

Original Article

ABCB1 3435 C > T and 1236 C > T and efficacy of sevoflurane-remifentanil on patients undergoing laparoscopic cholecystectomy

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Abstract: Aim: To explore the associations between *ABCB1* single nucleotide polymorphisms (SNPs) 1236 C > T and 3435 C > T, as well as the effect of sevoflurane-remifentanil on the patients undergoing laparoscopic cholecystectomy. Methods: For this study, a total number of 80 patients were recruited to undergo laparoscopic cholecystectomy, which resulted in the verification of genotype frequency and allele frequency distributions at 1236 C > T and 3435 C > T in *ABCB1* gene. Results: The patients with TT genotype had significantly shorter anesthesia induction time than those with CC and CT genotype at both 1236 C > T and 3435 C > T ($P = 0.004$). The patients with TT had significantly higher OAAS scores and shorter extubation time compared to those with CC and CT genotype at both 1236 C > T and 3435 C > T (all $P < 0.05$). In addition, patients with 3435TT spent significantly less time regaining a sense of orientation than those with 3435CC and 3435CT (all $P < 0.05$). The remifentanil dosage for patients with 1236TT was significantly lower than that for patients with 1236CC and 1236CT both at T_1 and T_2 (all $P < 0.05$); a significantly lower dosage of remifentanil was recorded in patients with 3435TT compared to patients with 3435CC and 3435CT at T_1 . Patients with 3435TT had significantly higher incidence of respiratory depression than patients with 3435CT and 3435CC (both $P < 0.05$). Conclusion: Patients with *ABCB1* 1236TT or 3435TT may have better response to analgesia but patients with 3435TT have a high risk of respiratory depression after having undergone laparoscopic cholecystectomy.

Keywords: *ABCB1*, single nucleotide polymorphism, 1236 C > T, 3435 C > T, laparoscopic cholecystectomy, sevoflurane-remifentanil, anesthetic effect

Introduction

Laparoscopic cholecystectomy is widely accepted among doctors and patients for its simplicity, as well as a lower rate in operational sequel, rapid recovery and less complication after operation [1, 2]. Due to its short operation time and high stimulus intensity, laparoscopic cholecystectomy requires anesthesia not only for safety and effectiveness, but also for good analgesia quality and less adverse effects [3]. Usually, anesthesia may cause postoperative side effects such as excessive sedation, respiratory depression, nausea, emesis and bradycardia, which may bring about a longer operation cycle, worse clinical outcomes and lower patient satisfaction [4, 5]. To our knowledge,

drug response may vary between individuals, and individual susceptibility plays an important role in the drug therapy for its participation in toxicity or inadequate treatment [6]. Therefore, an individualized anesthesia plot/plan is very necessary in order to lower the chance of adverse events from happening. Recently, the association between genetic polymorphisms and drug response have aroused increasing interest for gene variation's effectiveness in tracking the differences among individuals [7].

ABCB1/MDR1 is identified as a multidrug resistant gene which encodes P-glycoprotein (P-gp), an active drug efflux transporter and an important biological gatekeeper to limiting the accumulation of xenobiotics [8]. A variety of drugs,

such as chemotherapeutic agents, cardiac drugs, antibiotics, steroids and antiretroviral drugs, are proved to be excellent substrates of *ABCB1* [9]. Several studies reported a significant association between gene polymorphism and drug response [10, 11]. In this context, we hypothesize that the genotyping in *ABCB1* may help make an individualized anesthesia scheme for Chinese patients undergoing laparoscopic cholecystectomy.

In the present study, we compared the anesthetic effect, analgesia quality, dosage of remifentanyl and adverse effect in patients with different genotypes at *ABCB1* single nucleotide polymorphisms (SNPs), 1236 C > T and 3435 C > T, after anesthesia with sevoflurane-remifentanyl, "aiming to explore the associations" between *ABCB1* polymorphisms and the patients' response to anesthesia with sevoflurane-remifentanyl.

