Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.822786

Anatolian Curr Med J 2021; 3(1); 59-65

The effect of opioid receptor gene polymorphism (A118g) on postop tramadol consumption after gynecologic surgery performed with pfannenstiel incision

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Cite this article as: Güven BB, Şen H, Özkan S, Dağlı G. The effect of opioid receptor gene polymorphism (A118g) on postop tramadol consumption after gynecologic surgery performed with pfannenstiel incision. Anatolian Curr Med J 2021; 3(1); 59-65.

ABSTRACT

Aim: The analgesic efficacy and side effects of opioid medications show great inter-individual differences. Genetic studies have indicated that this difference is considerably associated with the relationship between opioid and receptor. Therefore, in this study it was aimed to investigate the effect of A118G polymorphism on postoperative tramadol consumption and opioid-related side-effects after gynecological surgery performed with a pfannenstiel incision.

Material and Method: Evaluation was made of 80 patients with I-II ASA status, scheduled for gynecological surgery performed with a pfannenstiel incision under general anesthesia. Genomic DNA was extracted from the blood samples. After surgery, all of the patients were equipped with an intravenous Tramadol patient-controlled analgesia device and tramadol consumption was measured. Pain scores were measured with a numerical rating scale. All assessments were performed prior to gene analysis. In order to detect the genotype for A118G single point mutation, Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) methods were used.

Results: The study included 80 patients were included. Of these, 60 (75%) patients were detected to have homozygous 118AA (AA) genotype and 20 (25%) patients to have heterozygous 118AG (AG). No patients with homozygous 118GG (GG mutant) genotype were detected. Patients were divided into 2 separate groups based on their genotypes. The postoperative total tramadol consumption (p=0.043), pain score (p=0.031) and patient satisfaction (p=0.026) in the AG group were significantly higher than in the AA group. No statistically significant difference (p=0.063) was detected between the groups in respect of side-effects.

Conclusions: A118G polymorphism detected in the μ-opioid receptor gene has an effect on postoperative tramadol consumption.

Keywords: Postoperative pain, A118G polymorphism, tramadol, Mu opioid receptor

INTRODUCTİON

The Pfannenstiel incision is commonly used in gynecological surgery as it provides good exploration. However, the severity, nature and duration of post-operative pain is extremely high. The most common and efficient method used for pain relief in this period is opioid use. In general clinical practice, opioid analgesic medications such as morphine, fentanyl and tramadol are used for the treatment of moderate to severe post-operative pain. However, the analgesic efficacy and side effects of opioid medications show great inter-individual differences. Genetic studies have indicated that this difference is not only associated with the severity and nature (neuropathic/nociceptive) of the painful stimulant or the bioavailability of opioid, but is also associated with the relationship between opioid and receptor (1-4).

Opioid analgesic medications used in clinical practice, exert their effects by affecting mu opioid receptors (MOR). Therefore, the primary candidate gene most held responsible for the difference in sensitivity to opioid medications, is the OPRM1 gene coding MOR. To date, more than a hundred single point mutations have been detected (5) in the OPRM1 gene which is in the q24-q25 region of chromosome 6. Of these mutations, 24 have been shown to cause amino acid changes in receptor protein. The most common and the most intriguing of these is A118G single point mutation in which a guanine

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Received: 09.11.2020 **Accepted:** 12.01.2021

nucleotide replaces the adenine nucleotide in the 118th row in Exon 1. A118G mutation replaces the asparagine amino acid in the 40th row of MOR protein with aspartate (N40D), and this causes relocation of the Nglycosylation region in the extracellular part of MOR. With this change, N40D mutant receptors are coded. In vitro studies have shown that this change increases the receptor binding capacity of ß-endorphin threefold. The change in the binding affinity of ligand causes the analgesic effects of opioids (6). Therefore, A118G mutation is the most emphasized mutation when clinical effects of opioid analgesics are studied.

