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Influence of Opioid Receptor Gene Polymorphisms on the Analgesic Effects of Fentanyl and Alfentanil in Pediatric Perioperative Patients

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ABSTRACT

Genetic variation in the μ-opioid receptor gene (OPRM1) is considered one of the contributors to interindividual differences in responses to opioid analgesics in pediatric patients. This study aimed to explore the relationship between OPRM1 polymorphisms and the occurrence of acute postoperative pain across different pediatric age groups. This prospective investigation included 110 children undergoing plastic or orthopedic surgical procedures. Participants were genotyped and then randomly allocated to receive either fentanyl or alfentanil for analgesia. Postoperative pain intensity was assessed using the Numerical Rating Scale (0–10). All enrolled patients were evaluated for the OPRM1 118A > G (rs1799971) genetic polymorphism. In school-aged children younger than 11 years, those with the OPRM1 AA genotype demonstrated a significantly higher body mass index (BMI) ($P < 0.05$). Among participants older than 12 years, carriers of the OPRM1 G allele exhibited greater postoperative pain sensitivity and intensity than AA genotype carriers (4.91 ± 2.17 vs 3.28 ± 1.95; $P < 0.05$). The OPRM1 118A > G polymorphism may contribute to differences in postoperative pain perception among children aged 12 years or older. It could serve as a marker to guide individualized analgesic dosing, although dose adjustments should ultimately be based on clinical requirements rather than genotype alone. In younger children, carriers of the OPRM1 118G allele may exhibit a lower risk of obesity, possibly related to reduced μ-opioid receptor (MOP) expression.

Keywords: Pain, Polymorphism, Children, Opioid, *OPRM1*

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Introduction

Opioids are widely used for the treatment of both acute and chronic pain, with fentanyl and alfentanil being commonly administered to control perioperative pain in surgical patients. These agents exert their analgesic effects primarily by activating μ-opioid receptors (MOR). Their clinical efficacy is influenced by properties such as lipid solubility and receptor affinity [1]. However, opioid administration is often complicated by marked interindividual variability in both required dosing and the occurrence of adverse effects [2].

In pediatric populations, this variability has been reported across age, sex, ethnicity, body weight, and surgical factors, such as procedure type and duration [3-5]. In addition, variability in MOR expression and distribution, along with genetic polymorphisms affecting opioid pharmacokinetics and pharmacodynamics, may further contribute to differences in analgesic response [6, 7].

Single-nucleotide polymorphisms (SNPs) in genes involved in pain pathways are thought to explain a substantial proportion of the variability in pain perception and analgesic response, potentially accounting for up to 30% of opioid dose requirements [8]. Among these, the OPRM1 118A > G (rs1799971) variant is the most extensively

studied. The presence of the G allele has been associated in several reports with reduced analgesic efficacy of standard opioid dosing [9-12]. This polymorphism may influence MOR expression and signaling in the central nervous system, thereby modifying receptor function and clinical opioid effects [13, 14].

Although previous studies have examined the relationship between OPRM1 variants and opioid dosing requirements, findings have been inconsistent [15, 16]. Furthermore, there are currently no clear clinical guidelines for interpreting these genetic variants, and data in pediatric populations remain limited [7].

This study aimed to examine whether the OPRM1 118A>G (rs1799971) polymorphism is associated with intraoperative requirements for fentanyl and alfentanil, as well as postoperative pain intensity, in pediatric patients across different age groups.

Materials and Methods

Patients

A total of 110 pediatric patients treated at the Pediatric Surgery and Orthopedics Clinic of the University Clinical Centre of Niš were enrolled in this prospective study. Before surgery, written informed consent was obtained from parents or legal guardians during the study period (2021–2023). Ethical approval was granted by the Ethics Committee of the University Clinical Centre of Niš (No. 28355/7, 21.09.2022) and the Ethics Committee of the Faculty of Medicine, University of Niš (No. 12-10650/2-5, 03.10.2022). The investigation followed the principles of the Declaration of Helsinki and adhered to Good Clinical and Laboratory Practice standards [17].

