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ORIGINAL RESEARCH

The Impact of Opioid Receptor Gene Polymorphism on Fentanyl and Alfentanil's Analgesic Effects in the Pediatric Perioperative Period

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Introduction: The polymorphism of the gene coding mu-opioid receptor (*OPRM1*) is one of the factors contributing to the variability in the response to opioid analgesics in children. The goal of this study is to investigate its role in association with postoperative acute pain in children of various ages.

Methods: This prospective study analyzed 110 pediatric patients, after plastic or orthopedic surgery, who were genotyped and randomly assigned to receive fentanyl or alfentanil. Postoperative pain was rated using Numerical Rating Scale (0–10). All the patients were genotyped for*OPRM1 118A>G* (*rs1799971*) gene polymorphism.

Results: School children under the age of 11 with the *OPRM1 AA* genotype were shown to have a higher BMI ($p<0.05$). Children over the age of 12 carrying G allele *OPRM1*, had increased postoperative pain sensitivity and intensity (3.28±1.95 vs 4.91±2.17; $p<0.05$), as compared to *AA* allele carriers.

Discussion: *OPRM1 118A>G* polymorphism may explain the variation in the perception of postoperative pain in children over the age of 12 and may be a useful predictor for adjusting the dose of analgesics, but the dose is relative to the patient's needs regardless of his genetic characteristics. In younger children, carriers of polymorphic *OPRM1 118G* allele may be protected from obesity, due to diminished *MOP* expression.

Keywords: polymorphism, *OPRM1*, opioid, pain, children

Introduction

The primary application of opioids is the management of both acute and chronic pain. Fentanyl and alfentanil are the opioids that are most frequently used to avoid acute pain during surgery. These drugs achieve their analgesic effect by binding to mu-opioid receptors (*MOP*). The potency and degree of lipid solubility of these drugs affect their analgesic effects.[1] Their administration is further complicated by significant interindividual variations in dosage and adverse effect incidence.[2] Children of various ages, sexes, ethnicities, weights, types, or duration of surgery have all had this interindividual variability in opioid dosage documented.[3–5] Additionally, the individual expression and distribution of *MOP* as well as gene polymorphism, which can affect the pharmacokinetics and pharmacodynamics of analgesics, was observed.[6,7] As a result, variations in pain perception or analgesic response to a painful procedure may be caused by single nucleotide polymorphisms (SNPs) in the DNA molecule that

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encode a protein involved in the pain pathway. It is assumed that gene polymorphisms may account for up to 30% in the variability of the opioid dose needed.[8] The *118A > G (rs1799971)* SNP in the mu-opioid receptor 1 (*OPRM1*) gene is one of the SNPs that is most frequently investigated for the modulation of opioid analgesic response, showing that G allele is associated with less effective pain relief with the use of standardly dosed opioid analgesics.[9–12] This*OPRM1* receptor polymorphism can alter *MOP* signaling and/or expression in the human brain, which alters the functional characteristics of the opioid receptor and results in a variety of opioid analgesic effects.[13,14] The effects of *OPRM1* gene polymorphisms on opioid analgesic dose were previously investigated, however the outcomes varied.[15,16] Up to date, there are no clear recommendations on the interpretation of these genetic variants in a clinical setting, as well as little data on its impact on opioid use in the children's population.[7]

Objective

This study aims to investigate the relationship between the *OPRM1* gene polymorphism *118A > G (rs1799971)* and the dosage of fentanyl and alfentanil used intraoperatively as well as the level of postoperative pain in children of various ages.

Materials and Methods

Patients

110 patients of the Pediatric Surgery and Orthopedics Clinic at the Niš University Clinical Centre were analyzed in this prospective study. Informed parental or guardian consent was required preoperatively for this type of study in the period from 2021 to 2023. The Ethics Committee of the Niš University Clinical Centre and the Ethics Committee of the Faculty of Medicine of the University of Niš both gave their approval to the study (number 28355/7 of 21.09.2022 and 12-10650/2-5 of 03.10.2022). The study protocol complied with the guidelines outlined in the Helsinki Declaration and conducted with the ethical principles of Good Clinical and Laboratory Practices.[17]

Children between the ages of 6 and 18 who have physical status I or II, according to the American Society of Anesthesiologists (ASA), underwent elective plastic and orthopedic surgery. The study eliminated any patients who had a history of chronic illnesses, hepatic or renal failure, immunodeficiency, or an infectious condition.

