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Original Article

Effect of intercostal nerve block combined with oxycodone on the postoperative cognitive ability in elderly patients undergoing radical resection of lung cancer

Qiang Wang[1], Jiao Guo[2], Minna Hou[2]

[1]*Department of Anesthesiology, The First Affiliated Hospital of Xi'an Jiaotong University, No. 277, Yanta West Road, Xi'an 710000, Shaanxi, P. R. China;* [2]*Department of Anesthesiology, Shaanxi Provincial People's Hospital, 256 Youyi West Road, Xi'an 710000, Shaanxi, P. R. China*

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Abstract: Objective: To explore the effect of intercostal nerve block (INB) combined with oxycodone on the postoperative cognitive ability in elderly patients undergoing radical resection of lung cancer (LC). Methods: A total of 135 elderly patients who underwent radical LC operations in our hospital from April 2019 to July 2021 were enrolled for retrospective analysis. There are 71 patients, who received INB with 0.5% ropivacaine 20 mL and oxycodone 5 mg (intravenous injection) before chest closure, were assigned to the observation group (OG), while 64 patients, who received a single oxycodone injection (5 mg) into the anterior thoracic vein, were assigned as the control group (CG). The cognitive function of patients was assessed by a mini mental state examination (MMSE) before and 24 h after operation. Also, the visual analogue scale (VAS), sedation score (Ramsay) and the occurrence of adverse reactions within 48 h after surgery were compared. Additionally, the changes of heart rate (HR), blood oxygen saturation (SpO_2) and central venous pressure (CAP) at 4 h, 8 h, 12 h and 24 h after operation were observed, and the pressure times of analgesia pump within 24 h and the satisfaction rates of postoperative analgesia were compared between the two groups. Results: After operation, compared with the CG, the MMSE in the OG was dramatically higher ($P<0.05$), while the incidence of adverse reactions ($P<0.05$) and the VAS score ($P<0.05$) in the OG were significantly lower. There was no remarkable difference in postoperative HR, SpO_2 and MAP between the two groups ($P>0.05$). The number of postoperative analgesia pump pressing in the OG was lower than that in the CG ($P<0.05$), and the satisfaction rate of postoperative analgesia in the OG was higher ($P<0.05$). Conclusion: INB combined with oxycodone has a better application effect in senile LC radical operation. It can improve the postoperative cognitive function and reduce postoperative adverse reactions and pain with high safety.

Keywords: Intercostal nerve block, oxycodone, senile LC radical operation, postoperative cognitive ability

Introduction

Lung cancer (LC) is a malignancy originating from the bronchial mucosa or glands of the lungs [1]. The etiology has not yet been fully clarified, and smoking, genetics and history of lung disease are all pathogenic factors [2]. The most common clinical symptom of LC in the early stage is coughing, and some patients also have irregular chest pain, hemoptysis, dyspnea, etc. The relevant clinical symptoms are the size, type, and development stage of the tumor [3]. LC is a disease with extremely high morbidity and mortality worldwide, posing a serious threat to human's life safety [4]. At present, surgery is the first choice and the main method for LC treatment. However, the surgical trauma due to invasive operation not only increases the pain of patients, but also easily leads to a series of complications, which has an adverse effect on their prognosis, especially in the elderly [5]. Thus, perioperative pain management is vital to accelerate the recovery of elderly patients and achieve ideal therapeutic effects.

With the development of visualization of medical technology, the application of intercostal

nerve block (INB) in early analgesia after thoracotomy is gradually increasing. Blocking the signal transduction of somatic pain by impeding the intercostal nerve at the pain site of the operation has fewer complications and is easy to operate, with good analgesic effect [6]. Nevertheless, many experimental studies have found that there are still some shortcomings, and many scholars have pointed out that INB can not relieve visceral pain in patients [7, 8]. Oxycodone, as an opioid anesthetic, is also frequently-used in clinical practice, and it has a marked analgesic effect on reducing neuralgia and visceral pain [9]. At present, oxycodone has achieved excellent results in radical resection of LC. Studies have shown that the use of oxycodone can not only effectively ameoliarate the pain of patients, but also effectively protect their neurological function, so as to improve their postoperative cognitive function [10, 11]. INB anesthesia is a method with less nerve injury [12]. Hence, we speculate that the application of INB combined with oxycodone in elderly patients undergoing radical LC may improve the efficacy. To verify the conjecture, a detailed study was carried out to observe the effect of INB combined with oxycodone, so as to provide accurate guidance and reference for analgesic intervention in elderly patients undergoing radical LC surgery in the future.

