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Correlation of ADRB1 rs1801253 Polymorphism with Analgesic Effect of Fentanyl After Cancer Surgeries

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AB 1 Wei Wei*
AB 1 Yanli Tian*
BD 2 Chunlei Zhao
CD 1 Zhifu Sui
EF 1 Chang Liu
DE 1 Congmin Wang
AG 1 Rongya Yang

1 Department of Dermatology, The General Hospital of Beijing Military Command, Beijing, P.R. China
2 Hengshui Cardiovascular Hospital, Hengshui, Hebei, P.R. China

* Co-first authors; Wei Wei and Yanli Tian

Corresponding Author: Rongya Yang, e-mail: yangrnogya@126.com
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Background: Our study aimed to explore the association between β_1-adrenoceptor (*ADRB1*) rs1801253 polymorphism and analgesic effect of fentanyl after cancer surgeries in Chinese Han populations.

Material/Methods: Postoperative fentanyl consumption of 120 patients for analgesia was recorded. Genotype distributions were detected by allele specific amplification-polymerase chain reaction (ASA-PCR) method. Postoperative pain was measured by visual analogue scale (VAS) method. Differences in postoperative VAS score and postoperative fentanyl consumption for analgesia in different genotype groups were compared by analysis of variance (ANOVA). Preoperative cold pressor-induced pain test was also performed to test the analgesic effect of fentanyl.

Results: Frequencies of Gly/Gly, Gly/Arg, Arg/Arg genotypes were 45.0%, 38.3%, and 16.7%, respectively, and passed the Hardy-Weinberg Equilibrium (HWE) test. The mean arterial pressure (MAP) and the heart rate (HR) had no significant differences at different times. After surgery, the VAS score and fentanyl consumption in Arg/Arg group were significantly higher than in other groups at the postoperative 2nd hour, but the differences were not obvious at the 4th hour, 24th hour, and the 48th hour. The results suggest that the Arg/Arg homozygote increased susceptibility to postoperative pain. The preoperative cold pressor-induced pain test suggested that individuals with Arg/Arg genotype showed worse analgesic effect of fentanyl compared to other genotypes.

Conclusions: In Chinese Han populations, *ADRB1* rs1801253 polymorphism might be associated with the analgesic effect of fentanyl after cancer surgery.

MeSH Keywords: Analgesics • Fentanyl • Pain, Postoperative • Polymorphism, Genetic

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Background

Postoperative pain is a kind of physiological reaction of the human body to the disease itself and to the operation wound, and is reflected in acute physical pain as well as severe mental pain. A good postoperative analgesic effect is significant to the recovery from diseases [1]. Postoperative pain is an important postoperative complication which can cause great sufferings to patients. Fentanyl has obvious analgesic effect, and has little influence on visceral functions, so it is widely used for postoperative analgesia in patients after abdominal surgeries [2]. However, there are significant individual differences in the postoperative consumption and analgesic effect of fentanyl [3]. Pain perception is a complex physiological regulation process which is affected by various factors such as environmental and genetic factors [4]. The influences of genetic factors on the analgesic effect of fentanyl are still not very clear.

Fentanyl is a kind of opioid analgesic widely used in clinic. Due to high lipophilicity, low molecular weight, and optimal skin flux, it could be absorbed easily through skin. It is commonly thought that the metabolism of fentanyl is controlled by CYP3A [5,6]. To date, extensive efforts have been taken to clarify how the genetic factors regulate the analgesic effects of fentanyl. It has been reported that CYP3A5 polymorphisms could results in the adverse effects of fentanyl: delirium, gastrointestinal dysfunction and respiratory depression [6]. Additionally, the passage of fentanyl through blood-brain barrier is regulated by ABCB1 [7]. Further study showed ABCB1 genetic mutations could brings about respiratory suppression of patients with intravenous fentanyl therapy [8]. CYP3A4 is the main enzyme in the metabolism of fentanyl [9,10]. The activity of it determines the inter-individual variability in clinical effects of fentanyl.