Anesthesia Protocol

In order to achieve general anesthesia, intravenous doses of propofol 2.5 mg/kg, alfentanil 10 mcg/kg or fentanyl 1 mcg/kg, and the muscle relaxant rocuronium 0.6 mg/kg, were administered. Patients were connected to mechanical ventilation (volume-controlled ventilation) following tracheal intubation until normocapnia was achieved. Propofol (6 mg/kg/h), intermittent boluses of alfentanil 10 mcg/kg or fentanyl 1 mcg/kg, and the use of oxygen and medical air were used to maintain anesthesia. With the use of atropine (0.01 mg/kg) and prostigmine (0.025 mg/kg), the neuromuscular block was reversed. The patients were extubated after achieving spontaneous breathing, and they were then moved, over the course of the following 30 min, first to the Post Anesthesia Care Unit and then to the Surgical Department. At the end of surgery, a single dose of fentanyl or alfentanil was administered for postoperative analgesia.

Monitoring

ECG, pulse oximeter, and non-invasive blood pressure measurement were used to monitor patients. Monitoring of heart rate and systolic and diastolic pressure was used to determine the level of pain during the procedure. In addition, the total quantity of fentanyl or alfentanil, the number of opioid doses administered during surgery, the total dose of propofol, the length of the procedure, and the anesthesia were all monitored.

In the first hour following surgery, postoperative pain assessment was evaluated using a Numerical Rating Scale (NRS). This scale is the simplest and most commonly used scale for older children who can count and understand numbers.[18] The level of pain was rated from 0 to 10 (0- no pain at all, 10- The worst pain imaginable), by the children themselves or with the help of the legal parent/guardian.

Patients' characteristics, as well as the drug dosing regimens are shown in Table 1.

School children, between the ages of 6 and 11 (45 patients), and adolescent children, between the ages of 12 and 18 (65 patients), were split into two groups based on age.

Table 1 Patients' Baseline Characteristics, Drug Dosing Regimens, and Postoperative Pain Level According to the Opioid Used

	Fentanyl	Alfentanil	X2 or Z or t (p)
Gender (male)	39 (67.2%)	45 (86.5%)	**4.638 (0.024)**
Age (years)	12.0 (9.0–15.0)	13.0 (10.0–15.0)	0.722 (0.470)
Age (elder children)	34 (58.6%)	31 (59.6%)	0.000 (1.000)
TBW (kg)	48.67±18.84	51.96±18.26	0.928 (0.356)
TBH (cm)	153.19±19.78	157.12±19.55	1.045 (0.298)
BMI (kg/m2)	19.4 (17.0–22.4)	19.9 (17.6–23.4)	0.910 (0.363)
ASA (II)	7 (12.1%)	5 (9.6%)	0.011 (0.916)
HR (1/min.)	104.22±17.67	107.40±14.60	1.048 (0.297)
SBP (mmHg)	110.0 (110.0–120.0)	110.0 (110.0–120.0)	1.106 (0.269)
DBP (mmHg)	67.24±7.90	65.96±7.74	0.857 (0.394)
Postoperative pain (0–10)	3.32±2.28	3.38±2.47	0.131 (0.896)
Opioid dose (mg)	150.0 (100.0–210.0)	1500.0 (1112.5–2100.0)	
Equivalent fentanyl dose (mg)	150.0 (100.0–210.0)	150.0 (111.2–210.0)	0.943 (0.346)
Number of opioid doses	3.24±1.01	3.31±1.02	0.341 (0.733)
Propofol dose (mg)	325.0 (220.0–500.0)	405.0 (240.0–555.0)	1.036 (0.300)
Anesthesia time (min.)	70.0 (48.8–95.0)	60.0 (46.2–85.0)	0.733 (0.464)
Surgery time (min.)	45.0 (35.0–70.0)	40.0 (25.0–60.0)	1.659 (0.097)

Note: Bold text: p<0.05.

Material Sampling

Peripheral venous blood samples (2 mL) for DNA extraction were collected prior to surgery in a tube containing EDTA as an anticoagulant, and immediately frozen and stored at −20°C until further processing.