Materials and methods

Ethic statement

This study was carried out in strict consistence with the protocols established by the Ethics Committee of Yishui Central Hospital of Linyi, Linyi, China. All the experimental procedures in this study were in accordance with the Declaration of Helsinki [12]. Informed consents were obtained from all subjects participating in this study which was approved by the local institutional review board.

Study subject

We randomly recruited 91 patients who were diagnosed with benign gallbladder diseases at the American Society of Anesthesiologists (ASA) all of whom had received laparoscopic cholecystectomy at Yishui Central Hospital of Linyi between March 2015 and May 2015. All 91 patients had indications (symptomatic gallstones > 3 cm in diameter, fulfilled gallstones, chronic cholecystitis, and polypoid lesions in gallbladder) for laparoscopic cholecystectomy: we excluded patients who had acute cholecystitis accompanied by severe complications, acute gallstone pancreatitis, acute cholangitis, primary choledocholithiasis, hepatolithiasis; patients with severe renal and hepatic diseases, diabetes and depression; patients with a longstanding use of painkillers and patients

allergic to tranquilizers and opioids. All patients were Han Chinese and blood samples were collected from their peripheral veins. Among the 91 patients, 7 dropped out during the observation for the presence of such side effects as nausea and emesis, and another 4 were lost for the failure of DNA extraction. Finally, our study gathered clinical data of 80 patients (43 males and 37 females) with a mean age of 34.8 ± 7.4 years old, mean weight of 56.2 ± 5.4 kg, and mean operation time of 52.23 ± 11.99 min.

Anesthesia method

All 80 patients were required to fast for 12 hours before operation and no other drugs were administered to them other than intramuscular injection of 0.5 mg atropine (Guangzhou Baiyunshan Hanfang Pharmaceutical Co. Ltd., Guangzhou, China) and 0.1 g phenobarbital sodium (Shanghai Xinya Pharmaceutical Co. Ltd., Shanghai, China) 30 mins before operation. Upon entering the operation room, the operators established a vein passage on the patients' forearm, followed by nasal rhinal, regular electrocardiogram monitoring and vital-signs monitoring. For anesthesia induction, midazolam (0.04 mg/kg; Renfu Pharmaceutical Co., Ltd, Yichang, Hubei), fentanyl (5 µg/kg; Renfu Pharmaceutical Co., Ltd, Yichang, Hubei) and vecuronium bromide (0.12 mg/kg) were injected in turns, then trachea cannula was conducted and a respirator was used to maintain oxygen flow rate of 1.5 L/min at a frequency of 12~20 times/min and tidal volume of 8~12 ml/kg. After the fixation of endotracheal tube, sevoflurane (at a concentration of 2%~4%; Maruishi Pharmaceutical co., Ltd, Japan) was used for inhalation anesthesia which lasted through the whole operation and then remifentanyl (0.005~0.5 g/(kg·h); Renfu Pharmaceutical Co., Ltd, Yichang, Hubei) was pumped in with a micro pump. During the anesthesia induction, the anesthesia depth was regulated according to the changes observed by vital-signs monitoring and vecuronium bromide (0.05 mg/kg; Jiangsu HaiCi Biological Pharmaceutical Co., Ltd., Yangtze River Pharmaceutical Group, Taizhou, Jiangsu) was injected to relax the muscle if necessary. Through the laparoscopic cholecystectomy, pneumoperitoneum was performed with carbon dioxide (CO₂), limiting the intra-abdominal pressure to 12~14 mmHg. On-

Table 1. The primer sequences of *ABCB1* single nucleotide polymorphisms, 1236 C > T and 3435 C > T

