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CLINICAL TRIAL REPORT

Lower Background Infusion of Oxycodone for Patient-Controlled Intravenous Analgesia, Combined with Ropivacaine Intercostal Nerve Block, in Patients Undergoing Thoracoscopic Lobectomy for Lung Cancer: A Randomized, Double-Blind, Controlled Clinical Trial

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Purpose: To compare the efficacy of a lower dose background infusion of oxycodone for patient-controlled intravenous analgesia (PCIA) with the conventional dose, following intercostal nerve block, for the management of postoperative pain in patients undergoing thoracoscopic lobectomy for lung cancer.

Patients and Methods: This was a prospective, single-center, randomized, parallel-group, double-blind, controlled clinical trial. In total, 155 patients scheduled for elective radical lobectomy via video-assisted thoracoscopy were recruited from December 2018 to July 2019, of whom 140 were ultimately included in the study population. Patients were randomized to receive either oxycodone 0.25 mg/h (low-dose group, n=70) or oxycodone 0.5 mg/h (control group, n=70) as a background infusion for PCIA, following ropivacaine intercostal nerve block, for postoperative pain management. The primary endpoints were rest and dynamic visual analogue scale (VAS) scores within 72 h of the operation. The secondary endpoints were patient satisfaction scores, consumption of postoperative analgesics, times of patient-controlled analgesia (PCA), and adverse events.

Results: All 140 enrolled patients completed the study requirements and were included in the final analysis. The rest and dynamic VAS scores at 4 h, 24 h, 48 h, and 72 h postoperative were comparable between the low-dose group and the control group ($P>0.05$). However, the low-dose group had statistically significantly higher patient satisfaction scores ($P<0.001$) and lower postoperative analgesic consumption ($P<0.001$) as well as lower incidence of nausea and vomiting ($P<0.05$). The times of PCA was not statistically significantly different between the two groups, and no serious adverse events occurred in either group ($P>0.05$).

Conclusion: A low-dose background infusion of oxycodone for postoperative PCIA can achieve a comparable analgesic effect to the conventional dose after thoracoscopic lobectomy for lung cancer. Furthermore, the low-dose regimen was associated with reduced consumption of oxycodone and increased patient satisfaction.

Keywords: oxycodone, postoperative analgesia, patient-controlled intravenous analgesia, radical resection of lung cancer

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Introduction

Although thoracoscopic surgery is associated with less postoperative pain than thoracotomy, thoracoscopic patients still suffer from moderate to severe pain, largely owing to the intraoperative interaction of thoracoscopic devices with the ribs, which may lead to intercostal neuropathy or neuroma.[1] Thoracoscopic cannulas can also cause postoperative pain, as they can result in compression or damage of the intercostal nerves when placed between the ribs. Furthermore, closed thoracic drainage tubes (CTDTs) are often a major cause of pain and discomfort in patients who have undergone thoracic surgery and are sometimes associated with a higher degree of pain than that caused by incisions, as the CTDT may result in strong stimulation of the pleura.[2] Intercostal nerve injury frequently leads to neurological pain, whereas CTDT stimulation often leads to visceral pain, resulting in pain after thoracoscopic surgery that is both neurological and visceral.[3]

Oxycodone is an agonist of μ- and κ-opioid receptors that can neutralize both neurological[4] and visceral pain[5] and has been widely used for postoperative analgesia through patient-controlled intravenous analgesia (PCIA) with an apparent effect.[6–8] At present, the routine background dose of oxycodone for PCIA, to ensure the continuity and effectiveness of the analgesic effect, is 0.5 mg/h to 1 mg/h.[9] However, higher doses of oxycodone may lead to overdose and increase the incidence of adverse events such as dizziness, nausea, and vomiting.[10] Time-scheduled decremental infusion of oxycodone for PCIA, and even no background infusion, have been reported;[11–13] however, the optimal approach and dose of oxycodone for PCIA remain unclear. What's more, intercostal nerve block has been widely used for thoracic patients as part of a multimodal analgesia approach in line with the trend of rapid rehabilitation, but the use of intercostal nerve block followed by postoperative oxycodone PCIA has not been widely studied.