Genomic DNA was extracted from blood using a commercial kit on silica-based columns. The Real-Time PCR method of commercially available Master Mix and an assay containing appropriate probes and primers (Applied Biosystems, commercial probe and primers: C___8950074_1_) were used to examine the gene polymorphism *118A > G (rs1799971)* on the *OPRM1* gene. The Real-Time PCR was performed in accordance with manufacturer's instructions.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS v. 25, Chicago, IL, USA). Depending on the normality of distribution, continuous variables are presented as means with standard deviation, or as median with interquartile range. Categorical variables are presented in terms of absolute and frequency. The differences between the two study groups were tested by parametric Student's *t*-test, or non-parametric Mann–Whitney *U*-test and Fischer's exact test. Standard linear univariate and multivariate regression was performed to determine statistically significant predictors of the postoperative pain level. Statistical significance was measured at level p<0.05.

Results

The study group included 110 patients, 84 male (76.4%) and 26 female (23.6%) aged from 6 to 18 years.

The average age was 12.24±3.38 years, and 45 patients (40.9%) were 11 years old or younger. They were anesthetized by propofol, and analgesia was obtained using an opioid analgesic, fentanyl (52.7%) or alfentanil (47.3%). Opioid analgesic was administered intermittently in boluses intravenously in standard doses during the intraoperative period of general anesthesia. Since fentanyl is approximately 10 times stronger, we have calculated fentanyl equivalent doses for all the patients in alfentanil group dividing by 10.[19]

The only statistically significant difference between alfentanil and fentanyl groups was a higher frequency of male patients in alfentanil group ($p<0.05$) as shown in Table 1.

OPRM1 118A>G polymorphism frequency

Polymorphic G allele was present in a study sample with a frequency of 0.152. Based on Hardy-Weinberg equilibrium, the obtained genotype frequencies do not deviate significantly from the expected. The allele and genotype frequencies are presented in Table 2.

Due to the low frequency of *GG* genotype, patients were divided into wild-type carriers (*AA* genotype) and *G* allele carriers (heterozygous or homozygous). Their characteristics, in association with *OPRM1* genotype, are presented in Table 3. There were no statistically significant differences between these two groups in any of the characteristics or the dosing regimens. Although the difference was not significant, the carriers with the *G* allele had more opioid doses per patient than *AA* genotype carriers (3.62±1.13 vs 3.17±0.96, p=0.076).

OPRM1 polymorphism and postoperative pain in school children and adolescents

Subsequently, we have analyzed the *OPRM1* genotype effects separately in school children and adolescents group (Table 4 and Table 5). In school children, the only statistically significant difference noted is that *AA* patients had a higher

Table 2 *OPRM1* Allele and Genotype Frequencies

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	

Table 3 Patients' Baseline Characteristics, Drug Dosing Regimens, and Postoperative Pain Level According to *OPRM1* Genotype

	AA	***AG+GG***	**X2 or Z or t (p)**
Opioid (fentanyl)	45 (53.6%)	13 (50.0%)	0.009 (0.824)
Gender (male)	64 (76.2%)	20 (76.9%)	0.000 (1.000)
Age (years)	13.0 (10.0–15.0)	10.5 (9.0–14.0)	1.806 (0.071)
Age (elder children)	53 (63.1%)	12 (46.2%)	1.709 (0.171)
TBW (kg)	52.10±18.11	44.19±19.04	1.921 (0.057)
TBH (cm)	156.85±19.41	149.23±19.78	1.740 (0.085)
BMI (kg/m2)	20.2 (17.6–23.2)	18.9 (15.0–21.8)	1.763 (0.078)
ASA (II)	11 (13.1%)	1 (3.8%)	0.925 (0.287)
HR (1/min.)	105.96±17.47	105.96±12.00	0.084 (0.934)

(*Continued*)

Table 3 (Continued).

	AA	*AG+GG*	X2 or Z or t (p)
SBP (mmHg)	110.0 (110.0–120.0)	110.0 (110.0–120.0)	1.608 (0.108)
DBP (mmHg)	67.14±7.85	65.00±7.62	1.225 (0.223)
Postoperative pain (0–10)	3.18±2.31	3.91±2.50	1.312 (0.193)
Fentanyl equivalent dose (mg)	150.0 (105.0–210.0)	147.5 (100.0–213.8)	0.635 (0.525)
Number of opioid doses	3.17±0.96	3.62±1.13	1.827 (0.076)
Propofol dose (mg)	400.0 (242.5–507.5)	302.5 (215.0–472.5)	0.904 (0.366)
Anesthesia time (min.)	65.0 (46.2–90.0)	72.5 (48.8–92.5)	0.420 (0.674)
Surgery time (min.)	40.0 (30.0–65.0)	45.0 (30.0–65.0)	0.375 (0.708)

