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ORIGINAL RESEARCH

Genetic Polymorphisms of Cytokines Might Affect Postoperative Sufentanil Dosage for Analgesia in Patients

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Objective: To explore the effect of genetic polymorphisms of cytokines on the dosage of sufentanil for patient-controlled intravenous analgesia (PCIA) after radical lung cancer surgery.

Methods: A total of 100 patients, aged 18 years and above, with ASA grade Ⅰ-Ⅱ and body mass index (BMI) 18.5 to 30, and who were scheduled for radical lung cancer surgery under total intravenous anaesthesia with PCIA of sufentanil from September 2015 to March 2016, were selected. DNA was collected from peripheral blood samples before surgery, and the iMLDRTM multiple single-nucleotide polymorphism typing kit was used to detect 16 related single-nucleotide polymorphism (SNP) sites of interleukin-1A (IL-1A), interleukin-1β (IL-1β), interleukin-1RN (IL-1RN), interleukin-6 (IL-6), C-X-C motif chemokine ligand 8 (CXCL8), interleukin-10 (IL-10), tumour necrosis factor (TNF), nuclear factor kappa-B1 (NFκB1), REL (REL proto-oncogene, NF-kB subunit), and nuclear factor kappa-B inhibitor alpha (NFκBIA). The general characteristics of patients, surgery and anaesthesia data, postoperative resting VAS pain scores, postoperative opioid dosages of sufentanil for PCIA and opioid-related adverse events were recorded. The effects of the examined genetic polymorphisms of the cytokines on the dosage of sufentanil were analysed.

Results: Eight of 100 patients withdrew for various reasons, and, eventually, 92 patients were included. The patients' resting visual analogue scale (VAS) scores at 24 h, 48 h, and 72 h after surgery were 2.3 ± 1.2, 2.0 ± 0.9, and 1.9 ± 1.0, respectively. The total amounts of sufentanil used were 34.7 ± 10.5 μg, 65.2 ± 13.7 μg, and 94.7 ± 11.6 μg, respectively. We found that the TT genotype of NFκBIA rs696 had higher PCIA sufentanil dosages than the CC genotype and the CT genotype at 48–72 h postoperation (p=0.023, p=0.025, respectively).

Conclusion: The genetic polymorphisms of the cytokine NFκBIA rs696 might affect the dosage of sufentanil for PCIA after radical lung cancer surgery. The specific mechanism needs further study.

Keywords: genetic polymorphisms, single-nucleotide polymorphism, SNP, patient-controlled intravenous analgesia, PCIA, nuclear factor kappa-B inhibitor alpha, NFκBIA

Background

How to effectively alleviate postoperative pain to accelerate patients' recovery after surgery, especially after thoracic surgery, remains a medical challenge today.[1,2] These patients may endure severe postoperative acute pain due to skin and deep soft tissue damage, rib or sternal fractures, lung tissue damage and the placement of closed drainage tubes in the thoracic cavity. Poorly controlled acute postoperative

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pain during the first 3 days after surgery correlates with persistent chronic post-thoracotomy pain at 6 months, which can develop to chronic pain syndrome.[3]

Currently, a multimodal analgesia approach consisting of non-steroidal anti-inflammatory analgesics, nerve blocks and opioids during perioperative analgesia of thoracic surgery has been highly recommended and adopted.[4] The application of opioids using patient-controlled intravenous analgesia (PCIA) technology is one of the main analgesic methods after thoracic surgery.[5] Sufentanil is widely used in postoperative analgesia because of its strong analgesic effects, insignificant accumulation, rapid clearance, minor effects on circulation, weak respiratory depression and low incidence of nausea and vomiting.[6–8]

In postoperative multimodal analgesia, opioids remain the cornerstone. An insufficient dosage of opioids may lead to a poor analgesic effect, which will then inevitably affect patients' recovery after surgery. An overdose of opioids will lead to serious adverse reactions such as excessive sedation and respiratory depression. Therefore, individualized therapy of opioids for postoperative analgesia is the key point for patients' safety while promoting patients' Enhanced Recovery After Surgery (ERAS).

