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Original Article

Study on individualized analgesia guided by *CYP3A4/5* polymorphisms in perioperative thoracoscopic surgery

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Abstract: Objective: To explore the significance of CYP3A4 and CYP3A5 genetic polymorphisms in achieving personalized fentanyl application in patients undergoing thoracoscopic operation. Methods: This was a retrospective study. One hundred patients with lung cancer received thoracoscopic surgery operation under the conditions of general anesthesia. According to the results of individualized analgesia guided by CYP3A4/5 polymorphisms, the patients were assigned into three groups: group I (the wild-type homozygote, the induced dosage of fentanyl: 6 μg/kg, the background infusion rate of patient-controlled intravenous analgesia (PCIA): 2 mL/h), group II (the heterozygote, the induced dosage of fentanyl: 5 μg/kg, the background infusion rate of PCIA: 1.5 mL/h), and group III (the mutant homozygote, the induced dosage of fentanyl: 4 μg/kg, the background infusion rate of PCIA: 1 mL/h). The locking-time was 15 min. A visual analog scale (VAS) score less than 3 points suggested effective analgesia. The times of operation and recovery were examined. Surgical plethysmography index (SPI), blood glucose levels, VAS and bruggemann comfort scale (BCS) scores at different time points were recorded, respectively. Total consumption of fentanyl, the effective time of PCIA compression, and the incidence of adverse drug reactions were also recorded. Results: There were no statistical differences in SPI, blood glucose level, VAS, BCS scores and incidence of adverse reactions among the three groups. In term of intraoperative, postoperative fentanyl doses and the amount of effective PCA, significant differences were found among the groups ($P < 0.05$). Conclusion: According to the genotype of *CYP3A4/CYP3A5*, an individualized application of fentanyl is feasible.

Keywords: Fentanyl, CYP3A4, CYP3A5

Introduction

Fentanyl is a μ-opioid receptor agonist. It is commonly applied for induction and maintenance of anesthesia, postoperative analgesia, and treatment of acute and chronic pain. Fentanyl can easily cross the blood-brain barrier due to its high lipophilicity, and its effects are 75-200 times stronger than morphine [1-3]. However, it is difficult to accurately determine the appropriate therapeutic dose of fentanyl, because the effective dose of fentanyl for pain control is highly varied [4]. Additionally, fentanyl-related adverse reactions vary greatly among individuals. Individual differences in fentanyl sensitivity may be related to genetic factors, sex, age, weight, and organ function.

Fentanyl is metabolized by oxidative N-dealkylation in the liver [5]. A pharmacogenomics study showed that fentanyl is mainly metabolized to its inactive and non-toxic form (norfentanyl) by the cytochrome P450 (CYP)3A enzyme [6]. Norfentanyl is mainly eliminated via the kidneys. CYP3A4 and CYP3A5 belong to the CYP3A subfamily of P450 enzymes and are the most abundant cytochrome oxidases in the human body [7]. The *CYP3A4* gene is located on chromosome 7 7q21.1-q22.1, and this gene encodes 30-40% of all CYP enzymes. CYP3A4 is mainly distributed in the liver and intestines, and it participates in the oxidative metabolism of approximately 45-60% of drugs [8], including fentanyl.

One study [9] showed that single-nucleotide polymorphisms (SNPs) of *CYP3A4* affect the expression and activity of its enzymes. The expression of CYP3A4 can differ by 40-fold between individuals [10], triggering differences

in the pharmacokinetics of fentanyl and leading to different plasma concentrations and patient responses to treatment. CYP3A4*1G (rs2242480) is a major and the most frequent SNP of *CYP3A4* [11], which is closely related to fentanyl metabolism. The mutation occurs at the tenth intron (G > A; wild type: CYP3A4*1/*1; heterozygous: CYP3A4*1/*1G; mutant: CYP3A4*1G/*1G). A recent meta-analysis showed that patients who had CYP3A4*1G required lower amounts of fentanyl for postoperative pain control [12]. Like *CYP3A4*, *CYP3A5* is associated with multiple SNPs. These SNPs affect the rate of fentanyl elimination through the kidneys and influence fentanyl metabolism [13]. Much importance has been attached to the site of CYP3A5*3. It has the highest mutation frequency [14], reaching approximately 70-90% in the Chinese population. The mutation appears at the third intron (A > G; mutant: CYP3A5*3/*3; heterozygous: CYP3A5*1/*3; wild type: CYP3A5*1/*1). There is a 10-40-fold difference in the mutated enzyme.

