International Journal of Surgery 69 (2019) 132–138

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Optimal dose of ropivacaine for relieving cough-pain after video-assisted thoracoscopic lobectomy by single intrapleural injection: A randomized, double-blind, controlled study

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ARTICLE INFO

Keywords:
Intrapleural analgesia
Coughing-pain
Ropivacaine
Dosage

ABSTRACT

Background: Pain due to coughing after thoracoscopic surgery remains a clinical problem, and its relief by intrapleural analgesia has not been extensively studied. This study attempts to determine the suitable volume of 0.75% ropivacaine needed for intrapleural analgesia after thoracoscopic surgery.
Methods: A double-blind, randomized, controlled trial was performed. Forty-five patients were randomly divided into three groups: R20, R15, and R10 (n = 15); 20 ml, 15 ml, or 10 ml of 0.75% ropivacaine was injected into the pleural cavity of each patient in the 3 groups, respectively, when the pain score from postoperative coughing was ≥4. The primary outcome was pain score upon coughing (C-NRS), and the secondary outcomes were pain score at rest (R-NRS), morphine consumption, time of onset, and duration of intrapleural analgesia.
Results: All patients in the R20 and R15 groups reported effective pain relief after intrapleural injection when postoperative coughing occurred. However, only 7 patients in the R10 group reported effective relief of pain. Compared with the patients in the R10 group, patients in the R20 and R15 groups had lower C-NRS scores, less morphine consumption at 8 h and 24 h, a shorter time to pain relief, and a longer duration of analgesia. There was no significant difference of R-NRS among the three groups.
Conclusion: Intrapleural analgesia with 0.75% ropivacaine at a volume of 15 ml or 20 ml effectively relieved pain due to coughing after thoracoscopic surgery.
Trial registration: ChiCTR1800017515.

1. Introduction

Lung cancer has been the most commonly diagnosed cancer and the primary cause of death due to cancer during the past several decades, especially in males [1–3]. Surgery remains the mainstay of lung cancer treatment. Recently, video-assisted thoracoscopic surgery (VATS) has been extensively used, as it is less invasive than thoracotomy [4]. However, postoperative pain remains the primary patient complaint, especially with regard to coughing in the early postoperative period after VATS [5].

Intuitively, pain from coughing can be attributed to the friction between the chest drain and the surrounding tissue, and pain is significantly reduced when the chest drains are removed. Moreover, limiting the number of chest drains after thoracotomy can significantly reduce patient discomfort [6]. Pain is usually addressed through epidural analgesia, intravenous analgesia, and/or thoracic paravertebral blocks. Epidural analgesia is not always possible and has the associated risks. A single paravertebral block of bupivacaine significantly relieved pain after thoracoscopic lung surgery, but the analgesic effect lasted for only 6 h [7]. Continuous paravertebral block and continuous epidural block had similar imperfect analgesic effects, and the mean pain score of coughing was > 4 [8]. Furthermore, it has been reported that 30-50% of patients who have paravertebral catheters and 40-45% of those with continuous-block catheters may encounter displacement [9,10].

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https://doi.org/10.1016/j.ijsu.2019.05.013
Received 26 February 2019; Received in revised form 11 April 2019; Accepted 21 May 2019
Available online 29 May 2019

Interpleural analgesia was first described in 1986 [11]. It is safe and convenient when catheter placement is performed by surgeons during the surgical procedure under direct vision. However, it can be controversial with regard to analgesia after thoracotomy because of the insufficient pain reduction. This is because the distribution of local anesthetics in the pleural cavity is limited by the dilutional effect of fluid and blood drainage, the combination of proteins with local anesthetics, and the leakage of the local anesthetic through the chest drains [12]. Additionally, various surgical and analgesia methods may also effect intrapleural analgesia [13,14]. However, VATS has led to a more effective abatement of bleeding in the operative field, a reduction in postoperative thoracic effusions, a decreased indwelling time of chest drains, and less rib manipulation, leading to less postoperative pain [15]. Contemporary changes in surgical methods and pain have warranted a reassessment of the role of intrapleural analgesia. Demmy et al. [16] found that pain was successfully controlled regardless of whether an intermittent or a continuous intrapleural bupivacaine injection was used. Silva et al. [17] found that a single intrapleural injection of 0.5% ropivacaine (20 ml) reduced the pain score at 2 h postoperatively (an average of 2 points) after thoracoscopic sympathectomy. However, dosing studies on intrapleural injection of ropivacaine to relieve pain due to coughing after thoracoscopic surgery have not been adequately conducted.