However, the dosage of opioids shows significant differences amongst individuals in PCIA. In the past, these differences were attributed to related factors such as patient's age, gender, weight, surgical trauma, and anaesthesia. In recent years, many studies have confirmed that genetic factors such as single-nucleotide polymorphisms (SNPs) do have great impact on postoperative analgesia, especially on the absorption, transport, metabolism, elimination and efficacy of opioids.[9–18] Lee et al,[12] found that a genetic polymorphism at the μ-opioid receptor gene (OPRM1) A118G influenced the analgesic effect of morphine for immediate acute postoperative pain in children. Zhang et al,[17] found that catechol-O-methyl transferase (COMT) gene haplotype contributed to the individual variation of postoperative analgesia with fentanyl. Yuan et al,[18] found that the CYP3A4*1G genetic polymorphism decreases the metabolism of fentanyl in human liver microsomes obtained from Chinese patients. Therefore, are there any other factors that affect the dosage of opioids in genetic polymorphisms?

Thoracic surgery is often accompanied by an increased level of various immune inflammation-related cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10).[19] Surgery-related stimuli will induce the release of inflammatory cytokines that have immunoregulatory functions or inflammatory or anti-inflammatory effects. Different dosages of opioids are needed for postoperative pain, which is closely related to the release of cytokines or inflammatory factors such as interleukin (IL), tumour necrosis factor-alpha (TNF-α), etc.[20–22] Cytokines modulate nociceptive signalling during acute inflammation and following tissue injury, and they may cause significant inter-individual variability in postoperative pain (including development, intensity, and resolution of pain).[23,24] Central cytokines and chemokines are powerful neuromodulators and play a significant role in inducing hyperalgesia and allodynia after central nervous system administration, and they drive widespread chronic pain via central sensitization.[25] We speculate that the genetic polymorphisms of cytokines related to perioperative immune inflammation may affect the postoperative PCIA sufentanil dosage. For this reason, this study intends to explore the effect of genetic polymorphisms of cytokines on the dosage of PCIA sufentanil after radical lung cancer surgery to provide a theoretical basis for the development of an individual PCIA sufentanil scheme.

Objects and Methods

Research Objects

The study was conducted in accordance with the Declaration of Helsinki, and that the patient consent was written informed consent. The trial has been approved by the Ethics Committee of the First Affiliated Hospital Zhejiang University School of Medicine (2015 [254]), and consents were obtained from patients and their families.

Inclusion Criteria

100 patients who were diagnosed with lung cancer in the hospital from September 2015 to March 2016, were selected and received radical lung cancer surgery under total intravenous anaesthesia. They were aged ≥18 years with no gender restriction and had ASA grade Ⅰ-Ⅱ and BMI 18.5–30.

Exclusion Criteria

Patients who were unable to be treated under parecoxib sodium for postoperative analgesia for various reasons, with severe neurological and psychiatric disorders, who were on non-steroidal or opioid analgesics for a long time, or who had a total Hamilton Anxiety Scale score ≥ 7 points or Hamilton Depression Scale ≥ 8 points.

Methods

Anaesthesia and Analgesia

Patients were routinely monitored for ECG, blood pressure, and oxygen saturation after entering the operating room. Invasive arterial pressure monitoring was done in the radial artery of the non-operative side of the lung. Total intravenous anaesthesia was induced with 0.05 mg/kg midazolam, 2 mg/kg propofol, 0.6 mg/kg rocuronium and 0.3 μg/kg sufentanil. A double-lumen endotracheal tube (males #37–39, females #32–35, where the appropriate double tracheal model was selected based on the CT measurement of the tracheal diameter) was inserted 5 mins later. A fibreoptic bronchoscope was used to confirm the location of the tube. An 8 mL/kg tidal volume (VT), 60% fraction of O_2 inspiration (FiO_2), and respiratory rate (RR) of 12 times/min were used for double lung ventilation, adjusting the RR exhalation to maintain $PaCO_2$ at 35–45 mmHg.