Considering that oxycodone has a rapid onset (2 to 3 min), a strong analgesic effect, and a long acting time (3.5 to 4.0 h),[14] we hypothesized that a lower background dose of oxycodone for PCIA, especially as part of a multimodal analgesia approach, may achieve a comparable analgesic effect to the conventional dose after thoracoscopic lobectomy for lung cancer with reduced consumption of oxycodone and improved patients' experience. In this study, we assessed the efficacy and safety of a low-dose background infusion of oxycodone for PCIA, following ropivacaine intercostal nerve block, for postoperative pain management in patients who underwent thoracoscopic lobectomy for lung cancer.

Materials and Methods

This was a prospective, single-center, randomized, parallel-group, double-blind, controlled clinical trial. Participants were randomized into 1 of 2 groups at a ratio of 1:1. The study was approved by the Medical Ethics Committee of Peking University Cancer Hospital (approval no. 2016YJZ11) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. The study was registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn) under the accession number ChiCTR1800016369.

Participants

In total, 155 patients with lung cancer who were scheduled for elective radical lobectomy via video-assisted thoracoscopy between December 1, 2018 and July 31, 2019 were recruited from the First Department of Thoracic Surgery, Peking University Cancer Hospital.

The main inclusion criteria was American Society of Anesthesiologists classification I or II. Exclusion criteria included (1) chronic pain; (2) long-term use of analgesics, sedatives, or antidepressants; (3) alcohol abuse; (4) use of sedatives, antiemetics, or antipruritics 24 h before surgery; (5) pregnant (6) or lactating; (7) scheduled to undergo a two-sided procedure; (8) reopening of the chest within 48 h of the operation; (9) and inability to score pain accurately.

Interventions

All patients received routine monitoring once they entered the operating room and the peripheral vein access was established. Patients then received total intravenous anesthesia. For induction of anesthesia, propofol 1 to 3 mg/kg, sulfentanyl 0.4 μg/kg, and rocuronium 0.6 mg/kg were administered. After endotracheal intubation, mechanical ventilation was conducted at a tidal volume of 8 mL/kg, respiratory rate of 12 to 14/min, and inspiration: expiration ratio of 1.0:1.5, with 60% oxygen at 1 L/min flow rate, positive end-expiratory pressure of 0 cm H_2O, and end-tidal PCO_2 of 30 to 40 mmHg (1 mmHg=0.133 kPa). For maintenance of anesthesia, an intravenous infusion of propofol 120 to 200 μg/kg/min and remifentanil 0.2 to 0.3 μg/kg/min was given with an intravenous injection of

cisatracurium 0.2 mg/kg at a 30-min interval to maintain blood pressure and heart rate within <20% deviation from baseline and bispectral index at 40 to 60. During the operation, Ringer's lactate solution and 6% hydroxyethyl starch (130/0.4) were infused intravenously at a ratio of 1:1 and at a total infusion speed of 8 to 12 mL/kg/h. At 30 min before the end of the operation, administration of the cisatracurium and remifentanil was stopped, and the patient was given an injection of oxycodone 0.05 mg/kg (batch number: BE123; Hamol, Nottingham, UK). Before the chest was closed, intercostal nerve block was performed on the operation segment (T2-T8) by the surgeon with 0.375% ropivacaine 2 mL for each point. At the end of the operation, When the patient begins to breathe autonomously, atropine 1 mg and neostigmine 2 mg were injected intravenously to antagonize the effect of residual muscle relaxants. The endotracheal tube was removed after satisfactory recovery of respiration.

After extraction of the endotracheal tube, if the visual analog scale (VAS) score was ≥4, an intravenous injection of oxycodone 2 mg was repeatedly given, at 5-min intervals, until the VAS score reached ≤3; the dose of oxycodone used for titration was recorded. PCIA was then initiated using the AutoMed 3000 pain pump (Woo Young, Korea). The PCIA drug solution consisted of oxycodone hydrochloride 50 mg and tropisetron 20 mg/100 mL of saline. The PCIA pump was set as follows: precharge 2 mL, patient-controlled analgesia (PCA) 2 mL per time and lockout interval of 10 min; For the low-dose group, the background infusion rate was 0.5 mL/h (oxycodone 0.25 mg/h), whereas for the control group, the background infusion rate was 1.0 mL/h (oxycodone 0.5 mg/h).

Outcomes

The primary endpoints were rest and dynamic VAS scores, scored by nurse anesthetists blinded to group assignment at 4 h, 24 h, 48 h, and 72 h after the operation. Dynamic VAS was defined as VAS when coughing.

