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Original Article

CYP2D6 gene polymorphisms influence postoperative pain sensitivity and drug response in lung cancer surgery

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Abstract: Objective: To investigate the role of CYP2D6 gene polymorphism expression in postoperative pain sensitivity and individualized drug response in lung cancer patients undergoing thoracoscopic surgery. Methods: Sixty patients (aged 40-80 years, ASA I-III) undergoing thoracoscopic lung surgery between January 2024 and March 2025 were enrolled. Preoperative blood samples were collected to assess CYP2D6 gene expression. Based on enzyme activity, patients were divided into two groups: Group I (high CYP2D6 expression, n=30) and Group II (low expression, n=30). All patients received standardized anesthesia and postoperative analgesia with tramadol. Evaluated outcomes included: CYP2D6 gene activity; pain scores at 2, 4, 6, 8, and 10 hours postoperatively (VAS); PCA pump usage; ST-T segment changes on ECG; incidence of adverse events (sweating, nausea, vomiting, urinary retention); time to first cough and ambulation; and length of hospital stay. Results: Group I showed significantly higher CYP2D6 expression (P<0.01). Postoperative VAS scores and PCA usage (T2-T5) were significantly greater in Group I (P<0.01). ST-T changes were more pronounced in Group I at T2 and T5 (P<0.01). Group II had a higher incidence of adverse reactions (P<0.05) but demonstrated earlier coughing, earlier ambulation, and shorter hospital stays (P<0.01). No significant differences in age, weight, height, BMI, or surgical time were observed. Conclusion: Patients with low CYP2D6 activity experienced stronger and longer analgesic effects after surgery. CYP2D6 genotyping may support personalized pain management in lung cancer surgery, promoting enhanced recovery (ERAS) and reduced hospital burden.

Keywords: CYP2D6, genetic polymorphism, PCA, lung cancer, ERAS

Introduction

Lung cancer remains one of the most prevalent malignancies and a leading cause of cancer-related mortality worldwide [1-3]. In China, it ranks first in both incidence and mortality among all cancers [4]. Surgical resection remains the cornerstone of curative treatment for lung cancer [5-7]. However, thoracic surgery is associated with severe postoperative pain, significant intraoperative hemodynamic fluctuations, and a high risk of complications such as arrhythmias, respiratory depression, nausea, and circulatory instability [8-10]. These factors not only delay postoperative recovery but also increase hospital stay and healthcare burden. Therefore, effective postoperative pain control and individualized anesthetic management have become essential components of perioperative care.

In recent years, the Enhanced Recovery After Surgery (ERAS) concept has gained increasing attention in thoracic surgery. ERAS emphasizes evidence-based, multidisciplinary strategies to reduce surgical stress, minimize postoperative complications, and accelerate functional recovery through optimized anesthesia, analgesia, and perioperative management [11-13]. Within this framework, understanding interindividual variability in analgesic response has become a crucial step toward precision medicine.

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The cytochrome P450 2D6 (CYP2D6) enzyme plays a pivotal role in drug metabolism, particularly in the biotransformation of opioids such as codeine and tramadol into their active metabolites (e.g., O-desmethyltramadol), which exert stronger analgesic effects [14, 15]. Genetic polymorphisms in the CYP2D6 gene lead to considerable interindividual differences in enzyme activity, classifying individuals as poor, intermediate, extensive, or ultrarapid metabolizers. These variations significantly influence pain perception and postoperative analgesic efficacy. Previous studies have shown that patients with higher CYP2D6 activity metabolize opioids more rapidly, resulting in lower plasma concentrations of active metabolites and reduced analgesic effects, whereas those with lower activity experience prolonged analgesia or heightened adverse reactions [16-18]. This pharmacogenetic diversity underscores the need for personalized pain management strategies in surgical patients, particularly those undergoing thoracic surgery.

Therefore, this study aimed to evaluate the influence of CYP2D6 gene polymorphisms on postoperative pain susceptibility and variability in tramadol response among patients with lung cancer undergoing thoracoscopic surgery. By investigating the relationship between CYP2D6 enzyme activity, analgesic efficacy, and clinical outcomes, this research seeks to provide a foundation for individualized analgesic regimens, improve postoperative pain control, and enhance recovery in accordance with ERAS principles.

Methods

General information

This study was approved by the medical ethics committee of Jilin cancer hospital, and informed consent was obtained from all the patients or their guardians. Sixty patients (aged 40-80 years) were selected for thoracoscopic radical lung cancer surgery at our hospital from January 2024 to March 2025, with an ASA classification of I-III, with approval by the ethics committee of this hospital and informed consent signed by the patient or their family members. The exclusion criteria were severe cardiac or pulmonary dysfunction (cardiac function >3), severe hypertension (hypertension >3), severe liver or kidney dysfunction, coagulation disorders, and a history of diabetes or hypothyroidism.

