MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2020; 26: e924153
DOI: 10.12659/MSM.924153

Received: 2020.03.10
Accepted: 2020.04.08
Available online: 2020.05.06
Published: 2020.05.13

Influences of *UGT2B7* rs7439366 and rs12233719 Polymorphisms on Fentanyl Sensitivity in Chinese Gynecologic Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

DEF 1 Zhenling Yang
CEFG 2 Qingfeng Yin
ABC 3,4 Xiaodong Li

1 The Pain Management Department, The First Affiliated Hospital of Henan University, Kaifeng, Henan, P.R. China
2 Institute of Evidence-Based Medicine and Clinical Transformation, Henan University, Kaifeng, Henan, P.R. China
3 Institutes of Evidence-Based Medicine and Knowledge Translation, Henan University, Kaifeng, Henan, P.R. China
4 Huaihe Hospital of Henan University, Kaifeng, Henan, P.R. China

Corresponding Author: Xiaodong Li, e-mail: yxcbetgg@126.com
Source of support: Departmental sources

Background: This study discussed potential influences of UDP glucuronosyltransferase family 2 member B7 (*UGT2B7*) rs7439366 and rs12233719 polymorphisms on fentanyl sensitivity among Chinese gynecologic patients.

Material/Methods: *UGT2B7* polymorphisms were genotyped by polymerase chain reaction (PCR) and direct sequencing. Before surgery, baseline latency to pain perception (PPLpre) and pain perception latency of the dominant hand (PPLpost) at 3 minutes after injecting fentanyl were measured by cold pressor-induced pain test. Perioperative fentanyl adoption referred to the total of fentanyl administration during and after operation. Intensity of spontaneous pain was appraised adopting 100-mm visual analog scale (VAS). Factorial analysis was performed by Mann-Whitney U test and Kruskal-Wallis H test.

Results: Significant differences of PPLpost (CC/CT/TT, P=0.038) and preoperative analgesic effect (CC/CT/TT, P=0.028) were discovered between the rs7439366 genotypes. PPLpost was significantly different between the CT and TT groups (P=0.009) and the CC+CT and TT groups (P=0.026). Preoperative analgesic effect was significantly different between the CT and TT groups (P=0.007) and the CC+CT and TT groups (P=0.009). All of the clinical features studied had no close association with rs12233719 SNP.

Conclusions: Gynecologic patients with rs7439366 TT genotype had significantly lower fentanyl sensitivity than the other 2 genotype carriers.

MeSH Keywords: Androgen-Insensitivity Syndrome • Fentanyl • Polymorphism, Single-Stranded Conformational

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/924153

1495 3 — 32

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Background

Gynecopathy is a group of diseases of the female reproductive system. It mainly includes 7 types: gynecological inflammation, artificial abortion, venereal diseases, irregular menstruation, infertility, gynecological plastic surgery and gynecological tumors [1–10]. Management for several gynecopathies requires surgery [11,12]. Control of pain during gynecologic surgery is important for patient consolation and operation success [13,14]. Pain for gynecologic patients before and during surgery may increase the healthcare burden [15]. Individual sensitivity for pain is considered to be determined by genetic background. Several genes have been linked to pain sensitivity [16,17].

Various analgesic drugs are used for pain during surgery, especially opioids [18]. However, many drugs had severe side effects [19]. Fentanyl has become the most common opioid for analgesia both at intra-operation and post-operation stages, taking the place of morphine due to its lesser side effect profile [20,21]. Analgesic efficacy of fentanyl is affected by multiple factors, including genes such as *MDR*, *OPRM1*, *ABCB1*, and *UGT2B7*) [22-25].