A protective ventilation strategy was used for single lung ventilation with a VT of 6 mL/kg, FiO_2 of 60–100% (as low as possible), RR at 12–16 times/min, positive end-expiratory pressure ventilation (5 cm H_2O) and intermittent lung dilatation to maintain a $PaCO_2$ of 35–45 mmHg. Anaesthesia was maintained with 6 mg kg^{-1} h^{-1} propofol, 0.05 μg kg^{-1} min^{-1} remifentanil and 0.15 mg/kg rocuronium (every 40 mins).

Sufentanil (0.2 μg/kg) was intravenously administered 2 minutes before the incision, and the concentrations of remifentanil and propofol were adjusted according to the Bispectral Index (BIS) value and blood pressure. The BIS value was maintained at 40–60, ensuring that the blood pressure fluctuation range did not exceed ± 20% of the base value. Palonosetron hydrochloride at 0.25 mg was injected 30 mins before the end of surgery to prevent postoperative nausea and vomiting. Anaesthesia maintenance medications were discontinued 5 minutes before surgery. All of these operations were performed under a three-hole full-thoracoscopy by the same group of doctors. Patients were transferred to the postanaesthesia care unit (PACU) for anaesthesia resuscitation and extubation after the operation.

Multimodal analgesia was used during the perioperative period. Sufentanil (0.2 μg/kg) was intravenously injected 30 minutes prior to the end of the operation. Parecoxib sodium (40 mg) was intravenously injected before the operation and then twice daily for three consecutive days. When the chest was closed, a 0.50% ropivacaine 10 mL incision was used for local infiltration, and PCIA was used for postoperative analgesia. PCIA (sufentanil, 100 μg/250 mL) was used for 72 h for postoperative acute pain control. The parameters were set as follows:

- load 5 μg, background infusion rate of 3 μg/h,
- bolus 2 μg, lock time 10 min, lock dosage of 20 μg/h.

When the patient had a VAS score ≥ 4 points at the ward, a bolus of 2 μg Sufentanil was used after the patient pressed once. If the VAS score was still ≥ 4 points after two consecutive valid pressures, tramadol 100 mg hydrochloride were intramuscularly injected for analgesia. When the patient had a VAS score ≥ 7 points, Acute Pain Service was also called in to adjust the PCIA parameters to control the patient's VAS score to ≤3 points. PCIA ceased after 3 days and if the VAS score remained ≥ 4 points, 200 mg celecoxib capsules were given.

The resting VAS pain score and the dosages of sufentanil at 24 h, 48 h, and 72 h after surgery were recorded. Tramadol was converted to equivalent sufentanil (100 mg tramadol are equivalent to 13.3 μg sufentanil) [26] for statistical purposes. Postoperative nausea, vomiting, pruritus, sedation, respiratory depression, hypotension and other related adverse reactions were recorded.

Detection of SNPs

A total of 16 polymorphisms (SNPs) of cytokines were selected according to a literature search. Table 1 shows the primers that were selected for polymorphism genotyping. After patient entered the room, 2 mL of venous blood were drawn and injected into an ETDA anticoagulation tube and stored in a refrigerator at 4 °C. Genomic DNA was extracted from the blood using a Maxwell 16 Blood DNA purification kit (Shanghai shengzhao biotechnology co., LTD). The iMLDRTM multiple SNP typing kit (Shanghai shengzhao biotechnology co., LTD) was used to type the SNPs of the samples.[27] Raw data collected on the sequencer were analysed by GeneMapper 4.0 (Applied Biosystems, USA).

Statistical Methods

SPSS 19.0 statistical software was used for analytical purposes. The results of the measurement data conforming to a normal distribution are expressed as the means ± standard deviation ($\bar{x} \pm sd$). To test whether alleles and genotypes meet Hardy-Weinberg equilibrium, the χ^2 test was used. Data between multiple groups were compared using a single factor analysis of variance (ANOVA). Grade

Table 1 Selected Polymorphisms (SNPs)

