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Correlation between gene polymorphism and opioid efficacy in patients with gastric or intestinal cancer

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Abstract. – OBJECTIVE: To explore the correlation between gene polymorphism and opioid efficacy in patients with gastric or intestinal cancer.

PATIENTS AND METHODS: Fifty-nine patients who underwent laparoscopic surgery for gastric or intestinal cancer under general anesthesia were included and randomly divided into oxycodone (n=30) and sufentanil groups (n=29) by reproducible random number generation method. Single nucleotide polymorphisms (SNPs) of four alleles: μ-opioid receptor gene OPRM1 A118G, cytochrome P450 (CPY450) enzyme system: CPY3A4*1G, CYP3A5*3, and CYP2D6*10 were detected by PCR-pyrosequencing. Patients in sufentanil group received intravenous sufentanil injection during anesthesia induction, intraoperative maintenance, and postoperative analgesia, while those in oxycodone group received oxycodone. Patients' postoperative VAS score, opioid use, and prevalence of adverse reactions were recorded.

RESULTS: The genotype distribution of OPRM1 A118G, CYP3A4*1G, CYP3A5*3, and CYP2D6*10 in Chinese gastric cancer/intestinal cancer patients accorded with the Hardy-Weinberg law ($p>0.05$). OPRM1 A118G polymorphism correlated with postoperative VAS score and medication dosage, in oxycodone group ($p<0.05$), while it didn't with those of sufentanil group. The VAS scores in GG group were higher than that in AA group and AG group at T6-T9, ($p<0.05$); the postoperative pain remedies times in GG group were more than that in the AA and AG groups ($p=0.002$). CYP3A4*1G polymorphism related to postoperative VAS score, medication dosage and prevalence of adverse reactions in sufentanil group ($p<0.05$), while it didn't with those of oxycodone group ($p>0.05$). The total intraoperative medication in AA group was less than that in GG and GA groups ($p<0.01$), with a higher prevalence of respiratory depression ($p=0.01$). Nor was there any correlation of CYP3A5*3 and CYP2D6*10 polymorphisms with the efficacy, postoperative VAS score, pain remedies times, postoperative 24 h medication dosage, or prevalence of adverse reactions in oxycodone and sufentanil groups.

CONCLUSIONS: Gene polymorphism affects the efficacy and adverse reactions of opioids in patients undergoing laparoscopic gastric or intestinal cancer surgery.

Key Words:
Sufentanil, Oxycodone, Perioperative analgesia, Gene polymorphism, OPRM1, CYP450.

Introduction

Gastric cancer and intestinal cancer are common tumors of the digestive system, and surgery remains the key treatment method. However, radical resection of abdominal tumor has drawbacks such as large surgical trauma and severe perioperative pain, and the latter will have a certain impact on the curative effect of patients[1]. This is worsened by the fact that the conventional μ-opioid receptor agonists exert a poor effect on controlling visceral pain and are thus less satisfied by patients. Therefore, visceral pain has become an obstinate obstacle in perioperative pain treatment for patients undergoing abdominal surgery such as gastric cancer/intestinal cancer[2]. At present, opioids remain the essential drugs for the treatment and control of perioperative pain in patients with gastric or intestinal cancer surgery. Among them, sufentanil, a μ-opioid receptor agonist, has a strong analgesic effect and a short half-life[3]. However, due to its dose-related adverse reactions, it affects the efficacy of the drug in abdominal surgery[4]. Oxycodone is a new generation of μ- and κ-opioid receptor agonist, whose κ-receptor agonist effect can effectively relieve visceral pain[5]. It is valuable to find the more suitable drug in the two drugs for perioperative pain management in gastrointestinal surgery.

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Cytochrome P450 (CYP450) is a kind of catalytic enzyme that plays a vital part in cell biochemical reactions. The genes related to opioid metabolism that have been studied more in CYP450 enzyme series are CYP2D6, CPY3A4, and CPY3A5[6]. Among them, the formation of methyloxycodone (74%) catalyzed by CYP3A4/5 enzyme is the primary metabolic pathway of oxycodone, second by the formation of oxymorone (2.9%) catalyzed by CYP2D6 enzyme and finally noroxymorphone is produced by the interaction of CYP3A4 and CYP2D6 enzymes[7]. While the main metabolic pathway of sufentanil is CYP3A4/5, which is responsible for its N-dealkylation and O-demethylation and is then metabolized by the liver, whose metabolic pathway shares the similarity with that of fentanil and alfentanil[8]. OPRM1, a genetic locus encoded by the μ-opioid receptor (OPRM1), is the main locus where endogenous opioid peptides and opioids play a role, so OPRM1 is the principal candidate gene for evaluating the efficacy of opioids. Among these genes, CYP3A4*1G, CYP3A5*3, and CYP2D6*10 and OPRM1 A118G are alleles with the highest mutation frequency in Chinese Han population[9]. Therefore, it is speculated that the OPRM1 A118G, CYP3A4*1G, CYP3A5*3, and CYP2D6*10 alleles produce market effect on the pharmacokinetics and pharmacodynamics of sufentanil and oxycodone, and their gene polymorphisms may affect the efficacy of sufentanil and oxycodone.

Today, clinical research on sufentanil and oxycodone mainly focuses on the comparison of visceral analgesia and postoperative analgesia, while little has done on the perioperative use of sufentanil and oxycodone from the perspective of gene polymorphism in gastric and intestinal cancer patients. Therefore, this study sets out to detect the genotypes of four alleles of OPRM1 A118G, CYP3A4*1G, CYP3A5*3, and CYP2D6*10 in Chinese Han patients with gastric or intestinal cancer, and to explain individual differences in drug efficacy and adverse reactions of oxycodone and sufentanil from the perspective of genetics, so as to guide the treatment of opioids with gene variation and provide reference for clinical individualized medication.

Patients and Methods

General Information

From April 2016 to October 2016, 59 patients aged between 18-65, with ASA grade of I-III and BMI of 18-25, who underwent laparoscopic surgery for gastric or intestinal cancer under general anesthesia in the general surgery department of our hospital were enrolled. Postoperative patient control analgesia (PCA) was performed on all patients. The study subjects were randomized into oxycodone group and sufentanil group using a reproducible random number generation method, with 30 in oxycodone group and 29 in sufentanil group. Patients' grouping numbers were all kept secret in sealed envelopes until the anesthesia induction conducted by anesthesiologists, who were in charge of anesthetic drugs. Data collection before, during and after surgery, as well as the scoring of various indicators, was under the charge of an experimental researcher. The double-blind study method was employed in this investigation, i.e., the study researcher did not know the grouping of patients or the anesthesia scheme, nor did the patients themselves know their grouping and medication, and the data collection and scoring of all patients in this study were conducted by the same study researcher. After the experiment, the data were collated and processed by a full-time statistician.

Written informed consent of the study and anesthesia were obtained from all patients before surgery. Exclusion criteria: patients allergic to opioids or other components of opioid preparations; patients with upper respiratory tract infection within 2 weeks, who had used hormones and bronchodilators 2 weeks before surgery; patients with serious heart, brain, liver, kidney, and other system diseases; patients in pregnancy; patients underwent a tracheostomy; patients with face, neck or chest wall deformities; patients with a preoperative determination of a history of mental and neurological diseases before surgery; patients with a long history of smoking and drinking; patients with a chronic pain or a long history of antipsychotic or opioid use; patients who had taken CYP450 inhibitor or activator within 1 month before surgery; patients unwilling or unable to provide informed consent. This investigation has been registered in the Chinese Clinical Trial Registry (Registration No.: ChiCTR-PR-16007775) and approved by the Medical Ethics Committee of Shanghai Changzheng Hospital [Approval No.: CZEC (2015) -32].