This study aimed to guide the individualized clinical application of fentanyl in thoracoscopic surgery based on *CYP3A4* and *CYP3A5* genotyping to improve the accuracy and effectiveness of drug use and decrease the occurrence of related adverse reactions.

Materials and methods

Patients

This research was approved by the Ethics Committee of the First Affiliated Hospital of Jiaxing University (approval no. 2017-177) and it was a retrospective study. All patients or their families signed written informed consent before surgery. The study included 100 patients aged 40-65 years with a body mass index (BMI) of < 30 kg/m^2 and American Society of Anesthesiologists physical status of I or II. These patients were scheduled to undergo radical thoracoscopic surgery for lung cancer between January 2018 and December 2018. All patients were Chinese Han individuals who resided in the Zhejiang Province of China.

The exclusion criteria were as follows: patients with hepatic or renal dysfunction, diabetes mellitus, hyperthyroidism, a history of significant cardiovascular disease or long-term use of analgesics, psychotropic drugs, or cortisol drugs; patients with opioid intolerance; patients who refused to use patient-controlled intravenous analgesia (PCIA) after surgery; patients who had general anesthesia within 3 months; patients in pregnancy or lactation; and patients with consumption of drugs or food known to inhibit or induce CYP3A enzyme expression within 2 weeks before surgery.

Genotyping assays

CYP3A4 and *CYP3A5* were examined in patients on the day before surgery. First, each patient rinsed their mouth with clean water and removed impurities from the oral cavity. Subsequently, a buccal swab was used to scrape the oral wall cells and marked separately and stored in a dedicated saliva preservation test tube. The marked preservation tube was placed in a shaking mixer with a constant temperature that was run according to a set procedure (56°C, 15 min, 800 rpm). After the instrument was stopped, the preservation tube was mixed with a nucleic acid extraction reagent (Mohe Medical Technology Co., Ltd.). After DNA was extracted, the concentration was titrated in a Fluo-100 fluorometer (Hangzhou Aosheng Instrument Co., Ltd.). In cases where the DNA concentration was > 5 ng/μl, the *CYP3A4*1G* and *CYP3A5*3* genotypes were detected on the fluorescent quantitative polymerase chain reaction instrument (Shanghai Omar Biotechnology Co., Ltd.) using the TaqMan probe method. If the DNA concentration was < 5 ng/μl, the titration concentration was doubled or the patient's oral wall cell samples were collected again to extract DNA and improve the accuracy of the genetic test results.

Among the 100 patients, 2 were excluded from the study due to unsuccessful classification; thus, 98 patients were finally included. According to the genotyping results, patients were assigned into the following groups: group I: wild-type homozygote group (*CYP3A4*1/*1*; *CYP3A5*1/*1*); group II: heterozygote group; and group III: mutant homozygote group (*CYP3A4*1G/*1G*; *CYP3A5*3/*3*).

Anesthetic procedure

No premedication was used. All patients underwent routine fasting and drinking. Electrocardiography results, mean arterial pressure, heart rate, pulse oxygen saturation (SpO_2),