Site	Primer sequence	Length of the target fragment
1236 C > T	Forward: 5'-TTCACCTCAGTTACCCATC-3'	315 bp
	Reverse: 5'-CATAGAGCCTCTGCATCA-3'	
3435 C > T	Forward: 5'-GATCTGTGAACCTTGTGTTTCA-3'	197 bp
	Reverse: 5'-GAAGAGAGACTTACATTAGGC-3'	

ce all endoscopic operations came to an end, the pneumoperitoneum and the inhalation anesthesia were stopped and the oxygen rate was upregulated to 5 ml/min. After finishing the whole operation, the operators closed the micro pump and stopped using anesthetic drugs. The endotracheal tube was removed when the patients regained consciousness, autonomous respiration and swallowing reflex. If pain reflexes such as body movement, moaning and frowning were observed during the operation, disoprolol (0.5~1 mg/kg; Astra Zeneca, Italy) was used to ease the pain.

Monitoring indexes

The systolic blood pressure (SBP), heart rate (HR) and saturation of blood oxygen (SpO₂) were recorded at the beginning of anesthesia induction (T₀), 10 mins after pneumoperitoneum (T₁) and during the withdrawal of remifentanil (T₂). Using Observer's Assessment of Alertness/Sedation Scale (OAAS), the anesthetic effect was leveled on the basis of alertness at extubation. The score system of OAAS was the following: quick response to naming at a normal volume (5 points); total awareness but with a slow response to naming at a normal volume and speaking relatively slow (4 points); responding only to naming at a high volume or repeated naming with unclear articulation and glassy eyes (3 points); responding to slight pushing and tapping with a tied tongue and glassy eyes (2 points); no response to slight pushing or tapping and being lethargic (1 point). In addition, we also recorded the time to regaining consciousness (time from end of surgery to full consciousness), the recovery time for regaining orientation (finger to nose test) and such adverse effects as respiratory depression (respiratory rate < 12 times/min or respiratory standstill for 15 s), abdominal pain after operation and emesis [13].

Detection of *ABCB1* polymorphisms

The primer sequences of *ABCB1* 1236 C > T and *ABCB1* 3435 C > T were listed in **Table 1**. The genotyping of 1236 C > T and 3435 C > T was performed under the following PCR system (20 µl): genome DNA (1 µl), forward and reverse primers (50 pmol/L), DNA polymerase (Taq polymerase; 0.12 µl), dNTPs (0.28 µl), 10 × Buffer (2.0 µl), Mg²⁺ (1.6 µl). The PCR protocol consisted of 37 cycles of 5-min initial denaturation at 94°C, 40-s denaturation at 94°C, 35-s annealing at 54~58°C, 40-s extension at 72°C. The suitable incision enzyme for the mutation site of 1236 C > T was BsuRI and that for the mutation site of 3435 C > T was BfuCI. The PCR products were analyzed with the incision enzyme at a ratio of 1.5 µl/8 µl and the enzyme-digested product was electrophoresed in 3% agarose gel at a voltage of 120 V for 40 min, which the electrophoresed products observed under 300-nm ultraviolet light and photographed. Using DNAMAN software, we figured out the incision enzymes for the mutation sites 1236 C > T and 3435 C > T and the results of electrophoresis as shown in **Figure 1**.

Statistical analysis

Data analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago, USA). The Hardy-Weinberg equilibrium tests on the genotype frequency and allele frequency in *ABCB1* 1236 C > T and 3435 C > T were conducted with χ^2 test. The measurement data that meet the normal distribution were expressed as mean ± standard deviation (SD). One-Way analysis of variance (ANOVA) was used to analyze the comparison on SBP, HR, SpO₂, extubation time, OAAS score, the recovery time for regaining orientation and the dosage of remifentanil among the patients with genotypes in *ABCB1* 1236 C > T and 3435 C > T, while comparisons between two genotypes were analyzed by least significant difference (LSD-t). The comparisons between the dosages of remifentanil at different timings during the operation were performed with Kruskal-Wallis H test. The count data were expressed as numbers or percentages, and the relationship between *ABCB1* genotypes and adverse effects of anesthesia were analyzed by χ^2 test. $P < 0.05$ was considered as statistically significant.