The secondary endpoints were patient satisfaction score, dose of analgesics consumed in PCIA, the times of PCA, the dose of remedial drugs (analgesic and antiemetic), and the incidence of adverse events within 72 h after the operation (also recorded by nurse anesthetists). Patient satisfaction scores for postoperative analgesia were as follows: 5, very satisfied; 4, satisfied; 3, not sure; 2, unsatisfied; 1, very unsatisfied.

Sample Size

The difference in VAS scores between the two groups was analyzed using Student's *t* test. The difference in VAS scores and tolerance between the two groups was expected to be 20%, and the maximum tolerance was expected to be 30%. The statistical significance level was set at α bilateral = 0.05, the test efficiency was set at 0.8, and the minimum sample size was calculated to be 148 cases, with the potential of 5% dropout and loss to follow-up.

Randomization

Eligible patients were randomized to receive either a low-dose or a conventional-dose background infusion of oxycodone for postoperative PCIA. The allocation sequence was generated using a computer program by a staff member not otherwise involved in the trial. Concealment was performed using opaque envelopes that were opened upon the patient's arrival in the operating room.

Blinding

This was a double-blind trial. The patients and the nurse anesthetists in charge of the postoperative follow-up were blinded to group assignment. The anesthesiologist and the surgeons were also blinded to group assignments. Data were recorded using a standardized study case report form and were later entered into a computerized database.

Statistics

Continuous data were expressed as mean ± standard deviation (SD) and compared using Student's *t* test. Categorical data were compared using the χ^2 test. Grading data were compared using the rank and balance test. Variance analysis of repeated measurement data was used for comparisons at different time points. Statistical analyses were performed using SPSS software (version 22.0, SPSS, Chicago, IL, USA). $P<0.05$ (2-sided) was considered statistically significant.

Results

Demographic Characteristics and Intraoperative Data

The study flowchart is shown in Figure 1. In total, 155 patients were scheduled for thoracoscopic lobectomy for lung cancer during the study period. Nine patients who declined to participate in the study were excluded. Therefore, 146 patients were randomized to either the low-dose group or the control group. Three patients in

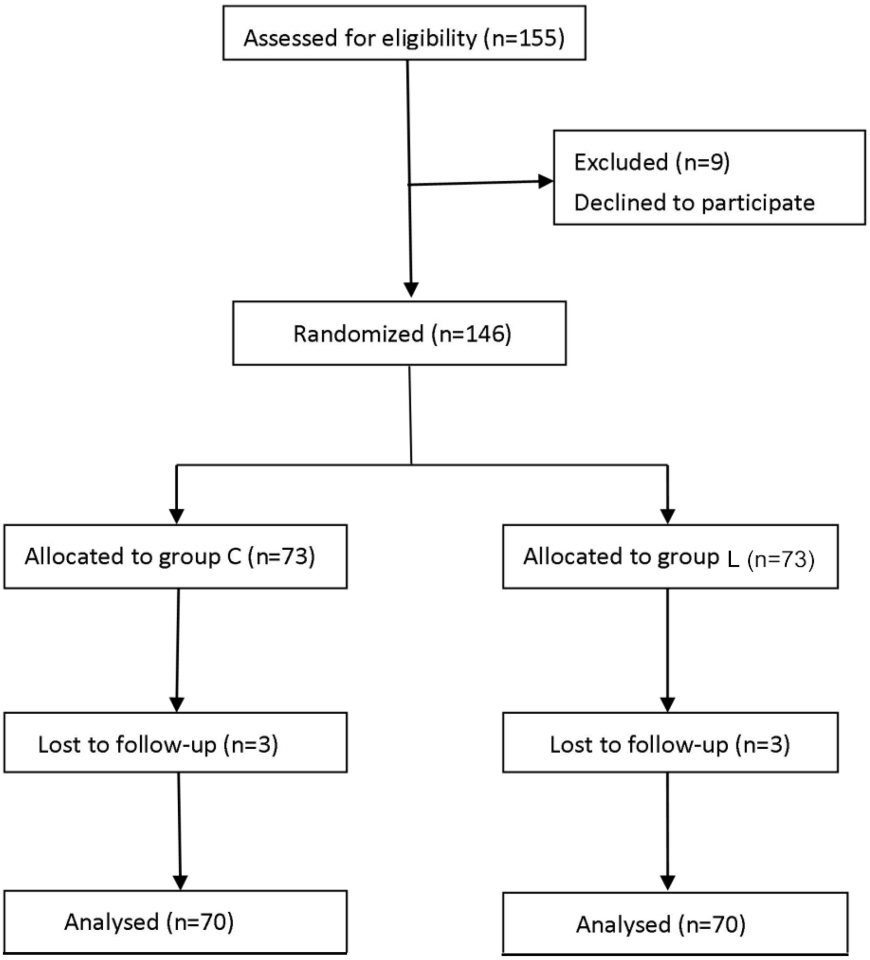

Figure 1 Study flowchart.

