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Research Article

The Effect of Opioid Receptor Gene Polymorphism (A118G) on Tramadol Consumption After Caesarean Section

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Abstract

Objectives: The efficacy of opioid analgesics is related to the μ-opioid receptor gene. The aim of this study was to determine the frequency of opioid receptor gene polymorphism at position 118 and response to tramadol for postcesarean analgesia.

Methods: We recruited 100 patients aged between 18–45 years, who could use patient-controlled analgesia (PCA) device and express their pain severity with visual rating scale (VRS), and had ASA I-II, undergoing cesarean section under spinal anesthesia. Blood samples were genotyped for the A118G polymorphism-A118 homozygous (AA), heterozygous (AG), or homozygous for the G allele (GG). Pain scores, the severity of nausea and vomiting, other complicaitons and the total self-administered intravenous tramadol consumption were recorded for the first 24 postoperative hours.

Results: Among the 100 patients in the study, 77 (77%) had a genotype of homozygous 118AA (AA normal), 19 (19%) were heterozygous 118AG (AG), and the remaining four (4%) were genotype homozygous 118GG (GG mutant type). The patients were divided into 3 groups. Compared to that in patients with AG genotype, those with AA homozygous genotype had significantly higher time to the first analgesic, lower dose of total additional analgesic, and higher patient satisfaction scores. Nausea and vomiting scores of patients with GG homozygous genotype were significantly higher.

Conclusion: In conclusion, A118G polymorphism is associated with variations in tramadol consumption and pain scores. The relative rare frequency of the patients who have 118GG homozygous gene within the Turkish population implies that it could be safe to use tramadol for postoperative analgesia.

Keywords: Opioid analgesics, tramadol, μ-opioid receptor gene

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Pain perception varies widely among individuals. Despite new analgesics and new methods, patients still experience severe pain after surgery.[1] Tramadol is a commonly used opioid analgesic for relieving post-cesarean pain.[2-5] Opioid analgesics act on μ-opioid receptors. However, the efficacy of opioid analgesics exhibits great variations between individuals,[6] which has been attributed to polymorphism in the μ-opioid receptor gene.[7]

Genetic factors were reported to be responsible for 50% of adverse effects and 20-40% of individual differences in response to the drug.[8, 9]

More than 250 single-point mutations were identified in the μ-opioid receptor gene. The A118G mutation slows transcription of the μ-opioid receptor gene and alters the amino acid sequence. Therefore, it was the most addressed mutation while studying the clinical effects of opioid analgesics.[6]

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Opioid use is a matter of concern due to many adverse effects, complications like respiratory depression, and potential for addiction. Ensuring lowest effective dose of the opioid is the main strategy for reducing these drawbacks. [10] On the other hand, the presence of μ-opioid receptor gene polymorphism is an independent risk factor. In postcesarean setting, opioid-related side effects could be more common with a potential impact on the newborn after excretion of the opioid and its metabolites to the breastmilk. Therefore, consideration of polymorphism appears to be especially critical after cesarean section.

Compared to that seen in other potent opioids, tramadol is widely used in patient-controlled analgesia because it causes less respiratory depression, less sedation, and is highly effective in postoperative analgesia.[5] The effect of tramadol, a μ-opioid receptor agonist, varies among individuals, making it difficult to determine the appropriate analgesic regimen for each patient. Therefore, in addition to the known risk factors that underlie this variation, revealing many unknown risk factors such as μ-opioid receptor gene polymorphism through technological advances could help to minimize opioid-related adverse effects and guide individualization of effective analgesic protocols.[11]

The aim of this study was to determine the frequency of opioid receptor gene polymorphism and its effect on postoperative tramadol use and pain severity in our patient population as well as to evaluate its association with opioid-induced adverse effects such as nausea, vomiting, and sedation.

Methods

After being approved by Ethics Committee of GATA (03.10.2010-165), this study was performed in Anesthesiology and Reanimation Clinic of the GATA Haydarpasa Training Hospital. Provided that they gave written informed consent, we recruited 100 patients aged between 18–45 years, who could use patient-controlled analgesia (PCA) device and express their pain severity with visual rating scale (VRS), and had ASA I-II undergoing cesarean section under spinal anesthesia. Exclusion criteria were drug or substance dependence, history of chronic analgesic use, cardiac, renal, hepatic, or hematological disease, fetal abnormality, placenta previa, ablatio placenta, history of allergy against amide local anesthetics, failed spinal anesthesia attempt, coagulopathy. The patients were informed about the study in the preoperative visit performed one day before the surgery. The patients who were included in the study were told about the VRS we used to evaluate pain. In VRS, 0 denoted no pain and 10 denoted the most severe pain possible; for which the patients were asked to grade their pain verbally between these numbers.

