, Post: After surgery, IL4: delta Interleukin 4, IL6: delta Interleukin 6.

Table 3: Association of Ethnicity with OPRM Gene Polymorphism A118G

Ethnic	**Polymorphism OPRM A118G**			**Total**	**p**
	***Wild Type* (AA)**	***Heterozygous Mutant (*AG)**	***Homozygous Mutant* (GG)**		
Minangkabau	12 (20%)	31 (51.7%)	17 (28.3%)	60 (100%)	0.36
Non-Minangkabau	10 (33.3%)	12 (40%)	8 (26.7%)	30 (100%)	

Table 4: Association of OPRM1 A118G Gene Polymorphism with Changes in Pain Sensitivity in Ethnic Minangkabau

Genotype OPRM1	**NRS Before Surgery (median (min-max))**	**P**	**NRS After Surgery (median (min-max))**	**p**	**Δ NRS (median (min-max))**	**p**
*Wild Type (*AA)	1 (0-3)	0.44	3 (1-5)	0.45	2 (0-5)	**0.57**
Heterozygous Mutant (AG)	2 (0-3)		3 (1-6)		2 (0-5)	
Homozygous Mutant (GG)	2 (0-3)		3 (1-7)		2 (0-5)	

Min: minimum value, Max: maximum value, NRS: *Numeric Rating Scale*

Table 5: Association of OPRM1 A118G Gene Polymorphism with Changes in Pain Sensitivity in Non-Minangkabau

OPRM1 Genotype	NRS Before Surgery (median (min-max))	p	NRS After Surgery (median (min-max))	p	Δ NRS (median (min-max))	p
*Wild Type (*AA)	1 (0-2)		3 (1-5)		1.5 (0-5)	
Heterozygous Mutant (AG)	1 (0-3)	0.74	3 (2-6)	0.13	2 (0-5)	0.26
Homozygous Mutant (GG)	1 (0-2)		2 (1-4)		1 (0-3)	

Min: minimum score, Max: maximum value, NRS: *Numeric Rating Scale Scale*

Table 6: Association of Sample Characteristics with COMT Gene Polymorphism G158A

Sample Characteristics	*Wild Type* (GG) (median (min-max))	*Heterozygous Mutant* (GA) (median (min-max))	*Homozygous Mutant* (AA) (median (min-max))	p
Age (years)	47 (16-64)	49 (16-65)	38 (24-61)	0.23
Gender (M/F)	50 (20/30)	32 (11/21)	8 (1/ 7)	0.31
BMI (Kg m^{-2})	22.67 (15.62-34.15)	22.43 (14.12-35.67)	24.38 (16-30)	0.36
Total Fentanyl dose (mg)	200 (100-450)	200 (100-500)	200 (100-350)	0.19

Min: Minimum value, Max: Maximum value, BMI: *Body Mass Index*, IL4: delta Interleukin 4, IL6 : delta Interleukin 6

The occurrence of the OPRM1 A118G gene polymorphism in each ethnic group can be different. In the Minangkabau ethnic group, the percentage of wild type (AA) (20%), homozygous mutants (GG) (28.3%), and heterozygous mutants (GA) (51.7%). Meanwhile, in non-Minangkabau ethnic groups, the percentage of wild type (AA) (33.3%), homozygous mutants (GG) (26.7%), and heterozygous (GA) (40%). Both ethnic groups showed that heterozygous mutants were the most common mutations.

The demographic results of the OPRM1 A118G gene polymorphism that were found were the same as the demographic results of Asian Ethnics in general. Research conducted on Asian races in China in 2011 and 2013 found mutations (AG + GG) A118G is more dominant than the wild type (51.5% and 63.5%, respectively) (12, 13). Research conducted on Asian Ethnics in East India showed the same results. The percentage distribution of OPRM1 A118G gene polymorphisms was dominated by the mutant group compared to the *wild* type (61.3% vs 38.6%) (14).