Experimental Materials and Reagents

MAGEN Blood DNA Extraction Kit (Guangzhou Magen Biology Co., Ltd., Guangzhou, China); TaKaRa PCR Kit (TaKaRa Bio Company, Mountain View, CA, USA); QIAGEN Sequencing

Reaction Kit (QIAGEN Company, Hilden, Germany); PCR and pyrosequencing supporting reagents (Changsha 3G Biotechnology Co., Ltd., Changsha, China); PyroMark Q24 Pyrophosphate Detection Sequencing Instrument (QIAGEN, Hilden, Germany); LifePro PCR Gene Amplifier (Hangzhou Bioer Technology Co., Ltd., Hangzhou, China); Oxycodone Hydrochloride Injection (Batch No.: BN868, Specification: 10 mg, Mundipharma Pharmaceutical Co., Ltd., Beijing, China); Sufentanil Citrate (Batch No.: 1161005, Specification: 50 μg, Yichang Humanwell Pharmaceutical Co. Ltd., Yichang, China); Midazolam (Batch No.: 20160504, Specification: 5 mg, Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China); 1% Lipofen (Batch No.: 116227033, Specification: 20 mg, B. Braun Medical Co., Ltd., Melsungen, Hessen, Germany); Cisatracurium besilatet (Batch No.:160605, Specification: 5 mg, Zhejiang Xianchen Pharmaceutical Co., Ltd., Taizhou, China); 2% Propofol (Batch No.: 1610089, Specification: 200 mg, Fresenius Kabi SSPC Pharmaceutical Co., Ltd., Beijing, China); Dolasetron (Batch No.: 20160602, Specifications: 12.5 mg, Liaoning Haisi Technology Co., Ltd., Anshan, China); Sevoflurane (Batch No.: 16110331, Specifications: 150 ml, Shanghai Hengrui Pharmacutical Co., Ltd., Shanghai, China); Sodium Lactate Ringer Injection (Batch No.: 160802, Specifications: 500 ml, Shanghai Changzheng Hospital, Shanghai, China).

Anesthesia Method

All patients were not premedicated before entering the operating room. While upon admission, noninvasive blood pressure, electrocardiogram, and pulse oxygen saturation were monitored. Then, a liquid pathway was established to monitor the invasive arterial blood pressure by radial artery puncture and catheterization under local anesthesia. Anesthesia induction: intravenous injection of midazolam (0.05 mg/kg), propofol (1-2 mg/kg), cisatracurium besilate (0.2 mg/kg). Oxycodone group was injected with oxycodone (0.3 mg/kg), while sufentanil group with sufentanil (0.3 μg/kg) along with the anesthesia induction. Three min later, when muscle relaxation was complete and bispectral index (BIS) was below 60, mechanical controlled ventilation with tracheal intubation was performed. The tidal volume was set at 6-8 mL/kg and the respiratory frequency at 10-14 times/min, and the end-expiratory carbon dioxide partial pressure was kept at 35-45 mmHg. Combined intravenous and inhalation anesthesia was applied during the surgery, target-controlled infusion (TCI) of 2% propofol was used to maintain the plasma concentration between 1.5-2.5 mg/mL, and the concentration of sevoflurane between 1-1.5%. BIS was kept between 40-60 by adjusting the concentration of propofol and sevoflurane, while cisatracurium besylate was intermittently intravenously injected at 0.1 mg/kg/h to hold essential muscle relaxation. Opioids were added if the blood pressure or heart rate exceeded 20% of the baseline value, patients in sufentanil group were supplemented with sufentanil at 0.1 μg/kg, and patients in oxycodone group were treated with oxycodone at 0.1 mg/kg. Thirty minutes before the end of the operation, both groups received an intravenous injection, with 0.1 mg/kg of oxycodone and 0.1 μg/kg of sufentanil in oxycodone group and sufentanil group, respectively. Meanwhile, the two groups were given 40 mg of parecoxib sodium for prophylactic analgesia. Five min before the end of the operation, all anesthetic drugs were stopped, PCA analgesic pump was connected, and dolasetron was given 12.5 mg to prevent nausea and vomiting. After the operation, when the patient was awake and the swallowing reflex and spontaneous breathing were fully recovered, the tracheal tube was removed by sputum suction and sent to post-anesthesia care unit (PACU) for observation. Treatment of special intraoperative conditions: in case of intraoperative hypotension (SBP<85 mmHg), the infusion of succinimide gelatin injection should be first accelerated to expand the volume, and the depth of anesthesia should be reduced appropriately; if ineffective, ephedrine injection 5-10 mg should be given intravenously to raise the blood pressure. If bradycardia (HR<50 beats/min) occurred, 0.2-0.5 mg atropine was given to increase heart rate. If the blood pressure was still higher than 20% of the baseline blood pressure or continues to rise after deepening anesthesia, 0.2 mg Peldipine (nicardipine) was rendered to control blood pressure.

Postoperative Analgesia

During the observation in the PACU, patients' pain degree was evaluated and pain remedies were conducted for those with VAS >4 points: patients in oxycodone group received intravenous injection of 0.1 mg/kg of oxycodone, while those in sufentanil group were treated with intravenous injection of 0.1 μg/kg of sufentanil, and the administration methods were titrated with small doses, i.e., half of the dose was given first, followed by

a 5-min observation to clear the symptoms of excessive sedation and respiratory depression. Then, the remaining dose was given until VAS <4 points. The patients were observed in PACU for 2 h, and were sent back to the ward when they were fully awake, quiet and cooperative with VAS <4 points.

PCA was applied to all patients. The volume of analgesia pump (Sujia, Zhejiang) was 100 ml. The administration mode was continuous administration + patient-controlled administration (CBI+PCA), flow rate: 2 ml/h, dosage of self-controlled solution: 0.5 ml/time, interval time: 15 min. The formula of the analgesic pump in sufentanil group was 1.6 μg/kg sufentanil diluted into 100 ml normal saline, and that of oxycodone group was 0.8 mg/kg oxycodone diluted into 100 ml normal saline. Besides, 12.5 mg dolasetron was added to the PCA formula of both groups to prevent nausea and vomiting.

During the postoperative observation, if patients presented excessive sedation (Ramsay >4 points), 5 mg flumazenil was given for antagonism. If uncontrollable dysphoria found with RS score >2 points, the patient was sedated with propofol and dexmedetomidine. In case of opioid overdose after surgery, including severe nausea and vomiting (vomiting more than 6 times), severe respiratory depression (oxygen SPO2 <90% or apnea more than 12S) or by excessive sedation (Ramsay> 4 points), 30 mg nalmefene was administered to antagonize, the analgesic pump was temporarily stopped, and the patient who was antagonized with nalmefene was excluded from the test.

Genotype Detection

Before the operation, 2 ml of venous blood was extracted from peripheral veins, placed in ethylenediaminetetraacetic acid-2K (EDTA-2K) anticoagulant tubes, marked with patient information, and then sent to the clinical drug testing center of our hospital for detection. PCR-pyrophosphate sequencing was employed to detect the Single nucleotide polymorphisms (SNPs) of OPRM1 A11G, CPY3A4*1G, CYP3A5*3, and CYP2D6*10 alleles. In addition, the collected whole blood samples were extracted with the whole blood DNA extraction kit produced by MAGEN company, and the obtained nucleic acid was stored at –20°C. PyroMark Assay Design 2.0 was adopted to design reference primers using the complete gene sequence of the national center for biotechnology information (NCBI) as the template. PCR specific primers were designed independently in the conservative section, and one of the primers was purified by biotin labeling and HPLC at the 5' end. Specific primer designs for four genes are shown in Table I. The extracted nucleic acid was used as a template for PCR reaction. PCR reaction system: 5 μl of 10×PCR Buffer, 3 μl of dNTPs, 1 μl of forward primer, 1 μl of reverse primer, 0.5 μl of Taq DNA polymerase, 2 μl of DNA template, and sterile water were added to increase the reaction volume to 50. The PCR reaction conditions were pre-denaturation at 95°C for 5 min, and then amplification for 35 cycles: denaturation at 95°C for 30s, annealing at 60°C for 30 s, extension at 72°C for 30 s, and finally extension at 72°C for 7 min, and storage at

Table I. Primer design of different genes.

Genotype	Primer name	Primer sequence	Biotin labeling	Fragment size (bp)
CYP2D6*10	CYP2D6-F-188-3 CYP2D6-R-188-3 CYP2D6-S-188-3	GCCGTGATAGTGGCCATCTT TCGAAGCAGTATGGTGTGTTCT GGCAGGGGGCCTGGT	Biotin	263 bp
CYP3A4*1G	CYP3A4*1G-F CYP3A4*1G-R CYP3A4*1G-S	CGAGCAGTGTTCTCTCCTTCATTA GGCATTTTTGCTAAGGTTTCAC CCCTCCTTCTCCATGTA	Biotin	215 bp
CYP3A5*3	CYP3A5*3-F CYP3A5*3-R CYP3A5*3-S	ACCCAGCTTAACGAATGCTCTA CAGGAAGCCAGACTTTGATCATTA CCAAACAGGGAAGAGATA	Biotin	243 bp
OPRM1 A118G	OPRM1-F OPRM1-R OPRM1-S	GCACTGATGCCTTGGCGTAC GTCTCTCCCGCCCAGGTC CAACTTGTCCCACTTAGAT	Biotin	191 bp

Table II. Pyrosequencing of different genes.