No.	SNP	Gene	Allele	Wild-Type	Polymorphic
1	rs17561	IL-1A	C>A	C	A
2	rs1800587	IL-1A	G>A	G	A
3	rs1143634	IL-1β	G>A	G	A
4	rs16944	IL-1β	A>G	A	G
5	rs419598	IL-1RN	T>C	T	C
6	rs1800795	IL-6	C>G	C	G
7	rs4073	CXCL8	A>T	A	T
8	rs1800871	IL-10	A>G	A	G
9	rs1800872	IL-10	T>G	T	G
10	rs1800896	IL-10	T>C	T	C
11	rs1800629	TNF	G>A	G	A
12	rs28362491	NFκB1	delATTG	-	delATTG
13	rs3774932	NFκB1	A>G	A	G
14	rs842647	REL	G>A	G	A
15	rs8904	NF-κBIA	G>A	G	A
16	rs696	NF-κBIA	C>T	C	T

count data were tested by χ^2. A difference of $P < 0.05$ was statistically significant.

Results

General Information

Of these 100 selected patients, 8 were excluded as they failed to meet the test protocol, and 92 patients were enrolled, consisting of 58 males and 34 females. Their average age was 58.9 ± 10.3 years and BMI 22.2 ± 2.6. Details of characteristics of patients enrolled can be found in Table 2.

Table 2 Characteristics of Enrolled Patients (n=92)

Patients' Characteristics	Value
Age (years)	58.9 ± 10.3
Gender (male/female)	58/34
BMI (kg/m^2)	22.2 ± 2.6
ASA classification (grade Ⅰ/Ⅱ)	9/83
Medical comorbidities	
Hypertension (yes/no)	31/61
Diabetes mellitus (yes/no)	7/85
History of surgery (yes/no)	32/60
Occupation (worker/farmer/civil service/retirement/other)	37/13/6/21/15
Education (college/middle school/primary school/illiterate)	18/46/24/4

Note: Data are expressed as the frequencies or mean ± SD, as appropriate.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Surgery and Anaesthesia Information

Of all 92 patients, the surgical time was 113.1 ± 41.8 min, volume of blood loss was 59.2±55.9 mL, urine output was 231.7±185.1 mL, infusion volume was 1117.9±341.1 mL and length of incision was 8.1±2.7 cm. For dosages of intraoperative anaesthetics: sufentanil was 55.8±9.4 μg, remifentanil was 741.4±321.5 μg, and propofol was 902.2±274.2 mg. The details of surgery and anaesthesia information of patients enrolled can be found in Table 3.

Follow-Up of Postoperative Analgesia and Adverse Reactions

The follow-up resting VAS pain scores of the 92 patients at 24 h, 48 h–72 h after operation were 2.3 ± 1.2, 2.0 ± 0.9 and 1.9 ± 1.0, respectively. The total amounts of sufentanil used were 34.7 ± 10.5 μg, 65.2 ± 13.7 μg and 94.7 ± 11.6 μg, respectively (Table 3).

Within 72 h after surgery, the patients in each group had no sedation or respiratory depression. Forty-one patients had nausea with an incidence of 44.56%, 8 patients had vomiting with an incidence rate of 8.69%, 3 patients had pruritus with an incidence rate of 3.26% and 2 patients had hypotension with an incidence rate of 2.17%.

Table 3 Surgery and Anaesthesia Data, Resting VAS Pain Score, Opioid Dosage, and Opioid-Related Adverse Events Within 72 h Post-Op (n=92)

Item	Value
Surgery and anaesthesia data	
Operation time (min)	113.1 ± 41.8
Volume of blood loss (mL)	59.2 ± 55.9
Infusion volume (mL)	1275.5 ± 366.7
Urine output (mL)	231.7 ± 185.1
Length of the incision (cm)	8.1± 2.7
Intraoperative anaesthetics	
Sufentanil (μg)	55.8 ± 9.4
Remifentanil (μg)	741.4 ± 321.5
Propofol (mg)	902.2 ± 274.2
Resting VAS pain score	
24 h post-op	2.3 ± 1.2
48 h post-op	2.0 ± 0.9
72 h post-op	1.9 ± 1.0
Sufentanil dosage (μg)	
24 h post-op	34.7 ± 10.5
48 h post-op	65.2 ± 13.7
72 h post-op	94.7 ± 11.6

Note: Data are expressed as the mean ± SD.
Abbreviations: VAS, visual analogue scale; 24 h post-op, 24 h postoperation; 48 h post-op, 48 h postoperation; 72 h post-op, 72 h postoperation.