Previous studies indicated that adrenergic system plays an important role in the pain mechanism and analgesic mechanism of the human body [11]. In 1948, the adrenergic receptor theory was reported [12]. The adrenergic receptor, located in the cell membrane of the sympathetic nerve postganglionic fiber effector, can combine with adrenalin and norepinephrine [13]. Multiple species identification results have revealed that the adrenergic receptor has 9 different subtypes: α_{1A}, α_{1B}, α_{1D}, $\alpha_{2A-2C,}$ and β_{1-3} [5]. β_1-adrenoceptor (*ADRB1*) gene is located on the short arm q25.3 of chromosome 10, and has no introns [15]. It has been reported that esmolol is proved to be a selective *ADRB1* antagonist by formalin tests of rats [16]. Furthermore, *ADRB1* is associated with the analgesic effect of morphine [17]. Research indicated that *ADRB1* was significantly associated with painful stimulation [18], but research on the correlation between *ADRB1* polymorphisms and analgesic fentanyl is sparse.

Therefore, we conducted this study to investigate the relationship between *ADRB1* rs1801253 polymorphism and the effect of fentanyl after surgery on cancer patients in Chinese Han populations.

Material and Methods

General materials

We randomly selected 120 patients (63 males and 57 females) who had undergone cancer operations. The involved cancers were lung cancer (14), esophageal cancer (18), tongue cancer (33), gastric cancer (20), pancreatic cancer (11), and prostatic cancer (24). They were aged 21~73 years old, at American Society of Anesthesiologists (ASA) physical status classification I~II grade, had a body mass index (BMI) of 21~25 kg/m^2, and an operation duration of 1~3 h.

The patients had all accepted training about how to use the visual analogue scale (VAS) method (0: painlessness; 10: severe pain) and the patient-controlled analgesia (PCA) device. Patients who had the following characteristics were precluded: drinking and smoking a (≥80 g/day for >10 years; 20 cigarettes/day for >3 months), medical histories of hepatic and renal dysfunction (hepatic adipose infiltration, alcoholic liver disease, pathogen infection and cirrhosis; uremia, nephrophthisis, glomerular nephritis and pyelonephritis), severe cardiovascular disease (coronary heart disease, cerebral thrombosis, hyperlipemia, angina pectoris and myocardial infarction), diabetes (Type 1 and Type 2 diabetes mellitus), psychosis (schizophrenia, depression, obsession, phobia and personality disturbance), epilepsy (all types), opiate addiction (1 time/week for 3 weeks), and vomiting (1 time/day) or using antiemetics (thiadiazide and antihistamine drugs) within 24 h before the surgery.

Preoperative cold pressor-induced pain test

In a 26°C operating room, the patients were treated with an intravenous bolus injection of fentanyl at 2 μg/kg, then the cold pressor-induced pain test was conducted before and 3 min after the treatments, according to previous studies [19,20]. Firstly, the dominant hand of each patient was immersed in the ice-cold water. According to the instructions, the patients keep the hand in the water calmly until they felt some pain. The duration to pain perception (PPLpre) was measured as the immersion time of the hand in the water before fentanyl injection. To avoid tissue damage, the cut-off time was set as 150 s. The following test was conducted until the hand was warmed, along without any sensation of cold. Three minutes after the fentanyl injection, pain perception latency of the dominant hand (PPLpost) was tested. The difference between PPLpost and PPLpre (PPLpost -PPLpre) represent the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test.