Table 7: Association between Ethnicity and Gene Polymorphism COMT G158A

Ethnic	Polymorphism COMT G158A			Total	p
	Wild Type (GG)	*Mutant Heterozygous (*GA)	*Mutant Homozygous* (AA)		
Minangkabau	28 (46.7%)	26 (43.3%)	6 (10%)	60 (100%)	0.53
Non-Minangkabau	22 (73.3%)	6 (20%)	2 (6.7%)	30 (100%)	

Table 8: The Association of COMT G158A Gene Polymorphism with Changes in Pain Sensitivity in Ethnic Minangkabau

COMT Genotype	NRS Before Surgery (median (min-max))	p	NRS After Surgery (median (min-max))	p	Δ NRS (median (min-max))	p
*Wild Type (*GG)	1 (0-3)		3 (1-7)		2 (0-5)	
Heterozygous Mutant (GA)	2 (0-3)	0.31	3 (1-6)	0.77	2 (0-4)	0.65
Homozygous Mutant (AA)	1.5 (0-2)		3.5 (2-5)		2 (1-3)	

Min: minimum value, Max: maximum value, NRS: *Numeric Rating Scale*

Research conducted by Daisuke Nishizawa on people in Japan found that 72.4% of the total sample had mutations in the OPRM1 A118G (AG+GG) gene (15). In a study conducted on Asian Ethnics in Malaysia, the same demographic results were also found. The OPRM1 A118G (GA+GG) gene mutation has a higher percentage than the *wild type* (65% vs 35% respectively) (16).

Meanwhile, the distribution of the OPRM1 A118G gene polymorphism that was found was different from the results obtained from several studies on Caucasian ethnicity. Research on the OPRM1 A118G polymorphism conducted on Caucasian races in several places such as the USA, Italy, and Switzerland found the percentage of the G allele (AG+GG) of (39.7%; 42.1%; 48.6% respectively) of the total examined sample (17, 18). A study in San Antonio, USA that took a sample of the average student at a university, showed that the *wild type* (AA) was (60%) more dominant than homozygous mutants. (GG) (3.4%), and heterozygous mutants (36.2%) (19). Another study by Miranda R et al showed that of the total 107 Caucasian ethnic samples studied, only 32 samples (29.9%) had the G allele (GA+GG) in the OPRM1 gene (20). The data obtained in the Caucasian Ethnic population from Central Sweden showed that the G allele polymorphism (GA+GG) only occurred in 30% of the 299 samples examined. Central Swedes were chosen because they are ethnically indigenous with a low level of a mix-up with surrounding populations such as Finns, Baltic Peoples, Central Europeans, and Southern Europeans. So for gene genotypes, this sample is separate and pure from genes in Caucasian ethnicity in general; A considerable number of the normal population are prone to "subnormal OPRM1 or CYP2D6", potentially leading to "analgesic dose adjustment" or "analgesic choice" (21).

Table 9: The Association of COMT G158A Gene Polymorphism with Changes in Pain Sensitivity in Non-Minangkabau Ethics

COMT Genotype	NRS Before Surgery (median (min-max))	p	NRS After Surgery (median (min-max))	p	Δ NRS (median (min-max))	p
*Wild Type (*GG)	1 (0-3)	0.60	3 (1-6)	0.85	1.5 (0-5)	0.90
Heterozygous Mutant (GA)	1.5 (0-3)		3 (2-6)		2 (1-3)	
Homozygous Mutant (AA)	1.5 (1-2)		3 (3-3)		1.5 (1-2)	

Min: minimum score, Max: maximum value, NRS: *Numeric Rating Scale*

Research of the distribution in both Asian and Caucasian ethnic groups showed that the OPRM1 gene mutation is dominant in Asian ethnic groups rather than Caucasians. This result is in line with several direct comparison studies between Asian and Caucasian ethnicities. A study by Kreek et al found that the prevalence of the G allele in the OPRM1 gene in Asian populations was significantly higher than in Caucasians 50% and 15%-30%, respectively) (22). A meta-analysis study conducted by Chen *et al* found that from 1900 samples of mixed Asian and Caucasian races mutations occurred (GA+GG) as much as 36.04% in Asian races and 11.52% in Caucasian races (23). The distribution of the OPRM1 A118G gene polymorphism on Asian Ethnics in Indonesia, which are divided into Minangkabau and Non-Minangkabau Ethnics, have the same characteristics as other Asian Ethnics.

The OPRM1 gene is the gene encoding the opioid receptor. Several SNPs in the OPRM1 gene have been identified to affect the opioid receptor. (24) More than 700 SNPs have been identified in the OPRM1 gene (refer to the dbSNP database of the NCBI database). A118G mutations are the most common SNPs causing changes in the effects of the opioid receptor gene, where substitution from A to G in exon 1 results in an amino acid exchange at position 40 from asparagine to aspartate (N40D). This exchange was correlated with mRNA stability and opiate sensitivity, including analgesic effects, tolerance, and opiate dependence (25, 26).

