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Abstract

Background: Studies have confirmed that CYP3A4 and CYP3A5 genotypes affect fentanyl metabolism in vivo. This study explores the application value of CYP3A4 and CYP3A5 genetic polymorphism in the individualized use of fentanyl in thoracoscopic surgery.
Methods: One hundred American Society of Anesthesiologists physical status I or II patients, aged 40–65 years, with a body mass index of <30 kg/㎡ were scheduled for thoracoscopic surgery for lung cancer under general anesthesia. The patients were divided into the wild homozygote group (group I), heterozygote group (group II), and mutant homozygote group (group III) according to gene detection results. The induction dose of fentanyl was 6 μg/kg, 5 μg/kg, and 4 μg/kg, respectively; the background infusion rate of patient-controlled intravenous analgesia (PCIA) was 2 mL/h, 1.5 mL/h, and 1 mL/h, respectively; the patient-controlled analgesia (PCA) dose was 2 mL, 1.5 mL, and 1 mL, respectively; the locking time was 15 min; and the visual analog scale (VAS) score of ≤ 3 was used as the effective analgesia. The operation and recovery times were recorded. Surgical plethysmography index (SPI) and blood glucose levels were recorded on admission, immediately after tracheal intubation, during skin cutting, during surgery for 1 h, and during skin suturing. Furthermore, the VAS and Bruggemann comfort scale (BCS) scores were recorded in the resting states of immediate consciousness and 6 h, 12 h, 24 h, and 48 h after the operation. The total fentanyl consumption, the effective times of PCIA compression, and the incidence of adverse drug reactions (nausea, vomiting, itching, sleepiness, and respiratory depression) were recorded during the operation and within 48 h after the operation.
Results: No significant intergroup differences in terms of SPI and blood glucose levels ($p > 0.05$) were observed. No statistically significant difference in VAS and BCS scores was found after operation ($p > 0.05$). The intraoperative and postoperative fentanyl doses and the amount of effective PCA decreased in all groups ($p < 0.05$). There were no significant differences in the incidence of adverse reactions within 48 h after surgery between all groups ($p > 0.05$).
Conclusion: This study suggests that it is feasible to use individualized application of fentanyl according to CYP3A4 and CYP3A5 genotypes.
Key words fentanyl, CYP3A4, CYP3A5

Background

Fentanyl is an μ-opioid receptor agonist. It is widely used for induction and maintenance of anesthesia, postoperative analgesia, and treatment of acute and chronic pain. Because fentanyl has high lipophilicity, it easily crosses the blood–brain barrier, and its effects are 75–200 times stronger than morphine [1][3].The appropriate therapeutic dose of fentanyl is difficult to accurately determine because the effective dose of fentanyl for pain control is individualized 错误!未找到引用源。. Additionally, fentanyl-related adverse reactions vary greatly among individuals. Individual differences in fentanyl sensitivity may be related to genetic factors, gender, age, weight, and organ function.

Fentanyl is metabolized by undergoing oxidative N-dealkylation in the liver[4]. A pharmacogenomics study has shown that fentanyl is mainly metabolized to its inactive and nontoxic norfentanyl form by cytochrome P450 [6](CYP) 3A enzyme. Norfentanyl is eliminated mainly via the kidneys. CYP3A4 and CYP3A5 belong to the CYP3A subfamily of the P450 enzyme system and are the most abundant cytochrome oxidases in the human body 错误!未找到引用源。. The CYP3A4 gene is located on chromosome 7 7q21.1–q22.1, accounting for 30%–40% of the total P450 enzyme system; it is mainly distributed in the liver and intestines, and it can participate in the oxidative metabolism of approximately 45%–60% of drugs[8] including fentanyl. Studies have shown that[9] single nucleotide polymorphism (SNP) of CYP3A4 affects the expression and activity of its enzymes. The expression of CYP3A4 can cause a 40-fold difference between individuals[10], triggering changes in the pharmacokinetics of fentanyl and leading to different plasma concentrations and patient responses to treatment. The CYP3A4*1G (rs2242480) is a major site of SNPs and the most frequently mutated site in CYP3A4 错误!未找到引用源。. It is closely related to fentanyl metabolism. The mutation occurs at the 10th intron (G > A; the wild type: CYP3A4*1/*1; the heterozygous type: CYP3A4*1/*1G; and the mutant type: CYP3A4*1G/*1G). A recent meta-analysis reported that patients with CYP3A4*1G consumed lower amounts of fentanyl for postoperative pain control[12]. In addition, CYP3A5 has multiple SNPs, which are mostly expressed outside the liver, that affect the rate of fentanyl excretion through the kidneys and participate in the fentanyl metabolism [13]. Most attention has been paid to the site of CYP3A5*3. It has the highest mutation frequency[14], reaching approximately 70%–90% in the Chinese population. The mutation occurs at the third intron (A > G; the wild type: CYP3A5 *1/*1; the heterozygous type: CYP3A5*1/*3; and the mutant type: CYP3A5*3/*3). There is a 10–40-fold difference in the mutated enzyme.