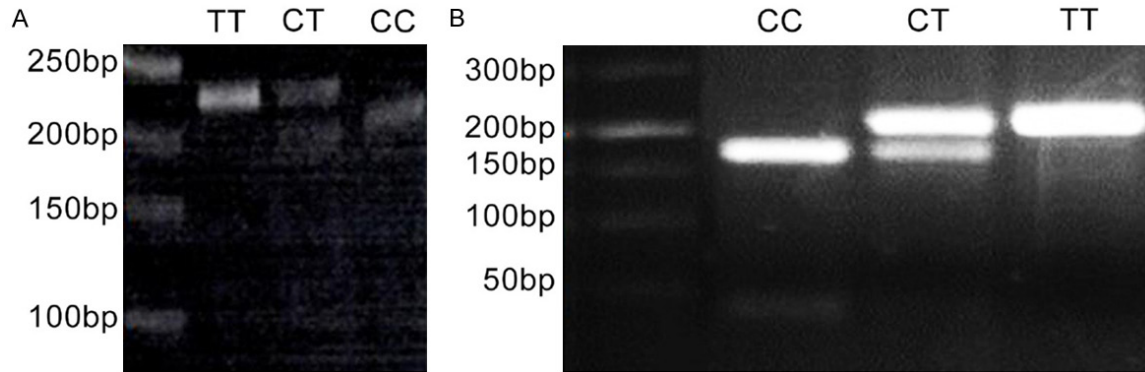


Figure 1. Electrophoretograms of digested PCR products: A. BsuR I-digested PCR products of 1236 C > T; B. BfuC I-digested PCR products of 3435 C > T. Note: 1236TT = 252 bp; 1236CT = 252 bp/218 bp; 1236CC = 218 bp; 3435TT = 197 bp; 3435CT = 197 bp/158 bp; 3435CC = 158 bp; PCR, polymerase chain reaction.

Table 2. The distribution of the genotype frequency and allele frequency in *ABCB1* gene

Genotype	Actual number of cases (frequency)	Theoretical number of cases (frequency)	χ^2	P
1236 C > T	80		0.02	0.89
CC	15 (18.75%)	15.31 (19.14%)		
CT	40 (50.00%)	39.38 (49.22%)		
TT	25 (31.25%)	25.31 (31.64%)		
Allele T	45 (56.25%)			
3435 C > T	80		0.00	0.96
CC	30 (38.75%)	30.01 (37.52%)		
CT	38 (46.25%)	37.98 (47.47%)		
TT	12 (15.0%)	12.01 (15.01%)		
Allele T	31 (38.75%)			

Results

Distribution of genotype frequency and allele frequency in *ABCB1*

The distribution of genotype frequency and allele frequency in *ABCB1* complied with the Hardy-Weinberg law, as shown in **Table 2**. At 1236 C > T, the mutation frequency of allele T was 56.25% ($\chi^2 = 0.02$, $P = 0.89 > 0.05$), with 15 of CC wild-type homozygote, 40 of TC mutant heterozygote and 25 of TT mutant homozygote. At 3435 C > T, the mutation frequency of allele T was 38.75% ($\chi^2 = 0.00$, $P = 0.96 > 0.05$), with 30 of CC wild-type homozygote, 38 of TC mutant heterozygote and 12 of TT mutant homozygote.

Genotypes and anesthetic effect

The relationships between genotypes and anesthetic effect were shown in **Table 3**. The

expression of SBP, HR and SpO₂ was closely observed at the beginning of anesthesia induction and during the operation. No significant differences among the expressions of SpO₂ at T₀, T₁ and T₂ were identified among the included cases (all $P > 0.05$). The anesthesia induction time of patients with 1236TT and 3435TT was significantly shorter than that of patients with CC and CT genotype at both 1236 C > T and 3435 C > T ($P = 0.004$). In patients with 1236CC, 1236CT, 3435CC and 3435CT, a significantly higher expression of SBP and HR was observed at T₁ than that at T₀ (all $P < 0.05$), while in patients

with 1236TT and 3435CT, no significant difference was found between the expressions of SBP and HR at T₁ and T₀ (all $P > 0.05$). At T₂, patients with 1236CC, 1236CT, 3435CC and 3435CT presented a significantly decreased expression of SBP and HR than they did at T₀ (all $P < 0.05$), while patients with 1236TT and 3435TT had no changes in their expressions of SBP and HR, compared with those at T₀ (all $P > 0.05$).