Data and methods

Patient data

A total of 135 elderly patients who underwent radical LC operation in our hospital from April 2019 to July 2021 were enrolled into this research. Of these, 71 patients who received INB with 0.5% ropivacaine 20 mL and intravenous injection of oxycodone 5 mg before chest closure were included in the observation group (OG), while 64 who received a single injection of oxycodone 5 mg into the anterior thoracic vein were regarded as the control group (CG). This research met the requirements of the Medical Ethics Committee and was reviewed and approved by our hospital, ethical approval number: 201903017.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with conditions in accordance with the clinical manifestation of LC [13], and were diagnosed as LC after pathological biopsy in our hospital, and met the indication of radical operation of LC [14]. (2) Patients were 60 to 75 years old. (3) Those with complete case data. (4) Those agreed to participate in this research. (5) Patients did not have adjuvant treatment before admission. (6) Unconscious disturbance before operation.

Exclusion criteria: (1) Patients with contraindication of narcotic drugs. (2) Patients with mental illness. (3) Those complicated with major diseases. (4) Patients with abnormal liver or kidney function. (5) Patients who took opioids for a long time. (6) Patients were transferred to the hospital.

Methods

No sedative was used before operation. After the patient entered the operating room, the venous access was opened. Blood pressure, electrocardiogram (ECG) and pulse oxygen saturation were monitored routinely, and the pressure was measured by radial artery puncture under local anesthesia. Methylprednisolone was intravenously injected (Pfizer Pharmaceutical Co., Ltd.) before anesthesia induction. Rapid sequence induction was performed: midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., SFDA Approval No. H20143222) 0.03 mg/kg, etomidate (Jiangsu Hengrui Pharmaceutical Co., Ltd., SFDA Approval No. H32022-379) 0.25 mg/kg, sufentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., SFDA Approval No. H20143314) 0.5 μg/kg, rocuronium (Shanghai Hengrui Pharmaceutical Co., Ltd., SFDA Approval No. H20061298) 50 mg. After pure oxygen mask ventilation for 3 min, double-lumen bronchial intubation was performed under laryngoscope. Auscultation or fiberoptic bronchoscopy confirmed that one-lung ventilation was good, and then connected to the anesthetic machine to control breathing. Bi-lung ventilation parameters: Tidal volume 8 mL/kg, respiratory rate 12 times/min. One-lung ventilation parameters: Tidal volume 5-6 mL/kg, respiratory rate 14-16 times/min. Respiratory ratio 1:1.5, oxygen flow 2 L/min, oxygen volume fraction 100%. Anesthesia maintenance: Propofol (Hebei Yipin Pharmaceutical Co., Ltd., SFDA Approval No. H20093542) 4-5 mg/kg/h, remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd., SFDA Approval No. H20143315) 0.2-0.3 μg/kg/min. Sodium lactate Ringer's solution (Anhui Fengyuan Pharmaceutical Co., Ltd.,

SFDA Approval No. H34021876) 4 mL/kg/h was infused intravenously during one-lung ventilation. Anesthesia maintenance drugs were stopped, and analgesia was given at the end of the operation. In CG, oxycodone [Mundipharma (China) Pharmaceutical Co., Ltd., imported Drug Registration No. H20130314] 5 mg was injected intravenously before closing. Sufentanil 150 μg + oxycodone 20 mg + ondansetron 16 mg was diluted to 100 mL with normal saline during skin sewing, and patient-controlled analgesia was performed. In OG, altogether 7.5 g/L ropivacaine injection 20 mL and intravenous injection of oxycodone 5 mg were given before thoracoscopy for INB. The rest were the same as above. For INB, before closing the thoracic cavity, the surgeon used 7.5 g/L ropivacaine injection 20 mL to block the incision and the intercostal nerve in the upper and lower part of the incision and the intercostal nerve where the thoracic drainage tube was located under thoracoscopic direct vision. The intercostal nerve was punctured outward from the parietal pleura to avoid the intercostal vessels, and 5 mL was injected into each intercostal cavity.