This study intends to guide the individualized clinical application of fentanyl in thoracoscopic surgery based on the patient's CYP3A4 and CYP3A5 genotyping to improve the accuracy and effectiveness of drug use and reduce the occurrence of related adverse reactions.

Methods

Patients

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

and reside in the Zhejiang Province of China.

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

Genotyping assays

The CYP3A4 and CYP3A5 genes were tested on the patients enrolled the day before surgery. The genotyping procedure was as follows: the patient rinses their mouth with clean water and removes impurities in the oral cavity; subsequently, a buccal swab was used to scrape the oral wall cells and was marked separately and stored in a dedicated saliva preservation test tube. The marked preservation tube is placed in a constant temperature shaking mixer that is run according to the set procedure (56°C, 15 min, and 800 rpm). After the instrument is stopped, the preservation tube is mixed with a nucleic acid extraction reagent (Mohe Medical Technology Co., Ltd.) for extraction. After the DNA was extracted, the concentration was titrated in a Fluo-100 fluorometer (Hangzhou Aosheng Instrument Co., Ltd.). In cases when the DNA concentration is >5 ng/μl, the genotypes of CYP3A4*1G and CYP3A5*3 can be detected on a fluorescent quantitative polymerase chain reaction instrument (Shanghai Omar Biotechnology Co., Ltd.) using the TaqMan probe method. If the DNA concentration is <5 ng/μl, the titration concentration can be doubled or the patient's oral wall cell samples can be 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, and 98 patients were finally included. According to the genotype results, the patients were divided into three groups: group I was the wild-type homozygous group (CYP3A4*1/*1; CYP3A5*1/*1), group II was the heterozygous group, and group III was the mutant-type homozygous group (CYP3A4*1G/*1G; CYP3A5*3/*3).

Anesthetic procedure

No premedication was used. All patients underwent routine fasting and drinking. Electrocardiogram, heart rate (HR), mean arterial pressure (MAP), pulse oxygen saturation (SpO2), state entropy (SE), response entropy (RE), surgical plethysmography index (SPI), and nose temperature were monitored after the patients entered the operating room. Then, upper limb venous access was opened and ultrasound-guided radial artery and internal jugular vein puncture catheterization was performed; this was followed by sequential intravenous administration of 2 mg/kg propofol, 0.2 mg/kg cis-atracurium, and different doses of fentanyl (Yichang Renfu Medicine, batch number: 91D03101)—6 μg/kg in group I, 5 μg/kg in group II, and 4 μg/kg in group III—as anesthesia induction. 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 performed. 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 maintained between 35 mmHg and 45 mmHg (1 mmHg = 0.133 kPa) by mechanical ventilation. The oxygen flow rate was set to 2 L/min during the operation. Intravenous anesthesia along with inhalation