Preliminary Analysis of Genetic Polymorphisms of Cytokines on the Dosage of PCIA Sufentanil After Radical Lung Cancer Surgery

The detection found that the variant frequencies of rs1800795 and rs1143634 were 100% and 0.5%, respectively, which were similar to the variant frequencies in the East Asian population.

No significant difference was detected in the dosage of sufentanil at 72 h postoperative in many SNPs (ie, rs17561 C> A, rs1800587 G> A, rs16944 G> A, rs419598 T> C, rs4073 A> T, rs1800871 A> G, rs1800872 T> G, rs1800896 T> C, rs1800629 G> A, rs28362491 delATTG, rs3774932 A> G, rs842647 G> A, and rs8904 G> A) ($p>0.05$). The dosage of sufentanil between different genotype groups of rs696 C> T ($p<0.05$) was statistically significant at 72 h after operation, as shown in Table 4.

The Rs696 Polymorphism Might Affect Postoperative Sufentanil Dosage for Analgesia in Patients After Radical Lung Cancer Surgery

Rs696 Genotype and Allele Frequency Analysis

The analysis showed that the variant frequency of the rs696 C> T allele in patients with lung cancer surgery was 35.3%. The distribution of alleles and genotypes were in accordance with Hardy-Weinberg equilibrium ($p>0.05$). Patients were divided into wild-type homozygous (CC group), heterozygous (CT group) and homozygous (TT group) according to their genotypes. The rs696 C> T genotype and allele frequencies are shown in Table 5.

Analysis of the General Characteristics, Surgery and Anaesthesia Data, and Opioid-Related Adverse Events

Patients were grouped according to the direct sequencing results of the rs696 C> T genotype. There was no significant difference in age, gender, BMI, ASA classification, medical comorbidities, occupation or education in each group ($p>0.05$) (Table 6). There was no statistically significant difference in the surgical time, volume of blood loss, infusion volume, urine volume, length of incision, or intraoperative dosages of sufentanil, remifentanil and propofol in each group ($p> 0.05$) (Table 6).

Within 72 h postoperation, the patients in each group were followed-up without hypersedation or respiratory depression. There were no significant differences in nausea, vomiting, pruritus or hypotension in the three groups ($p>0.05$) (Table 6).

Comparison of the Resting VAS Pain Scores and PCIA Sufentanil Dosages Within 72 h of Each Group

The resting VAS pain scores of the three groups were not significantly different ($p>0.05$) (Figure 1A). The dosages of PCIA sufentanil of three groups were not significantly different at 24 h postoperation ($p>0.05$) (Figure 1B). The dosage of PCIA sufentanil in the TT group was higher than that in the CC group and the CT group at 48–72 h postoperation ($p<0.05$) (Figure 1B). There was no significant difference in the dosage of PCIA sufentanil between the CC group and the CT group at 48–72 h postoperation ($p>0.05$) (Figure 1B).

Discussion

The present study aims to explore the effect of genetic polymorphisms of cytokines on the dosage of sufentanil for PCIA after radical lung cancer surgery. This study demonstrated that the dosage of PCIA sufentanil in the homozygous TT genotype of rs696 was higher than that in the wild-type homozygous CC and the heterozygous CT genotypes at 48–72 h postoperation, suggesting that the rs696 genetic polymorphism may cause individual differences in the analgesic effect of PCIA sufentanil after radical lung cancer surgery.