the low-dose group and 3 patients in the control group were unable to describe accurate pain scores and were excluded from the final analysis. The final analysis included 140 patients: 70 patients in the low-dose group and 70 patients in the control group. The two groups were comparable in terms of demographic variables, intraoperative data, and dose of oxycodone used for titration before PCIA (Table 1).

Postoperative VAS Scores

To assess the efficacy of the two approaches, the rest and dynamic VAS scores were recorded at 4 h, 24 h, 48 h, and 72 h postoperative. There were no statistically significant differences in VAS scores between the two groups, indicating that, in combination with ropivacaine intercostal nerve block, a low-dose background infusion was as effective as a conventional-dose background infusion of oxycodone for PCIA (Figure 2).

Dose of Analgesics Consumed Postoperatively

To assess analgesics consumed postoperatively between the two groups, the dose of analgesics consumed in PCIA, the dose of postoperative remedial analgesics, and the number of times of PCA were recorded. The dose of analgesics consumed in PCIA was not statistically significantly different between the two groups within the first 4 h after operation; however, at 24 h, 48 h, and 72 h postoperative, the dose of analgesics consumed was statistically significantly lower in the low-dose group than in the control group. When the VAS score ≥4 and the patients complained of pain even after the use of PCIA, the rescue analgesics (morphine) will be given. The dose of postoperative rescue analgesics, the total times of PCA, and the times of effective/invalid PCA were not statistically significantly different between the two groups (Table 2).

Table 1 Demographic Characteristics and Intraoperative Data

Variables	Low-Dose (n=70)	Control (n=70)	*P* value
Age, years	55.5 ± 3.6	55.9 ± 3.4	0.456
Sex, female/male	32/38	29/41	0.733
BMI, kg/m^2	23.3 ± 0.9	23.6 ± 1.0	0.104
ASA, I/II	27/43	31 /39	0.607
Duration of surgery, min	95.9 ± 7.8	95.0 ± 7.5	0.480
Type of surgery			>0.999
Right VATS lobectomy	34 (48.6)	33 (47.1)	
Left VATS lobectomy	36 (51.4)	37 (52.9)	
Estimated blood loss, mL	96.7 ± 134.8	74.4 ± 85.3	0.244
Titration dose before PCIA			0.946
Oxycodone, mg	1.1 ± 1.2	1.1 ± 1.3	

Note: Data are expressed as mean ± standard deviation or no. (%).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; PCIA, patient-controlled intravenous analgesia; VATS, video-assisted thoracoscopic surgery.

Postoperative Nausea and Vomiting

The incidence of nausea was statistically significantly lower in the low-dose group at 5 to 24 h, 24 to 48 h, and 48 to 72 h postoperative. Similarly, the incidence of vomiting was statistically significantly lower in the low-dose group at 5 to 24 h and 24 to 48 h (Table 3).

Other Adverse Effects

No patients were admitted to the ICU after surgery. Incidence of postoperative dizziness and respiratory rate (used to assess the risk of respiratory depression) were not statistically significantly different between the two groups. No serious adverse events occurred in either group (Table 3).