Human UDP glucuronosyltransferase family 2 member B7 (*UGT2B7*) gene is located at chromosome 4q13.2. The UGT2B7 protein imposes vital influences on eliminating potentially toxic xenobiotics [26]. Single nucleotide polymorphisms (SNPs) in the *UGT2B7* gene might change its enzyme activity, and then alter its function. rs7439366 (c.802C>T) is a T to C mutation at exon 2 base 802 of the gene, which induces the 268 amino acid to change from tyrosine to histidine. rs12233719 (c. 211G>T, p.Ala71Thr) is a missense mutation in exon 1. These 2 SNPs of the *UGT2B7* gene, as missense mutations, could decrease, increase, or not affect the activity of *UGT2B7* enzymes [27]. It has been found that these SNPs also contribute to the pharmacokinetics of many drugs [28,29]. Therefore, we speculated that these 2 SNPs might contribute to the sensitivity of fentanyl during an operation.

This study aimed to explore the influences of *UGT2B7* rs7439366 and rs12233719 polymorphisms on fentanyl sensitivity in Chinese gynecologic patients.

Material and Methods

Sample collection

This study obtained the approval of the Ethic Committee of the Institutes of Evidence-Based Medicine and Knowledge Translation, Henan University. Written informed consent was signed by every patient or their guardian.

Gynecologic patients who had gynecological surgery at the Institutes of Evidence-Based Medicine and Knowledge Translation, Henan University were recruited for our research. These patients were diagnosed by endoscope and B-mode ultrasonography by 2 gynecologists. All of the patients were 20 to 50 years old. Patients with psychiatric diseases, cardiovascular and cerebrovascular diseases, hepatic or renal diseases, diabetes mellitus; history of alcohol or drug abuse; or use of chronic pain medication were excluded from this study. Patients with severe adverse events for fentanyl were excluded from this study.

2 Preoperative cold pressor-induced pain test

Before surgery, baseline latency to pain perception (PPLpre) and pain perception latency of the dominant hand (PPLpost) at 3 minutes after injecting fentanyl were measured by cold pressor-induced pain test following methodology from a previous study [30]. Fentanyl sensitivity (analgesic effect before operation) stood for divergence between PPLpost and PPLpre (PPLpost-PPLpre).

Postoperative pain management

Fentanyl use during the intraoperative period and intravenous patient-controlled analgesia (PCA) fentanyl employment in the first 24 hours after operation were documented. Fentanyl dosage administered intraoperatively and postoperatively were decided by body weight [31]. Perioperative fentanyl use was defined as the sum of intraoperative fentanyl use and postoperative fentanyl use. Intensity of spontaneous pain was appraised at 3 hours and 24 hours after operation utilizing 100-mm visual analog scale (VAS), with 0 mm referring to no pain while 100 mm to the worst pain imaginable.

DNA extraction and genotyping method

Blood samples were collected from every participate at the morning, then put into the blood collection tubes containing EDTA-Na_2. Total DNA were extracted from whole blood using RelaxGene Blood DNA System (TIANGEN, Beijing).

PCR primers of the *UGT2B7* gene rs7439366 and rs12233719 polymorphisms were designed by Primer Premer 5.0 and synthesized by Sangon Biotech (Shanghai) Co., Ltd. Target sequences were amplified by polymerase chain reaction (PCR) and sequenced by direct sequencing method.

Statistical analysis

Genotype and allele frequencies of the *UGT2B7* SNPs were performed by direct counting. Hardy-Weinberg equilibrium (HWE) was used to assess the representativeness of participants.

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Table 1. Basic and clinical features of patients.

Features	Mean±SD	Range
Age (years)	34.95±8.02	20–50
Body weight (kg)	53.70±8.88	30–80
PPLpre (s)	15.89±9.84	1–93
PPLpost (s)	31.95±16.02	4–103
Preoperative analgesic effect (s)	16.06±11.79	–34–57
Intraoperative fentanyl use (μg/kg)	4.01±2.52	0–13.6
24h postoperative fentanyl use (μg/kg)	2.61±2.59	0–13.8
Perioperative fentanyl use (μg/kg)	6.62±4.12	0.2–25.2
VAS score at 3 hours (mm)	28.83±12.49	0–90
VAS score at 24 hours (mm)	26.17±11.86	0–84

Mean±standard deviation (mean±SD) was used to present the quantitative variables. Factorial analysis between 2 factors was performed by Mann-Whitney U test. Factorial analysis between 3 factors was performed by Kruskal-Wallis H test. Data analysis was performed by SPSS 18.0. Cutoff *P* value for statistical significance was set to 0.05. Bonferroni method was used to adjust the *P* value for multiple-comparison tests.