Postoperative pain is closely related to inflammatory cytokines. Inflammation gene polymorphisms have significant importance in modulating pain severity.[28] We hypothesized that genetic polymorphisms of cytokines might affect the dosage of postoperative opioids. To this end, we wanted to explore whether or not the genetic polymorphisms of cytokines affect the dosage of PCIA sufentanil after radical lung cancer surgery. After reviewing the available studies, we found that IL-1A,[24,29–31] IL-1β,[24,29,31,32] IL-1RN,[24,29,33] IL-6,[24,29,34,35] CXCL8,[24,29,35,36] IL-10,[24,29] TNF,[20,24,28] NFκB1,[24,29,37] REL[37] and NFκBIA[24,37] are closely related to pain. After searching the NCBI SNP database (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Snp) and inputting related genes, 16 related genetic polymorphism sites were selected with a variant frequency> 5%. We did not find that these SNPs

Table 4 Preliminary Analysis of the Effect of Genetic Polymorphisms of Cytokines on the Dosage of PCIA Sufentanil After Radical Lung Cancer Surgery

SNP Site	Genotype	Quantity	p value[a]	Sufentanil Dosage (μg)	p value[b]
IL-1A					
rs17561	CC	79	0.77	95.2 ± 11.3	0.179
	CA	13		90.6 ± 11.3	
	AA	0			
rs1800587	GG	79	0.77	95.2 ± 11.3	0.179
	GA	13		90.6 ± 11.3	
	AA	0			
IL-1β					
rs16944	AA	17	0.87	92.2 ± 10.0	0.372
	GA	48		96.1 ± 12.0	
	GG	27		93.3 ± 10.8	
IL-1RN					
rs419598	TT	85	0.93	94.5 ± 11.5	0.945
	CT	7		94.8 ± 9.8	
	CC	0			
CXCL8					
rs4073	AA	8	0.70	95.6 ± 9.0	0.802
	TA	44		93.7 ± 9.8	
	TT	40		95.2 ± 13.2	
IL-10					
rs1800871	AA	45	0.67	93.2 ± 9.8	0.416
	GA	36		96.5 ± 13.7	
	GG	11		93.8 ± 7.6	
rs1800872	TT	45	0.67	93.2 ± 9.8	0.416
	GT	36		96.5 ± 13.7	
	GG	11		93.8 ± 7.6	
rs1800896	TT	74	0.62	93.7 ± 11.0	0.141
	CT	16		99.4 ± 12.3	
	CC	2		88.8 ± 3.3	
TNF					
rs1800629	GG	81	0.83	94.6 ± 11.5	0.968
	GA	11		94.4 ± 10.5	
	AA	0			
NFκB1					
rs28362491	ins/ins	74	0.62	93.7 ± 11.0	0.141
	ins/del	16		99.4 ± 12.3	
	del/del	2		88.8 ± 3.3	
rs3774932	AA	32	0.82	95.1 ± 10.3	0.361
	GA	42		95.6 ± 10.0	
	GG	18		91.1 ± 15.3	
REL					
rs842647	GG	66	0.72	95.4 ± 12.1	0.456
	GA	25		92.6 ± 9.1	
	AA	1		86.4	

(*Continued*)

Table 4 (Continued).

SNP Site	Genotype	Quantity	p value[a]	Sufentanil Dosage (μg)	p value[b]
NFκBIA					
rs8904	GG	37	0.80	93.0 ± 12.1	0.052
	GA	45		94.3 ± 9.5	
	AA	10		103.0 ± 15.6	
rs696	CC	36	0.53	93.2 ± 12.2	0.025*
	CT	47		93.9 ± 9.5	
	TT	9		104.6 ± 15.6	

Notes: Data are expressed as the frequencies or mean ± SD, as appropriate. p value[a] for Hardy–Weinberg analyses of different genotypes; p value[b] for PCIA sufentanil dosage of different genotypes; *The difference in the dosage of PCIA sufentanil between three groups was significant, $p < 0.05$.

Abbreviations: SNP, single-nucleotide polymorphism; IL-1A, interleukin-1A; IL-1β, interleukin-1β; IL-1RN, interleukin-1RN; CXCL8, C-X-C motif chemokine ligand 8; IL-10, interleukin-10; NFκB1, nuclear factor kappa-B1; REL, a member of the nuclear factor κB gene family; TNF, tumour necrosis factor-alpha; NFκBIA, nuclear factor kappa-B inhibitor alpha.