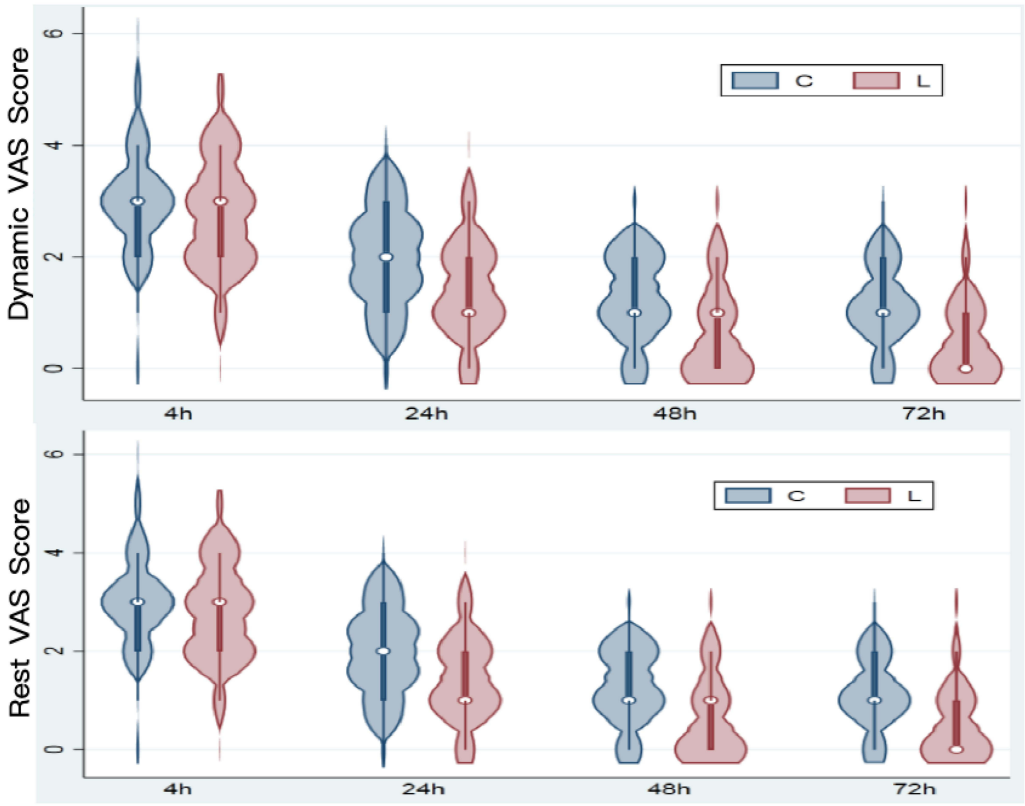

Figure 2 Postoperative rest and dynamic visual analog scale (VAS) scores for the two groups. There were no statistically significant differences in VAS scores between the two groups at 4 h, 24 h, 48 h, and 72 h postoperative (all *P*>0.05).
Abbreviations: C, control; L, low dose.

Table 2 Analgesics Consumed in PCIA, Times of PCA and Remedial Drugs Consumed Postoperatively

Variables	Low-Dose (n=70)	Control (n=70)	*P* value
Analgesics consumed in PCIA, mL			
4 h after operation	4.89 ± 1.21	6.77 ± 1.04	**<0.001**
24 h after operation	19.29 ± 2.53	27.91 ± 2.11	**<0.001**
48 h after operation	31.17 ± 3.46	51.46 ± 3.61	**<0.001**
72 h after operation	52.31 ± 4.02	88.51 ± 4.71	**<0.001**
Number of times of PCA			
Total PCA	8.20 ± 2.25	8.44 ± 2.63	0.558
Effective PCA	7.16 ± 2.01	7.26 ± 2.36	0.788
Invalid PCA	1.04 ± 1.11	1.20 ± 1.22	0.427
Dose of remedial drugs			
Morphine, mg	0.64 ± 2.54	0.59 ± 2.49	0.893
Tropisetron, mg	0.36 ± 1.77	2.14 ± 3.36	**<0.001**

Note: Data are expressed as mean ± standard deviation. Bold indicates $P<0.05$.
Abbreviations: PCA, patient-controlled analgesia; PCIA, patient-controlled intravenous analgesia.

Patient Satisfaction Scores

Patient satisfaction scores with the effect of postoperative analgesia were higher in the low-dose group than in the control group (Table 3).

Discussion

We compared the analgesic effects of a low-dose and a conventional-dose background infusion of oxycodone for PCIA in patients who underwent radical thoracoscopic lung cancer surgery. Ropivacaine intercostal nerve block was administered in all patients near the end of the operation. The analgesic effect was comparable between the two groups, whereas patient satisfaction scores were higher and PCIA consumption and postoperative nausea and vomiting were lower in the low-dose group.