Results

Basic and clinical features of subjects

Our research covered 293 gynecologic sufferers, with the mean age of 34.95 ± 8.02 years old (Table 1). Distributions of basic and clinical features of patients did not conform with normal distribution (Table 1, all $P<0.001$).

CC, CT, and TT genotype frequencies of rs7439366 were 37.88%, 50.51% and 11.60% respectively. Frequencies of rs12233719 GG, GT and TT genotypes were 70.99%, 25.94%, and 3.07% respectively. Genotype distributions of these 2 SNPs were in accordance with HWE test (Table 2).

Association analysis between clinical features and *UGT2B7* SNPs

PPLpre, PPLpost, and preoperative analgesic effect had highest levels in patients with rs7439366 CT genotype and lowest levels in patients with TT genotype (Table 2). Significant differences of PPLpost (CC/CT/TT, $P=0.038$) and preoperative analgesic effect (CC/CT/TT, $P=0.028$) have been discovered between each rs7439366 genotypes (Table 3). No significant difference was discovered in PPLpre, fentanyl adoption during operation, fentanyl employment within 24 hours after operation, perioperative fentanyl administration, VAS score at 24 hours between each rs7439366 genotypes (Table 3).

PPLpost was significantly different between the CT and TT groups ($P=0.009$) and the CC+CT and TT groups ($P=0.026$). Preoperative analgesic effect was significantly different between the CT and TT groups ($P=0.007$) and the CC+CT and TT groups ($P=0.009$) (Table 3). Factorial analysis between 2 factors for other clinical features did not found any significant differences ($P>0.05$).

All of the clinical features had no close association with rs12233719 SNP (data not shown).

Discussion

In this study, we found that PPLpre, PPLpost, and preoperative analgesic effect had the highest levels in gynecologic patients with rs7439366 CT genotype and lowest levels in patients with TT genotype. However, Kruskal-Wallis H test revealed that only PPLpost and preoperative analgesic effect had significant difference among the 3 rs7439366 genotypes. Mann-Whitney U test showed that PPLpost had distinctly lower levels in the TT group than in the CT group and the CC+CT group. Preoperative analgesic effect was significantly different between the CT and TT groups and the CC+CT and TT groups. However, PPLpre had no obvious difference between the rs7439366 genotypes. These results indicated that gynecologic patients with rs7439366 TT genotype had significantly higher fentanyl sensitivity than other 2 genotype carriers. That was in accordance with a previous study. Muraoka et al. demonstrated that PPLpost-PPLpre was significantly different between 3 rs7439366 genotypes in cold pressor-induced pain test for patients experiencing orthognathic surgery [31]. They suggested that rs7439366 C allele could elevate the fentanyl analgesic effect.

No significant difference was discovered in fentanyl adoption during operation, fentanyl employment within 24 hours after operation, perioperative fentanyl administration, or VAS score at 24 hours between each rs7439366 genotypes, although patients with rs7439366 TT genotype had lower levels of perioperative fentanyl administration and VAS pain score at 24 hours. These results suggested that rs7439366 had no significant association with fentanyl analgesic effect. Our findings were similar to the results found by Muraoka et al. [31].

PPLpost, analgesic effect before operation and VAS pain score at 24 hours had lower levels in rs12233719 TT genotype carriers, but without substantial divergence. Meanwhile, fentanyl

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Table 2. Clinical features among different genotypes.