Prior to the spinal block procedure, standard monitoring was initiated with administration of 10 ml/kg 0.9% serum physiologic solution. The spinal block was made from the midline through the L3-L4 or L4-L5 intervertebral space in the sitting position. In the recovery room, the PCA device was inserted and the device was prepared to deliver 3 mg/ml tramadol. The bolus dose was set at 20 mg, the locked time was 20 min with a maximal dose of 150 mg for 4 hours. When VRS > 5 during follow-up, 20 mg bolus tramadol was administered for rescue analgesia and the time was recorded. Cases were visited at 1, 4, 8, 12, 16, 20 and 24 hours postoperatively. We recorded heart rate, systolic and diastolic blood pressure, mean arterial pressure, oxygen saturation, respiratory rate, VRS, sedation score, additional analgesic requirement, required and total tramadol use, adverse effects, and complications. Patient satisfaction was evaluated by VRS (0-10) at 24th postoperative hour. Sedation level was assessed by a 4-point scale (1: awake 2: sleepy 3: arousable 4: in deep sleep). Nausea and vomiting (0: nausea; 1: nausea and vomiting; 2: nausea and vomiting) were evaluated with a 3-point scale.

Following the surgery, when the patients were taken to the recovery room, 2 ml-blood sample was collected into the whole blood tube. Genomic DNA was isolated from whole blood by Quiagen DNA extraction kit using standard phenol chloroform procedure. PCR and RFLP methods were used to determine genotype of A118G single nucleotide point-mutation polymorphism. For gene amplification, 5'-GGT-CAACTTGTCCCACTTAGATCGC-3 'was used as the forward primer and 5'-AATCACATACATGACCAGGAAGTT-3' base sequence (Ferme ntas Life Sciences) was used as the reverse primer. After amplification, PCR products of 193 bases were obtained. While excising of the genes carrying A allele with restriction enzymes formed a single band of 193 bases, whereas excising of the genes with G allele formed two fragments of 169 and 24 bases. The DNA fragments were electrophoresed in 2% agarose gel. Bands of DNA fragments were visualized under ultraviolet light (Fig. 2).

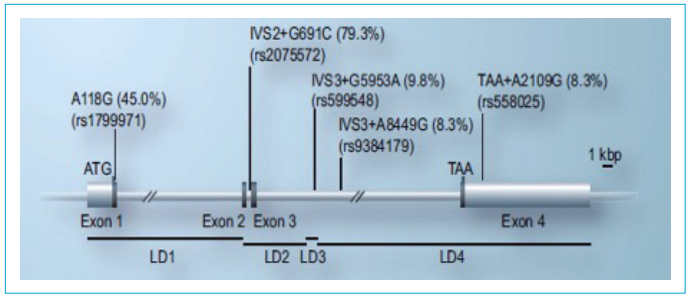

Figure 1. Schematic illustration of the μ-opioid receptor gene.

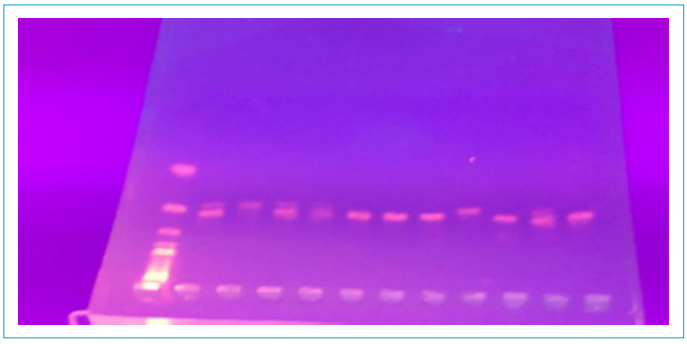

Figure 2. Imaging of bands of DNA fragment under ultraviolet light.

Statistical Analysis

Data were expressed as mean±standard deviation values and numbers and/or percentages where appropriate. Statistical analyses were performed through SPSS 15.0 software. Parametric variables were compared by Mann Whitney U test and temporal pattern was compared through Wilcoxon test. An overall type I error of 5% was used to infer statistical significance.

Results

Among the 100 patients in the study, 77 (77%) had a genotype of homozygous 118AA (AA normal), 19 (19%) were heterozygous 118AG (AG), and the remaining four (4%) were genotype homozygous 118GG (GG mutant type). In our study, we found the frequency of G allele as 23% and homozygous GG allele as 4%. The patients were divided into 3 groups according to their genotypes and all data of the patients were compared between the 3 groups. The mean age and height of patients with AA homozygous genotype were significantly lower than those with AG genotype (Tables 1, 2).

