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Original Article

Effects of OPRM1, ABCB1 and CYP2D6 single nucleotide polymorphisms on clinical efficacy of sufentanil-propofol anesthesia in patients undergoing gynecologic laparoscopic surgery: a preliminary study

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Abstract: *Background:* Genetic polymorphism may have been implicated in drug metabolism and drug targets or drug receptor, leading to interindividual variability in drug disposition and efficacy. This study investigated the effects of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 polymorphisms on anesthetic efficacy of sufentanil-propofol in patients undergoing gynecologic laparoscopic surgery. *Methods:* Between August 2000 and December 2011, one hundred and eighty-seven female patients with ovarian cyst enucleation, ectopic pregnancy (EP) or hysterectomy received gynecologic laparoscopic surgery at our hospital. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for detecting the polymorphisms of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10. *Results:* Average breathing rate and SpO_2 in the mutant homozygote (GG) of *OPRM1* All8G allele decreased at before intubation (T_1) and during intubation (T_2) compared with wild-type homozygote (AA) and heterozygote (AG) (all $P<0.05$). Average heart rate (HR) and mean arterial pressure (MAP) in the mutant homozygote (CC) of *CYP2D6**10 decreased before induction (T_1) and during intubation (T_2) compared with those in the wild-type homozygote (TT) and heterozygote (CT) (all $P<0.05$). Higher recovery degree and increased extubation time were found in the mutant homozygote compared with those in the wild-type homozygote and the heterozygote in allele of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 (both $P<0.05$). Besides, in mutant homozygote of *CYP2D6**10, 12.5% bradycardia occurred, and evident difference was observed in mutant homozygote when compared with wild-type homozygote and heterozygote (all $P<0.05$). *Conclusion:* These findings reveal that *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 gene polymorphisms have negative effects on anesthetic efficacy of sufentanil-propofol in patients receiving gynecologic laparoscopic surgery.

Keywords: *OPRM1* All8G, *ABCB1* C3435T, *CYP2D6*10, gynecologic* laparoscopic surgery, sufentanil-propofol, anesthesia

Introduction

Laparoscopic surgery, also known as minimally invasive surgery, is conducted far from their location via small incisions (0.5~1.5 cm) elsewhere in the body [1]. Laparoscopy has become the standard method for paediatric, gynaecological as well as general urological surgery [2-5]. Laparoscopic surgery has been widely used with several advantages, such as less postoperative pain, reduced surgical trauma, reduced recovery time, and better cosmetic results; however, it has several disadvantages, like awkward instruments with fulcrum effects, increased static postural stress, as well as an unstable camera platform [1, 6-8]. Continuous infusion of intravenous anesthetic propofol is widely used in laparoscopic surgery for rapid recovery and better antiemetic property that lasts long into post-operative period and reduces the risk of postoperative nausea and vomiting [9]. Sufentanil is also known as an alternative opioid with fewer side effects than morphine, higher affinity for μ receptors and longer lasting of efficacy after surgery [10]. Furthermore, genetic polymorphism may have been

Table 1. Primer sequences of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 genepolymorphisms

Sites	Primer sequences	Annealing temperature	Annealing time	Cycle number
OPRM1 A118G	F: 5'-GGTCAACTTGTCCCACTTAGATCGC-3'	62°C	60 s	38
	R: 5'-AATCACATACATGACCAGGAAGTTT-3'			
ABCBI C3435T	F: 5'-GATCTGTGAACTCTTGTTTTCA-3'	58°C	45 s	40
	R: 5'-GAAGAGAGACTIACATTAGGC-3'			
*CYP2D6**10	F: 5'-TCAACACAGCAGGTTCA-3'	52°C	45 s	35
	R: 5'-CTGTGGTTTCACCCACC-3'			

OPRM1: Opioid receptor mu 1; *ABCBI*: ATP-binding cassette B1; *CYP2D6*: Cytochrome P450 2D6; F: forward; R: reverse.

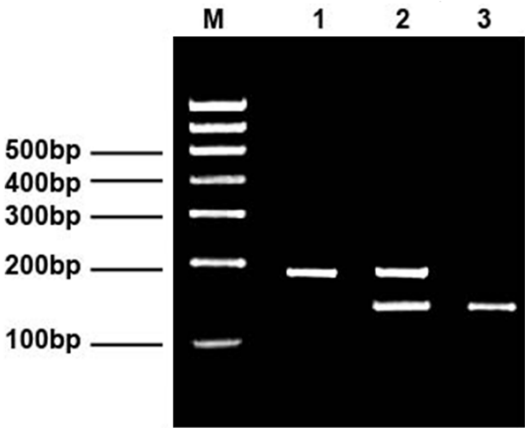

Figure 1. Electrophoretogram of PCR amplified product of *OPRM1* (PCR: polymerase chain reaction; M: DNA marker; 1: enzyme-digested product of AA homozygote; 2: enzyme-digested product of AG heterozygote; 3: enzyme-digested product of GG homozygote).

implicated in drug metabolism and drug targets or drug receptor, resulting in inter-individual variability in drug disposition and efficacy [11, 12].