Gene	Mode	Sequence to analyze	Sequencing direction
CYP3A4 *1G	AQ	C/TCATCCACTCACCTTATTGGG	Reverse
CYP3A5*3	AQ	C/TTGAAAGACAAAAGAGCTCTTTAAAG	Reverse
CYP2D6 *10	AQ	GA/GGTAGCGTGCAGCCCAGCGTTGGCGC	Reverse
OPRM1 A118G	AQ	GGCA/GACCTGTCCGACCCATGCGGTCCGAA	Forward

12°C. Pyrosequencing analysis of CYP2D6*10, CPY3A4*1G, CYP3A5*3, and OPRM1 A118G genes were performed using the corresponding sequencing primer and sequence program (AQ mode; Table II).

Sequencing Data Analysis

PyroMark Q24 pyrosequencing instrument matching analysis software was applied for AQ analysis of all sequencing results. PyroMark Q24 software further evaluated the detected peak map and gave the base alignment of the detected sequence ends to determine the genotype of the tested gene.

Statistical Analysis

Data analysis was performed using SPSS 20.0 statistical software (IBM, Armonk, NY, USA), and the measurement data was expressed as mean ± standard deviation (X±S). One-way ANOVA was employed and LSD-*t*-test is adopted for pairwise comparison in the case that the measurement data of these three groups were subject to normal distribution and homogeneity of variance. Otherwise, the Kruskal-Wallis H and Nemenyi tests were employed, with the latter for pairwise comparison. Variance analysis of repeated measurements was applied for comparison among different groups and at different time points. When it came to two-factor and two-level data analysis, the variance analysis of factorial design data was utilized. The counting data were expressed by rate or composition ratio. Chi-square test or Fisher's exact probability method was used to detect whether the distribution of alleles and genotypes was consistent with the Hardy-Weinberg law. $p<0.05$ indicated that the difference was statistically significant.

Results

General Information

The preoperative general information did not differ significantly between oxycodone group and sufentanil group ($p>0.05$; Table III).

Table III. Comparison of general information between the two groups.

Variables	Oxycodone group	Sufentanil group	$Z/\chi^2/t$	*p*
Gender (male/female)			0.425	0.515
Male	22 (73.33)	19 (65.52)		
Female	8 (26.67)	10 (26.67)		
Type of surgery (stomach/intestine)		0.136	0.712	
Stomach	20 (66.67)	18 (62.07)		
Intestine	10 (33.33)	11 (37.93)		
Smoking (yes/no)		0.167	0.683	
Yes	14 (46.67)	12 (41.38)		
No	16 (53.33)	17 (58.62)		
ASA grade (I/II/III)			-0.672	0.502
I	7 (23.33)	5 (17.24)		
II	20 (66.67)	20 (68.97)		
III	3 (10.00)	4 (13.79)		
Age (year)	57.13±7.10	55.93±7.21	0.645	0.521
Height (cm)	167.97±8.03	165.34±6.64	1.364	0.178
Weight (kg)	61.33±9.68	59.52±8.46	0.766	0.447
BMI	21.67±2.53	21.71±2.33	-0.071	0.943
Duration of surgery (min)	154.53±27.30	160.00±24.46	-0.809	0.422
Anxiety score	42.67±10.68	41.79±8.83	0.342	0.734

Allele Frequency in Patients With Gastric or Intestinal Cancer

OPRM1 A118G allele

According to the results of pyrosequencing, OPRM1 A118G gene was classified into AA, AG, and GG genotypes, and the OPRM1 A118G mutation allele frequency was 35.6%. Chi-square test demonstrated that the distribution of genotypes in groups AA, AG, and GG conformed to the Hardy-Weinberg law (p=0.522), indicating that the distribution of genotypes in this population had reached the genetic equilibrium and had group representation (Figure 1, Table IV).

*CYP3A4*1G allele*

Genotyping was conducted according to pyrosequencing results, and CYP3A4*1G genes were classified into GG, GA, and AA genotypes. The mutation allele frequency of CYP3A4*1G was 23.7%. Chi-square test revealed that the distribution of GG, GA and AA genotypes was in line with Hardy-Weinberg's law (p=0.993), suggesting that the distribution of CYP3A4*1G genes in this population had reached genetic equilibrium and had group representation (Figure 2, Table V).

*CYP3A5*3 allele*

According to the results of pyrosequencing, the CYP3A5*3 genotype was classified into AA, AG, and GG genotypes, and the CYP3A5*3 mutant allele frequency was 72.9%. The distribution of genotypes in groups AA, AG, and GG detected by Chi-square test accorded with the Hardy-Weinberg law (p=0.846), indicating that the distribution of CYP3A5*3 genes in this population had reached genetic equilibrium and had group representation (Figure 3, Table VI).

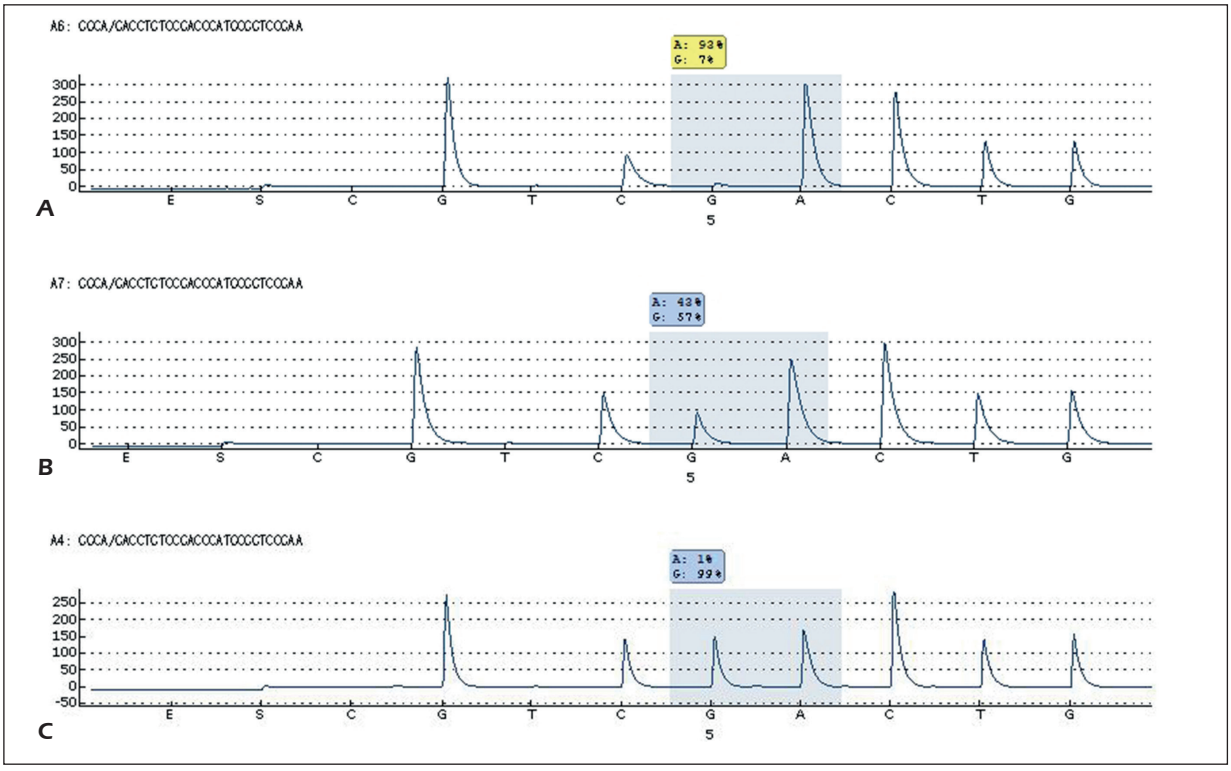

Figure 1. OPRM1 A118G gene sequencing. **A**, AA wild type. **B**, AG mutant heterozygote. **C**, GG mutant homozygote.

Table IV. OPRM1 A118G genotype and allele frequency.