Tramadol is a central acting, synthetic analgesic that inhibits presynaptic reuptake of noradrenaline and serotonin in addition to a MOR-agonist effect. Thus, it potentialises the endogenous analgesia system by both the opioid agonist mechanism and the monoaminergic effect (7). In this respect, tramadol may be considered to have both an analgesic and an adjuvant effect. The additive effect obtained with these two mechanisms with its apparent anti-nociception and fewer side effects, have made tramadol a commonly used medication in clinical practice for the treatment of postoperative pain with PCA (patient controlled analgesia) technique.

To the best of our knowledge, this is the first study to explore the relationship between A118G mutation and tramadol for the treatment of postoperative pain. In this study, it was aimed to investigate the effect of A118G polymorphism on postoperative tramadol consumption.

MATERIAL AND METHOD

This prospective observational study was approved by Clinical Trials Ethics Committee of Istanbul Faculty of Medicine, Istanbul University, Turkey. This current research included a total of 80 patients, aged 18-65 years, with American Society of Anesthesiologists (ASA) Classification I-II, undergoing a gynecological operation with a Pfannenstiel incision.

Patients with severe heart disease, kidney disease, epilepsy and convulsion history, antidepressant use, liver disease, neuropsychiatric disease, history of chronic analgesic use, who could not comply with PCA use, who were allergic to the drugs used in the study, who did not agree to participate in the study, or who could not be communicated with, were excluded from the study.

The study was conducted in line with the Declaration of Helsinki and written consent was obtained from all patients included in the study. The patients who agreed to participate in the study, were informed about the Numerical Rating Scale (NRS) which was used for the assessment of pain, in which 0 = no pain and 10 = the greatest possible pain, and patients were requested to verbally grade their pain between these numbers.

In the operating theater, standard monitors were applied for all patients. A 20G venous canule was inserted through a non-dominant side vein in the antecubital region, and 2 ml of blood was taken into an EDTA tube from the same place before any further intervention. Following the blood sample, 0.9% NaCl infusion was initiated. Blood samples were stored at +2°C.

Patients were intubated following induction with 2 mg/kg of propofol, 2 mcg/kg of fentanyl and 0.5 mg/kg of rocuronium, and maintenance of anesthesia was obtained with 1-2% sevoflurane anesthesia in 50/50% O_2/N_2O mixture. Ventilation was maintained to keep $EtCO_2$ pressure between 35-40 mmHg. Towards the end of the operation, all patients were stitched with subcutaneous sutures and tramadol HCl 0.5 mg/kg was administered IV.

After surgery, the time of arrival in the recovery unit was defined as time 0. All of the patients were equipped with an intravenous PCA device set to the following regimen: bolus dose of 20 mg tramadol, lockout of 15 min, and 150 mg of 4-hour dose limit up to 24 hours for treatment of postoperative pain. During the follow-up, NRS >4 was considered as insufficient analgesia, and 20 mg tramadol was administered IV as rescue analgesia, and the time was recorded.

Patients were visited at postoperative 1st, 4th, 6th, 12th, 18th, 24th hours and their condition was recorded. Heart rate (HR), systolic blood pressure (SBP), NRS, sedation score, additional analgesic requirement, the amount of total consumed tramadol, and side effects (nausea, vomiting, itching, sedation, hypotension, bradicardia, respiratory depression, dizziness, headache) were followed-up and recorded. Patient satisfaction was evaluated with NRS (0=not satisfied at all, 10=very satisfied) at postoperative 24th hour. Sedation score was evaluated with a 4-point scale (0: awake 1: sleepy 2: can be woken 3: deep sleep). Nausea-Vomiting (0: no nausea; 1: nausea without vomiting; 2: nausea and vomiting) was evaluated with a 3-point scale. All assessments were performed and recorded before gene analyses.