Table 5 NFκBIA Rs696 C> T Genotypes and Allele Frequency

Allele				Genotypes			
	C	T	Total	CC	CT	TT	Total
Quantity	119	65	184	36	47	9	92
Frequency (%)	64.67%	35.33%	100%	39.13%	51.09%	9.78%	100%

(ie, rs17561 C> A, rs1800587 G> A, rs16944 G>A, rs419598 T> C, rs1800629 G> A, rs28362491 delATTG, rs3774932 A> G, and rs842647 G> A) were associated with dosage of PCIA sufentanil, which may be related to factors such as ethnic differences and population conditions. However, we found for the first time that the NFκBIA rs696 genetic polymorphism might have an impact on the dosage of PCIA sufentanil after radical lung cancer surgery.

Rs696 is located in the 3 prime UTR variants of the NFκBIA gene. Studies have shown that the frequency of rs696 C> T variants is related to differences in population and ethnicity. Americans have a variant frequency of 30% compared to Africans, who have a variant frequency of 65% and East Asians, who have a variant frequency of 39% (https://www.ncbi.nlm.nih.gov/snp/rs696 # frequency_ tab). In this study, the rs696 C>T variant frequency of patients with lung cancer was 35.3%, which was similar to that of the East Asian population, suggesting certain population representativeness.

NFκBIA genetic polymorphisms are related to a variety of inflammatory, autoimmune and tumour diseases.[20,24,29,37] Many of the same inflammatory factors that promote tumour growth are also hypothesized to function as pain modulators.[28] Reyes-Gibby et al,[28] found that an additive model for NFκBIA Ex6+50 C>T (rs8904) was predictive of severe pain in lung cancer patients. However, no relevant study has been conducted to examine NFκBIA genetic polymorphism and dosages of postoperative opioids.

The NFκBIA gene mainly encodes IκB, which inhibits the NF-κB signalling pathway under several physiological processes, such as by biasing NF-κB nucleocytoplasmic dynamics and blocking its DNA binding.[37,38] Inhibiting the NF-κB signalling pathway can effectively decrease levels of inflammatory cytokines and reduce the severity of pain.[37,39,40] Zhao et al,[41] found that the NFκBIA rs1957106 polymorphism is associated with lower mRNA and NFKBIA protein levels. We speculate that the homozygous TT genotype of rs696 might cause lower mRNA levels and protein expression of IκB,[41] decreasing the inhibitory function of the NF-κB signalling pathway and increasing the levels of perioperative inflammatory cytokines, which leads to increased postoperative pain and opioid dosage.

Table 6 Patients' Characteristics, Surgery and Anaesthesia Data, and Opioid-Related Adverse Events Based on the Different Genotypes of NFκBIA Rs696

	CC Group (n=36)	CT Group (n=47)	TT Group (n=9)	p value
Patients' characteristics				
Age (years)	58.1 ± 10.9	58.9 ± 10.2	61.7 ± 8.8	0.646
Gender (male/female)	22/14	32/15	4/5	0.394
BMI (kg/m^2)	21.7 ± 2.1	22.7 ± 2.7	21.5 ± 3.3	0.176
ASA classification (grade Ⅰ/Ⅱ)	4/42	5/42	0/9	0.375
Medical comorbidities				
Hypertension (yes/no)	4/32	3/44	0/9	0.352
Diabetes mellitus (yes/no)	14/22	15/32	2/7	0.588
History of surgery (yes/no)	9/27	19/28	4/5	0.272
Occupation (worker/farmer/civil service/retirement/other)	13/5/2/9/7	20/7/4/10/6	4/1/0/2/2	0.951
Education (primary/secondary/university/illiterate)	8/17/8/3	13/35/8/1	3/4/2/0	0.754
Surgery and anaesthesia data				
Operation time (min)	118.8 ± 50.0	106.3 ± 33.6	125.5 ± 43.3	0.263
Volume of blood loss (mL)	58.4 ± 52.9	60.6 ± 62.3	55.5 ± 30.8	0.964
Infusion volume (mL)	1333.3 ± 348.4	1241.4 ± 378.0	1222.2 ± 384.1	0.480
Urine output (mL)	280.0 ± 243.0	197.4 ± 130.9	217.7 ± 123.4	0.128
Length of incision (cm)	8.0 ± 3.0	8.2 ± 2.6	8.2 ± 1.5	0.919
Intraoperative anaesthetics				
Sufentanil (μg)	55.0 ± 9.3	57.0 ± 9.4	52.9 ± 9.7	0.395
Remifentanil (μg)	758.0 ± 393.4	721.2 ± 259.6	779.8 ± 325.2	0.818
Propofol (mg)	894.9 ± 307.1	900.1 ± 249.3	942.5 ± 288.6	0.897
Opioid-related adverse events				
Hypersedation (yes/no)	0/36	0/47	0/9	
Respiratory depression (yes/no)	0/36	0/47	0/9	
Nausea (yes/no)	13/23	25/23	3/6	0.230
Vomiting (yes/no)	3/33	4/43	1/8	0.966
Pruritus (yes/no)	2/34	1/46	0/9	0.519
Hypotension (yes/no)	1/35	0/47	1/8	0.146