Outcome measures

The cognitive function of patients was assessed by the mini mental state examination (MMSE) [15] before and 24 h after the operation, the lower the MMSE score, the more severe the neurological dysfunction. The Visual Analogue Scale/Score (VAS) [16], Ramsay sedation scores (Ramsay) [17] and the occurrence of adverse reactions within 48 h after operation were compared, the higher the VAS score, the more obvious the pain, while the higher the Ramsay score, the more significant the sedative effect. The changes of heart rate (HR), blood oxygen saturation (SpO_2) and mean arterial pressure (MAP) were observed at 4 h, 8 h, 12 h and 24 h after operation. The times of analgesic pump pressing and the satisfaction rate of postoperative analgesia were compared between the two groups.

Statistical methods

The data were processed by the statistical software SPSS23.0. The counting data were expressed as rate, and those between groups were compared by chi-square test. The measurement data in accordance with normal distribution were expressed as (mean ± standard deviation) and tested by t-test. One-way ANOVA and LSD post hoc test were applied to comparison between multiple groups, and logistic regression analysis was conducted for correlated factors. The difference was considered to be statistically significant when $P<0.05$.

Results

Baseline data of two groups of patients

The age, sex, BMI, smoking history, drinking history, place of residence, education level, nationality and other baseline data between the two groups of patients were compared, no significant difference was found, showing experimental comparability ($P>0.05$) (**Table 1**).

Comparison of cognitive function in patients

The MMSE scores between the two groups were compared before and 24 h after operation. The results manifested that there was no difference between the two groups before operation ($P>0.05$), but the MMSE score decreased within 24 h after operation, and the score in the CG decreased more obviously ($P<0.05$) (**Figure 1**).

VAS and Ramsay scores of two groups after operation

The VAS and Ramsay scores between the two groups within 48 h after operation were compared. It was revealed that the VAS of the OG was lower than that of the CG within 48 h after operation ($P<0.05$). There was no remarkable difference in Ramsay scores between the two groups ($P>0.05$) (**Figure 2**).

Changes of HR, SpO_2 and MAP in both groups after operation

The changes of HR, SpO_2 and MAP were compared between the two groups at 4 h, 8 h, 12 h and 24 h after operation. It was revealed that there was no marked difference in HR, SpO_2 and MAP between the two groups at different time after operation ($P>0.05$) (**Figure 3**).

Comparison of pressing times of analgesic pump between the two groups

After comparing the times of analgesia pump pressing within 12 h and 24 h between the two groups, we found that the times in the OG were less than those in the CG ($P<0.05$), as shown in **Figure 4**.

Table 1. Baseline data

	Observation group (n=71)	Control group (n=64)	t or x^2	P
Age	63.6±6.4	63.1±4.7	5.0213	0.609
Sex			0.044	0.835
Male	51 (71.83)	47 (73.44)		
Female	20 (28.17)	17 (26.56)		
BMI (kg/m^2)	26.7±2.8	27.0±2.5	0.654	0.514
Smoking			0.596	0.440
Yes	49 (69.01)	48 (75.00)		
No	22 (30.99)	16 (25.00)		
Drinking			0.032	0.859
Yes	52 (73.24)	46 (71.88)		
No	19 (26.76)	18 (28.13)		
Place of residence			0.010	0.919
Cities and towns	46 (64.79)	42 (65.63)		
Countryside	25 (35.21)	22 (34.38)		
Education level			0.005	0.945
Below high school	54 (76.06)	49 (76.56)		
High school or above	17 (23.94)	15 (23.44)		
Nationality			0.061	0.804
The Han nationality	67 (94.37)	61 (95.31)		
Minority nationality	4 (5.63)	3 (4.69)		
Type of operation			0.522	0.770
Local excision	29 (40.85)	30 (46.88)		
Lobectomy	34 (47.89)	28 (43.75)		
Total pneumonectomy	8 (11.27)	6 (9.38)		