Children aged 6–18 years with ASA physical status I–II scheduled for elective plastic or orthopedic procedures were included. Exclusion criteria comprised chronic systemic diseases, hepatic or renal impairment, immunodeficiency disorders, and active infections.

Anesthesia protocol

Anesthesia was initiated intravenously with propofol 2.5 mg/kg, combined with either fentanyl 1 μg/kg or alfentanil 10 μg/kg, and rocuronium 0.6 mg/kg to facilitate tracheal intubation. After airway securing, patients were ventilated using volume-controlled mechanical ventilation until normocapnia was confirmed.

Maintenance of anesthesia consisted of a continuous propofol infusion at 6 mg/kg/h, with supplemental bolus doses of fentanyl (1 μg/kg) or alfentanil (10 μg/kg) as required, along with oxygen–air mixture support. Neuromuscular blockade was antagonized using atropine (0.01 mg/kg) and neostigmine/prostigmine (0.025 mg/kg).

Following recovery of spontaneous respiration, patients were extubated and transferred to the post-anesthesia care unit and, subsequently, to the surgical ward within 30 minutes. At the end of surgery, an additional single dose of fentanyl or alfentanil was given for postoperative analgesia.

Monitoring

Patients were continuously monitored using electrocardiography (ECG), pulse oximetry, and non-invasive blood pressure measurements. Hemodynamic variables, including heart rate and systolic and diastolic blood pressure, were also recorded and used as indirect indicators of intraoperative nociception.

Additional perioperative data collected included total opioid consumption (fentanyl or alfentanil), number of intraoperative opioid boluses, overall propofol dose, and duration of both surgery and anesthesia.

Postoperative pain was assessed within the first hour after surgery using the Numerical Rating Scale (NRS), which is appropriate for older pediatric patients capable of understanding numerical evaluation [18]. Pain intensity was scored from 0 (no pain) to 10 (worst imaginable pain) based on patient self-report or, when necessary, with assistance from a parent or legal guardian.

Baseline patient characteristics, administered drug regimens, and postoperative pain outcomes are summarized in **Table 1.**

Table 1. Patient characteristics, anesthetic drug use, and postoperative pain according to opioid type.

Variable	X^2 / Z / t (P-value)	Alfentanil	Fentanyl
Male sex	4.638 (0.024)	45 (86.5%)	39 (67.2%)
Age (years)	0.722 (0.470)	13.0 (10.0–15.0)	12.0 (9.0–15.0)
Older children category	0.000 (1.000)	31 (59.6%)	34 (58.6%)

Total body weight (kg)	0.928 (0.356)	51.96 ± 18.26	48.67 ± 18.84
Total body height (cm)	1.045 (0.298)	157.12 ± 19.55	153.19 ± 19.78
Body mass index (kg/m²)	0.910 (0.363)	19.9 (17.6–23.4)	19.4 (17.0–22.4)
ASA class II	0.011 (0.916)	5 (9.6%)	7 (12.1%)
Heart rate (beats/min)	1.048 (0.297)	107.40 ± 14.60	104.22 ± 17.67
Systolic blood pressure (mmHg)	1.106 (0.269)	110.0 (110.0–120.0)	110.0 (110.0–120.0)
Diastolic blood pressure (mmHg)	0.857 (0.394)	65.96 ± 7.74	67.24 ± 7.90
Postoperative pain score (0–10)	0.131 (0.896)	3.38 ± 2.47	3.32 ± 2.28
Opioid dosage (mg)		1500.0 (1112.5–2100.0)	150.0 (100.0–210.0)
Fentanyl-equivalent dose (mg)	0.943 (0.346)	150.0 (111.2–210.0)	150.0 (100.0–210.0)
Number of opioid administrations	0.341 (0.733)	3.31 ± 1.02	3.24 ± 1.01
Propofol administered (mg)	1.036 (0.300)	405.0 (240.0–555.0)	325.0 (220.0–500.0)
Duration of anesthesia (min)	0.733 (0.464)	60.0 (46.2–85.0)	70.0 (48.8–95.0)
Operative time (min)	1.659 (0.097)	40.0 (25.0–60.0)	45.0 (35.0–70.0)

Note: Statistically significant differences are indicated in bold ($P < 0.05$).
Participants were stratified into two age-based subgroups: school-aged children (6–11 years; n = 45) and adolescents (12–18 years; n = 65).