Patients with heart rate of <50 beat/min were considered bradycardic and 0.5 mg IV atropine was planned to be administered for bradycardia. Patients with a nausea-vomiting score of 2 were planned to be given 10 mg IV metoclopramide. In case of itching, 1 mg pheniramine maleate IV was planned to be administered. A 2 ml blood sample was withdrawn into an EDTA tube from each of the 80 patients. Genomic DNA was isolated from these blood samples with the Roche High Pure PCR template preparation kit. In order to detect the genotype for A118G

single point mutation, polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) methods were used. In order to reproduce the A118G single point polymorphism, 5'-GGTCAACTTGTCCC ACTTAGATCGC-3' base sequence was used as forward primary and 5'-AATCACATACA TGACCAGGAAGTTT-3' as reverse primary. For PCR reactions, a total of 20 JL mixture was prepared with 10 JL PCR master mix, 1 JL primary forward, 1 JL primary reverse, 2 JL sample DNA and 6 JL H_2O and placed into the PCR device. For the DNA amplification process, samples were kept at 94°C for 3 minutes, then at 94°C for 30 seconds, at 60°C for 1 minute, and at 72°C for 1 minute in order to be 38 rotation. Following the rotation, each sample was kept at 72°C for 10 minutes. Following the amplification process with PCR, the PCR product consisting of 10 JL 193 bases was kept at 37°C for at least 12 hours with 20 U Bsh1236 I restriction enzyme, and thereby sections emerged. The obtained PCR product sections were moved towards electrophoresis by adding 5 JL ethidium bromide in 2% agarose gel. Bands of DNA fragments were observed under ultraviolet light with the help of the Kodak Gel Logic 200 device (**Figure 1**). There was one band consisting of 193 bases in the images of A alleles, while there were two bands consisting of 169 and 24 bases respectively, in the images of G alleles due to section by restriction enzyme.

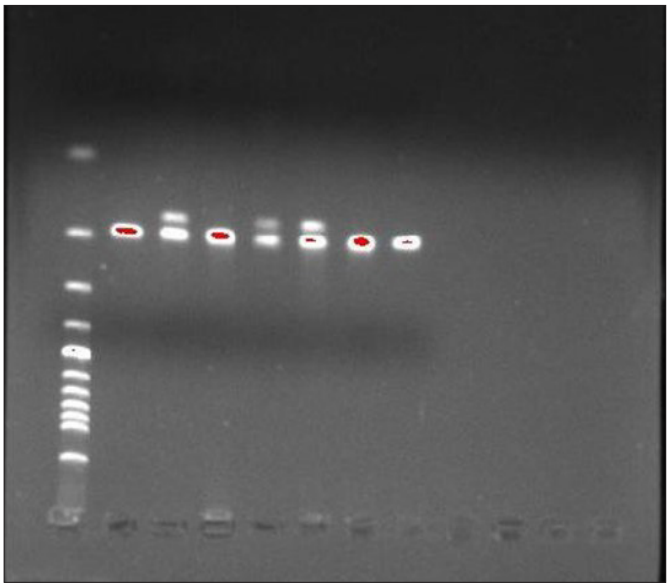

Figure 1. Electrophoresis images of bands of DNA fragments (Out of 7 DNA fragments, 3 of them are G alleles, 4 of them are A alleles)

Statistical Analysis

After the data obtained in the study was computerized, SPSS (Statistical Package for Social Sciences) 15.0 software was used for statistical analyses. Descriptive statistics were stated as frequency, percentage, mean and standard deviation. The accordance of data to normal distribution was checked with the Kolmogorov-Smirnov test, and then the Student's t-test was used for normally distributed parameters, and the Mann Whitney U test was used for non-normally distributed parameters. The Chi square test was used for intergroup comparison of discrete variates. A value of $p<0.05$ was accepted as statistically significant.

RESULTS

The study included 80 patients. No patient was excluded. As a result of genetic analyses, 60 (75%) patients were detected to have homozygous 118AA (AA) genotype and 20 (25%) patients to have heterozygous 118AG (AG). No patients with homozygous 118GG (GG mutant) genotype were detected. Patients were divided into 2 separate groups based on their genotypes, and all data regarding the patients were compared between these 2 groups.