	A118G genotype				A118G allele		
	AA	AG	GG	Total	A	G	Total
No. of cases	22	32	5	59	38	21	59
Frequency (%)	37.3	54.2	8.5	100	64.4	35.6	100

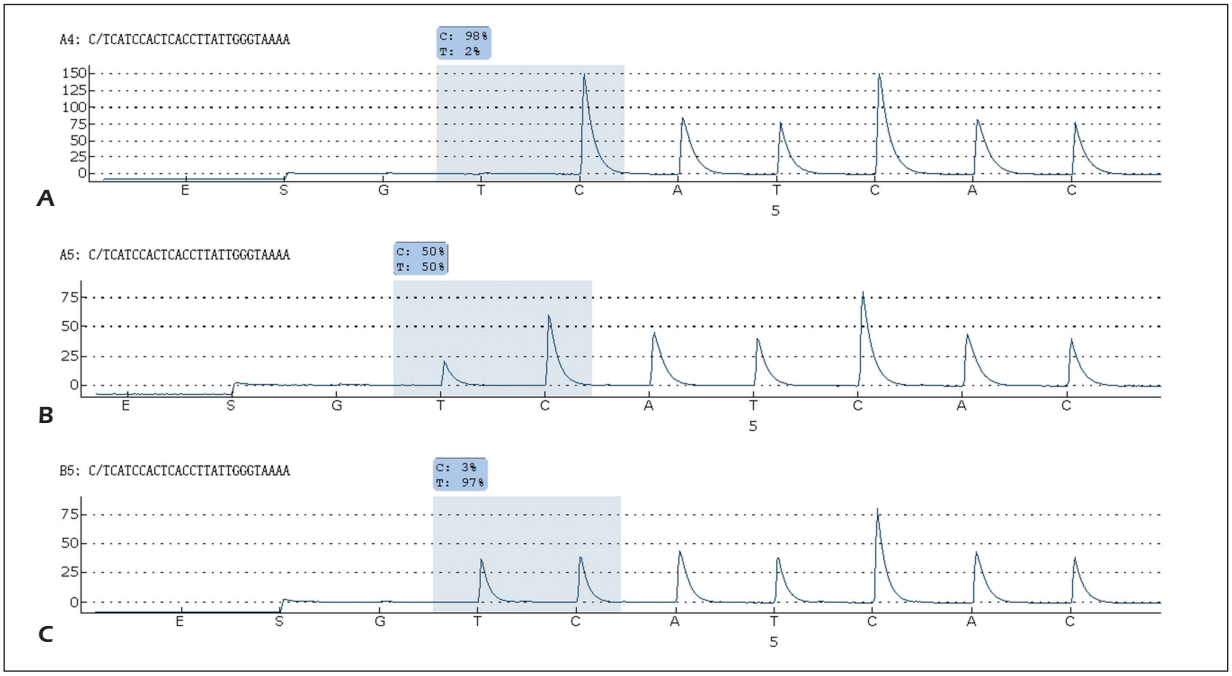

Figure 2. CYP3A4*1G gene sequencing. **A**, GG wild type. **B**, GA mutant heterozygote. **C**, AA mutant homozygote.

Table V. CYP3A4*1G genotype and allele frequency.

	CYP3A4*1G genotype				CYP3A4*1G allele		
	GG	GA	AA	Total	G	A	Total
No. of cases	34	22	3	59	45	14	59
Frequency (%)	57.6	37.3	5.1	100	76.3	23.7	100

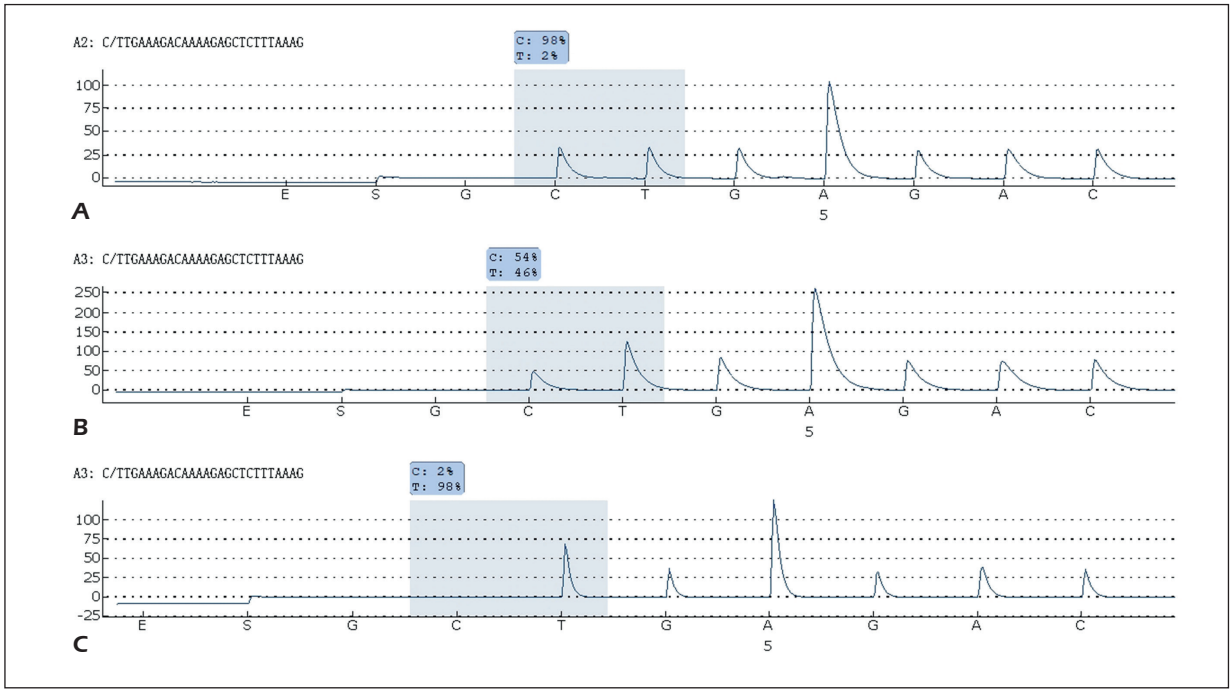

Figure 3. CYP3A5*3 gene sequencing. **A**, AA wild type. **B**, AG mutant heterozygote. **C**, GG mutant homozygote.

Table VI. CYP3A5*3 genotype and allele frequency.

	CYP3A5*3 genotype				CYP3A5*3 allele		
	AA	AG	GG	Total	A	G	Total
No. of cases	3	26	30	59	32	86	118
Frequency (%)	5.1	44.1	50.8	100	27.1	72.9	100

*CYP2D6*10 allele*

Genotyping was conducted according to pyrosequencing results, which classified CYP2D6*10 genotypes into CC, CT and TT genotypes, and the mutation allele frequency of CYP2D6*10 was 56.7%. Chi-square test showed that the genotype distribution of CC, CT, and TT accorded with Hardy-Weinberg law (p=0.755), indicating that the population of CYP2D6*10 gene distribution has reached genetic equilibrium, with group representation (Figure 4, Table VII).

Correlation of OPRM1 A118G Polymorphism With Oxycodone and Sufentanil

The correlation between OPRM1 A118G polymorphism and VAS score in oxycodone group was found to be statistically significant at time points T6, T7, T8, T9, and T12 among the three groups (p<0.05). Further pairwise comparison showed that at the time points of T6, T7, T8, and T9, the GG group was higher than the AA and AG groups. At T10 and T12, GG group and AG group