We hypothesized that there was a dose effect with a single intrapleural injection of 0.75% ropivacaine in relieving coughing pain after thoracoscopic surgery. Therefore, we conducted a study using protocols of 20 ml, 15 ml, or 10 ml of 0.75% ropivacaine after VATS to determine the optimal dose for intrapleural analgesia. The primary outcome was pain score on coughing (C-NRS), and the secondary outcomes were pain scores at rest (R-NRS), morphine consumption, time of onset, and duration of intrapleural analgesia.

2. Material and methods

2.1. Participants

This double-blind, randomized trial was approved by Ethics Committee, and a written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment in the Clinical Trial Registry. The inclusion criterion was patients scheduled for video-assisted thoracoscopic lobectomy. Exclusion criteria were age < 18 years, ASA > III, allergies to ropivacaine and parecoxib or adverse interactions/side effects of ropivacaine, recent thoracic infection, a history of previous lung surgery, a history of chronic pain, serious hepatic or renal insufficiency, current opioid use, alcohol or opioid dependence, psychiatric disorders, those with inability to complete a numerical rating scale measurement, or patients whose C-NRS after surgery was < 4 within 2 h in the PACU.

This study has been reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. All authors had access to the study data and reviewed and approved the final manuscript.

2.2. Study design

Patients received no preoperative medications, were routinely forbidden smoking for 2 weeks, under fasting for 6 h, and deprived of water 2 h before surgery. Patients were instructed how to express pain intensity using the NRS (0 = no pain, 10 = the worst imaginable pain) on the day before surgery. Patients were monitored by electrocardiography (ECG), invasive arterial blood pressure (IBP), pulse oximetry (SpO_2), and bispectral index (BIS). All patients had peripheral venous access established in an upper limb. General anesthesia was induced by intravenous infusion of sufentanil (0.3 μg kg^{-1}) or propofol (2 mg kg^{-1}), and this was followed by rocuronium (0.6 mg kg^{-1}) for facilitation of intubation using a selective endobronchial tube with positioning guided by fiberoptic bronchoscopy. All patients underwent two port incisions, that is, one is a 1 cm incision in the seventh or the eighth intercostal space in the mid-axillary line for observation, and the other is a 4 cm incision in the fourth or the fifth intercostal space in the anterior axillary line for operation. Morphine 0.1 mg kg^{-1} was administered before skin incision. Anesthesia was maintained with intravenous propofol (4-6 mg kg^{-1} h^{-1}), remifentanil (5-6 μg kg^{-1} h^{-1}), and sevoflurane (1%–2%) in oxygen. The BIS index was maintained between 45 and 60. The surgeon confirmed that there was no bleeding in the chest and that any residual lavage fluid and blood were fully removed before placing the chest drain(s) (F26, Suzhou Instrument Standard 2015266086, Suzhou McLean Medical Instrument Products Co., Ltd, China). On completion of the procedure, incisions were infiltrated with 0.375% ropivacaine with a maximum volume of 20 ml. After extubation, the patient was transferred to the post-anesthesia care unit and observed for 2 h. All patients were given parecoxib 40 mg twice daily for 2 postoperative days.

2.3. Intrapleural analgesia

Before closing the chest, an epidural catheter with three orifices (National Machinery Standard 20173664119, Zhejiang Haisheng Medical Devices Co., Ltd., Shaoxing, Zhejiang) was placed into the side hole of the chest drain and into the chest cavity for injection of ropivacaine.