The demographic data of the subjects were compared statistically. No statistically significant difference was detected between the two groups in respect of age, body weight, height, ASA classification, anesthesia duration and type of operation **(Table 1)**. There was also no difference between the groups in the postoperative hemodynamic parameters of the patients.

Table 1. Demographic data regarding groups.

	AA (n:60)	AG (n:20)	p value
Age (years)	46.80±12.55	47.60±12.89	0.807
Body weight (kg)	69.98±12.70	66.90±11.91	0.343
Length (cm)	161.95±4.88	159.60±6.46	0.091
Anesthesia duration (min)	118.53±49.48	145.00±64.48	0.059
ASA (I/II)	38/22	15/5	0.420
Type of Operation			
TAH+BSO	15	8	0.256
TAH	24	8	1.00
Myomectomy	21	4	0.272

No statistical significant differences were observed between groups. Data were given as numerical, mean and standard deviation (SD).

When the postoperative NRS values of the patients were compared, the NRS values in the patient group carrying the AG heterozygous allele were higher than those of the patient group carrying the AA homozygous allele at 1st hour and this was statistically significant **(Figure 2)**.

There was a significant statistical difference between the two groups in respect of the total consumption of PCA tramadol. Postoperative total tramadol consumption in the patient group carrying the AG heterozygous allele was statistically significantly higher than in the patient group carrying the AA homozygous allele at 1st, 4th and 24th hours **(Figure 3)**.

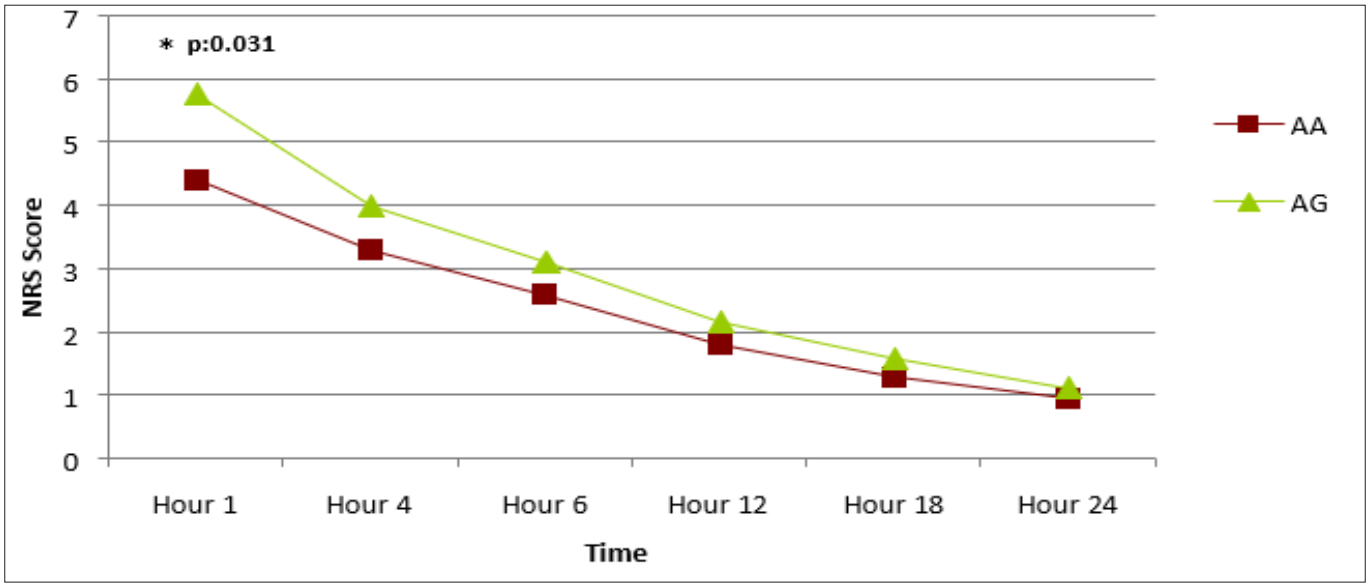

Figure 2. NRS values of the groups (The Chi square test was used for intergroup comparison) AA: The patient group carrying the AA heterozygous allele, AG: The patient group carrying the AG heterozygous allele, * Statistically significant difference