Previous study showed that a background infusion of oxycodone of 0.5–1 mg/h could achieve satisfactory postoperative analgesic effects in patients after surgery, but postoperative nausea and vomiting were observed.[7,9,10] Other studies have reported that a low dose of oxycodone can achieve a good analgesic effect and is associated with fewer side effects.[4,12] Therefore, in our trial, we set the background infusion dose of oxycodone in the control group at conventional 0.5 mg/h, and tried to investigate

Table 3 Incidence of Adverse Events and Patient Satisfaction Scores

Variables	Low-Dose (n=70)	Control (n=70)	P value
Patients with nausea			
1–4 h after operation	6 (8.6)	6 (8.6)	>0.999
4–24 h after operation	4 (5.7)	14 (20.0)	**0.021**
24–48 h after operation	2 (2.9)	17 (24.3)	**<0.001**
48–72 h after operation	0 (0)	10 (14.3)	**0.001**
Patients with vomiting			
1–4 h after operation	2 (2.9)	3 (4.3)	>0.999
4–24 h after operation	1 (1.4)	8 (11.4)	**0.033**
24–48 h after operation	1 (1.4)	10 (14.3)	**0.009**
48–72 h after operation	0 (0)	5 (7.1)	0.058
Patients with dizziness	4 (5.7)	5 (7.1)	>0.999
Respiratory rate, times/min[a]	13.54 ± 1.47	13.50 ± 1.42	0.861
Patient satisfaction score[b]	4.79 ± 0.41	3.80 ± 0.73	**<0.001**

Note: Data are expressed as mean ± standard deviation or no. (%). Bold indicates $P<0.05$. [a]Used to assess the risk of respiratory depression. [b]Patient satisfaction score: 5, very satisfied; 4, satisfied; 3, not sure; 2, unsatisfied; 1, very unsatisfied.

a background infusion dose of 0.25 mg/h, with the goals of achieving satisfactory analgesia and reducing side effects, following ropivacaine intercostal nerve block, for postoperative pain management.

All patients with a VAS score ≥4 after removal of the endotracheal tube received intravenous titration of oxycodone until VAS was ≤3. The titration levels of the two groups were not statistically significantly different, which indicates that the patients had comparable degrees of pain immediately after surgery and similar sensitivity to oxycodone. In the present study, consumption of analgesics was evaluated at 4 h, 24 h, 48 h, and 72 h postoperative, as the basic metabolism of anesthetic analgesics was expected to be complete by 4 h postoperative,[15] the CTDT was most often removed at approximately 48 h (which would largely relieve related pain), and the postoperative analgesia for this type of operation regularly lasts 72 h.[10] Rest and dynamic VAS scores were comparable between the two groups and were <3 at all selected time points, indicating that both approaches provide adequate analgesia for patients undergoing radical surgery for lung cancer via thoracoscopy.

Patient satisfaction scores in the low-dose group were statistically significantly higher than those in the control group, which may be due to the lower incidence of postoperative nausea and vomiting in the low-dose group. Studies have shown that postoperative analgesia with oxycodone is often accompanied by nausea, vomiting, dizziness, fatigue, and other complications, and the incidence of these increase with the dose of oxycodone and the duration of use.[7,8,16] The precise mechanisms of oxycodone-induced nausea and vomiting are not known with certainty, although such side effects may be due to multiple opioid effects, such as enhanced vestibular sensitivity, direct effects on the chemoreceptor trigger zone, and delayed gastric emptying.[17] In the present study, we have shown that a lower background dose of oxycodone for PCIA may decrease the incidence of postoperative nausea and vomiting and analgesia-related adverse events, owing to the substantial reduction in the amount of analgesics consumed postoperatively.

In line with the trend of rapid rehabilitation, intercostal nerve block has been widely used as part of a multimodal analgesia approach for thoracic patients.[13] In the present study, ropivacaine was used for intercostal nerve block, the effect of which usually lasted approximately 10 h.[18] Studies have shown that the primary pain caused by skin incision subsides within 1 h, whereas severe secondary pain can last until the early postoperative period.[19] Previous studies have also found that the degree of postoperative pain is highest at 4 h after surgery and then declines thereafter.[20,21] Therefore, in the first few hours after surgery, ropivacaine intercostal nerve block may contribute substantially to the satisfied analgesia of patients in both groups.

The limitations of this study include its small sample size. In addition, the study was performed at a single institution, which may limit the generalizability of our results.

In conclusion, a low-dose (0.25 mg/h) background infusion of oxycodone in PCIA, following ropivacaine intercostal nerve block, is safe and effective for postoperative pain management in patients undergoing thoracoscopic lobectomy for lung cancer, with comparable analgesic effect to the conventional dose, but reduced consumption of oxycodone and increased patient satisfaction.

Data Sharing Statement

All the data in the manuscript are available upon reasonable request from the corresponding author.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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