Genotypes and postoperative analgesia quality

The associations of genotypes to the extubation time, OAAS score and time for regaining orientation were presented in **Table 4**. After operation, patients with 1236TT and 3435TT scored significantly higher and also had a shorter extubation time than those with CC and CT genotype at both 1236 C > T and 3435 C > T (all $P < 0.05$). In addition, patients with 3435TT

Table 3. The associations of genotype and anesthetic effect

Genotype	Anesthesia induction time (s)	T ₀			T ₁			T ₂		
		SBP (mmHg)	HR (times/ min)	SpO ₂ (%)	SBP (mmHg)	HR (times/ min)	SpO ₂ (%)	SBP (mmHg)	HR (times/ min)	SpO ₂ (%)
1236 C > T										
CC	73.0 ± 8.0	128.4 ± 11.3	66.5 ± 9.4	98.2 ± 0.15	135.7 ± 9.8*	78.4 ± 8.6*	99.5 ± 0.13	110.5 ± 12.3*	55.3 ± 8.7*	99.5 ± 0.15
CT	71.0 ± 6.0	124.7 ± 10.6	68.2 ± 10.1	98.4 ± 0.18	138.5 ± 9.4*	79.2 ± 7.9*	99.2 ± 0.15	112.3 ± 10.5*	54.6 ± 9.2*	99.4 ± 0.17
TT	64.0 ± 6.0*	125.1 ± 12.7	67.5 ± 9.8	98.9 ± 0.16	125.3 ± 8.6	67.8 ± 7.5	99.1 ± 0.11	126.4 ± 11.6	67.8 ± 8.4	99.5 ± 0.13
3435 C > T										
CC	69.0 ± 8.0	127.7 ± 12.5	65.7 ± 8.6	98.3 ± 0.19	136.6 ± 9.1*	80.2 ± 7.4*	99.4 ± 0.19	105.7 ± 10.1*	53.7 ± 6.7*	99.5 ± 0.18
CT	67.0 ± 6.0	125.0 ± 10.7	67.7 ± 9.9	98.6 ± 0.31	134.4 ± 11.5*	77.7 ± 9.9*	99.2 ± 0.11	118.6 ± 12.8*	58.0 ± 10.8*	99.4 ± 0.15
TT	63.0 ± 4.0*	127.7 ± 13.5	68.2 ± 3.9	98.9 ± 0.14	125.5 ± 7.5	67.3 ± 5.7	99.1 ± 0.13	126.3 ± 12.3	67.5 ± 10.7	99.5 ± 0.10

Note: *refers to $P < 0.05$ in the comparison with the value at the beginning of anesthesia induction.

Table 4. The association between genotype and analgesia quality

Genotype	Extubation time (min)	P value	OAAS score	P value	Time for regaining orientation (min)	P value
1236 C > T						
CC	11.86 ± 5.41	0.045	3.10 ± 0.25		4.69 ± 0.41	0.037
CT	12.98 ± 5.13		3.21 ± 0.22	< 0.001	4.73 ± 0.48	
	9.70 ± 4.72 [#]		3.50 ± 0.36 ^{*,#}		4.44 ± 0.40 [#]	
3435 C > T						
CC	12.55 ± 4.93	0.044	3.10 ± 0.25		4.69 ± 0.54	0.010
CT	12.19 ± 5.66		3.25 ± 0.20 [*]	< 0.001	4.70 ± 0.38	
TT	8.34 ± 2.74 [*]		3.75 ± 0.25 ^{*,#}		4.26 ± 0.34 ^{*,#}	

Note: ^{*}refers to $P < 0.05$ in the comparison with patients with CC genotype; [#]refers to $P < 0.05$ in the comparison with patients with CT genotype.

spent significantly less time regaining orientation after operation than those with 34345CC and 3435CT (all $P < 0.05$).