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Preoperative anesthesia

Seventy patients all received general anesthesia; 2 mg of midazolam, 0.2 mg of fentanyl, and 70~120 mg of propofol were intravenously injected. After the patients became unconscious, 20 mg of cisatracurium was intravenously injected. Mechanical ventilation was performed after tracheal intubation. Anesthesia was maintained as follows: propofol, fentanyl, and cisatracurium were continuously pumped in by a micro-pump; then sevoflurane was inhaled in; the pumping speed and the inhaling speed of drugs were adjusted according to changes of hemodynamics during the surgery; after the skin was sutured, the use of anaesthetic was stopped and 0.5 mg of atropine and 1 mg of neostigmine were intravenously injected; and after the patients became awake, the tracheal tube was pulled out and the patients were sent to the post-anesthesia care units (PACUs) for observation.

Postoperative analgesia

Basic physiological parameters (including blood pressure, pulse, oxygen saturation and consciousness) of the patients were assessed immediately after they entered in the PACUs. Then VAS was performed to assess the pain of the patients (0: painlessness; 10: severe pain). If the patients could not stand the severe pain, then fentanyl was intravenously injected to control the VAS score at below 3. In this case, the PCA pump was connected to achieve electronic intravenous injection of fentanyl for 48 h. If the analgesic effect was not good (VAS>3 in resting state), then an extra 50 mg of fentanyl was intravenously injected 1 time. The patients and family members were told to control the pump for analgesia by themselves to maintain the VAS score below 3. Postoperative follow-ups continued for 48 h, and the fentanyl consumption for analgesia at 2, 4, 24, and 48 h was recorded.

Genotype analyses

After the anesthesia induction ended, 2 ml of blood was collected, and then it was treated with ethylene diamine tetraacetic acid (EDTA), and finally stored in a –80°C refrigerator. DNA was extracted via phenol/chloroform extracting method. Reagents and instruments were respectively as follows: Taq DNA polymerase (Promega, USA), dNTP (Beijing Nobleryder Biotech Cor., Ltd.), PCR instrument (Perkin Elmer, USA), high-speed and low-temperature centrifuge (Sigma, Germany), and electrophoresis apparatus (Pharmacia, Italy); and agarose gel, loading buffer, and ethidium bromide. Allele specific primers were designed by using the strictest principle of 3'-terminal base matching between primers in PCR amplification. There were 3 amplification results: the wild allele was obtained when the wild allele specific primer was amplified; the mutant allele was carried when the ordinary primer obtained amplification product; and the heterozygote was carried when the wild allele specific primer and the ordinary primer both obtained amplification product.

Observation index

The pain degree (VAS), blood pressure, heart rate, finger pulse, and oxygen saturation (SpO_2) in resting state at 2, 4, 24, and 48 h after the surgery were assessed. VAS method was adopted to assess the degree and frequency of pain during the 48 h after the surgery.

Statistical analyses

All the analyses were performed with SPSS 18.0. The measurement data are represented by $\bar{\chi}\pm s$. The Hardy-Weinberg equilibrium (HWE) was checked by χ^2 test [21,22]. Differences in postoperative VAS score and postoperative fentanyl consumption for analgesia among different genotype groups were compared by analysis of variance (ANOVA) [23–25]. Comparisons of the fentanyl consumption between different genotype groups during the 48 h after the surgery were made through variance analysis. The VAS was checked with non-parametric test (Kruskall-Wallis H test). The differences were statistically significant only when $P<0.05$.

Results

Genotype groups

According to the genotypes of *ADRB1* rs1801253 polymorphism, the 120 patients were divided into 3 groups. Fifty-four patients (45%) were in the wild homozygote (Gly/Gly) group, 46 (38.3%) were in the heterozygote (Arg/Gly) group, and 20 (16.7%) were in the mutant homozygote (Arg/Arg) group. The allele distribution of *ADRB1* rs1801253 polymorphism accorded with HWE ($P>0.05$).

General clinical features

Distributions of age, sex, operation duration, height, and weight among the 3 genotype groups had no statistical significance differences ($P>0.05$, Table 1). To clarify the association of each genotype with analgesic effect of fentanyl, we performed the preoperative cold pressor-induced pain test. The results indicated that the patients with Arg/Arg genotype showed better analgesic effect of fentanyl ($P<0.05$, Table 1). Therefore, we concluded that *ADRB1* rs1801253 polymorphism was correlated with analgesic effect of fentanyl.