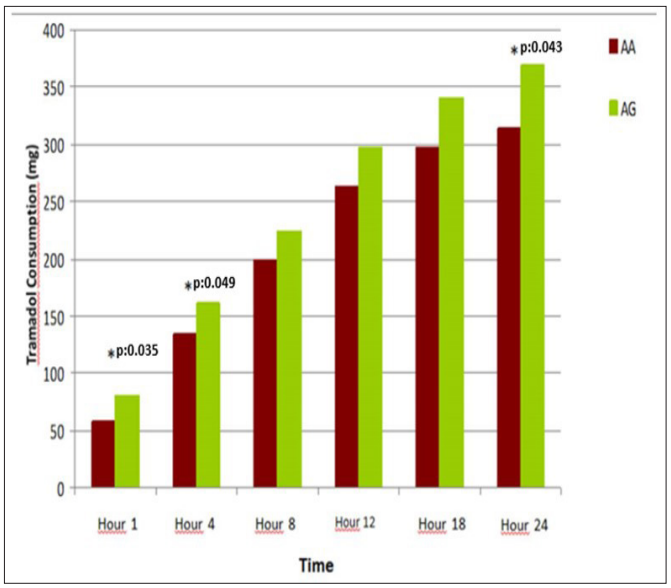

Figure 3. Total tramadol consumption graph of the groups (mg) (The Chi square test was used for intergroup comparison) AA: The patient group carrying the AA heterozygous allele, AG: The patient group carrying the AG heterozygous allele, * Statistically significant difference

The number of patients needed postoperative additional analgesic in both groups is given in **Table 2**. While the percentage of the patients needing additional analgesic in the patient group carrying the heterozygous allele was higher, no statistically significant difference was detected between the groups. There was also no difference between the two groups in the total additional analgesic amount and first analgesic time.

When the groups were compared for patient satisfaction, it was found to be statistically significantly low in the patient group carrying the AG heterozygous allele compared to the patient group carrying the AA homozygous allele **(Table 2)**.

Table 2. The number of patients needing additional analgesic in both groups and their satisfaction scores

	AA (n =60)	AG (n =20)	P value
Number of patients needing additional analgesic	32 (53%)	14 (70%)	0.192
Patient satisfaction	9.27±1.06	8.65±1.04	0.026 *

* Statistically significant difference found between the two groups.

When the study subjects were compared in respect of nausea-vomiting, the nausea-vomiting scores of the patients with the AA homozygous genotype were higher than those of the patients with the AG heterozygous genotype by percentage **(Table 3)**. However, no statistically significant difference was detected (p= 0.063). When the incidence of side-effects was evaluated, 1 patient had bradycardia in the patient group carrying the AG heterozygous allele, and 1 patient had hypotension and dizziness in the patient group carrying the AA homozygous allele. No other opioid side-effects such as itching and respiratory depression were observed in either of the groups. There was no statistically significant difference between the groups with regard to postoperative sedation score.

Table 3. Nausea-vomiting scores of the groups

			Nausea-vomiting Scores		Total
			1	2	
Group	AA	38	14 (23%)	8 (13%)	60
	AG	18	2 (10%)	0	20
Total		56	16 (20%)	8 (10%)	80

(0:No 1:Nausea 2:Vomiting)

DISCUSSION

No optimum medication or method for the treatment of postoperative pain that is free of side-effects has yet been found. Opioid analgesic medications such as morphine, fentanyl and tramadol are still essential for the treatment of moderate to severe postoperative pain. The minimum efficient analgesic concentrations of opioids necessary for satisfactory analgesia show important inter-individual differences (3). Therefore, the key analgesia principle to reduce or eliminate the side-effects of opioids, should be to individualize the opioid choice for the treatment of postoperative pain and minimize the dose.