Material sampling

Peripheral blood (2 mL) was drawn from each participant before surgery for genetic analysis. Samples were collected into EDTA-containing tubes to prevent coagulation, then promptly frozen and stored at −20 °C until DNA isolation.

Genomic DNA was subsequently isolated from whole blood using a silica column–based commercial extraction kit. Detection of the OPRM1 118A > G (rs1799971) polymorphism was performed by real-time PCR using a commercially prepared master mix together with validated allele-specific primers and probes (Applied Biosystems assay: C___8950074_1_). All procedures were carried out according to the manufacturer's protocol.

Statistical analysis

Data processing and evaluation were carried out with the Statistical Package for Social Sciences (SPSS v. 25, Chicago, IL, USA). Based on the data distribution, continuous measures were summarized as either the mean with standard deviation or the median with interquartile range. Categorical measures were described using absolute numbers alongside their corresponding percentages. Group comparisons between the two study arms were undertaken with the parametric Student's t-test, or the non-parametric Mann–Whitney U-test and Fisher's exact test. To ascertain which factors independently and significantly forecast postoperative pain severity, standard linear regression models (both univariate and multivariate) were applied. The threshold for statistical significance was fixed at $P < 0.05$.

Results and Discussion

A total of 110 pediatric patients were included in the analysis, comprising 84 boys (76.4%) and 26 girls (23.6%), aged 6 to 18 years. The mean age was 12.24 ± 3.38 years, and 45 children (40.9%) were aged 11 years or younger. All patients received propofol for induction and maintenance of anesthesia, while intraoperative analgesia was provided using either fentanyl (52.7%) or alfentanil (47.3%) administered as intermittent intravenous boluses according to standard dosing protocols. To allow comparison between opioids, alfentanil doses were converted into fentanyl-equivalent doses using a 10:1 potency ratio [19].

Baseline comparison revealed no significant differences between the two opioid groups, except for a higher proportion of male patients in the alfentanil group ($P < 0.05$), as shown in **Table 1.**

OPRM1 118A > G polymorphism frequency

The polymorphic G variant was detected with an overall frequency of 0.152 in the analyzed cohort. Genotype distribution analysis confirmed the Hardy–Weinberg equilibrium, with no statistically significant differences between observed and expected values. The detailed distribution of alleles and genotypes is provided in **Table 2.**

Table 2. Distribution of OPRM1 alleles and genotypes.

Allele		Genotype	
A	**191 (86.8%)**	**AA**	**84 (76.4%)**
G	29 (15.2%)	AG	23 (20.9%)
		GG	3 (2.7%)
Hardy-Weinberg equilibrium		X2=0.823, p=0.364	

Because the GG genotype was rare, participants were grouped into two categories: AA homozygotes (wild-type) and carriers of the G allele (AG and GG combined). The comparison of baseline features and perioperative variables according to OPRM1 genotype is summarized in **Table 3.**

No statistically significant differences were observed between the two groups in demographic characteristics or anesthetic dosing regimens. However, a trend toward a higher number of opioid administrations per patient was noted in G allele carriers compared with AA individuals (3.62 ± 1.13 vs 3.17 ± 0.96), although this did not reach statistical significance (p = 0.076).

Table 3. Patient characteristics, anesthetic dosing, and postoperative pain outcomes according to OPRM1 genotype.