When the patients entered the PACU, we immediately evaluated the R-NRS and C-NRS and then assessed the NRS every 10 min or the patient reported an increase in NRS. If the C-NRS ≥ 4, we preferred to administer an intrapleural ropivacaine injection. If the NRS was still ≥4 after half an hour of intrapleural administration, we provided morphine titration. For patients with a C-NRS always < 4 within 2 h in the PACU, we did not take any measures. These patients were excluded and took the intravenous morphine PCA before returning to the ward.

When the patients were given an intrapleural injection with ropivacaine 20 ml, 15 ml, or 10 ml, the time was recorded. At the same time, the chest drain was clamped for 10 min. Patients were assigned to groups using a computerized random number generator (by a nurse). For investigational purposes, the time point “0” was defined upon the completion of the intrapleural injection; the initial NRS before intrapleural injection was defined as the baseline score. This study was double-blinded. Ropivacaine was prepared in a 20 ml syringe covered with a black cloth, thereby blinding the provider and the patient as to the contents of the syringe and then injected by an anesthesiologist for 2-3 min. Pain assessment was conducted by a second anesthesiologist to ensure this trial was double-blinded. Patients were assessed at 2-min increments beginning 2 min after intrapleural injection assessment continued to 30 min. Effective analgesia was defined as the NRS < 4 or fall ≥3 (on coughing) at 30 min. Otherwise, the intrapleural analgesia was considered as failed; then morphine was administered intravenously for analgesia. The drains of all patients were retained for the entire period of observation of 24 h. All patients received postoperative intravenous patient-controlled analgesia (PCV) (SU Food drug supervision and production No. 20020280, Nantong AIPU Medical Technology Co., Ltd., Jiangsu) with morphine, programmed to provide a 1 mg bolus with a lockout time of 5 min.

2.4. Data collection

Data of intrapleural analgesia efficacy, onset time, and duration of intrapleural analgesia were collected. Intrapleural analgesia onset was defined as the time from the end of ropivacaine injection to C-NRS < 4 or fall ≥3. Intrapleural analgesia duration was defined as the time from intrapleural analgesia onset to C-NRS ≥ 4 or an increase of ≥2 again. One hour after intrapleural injection, to assess bilateral chest wall sensory plane, ice was applied, as well as a pinprick, on the front and the lateral chest wall (assessment of the healthy side as a contrast) to

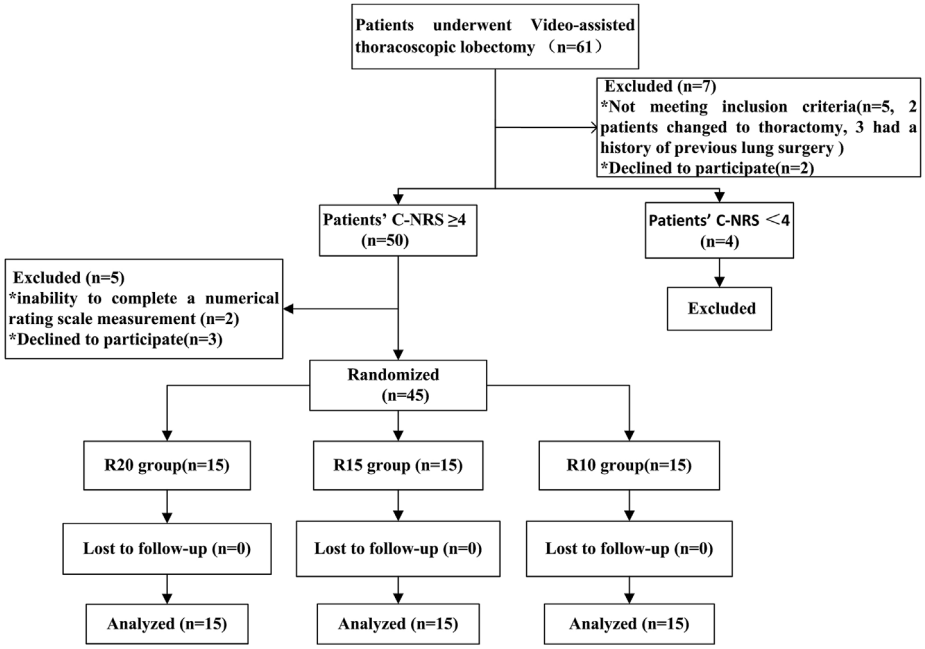

Fig. 1. Flow diagram of patients enrolled in the study. R20 group, 20 ml of 0.75% ropivacaine as intrapleural injection; R15 group, 15 ml of 0.75% ropivacaine as intrapleural injection, and R10 group, 10 ml of 0.75% ropivacaine as intrapleural injection.