Genotypes and dosage of remifentanil

Through the whole operation, remifentanil was used for analgesia. The dosage of remifentanil for patients with 1236TT was significantly lower than that for patients with 1236CC and 1236CT both at T_1 and T_2 (all $P < 0.05$); a significantly lower dosage of remifentanil was recorded in patients with 3435TT compared with patients with 3435CC and 3435CT at T_1 , while no significant difference in the dosage of remifentanil was observed at T_2 (Figure 2).

Genotypes and adverse effects of anesthesia

Remifentanil was a typical μ -opioid receptor, of which the major adverse effects were excessive sedation, respiratory depression, nausea, emesis and bradycardia. In our study, no excessive sedation was found and the incidence of nausea, emesis and respiratory depression was 37.5% (30 cases), 17.5% (14 cases) and 12.5% (10 cases), respectively. No significant difference in the incidence of nausea and emesis was found among the patients (all $P > 0.05$). The patients with 3435TT had significantly higher incidence of respiratory depression than patients with 3435CT and 3435CC (both $P < 0.05$) (Table 5).

Discussion

Sevoflurane-remifentanil is a common anesthesia scheme for surgeries [14, 15]. It has been suggested that ABCB1 gene is associat-

ed with the anesthetic effect and Caucasian patients with 6T genotype and T3435T genotype show the least respiratory depression rate at 2-7 min after fentanyl injection [16]. With this study, we aim to investigate the effects of ABCB1 1236 C > T and 3435 C > T polymorphisms, two most-studied ABCB1 SNPs [17, 18], on the drug response

of Chinese patients who received laparoscopic cholecystectomy to sevoflurane-remifentanil.

In our study, we observed an increase of SBP and HR expression in patients with CC genotype and CT genotype at 1236 C > T and 3435 C > T 10 mins after pneumoperitoneum while decreased SBP and HR expression when anesthesia induction ended, suggesting that patients with CC genotype and CT genotype didn't have a good response to sevoflurane. However, patients with 1236TT and 3435TT presented no significant changes in the expression of SBP and HR and had a shorter time for anesthesia induction than those patients with CC genotype and CT genotype. On this ground, we suggested that a patient's drug response varies with the ABCB1 genotype he has, implying a close association between ABCB1 polymorphism and patients' response to anesthesia induction. In consistence with our study, Mukonzo et al. observed strong association between efavirenz relative bioavailability and ABCB1 3435 C > T polymorphism, an encouragement to look into the genotype of the patients for predicting the drug response [19]. Moreover, we also observed that patients with 1236TT and 3435TT had higher OAAS scores and shorter extubation time, as well as shorter time for regaining orientation and indications of higher analgesia quality. As suggested, ABCB1 gene is a drug-transporter, which is responsible for the disposition of xenobiotic, regulating bioavailability and reducing cell toxicity of a variety of drugs [20]. After carrying out anesthesia induction, we believe that ABCB1 gene may act as a cleaner, preventing the linger of sevoflurane in patients with 1236TT and 3435TT. Meng et al. found