The μ-opioid receptors (MOR) are known as a kind of opioid receptors with an endogenous ligand and beta-endorphin [13]. The human *MOR* gene, opioid receptor mu 1 (*OPRM1*), which belongs to the 7-transmembrane domain, is mapped to chromosome 6q24-q25 and consists of approximately nine exons and spans more than 200 kb [14]. Evidence has demonstrated that *OPRM1* was observed to be correlated with analgesia [13]. ATP-binding cassette B1 (ABCB1), also known as multidrug resistance (MDR) 1 or P-glycoprotein (P-gp), is deemed as one of ATP-binding cassette (ABC) transporters in ABC superfamily, and mainly acts as a drug efflux pump lowering the intracellular concentration of cytotoxic drugs [15, 16]. The *ABCB1* gene (located on chromosome 7) encodes P-gp, an efflux transporter in plasma membrane and consists of 28 exons [17, 18]. Cytochrome P450 2D6 (CYP2D6) is deemed as one of the most important enzymes related to the metabolism of xenobiotics in the body [19]. The *CYP2D6* gene (subfamily D, polypeptide 6) is located on chromosome 22 q 13.1-13.2 and lies close to the *CYP2D7* and *CYP2D8* pseudogenes, with more than 300 genetic variants and 128 different alleles [20]. CYP2D6 is also responsible for metabolism and elimination of about 25% of clinical drugs, in which the process is known to be O-demethylation [21]. Nevertheless, no detailed information concerning the effects of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 gene polymorphisms on anesthetic efficacy of patients receiving gynecologic laparoscopic surgery with sufentanil-propofolin was previously reported. In this case, we conducted the present study to further investigate the effects.

Material and methods

Ethical statement

This study was approved by the Ethical Committee of the Shanghai First Maternity and Infant Hospital. Written informed consents were obtained from all study subjects. This study complied with the guidelines and principles of the Declaration of Helsinki [22].

Study subjects

Between August 2000 and December 2011, one hundred and eighty-seven female patients (age range: 29~59 years old) with enucleation of ovarian cyst, ectopic pregnancy (EP) and hysterectomy who underwent gynecologic laparoscopic surgery at selected time were enrolled in our study. The body mass index (BMI) of all patients was in the normal range (1 ± 20%),

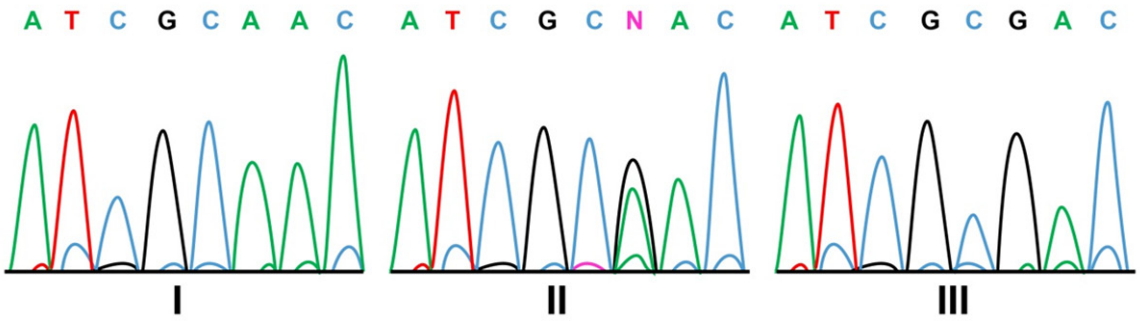

Figure 2. Sequencing diagram of *OPRM1* A118G allele (I: AA homozygote; II: AG heterozygote; III: GG homozygote).

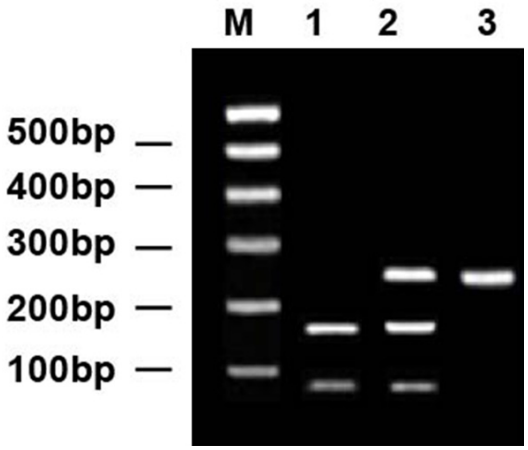

Figure 3. Electrophoretogram of PCR amplified product of *ABCB1* (PCR: polymerase chain reaction; M: DL2000 DNA marker; 1: enzyme-digested products of CC homozygote; 2: enzyme-digested products of CT heterozygote; 3: enzyme-digested products of TT homozygote).

and the American Society of Anesthesiologists (ASA) classification was at level I or II [23]. The exclusion criteria were: (1) patients with a history of smoking and excessive drinking; (2) patients with angiocardiopathy and diabetes mellitus who require long term medication; (3) chronic pain patients; (4) patients receiving surgery again within three months due to complications after surgery; (5) patients with severe liver and kidney dysfunction; (6) patients with severe cardiac and pulmonary dysfunction; (7) patients with depression; and (8) patients with other mental disorders.

Anesthetic methods

All patients took no drugs before surgery, and patients underwent fasting and water deprivation before surgery for 12 h and 4 h, respectively. The unified total intravenous anesthesia was conducted for all patients, and conventional vital signs of the patients were monitored after entering operation room.