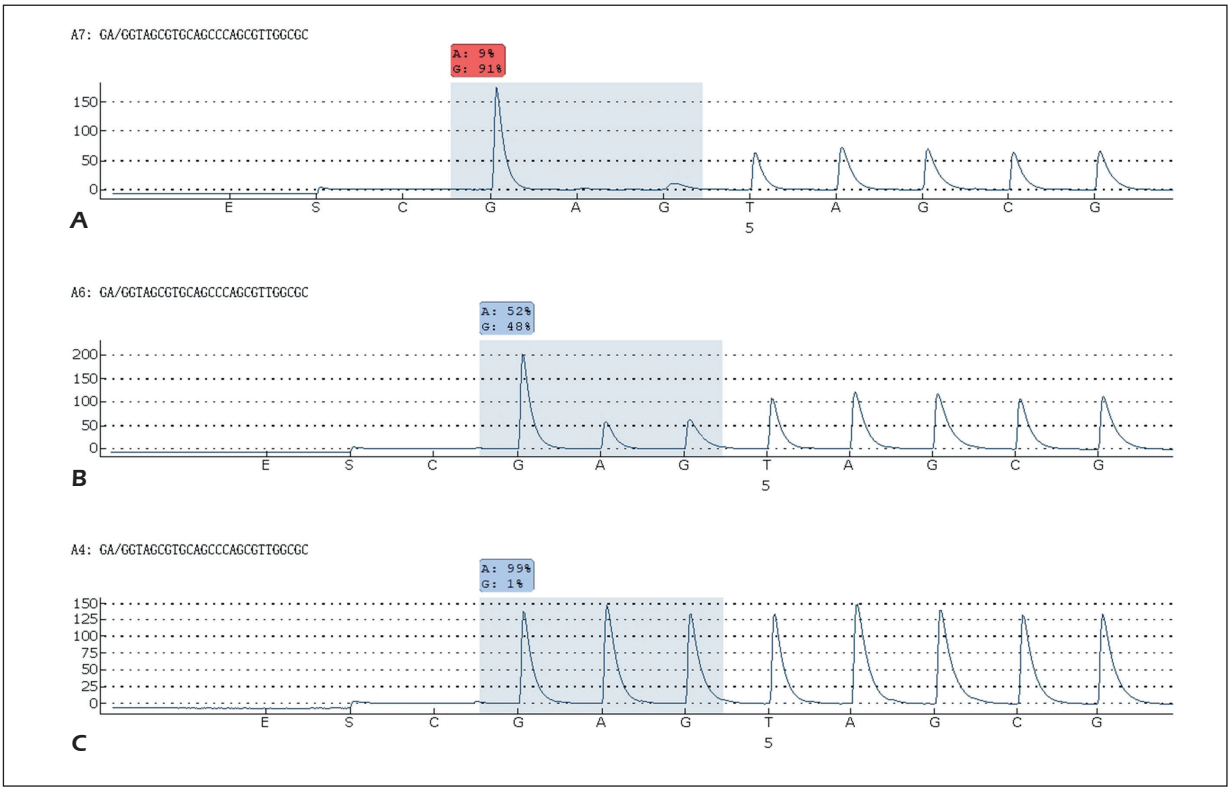

Figure 4. CYP2D6*10 gene sequencing. **A**, CC wild type. **B**, CT mutant heterozygote. **C**, TT mutant homozygote.

Table VII. CYP2D6*10 genotype and allele frequency.

	CYP2D6*10 genotype				CYP2D6*10 allele		
	CC	CT	TT	Total	C	T	Total
No. of cases	13	25	21	59	25.5	33.5	59
Frequency (%)	22	42.4	35.5	100	43.3	56.7	100

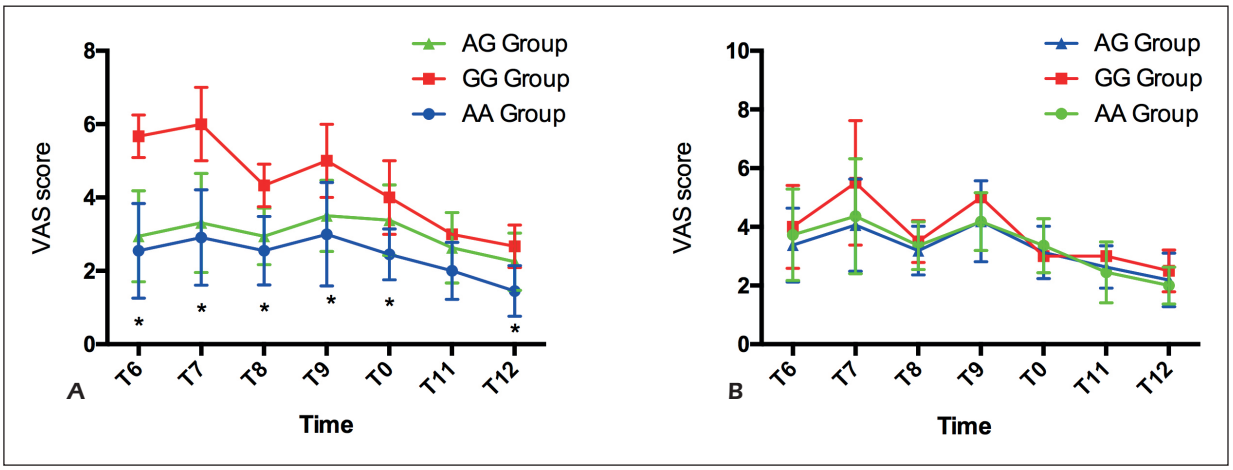

Figure 5. Correlation between OPRM1 A118G polymorphism and VAS scores in oxycodone group and sufentanil group. **A**, The oxycodone group. **B**, The sufentanil group. *Indicated $p<0.05$.

were higher than AA group. In contrast, the correlation between OPRM1 A118G polymorphism and VAS score in sufentanil group did not identify any statistical significance among the three genotypes ($p>0.05$; Figure 5). The comparison of the dosage of oxycodone demonstrated that patients in GG group needed more pain remedies than those in AA and AG groups ($p<0.05$). However, when comparing the total dosage of oxycodone and postoperative 24hPCA, no significant difference was observed between different genomes ($p>0.05$). As for the dosage of sufentanil, the number of times of pain remedies in PACU, the total intraoperative dosage of sufentanil and the total dosage of postoperative 24hPCA in the three groups did not differ significantly ($p>0.05$), nor there was any significant difference in the prevalence of adverse reactions between OPRM1 A118G genotypes in patients treated with oxycodone and sufentanil ($p>0.05$; Tables VIII-XI).

*Correlation of CYP3A4*1G Polymorphism With Oxycodone and Sufentanil*

Comparison of the correlation between the polymorphism of CYP3A4*1G allele and VAS score in oxycodone group showed no statistically significant difference among the three genotypes ($p=0.350$). Comparing the correlation between the polymorphism of CYP3A4*1G allele and VAS score in sufentanil group, it was found that at the time points of T7, T9, and T11, the difference among the three groups was statistically significant ($p<0.05$). Further pairwise comparison revealed that VAS scores of AA group were lower than those of GG group and GA group at the time points of T7, T9, and T11 ($p<0.05$; Figure 6). The number of times of pain remedies in PACU, the total dosage of intraoperative oxycodone and the total dosage of postoperative 24hPCA in patients with three genotypes

Table VIII. Medications of different genotypes of OPRM1 A188G (the oxycodone group).

Variables	AA group (n=11)	GG group (n=3)	AG group (n=16)	Z/F	p
Pain remedies (times)					
0	10	0	13	12.053	0.002
1	1	2	3		
2	0	1	0		
Total intraoperative dosage (mg/kg)	0.41±0.03	0.43±0.06	0.4±0.03	0.087	0.917
Total dosage 24 hours after surgery (mg/kg)	0.41±0.02	0.43±0.01	0.41±0.01	2.684	0.086

Table IX. Medications of different genotypes of OPRM1 A118G (sufentanil group).

Variables	AA group (n=11)	GG group (n=2)	AG group (n=16)	Z/F	p
Pain remedies					
0	7	1	10	0.124	0.940
1	4	1	5		
2	0	0	1		
Total intraoperative dosage (μg/kg)	0.82±0.09	0.85±0.07	0.86±0.08	0.935	0.405
Total dosage 24 hours after surgery (μg/kg)	0.84±0.02	0.82±0.01	0.83±0.02	0.611	0.550

Table X. Adverse reactions of OPRM1 A118G with different genotypes (oxycodone group).

Variables	AA group (n=11)	GG group (n=3)	AG group (n=16)	χ^2	p
Nausea	4	0	4	1.643	0.440
Vomiting	3	0	3	1.129	0.569
Dysphoria	1	0	2	0.455	0.797
Respiratory depression	0	0	1	0.905	0.636

Table XI. Adverse reactions of OPRM1 A118G with different genotypes (sufentanil group).

Variables	AA group (n=11)	GG group (n=2)	AG group (n=16)	χ^2	p
Nausea	1	0	5	2.511	0.285
Vomiting	1	0	5	2.511	0.285
Dysphoria	2	1	6	1.498	0.473
Respiratory depression	0	0	1	0.842	0.657

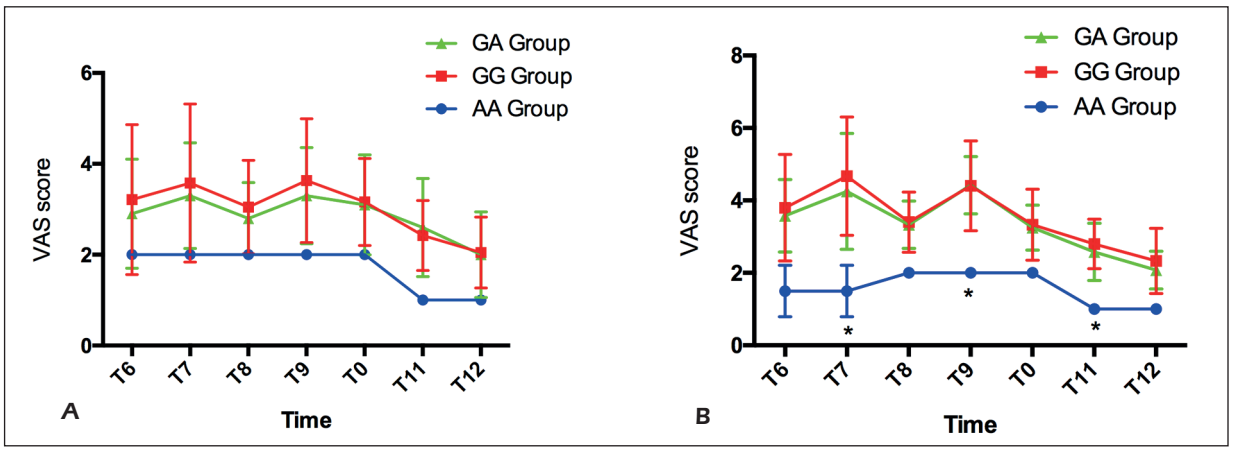

Figure 6. Correlation between CYP3A4*1G polymorphism and VAS scores in oxycodone group and sufentanil group. **A**, The oxycodone group. **B**, The sufentanil group. *Indicated $p<0.05$.