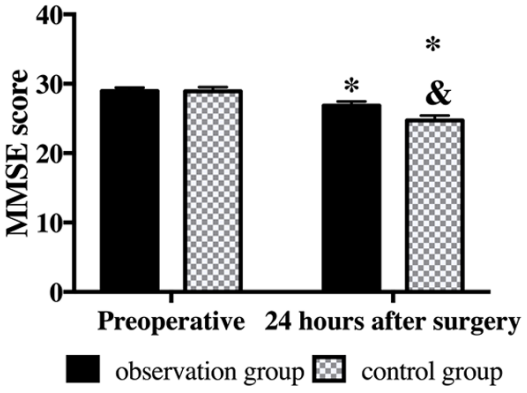

Figure 1. MMSE scores before and 24 h after operation in both groups. Note: * means P<0.05 compared with before operation; & means P<0.05 compared with observation group.

Occurrence of postoperative adverse reactions in both groups

The occurrence of postoperative adverse reactions between the two groups were compared. It was found that the total incidence of adverse reactions in the OG was 15.49%, which was lower than 37.50% in the CG (P<0.05), as shown in **Table 2**.

Comparison of satisfaction rate of postoperative analgesia between the two groups

The satisfaction rate of postoperative analgesia between the two groups was compared. It showed that compared with the CG, the most satisfaction rate of the OG was higher (P= 0.001), and the rate that needs to be improved was lower (P=0.001) (**Table 3**).

Analysis of related factors affecting postoperative cognitive impairment

Univariate analysis was conducted between patients with postoperative cognitive impairment (n=25) and those without cognitive impairment (n=110). It turned out that sex, BMI, smoking, drinking, place of residence, education and nationality were not single factors

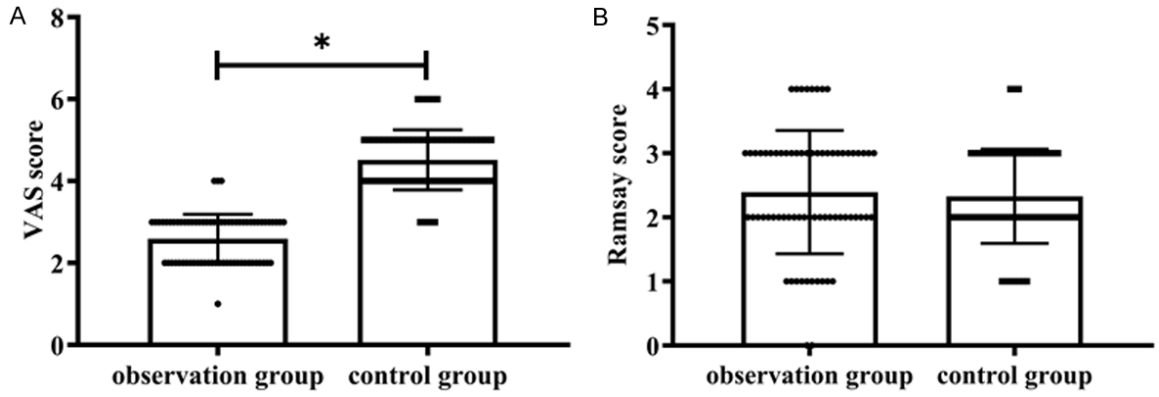

Figure 2. VAS and Ramsay scores within 48 h after operation in both groups. A. VAS scores; B. Ramsay scores; Note: * denotes P<0.05 compared with the observation group.