Methodology

Anesthesia monitoring: All patients entering the operating room are routinely connected to two peripheral venous access lines in the lower limbs, and the Delger anesthesia system is used to monitor vital signs continuously. Blood pressure monitoring includes four limb leads and one chest lead, measuring heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SPO_2), and the bispectral index (BIS). During surgery, the concentration of inhaled and exhaled sevoflurane is monitored in real time, along with temperature and muscle relaxation monitoring.

Anesthesia methods: Before the operation, a 5 ml blood sample for gene expression activity testing was taken from each patient, and patients were subsequently randomly divided into two groups (30 patients each) on the basis of enzyme activity levels in a double-blind design. The Group I patients presented high CYP2D6 enzyme activity, whereas the Group II patients presented low enzyme activity. The general anesthesia induction protocol for both groups was as follows: intravenous administration of midazolam at 0.02-0.04 mg/kg, sufentanil at 0.2-0.3 μg/kg, propofol at 1.0-1.2 mg/kg, etomidate at 0.15-0.25 μg/kg, and succinate atracurium at 0.15-0.2 mg/kg (3-4 times the ED95 dose). After satisfactory anesthesia depth (BIS value between 40 and 60) was achieved, a double-lumen bronchial tube was inserted using a visual laryngoscope, and an immediate positioning check with a fiberoptic bronchoscope was performed to ensure accurate positioning of the double-lumen tube.

The drug regimen for maintaining anesthesia during surgery was the same in both groups. Both groups received a combination of intravenous and inhalation general anesthesia: continuous target-controlled infusion (TCI) of remifentanil at 0.1-0.2 ng/ml and continuous inhalation of sevoflurane at 1.0-1.5 MAC to maintain sedation. Fentanyl and succinylcholine were added as needed through bispectral index (BIS) monitoring and muscle tone monitoring. During surgery, mechanical ventilation was used to control respiration, with tidal volumes ranging from 6-8 ml/kg. The respiratory rate was adjusted to 10-12 breaths per minute on the basis of end-tidal CO_2 partial pressure (maintaining CO_2 partial pressure within the

range of 35-45 mmHg), ensuring that the SPO_2 level remained >90% during surgery.

After the procedure, once both groups of patients regained good consciousness and all reflexes, suctioning and lung percussion were performed. The double-lumen bronchial tube was removed after the patients naturally regained full awareness. Auscultation revealed clear breath sounds on both sides of the lungs, with no complications such as atelectasis. The frequency of spontaneous breathing reached 10-12 times per minute, and the tidal volume was maintained at 6-8 ml/kg. There was no pain at the surgical site or drainage sites, and vital signs were stable. The patients safely returned to the intensive care unit.

Analgesic methods: All patients were given tramadol for pain relief after receiving general anesthesia. Postoperative patient-controlled analgesia was started 2 h after surgery, and the expected duration of analgesia was 48 hours. The drug combination regimen included tramadol at a concentration of 18 mg/h + 100 ml of normal saline.

Observation indicators

CYP2D6 gene expression activity: Five milliliters of blood was drawn from all patients before surgery to detect the expression activity of the CYP2D6 gene, and the activity of the enzyme was recorded for comparison.

Pain conditions: The resting incision pain levels at 2 h (T_1), 4 h (T_2), 6 h (T_3), 8 h (T_4), and 10 h (T_5) post-surgery were recorded for both groups of patients via the VAS. For the VAS score, 0 indicates no pain, and 10 indicates unbearable severe pain. The number of PCA pump presses was recorded at 2 h, 4 h, 8 h, and 12 h post-surgery and compared between groups.

Changes in the ST-T of the ECG: Changes in the ST-T of the ECG at different time points after surgery.

Postoperative adverse reactions: The incidence of adverse reactions, including sweating, nausea, vomiting and urinary retention, within 12 h after surgery in the two groups of patients was recorded, and the incidence of adverse reactions was calculated.

Statistical analysis

For these experiments, SPSS version 21.0 software was used for statistical analysis. Measurement data with a normal distribution were expressed as the mean ± standard deviation ($\bar{x} \pm s$), and comparisons between groups were performed using the independent-sample t-test. Count data were expressed as frequencies and percentages (n, %) and analyzed using the chi-square (χ^2) test. A *P*-value <0.01 was considered statistically significant.

Results

Comparisons of general data such as age, height and weight between the two groups revealed no significant differences (P>0.05).

Comparison of CYP2D6 gene expression activity in the blood between the two groups revealed that the expression in Group I was significantly greater than that in Group II (P<0.01).