SNP	N (%)	PPLpre (s)	PPLpost (s)	Preoperative analgesic effect (s)	Intraoperative fentanyl use (μg/kg)
rs7439366					
CC	111 (37.88)	15.41±8.40	31.45±17.58	16.05±11.96	4.21±2.56
CT	148 (50.51)	16.55±11.08	33.52±15.69	16.97±12.19	3.88±2.57
TT	34 (11.60)	14.59±8.42	26.76±10.31	12.18±8.46	3.96±2.24
P_{HWE}	0.145				
rs12233719					
GG	208 (70.99)	16.25±10.28	32.17±16.11	15.92±11.91	3.99±2.63
GT	76 (25.94)	14.83±8.89	31.95±16.24	17.12±11.33	4.02±2.15
TT	9 (3.07)	16.44±6.89	26.89±12.68	10.44±12.43	4.48±3.17
P_{HWE}	0.256				

SNP	N (%)	Postoperative fentanyl use (μg/kg)	Perioperative fentanyl use (μg/kg)	VAS pain score at 3 h (mm)	VAS pain score at 24 h (mm)
rs7439366					
CC	111 (37.88)	2.74±2.66	6.95±4.35	28.05±12.13	25.53±11.85
CT	148 (50.51)	2.67±2.72	6.55±4.13	29.77±13.15	27.00±11.97
TT	34 (11.60)	1.87±1.50	5.83±3.12	27.29±10.54	25.53±11.48
P_{HWE}	0.145				
rs12233719					
GG	208 (70.99)	2.58±2.55	6.57±4.26	28.43±12.91	25.85±12.29
GT	76 (25.94)	2.67±2.81	6.69±3.73	30.33±11.64	27.51±10.89
TT	9 (3.07)	2.66±1.59	7.13±4.29	25.44±8.68	22.33±9.08
P_{HWE}	0.256				

Table 3. Association analysis between clinical features and rs7439366.

Features	CC/CT/TT (Kruskal-Wallis)	CC/CT (Mann-Whitney)	CC/TT (Mann-Whitney)	CT/TT (Mann-Whitney)	CC+CT/TT (Mann-Whitney)	CC/CT+TT (Mann-Whitney)
PPLpre (s)	0.599	0.565	0.547	0.345	0.401	0.761
PPLpost (s)	0.038*	0.224	0.146	0.009**	0.026*	0.557
Preoperative analgesic effect (s)	0.028*	0.563	0.028	0.007**	0.009*	0.859
Intraoperative fentanyl use (μg/kg)	0.422	0.207	0.529	0.634	0.995	0.207
24 h postoperative fentanyl use (μg/kg)	0.302	0.480	0.109	0.297	0.173	0.277
Perioperative fentanyl use (μg/kg)	0.549	0.650	0.254	0.439	0.323	0.464
VAS score at 24 h (mm)	0.491	0.313	0.785	0.377	0.514	0.440

* $P<0.05$; ** $P<0.017$ (significant level which was adjusted by Bonferroni method).

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adoption during operation, fentanyl employment within 24 hours after operation, and perioperative fentanyl administration also had no obvious difference between rs12233719 genotypes. Consequently, rs12233719 SNP was not related to individual sensitivity to or analgesic effect of fentanyl. As far as we know, our research, for the first time, explored potential connection for rs12233719 to fentanyl sensitivity. Besides, Tian and colleagues demonstrated that rs12233719 had no remarkable link to the severity of withdrawal symptoms in patients with methadone treatment [32].

Several limitations of our present study should be noted. First of all, we only focused on female patients; whether the study findings could be repeated in male patients is not known. Secondly, subgroup analysis based on the type gynecologic operation were not carried out. Thirdly, analgesia of pain during operation was affected by many factors, such as the type and dosage of anesthetics and genetic background. These factors usually effect the individual sensitivity for fentanyl. However, anesthetics and other genetic mutations were not considered in this study. In addition, linkage disequilibrium of rs7439366 with other candidate genes and SNPs might contribute to individual sensitivity of fentanyl. Further studies with rigorous experimental design will be performed in the future to verify our study findings.

Conclusions

In conclusion, gynecologic patients with rs7439366 TT genotype had significantly lower fentanyl sensitivity than other 2 genotype carriers, but had no influence on the fentanyl analgesic effect at the intra- and post-operation period.

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