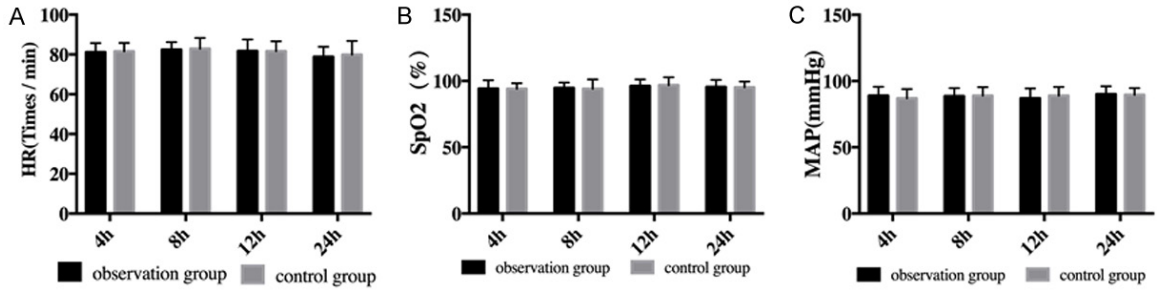

Figure 3. Changes of HR, SpO_2 and MAP levels at 4 h, 8 h, 12 h and 24 h after operation in both groups. A. Comparison of HR between the two groups; B. Comparison of SpO_2 between the two groups; C. Comparison of MAP between the two groups.

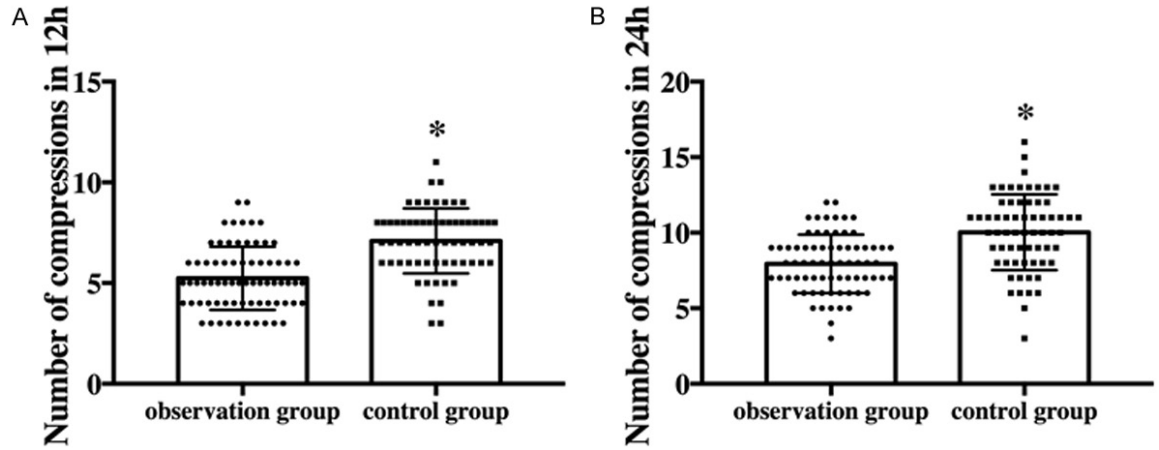

Figure 4. The times of analgesia pump pressing within 12 h and 24 h in both groups. A. The times of analgesia pump pressing within 12 h in both groups; B. The times of analgesia pump pressing in both groups within 24 h. Note: * means P<0.05 compared with the observation group.

affecting postoperative cognitive impairment (P>0.05). Age, time of postoperative mechanical ventilation, mode of anesthesia and type of operation were single factors affecting postoperative cognitive impairment (P<0.05) (**Table 4**). Then, the above indexes were assigned and

Table 2. Incidence of adverse reactions

	Observation group (n=71)	Control group (n=64)	x^2	P
Nausea and vomiting	0 (0.00)	1 (1.56)		
Dizziness and headache	1 (1.41)	2 (3.13)		
Hypotension	0 (0.00)	1 (1.56)		
Lethargy	1 (1.41)	2 (3.13)		
Skin itch	1 (1.41)	1 (1.56)		
Cognitive impairment	8 (11.27)	17 (26.56)		
Total incidence rate (%)	15.49	37.50	8.488	0.004