Anesthesia induction was conducted via intravenous injection with 2 μg/kg sulfentanyl (Jiangsu Nhwa Pharmaceutical Co., Ltd, license number: H20113509), 0.5 mg/kg propofol (license number: H20100646, CordenPharma SPA Company, Italy), and 1.5 mg/kg vecuronium bromide (injected after patients were asleep) (Zhejiang Xianju Pharmaceutical Co., Ltd, license number: H19991172). After muscle relaxation, a tracheal catheter was inserted for mechanical ventilation to maintain breathe. Maintenance of anesthesia: 0.1~0.2 mg/kg rocuronium was intermittently intravenously injected during surgery for maintaining muscle relaxation, and sulfentanyl (0.1~0.2 mg/kg/min) and propofol (6~8 mg/kg/h) were continuously intravenously injected by infusion pump. Infusion rates of sulfentanyl and propofol were adjusted for making the depth of anesthesia adapted to intensity of surgical stimulation to let fluctuation of blood pressure within a normal range (no more than 20% of the base value). The use of all anaesthetic drugs was stopped after surgery. The tracheal tubes were removed from the patients when they regained consciousness with satisfactory recovery of spontaneous breathing, and the visual analog scale (VAS) was immediately recorded. If the VAS score >3 points, patients would be intravenous injected with sulfentanyl (20 pg/5 min) and titration to let VAS score ≤3 points, and then the titration dosage of sulfentanyl was recorded.

Outcome measures

Data, including breathing rate, oxygen saturation (SpO_2), heart rate (HR), and mean arterial

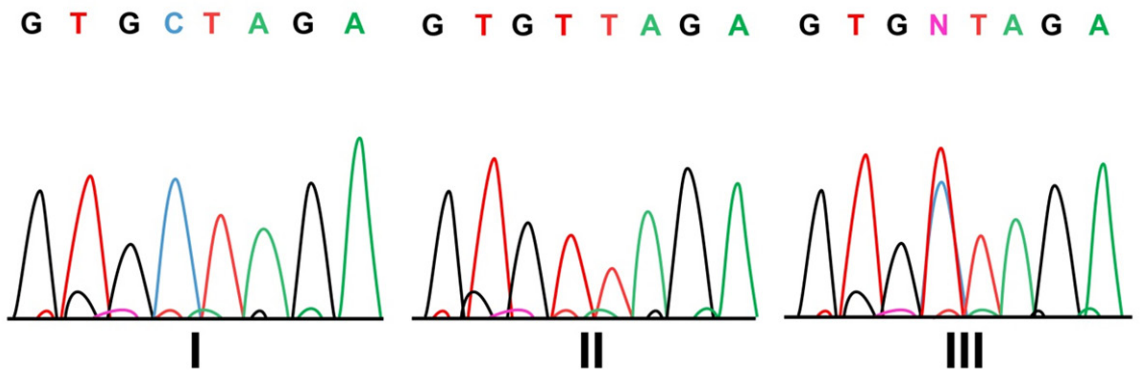

Figure 4. Sequencing diagram of *ABCB1* C3435T allele (I: CC homozygote; II: TT homozygote; III: CT heterozygote).

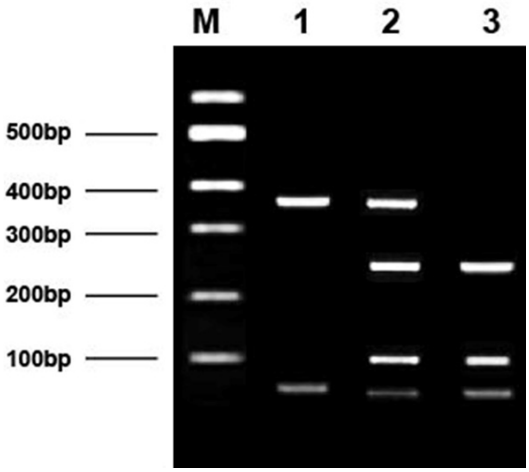

Figure 5. Electrophoretogram of PCR amplified product of *CYP2D6* (PCR: polymerase chain reaction; M: 100 bp DNA marker; 1: enzyme-digested products of CC homozygote; 2: enzyme-digested products of CT heterozygote; 3: enzyme-digested products of TT homozygote).

pressure (MAP), was monitored and recorded before anesthesia induction (T_0), before intubation (T_1), during intubation (T_2), during extubation (T_3), and after surgery (T_4). Moreover, induction time (from injection of drug to anesthesia state), maint-enance of anesthesia, recovery time, recovery degree, extubation time, postoperative nausea, bucking, bradycardia, tachycardia and other adverse reactions were also recorded.

Detection of gene polymorphism

Gene polymorphism was detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and 2% agarose gel electrophoresis. The reliability of these methods is verified by direct sequencing of PCR products. Peripheral blood was collected and ethylenediaminetetracetic acid (EDTA) was added. The Blood Genome DNA Extraction Kit (Takara Biotechnology [Dalian] co., LTD) was used to extract genomic DNA from peripheral blood. In the high salt state, the silicon membrane was adsorbed DNA, while the DNA was eluted in a low salt or aqueous solution state. DNA density was adjusted to 100 ng/μL, and then stored at -20°C in refrigerator. The Premier 5.0 was used to design primer which was synthesized by Shanghai Sangon Biotech Co., Ltd. (Shanghai, China). **Table 1** shows the primer sequences.

*Genotyping of OPRM1 All8G, ABCB1 C3435T and CYP2D6*10*

Base mutation of the A118G site resulted in the production of the recognition site of restriction enzyme Bsh I236 I in PCR amplified products. This 193 bp PCR amplified product can be digested into two fragments: 169 bp and 24 bp (**Figure 1**). The PCR amplified product of wild-type homozygote (AA) remains 193 bp. While, PCR amplified product of mutant homozygote (GG) was cut into 169 bp (the only one can be seen in electrophoretogram) and 24 bp (the 24 bp fragment is not seen in the agarose gel) by Bsh I236 I. As for heterozygote (AG), there were three fragments cut by Bsh I236 I, including 193 bp, 169 bp and 24 bp fragments (the 24 bp fragment is not seen in the agarose gel) (**Figure 2**).