state entropy (SE), response entropy, surgical plethysmography index (SPI), and nasal temperature were monitored after patients entered the surgery room. Then, upper limb venous access was opened, and ultrasound-guided radial artery and internal jugular vein puncture catheterization were performed, followed by sequential intravenous administration of 2 mg/kg propofol, 0.2 mg/kg cis-atracurium, and varying doses of fentanyl (Yichang Renfu Medicine, batch number: 91D03101) for induction of anesthesia. The dose of fentanyl was 6 μg/kg in group I, 5 μg/kg in group II, and 4 μg/kg in group III. A double-lumen bronchial catheter was inserted through the mouth after the mask was pressurized to oxygen, and nitrogen was removed for 4.5 min. After a fiberoptic bronchoscope and stethoscope confirmed that the catheter position was correct, mechanical ventilation was conducted. The parameter ratio of the ventilator was set to 1:2; the tidal volume was 8-10 mL/kg for bilateral lung ventilation and 4-6 mL/kg for single-lung ventilation. End-tidal carbon dioxide was kept at 35-45 mmHg (1 mmHg = 0.133 kPa) by mechanical ventilation. The rate of oxygen flow was set to 2 L/min during surgery. Intravenous anesthesia along with inhalational anesthesia was administered to maintain anesthesia. The dose of inhaled sevoflurane was 1.0 MAC, and 0.5 $\mu g \cdot kg^{-1}h^{-1}$ dexmedetomidine hydrochloride was infused intravenously. The initial plasma concentration of propofol target-controlled infusion was set to 2 μg/mL. The concentration of propofol was adjusted according to SE, with an amplitude of 0.1 μg/mL each time, to maintain SE at 40-60. The dosage of fentanyl was adjusted according to the SPI value. The target SPI value was 40-50. When the SPI value was > 55, 1 μg/kg fentanyl was added. Then, 0.05 mg/kg cis-atracurium was intravenously injected every 40-50 min to maintain muscle relaxation. Propofol and dexmedetomidine concentrations were decreased when persistent hypotension occurred. When hypotension could not be corrected or the RE value was > 60, phenylephrine was administered to maintain a stable circulation. Sodium lactate Ringer's solution and hydroxyethyl starch 130/0.4 were infused intravenously to supplement the blood volume. Concentrated red blood cells were infused when hemoglobin concentration was < 70 g/L. Consequently, 5 mg tropisetron was injected intravenously about 15 min before the end of operation to prevent PONV events. At the end of surgery, sevoflurane, dexmedetomidine, and propofol were discontinued, and the patient was sent to the care unit of post-anesthesia. The tracheal tube was removed when patients were awake with their eyes open, spontaneous breathing tidal volume reached 5-8 mL/kg, and the rate of respiratory was 14-18 breaths/min. Patients were under observation for 30 min and returned to the ward when the partial pressure of oxygen was > 70 mmHg and SpO_2 was > 95% in inhaled air.

Postoperative analgesia

After surgery, the REHN (11) wireless electronic analgesia pump (Jiangsu Renxian Medical Technology Co., Ltd.) was connected for PCIA. PCIA analgesics consisted of 1.0 mg fentanyl and 6 mg granisetron with 0.9% normal saline (NS) diluted to 100 mL. The rate of background infusion was 2 mL per hour, and the dose of PCA was 2 mL in group I. In group II, the rate of background infusion was 1.5 mL per hour, and the dose of PCA was 1.5 mL. In group III, the rate of background infusion was 0.5 mL per-hour, and the dose of PCA was 0.5 mL. The lockout time was 15 min in all groups. All patients received analgesia until 48 h postoperatively. The analgesic pump was operated by the patient according to the degree of pain. All patients were scored using VAS scale (0-10 points), and a VAS score less than 3 points was defined as effective analgesia. The REHN mobile ward round application was installed on a mobile phone to observe the effective number of compressions of the analgesic pump and the total consumption of fentanyl in real time.