Intraoperative circulatory state

As shown in Table 2, the mean arterial pressure (MAP) and the heart rate (HR) of patients in the 3 groups were measured and

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Table 1. General clinical features and operation durations ($\bar{\chi}$±s).

Groups	Gly/Gly (n=54)	Gly/Arg (n=46)	Arg/Arg (n=20)
Age (year)	54.2±9.4	57.9±8.4	58.1±7.8
Weight (kg)	55.2±10.3	57.0±6.4	61.4±7.2
Height (cm)	169.4±6.8	169.7±7.8	168.4±8.7
Sex (male/female)	30/26	23/21	13/7
Operation duration (min)	214.6±43.8	196.4±56.9	206±48.4
PPLpre (s)	32.0±5.5	31.0±2.3	12.5±1.0
Analgesic effect (PPLpost-PPLpre) (s)	44.5±6.4	40.5±2.0	11.0±0.8

Table 2. Hemodynamic parameters in patients with different genotype ($\bar{\chi}$±s).

Parameter	After entered operating room	CO_2 pneumoperitoneum	After surgery	Before extubation
MAP (mmHg)				
Gly/Gly	74.3±21.3	75.8±18.4	74.3±14.6	70.1±16.4
Gly/Arg	68.7±12.6	75.3±15.9	76.4±14.0	69.8±12.4
Arg/Arg	67.9±19.6	75.4±20.1	76.4±19.9	74.2±9.7
HR (times/min)				
Gly/Gly	81.4±17.1	76.4±23.1	74.6±19.4	76.1±21.5
Gly/Arg	75.3±14.9	73.5±18.4	74.6±12.3	71.3±13.0
Arg/Arg	72.6±15.1	74.3±10.3	71.3±11.2	71.6±9.4

recorded at different times, at the very moments the patients entered in the operating room, when surgery ended, and before extubation. The changes of MAP and HR had no significant differences in the 3 groups during different periods ($P>0.05$). During the CO_2 pneumoperitoneum, there were still no significant differences in the 2items between the 3 groups ($P>0.05$).

Fentanyl consumption

At 4, 24, and 48 h after the surgery, the differences in fentanyl consumption among the 3 groups were not statistically significant ($P>0.05$). At 2 h after the surgery, the fentanyl consumption of the Arg/Arg group was significantly higher than that of the Gly/Gly group and Gly/Arg group ($P<0.05$), but the difference in fentanyl consumption between the Gly/Arg group and Gly/Gly group had no statistical significance ($P>0.05$, Table 3).

Postoperative VAS score

Compared with Gly/Gly group, postoperative VAS score of Arg/Arg group was significantly higher ($P<0.05$) at 2 h after surgery. There was no significant difference in VAS scores at 4, 24, and 48 h after the surgery among the 3 groups ($P>0.05$, Table 4).

Discussion

Fentanyl is currently the most commonly used opioid drug, and is often used for preoperative, intraoperative, and postoperative analgesia, as well as the treatment of terminal cancer. However, there are significant differences in sensitivities to fentanyl in clinical use between patients due to individual differences. Individual difference is mainly reflected in the different demands for drugs, as well as the different incidences of adverse reactions [26]. In recent years, many scholars have found that the individual differences in fentanyl use are closely associated with human genes [27]. With the development in genomic sequencing, it has become possible to comprehensively and thoroughly explore the genomic mutations and polymorphisms of different individuals and groups. Furthermore, genetic characteristics are expected to become guidance for preventive measures of diseases in clinic. Currently, the association of sympathetic nerves in the automatic nervous system (ANS) with the analgesic effect of fentanyl has become a research hotspot.

ADRB1 plays an important role in mediating of signal transduction of the sympathetico-adrenal system. *ADRB1* gene has

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Table 3. Postoperative fentanyl consumption in 3 groups ($\bar{\chi}$±s).