Table 3. Satisfaction rate of postoperative analgesia in both groups

	Observation group (n=71)	Control group (n=64)	x^2	P
Very satisfied	43 (60.56)	20 (31.25)	11.620	0.001
Satisfied	24 (33.80)	25 (39.06)	0.403	0.526
Need to be improved	3 (4.23)	15 (23.44)	10.750	0.001
Not satisfied	1 (1.41)	4 (6.25)	2.212	0.137

Logistic regression analysis was performed. It manifested that age, time of postoperative mechanical ventilation, mode of anesthesia and type of operation were independent factors affecting postoperative cognitive impairment (P<0.001) (**Table 5**).

Discussion

With the aging of the population, the morbidity and mortality of LC are increasing, which is a serious threat to human life and health [18]. Radical surgery is the basic surgical method for LC treatment (i.e. removal of lesions and dissection of lymph nodes). Although this method is very mature and widely used in clinical treatment, the incidence of postoperative complications increases due to surgical incision and pain, etc., especially in the elderly with poor conditions, and the prognosis is poor [19]. Some scholars have pointed out that the prognosis of LC patients is related to the mode of surgical anesthesia [20]. INB has been proved to have significant analgesic effect, but it cannot block visceral pain. Oxycodone is a μ and κ double receptor agonist, which is better than μ receptor agonist only in inhibiting visceral pain and neuralgia. It can make up for the defect of INB. Based on this, the combination of the two was applied to elderly patients undergoing radical LC in this research, and the effect was observed.

First of all, in the evaluation of the cognitive function of both groups of patients before and after operation, we found that patients in the OG had better cognitive function after operation, which suggested that INB combined with oxycodone had less impact on the cognitive function of patients undergoing LC radical operation. In previous studies, we also discovered that patients with INB and oxycodone had higher cognitive function scores after thoracoscopic lobectomy [10], which can also support the results of this experiment. Moreover, in comparison of pain between the two groups, we also found that patients in the OG had lower pain experience after operation, suggesting betterperformance of INB combined with oxycodone in LC radical operation. As one of the most commonly-used methods of anesthesia and analgesia, INB has the advantage of being operated under video-assisted thoracoscopy to avoid the risk of accidental entry into blood vessels and pneumothorax [12]. At the same time, the diffusion area and situation of local anesthetics in the human body can be observed by video-assisted thoracoscopy, and the time of single block can be maintained at 6-24 h [21]. Research has shown that blocking nociceptive conduction to the spinal cord through INB can improve the effect of early postoperative analgesia [22]. We speculate that this is also the main reason for the marked decrease in the number of postoperative analgesia pump presse in the OG. However, INB has no obvious effect on visceral analgesia, and muscle and organ pain caused by intercostal nerve injury is the main cause of pain after thoracotomy [23]. Thus, when using INB, it is suggested to use

Table 4. Univariate analysis of postoperative cognitive impairment

	Patients with cognitive impairment (n=25)	Patients without cognitive impairment (n=110)	t or x^2	P
Age	66.8±5.2	60.4±6.1	4.857	<0.001
Sex			0.005	0.941
Male	18 (72.00)	80 (72.73)		
Female	7 (28.00)	30 (27.27)		
BMI (kg/m^2)	26.8±3.1	27.4±2.4	1.066	0.288
Smoking			0.225	0.635
Yes	17 (68.00)	80 (72.73)		
No	8 (32.00)	30 (27.27)		
Drinking			0.179	0.672
Yes	19 (76.00)	79 (71.82)		
No	6 (24.00)	31 (28.18)		
Place of residence			0.364	0.547
Cities and towns	15 (60.00)	73 (66.36)		
Countryside	10 (40.00)	37 (33.64)		
Educational level			1.168	0.280
Below high school	17 (68.00)	86 (78.18)		
High school and above	8 (32.00)	24 (21.82)		
Nationality			0.495	0.482
Han	23 (92.00)	105 (95.45)		
Minority nationality	2 (8.00)	5 (4.55)		
Type of operation			10.390	0.006
Local excision	8 (32.00)	51 (46.36)		
Lobectomy	10 (40.00)	52 (47.27)		
Total pneumonectomy	7 (28.00)	7 (6.36)		
Anesthesia method			5.218	0.022
Ropivacaine + oxycodone	8 (32.00)	63 (57.27)		
Oxycodone	17 (68.00)	47 (42.73)		
Postoperative ventilation duration			4.485	0.342
≥72 h	17 (68.00)	49 (44.55)		
<72 h	8 (32.00)	61 (55.45)		