Table 1. Demographic characteristics of the patients

	AA (n=77)	AG (n=19)	GG (n=4)
Age, years	31.7±4.3	35.4±2.7	32.8±3.3
Body weight, kg	76.7±8.0	77.1±8.2	70.3±4.7
Height, cm	163.9±4.7	167.7±2.1	157.8±6.7
Duration of anesthesia, min	62.2±9.6	63.0±5.5	63.0±5.5
Gestational age, week	37.9±1.0	37.9±0.9	37.9±0.9
ASA (I/II)	53/24	14/5	3/1

Table 2. The comparison of the demographic characteristics of the study groups

	AA vs. AG	AA vs. GG	AG vs. GG
Age	p<0.01	p=0.59	p=0.09
Height	p<0.01	p=0.08	p<0.01
Body weight	p=0.79	p=0.06	p=0.11

Postoperative hemodynamic parameters of the patients from different genotypes did not significantly differ except that those with GG homozygous genotype had significantly lower HR at hour 1, 12, and 20 compared to that in AA and AG groups. No statistically significant difference was found between the maximum sensory block levels of the study groups (Table 3).

The comparison of resting VRS (rVRS) between the study groups showed that rVRS values were significantly higher in those with AG heterozygous genotype than that in AA homozygous genotype at hour 16, 20, and 24 (Fig. 3).

Postoperative tramadol consumption at hour 12, 16, 20 and 24 were significantly higher in patients with AG heterozygous genotype than in patients with AA homozygous genotype.

The mere exception was that tramadol consumpiton was significantly lower in the patient group with GG homozygous genotype compared to that in patients with AG genotype.

The groups did not show statistical difference in terms of the first 24-hour total tramadol consumption postoperatively (Table 4).

There was no statistically significant difference between patients with different genotypes when PCA device and analgesic demands were compared in the postoperative period.

Compared to that in patients with AG heterozygous genotype, those with AA homozygous genotype had significantly higher time to the first analgesic, lower dose of total additional analgesic, and higher patient satisfaction score (Fig. 4, Table 5).

Table 3. Maximum level of the sensory block in the study groups

	AA (n=77)	AG (n=19)	GG (n=4)
T4, n (%)	12 (16)	1 (5)	0 (0)
T5, n (%)	26 (34)	8 (42)	1 (25)
T6, n (%)	39 (50)	10 (53)	3 (75)

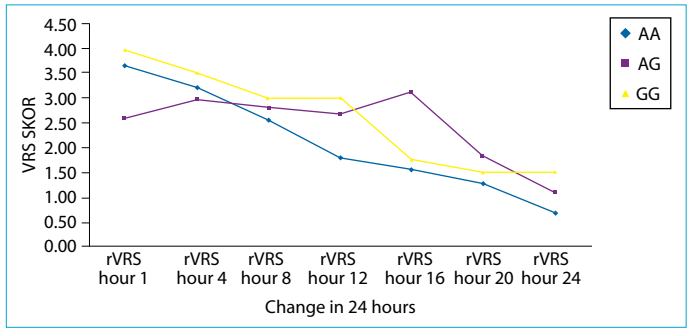

Figure 3. Resting VRS (rVRS) scores in the study groups. VRS, visual rating scale.

Table 4. The comparison of the total postoperative tramadol consumption in the study groups

Hour	1	4	8	12	16	20	24
AA-AG	p=0.54	p=0.94	p=0.81	p=0.11	p=0.86	p=0.98	p=0.43
AA-GG	p=0.13	p=0.25	p=0.15	p=0.32	p=0.91	p=0.90	p=0.87
AG-GG	p=0.29	p=0.51	p=0.40	p=0.40	p=0.71	p=0.90	p=0.67

Table 5. The comparison of the study groups in terms of analgesic-related parameters and satisfaction

	Time to first analgesic dose	Total dose of the additional analgesic	Patient satisfaction score
AA-AG	p=0.03	p=0.01	p=0.04
AA-GG	p=0.15	p=0.40	p=0.88
AG-GG	p=0.67	p=0.12	p=0.21

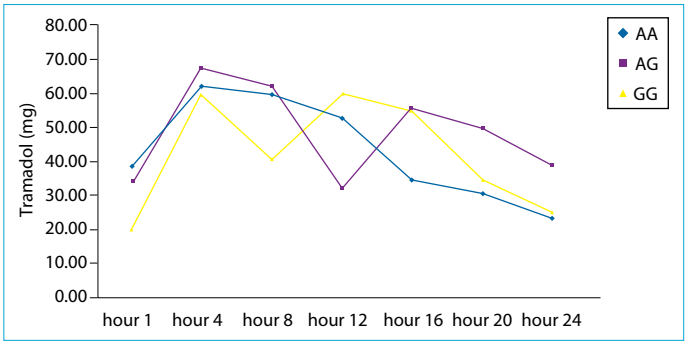

Figure 4. Dose of tramadol used by the study groups within first 24 hours.