Observation index

Primary indexes: The genotypes of all patients were recorded, and patients were categorized accordingly. The operation time and wake-up time (the time from stopping general anesthesia to removal of the tracheal tube) were recorded. *Secondary indexes:* The SPI and blood glucose values were recorded at the time of entry (T1), immediately after tracheal intubation (T2), during skin incision (T3), during surgery for 1 h (T4), and during skin suturing (T5). The resting VAS scores of all patients were recorded immediately after recovery of consciousness and at 6, 12, 24, and 48 h after operation to evaluate

Table 1. Demographic and clinical characteristics of patients in the three groups

Group	n	Age (years old)	BMI (kg/m^2)	Operation time (min)	Recovery time (min)
I	20	50.15 ± 5.37	23.21 ± 2.02	98.70 ± 16.36	21.40 ± 4.37
II	70	49.94 ± 6.00	22.41 ± 1.56	101.44 ± 16.57	21.83 ± 4.15
III	8	53.88 ± 6.06	23.16 ± 2.09	102.63 ± 15.81	21.88 ± 3.44
F value		1.618	2.127	0.259	0.087
p value		0.204	0.125	0.772	0.916

Data are expressed as number and mean ± standard deviation. BMI, body mass index.

Table 2. Genotyping of all patients

Group	Genotype		n (n%)	Genotype
	CYP3A4	CYP3A5		
I	*1/*1	*1/*1	20 (20.41)	Wild-type homozygote
II	*1/*1G	*1/*1	70 (71.43)	Heterozygote
	*1/*1	*1/*3		
	*1/*1G			
	*1/*1	*3/*3		
	*1/*1G			
	*1G/*1G	*1/*1		
		*1/*3		
III	*1G/*1G	*3/*3	8 (8.16)	Mutant homozygote

Data are expressed as number (%).

the degree of postoperative analgesia. Patient comfort level was evaluated using the Bruggemann comfort scale (BCS). The BCS scoring standards were as follows: 0 = persistent pain; 1 = painless when quiet or severe pain when breathing deeply or coughing; 2 = painless when lying flat or mild pain when breathing deeply or coughing; 3 = painless when breathing deeply; and 4 = painless even when coughing. Fentanyl consumption during surgery and within 48 h after operation was recorded. In addition, the effective number of PCIA compressions was recorded. The fentanyl-related adverse reaction within 48 h after operation, such as sedation, respiratory depression, PONV, itching, and lethargy, was observed.

Statistical processing

The Statistical Package for the Social Sciences, version 20.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Normally distributed quantitative data were expressed as mean ± standard deviation (SD). One-way ANOVA and LSD test were applied to analyze the data among three groups. And t test was applied to examine the differences between two groups. Count data were presented as rate (%) and were analyzed by the χ^2 test or Fisher's exact probability test. $P \leq 0.05$ suggested statistically significant differences.

Results

Comparison of general data

In total, 100 patients were recruited in this study, and their demographic and clinical information are shown in **Table 1**. Two of 100 patients dropped out of this study due to unsuccessful classification; thus, 98 patients were finally included. According to the results of genotyping, patients were assigned into three groups: group I: wild-type homozygote group (*CYP3A4*1/*1*; *CYP3A5*1/*1*); group II: heterozygote group; and group III: mutant homozygote group (*CYP3A4*1G/*1G*; *CYP3A5*3/*3*). Twenty patients (20.41%) were classed as wild-type homozygotes, 70 patients (71.43%) were classed as heterozygotes, and 8 patients (8.16%) were classed as mutant homozygotes (**Table 2**). Among the 98 enrolled patients, the *CYP3A4*1/*1* + *CYP3A5*1/*1* allele frequency was 56.13%, and the *CYP3A4*1G/*1G* + *CYP3A5*3/*3* allele frequency was 43.88%. The allele frequency was consistent with the Hardy-Weinberg equilibrium (χ^2 = 0.705; *P* = 0.401) (**Table 3**). No statistical differences in BMI, age, the time of operation, or recovery time were observed among the three groups (*P* > 0.05) (**Table 3**). No patients required rescue analgesics for insufficient postoperative analgesia, and no patients requested termination of PCA due to adverse reactions.

Comparison of blood glucose and SPI values

We compared the blood glucose and SPI values among the three groups at various points during surgery (**Tables 4** and **5**). For all groups,

Table 3. Allele frequency

Project	Allele frequency		Total
	CYP3A4*1/*1 + CYP3A5*1/*1	CYP3A4*1G/*1G + CYP3A5*3/*3	
n	55	43	98
n %	56.13	43.88	100.0

Data are expressed as number and number %.