Table 4 Patients' Baseline Characteristics, Drug Dosing Regimens, and Postoperative Pain Level According to *OPRM1* Genotype in School Children (6–11 Years Old)

	AA	*AG+GG*	X2 or Z or t (p)
Opioid (fentanyl)	15 (48.4%)	6 (42.9%)	0.000 (1.000)
Gender (male)	22 (71.0%)	12 (85.7%)	0.477 (0.458)
Age (years)	8.84±1.55	8.57±1.60	0.530 (0.599)
TBW (kg)	35.52±10.33	30.14±8.70	1.691 (0.098)
TBH (cm)	137.03±12.70	134.21±11.30	0.712 (0.480)
BMI (kg/m2)	18.56±3.03	16.43±2.63	**2.266 (0.029)**
ASA (II)	5 (16.1%)	1 (7.1%)	0.674 (0.648)
HR (1/min.)	113.71±16.02	110.71±10.72	0.636 (0.528)
SBP (mmHg)	109.19±7.87	108.57±7.70	0.247 (0.806)
DBP (mmHg)	60.0 (60.0–70.0)	60.0 (60.0–60.0)	1.296 (0.195)
Postoperative pain (0–10)	3.00±2.83	3.00±2.52	0.000 (1.000)
Fentanyl equivalent dose (mg)	112.19±35.57	110.71±41.41	0.123 (0.903)
Number of opioid doses	3.23±0.76	3.71±1.07	1.542 (0.139)
Propofol dose (mg)	257.81±103.18	250.0±80.02	0.250 (0.803)
Anesthesia time (min.)	55.0 (45.0–75.0)	55.0 (48.8–85.0)	1.064 (0.287)
Surgery time (min.)	40.0 (25.0–45.0)	40.0 (30.0–64.8)	1.198 (0.231)

Note: Bold text: p<0.05.

BMI (p<0.05). In 12 year old children and older, significantly higher level of postoperative pain was observed in *G* carriers (p<0.05), despite all the other characteristics and drug dosing were similar.

In adolescents, the postoperative pain level was 3.60±2.08 (from 1 to 9). The only statistically significant predictor of the postoperative pain level was *OPRM1* genotype (F=5.984, p<0.05). The variance in the postoperative pain level is in 8.2% explained by the presence of G alleles in the genotype – each *G* allele increases the pain level by 1.3 (95% CI=0.2–2.4) (p<0.05). No statistically significant predictor of postoperative pain level in school children was observed.

Table 5 Patients' Baseline Characteristics, Drug Dosing Regimens, and Postoperative Pain Level According to *OPRM1* Genotype in Adolescents (12–18 Years Old)

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

Note: Bold text: p<0.05.

Discussion

Single nucleotide polymorphisms (SNPs) in the pain pathway have been linked to variations in pain perception or analgesic response following painful procedures, according to a number of studies.[20–25] We have determined the frequency of the polymorphic *G* allele of 15.2%. In the school-aged and adolescent groups of children, according to our prospective study, the total dose and the number of repeated doses of both analgesics were similar. In both genotype groups*OPRM1* genotype had no impact on the intraoperative dosing regimen of fentanyl and alfentanil. Regardless, postoperative pain was considerably higher in children over the age of 12, who were carriers of the G allele of the gene polymorphism *OPRM1 118A>G*. Therefore, the *OPRM1* genotype can be used in predicting the severity of postoperative pain and modifying the dose of opioid analgesics, based on the child's age.

The intensity of postoperative pain in children can depend on numerous factors such as age, multiple localization of pain, presence of depression, previous hospitalizations, absence from school and disability due to pain.[26] The retrospective study by Avian et al[27] showed an increased pain rating with age. The reason for that is in increased vocalization of pain and better presentation of pain of older children. This is in agreement with our finding that postoperative pain was significantly higher in children over the age of 12. At the same time, these patients were carriers of the *G* allele of the gene polymorphism *OPRM1 118A>G*.