anesthesia was administered to maintain anesthesia. The inhaled sevoflurane dose was 1.0 MAC, and 0.5 μg·kg^{-1}h^{-1} dexmedetomidine hydrochloride was infused intravenously. The initial plasma concentration of propofol target-controlled infusion is set to 2 μg/mL. The concentration of propofol is 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 is 40–50. When the SPI is more than 55, 1 μg/kg fentanyl was added. Then, 0.05 mg/kg cisatracurium was intravenously injected every 40–50 min to maintain muscle relaxation. Propofol and dexmedetomidine concentrations were decreased when persistent hypotension occurred. When hypotension cannot be corrected or the RE value was >60, phenylephrine was administered to maintain stable circulation. Sodium lactate Ringer's solution and hydroxyethyl starch 130/0.4 were infused intravenously to supplement blood volume. Concentrated red blood cells were infused when the hemoglobin level was <70 g/L. Consequently, 5 mg tropisetron was injected intravenously approximately 15 min before the end of surgery to prevent postoperative nausea and vomiting (PONV). At the end of the operation, sevoflurane, dexmedetomidine, and propofol were discontinued, and the patient was sent to the postanesthesia care unit. The tracheal tube can be removed when the patient is awake, eyes are open, the spontaneous breathing tidal volume reaches 5–8 mL/kg, and the respiratory rate is 14–18 cycles/min. The patients were under observation for 30 min and returned to the ward when the partial pressure of oxygen was >70 mmHg and SpO2 was >95% under inhaled air conditions.

Postoperative analgesia

After the operation, 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 diluted to 100 mL. The background infusion rate was 2 mL/h and the PCA dose was 2 mL in group I; the background infusion rate was 1.5 mL/h and the PCA dose was 1.5 mL in group II; and the background infusion rate was 0.5 mL/h and the PCA dose was 0.5 ml in group III, with a lockout time of 15 min. 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 on an 11-point VAS (0 = no pain; 10 = unbearable pain), and a VAS score of ≤3 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

The genotypes of all patients were recoded, and the patients were categorized accordingly; the operation and wake-up (the time from the stopping of general anesthetics to the removal of the tracheal tube) times were recorded. Furthermore, 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 suturing of the skin (T5). The resting VAS scores of all patients were recorded immediately after the recovery of consciousness, 6 h, 12 h, 24 h, and 48 h after surgery to evaluate the degree of postoperative analgesia. Patient comfort level was evaluated using the Bruggemann comfort scale (BCS). The BCS scoring standards were as follows: 0 means persistent pain; 1 means painless when quiet or severe pain when breathing deeply or coughing; 2 means painless when lying flat or mild pain when

breathing deeply or coughing; 3 means painless when breathing deeply; and 4 means painless even when coughing. The consumption of fentanyl during the operation and within 48 h after surgery was recorded, respectively. In addition, the effective number of PCIA compressions was recorded; the incidence of fentanyl-related adverse reactions within 48 h after surgery, such as sedation, respiratory depression, PONV, itching, and lethargy, was recorded.

Statistical processing

Data were analyzed using Statistical Package for the Social Sciences, version 20.0 (IBM Corp., Armonk, NY, USA). Normally distributed quantitative data are expressed as means ± standard deviation (SD). A group t-test was used to determine the intergroup differences. Count data are presented as rate (%), using a χ^2 test or Fish's exact probability test. *P* values of ≤0.05 indicated statistical significance.

Results

In total, 100 patients were recruited in this study, and their demographic and clinical characteristics are summarized in Table 3. Two of the 100 patients were excluded from the study owing to unsuccessful classification, and finally, 98 patients were included. According to the genotype results, the patients were divided into three groups: group I was the wild-type homozygous group (CYP3A4*1/*1; CYP3A5*1/*1), group II was the heterozygous group, and group III was the mutant-type homozygous group (CYP3A4*1G/*1G; CYP3A5*3/*3). Twenty patients (20.41%) had wild-type homozygotes, 70 patients (71.43%) had heterozygotes, and 8 patients (8.16%) had mutant-type homozygotes (Table 1). 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%, and the allele frequency was consistent with the Hardy–Weinberg equilibrium (χ^2 = 0.705; p = 0.401) (Table 2). No significant differences in age, BMI, operation time, and recovery time were observed between the three groups (p > 0.05) (Table 3). No patients needed rescue analgesics for insufficient postoperative analgesia, and no patients requested termination of PCA due to adverse reactions.

Table 1. Genotyping of all patients.

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

Ⅲ	*1G/*1G	*3/*3	8(8.16)	Mutant homozygous

Data are expressed as numbers and number%.

Table 2. Allele frequency.

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

Data were expressed as numbers and number%.

Table 3. Demographic and clinical characteristics between the different genotypic groups.

Group	n	Year	BMI（kg/m2）	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

Data are expressed as numbers and means ± SD. BMI, body mass index.