PCR amplified product of *ABCB1* C3435T was 244 bp. The T allele of *ABCB1* C3435T failed to be recognized, while C allele was cut into two fragments (175 bp and 69 bp). So, TT genotype

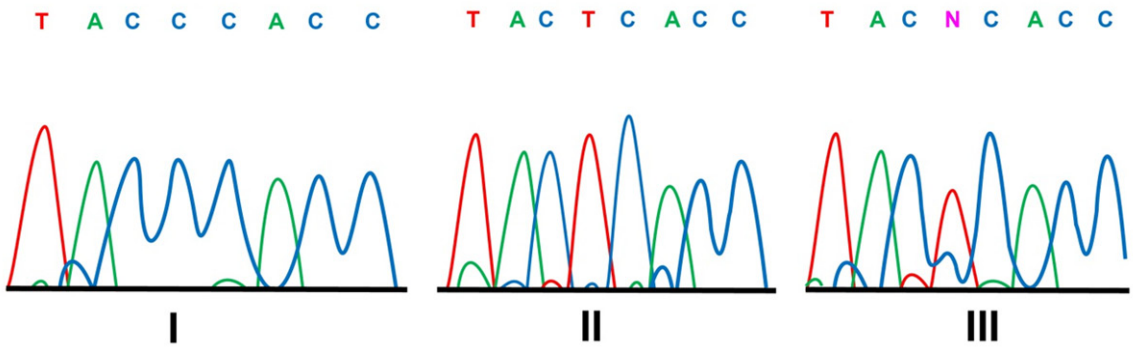

Figure 6. Sequencing diagram of *CYP2D6**10 allele (I: CC homozygote; II: TT homozygote; III: CT heterozygote).

Table 2. Baseline characteristics of patients with different genotypes of *OPRM1* All8G, *ABCB1*C3435T and *CYP2D6**10

Genotypes	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)	Operation time (min)	Dosage of sufentanil (ug)	Anesthesia time (min)
OPRM1 All8G							
AA	41.4 ± 5.8	59.8 ± 5.9	158.2 ± 5.8	23.6 ± 1.8	86.9 ± 22.8	879.8 ± 215.8	96.6 ± 24.9
AG	42.6 ± 4.6	60.5 ± 6.3	157.2 ± 4.4	24.2 ± 1.9	86.4 ± 22.1	911.7 ± 225.6	97.3 ± 25.5
GG	43.2 ± 6.2	59.9 ± 7.6	159.1 ± 4.9	23.7 ± 1.4	86.8 ± 17.8	887.6 ± 193.2	98.2 ± 23.6
ABCB1 C3435T							
CC	42.2 ± 5.8	61.0 ± 5.7	158.4 ± 5.8	23.6 ± 1.6	87.5 ± 21.7	879.4 ± 223.8	94.6 ± 24.9
CT	42.0 ± 5.8	59.8 ± 6.8	157.8 ± 5.0	24.0 ± 1.9	86.1 ± 22.7	906.8 ± 217.3	98.4 ± 24.8
TT	42.3 ± 4.3	59.3 ± 5.5	157.4 ± 4.2	24.1 ± 2.0	87.2 ± 18.6	876.3 ± 189.7	99.1 ± 25.1
*CYP2D6*10*							
CC	42.3 ± 5.1	59.5 ± 6.3	158.1 ± 5.2	24.0 ± 1.9	86.6 ± 23.5	892.1 ± 248.9	97.2 ± 19.7
CT	41.6 ± 5.4	60.6 ± 6.4	158.2 ± 5.4	23.7 ± 1.8	87.2 ± 23.0	894.7 ± 200.4	98.5 ± 25.5
TT	42.6 ± 5.8	59.7 ± 6.2	157.5 ± 5.0	24.0 ± 1.7	86.2 ± 19.5	890.7 ± 222.3	95.2 ± 26.4

BMI: body mass index; *OPRM1*: Opioid receptor mu 1; *ABCBI*: ATP-binding cassette B1; *CYP2D6*: CytochromeP450 2D6.

presented one fragment (244 bp), CC genotype showed two fragments (175 bp and 69 bp), and CT genotype had three fragments (244 bp, 175 bp and 69 bp) (**Figure 3**). BigDyeterminator v3.1 sequencing reagent was added into PCR amplified product (50 uL) of some samples, and then the samples were analyzed by ABI-PRISM3730 sequenator to further confirm the accuracy and reliability of results obtained by PCR-PFLP (**Figure 4**).

PCR amplified product of *CYP2D6**10 was digested by HphI, and the PCR products of all samples were specific fragments of length 433 bp. And, CC genotype had 2 fragments of 362 bp and 71 bp; TT genotype had 3 fragment of 262 bp, 100 bp and 71 bp; CT genotype had 4 fragments of 362 bp, 262 bp, 100 bp and 71 bp (**Figure 5**). DNA sequence analysis revealed that the polymorphic site of the individual of the CC genotype detected by PCR-RFLP was C, the polymorphic site of TT was T and the polymorphic site of CT had two basic groups of C and T (**Figure 6**).