There was no significant difference in VAS scores between the two groups at T1 (P>0.05). The VAS scores of Group I were significantly greater than those of Group II at T2-T5 (P<0.01).

At the T1 time point, there was no significant difference in the number of PCA pump compressions between the two groups (P>0.05). The number of compressions in Group I was significantly greater than in Group II at the T2-T5 time points (P<0.01).

There was no significant difference in the ECG ST-T changes between the two groups at the T1 time point (P>0.05). At the T2-T5 time points, the decrease in ST-T changes in Group I was significantly greater than that in Group II (P<0.01).

Except for urinary retention, other adverse symptoms, such as sweating, nausea, and vomiting, were significantly different between the two groups. Overall, the frequency of adverse symptoms in Group II was significantly greater than that in Group I (P<0.05).

The number of postoperative hospitalization days in Group I was significantly greater than that in Group II (11.03±2.266 vs. 6.97±1.520, P<0.01).

The time until cough onset in Group I was significantly greater than that in Group II (19.40±4.484 vs. 8.13±1.978, P<0.01).

Table 1. Comparison of general characteristics ($\bar{X}$±S)

Variable	Group I (n=30)	Group II (n=30)	t-value	*p*-value
Age (years)	60.87±8.581	60.77±9.213	0.044	0.965
Weight (kg)	67.07±12.654	67.03±11.003	0.011	0.991
Height (cm)	164.53±9.024	165.40±7.054	-0.414	0.680
BMI (kg/m^2)	24.57±2.910	24.38±2.723	0.250	0.803
Surgery Time (min)	114.20±49.908	131.10±57.634	-1.214	0.230

This table presents the general demographic and baseline characteristics of patients in both groups. No statistically significant differences were found (P>0.05).

Table 2. Comparison of CYP2D6 gene expression activity in peripheral blood ($\bar{X}$±S)

Group	n	Gene Expression Level	t-value	*p*-value
I	30	1.38±0.472	10.512	<0.01**
II	30	0.46±0.089		

Gene expression levels of CYP2D6 were significantly higher in Group I compared to Group II (**P<0.01).

The amount of time until patients were able to get out of bed in Group I was significantly greater than that in Group II (56.20±15.153 vs. 31.30±10.449, P<0.01). See **Table 9**.

Discussion

This study analyzed the impact of CYP2D6 gene polymorphisms on postoperative pain susceptibility and drug treatment response in patients with lung cancer and revealed that the expression activity of the CYP2D6 gene is closely related to postoperative pain management, drug metabolism, and patient recovery. First, we analyzed the general characteristics of the patients, and the results showed no significant differences between the two groups (**Table 1**). CYP2D6 is the primary enzyme involved in the metabolism of tramadol into nortramadol (O-desmethyltramadol, ODT), the main active metabolite, which exerts stronger analgesic effects than tramadol. We detected CYP2D6 gene expression activity in both groups and found significant differences (**Table 2**).

Patients with higher CYP2D6 gene expression (Group I) had significantly greater VAS scores at all postoperative time points than those with lower gene expression (Group II) (**Table 3**). This suggests that higher enzyme activity accelerates drug metabolism, reduces effective drug concentrations, and weakens analgesic efficacy. This finding is consistent with prior studies showing that CYP2D6 polymorphisms alter metabolic rate, thereby influencing drug efficacy and duration [17, 18]. In addition, the number of PCA pump compressions was significantly greater in Group I (**Table 4**), reflecting increased demand for analgesia. This indicates that patients with higher CYP2D6 activity metabolize tramadol more rapidly and may require either dose adjustments or alternative analgesics not dependent on the CYP2D6 pathway.

At all postoperative time points, the reduction in ST-T segment changes was more pronounced in Group I (**Table 5**). This may reflect stronger stress responses due to insufficient analgesia, as pain stimulates sympathetic activation, myocardial ischemia, and ECG abnormalities [19-21]. Conversely, Group II showed a higher incidence of adverse reactions such as sweating, nausea, and urinary retention (**Table 6**). This may be attributed to slower metabolism and drug accumulation, underscoring the need for careful monitoring and dose adjustment in patients with lower CYP2D6 activity. Furthermore, the postoperative hospital stay was significantly shorter in Group II than in Group I (**Table 7**), likely due to better pain relief and fewer complications such as reluctance to ambulate or cough (**Table 8**). Improved pain control reduces adverse events, promotes early mobilization, and accelerates recovery, consistent with the ERAS philosophy [22-24].