We compared the blood glucose and SPI values of the three groups at various points during surgery (Tables 4 and 5). For all groups, blood glucose and SPI values were the highest immediately after intubation, and blood glucose levels continued to decrease from intubation to skin suturing. No statistically significant differences in SPI and blood glucose values were perceived between the three groups at the same time point during operation ($p > 0.05$).

Table 4. Comparison of SPI at different time points between the different genotypic 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

Data are expressed as numbers and means ± SD. SPI, surgical plethysmography index; T1, on admission; T2, immediately after tracheal intubation; T3, during skin incision; T4, during the operation for 1 h; T5, during skin suturing.

Table 5. Comparison of blood glucose levels at different time points between the different

genotypic 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

Data are expressed as numbers and means ± SD. T1, on admission; T2, immediately after tracheal intubation; T3, during skin cutting; T4, during the operation for 1 h; and T5, during skin suturing.

Tables 6 and 7 reveal the resting VAS and BCS scores of each genotype group at 0, 6, 12, 24, and 48 h after PCA initiation. The BCS scores of the three groups of patients continued to increase from 0 to 48 h after surgery. No significant differences in the VAS and BCS scores were found between the three groups at different time points after surgery ($p > 0.05$).

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

Group	n	VAS				
		Immediately after surgery	6h after operation	12h after operation	24h after operation	48h after operation
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

Data are expressed as numbers and means ± SD. VAS, visual analog scale.

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

Group	n	BCS				
		Immediately after surgery	6h after operation	12h after operation	24h after operation	48h after operation
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

Data are expressed as numbers and means ± SD. BCS, Bruggemann comfort scale.

In addition, the number of effective PCA compression and the total consumption of fentanyl during and after the operation were recorded in the three groups. For the three groups, the

consumption of fentanyl during the operation 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 homozygous group (CYP3A4*1/*1; CYP3A5*1/*1), 754.00 ± 29.54 μg in the heterozygous group, and 495.00 ± 9.26 μg in the mutant-type homozygous group (CYP3A4*1G/*1G; CYP3A5*3/*3) (Table 8). Statistical analysis showed that the intraoperative and postoperative fentanyl doses in the mutant-type homozygous group were significantly lower than those in the wild-type homozygous group ($p < 0.05$). The intraoperative and postoperative fentanyl doses and the number of effective PCA compression decreased in the three groups, and the difference was statistically significant (all $p < 0.05$) (Table 8).

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

Group	n	Intraoperative fentanyl usage (μg)	Postoperative fentanyl usage (μg)	Effective PCA times (times)
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

Data are expressed as numbers and means ± SD.

The results of the analysis of the side effects 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 and lethargy were found in the mutant-type homozygous group. No significant difference in the postoperative side effects was observed between the patients in each genotype group ($p > 0.05$). All patients did not experience excessive sedation, resulting in respiratory depression.

Table 9. Comparison of incidence of PONV, itching, and lethargy between the genotype 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）

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

Discussion

Fentanyl is a new type of analgesic drug developed and synthesized in the 1960s. It can stimulate μ opioid receptors and exert powerful analgesic effects[15]. It has been widely used in surgical anesthesia and treatment of acute and chronic pain. Fentanyl plays an important role in relieving postoperative pain, inhibiting excessive stress response, improving the quality of

patients' life, and promoting postoperative recovery[16]. However, it has many complications, such as delayed postoperative recovery, respiratory depression, nausea and vomiting, and increased incidence of chronic pain[4]. The analgesic effects and adverse reactions of fentanyl vary significantly between individuals[4], and the minimum 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 enzyme system, the main metabolic enzyme of fentanyl. The SNP of CYP3A4 and CYP3A5 affects the expression and activity of the enzyme and then leads 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 can quickly and accurately analyze the patient's genotype. According to the results of genotype testing, individualized fentanyl medication administration was implemented during the perioperative period. During anesthesia induction and surgical operations, if the anesthesia is too shallow, it will cause a strong stress response, consequently causing violent fluctuations in the circulation and even suppress immune function[17]. The SPI 错误!未找到引用源。 can be used as an effective indicator to quantify the intensity of analgesia during surgery, and blood glucose is a clinical stress indicator[19]. This study combines SPI and blood glucose values to analyze analgesic intensity and stress response. No patient showed obvious insufficiency of analgesia and severe stress response during surgery with strong noxious stress response[4], such as tracheal intubation and skin incision. It is suggested that with regard to the administration of individualized fentanyl analgesia, the analgesic effect and anti-stress ability of the three groups were similar. Owing to the similar degree of pain control, patients in the mutant-type homozygous group (CYP3A4*1G/*1G; CYP3A5*3/*3) required significantly less intraoperative fentanyl requirements. Furthermore, no adverse reactions, such as respiratory depression and delayed recovery, were observed during the resuscitation period of anesthesia.