Statistical analysis

Data analysis was conducted by SPSS 19.0 software (SPSS Inc, Chicago, IL, USA. Hardy-Weinberg's equilibrium was applied for examining the representative of enrolled patients [24]. Gene and allele frequencies were presented by ratio or percentage. χ^2 test was applied for testing whether the allele and genotype were in coincidence with Hardy-Weinberg's equilibrium. The age, weight, height, BMI, operation time, the dosage of sulfentanyl during operation, anesthesia time, induction time, maintenance of anesthesia, recovery time, recovery degree, and extubation time in different genotypes

Table 3. Genotypes and allele frequencies of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10

Sites		Cases	Frequency (%)	Hard-Weinberg test	
				χ^2	*P*
OPRM1 All8G	AA	91	48.7	2.821	0.093
	AG	70	37.4		
	GG	26	13.9		
	A	252	67.4		
	G	122	32.6		
ABCB1 C3435T	CC	70	37.4	1.000	0.317
	CT	94	50.3		
	TT	23	12.3		
	C	234	62.6		
	T	140	37.4		
*CYP2D6**10	CC	32	17.1	0.114	0.736
	CT	88	47.1		
	TT	67	35.8		
	C	152	40.6		
	T	222	59.4		

OPRM1: Opioid receptor mu 1; *ABCBI*: ATP-binding cassette B1; *CYP2D6*: Cytochrome P450 2D6.

were presented as mean ± standard deviation (SD), and the comparisons among them were conducted by One-Way analysis of variance (ANOVA); while, the comparisons between two groups were least significant difference (LSD). The paired *t*-test was applied for comparing breathing rate, SpO_2, HR, and MAP in same genotypes at different time points; the ANOVA was used for the comparison among them in different genotypes at the same time points, and the comparisons between two groups were LSD. Besides, comparison of adverse reaction rate between groups was measured by χ^2 test. *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 187 female patients (average age: 42.1 ± 5.5 years old; average weight: 60.1 ± 6.3 kg; average height: 158.0 ± 5.2 cm; average BMI: 23.8 ± 1.8 kg/m^2; average operation time: 86.7 ± 21.8 min; average dosage of sufentanil: 892.8 ± 216.0 μg; and average anesthesia time: 97.0 ± 24.9 min) received Pfannenstiel incision (length of incision: 8~10 cm). No significant difference was found on *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 in different genotypes of patients (all *P*>0.05) (**Table 2**).

*Genotype and allele frequency of OPRM1 All8G, ABCB1 C3435T and CYP2D6*10*

Genotyping was conducted according to electrophoretic pattern of enzyme-digested product. In *OPRM1* All8G, 91 cases (48.7%) were AA genotype, 70 cases (37.4%) were AG genotype and 26 (13.9%) were GG genotype. The A and G allele frequency of *OPRM1* All8G were 67.4% and 32.6%, respectively. In *ABCB1* C3435T, there were 70 CC genotypes (37.4%), 94 CT genotypes (50.3%) and 23 TT genotypes (12.3%). And the C and T allele frequency of *ABCB1* C3435T were 62.6% and 37.4%, separately. While, in *CYP2D6**10, 32 cases (17.1%) were CC genotype, 88 cases (47.1%) were CT genotype and 67 (35.8%) were TT genotype. The C and T allele frequency of *CYP2D6**10 were 40.6% and 59.4%, respectively. The genotypes and allele frequency were all in in coincidence with Hardy-Weinberg's equilibrium (all *P* >0.05), which affirmed the population representativeness (**Table 3**).

Effects of anaesthesia on respiratory and cardiovascular system

Average breathing rates of patients with AA, AG and GG genotypes in *OPRM1* All8G at T_0 were 17.9 ± 1.3 times/min, 18.1 ± 1.2 times/min and 17.4 ± 1.4 times/min, respectively. At T_1, the average breathing rates decreased to 10.5 ± 2.5 times/min, 10.3 ± 2.4 times/min and 8.2 ± 1.1 times/min, separately; while, average breathing rate at T_2 increased to 12.8 ± 2.3 times/min, 13.2 ± 2.8 times/min and 9.1 ± 1.6 times/min, respectively. Average breathing rate and SpO_2 in mutant homozygote of *OPRM1* All8G at T_1 and T_2 decreased, compared with those possessing wild-type homozygote and heterozygote, respectively (all *P*<0.05). No such significant difference was found in average breathing rate and SpO_2 of patients with mutant homozygote when compared with those with wild-type homozygote and heterozygote of *ABCB1* C3435T and *CYP2D6**10 (all *P*>0.05). The overall average breathing rate and SpO_2 showed a trend from decline to rise (**Table 4**).

Average HR of patients with CC, CT and TT genotypes in *CYP2D6**10 at T_0 were 82.3 ± 7.7