Variable	X^2 / Z / t (P-value)	AG + GG genotypes	AA genotype
Use of fentanyl	0.009 (0.824)	13 (50.0%)	45 (53.6%)
Male sex	0.000 (1.000)	20 (76.9%)	64 (76.2%)
Age (years)	1.806 (0.071)	10.5 (9.0–14.0)	13.0 (10.0–15.0)
Older children group	1.709 (0.171)	12 (46.2%)	53 (63.1%)
Total body weight (kg)	1.921 (0.057)	44.19 ± 19.04	52.10 ± 18.11
Total body height (cm)	1.740 (0.085)	149.23 ± 19.78	156.85 ± 19.41
Body mass index (kg/m²)	1.763 (0.078)	18.9 (15.0–21.8)	20.2 (17.6–23.2)
ASA class II	0.925 (0.287)	1 (3.8%)	11 (13.1%)
Heart rate (beats/min)	0.084 (0.934)	105.96 ± 12.00	105.96 ± 17.47
Systolic blood pressure (mmHg)	1.608 (0.108)	110.0 (110.0–120.0)	110.0 (110.0–120.0)
Diastolic blood pressure (mmHg)	1.225 (0.223)	65.00 ± 7.62	67.14 ± 7.85
Postoperative pain score (0–10)	1.312 (0.193)	3.91 ± 2.50	3.18 ± 2.31
Fentanyl-equivalent dose (mg)	0.635 (0.525)	147.5 (100.0–213.8)	150.0 (105.0–210.0)
Number of opioid administrations	1.827 (0.076)	3.62 ± 1.13	3.17 ± 0.96
Propofol administered (mg)	0.904 (0.366)	302.5 (215.0–472.5)	400.0 (242.5–507.5)
Duration of anesthesia (min)	0.420 (0.674)	72.5 (48.8–92.5)	65.0 (46.2–90.0)
Surgical duration (min)	0.375 (0.708)	45.0 (30.0–65.0)	40.0 (30.0–65.0)

OPRM1 polymorphism and postoperative pain in school children and adolescents

Subgroup analyses were then performed separately for school-aged children and adolescents **(Tables 4 and 5).**

In the 6–11-year age group, a statistically significant difference was observed only in body mass index (BMI), which was higher in AA genotype carriers (P < 0.05). All other demographic variables, anesthetic doses, and perioperative parameters were comparable between genotype groups.

In contrast, among participants aged 12 years and older, carriers of the G allele experienced significantly greater postoperative pain compared with AA individuals (P < 0.05), despite similar baseline characteristics and opioid dosing across groups.

Table 4. Patient characteristics, anesthetic dosing, and postoperative pain according to OPRM1 genotype in school-aged children (6–11 years).

Variable	X^2 / Z / t (P-value)	AG + GG genotypes	AA genotype
Fentanyl administration	0.000 (1.000)	6 (42.9%)	15 (48.4%)
Male sex	0.477 (0.458)	12 (85.7%)	22 (71.0%)
Age (years)	0.530 (0.599)	8.57 ± 1.60	8.84 ± 1.55

Total body weight (kg)	1.691 (0.098)	30.14 ± 8.70	35.52 ± 10.33
Total body height (cm)	0.712 (0.480)	134.21 ± 11.30	137.03 ± 12.70
Body mass index (kg/m²)	2.266 (0.029)	16.43 ± 2.63	18.56 ± 3.03
ASA class II	0.674 (0.648)	1 (7.1%)	5 (16.1%)
Heart rate (beats/min)	0.636 (0.528)	110.71 ± 10.72	113.71 ± 16.02
Systolic blood pressure (mmHg)	0.247 (0.806)	108.57 ± 7.70	109.19 ± 7.87
Diastolic blood pressure (mmHg)	1.296 (0.195)	60.0 (60.0–60.0)	60.0 (60.0–70.0)
Postoperative pain score (0–10)	0.000 (1.000)	3.00 ± 2.52	3.00 ± 2.83
Fentanyl-equivalent dose (mg)	0.123 (0.903)	110.71 ± 41.41	112.19 ± 35.57
Number of opioid administrations	1.542 (0.139)	3.71 ± 1.07	3.23 ± 0.76
Propofol administered (mg)	0.250 (0.803)	250.0 ± 80.02	257.81 ± 103.18
Duration of anesthesia (min)	1.064 (0.287)	55.0 (48.8–85.0)	55.0 (45.0–75.0)
Operative duration (min)	1.198 (0.231)	40.0 (30.0–64.8)	40.0 (25.0–45.0)

Note: Results with statistical significance are highlighted in bold ($P < 0.05$).