assess the sensation on both sides of the chest wall. To avoid disturbing sleeping patients on the wards, patients were told to notify the staff to assess the NRS if they thought the characteristics of their pain had changed at 8-24 h after intrapleural injection.

2.5. NRS

The NRS was assessed initially and at 30 min, and then at 1, 2, 3, 4, 5, 6, 7, 8, and 24 h after intrapleural injection when patients were both at rest (R-NRS) and coughing (C-NRS).

2.6. Cumulative morphine consumption

The cumulative morphine consumption at 8 h, 8-24 h, and 24 h was recorded.

2.7. Adverse events

Commonly recorded adverse events from morphine administration and local anesthetic toxicity were vomiting, nausea, and respiratory depression. Surgical complications such as bleeding, pneumothorax, and/or lung infection after surgery were also recorded.

2.8. Statistical analysis

The power analysis was based on the results of the preliminary study using Power Analysis and Sample Size (PASS11.0) software. Twenty-one patients were divided into three groups (n = 7) in the preliminary study; the mean and SD of the C-NRS 30 min after intrapleural injection in the R20, R15, and R10 groups was 2.36 ± 1.11, 2.21 ± 1.78, and 5.14 ± 2.54, respectively. We assumed a type I error of 0.05 and a power of 0.90, and the ANOVA was used. Nine patients required per group to determine a statistical significance among the three groups. Considering the loss potential and errors, it was determined that there should be 15 patients in each group for the trial.

Statistical analysis was performed using SPSS statistical software, version 19.0. Data were tested for normal distribution using the Shapiro–Wilk test. The measured data of normal distribution were expressed as mean ± standard deviation, and the data of non-normal distribution were expressed as median and interquartile range. Average age, body mass index (BMI), the time of surgery end to the first intrapleural injection, pre-administration NRS, ambulation time, discharge time, and duration of surgery were assessed by one-way analysis of variance (ANOVA) test. The pain assessment (R-NRS and C-NRS) was evaluated by ANOVA for repeated measurement. Pairwise comparisons were performed using the LSD test. $P < 0.05$ was considered statistically significant. Smoking habits, surgery category, intrapleural analgesia efficacy, and the probability of the occurrence of adverse events were determined using the chi-square test. The onset time and duration of intrapleural analgesia were studied using Kaplan–Meier analysis and compared using the log-rank test. ASA classification and cumulative morphine consumption at 8, 8-24, and 24 h after surgery were compared using an initial Kruskal–Wallis H-test. To reduce type I error, $P < 0.0167$ was considered as statistically significant difference when comparing two groups.

3. Results

A total of 61 patients underwent thoracoscopic lobectomy during the study period, 2 patients were converted to thoracotomy during surgery, 3 patients had a history of previous pulmonary surgery, and 2 patients refused to participate in the experiment. A total of 50 patients had C-NRS ≥ 4 after operation. Of them, 2 complained of pain but could not complete a numerical rating scale measurement after surgery, and 3 patients refused to receive intrapleural injection. Four of them had an NRS of less than 4 within 2 h in the resuscitation chamber; thus, they were excluded. Therefore, a total of 11 patients were excluded. Forty-five patients were enrolled and randomly assigned. All patients successfully completed the study procedures (Fig. 1). There was no significant difference in ASA classification, age, BMI, smoking habits, surgery category, surgery time, the time of surgery end to the first intrapleural injection, pre-administration NRS, ambulation, and discharge time among the three groups (Table 1).

3.1. Analgesia outcomes

There were 15 patients with effective analgesia in the R20 and R15 groups and only 7 patients with effective analgesia in the R10 group.

Table 1
Patient Demographics among three groups.