Table 5. Multivariate analysis of postoperative cognitive impairment

	β	Wald	SE	OR	95% CI	P
Age	0.705	7.776	0.042	1.924	1.124-2.994	<0.001
Type of anesthesia	1.058	10.341	0.051	2.007	1.904-2.354	<0.001
Type of operation	0.022	11.114	0.044	1.161	0.842-1.637	<0.001
Postoperative ventilation duration	0.668	8.424	0.024	1.862	1.771-1.924	<0.001

other anesthetics to improve the analgesic effect of surgery. Oxycodone, as one of the commonly-used anesthetic drugs in clinical medium and large surgery, has the same analgesic effect as morphine sulfate injection. It is a pure opioid μ and κ receptor agonist. It is easy to pass through the blood-brain barrier, with quick action, moderate action time and slight immunosuppressive effect [24]. Oxycodone, as the only opioid double receptor agonist that can be used clinically, has the effects of analgesia, sedation, anti-anxiety, antitussive and reducing smooth muscle tension. Because of its κ receptor activation, the adverse reactions such as nausea, vomiting and respiratory inhibition are mild [25], which makes oxycodone

even more suitable for relevant application. In this research, we also found that the incidence of postoperative adverse reactions in the OG was lower than that in the CG, which once again verified the safety of oxycodone. Furthermore, Li et al. confirmed that oxycodone anesthesia also reduced the incidence of postoperative adverse reactions in patients undergoing laparoscopic surgery [26], which was consistent with the results of this experiment. Furthermore, other studies have pointed out that the control of visceral pain is tied to κ receptor. Oxycodone can inhibit the injury to the upload center and produce analgesic effect by activating κ receptors in visceral afferent fibers, which can relieve visceral pain more effectively than other frequently-used opioids [27]. Visceral pain caused by stimulation of diaphragm, pleura and lung tissue by indwelling closed thoracic drainage tube after LC is often an essential cause of postoperative pain and discomfort, and the degree of pain is sometimes even higher than that of surgical poke itself [28]. Therefore, oxycodone analgesia anesthesia has unique advantages. Correlation factor analysis also found that the use of INB combined with oxycodone anesthesia was an independent factor affecting the postoperative period of LC radical surgery, which once again validated our finding. Finally, we compared the postoperative analgesia satisfaction between the two groups. The results demonstrated that patients in the OG had higher analgesia satisfaction rate, which indicated that INB combined with oxycodone during LC radical operation could provide patients better treatment experience.

Nevertheless, this research also has some limitations that need to be improved. For example, there are many ways of analgesia and anesthesia for LC radical surgery, but we only compared with patients who used oxycodone routinely. The difference between INB combined with oxycodone and other methods remains to be studied. In addition, patients in this research are all the elderly, which has a certain singularity in age coverage. In the future, we also need to analyze patients in different ages. Besides, we need to follow up the subjects for a longer time to further evaluate the effect of INB combined with oxycodone on the late prognosis of patients.

To sum up, INB combined with oxycodone has a better application effect in the elderly undergoing LC radical operation, improves postoperative cognitive function and reduces postoperative adverse reactions and pain with has high safety.

Disclosure of conflict of interest

None.

Address correspondence to: Jiao Guo, Department of Anesthesiology, Shaanxi Provincial People's Hospital, 256 Youyi West Road, Xi'an 710000, Shaanxi, P. R. China. Tel: +86-17392941816; E-mail: guojanesyy@163.com

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