For many years, tramadol has been used for the control of postoperative pain. Currently, it is one of the most frequently preferred opioid analgesics for the treatment of postoperative pain. Despite studies reporting favorable results with IV tramadol infusion in acute pain, there are also studies indicating that the efficacy is not optimal. These studies have shown that there are individual differences against opioid analgesics (3-6). It is well known that genetic structure plays an important role in the effects and toxicities of medications. Genetic factors affecting pharmacokinetics and pharmacodynamics may cause differences in effects, side-effects and toxicities of analgesics (1,3-7). In the present study, it was aimed to explore the effect of OPRM1 gene, one of the genetic factors most held responsible for individual differences in response to analgesics, on tramadol consumption in postoperative pain treatment.

Therefore, it was planned to investigate the A118G mutation in the exon 1 of OPRM1 that causes N40D mutant receptor formation. In an in vitro study about this mutation (8), it was shown that it increases the binding capacity of ß-endorphin to receptor by three times. In another in vitro study (9), it was shown that as a result of the mutation, mRNA expression decreases nearly 2-fold, and this causes more than a 10-fold decrease in OPRM1 protein levels. As a result of these molecular changes, it was thought that the effects of opioids used in clinical practice may be reduced in patients with A118G mutation.

In a search of literature, it was seen that studies of A118G mutation have been mostly on morphine, alfentanyl and fentanyl (10-12). Other than the study performed by Yu-Chang Liu et al. (13) with an oral combination preparation of paracetamol and tramadol (Ultracet) for the treatment of neuropathic pain induced by chemotherapeutics, no study could be found which investigated tramadol consumption in patient with A118G mutation.

The present study included 80 female patients who had an open abdominal surgical operation in a gynecological procedure with a Pfannenstiel incision. The Pfannenstiel incision (10-15 cm transverse incision passing approximately 2 cm above the symphysis pubis) is commonly used in gynecological surgery as it provides good exploration. It was possible to assess the efficacy of IV tramadol better in the postoperative period as the severity, nature and duration of postoperative pain is extremely high in patients operated on with a Pfannenstiel incision. In order to standardize the postoperative pain, three operation types with similar incision sizes (TAH+BSO, TAH and myomectomy) were included in the study.

The incidence of 118G allele has been reported as varying between 11-32% in previous studies (8,9,13,14). In the current study, the incidence of 118G allele was detected to be 25%. 60 patients (75%) were detected to have homozygous AA, 20 patients (25%) to have heterozygous AG genotype, and no patients were detected with homozygous GG genotype. There have been seen to be great differences between ethnicities, with 118G allele incidence reported as 14% in Caucasians, 30% in Taiwanese, 35% in Chinese, 47% in Indians, 44.9% in Japanese, and homozygous GG genotype allele incidence between 12-19% (15). In a study by Masakuza et al. (2) it was reported that individuals carrying G allele need more analgesic consumption to have the same analgesic effect as individuals carrying A allele. Thus, one of the most limiting factors of the current study is that no patients with homozygous (GG) allele were detected. Another limiting factor of the study is that the types of operations were not standard. Another is that tramadol shows analgesic activity by also inhibiting noradrenaline/serotonin re-uptake in addition to the mu opioid receptor.

Regarding the therapeutic outcomes caused by A118G polymorphism, most investigators have reported that A118G single point mutation causes a reduced antinociceptive effect of opioids (4,5,16). Caraco et al. (10) reported that patients with A118G polymorphism need high dose alfentanyl for the treatment of acute postoperative pain. Klepstad et al. (11) reported that morphine consumption is increased in cancer patients with A118G mutation. In a study performed with an oral combination preparation of tramadol and paracetamol (Ultracet) for the treatment of neuropathic pain, Yu-Chang Liu et al. (13) determined that the group with A118G mutation had higher VAS values and analgesic consumption. Supporting these results, in the current study, the group carrying the heterozygous allele was found to have significantly higher pain scores at postoperative 1st hour and total tramadol consumption at 1st, 4th and 24th hours in. The patient satisfaction score, which is an indicator for the success of postoperative pain treatment, was also found to be statistically significantly lower in the group carrying the heterozygous AG allele.