Variable	R20 group	R15 group	R10 group	P value
Age, y	55(14)	53(13)	62(8)	0.099
Sex, M/F	7/8	8/7	8/7	0.655
Body mass index(kg/m2)	23.5(1.9)	23.6(3.3)	23.5(2.7)	0.981
ASA				0.849
I	6	7	4	
II	7	7	8	
III	2	1	3	
Smoking habits, number of patients	4	3	5	0.912
Duration of surgery (h)	2.2(1.1)	1.7(0.6)	1.7(0.9)	0.250
Extent of pulmonary parenchyma resection, number of patients				0.988
Right upper lobe	3	5	4	
Right lower lobe	4	3	3	
Middle lobe	3	2	2	
Left upper lobe	3	4	3	
Left lower lobe	2	1	3	
The NRS score before intrapleural injection				
Rest	4.4(1.7)	4.7(2.2)	4.4(2.6)	0.862
Cough	7.0(1.5)	7.1(1.5)	7.3(0.9)	0.789
The time from surgery end to the first intrapleural injection (min)	23.47(7.56)	22.87(8.69)	22.62(8.34)	0.807
ambulation time (h)	17.68(5.59)	17.24(8.84)	21.12(11.47)	0.063
discharge time (day)	5.14(1.29)	4.07(1.03)	4.80(2.11)	0.173

Values are number (proportion) or means (SD). R20 group, 0.75% ropivacaine 20 ml intrapleural injection; R15 group, 0.75% ropivacaine 15 ml intrapleural injection, R10 group, 0.75% ropivacaine 10 ml intrapleural injection.

The difference among the three groups was statistically significant ($P < 0.001$) (Table 2).

The onset time of intrapleural analgesia in the R20 and R15 groups was significantly shorter than that in the R10 group (R20 vs. R10 group, P = 0.007, and R15 vs. R10 group, P = 0.009). There was no statistically significant difference between the R20 and R15 groups (P = 0.724) (Fig. 2A, Table 2).

The duration of intrapleural analgesia in the R20 and R15 groups was longer than that in the R10 group (R20 vs. R10 group, P = 0.009, and R15 vs. R10 group, P = 0.008). There was also no statistically significant difference between the R20 and R15 groups (P = 0.730) (Fig. 2B, Table 2).

3.2. Bilateral chest wall sensory plane

The sense of temperature (ice irritation test) and pain (pinprick test) did not show changes between the initial assessment and 1 h after intrapleural injection, suggesting that there was no chest wall sensory blockade.

3.3. NRS scores

There was no significant interaction between groups and times of R-NRS at different points of time (F = 1.358, P = 0.268). Compared with the R-NRS before intrapleural analgesia, it was significantly lower at all measured times (F = 20.599, $P < 0.001$). However, there was no significant difference among the three groups (P = 0.535) (Fig. 3A).

There was no significant interaction between groups and times of C-NRS at different points of time (F = 1.918, $P = 0.160$). Compared with the C-NRS before intrapleural analgesia, it was significantly lower at all measured times (F = 46.966, $P < 0.001$), and there was significant difference among the three groups (F = 3.426, P = 0.042) (Fig. 3B). The C-NRS scores in the R20 and R15 groups were lower than that in the R10 group (R20 vs. R10 group, P = 0.043; R15 vs. R10 group, P = 0.02).

3.4. Cumulative morphine consumption at 8, 8-24, and 24 h

The cumulative morphine consumption in R20 and R15 groups at 8 and 24 h was significantly less than that in the R10 group (morphine consumption at 8 h, R20 vs. R10 group, P = 0.007, R15 vs. R10 group, P = 0.012; morphine consumption at 24 h, R20 vs. R10 group, P = 0.001, R15 vs. R10 group, P = 0.006). There was no statistically significant difference between the R20 and R15 groups (morphine consumption at 8 h, R20 vs. R15 group, P = 0.697; morphine consumption at 24 h, R20 vs. R15 group, P = 0.0.616) Moreover, there was no significant difference at 8-24 h among the three groups (P = 0.091) (Table 2).