Table 4. Comparison of SPI at different time points among the three groups

Index	Group	n	T1	T2	T3	T4	T5
SPI	I	20	46.55 ± 3.38	69.25 ± 4.61	54.35 ± 3.69	42.95 ± 2.84	44.40 ± 3.35
	II	70	46.37 ± 3.27	69.39 ± 3.13	54.23 ± 3.80	42.89 ± 2.84	44.56 ± 3.05
	III	8	46.38 ± 3.02	69.25 ± 2.60	53.25 ± 1.83	42.25 ± 2.87	44.63 ± 3.33
F value			0.024	0.016	0.285	0.196	0.285
p value			0.977	0.985	0.753	0.822	0.753

Data are expressed as number and mean ± standard deviation. SPI, surgical plethysmography index; T1, on admission; T2, immediately after tracheal intubation; T3, during skin incision; T4, during surgery for 1 h; T5, during skin suturing.

Table 5. Comparison of blood glucose levels at different time points among the three groups

Index	Group	n	T1	T2	T3	T4	T5
Blood glucose (mmol/L)	I	20	5.55 ± 0.56	7.03 ± 0.63	6.28 ± 0.59	5.65 ± 0.44	5.51 ± 0.43
	II	70	5.51 ± 0.55	7.08 ± 0.64	6.44 ± 0.62	5.62 ± 0.48	5.54 ± 0.53
	III	8	5.43 ± 0.66	7.01 ± 0.61	6.44 ± 0.62	5.77 ± 0.45	5.59 ± 0.52
F value			0.129	0.764	0.560	0.382	0.072
p value			0.879	0.468	0.573	0.684	0.930

Data are expressed as number and mean ± standard deviation. T1, on admission; T2, immediately after tracheal intubation; T3, during skin cutting; T4, during surgery for 1 h; T5, during skin suturing.

Table 6. Comparison of VAS scores among the three groups at different time points after surgery

Group	n	VAS				
		Immediately after surgery	6 h after surgery	12 h after surgery	24 h after surgery	48 h after surgery
I	20	2.45 ± 0.83	2.35 ± 0.67	2.75 ± 0.64	2.15 ± 0.49	1.90 ± 0.55
II	70	2.50 ± 0.78	2.33 ± 0.68	2.56 ± 0.69	2.01 ± 0.58	1.87 ± 0.56
III	8	2.13 ± 0.64	2.25 ± 0.46	2.13 ± 0.64	2.00 ± 0.53	1.63 ± 0.52
F value		0.838	0.067	2.420	0.484	0.776
p value		0.436	0.936	0.094	0.618	0.463

Data are expressed as number and mean ± standard deviation. VAS, visual analog scale.

blood glucose and SPI values were highest immediately after intubation, and blood glucose levels continued to decrease from intubation to skin suturing. No significant differences in SPI or blood glucose values were identified among the three groups at comparable time points during surgery.

Comparison of VAS and BCS scores

Tables 6 and **7** reveal the resting VAS and BCS scores of each group at 0, 6, 12, 24, and 48 h after PCA initiation. The BCS scores of the three groups continued to increase from 0 to 48 h after surgery. No statistical differences in VAS and BCS scores were found among the three groups at different time points after surgery.

Comparison of fentanyl doses and effective PCA compressions

The number of effective PCA compressions and the total consumption of fentanyl during and

Table 7. Comparison of BCS scores among the three groups at different time points after surgery

Group	n	BCS				
		Immediately after surgery	6 h after surgery	12 h after surgery	24 h after surgery	48 h after surgery
I	20	2.80 ± 0.52	2.90 ± 0.45	3.05 ± 0.39	3.25 ± 0.44	3.50 ± 0.51
II	70	2.81 ± 0.54	2.93 ± 0.57	3.09 ± 0.37	3.23 ± 0.49	3.54 ± 0.50
III	8	2.75 ± 0.46	2.88 ± 0.64	3.13 ± 0.35	3.25 ± 0.46	3.63 ± 0.52
F value		0.053	0.047	0.129	0.02	0.177
p value		0.948	0.954	0.879	0.980	0.838

Data are expressed as number and mean ± standard deviation. BCS, Bruggemann comfort scale.