In the present study, especially in the early postoperative period, it was observed that the opioid consumption

amount and pain scores of the patients in the heterozygous group of AG were higher. If this mutation was known before the operation, one of the regional analgesia techniques could be preferred instead of the use of systemic opioid (tramadol) for postoperative analgesia in these patients. Many studies performed in the postoperative period have demonstrated that tramadol causes less respiratory depression, less sedation and affects the hemodynamic parameters less than strong opioids (17). In the current study, when side-effect incidence was evaluated, 1 patient had bradycardia, 1 patient had hypotension and dizziness, and none of the patients had any other opioid side-effects such as itching, respiratory depression or bradycardia.

One of common causes for nausea and vomiting in the postoperative period is the use of opioid derivatives and opioid-like medications such as tramadol. Reported effects of A118G polymorphism on nausea and vomiting caused by opioids in the postoperative period are contradictory. Zhang et al. (18) administered fentanyl with a PCA device for the first postoperative 24 hours in a study of 165 females, and no statistically significant difference was determined between 3 genotypes in respect of nausea-vomiting scores, although more fentanyl was consumed in patients carrying 118G allele (AG,GG), and less nausea and vomiting were detected than in the homozygous AA group. Similarly in the current study, the heterozygous AG group consumed more tramadol than the homozygous AA group but had lower nausea-vomiting scores. However, no statistically significant difference was found between the two groups. In order to explain this contradiction, there is a need for more participative studies considering the factors that affect nausea and vomiting in the postoperative period such as age, body mass index, tobacco use, motion sickness, preoperative anxiety level, chronic medication use, type of operation, and type and duration of anesthesia.

Studies conducted with the aim of finding an efficient solution for pain complaints, continue to improve in parallel with the advancements in technology and science. Pharmacogenetic investigations performed in the last decade, have indicated that many genetic factors cause different analgesic dose requirements for the patients with pain of similar severity and aspect. Genetic studies have indicated that this difference is not only associated with the severity and nature of the painful stimulant or the bioavailability of the opioid, but is also associated with the relationship between opioid and receptor (3). In addition, the importance of this study in clinical practice is that it can provide guidance on which of the systemic opioids or the other (regional) analgesia techniques used for postoperative analgesia is most appropriate for the patient with A118G mutation.

CONCLUSION

In this study it was determined that A118G polymorphism detected in mu opioid receptor increases the total tramadol consumption at postoperative 1st, 4th and 24th hours, and pain score at postoperative 1st hour, but does not cause a significant change in postoperative hemodynamics, first analgesic requirement time or the incidence of side-effects such as nausea, vomiting, and sedation, and decreases the patient satisfaction score. According to these results, patients with A118G polymorphism can be considered to have a reduced response to opioid derivate medications such as tramadol, and there is no negative effect with regards to the side-effect profile. In addition, this study indicated that it is more appropriate to prefer other analgesia techniques instead of systemic opioids in postoperative analgesia for patients with A118G polymorphism in terms of patient satisfaction. Further pharmacogenetic studies are required in this area to be able to achieve more efficient, individualized pain control.

ACKNOWLEDGMENT

We would like to thank Md. Kadir Hakan Cansız for English translation and poster arrangement for the congress.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Clinical Trials Ethics Committee of Istanbul Faculty of Medicine, Istanbul University, Turkey (F. No:2011/1890-820).

Informed Consent: Written informed consent was obtained from all participants who participated in this

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declared that this study was financially supported by the epidomylogical committee

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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