Group	Number	Fentanyl consumption (μg/kg)			
		2 h	4 h	24 h	48 h
Gly/Gly	54	1.1±0.4	2.3±1.1	9.4±2.0	16.1±3.8
Gly/Arg	46	1.2±0.6	2.5±1.4	9.7±2.4	16.4±3.0
Arg/Arg	20	2.2±0.5*	3.0±0.9	10.1±2.1	16.9±3.3

* P<0.05 when compared with Gly/Gly.

Table 4. Postoperative VAS score in different groups ($\bar{\chi}$±s).

Group	Number	VAS score			
		2 h	4 h	24 h	48 h
Gly/Gly	54	2.1±0.9	3.0±0.9	1.2±0.6	0.9±0.4
Gly/Arg	46	1.9±0.6	2.6±0.9	1.5±1.1	1.1±0.3
Arg/Arg	20	3.2±0.6*	3.1±0.8	2.0±0.7	1.8±0.5

* P<0.05 when compared with Gly/Gly.

the 2 most important single-nucleotide polymorphisms (SNPs): rs1801252 (Ser49Gly) and rs1801253 (Gly389Arg, C1165G). Gly389Arg polymorphism is caused by the replacement of 389 Gly near the carboxyl terminal by Arg [28], and Arg is a minor allele. Gly389Arg polymorphism is located in the 7th transmembrane domain near the cytoplasmic tail end, which is considered an important region for the coupling of receptors with Gs proteins. Various studies indicated that *ADRB1* gene is closely involved to sympathetic nervous system function [29–32]. Bruck et al. indicate that individuals carrying Arg389 have stronger sympathetic nervous system activity and plasma renin activity than those carrying Gly389 [33]. Therefore, *ADRB1* rs1801253 polymorphism has a definite influence on the sympathetic nervous system activity, that is, Arg389 homozygote could easily cause higher sympathetic nervous system activity. Recent studies mainly focused on the role of *ADRB1* gene in the pathogenesis of disease, and it has been found that *ADRB1* polymorphisms are related to various diseases [34–39]. Researches also found that the rs1801253 polymorphism was related with beta-blocker response [40–43]. This suggested to us that the rs1801253 has become increasingly important in the reaction to pain, and might be associated with analgesic effect.

We performed this study to determine the relationship between *ADRB1* rs1801253 polymorphisms and the analgesic effect of fentanyl in a Chinese Han population. In the intraoperative circulatory state, the MAP and HR had no significant difference among the 3 groups. After surgery, the Arg/Arg group had a high postoperative VAS score and fentanyl consumption compared with the Gly/Gly group, at 2, 4, 24, and 48 h, but an obvious difference only existed at 2 h after the surgery (P<0.05). The results indicated that Arg/Arg was the homozygote involved in susceptibility to postoperative pain. The preoperative cold pressor-induced pain test indicated that the analgesic effect of fentanyl was poor in the Arg/Arg group. This study revealed that *ADRB1* rs1801253 polymorphism was associated with the analgesic effect of fentanyl after cancer surgeries. This is in accord with previous study in Japan [44], which found that G allele of rs1801253 significantly reduced the analgesic effect of fentanyl after cosmetic surgery.

Conclusions

This result might provide guidance for the clinic treatment of postoperative pain, and supply evidence for researching and developing new treatment medicines.

Our study had many limitations, such as the small sample size and few measurement parameters. The study was conducted only based on 6 cancers without considering the variances in postoperative pain of all cancer types. The result was insufficient to clarify the mechanism of the analgesic effect of fentanyl. To clarify the possible mechanism or characteristics of the analgesic effect of fentanyl from the level of molecular genetics, further research with a large sample and containing more genes, SNPs, and measure parameters should be carried out.

Conflict of interest

We declare that we do not have any competing financial interest or conflict of interest.

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