presented no statistical significance ($p>0.05$). In contrast, the total dosage of intraoperative sufentanil was found to be statistically significant ($p<0.001$). Further pairwise comparisons exhibited that AA group was lower than GG group and GA group ($p<0.05$). However, the number of times of pain remedies in PACU and the total dosage of postoperative 24hPCA showed no statistically significant difference ($p>0.05$), nor there was any significant difference in the prevalence of adverse reactions between CYP3A4*1G genotypes in patients treated with oxycodone ($p>0.05$). In the CYP3A4*1G polymorphism of sufentanil patients, the prevalence of respiratory depression in AA group was higher than that in GG group and GA group, with statistically significant difference ($p=0.01$), while the prevalence of other adverse reactions did not differ significantly between the groups ($p>0.05$; Tables XII-XV).

Table XII. Medications of CYP3A4*1G with different genotypes (oxycodone group).

Variables	AA group (n=1)	GG group (n=19)	AG group (n=10)	Z/F	p
Pain remedies					
0	1	14	8	0.490	0.783
1	0	4	2		
2	0	1	0		
Total intraoperative dosage (mg/kg)	0.40	0.42±0.04	0.41±0.03	0.159	0.854
Total dosage 24 hours after surgery (mg/kg)	0.41	0.42±0.02	0.41±0.01	0.200	0.820

Table XIII. Medications of CYP3A4*1G with different genotypes (sufentanil group).

Variables	AA group (n=2)	GG group (n=15)	AG group (n=12)	Z/F	p
Pain remedies					
0	2	7	9	3.640	0.162
1	0	7	3		
2	0	1	0		
Total intraoperative dosage (μg/kg)	0.65±0.07	0.88±0.07	0.83±0.05	13.053	<0.001
Total dosage 24 hours after surgery (μg/kg)	0.81±0.01	0.83±0.02	0.84±0.02	1.901	0.170

Table XIV. Adverse reactions of CYP3A4*1G with different genotypes (oxycodone group).

Variables	AA group (n=1)	GG group (n=19)	AG group (n=10)	χ^2	p
Nausea	0	7	1	2.790	0.248
Vomiting	0	5	1	1.349	0.509
Dysphoria	0	3	0	1.930	0.381
Respiratory depression	0	0	1	2.069	0.355

Table XV. Adverse reactions of CYP3A4*1G with different genotypes (sufentanil group).

Variables	AA group (n=2)	GG group (n=15)	AG group (n=12)	χ^2	p
Nausea	1	2	3	1.678	0.432
Vomiting	1	2	3	1.678	0.432
Dysphoria	0	5	4	0.967	0.617
Respiratory depression	1	0	0	13.982	0.001

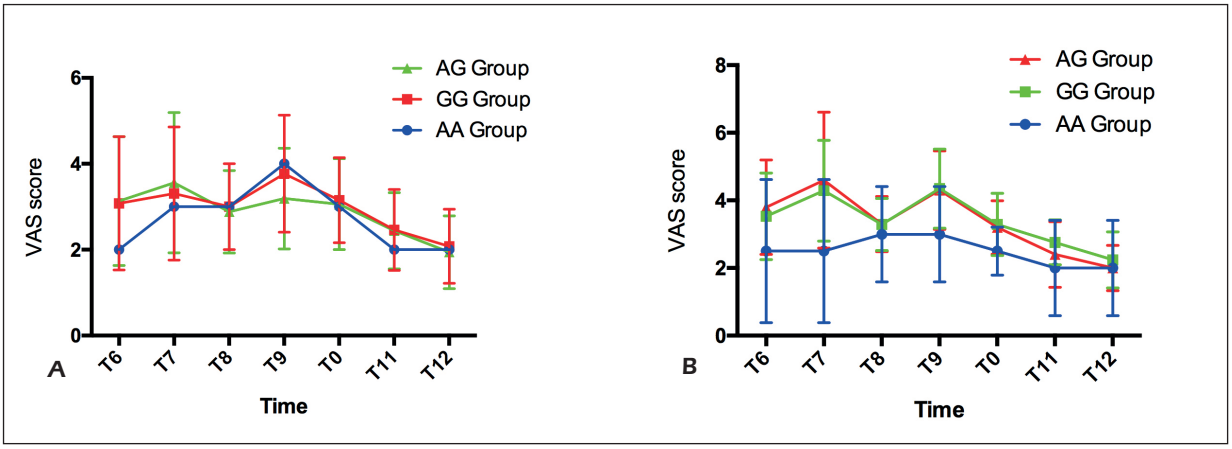

Figure 7. Correlation between CYP3A5*3 polymorphism and VAS scores in oxycodone goup and sufentanil group. **A**, The oxycodone group. **B**, The sufentanil group. *Indicated $p<0.05$.

*Correlation of CYP3A5*3 Polymorphism With Oxycodone and Sufentanil*

The correlation between the polymorphism of CYP3A5*3 allele and VAS score in the oxycodone group and sulfentanil group was compared, and no statistical significance was found among the three genotypes ($p=0.937$, $p=0.387$; Figure 7). The number of times of pain remedies in PACU, the total dosage of intraoperative oxycodone and postoperative 24hPCA in patients with three genotypes did not identify any significant difference after comparing the dosage of oxycodone ($p>0.05$). When it came to the dosage of sufentanil, it was found that the total intraoperative dosage of sufentanil was significantly different among the three genotypes ($p=0.012$). Further pairwise comparison between the two groups showed that GG group and AG group were both higher than AA group ($p<0.05$).

However, there was no significant difference among the groups as regards to the number of times pain remedies required in PACU and the total dosage of 24hPCA after operation ($p>0.05$), nor there was any significant difference in the prevalence of adverse reactions between CYP3A5*3 genotypes in sufentanil-treated patients and oxycodone-treated patients ($p>0.05$; Tables XVI-XIX).

*Correlation of CYP2D6*10 Polymorphism With Oxycodone and Sufentanil*

The correlation between the polymorphism of CYP2D6*10 allele and VAS score in the oxycodone group and sufentanil group was compared, and no statistical significance was found among the three genotypes ($p>0.05$; Figure 8). The comparison of oxycodone dosage indicated no significant differences concerning the times of pain remedies in PACU, the total dosage of in-

Table XVI. Medications of CYP3A5*3 with different genotypes (oxycodone group).

Variables	AA group (n=1)	GG group (n=13)	AG group (n=16)	Z/F	p
Pain remedies					
0	1	10	12	0.344	0.842
1	0	3	3		
2	0	1	1		
Total intraoperative dosage (mg/kg)	0.40	0.42±0.04	0.41±0.03	0.096	0.909
Total dosage 24 hours after surgery (mg/kg)	0.42	0.41±0.02	0.42±0.01	0.071	0.931

Table XVII. Medications of CYP3A5*3 with different genotypes (sufentanil group).

Variables	AA group (n=2)	GG group (n=17)	AG group (n=10)	Z/F	p
Pain remedies					
0	2	10	6	1.272	0.529
1	0	6	4		
2	0	1	0		
Total intraoperative dosage (μg/kg)	0.70±0.14	0.87±0.69	0.83±0.07	5.287	0.012
Total dosage 24 hours after surgery (μg/kg)	0.83±0.04	0.83±0.02	0.84±0.02	1.004	0.380

Table XVIII. Adverse reactions of CYP3A5*3 with different genotypes (oxycodone group).

Variables	AA group (n=1)	GG group (n=13)	AG group (n=16)	χ^2	p
Nausea	0	3	5	0.621	0.733
Vomiting	0	2	4	0.673	0.714
Dysphoria	0	1	2	0.299	0.861
Respiratory depression	0	0	1	0.9053	0.636

Table XIX. Adverse reactions of CYP3A5*3 with different genotypes (sufentanil group).