Table 4. Effects of sufentanil-propofol anesthesia on respiratory system

Indexes	Genotypes	T0	T1	T2	T3	T4
Breathing rate (times/min)	OPRM1 All8G					
	AA	17.9 ± 1.3	10.5 ± 2.5	12.8 ± 2.3	13.5 ± 2.6	15.1 ± 2.7
	AG	18.1 ± 1.2	10.3 ± 2.4	13.2 ± 2.8	13.6 ± 2.7	14.9 ± 2.4
	GG	17.4 ± 1.4	8.2 ± 1.1*	9.1 ± 1.6*	13.1 ± 2.9	14.6 ± 2.7
	ABCB1 C3435T					
	CC	18.0 ± 1.4	10.1 ± 2.4	12.4 ± 2.5	13.2 ± 2.6	14.8 ± 2.7
	CT	18.0 ± 1.2	10.1 ± 2.5	12.5 ± 2.9	13.6 ± 2.8	15.0 ± 2.5
	TT	17.5 ± 1.4	10.3 ± 2.2	12.5 ± 3.1	13.3 ± 2.9	15.1 ± 2.6
	CYP2D6*10					
	CC	17.9 ± 1.7	10.2 ± 2.0	12.5 ± 2.0	13.3 ± 2.8	15.2 ± 2.6
	CT	18.0 ± 1.1	10.1 ± 2.6	12.5 ± 2.9	13.5 ± 2.7	14.8 ± 2.6
	TT	17.8 ± 1.3	10.1 ± 2.4	12.3 ± 3.0	13.4 ± 2.8	15.1 ± 2.5
SpO_2 (%)	OPRM1 All8G					
	AA	96.2% ± 1.3%	94.2% ± 2.7%	96.2% ± 2.2%	95.9% ± 1.2%	96.3% ± 1.4%
	AG	95.5% ± 2.3%	93.8% ± 2.2%	96.5% ± 2.4%	96.0% ± 1.1%	96.2% ± 1.2%
	GG	95.9% ± 1.9%	87.6% ± 3.3%*	93.2% ± 3.6%*	96.1% ± 1.0%	96.4% ± 1.5%
	ABCB1 C3435T					
	CC	95.9% ± 1.4%	93.0% ± 3.6%	95.9% ± 2.3%	95.9% ± 1.1%	96.3% ± 1.4%
	CT	95.8% ± 2.0%	93.1% ± 3.5%	95.9% ± 2.9%	96.1% ± 1.2%	96.2% ± 1.3%
	TT	95.8% ± 2.3%	93.6% ± 2.6%	95.9% ± 3.0%	96.0% ± 1.0%	96.4% ± 1.3%
	CYP2D6*10					
	CC	95.8% ± 1.5%	93.3% ± 4.1%	95.9% ± 2.6%	96.0% ± 1.1%	96.3% ± 1.3%
	CT	96.0% ± 1.6%	93.1% ± 3.6%	96.0% ± 2.5%	96.0% ± 1.2%	96.2% ± 1.4%
	TT	95.7% ± 2.3%	93.0% ± 2.9%	95.8% ± 3.1%	96.0% ± 1.1%	96.4% ± 1.3%

SpO_2: oxygen saturation; *OPRM1*: Opioid receptor mu 1; *ABCBl*: ATP-binding cassette B1; *CYP2D6*:Cytochrome P450 2D6; *: significant difference was found in comparison between wild-type homozygote andmutant homozygote, mutant heterozygote (P<0.05); T_0: before anesthesia induction; T_1: before intubation; T_2: during intubation; T_3: during extubation; T_4: after surgery. P value was corrected by age, weight, height, BMI, operation time, the dosage of sulfentanyl during operation, and anesthesia time.

times/min, 81.8 ± 7.4 times/min and 80.9 ± 7.2 times/min, respectively. At T_1, the average HR decreased to 63.6 ± 6.5 times/min, 62.9 ± 6.7 times/min and 64.1 ± 7.1 times/min, separately; while, the average HR at T_2 increased to 69.7 ± 6.3 times/min, 70.2 ± 6.7 times/min and 69.5 ± 6.1 times/min, respectively. Significant difference was found in Average HR and MAP at T_1 and T_2 in patients with mutant homozygote when compared with patients with wild-type homozygote and heterozygote of *CYP2D6**10 (all P<0.05). No such significance was found in average HR and MAP of patients with mutant homozygote when compared with patients with wild-type homozygote and heterozygote of *ABCB1* C3435T and *OPRM1* All8G (all P>0.05) (**Table 5**).

Anaesthesia recovery

No significant difference was found in comparisons of induction time, maintenance of anesthesia, recovery time of patients with mutant homozygote when compared with patients with wild-type homozygote and heterozygote of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 (all P>0.05). Moreover, there was a rise of recovery degree and extubation time in patients with mutant homozygote when compared with those with wild-type homozygote and heterozygote of *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10, which suggest significant difference (both P<0.05) (**Table 6**).

Adverse reaction of anaesthesia

Nausea is the most common adverse reaction of sufentanil-propofol anesthesia, but the actual occurrence rate in our study was very low. Varying degrees of nausea occurred during surgery and recovery from sufentanil-propofol anesthesia in the patients with presence of the *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 polymorphisms, but no significant differences were observed in the patients with mutant homozygote when compared with those with