3.5. Adverse events

There was no statistically significant difference in nausea and vomiting between the groups (1, 3, and 3 in R20, R15, and R10 groups, respectively, P = 0.668). None of patients in the three groups had respiratory depression and local anesthetic toxicity. All patients had no surgical complications such as bleeding, pneumothorax, and/or lung infection after surgery.

4. Discussion

The results of this study demonstrated that 20 ml and 15 ml of 0.75% ropivacaine provide a better analgesic effect than the 10 ml dose. The effective analgesic results in patients in the R20 and R15 groups were significantly higher than that in the R10 group; the R20 and R15 groups had a lower C-NRS, less morphine consumption, shorter onset time, and a longer duration of analgesia.

The effect of intrapleural analgesia has remained controversial. Kambam et al. [11] and Mann et al. [18] used intrapleural analgesia for thoracotomy early and successfully relieved postoperative pain. On the contrary, Rosenberg [19] reported that neither a bolus injection of 0.5% bupivacaine 15-20 ml nor a continuous infusion of 0.25% bupivacaine 10 ml/h can effectively relieve pain. This was related to the limited

Table 2
Analgesia outcomes and cumulative morphine consumption.

	R20 Group	R15 Group	R10 Group	P value
The effective of intrapleural analgesia, effective/ineffective	15/0	15/0	7/8	< 0.001*
The onset time of intraleural analgesia, minute	6(4,10)	6(4,6)	30(10,30)	< 0.001*
The duration time of intraleural analgesia, minute	320(140,630)	320(230,570)	0(0,320)	0.005*
Cumulative morphine consumption				
0–8 h,mg	6(0,9)	6(0,9)	14(8,26)	0.009*
8–24 h, mg	9(6,16)	12(6,18)	15(12,17)	0.091
24 h, mg	15(12,21)	18(12,24)	26(20,41)	0.002*

Value are number or median (Q1–Q3), n = 15 for all groups. R20 group, 0.75%ropivacaine 20 ml intrapleural injection; R15 group, 0.75%ropivacaine 15 ml intrapleural injection, R10 group, 0.75%ropivacaine 10 ml intrapleural injection. *indicates statistically significant among three groups.

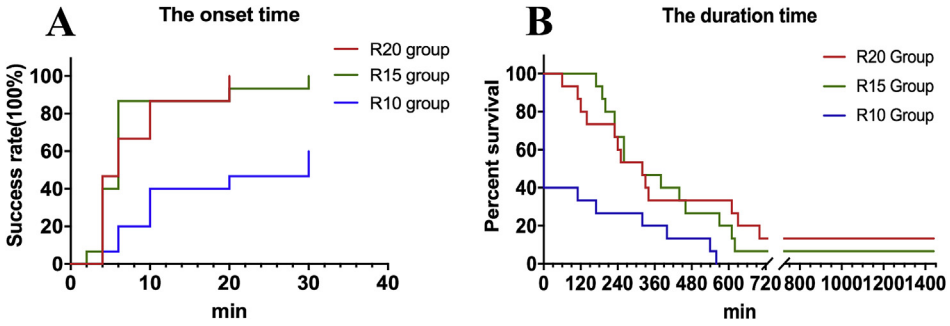

Fig. 2. The time of onset and duration of intrapleural analgesia in the 3 groups. Kaplan–Meier survival curves demonstrated that the median onset time of intrapleural analgesia in R20 and R15 groups was shorter than that of the R10 group (R20 versus R10, P = 0.007 and R15 versus R10, P = 0.009, R20 versus R15, P = 0.724), and the median duration time of intrapleural analgesia in R20 and R15 groups was longer than that in the R10 group (R20 versus R10, P = 0.009 and R15 versus R10, P = 0.008, R20 versus R15, P = 0.730). R20 indicates 20 mL of 0.75% ropivacaine as intrapleural injection, R15 indicates 15 mL of 0.75% ropivacaine as intrapleural injection, and R10 indicates 10 mL of 0.75% ropivacaine as intrapleural injection.