The patients in this study plan to undergo video-assisted thoracic surgery (VATS). Although VATS has many advantages, such as it is less invasive; it ensures quick recovery and light pain; it has a definite curative effect; and it is safe and reliable [20][21]. However, the 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 more likely to occur. Simultaneously, severe pain can easily induce a stress response. In addition, it causes tissue damage by destroying the immune system, affects the healing of surgical incisions, and increases the chance of infection. Therefore, perfect postoperative analgesia is crucial to promote the rapid recovery of patients who underwent VATS. Obvious individual differences in the analgesic effects and adverse reactions of PCIA exist. Some patients have inadequate analgesia, and other patients experience various adverse reactions and side effects due 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 showed that compared with the other two groups of patients, the mutant-type homozygous group (CYP3A4*1G/*1G; CYP3A5*3/*3) required significantly smaller fentanyl doses for postoperative pain control. This suggested that CYP3A4*1G/*1G and CYP3A5*3/*3 variant alleles play a key role in the changes in CYP3A4 and CYP3A5 enzyme activities and plasma fentanyl concentrations. Our findings are similar to those of other clinical studies after the treatment of gastrointestinal cancer and lower abdominal surgery. No significant intergroup difference in the VAS and BCS scores was observed at each time point within 48 h after surgery ($p > 0.05$). In addition, postoperative adverse reactions, such as nausea, vomiting, itching, and lethargy, did not occur in a statistically significant manner ($p > 0.05$). These findings suggest that the implementation of an individualized PCIA analgesia program can optimize pain management, provide better analgesia, increase patient comfort, and reduce complications.

Conclusion

In this study, the perioperative dose of fentanyl was appropriately adjusted individually based on the genotypes of the patients undergoing thoracoscopic radical resection for lung cancer. The results show that individualized administration can reduce the use of drugs and reduce adverse drug reactions under the premise of ensuring analgesic effects. This outcome is of great significance to promote the rapid recovery of patients and improve the comfort and satisfaction of patients after surgery. This study suggests that guiding the personalized medication of fentanyl based on the results of CYP3A4 and CYP3A5 gene testing is feasible. However, this study still has many limitations. First, the sample size is inadequate. Second, the pain at rest was evaluated instead of dynamic pain. Third, the blood concentrations of fentanyl and norfentanyl were not measured. Therefore, conducting a multicenter, large-sample clinical study on individualized fentanyl administration and analyzing the precise dosage of fentanyl in patients with different genotypes is warranted to more precisely guide individualized fentanyl administration.

Supplementary information

Abbreviations

PCIA: patient-controlled intravenous analgesia; PCA: patient-controlled analgesia; VAS: the visual analog scale; SPI: Surgical plethysmography index; BCS: Bruggemann comfort scale; CYP: cytochrome P450; SNP: single nucleotide polymorphism; BMI: body mass index; ASA: American Society of Anesthesiologists; HR: heart rate; MAP: mean arterial pressure; SpO2: pulse oxygen saturation; SE: state entropy; RE: response entropy; PONV: postoperative nausea and vomiting; SD: standard deviation; VATS: video-assisted thoracic surgery.

Ethics approval and consent to participate

Ethical approval for this study (Ethics Committee of the Affiliated Hospital of Jiaxing University) was provided by the Ethics Committee of the Affiliated Hospital of Jiaxing University (2017-177), Jiaxing, China on 12/25/2017.

Consent for publication

Not applicable.

Availability of data and material

All the patient information and research data can be inquired and used in the Ethics Committee of the Affiliated Hospital of Jiaxing University.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZXY conceived this study. YYB participated in the design of this study. KM performed the statistical analysis. SX and WSY carried out the study and collected important background information. WSY drafted the manuscript. All authors have participated in study discussion and manuscript preparation. All of the authors have read and approved the final manuscript.

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