Table 5. Effects of sufentanil-propofol anesthesia on cardiovascular system

Indexes	Genotypes	T0	T1	T2	T3	T4
HR (times/min)	OPRM1 All8G					
	AA	82.3 ± 7.7	63.6 ± 6.5	69.7 ± 6.3	68.4 ± 6.7	79.1 ± 6.3
	AG	81.8 ± 7.4	62.9 ± 6.7	70.2 ± 6.7	69.1 ± 6.4	78.9 ± 6.6
	GG	80.9 ± 7.2	64.1 ± 7.1	69.5 ± 6.1	68.9 ± 6.2	78.6 ± 6.7
	ABCB1 C3435T					
	CC	81.9 ± 7.7	63.7 ± 6.3	70.0 ± 6.3	68.6 ± 7.3	79.1 ± 6.3
	CT	82.0 ± 7.6	63.2 ± 7.0	69.8 ± 6.5	68.8 ± 6.0	78.9 ± 6.6
	TT	81.4 ± 6.8	63.2 ± 6.5	69.7 ± 6.2	68.6 ± 6.6	79.0 ± 6.3
	CYP2D6*10					
	CC	81.8 ± 7.2	65.0 ± 5.6	71.5 ± 6.4	68.6 ± 7.2	78.9 ± 5.8
	CT	82.2 ± 8.2	65.2 ± 6.1	71.3 ± 6.1	68.7 ± 7.2	79.0 ± 6.7
	TT	81.6 ± 6.7	60.2 ± 6.8*	67.1 ± 5.9*	68.8 ± 5.4	78.9 ± 6.4
MAP(mmHg)	OPRM1 All8G					
	AA	85.7 ± 7.4	80.6 ± 7.1	79.9 ± 7.1	80.4 ± 7.2	83.3 ± 6.8
	AG	86.1 ± 7.1	80.3 ± 7.4	79.2 ± 7.3	80.2 ± 6.6	83.5 ± 7.2
	GG	86.3 ± 7.3	80.1 ± 7.6	79.5 ± 6.9	80.6 ± 6.8	83.1 ± 6.9
	ABCB1 C3435T					
	CC	85.7 ± 7.7	80.4 ± 7.0	79.7 ± 7.0	80.4 ± 7.0	83.2 ± 6.6
	CT	86.1 ± 6.9	80.4 ± 7.3	79.4 ± 7.3	80.2 ± 6.9	83.4 ± 7.2
	TT	85.8 ± 7.8	80.4 ± 7.9	79.5 ± 6.6	80.5 ± 6.4	83.5 ± 7.0
	CYP2D6*10					
	CC	86.1 ± 7.0	82.3 ± 6.1	81.0 ± 6.5	80.2 ± 6.3	83.3 ± 6.0
	CT	85.9 ± 7.9	82.2 ± 5.5	80.8 ± 6.6	80.4 ± 7.3	83.2 ± 7.4
	TT	86.0 ± 6.7	77.2 ± 8.6*	77.0 ± 7.4*	80.3 ± 6.6	83.5 ± 6.8

HR: heart rate; MAP: mean arterial pressure; *OPRM1*: Opioid receptor mu 1; *ABCBI*: ATP-bindingcassette B1; *CYP2D6*: Cytochrome P450 2D6; *: significant difference was found in comparison betweenwild-type homozygote and mutant homozygote, mutant heterozygote ($P<0.05$); T_0: before anesthesiainduction; T_1: before intubatton; T_2: during intubatton; T_3: during extubation; T_4: after surgery. *P* value wascorrected by age, weight, height, BMI, operation time, the dosage of sulfentanyl during operation, andanesthesia time.

wild-type homozygote and heterozygote (all $P>0.05$). Secondly, bucking is another common adverse reaction, but no obvious bucking was found in our study. During anesthesia, 3%~13% bradycardia and 4%~13% tachycardia both occurred in patients with *OPRM1* All8G, *ABCB1* C3435T, however, no obvious difference was found in comparison among patients with different genotypes (all $P>0.05$). Besides, 12.5% bradycardia occurred in patients with CC of *CYP2D6**10, which had significant difference when compared with those with TT and CT (both $P<0.05$) (**Table 7**).

Discussion

This study revealed that *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 gene polymorphisms play important roles in anesthetic efficacy of sufentanil-propofol in patients undergoing gynecologic laparoscopic surgery.

Human gene polymorphism plays an important role in elucidating the susceptibility and survivability to diseases and drugs in human body, the diversity of clinical manifestations, and the response to medication [25]. Also, gene polymorphism can affect pharmacokinetic of anaesthesia due to changes of corresponding drug metabolic enzyme and drug transport protein absorption, distribution, transport, and metabolism of drugs [26].

Opioid drugs can inhibit the transmission of pain in the central nervous system, improve the pain threshold, and enhance the analgesic effect [27]. The *OPRM1* are considered the main effectors of analgesic effects that are acted upon by opioid drugs [28]. *OPRM1* gene is the main candidate gene affecting efficiency of opioid drugs, with more than 100 mutant sites among which A118G was the most common one [29]. Mutation of A118G is featured

Table 6. Recovery condition of anaesthesia in *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10

Genotypes	Induction time (s)	Maintenance of anesthesia (min)	Recovery time (min)	Score of recovery degree (points)	Extubation time (min)
OPRM1 All8G					
AA	31.2 ± 2.6	60.5 ± 8.5	10.4 ± 1.5	2.5 ± 1.2	11.0 ± 1.5
AG	32.0 ± 3.1	59.8 ± 6.7	11.0 ± 1.8	3.1 ± 1.6	10.7 ± 1.3
GG	30.9 ± 2.7	60.1 ± 7.7	10.5 ± 2.0	3.6 ± 1.2*	11.6 ± 1.2*
F	2.197	0.173	2.592	7.124	4.017
P	0.114	0.841	0.078	0.001	0.02
ABCB1 C3435T					
CC	31.3 ± 2.7	61.1 ± 8.6	10.4 ± 1.7	2.5 ± 1.3	10.9 ± 1.4
CT	31.5 ± 2.9	59.6 ± 7.0	10.9 ± 1.7	3.1 ± 1.6	10.8 ± 1.5
TT	31.4 ± 3.0	59.4 ± 7.8	10.6 ± 2.0	3.3 ± 1.2*	11.7 ± 1.1*
F	0.1	0.874	1.678	4.438	5.69
P	0.905	0.419	0.19	0.013	0.004
*CYP2D6**10					
CC	30.6 ± 2.8	60.2 ± 7.8	10.6 ± 1.6	2.6 ± 1.3	11.8 ± 1.2
CT	31.7 ± 2.8	59.6 ± 8.0	10.7 ± 1.6	2.8 ± 1.4	10.3 ± 1.6
TT	31.5 ± 2.9	60.8 ± 7.4	10.7 ± 2.1	3.2 ± 1.5*	15.7 ± 1.8*
F	1.788	0.457	0.041	18.72	3.364
P	0.17	0.634	0.96	<0.001	0.037