The results of the One way ANOVA test showed that there was no significant difference between the OPRM1 A118G gene polymorphism groups in NRS scores before surgery (P=0.44), NRS scores after surgery (P=0.45), and ΔNRS (P=0.57) on the Minangkabau Ethics. This study also did not find a significant difference between the OPRM1 A118G gene polymorphism groups in NRS scores before surgery (P=0.74), NRS scores after surgery (P=0.13), and ΔNRS (P=0.26) in non-Minangkabau ethnic groups.

The results obtained are in line with the results obtained by Ruth Landau et al, who also investigated the correlation between the OPRM1 A118G gene polymorphism and the efficiency of IV Fentanyl treatment in women who are about to give birth. Landau measured satisfaction with analgesic treatment for mothers who underwent surgery during childbirth and found no association between the OPRM1 gene A118G rs 1799971 polymorphism and anesthetic success (P=0.82; 95% CI,-17%-19%) (27). Zhang et al also investigated the effect of the OPRM1 A118G gene polymorphism on the postoperative analgesic requirement of fentanyl in patients undergoing radical gastrectomy. They reported that the OPRM1 A118G gene polymorphism did not play a role in determining postoperative fentanyl analgesic requirements (28). Walter et al in a meta-analysis study also found no significant association between the OPRM1 A118G genotype and pain management in patients with chronic pain, labor pain, and postoperative pain (29).

The results obtained have differences from several other studies. Another meta-analysis conducted by Zhicao Yu et al. found significant results where cancer patients with *wild-type* (AA) gene OPRM1 A118G required lower doses of opioids than the mutant group (GG, GA) to achieve the same therapeutic level (30). Another study showed a significant response in cancer patients who had polymorphisms OPRM1 A118G and COMT G158A to systemic opioid use. One study found that patients with the *wild-type* (AA) genotype required low doses of morphine to achieve the desired analgesic effect. Meanwhile, the mutant group required a higher dose of morphine up to twice to achieve the same effect (31).

Differences in the results of this study may be due to differences in pain modalities. The study that found a significant correlation between the OPRM1 polymorphism and pain sensitivity used samples with a history of chronic pain. Meanwhile, in this study, we took pain due to trauma from an acute surgical wound. Differences in opioid regimens between oral morphine and IV fentanyl may also allow differences in study results. In several studies, it was found that there was a significant correlation between the OPRM1 gene allele G (GA+GG) and the group that had opioid addiction (morphine) compared to the control group (14). Thus, there may be an association between the OPRM1 gene polymorphism with the type of opioid given. The OPRM1 gene that encodes for the opioid receptor clinically exhibits different pain responses. The difference in pain sensitivity in patients with the OPRM1 polymorphism is influenced by differences in

opioid receptor density to various opioid drugs. This is possible because of the different types of opioids given and the factor of long-term use of opioids due to chronic pain.

COMT G158A gene polymorphism is found in both Minangkabau and Non-Minangkabau ethnic groups. In the Minangkabau ethnic group, the percentage of wild type (GG) (43.3%), homozygous mutants (AA) (10%), and heterozygous mutants (GA) (46.7%). Meanwhile, non-Minangkabau ethnic groups have a percentage of wild type (GG) (73.3%), homozygous (AA) mutants (6.7%), and heterozygous (GA) (20%). In the Minangkabau ethnic group, heterozygous mutants are the most common polymorphisms. Meanwhile, in non-Minangkabau ethnic groups, the wild type. Research on the incidence of the COMT G158A gene polymorphism in samples from India showed the same results as the polymorphisms found in the Minangkabau ethnic group. P. Kumar et al found the frequency of COMT G/G, G/A, and A/A genotypes (48%, 40%, and 12% respectively). These results indicate that the P. Kumar sample is dominant for mutations in the COMT A158Met gene (32).

Research conducted on Caucasians in Spain showed the same results regarding the distribution of COMT gene mutations with a percentage of 61%, this number is more than the wild-type sample (33). This distribution is similar to that obtained by Cesar Fernandez et al who investigated the distribution of the COMT G158A gene polymorphism. Cesar found variations in the G/G, G/A, and A/A genotypes with percentages (i.e. 38%, 43%, and 19%, respectively). This shows that the COMT G158A mutation is the most dominant group of the total sample (34). The COMT gene mutant with the A allele was the most common mutant among all studied populations. According to a literature study on the distribution of mutations, the A allele was found to occur most frequently in the United States, Europe, China, and Japan with values (i.e. 0.56; 0.5; 0.27, and 0.64, respectively) (32).