Table 8. Comparison of intraoperative and postoperative fentanyl doses and effective PCA compressions among the three groups

Group	n	Intraoperative fentanyl usage (μg)	Postoperative fentanyl usage (μg)	Effective PCA compressions (number)
I	20	416.50 ± 48.80	986.25 ± 17.61	6.50 ± 1.40
II	70	335.50 ± 36.64	754.00 ± 29.54	3.23 ± 0.94
III	8	221.25 ± 28.00	495.00 ± 9.26	1.75 ± 0.71
F value		76.397	1101.932	95.251
p value		0.000	0.000	0.000
LSD-t value		0.000	0.000	0.000

Data are expressed as number and mean ± standard deviation.

Table 9. Comparison of the incidence of PONV, itching, and lethargy among the three groups

Group	PONV	Itching	Lethargy	Total
I	3 (15.0)	1 (5.0)	1 (5.0)	5 (25.0)
II	10 (14.3)	3 (4.29)	2 (2.86)	15 (21.43)
III	1 (12.5)	0 (0.0)	0 (0.0)	1 (12.5)
F value				5.14
p value				0.308

Data are expressed as number. PONV, postoperative nausea and vomiting.

after surgery were recorded in the three groups. For groups I, II, and III, the consumption of fentanyl during surgery was 416.50 ± 48.80 μg, 335.50 ± 36.64 μg, and 221.25 ± 28.00 μg, respectively (**Table 8**). Postoperative fentanyl consumption was 986.25 ± 17.61 μg in the wild-type homozygote group (*CYP3A4*1/*1*; *CYP3A5*1/*1*), 754.00 ± 29.54 μg in the heterozygote group, and 495.00 ± 9.26 μg in the mutant homozygote group (*CYP3A4*1G/*1G*; *CYP3A5*3/*3*) (**Table 8**). Statistical analysis showed that the intraoperative and postoperative doses of fentanyl in the mutant homozygote group were significantly lower compared with the wild-type homozygote group ($P < 0.05$). The intraoperative and postoperative doses of fentanyl and the number of effective PCA compressions were reduced in the three groups (all $P < 0.05$) (**Table 8**). Multiple comparisons showed significant differences among the three groups (all $t < 0.05$).

Comparison of side effects

The side effects in this study are summarized in **Table 9**. The main postoperative adverse reactions were PONV, itching, and lethargy. PONV occurred in 14 patients (14.28%), including three patients in group I (15%), 10 patients in group II (14.3%), and one patient in group III (12.5%). No itching or lethargy was noted in the mutant homozygote group. No statistical difference in postoperative side effects was found among the groups ($P > 0.05$). None of the patients experienced excessive sedation resulting in respiratory depression.

Discussion

Fentanyl is an analgesic drug that was developed and synthesized in the 1960s. It stimulates μ-opioid receptors to exert powerful analgesic effects [15]. It has been widely used in surgical anesthesia and in the therapy of acute and chronic pain. Fentanyl plays an important role in relieving postoperative pain, inhibiting excessive stress responses, improving quality of life for patients, and promoting postoperative recovery [16]. However, it is associated with many complications, such as delayed postoperative recovery, respiratory depression, nausea and vomiting, and an increased incidence of chronic pain [10]. The analgesic effects and adverse reactions of fentanyl vary markedly between individuals [4], and the mini-

mum effective dose can vary by 4-6 times. An important reason for this phenomenon is genetic polymorphism.

CYP3A4 and CYP3A5 belong to the CYP340 subfamily of P450 enzymes, which are the main metabolic enzymes responsible for fentanyl metabolism. SNPs of *CYP3A4* and *CYP3A5* affect the expression and activity of the encoded enzymes and can lead to changes in the pharmacokinetics of fentanyl. Among them, *CYP3A4*1G* and *CYP3A5*3* have the highest mutation rates.