Limitations to this research must also be acknowledged. First, this was a single-center study with a relatively small sample size, which may restrict external validity. Future multicenter studies with larger and more diverse

Table 3. VAS pain scores at different time points ($\bar{X}$±S)

Group	n	T1	T2	T3	T4	T5
I	30	1.63±0.490	4.00±0.643	5.27±0.640	5.67±0.711	6.50±0.630
II	30	1.50±0.509	2.40±0.621	3.50±0.509	4.37±0.669	4.73±0.785
t-value	-	1.034	9.798	11.841	7.294	9.616
p-value	-	0.305	<0.01**	<0.01**	<0.01**	<0.01**

Visual Analog Scale (VAS) pain scores were significantly lower in Group II at all time points except T1 (**P<0.01).

Table 4. Number of PCIA presses at different time points ($\bar{X}$±S)

Group	n	T1	T2	T3	T4	T5
I	30	0.87±0.571	4.70±1.149	6.70±1.119	9.00±1.017	9.60±1.453
II	30	0.73±0.450	2.63±0.718	3.33±1.028	3.90±1.029	4.37±1.033
t-value	-	1.004	8.352	12.135	19.308	16.079
p-value	-	0.319	<0.01**	<0.01**	<0.01**	<0.01**

Group II had significantly fewer PCIA pump presses at T2 through T5 compared to Group I (**P<0.01).

Table 5. ST-T changes at different time points ($\bar{X}$±S)

Group	n	T1	T2	T3	T4	T5
I	30	0.035±0.0082	0.089±0.020	0.12±0.021	0.15±0.024	0.15±0.019
II	30	0.026±0.0085	0.040±0.0093	0.04±0.010	0.04±0.011	0.04±0.010
t-value	-	3.866	12.374	17.798	23.597	27.987
p-value	-	>0.05	<0.01**	<0.01**	<0.01**	<0.01**

Legend: **ST-T changes were significantly more pronounced in Group I at time points T2 through T5 (P<0.01).

Table 6. Incidence of adverse reactions [n (%), n=30]

Group	n	Sweating	Nausea	Vomiting	Urinary Retention
I	30	3 (10%)	4 (13%)	6 (20%)	2 (7%)
II	30	10 (33%)	12 (40%)	16 (53%)	6 (20%)
χ^2	-	4.812	5.455	7.177	2.308
p-value	-	<0.05*	<0.05*	<0.01**	0.129

Group II had significantly higher rates of sweating, nausea, and vomiting compared to Group I (*P<0.05, **P<0.01).

Table 7. Postoperative length of hospital stay ($\bar{X}$±S)

Group	n	Length of Stay (days)	t-value	*p*-value
I	30	11.03±2.266	8.163	<0.01**
II	30	6.97±1.520		

Postoperative hospitalization duration was significantly shorter in Group II (**P<0.01).

Table 8. Time to first cough after surgery ($\bar{X}$±S)

Group	n	Time to Cough (h)	t-value	*p*-value
I	30	19.40±4.484	12.590	<0.01**
II	30	8.13±1.978		

Group II began coughing significantly earlier postoperatively than Group I (**P< 0.01).

cohorts are needed to confirm these findings. Second, follow-up was limited to the first 10 hours after surgery. Outcomes such as pain control, adverse events, and patient satisfaction were not assessed beyond this early period. Longer follow-up (24-72 hours or more) would provide a more complete understanding of the sustainability of analgesic benefits. Third, our outcomes mainly focused on objective measures such as pain scores, PCA

Table 9. Time to first ambulation after surgery ($\bar{X}$ ±S)

Group	n	Time to Ambulation (h)	t-value	*p*-value
I	30	56.20±15.153	7.410	<0.01**
II	30	31.30±10.449		

Group II was able to get out of bed significantly earlier postoperatively compared to Group I (**P<0.01).

pump use, ECG changes, and short-term complications. Although Ramsay scores provided indirect insights into patient comfort, subjective outcomes - such as postoperative satisfaction, intraoperative awareness, and psychological recovery - were not systematically assessed. Since these factors are integral to ERAS protocols, future research should incorporate validated patient-reported measures.

Finally, while this study emphasizes the pharmacogenetic role of CYP2D6, the heterogeneity of thoracoscopic procedures (lobectomy versus partial resection) and interindividual variability in surgical invasiveness could still influence hemodynamic and analgesic responses. Although operative time and baseline characteristics did not differ significantly between groups, multicenter studies across varied surgical contexts will be needed to strengthen internal validity.

In summary, CYP2D6 gene polymorphisms significantly impact postoperative pain management and drug metabolism in lung cancer. Preoperative detection of CYP2D6 activity may guide personalized analgesia strategies, optimize recovery, and reduce costs. Incorporating genetic testing alongside other biomarkers and clinical indicators could further enhance the precision of postoperative pain management. Future multicenter, prospective studies with extended follow-up, larger samples, and broader outcome measures are warranted to validate these findings and fully realize the potential of pharmacogenomics in ERAS pathways.

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Disclosure of conflict of interest

None.

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