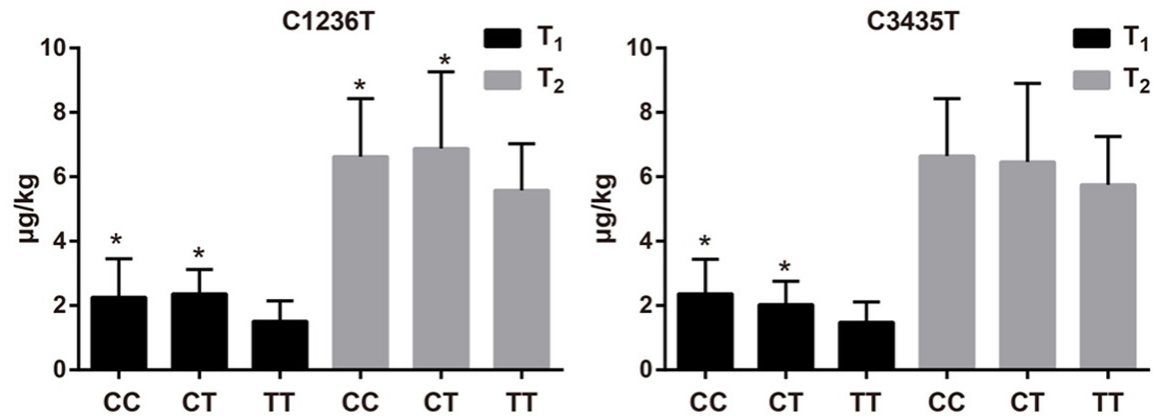


Figure 2. The comparisons between patients with different genotypes in the dosage of remifentanyl at 10 min after pneumoperitoneum (T₁) and at the withdrawal of remifentanyl (T₂). Note: *refers to $P < 0.05$ in the comparison with patients with TT genotype.

Table 5. The associations between genotype and adverse effects

Genotype	Number of cases	Nausea (%)	<i>P</i> value	Emesis (%)	<i>P</i> value	Respiratory depression (%)	<i>P</i> value
1236 C > T	80		0.897		0.964		0.468
CC	15	6 (40.0)		3 (20.0)		3 (20.0)	
CT	40	16 (40.0)		7 (17.5)		3 (7.5)	
TT	25	8 (32.0)		4 (16.0)		4 (16.0)	
3435 C > T	80		0.977		0.781		0.025
CC	30	11 (36.7)		4 (13.3)		3 (10.0)	
CT	38	14 (36.8)		8 (21.0)		2 (5.3)	
TT	12	5 (41.7)		2 (16.7)		5 (41.7)	

that Chinese epilepsy patients with *ABCB1* 3435TT had a lower carbamazepine concentration than those with *ABCB1* 3435CC [21].

Another important result in our study shows that *ABCB1* polymorphism is in strong association with the dose of remifentanyl during operation. Accordingly, Singh et al. suggested *ABCB1* polymorphism as a dosage-predictor in the administration of escitalopram for remission in major depression [22]. From the above, it is reasonable to conclude that through genotyping in *ABCB1*, we may be able to estimate the drug dose needed in the operation. According to our observation, patients with 3435TT were found to have a higher risk of respiratory depression. Fujita et al. also found that patients with *ABCB1* 3435TT had a higher frequency of vomiting [23]. However, the reason why patients *ABCB1* 3435TT have a higher susceptibility to adverse event remains to be explored in future studies.

Taken together, we hypothesize that we could use genotyping in *ABCB1* gene as a reference to predict intraindividual variation in drug response and therefore make clinical decision on the dosage of drug [24]. On the contrary, there is a meta-analysis which observed no association between *ABCB1* polymorphism and drug resistance [25].

A possible reason, as Wang et al suggested, is the lack of clinical utility for the inaccessibility of pharmacokinetic testing to the majority [26]. In the future, more efforts shall be made to explore the association of genotyping to intraindividual response to anesthesia with clinical studies of larger sample size.

To sum up, we provided compelling evidence that *ABCB1* 3435 C > T and 1236 C > T genotypes differentially influence the efficacy of sevoflurane-remifentanyl in the patients undergoing laparoscopic cholecystectomy, with *ABCB1* 1236TT and 3435TT of better response to analgesia but 3435TT of high risk of respiratory depression after laparoscopic cholecystectomy. However, a comprehensive study with larger sample size is still in want to further confirm the association between *ABCB1* polymorphisms and anesthesia.

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Disclosure of conflict of interest

None.

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