The genetic detection method used in this study quickly and accurately analyzed each patient's genotype. According to the results of genotyping, individualized fentanyl administration was implemented during the perioperative period. During anesthetic induction and surgery, if the anesthetic depth is too shallow, it will cause a strong stress response, consequently leading to violent fluctuations in the circulation and possible suppression of immune function [17]. The SPI can be used as an effective indicator to quantify the intensity of analgesia during surgery [18], while blood glucose is a clinical stress indicator [19]. This study combined SPI and blood glucose values to analyze analgesic intensity and the stress response. No patients showed obvious insufficiency of analgesia or a severe stress response during surgery in response to strong noxious stimuli, such as tracheal intubation and skin incision. With regard to the administration of individualized fentanyl, the analgesic effect and anti-stress ability were similar among the three groups. Owing to the similar degree of pain control, patients in the mutant homozygote group (*CYP3A4*1G/*1G*; *CYP3A5*3/*3*) required significantly less intraoperative fentanyl. Furthermore, no adverse reactions, such as respiratory depression or delayed recovery, were observed during the resuscitation period of anesthesia.

Patients in this study received video-assisted thoracic surgery (VATS). Although VATS has many advantages, such as minimal invasiveness, quick recovery time, minimal pain, definite curative effect, and good safety and reliability [20, 21], postoperative pain remains obvious. Severe pain prevents the patient from breathing deeply, coughing, and expectorating effectively. Pulmonary complications, such as atelectasis, lung infection, and pleural effusion, are also more likely to occur. Simultaneously, severe pain can easily induce a stress response. In addition, VATS causes tissue damage by destroying the immune system, which affects the healing of surgical incisions and increases the chance of infection. Therefore, optimal postoperative analgesia is crucial to promoting the rapid recovery of patients who undergo VATS. Obvious individual differences exist in the effects of analgesia and adverse reactions to PCIA. Some patients have inadequate analgesia, and other patients experience various adverse reactions and side effects in response to relatively large doses.

In this study, the conventional PCIA protocol was discarded, and different continuous background infusion rates and single-compression PCA doses were used. The results of this study show that in contrast to other two groups, the mutant homozygote group (*CYP3A4*1G/*1G*; *CYP3A5*3/*3*) required significantly lower fentanyl doses for postoperative pain control. This suggests that *CYP3A4*1G/*1G* and *CYP3A5*3/*3* variant alleles play a key role in CYP3A4 and CYP3A5 enzyme activity and plasma fentanyl concentrations. Our findings are similar to those of other clinical studies on the treatment of patients with gastrointestinal cancer and those undergoing lower abdominal surgery. No significant intergroup differences in VAS and BCS scores were observed at any time point within 48 h after operation. In addition, the adverse reaction following operations such as vomiting, nausea, itching, and lethargy did not differ in a statistically significant manner among groups. These results indicated that the implementation of an individualized PCIA analgesia program can optimize pain management, provide better analgesia and increase patient comfort without causing obvious complications.

This study has some limitations that should be noted. First, the sample size was inadequate. Second, pain at rest, instead of dynamic pain, was evaluated. Third, the blood concentrations of fentanyl and norfentanyl were not measured. Therefore, conducting a multicenter, large-sample size clinical study on individualized fentanyl administration to analyze the precise dosage of fentanyl in patients with different genotypes is

warranted to more precisely guide individualized fentanyl administration.

In this study, the perioperative dose of fentanyl was appropriately adjusted based on the genotypes of patients undergoing thoracoscopic radical resection for lung cancer. The results show that individualized administration of fentanyl can reduce the use of drugs and adverse drug reactions while still ensuring analgesic effects. This outcome is of great significance to promote rapid recovery and improve the comfort and satisfaction of patients after surgery. This study suggests that personalized administration of fentanyl based on the results of *CYP3A4* and *CYP3A5* genotyping is feasible.

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Disclosure of conflict of interest

None.

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