Adolescents with the *OPRM1 G* allele polymorphism experienced much higher level of postoperative pain, with each G allele raising pain level by 1.3 (95% CI=0.2–2.4), suggesting it may be a significant predictor of postoperative pain level. In a study by Lee et al,[9] a higher frequency of the *G* allele was found in 37.5% of children between the ages of 5 and 18, who underwent tonsillectomy. Patients with at least one *G* allele for *OPRM1 (AG/GG)* experienced more intense postoperative pain, after administration of morphine, in comparison to children with the *AA* genotype. Chidambaran et al[28] demonstrated that increased postoperative pain was linked to the G allele in children between the ages of 10 and

18. In addition to having a lower degree of postoperative analgesia after morphine administration, pediatric patients also have a lower risk of respiratory depression. In the study by Mamie et al,[29] children between the ages of 4 and 16 and with the *G* allele, had more postoperative pain than those with the *AA* genotype in the 24 hr following orthopedic or abdominal surgery.

In our study, the carriers of different alleles were similar concerning basic characteristics, except that school children patients younger than 12 years with the *AA* genotype had considerably higher BMIs, which was later shown not to be significant in predicting the intensity of postoperative pain. Previous study supported this finding that BMI is not associated with postoperative pain level in children.[30] There is a possible explanation of the higher BMI this group. *MOP* has a role in the control of adipose tissue deposition, dependent on age, gender, and type of diet.[31–33] Opioid neurotransmission plays a significant role in the rewarding and homeostatic mechanisms of obesity. In rat models, it was shown that a high-fat diet leads to epigenetic changes and up-regulation of *MOP*, linking receptor expression with obesity.[32] Additionally, these receptors are involved in the modulation of the dietary intake.[33] There are no data in the literature explaining the association between *OPRM1* genotype and BMI in children. Since the investigated *OPRM1* polymorphism affects receptor expression, we propose that polymorphic *MOP* may act protectively in younger children against obesity.

These polymorphism effects have been demonstrated in both pediatric and adult populations.[9,20–22,25,28,34,35] Similar results with adult patients were also obtained by Campa et al,[36] who demonstrated that one polymorphic G allele in the genotype is sufficient for the lower analgesic effect of opioids, which justifies the grouping of patients in our study into *AA* homozygotes and *G* allele carriers (*GA* + *GG*).

Additionally, it was found in the study conducted by Klepstad et al[37] that *118G/G* homozygotes require a larger dose of morphine to achieve analgesia in the first 48 hr following surgery compared to *118A/G* heterozygotes and *118A/A* homozygotes, which is in agreement with the study by Chou et al.[38] The results obtained in our study are in line with earlier studies. Higher doses of opioid analgesic were given to carriers of the polymorphic *G* allele. Although a larger sample size would have revealed the existence of a variation in opioid dosage between the two patient groups, this difference was not statistically significant. The *OPRM1 118A>G* polymorphism can affect the analgesic and respiratory-depressant effects of alfentanil in comparison to other opioid analgesics. Alfentanil's analgesic effects are thereby diminished in heterozygotes with only one *G* allele, and its respiratory-depressant effects are diminished in individuals who are homozygous carriers of the *118G* allele.[20] According to the studies stated above, there is statistically significant variation in dose based on *OPRM1* gene polymorphisms. However, other studies failed to demonstrate a variation in opioid dose in relation to *OPRM1* gene polymorphism.[16,39]

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 polymorphic *OPRM1 118G* allele may be protected from obesity due to diminished *MOP* expression.

Study Limitations

Given that children are the most vulnerable population and that this study was conducted in just one institution, the sample size is the study's most significant limitation. A larger sample size would make it possible to identify more variations among patients with different genotypes. For the same reason, the study group included patients treated with two different analgesics, fentanyl and alfentanil, although there is no evidence that the presence of the *OPRM1* polymorphism affects the effectiveness of these two opioid analgesics in a different way.

Conclusion

According to the results of our study, postoperative pain is much more common in children over the age of 12 who carry the G allele of the gene polymorphism *OPRM1 118A>G* (*rs1799971*). It could be a useful predictor of the severity of postoperative pain. Even though the *OPRM1* genotyping is not a routine test, an information on the presence of a polymorphic G allele could be useful in adjusting the dose of opioid analgesics in children of various ages, especially

adolescents, but the dose is relative to the patient's needs regardless of his genetic characteristics. Since the investigated *OPRM1* polymorphism affects diminished receptor expression, we propose that polymorphic *MOP* may act protectively in younger children against obesity.

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Disclosure

The authors report no conflicts of interest in this work.

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