Table 5. Baseline characteristics, perioperative drug administration, and postoperative pain outcomes stratified by OPRM1 genotype in adolescents aged 12–18 years.

	X2 or Z or t (p)	***AG+GG***	***AA***
Opioid (fentanyl)	0.247 (0.527)	34 (52.3%)	29 (41.7%)
Gender (male)	0.307 (0.449)	8 (66.7%)	42 (79.2%)
Age (years)	0.831 (0.409)	14.25 ± 1.82	14.74 ± 1.83
TBW (kg)	0.267 (0.790)	60.58 ± 13.80	61.79 ± 14.22
TBH (cm)	0.455 (0.651)	166.75 ± 10.82	168.43 ± 11.74
BMI (kg/m2)	0.275 (0.783)		
ASA (II)	0.450 (0.583)	0 (0.0%)	69 (11.3%)
HR (1/min.)	0.104 (0.918)	100.42 ± 11.37	100.94 ± 16.67
SBP (mmHg)	0.827 (0.408)	115.0 (110.0–120.0)	120.0 (110.0–120.0)
DBP (mmHg)	0.136 (0.892)	68.33 ± 8.35	68.68 ± 7.85
Postoperative pain (0–10)	**2.433 (0.018)**	4.91 ± 2.17	3.28 ± 1.95
Fentanyl equivalent dose (mg)	0.878 (0.380)	217.5 (150.0–257.5)	200.0 (150.0–225.0)
Number of opioid doses	1.024 (0.306)	3.0 (3.0–4.8)	3.0 (2.0–3.0)
Propofol dose (mg)	0.439 (0.662)	546.42 ± 262.38	513.36 ± 229.37
Anesthesia time (min.)	0.029 (0.977)	77.92 ± 28.96	78.21 ± 31.53
Surgery time (min.)	0.219 (0.827)	54.58 ± 27.67	56.54 ± 27.91

Note: Statistically significant results are indicated in bold ($P < 0.05$).

Among adolescents, the mean postoperative pain score was 3.60 ± 2.08 (range: 1–9). Regression analysis identified OPRM1 genotype as the only significant predictor of postoperative pain intensity ($F = 5.984$, $P < 0.05$). The model explained 8.2% of the variance in pain scores, and each G allele was associated with a 1.3-point increase in pain severity (95% CI: 0.2–2.4; $P < 0.05$).

In contrast, no significant predictors of postoperative pain were identified in the school-aged group.

Genetic variability within genes involved in nociception has been consistently reported to contribute to differences in both pain sensitivity and response to opioid analgesics during clinical pain stimuli [20-25]. In the current study, the G allele of the OPRM1 118A > G polymorphism was observed in 15.2% of participants. When analyzed separately by age category, no meaningful differences were detected in intraoperative opioid requirements between genotype groups, as both total opioid use and rescue dosing were comparable in school-aged children and adolescents. This indicates that OPRM1 variation did not significantly influence fentanyl or alfentanil dosing during surgery. However, a clear divergence emerged postoperatively, where adolescents older than 12 years carrying the G allele experienced higher pain scores compared with AA genotype carriers, suggesting a potential age-dependent genetic contribution to pain perception after surgery. Postoperative pain in children is shaped by a broad range of interacting factors, including developmental stage, pain distribution, psychological state, prior