Note: Data are expressed as the frequencies or mean ± SD, as appropriate.

Abbreviations: CC group, the wild-type homozygotes of NFκBIA rs696 CC group; CT group, the heterozygotes of NFκBIA rs696 CT group; TT group, the homozygotes of NFκBIA rs696 TT group; BMI, body mass index; ASA, American Society of Anesthesiologists.

Our study has some limitations. First, the preoperative pain state and use of steroids have not been considered in this study, but they may play a big role in determining inflammation and pain perception, and indirectly, the need for opioids. Second, we did not examine the levels of the corresponding cytokines and their changes in the blood. Third, only partial gene fragments, not complete genes, were detected in this study. The differences in the selected gene fragments may have a certain effect on the results, while the selected gene segments were highly representative with a variant frequency> 5%. Finally, the selected group of lung cancer patients in East Asia may have a certain effect on the results, and more studies might be needed to confirm our findings.

In summary, genetic polymorphisms of cytokines, specifically NFκBIA rs696, may be one of the individual genetic factors that causes a difference in the analgesic effect of PCIA sufentanil after radical lung cancer surgery.

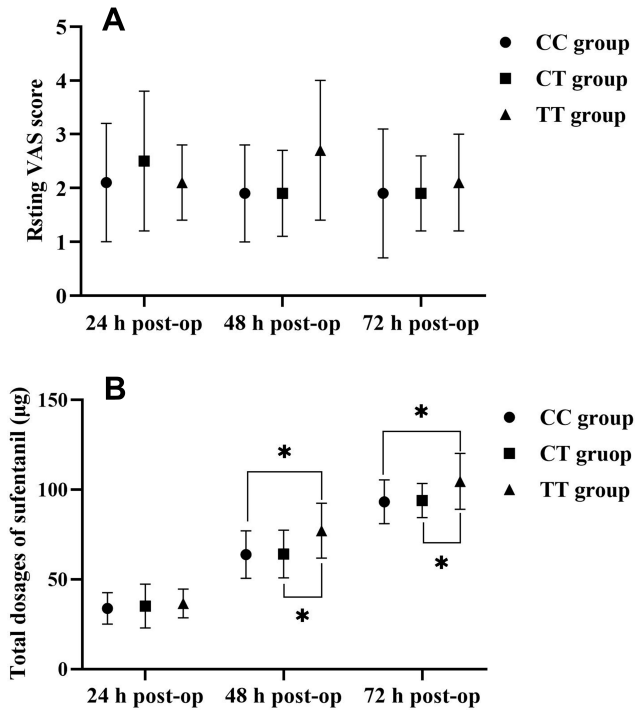

Figure 1 (**A** and **B**) Comparison of the resting VAS scores and PCIA sufentanil dosages within 72 h by the different genotypes of NFκBIA rs696. *The difference of the dosage of PCIA sufentanil between groups was significant, $p < 0.05$. **Abbreviations:** CC group, the wild-type homozygotes of NFκBIA rs696 CC group; CT group, the heterozygotes of NFκBIA rs696 CT group; TT group, the homozygotes of NFκBIA rs696 TT group; VAS, visual analogue scale; 24 h post-op, 24 h postoperation; 48 h post-op, 48 h postoperation; 72 h post-op, 72 h postoperation.

Disclosure

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