*: significant difference was found in comparison between wild-type homozygote and mutant homozygote, mutant heterozygote ($P<0.05$); *OPRM1*: Opioid receptor mu 1; *ABCBI*: ATP-binding cassette B1; *CYP2D6*: Cytochrome P450 2D6. *P* value was corrected by age, weight, height, BMI, operation time, the dosage of sulfentanyl during operation, and anesthesia time.

by the replacement at position 40 of the μ-opioid receptor from asparagine to aspartate (Asn40Asp) and can reduce the effectiveness of various opioid drugs [30, 31]. Patients carrying 118G allele may need increased administration of opioid drugs and decreased side effects, like nausea, vomiting and respiratory depression, which is linked to our results [32]. In our study, the mutation of *OPRM1* All8G was proved to have some effects on respiratory system of female patients receiving gynecologic laparoscopic surgery under sufentanil-propofol.

P-gp is a kind of glycoprotein which is expressed by multidrug resistance 1 (*ABCB1/MDR1* gene), with the function of efflux pump [33]. CC genotype of *ABCB1* may lead to increased activity of P-gp, whereas individuals with TT genotype have reduced P-gp activity and higher frequency of fentanyl induced central nervous system side effects [34]. Park et al. also revealed that clinical unwanted effects of fentanyl on respiration were related to *ABCB1* gene polymorphism [35]. In our study, with the investigation of sulfentanyl (derivative of fentanyl), we also revealed the association between *ABCB1* C3435T polymorphism and patients receiving gynecologic laparoscopic surgery under sufentanil-propofol. Consistent with our study, *Mukonzo* et al. observed correlation between efavirenz relative bioavailability and *ABCB1* 3435 C>T polymorphism, a chance for us to explore genotype of 3435 C>T carriers for predicting the drug response [36].

Some metabolic enzymes in CYP P450 family participate in the biotransformation of endogenous compounds to exogenous compounds. CYP2D6 is involved in the metabolism of opioid drugs [37, 38]. Gene polymorphism may influence the blood concentration of drug and its metabolites *in vivo* by altering the activity of metabolic enzymes and the recognition capability of specificity of substrate, which makes the change of absorption, distribution, elimination and toxicity of drugs *in vivo*, especially metabolism [39]. Allele combination result in *CYP2D6* phenotype including the ultra-rapid metabolizer (UM), the extensive metabolizer (EM), the intermediate metabolizer (IM) and the poor metabolizer (PM) [40]. People with PM phenotype for a particular enzyme would have higher circulating plasma concentrations after

Table 7. Adverse reaction of patients receiving sufentanil-propofol anesthesia

Genotypes	Cases (n)	Cases of nausea (%)	Cases of bucking (%)	Cases of bradycardia (%)	Cases of tachycardia (%)
OPRM1 All8G					
AA	91	30 (33.0)	1 (1.1)	5 (5.5)	6 (6.6)
AG	70	24 (34.3)	0 (0)	3 (4.3)	3 (4.3)
GG	26	9 (34.6)	0 (0)	1 (3.8)	1 (4.0)
χ2		0.021	1.047	0.171	0.45
P		0.99	0.592	0.918	0.781
ABCB1 C3435T					
CC	70	25 (35.7)	0 (0)	3 (4.3)	4 (5.7)
CT	94	30 (31.9)	1 (1.1)	5 (5.3)	6 (6.4)
TT	23	8 (34.8)	0 (0)	1 (4.5)	0 (0)
χ2		0.135	0.984	0.096	1.424
P		0.934	0.611	0.953	0.491
*CYP2D6**10					
CC	32	9 (28.1)	0 (0)	4 (12.5)	4 (12.5)
CT	88	22 (25.0)	1 (1.1)	5 (5.7)	4 (4.5)
TT	67	22 (32.8)	0 (1.5)	0 (0)*	2 (3.0)
χ2		0.637	0.456	6.848	1.729
P		0.727	0.796	0.033	0.421

*: significant difference was found in comparison between wild-type homozygote and mutant homozygote, mutant heterozygote ($P<0.05$); *OPRM1*: Opioid receptor mu 1; *ABCBI*: ATP-binding cassette B1; *CYP2D6*: Cytochrome P450 2D6. *P* value was corrected by age, weight, height, BMI, operation time, the dosage of sulfentanyl during operation, and anesthesia time.

administration of standard doses of drugs that are substrates for that enzyme [41]. *CYP2D6**10 belongs to PM phenotype and presents less production of drugs for relieving pain, and increasing of dosage may lead to increased side effects [40]. Also, patients carrying wild-type homozygote of *CYP2D6**10 need more dosage of Tramadol for analgesia compared with mutant homozygote and heterozygote carriers [42]. As seen in our results, wild-type homozygote in those three gene polymorphisms was all better than mutant homozygote and heterozygote under sufentanil-propofol.

Conclusion

Globally from our present study, it is apparent that *OPRM1* All8G, *ABCB1* C3435T and *CYP2D6**10 gene polymorphisms have negative effects on anesthetic efficacy of sufentanil-propofol in patients receiving gynecologic laparoscopic surgery, which can provide guide for personal treatment and anaesthesia of gynecologic laparoscopic surgery and improve adaptability of patients. However, further studies with the applications of genotyping and enzyme assay of receptor and metabolic enzyme should be conducted to strengthen the validity of our conclusion.

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