healthcare exposure, school absenteeism, and functional limitations related to pain [26]. Avian *et al*. [27] reported an age-related increase in reported pain intensity, which may be explained by improved pain recognition and expression in older children. This observation aligns with our results, which demonstrated increased postoperative pain in adolescents, particularly in those carrying the OPRM1 G allele. In our cohort, baseline characteristics were generally comparable between genotype groups. The only exception was a higher BMI observed in school-aged children (< 12 years) with the AA genotype; however, this difference was not associated with postoperative pain intensity in subsequent analyses. This is consistent with previous reports indicating that BMI is not a significant determinant of postoperative pain in pediatric populations [28]. The higher BMI observed in this subgroup may be explained by the involvement of the μ-opioid receptor (MOP) system in energy balance and adipose tissue regulation, which is influenced by factors such as age, sex, and dietary patterns [29-31]. Central opioid signaling has been implicated in both hedonic feeding and metabolic homeostasis. Experimental studies in animal models have shown that high-fat diets can induce epigenetic modifications and upregulation of MOR expression, suggesting a link between opioid receptor activity and obesity-related pathways [30]. Furthermore, MORs also participate in the regulation of food intake behavior [31]. Despite these experimental findings, clinical evidence directly linking the OPRM1 118A > G polymorphism with BMI in children remains lacking. Given that this variant may influence receptor expression and function, it is plausible that altered MOR activity could protect against increased adiposity in younger individuals, though this hypothesis requires further investigation. The influence of OPRM1 polymorphisms on opioid response has been reported in both pediatric and adult populations [9, 20-22, 25, 32-34]. Campa *et al*. [35] demonstrated that even a single G allele may be sufficient to reduce opioid analgesic efficacy, supporting our approach of grouping GA and GG genotypes. Similarly, Klepstad *et al*. [36] reported that homozygous 118G/G carriers required higher morphine doses in the early postoperative period than other genotypes, findings consistent with those of Chou *et al.* [37]. In our study, carriers of the G allele tended to receive higher doses of opioid analgesics, although this difference did not reach statistical significance. A larger sample size might have clarified potential differences in dosing requirements between genotype groups. Additionally, the OPRM1 118A > G polymorphism has been suggested to modulate both analgesic efficacy and respiratory depressive effects of certain opioids, including alfentanil, with reduced analgesia observed in heterozygous carriers and attenuated respiratory depression in homozygous G allele carriers [20]. While several studies have reported significant associations between OPRM1 genotype and opioid dose requirements, others have failed to confirm these findings, highlighting ongoing inconsistency in the literature [16, 38]. So far, only a few clinical studies have examined the impact of opioid receptor polymorphism on the analgesic effectiveness of fentanyl or alfentanil in young patients. The analgesic efficacy of these analgesics during the perioperative period requires further study in a larger sample of pediatric patients. In the future, it will be necessary to base clinical practice in the dosing of opioid analgesics on genetic variations in children. Moreover, in younger children, carriers of the polymorphic OPRM1 118G allele may be protected from obesity due to diminished MOP expression.

Given that pediatric patients are a particularly sensitive population and that the investigation was conducted at a single center, the relatively small sample size is the main limitation of this study. A larger cohort would likely allow detection of more subtle genotype-related differences between patients.

For similar reasons, both fentanyl and alfentanil were included as analgesic agents within the study population. However, current evidence does not indicate that the OPRM1 polymorphism differentially influences the analgesic efficacy of these two opioids.

Conclusion

Based on our findings, postoperative pain was more frequently observed in children older than 12 years carrying the G allele of the OPRM1 118A > G (rs1799971) polymorphism. This suggests that this genetic variant may serve as a potential indicator of higher postoperative pain risk.

Although routine genotyping for OPRM1 is not currently part of standard clinical practice, knowledge of G allele carriage may help guide more individualized opioid dosing strategies in pediatric patients, particularly adolescents. Nevertheless, analgesic dosing should always be based primarily on the individual clinical condition and pain response, rather than on genetic information alone.

Given that the studied polymorphism is associated with reduced μ-opioid receptor expression, it is also hypothesized that this variant may exert a protective effect against obesity in younger children.

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