Variables	AA group (n=2)	GG group (n=17)	AG group (n=10)	χ^2	p
Nausea	0	4	2	0.608	0.738
Vomiting	0	4	2	0.608	0.738
Dysphoria	0	5	4	1.296	0.523
Respiratory depression	0	0	1	1.968	0.374
Cough	0	3	2	0.608	0.738

traoperative oxycodone, and the total dosage of postoperative 24hPCA in patients with three genotypes (p>0.05). Nor any significant difference was identified in the three indicators mentioned above in terms of the dosage of sufentanil among the three groups (p>0.05). As for the prevalence of adverse reactions, no marked differences were observed among CYP2D6*10 genotypes in sufentanil-treated patients and oxycodone-treated patients (p>0.05; Tables XX-XXIII).

Interaction of OPRM1 A118G and CYP3A4*1G Genotypes in the Oxycodone Group

The comparison of VAS scores between OPRM1 A118G and CYP3A4*1G genotypes at different time points showed that there was no statistical difference in VAS scores between OPRM1 A118G and CYP3A4*1G genotypes (p>0.05; Table XXIV).

Interaction of CYP3A4*1G and CYP3A5*3 Polymorphism in the Sufentanil Group

Statistical analysis acquired from comparing the interaction of different genotypes of CYP3A4*1G and CYP3A5*3 in VAS score at different time points demonstrated that there was no significant difference in VAS score between different genotypes of CYP3A4*1G and CYP3A5*3 (p>0.05; Table XXV).

Discussion

From a genetic point of view, the single nucleotide polymorphisms (SNPs) of OPRM1 A118G, CYP3A4*1G, CYP3A5*3, and CYP2D6*10 genes in 59 Chinese Han patients with gastric or intestinal cancer were analyzed to discuss individual differences in drug efficacy and adverse reactions

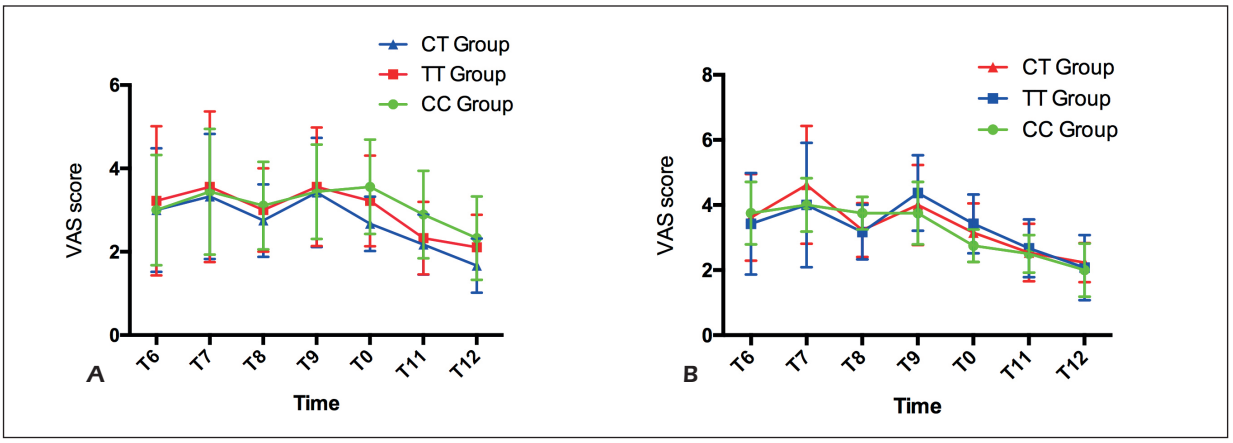

Figure 8. Correlation between CYP2D6*10 polymorphism and VAS scores in the oxycodone group and sufentanil group. **A**, The oxycodone group. **B**, The sufentanil group. *Indicated $p<0.05$.

of oxycodone and sufentanil in this study, in an attempt to guide opioid treatment with genetic variation, as well as to provide reference for clinical individualized medication.

OPRM1, a genetic locus encoded by the μ-opioid receptor (OPRM1) gene, is the principal locus where endogenous opioid peptides, oxycodone, and sufentanil play their roles. Therefore, OPRM1 acts as the primary candidate gene for evaluating the efficacy of opioids[10]. To assess the function of each allele, they were divided into the AA, AG, and GG groups according to its genotype. In this study, the polymorphism of OPRM1 A118G gene was found to be correlated with the postoperative VAS

Table XX. Medications of CYP2D6*10 with different genotypes (oxycodone group).

Variables	CC group (n=9)	TT group (n=9)	CT group (n=12)	Z/F	p
Pain remedies					
0	7	17	9	0.024	0.988
1	2	1	3		
2	0	1	0		
Total intraoperative dosage (mg/kg)	0.41±0.03	0.41±0.03	0.42±0.04	0.087	0.917
Total dosage 24 hours after surgery (mg/kg)	0.42±0.02	0.41±0.01	0.42±0.01	0.683	0.514

Table XXI. Medications of CYP2D6*10 with different genotypes (sufentanil group).

Variables	CC group (n=4)	TT group (n=12)	CT group (n=13)	Z/F	p
Pain remedies					
0	3	8	7	0.943	0.624
1	1	4	5		
2	0	0	1		
Total intraoperative dosage (μg/kg)	0.83±0.05	0.83±0.09	0.86±0.09	0.477	0.626
Total dosage 24 hours after surgery (μg/kg)	0.82±0.02	0.84±0.02	0.83±0.02	0.489	0.619

Table XXII. Adverse reactions of CYP2D6*10 with different genotypes (oxycodone group).

Variables	CC group (n=9)	TT group (n=9)	CT group (n=12)	χ^2	p
Nausea	3	0	5	4.858	0.088
Vomiting	2	0	4	3.611	0.164
Dysphoria	1	0	2	1.605	0.448
Respiratory depression	1	0	0	2.414	0.299

Table XXIII. Adverse reactions of CYP2D6*10 with different genotypes (sufentanil group).

Variables	CC group (n=4)	TT group (n=12)	CT group (n=13)	χ^2	p
Nausea	0	2	4	1.967	0.374
Vomiting	0	2	4	1.967	0.374
Dysphoria	0	4	5	2.165	0.339
Respiratory depression	0	0	1	1.275	0.529

Table XXIV. Interaction of two genotypes in VAS scoring at different time points (oxycodone group).

Genotype		N.	VAS (T6)	VAS (T7)	VAS (T8)	VAS (T9)
OPRM1	CYP3A4					
GA/AA	GG	17	2.88±1.41	3.24±1.48	2.88±0.93	3.41±1.23
GA/AA	AA/AG	10	2.60±0.97	3.00±1.05	2.60±0.70	3.10±1.10
GG	GG	2	6.00±0.00	6.50±0.71	4.50±0.71	5.50±0.71
GG	AA/AG	1	5.00	5.00	4.00	4.00

Table XXV. Interaction of two genotypes in VAS scoring at different time points (sufentanil group).

Genotype		N.	VAS (T6)	VAS (T7)	VAS (T8)	VAS (T9)
CYP3A4*1G	CYP3A5*3					
GG	GG	13	3.62±1.45	4.54±1.61	3.31±0.86	4.38±1.33
GG	AA/AG	2	5.00±1.41	5.50±2.12	4.00±0.00	4.50±0.71
GA/AA	GG	4	3.25±0.50	3.50±0.58	3.25±0.50	4.25±0.50
GA/AA	AA/AG	10	3.30±1.42	4.00±2.11	3.10±0.88	4.00±1.33

score and drug requirements in oxycodone group. The postoperative VAS score of GG patients was the highest and the number of times of pain remedies was more frequent, while the VAS score of AA patients was the lowest. Zhang et al[11] found in human cadaveric brain tissue that OPRM1 A118G polymorphism might affect the expression of μ opioid receptor mRNA, while in the corresponding mouse model, the 118G allele resulted in a 10-fold decrease in the protein level of the μ opioid receptor, thus reducing the number of receptors that can bind to opioids and the efficacy of opioids, which was consistent with the conclusion of this study. The current research also demonstrates that the analgesic effect and adverse reactions of sufentanil were not significantly correlated with OPRM1 A118G polymorphism as there was no significant difference in postoperative VAS score at different time points, number of pain remedies in PACU, total intraoperative dosage, total postoperative dosage of 24hPCA, and prevalence of adverse reactions between OPRM1 A118G polymorphism in sufentanil group. Hwang et al[12] analyzed the effects of OPRM1 A118G polymorphism on different opioid drugs, and the results showed that OPRM1 locus exhibited different binding force on different opioid substances, and OPRM1 A118G polymorphism affected the need for morphine intrauterine injection after surgery, but did not affect the need for fentanyl, which accorded with our results.