The study groups did not significantly differ in terms of complication rates, postoperative sedation score, and oxygen saturation.

Nausea and vomiting scores of patients with GG homozygous genotype were significantly higher than that in patients having the other genotypes tested in the study.

Discussion

Recently, several studies have examined the effect of A118G mutation in the μ-opioid receptor gene on postoperative opioid use in surgical patients, but no satisfactory data have been obtained.[12] Our study was the first to investigate the effect of A118G μ-opioid receptor gene polymorphism on tramadol use.

In a study with 120 Taiwanese patients undergoing total knee arthroplasty, where they reported that postoperative first 48 hours of morphine consumption was significantly higher in patients with 118GG homozygous genotype than that in patients with other genotypes.[13] The same authors' another study, which was conducted in 80 Taiwanese patients who underwent total abdominal hysterectomy, reported postoperative morphine use within first 24 hours was significantly higher in the 118GG homozygous patient group compared to the other patient groups.[14] A different study[6] also reported similar findings to the results of these two studies.[12, 13] On the other hand, the other study reported contradictory results in terms of postoperative first 24-hour morphine consumption in 74 colorectal surgery patients. The study showed no statistically significant difference between the first 24 hours of morphine use among patients with different genotypes.[15] Similarly, the other authors performed a study in 101 patients who underwent laparoscopic surgery and reported no significant relationship between A118G polymorphism and first 24-hour postoperative morphine consumption.[16] The results of our study were consistent with that reported by Coulbault, L. and Janicki, P.K., where we did not identify any association of postoperative total tramadol consumption and μ-opioid receptor gene polymorphism.[14, 16]

Another factor is ethnic differences. In a study 118G allele frequency reported as 5% in Caucasian Americans, 15% in African Americans and in Japanese frequency of 118G allele was reported as 44.9%.[6] Coulbault, L. and Janicki, P.K. reported the frequency of 118G allele as 12% and 16%, respectively whereas we detected the frequency of 118G allele in our study as 23%.[15, 16] Again, the frequency of homozygous allele of 118GG in these studies was 2% in the former study and only 1% in the latter,[15, 16] which was 4% in our study. We believe that the low frequency of homozygous allele of 118GG did not allow to show any statistically significant impact of A118G single-point mutation on postoperative tramadol use. This might be explained by the fact that the frequency of patients with G alleles may be low considering the findings from other studies and ethnic differences. This might be supported by the significantly higher rates of nausea and vomiting in patients with 118GG homozygous genotype.

In other studies the frequency of G allele was reported as 25% and 35%, respectively. These studies also reported homozygous 118GG allele frequency as 12% and 18%. Higher frequency of 118GG homozygous allele could allow for revealing the relevant association between A118G single-point mutation and postoperative morphine consumption.[13] Opioids showed less analgesic efficacy in patients carrying G allele. Such patients had an increased need for opioids to achieve similar analgesic effect as did the individuals carrying the A allele.[6] A study reported no difference in pain score between those having 118 AA homozygous genotype and 118AG heterozygous genotype.[17] However, in our study, the pain score was significantly lower in patients with the 118AA homozygous genotype than that in patients with the 118AG heterozygous genotype. However,

we did not find a statistically significant difference between patients with different genotypes in terms of the total tramadol dose consumed to provide adequate postoperative analgesia.

Conclusion

In conclusion, A118G polymorphism detected in μ-opioid receptor gene seems to be associated with individual variations in tramadol use and pain scores. The relative rare frequency of the patients who have 118GG homozygous gene within the Turkish population implies that it could be safe to use tramadol for postoperative analgesia.

Disclosures

Ethics Committee Approval: After being approved by Ethics Committee of GATA (03.10.2010-165), this study was performed in Anesthesiology and Reanimation Clinic of the GATA Haydarpasa Training Hospital.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.M.; Design – M.M.; Supervision – H.Ş.; Materials – M.M.; Data collection &/or processing – M.M.; Analysis and/or interpretation – M.M.; Literature search – M.M.; Writing – M.M.; Critical review – H.Ş.

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