The COMT G158A polymorphism has an important role in the nociceptive pain response. Cesar found that patients with genotype A/A experienced greater pain sensitivity than those with genotypes G/G and G/A (34). Mutations of the COMT gene at exon 4 expressed in the nervous system are mediated by pain perception through the regulation of catecholamine levels (35). The A/A genotype is known to have the highest pain sensitivity. This could be because, in patients with mutations in COMT G/A or A/A, it will decrease the work of the COMT enzyme which functions in catecholamine metabolism. The decrease in catecholamine metabolism causes an increase in the number of catecholamines that can stimulate 2-adrenergic receptors in the central nervous system, resulting in persistent pain effects (36).

The results of the One-way ANOVA test showed that there was no significant difference between the COMT gene polymorphism G158A, with the NRS score before surgery (P=0.31), NRS score after surgery (P=0.77), and ΔNRS(p=0.65) for the Minangkabau ethnicity. This study also did not find a significant difference between the OPRM1 A118G gene polymorphism with NRS scores before surgery (P=0.6), NRS scores after surgery (P=0.85), and ΔNRS (P=0.9) in non-Minangkabau ethnic groups.

In this study, no significant association was found between the COMT G158A gene polymorphism and pain sensitivity in patients before and after surgery. These results are different from those obtained by Sabine et al who conducted a study on pain sensitivity after the administration of morphine in post-cardiac surgery patients. Sabine found the COMT G158A polymorphism contributed to the variability of pain sensitivity experienced by cardiac surgery patients after morphine administration in the ICU (37). This difference is possible due to different types of opioids, different types of surgery, and differences in patient postoperative interventions. In the Sabine study, the opioid used was the morphine type, while in this study the fentanyl type of opioid was investigated. Sabine measured patients who underwent cardiac surgery while the sample of this study did not undergo cardiac surgery. The difference in postoperative intervention between postoperative tramadol administration and morphine-administered Sabine is also thought to be the reason for the difference in study results. Differences in the type of surgery, the variability of the type of opioid, and postoperative intervention are the causes of the differences in the results obtained (37).

In Fernandes' research in 2011 and 2012, there was a correlation between the COMT G158A

polymorphism and high hyperalgesia. Fernandes found this in pediatric patients with TTH and women with chronic breast cancer (38). Fernandez's research is different from trying to see patients who experience pain due to chronic disease while this study examines patients who experience pain due to chronic disease. acute process. There may be differences in the density of -opioid receptors in patients receiving long-term opioids due to chronic pain, so the results obtained are different from the sample in this study who did not have a history of long-term opioid consumption. However, clinically this was not found in the results obtained in this study.

Several studies also reported a non-significant correlation between COMT polymorphism and pain sensitivity. Kim et al in 2009 studied 221 patients who experienced acute pain after surgery and the results did not find a significant correlation between the COMT G158A gene polymorphism with pain sensitivity felt by patients who experienced acute trauma due to surgery (39). Another study conducted by Mogil in 2012 found a weak association between COMT polymorphisms and perceived pain sensitivity in patients with postoperative pain and chronic pain (40). Research conducted on healthy samples with pain and cold stimuli also showed a non-significant correlation. In this study, the COMT G158A polymorphism was found to not be affection sensitive due to a given pain stimulus (41). Theoretically, the COMT G158A gene polymorphism increases catecholamine levels which affect persistent pain sensation. However, clinically, several studies have also found an inadequate association between COMT polymorphisms and pain sensation in patients. The difference in the results of this study could be due to differences in the types of opioids, differences in postoperative interventions, and differences in the history of chronic diseases suffered by patients.

Conclusion

We conclude that polymorphism of OPRM and COMT genes are not contributed to the NRS discrepancy related to surgery in Minangkabau and Non-Minangkabau Ethnic.

Acknowledgment

The Authors would like to acknowledge the efforts of all of the team and patients who participate in this research, and also Dr. M Djamil Hospital, Andalas University Hospital, and the Biomedic laboratory of Andalas University for their kind help and support.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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