Cytochrome P450 (CYP450) is a widely existed catalytic enzyme, which implicates in the production of endogenous hormones and the metabolism of exogenous substances[13]. Among them, CYP3A, the primary pathway for nearly 50% of drug clearance metabolism, is the most abundant in the liver. It is highly variable in phenotype as a result of complex gene-environment interaction, which also leads to individual differences in the catabolism and absorption of opioids[14]. CYP3A enzyme is mainly constituted of CYP3A4 and CYP3A5, among which CYP3A4*1G and CYP3A5*3 are gene loci with high mutation frequency and great influence on function in the Chinese population. To assess the function of each allele, we divided the CYP3A4*1G genotype into three groups, i.e., the GG (wild type), GA (mutant heterozygote), and AA (mutant homozygote) groups. Likewise, the alleles of CYP3A5*3 were also classified into three groups, namely, AA group (wild type), AG group (mutant heterozygote), and GG group (mutant homozygote). This study revealed that the polymorphism of CYP3A4*1G and CYP3A5*3 genes was not significantly different from the VAS score at each postoperative time point, the number of times of pain remedies in PACU, the total dosage of intraoperative medication, the total dosage of 24hPCA, and the prevalence of adverse reactions in oxycodone group, indicating that the analgesic effect, medication dosage, and adverse reactions of oxycodone were not correlated with CYP3A4*1G or CYP3A5*3 polymorphism. The reason may be that the products of oxycodone catalyzed by CYP3A (CYP3A4/5) are both weaker opioid receptor agonists and cannot provide major analgesic effects due to their low osmotic pressure and difficulty in crossing the blood-brain barrier, plus the fact that most of the analgesic effect of oxycodone is still controlled by the drug itself, thus its metabolite contribution is negligible. Therefore, it is theoretically inferred that CYP3A4 and CYP3A5 polymorphism may not be significantly correlated with the analgesic effect and adverse reactions of oxycodone[15]. Meanwhile, Andreassen et al[16] supported that CYP3A4*1G and CYP3A5*3 polymorphism were not associated with the analgesic effects and adverse reactions of oxycodone, which was consistent with the results of this study. CYP3A4*1G polymorphism was related to the postoperative VAS score of sulfentanil group in the present study. At the time points of postoperative T7, T9, and T11, the VAS score ofAA group was lower than that of GG group and GA group. In addition, the total dosage of medication in the three genotypes of CYP3A4*1G patients was compared: AA group was lower than GG group and GA group, while in terms of adverse reactions, the prevalence of respiratory depression in AA group was higher than GG group and GA group, indicating that the CYP3A4*1G polymorphism was associated with the efficacy and adverse reactions of sufentanil. Kharasch et al[17] conducted a research on 12 healthy volunteers and showed that inhibition of CYP3A4 enzyme activity in intestinal or liver had little effect on fentanyl absorption and analgesic effect, but significantly changed the elimination and duration of fentanyl effect. Gao et al[18] found that in CYP3A4*1G mutant homozygote (AA type) patients, the effect of Avastatin on lowering blood lipid was significantly enhanced, the activity of CYP3A4 enzyme was decreased, and the drug concentration was significantly increased. The above conclusions agreed with the results of this study. Therefore, it can be explained that the carriers of allele A of CYP3A4*1G may cause gene mutation, resulting in decreased activity of CYP3A4 enzyme, abated metabolism of sufentanil, increased drug concentration, and prolonged duration of sufentanil, which is further manifested as enhanced analgesic effect, decreased amount of drugs required during operation, and lower postoperative VAS score. However, the increased concentration of sufentanil in AA patients also increased the prevalence of sufentanil dose-related adverse reaction, which is manifested in the increased prevalence of postoperative respiratory depression in mutant homozygous AA patients in this study.

CYP3A5*3 also plays an important role in the metabolism of sufentanil. Jin et al[19] performed biopsy and genetic analysis on 25 suspected fentanyl-poisoned cadavers and found that CYP3A5 implicated in the metabolism of fentanyl, while CYP3A5*3 mutant homozygote (GG) might weaken the metabolism of fentanyl. Hu et al[20] have displayed that 62% of the Chinese population with genotype of CYP3A5*3 mutant homozygous (GG) has no protein expression. Therefore, the blood concentration of opioid metabolized by CYP3A5 is increased, the duration of analgesic action is prolonged, and the amount of drugs required is decreased. In terms of adverse reactions, Ross et al[21] indicated that patients with CYP3A5*3 mutant homozygous (GG)

type accompanied with a higher prevalence of central adverse reactions like drowsiness, lethargy, hallucinations. Therefore, CYP3A5*3 polymorphism may be an important factor contributing to individual differences in analgesic effects and adverse reactions of opioids. However, no association was found between CYP3A5*3 polymorphism and the analgesic effect of sufentanil, postoperative 24 h medication dosage, and adverse reactions here. On the contrary, we drew an opposite conclusion, that is, the total intraoperative dosage of sufentanil used in GG group and AG group was higher than that in AA group, indicating that the amount of sufentanil needed in the wild type (AA) individuals was the smallest. The reasons for this result were analyzed as follows: first of all, the limited sample size leads to the shortage of some genotype. The frequency of AA genotype accounted merely for 8%, i.e., only 3 patients with CYP3A5 were AA genotype, with 2 in sufentanil group. While one of them CYP was3A4*1G mutant homozygous (AA type), which meant the intraoperative sufentanil dosage of this patient was significantly reduced. In addition, as explained above, homozygote AA with CYP3A4*1G mutation has the lowest postoperative VAS score, and the lowest amount of sufentanil needed during operation. Therefore, it is suspected that these inconsistencies are resulted from the interaction of genes.

According to the combination of alleles and their influence on enzyme activity, CYP2D6 is classified into 4 types: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultra-rapid metabolizer (UM). Several clinical studies have found that CYP2D6 polymorphism affects drug efficacy. For example, Gasche et al[22] indicated that CYP2D6UM could quickly convert codeine into morphine, which exerted a better analgesic effect and reduced the dosage of opioids, but it is prone to drug poisoning, resulting in respiratory depression, and other adverse reactions. In this study, however, CYP2D6*10 polymorphism was not found to be associated with oxycodone and sufentanil concerning postoperative VAS scores, medication dosage and adverse reactions. In a study conducted by Klepstad et al[23], among 2294 cancer patients, 445 patients received oxycodone, and 695 patients received fentanyl. The final results showed that CYP2D6 polymorphism was not associated with postoperative pain score of oxycodone and fentanyl, medication dosage, and adverse reactions, which were consistent with our conclusions.

According to present study, CYP3A4*1G was associated with the analgesic effect, medication dosage, and adverse reactions of sufentanil. CYP3A4 and CYP3A5 are the most important enzymes involved in sufentanil metabolism. With a 60% similarity in nucleotide sequences and a similar matrix, CYP3A4 and CYP3A5 are bound to with each other and jointly constitute the CYP3A monomer[24]. Theoretically, the combined effect of the two on the efficacy of sufentanil should be greater than that of a single gene. Based on that assumption, the interaction between CYP3A5*3 and CYP3A4*1G genes was further analyzed. However, due to the small sample size, we did not find that each genotype combination was associated with the analgesic effect, medication dosage or adverse reactions of sufentanil. Therefore, more clinical trials are needed in the future to further study gene-to-gene interactions.

Conclusions

Gene polymorphism in patients undergoing laparoscopic gastric or intestinal cancer surgery is associated with opioid efficacy and adverse reactions. OPRM1 A118G polymorphism is correlated with the postoperative VAS score of oxycodone as the GG genotype had the highest postoperative VAS score and required more pain remedies. CYP3A4*1G polymorphism was related to the postoperative VAS score of sufentanil as the AA genotype had the lowest postoperative VAS score, the least dosage of sufentanil required during surgery, but the prevalence of respiratory depression increased. Therefore, detection of OPRM1 A118G gene in patients treated with oxycodone can help to predict the efficacy of oxycodone, while the detection of CYP3A4*1G polymorphism in patients treated with sufentanil can help predict the efficacy and adverse reactions of sufentanil. However, there are some limitations in this study. Firstly, the blood drug concentration and corresponding enzyme activity of individuals with different genotypes were not detected, which result in a lack of some certain objective indicators. Secondly, the limited sample size may lead to the absence of statistical significance in some indicators. Therefore, more large-scale and prospective researches are to be carried out in the future.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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