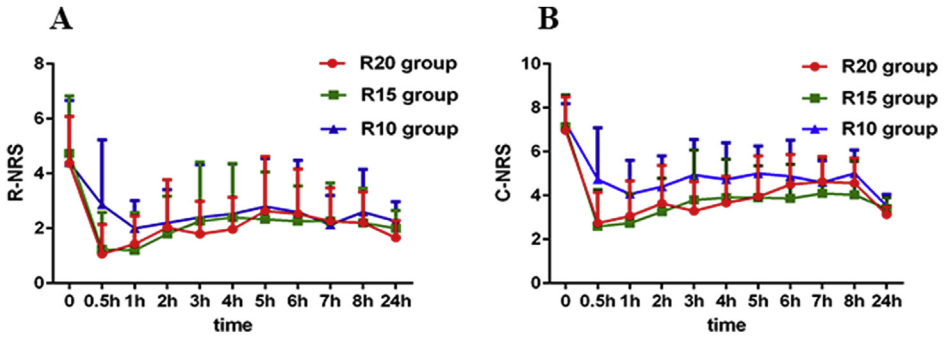

Fig. 3. R-NRS and C-NRS in the three groups. Mean (SD) numeric rating pain scores (NRS) at rest and on coughing assessed before intrapleural injection (time 0) and then 30 min, 1, 2, 3, 4, 5, 6, 7, 8, and 24 h after intrapleural injection evaluated using repeated measures analysis. Compared with NRS (R-NRS and C-NRS) at time 0 before intrapleural injection, the values were significantly lower at all measure of times after intrapleural injection ($p < 0.001$). However, the mean R-NRS values among the three groups demonstrated no significant differences (P = 0.535). There was a significant difference in the mean C-NRS values among the three groups (P = 0.042). The patients of R20 and R15 groups had lower C-NRS than those of the R10 group, and there was no significant difference between R20 and R15 groups (R20 versus R10, P = 0.043, R15 versus R10, P = 0.02, R20 versus R15, P = 0.748). R20 indicates 20 mL of 0.75% ropivacaine as intrapleural injection, R15 indicates 15 mL of 0.75% ropivacaine as intrapleural injection, and R10 indicates 10 mL of 0.75% ropivacaine as intrapleural injection.

distribution of local anesthetics in the pleural cavity, the diversity of previous surgical procedures, and postoperative pain management. By using VATS more frequently, surgeons have been able to significantly reduce postoperative incisional pain. Additionally, the use of local wound infiltration, intercostal nerve block, paravertebral block, nerve block, erectus spine muscle block, and serratus anterior plane block can be very helpful for incisional pain control [20,21]. In view of these interventions, pain caused by chest drains has become a more prominent concern, especially the pleural pain of coughing caused by chest drains. Previous studies found that the use of opioids such as morphine after thoracoscopic surgery is insufficient to control pain due to cough and causes side effects such as pruritus, sedation, and constipation, especially when used at high doses [22]. Although the patient will press PCA during cough, he is more inclined to force himself to not cough or cough slightly. The increased use of VATS, with its intrinsic reduction of postoperative pain, has presented the possibility of intrapleural injection of a local anesthetic as an effective analgesic. The special dual-lumen isolation tube designed by Demmy et al. [16] used for pleural drainage and intrapleural injection demonstrated an effective reduction of postoperative pain, and a reduction in opioid consumption at 24 h. During the 24 h observation period we studied, all patients retained the chest drains because they did not reach the extubation, and we used local wound infiltration for incisional pain control. In our study, 0.75% ropivacaine injection into the intrapleural space reliably reduced the pain of postoperative coughing.

Murphy et al. states that intrapleural analgesia can be mainly attributed to a multi-segmental intercostal nerve and visceral nerve blockade. If so, it could be used for the corresponding indications of pain treatment in breast, kidney, gallbladder, and thoracic surgery, as well as chronic pain [23]. McKenzie et al. injected India ink through an extradural catheter placed in the right interpleural space in cadavers at autopsy and found that the injected ink covered the chest wall, lung, diaphragm, and pooled in the paravertebral area [24]. Strømskag et al. injected 20 ml of 0.375% bupivacaine mixed with 10 ml of contrast medium into the intrapleural space and observed that the local anesthetic distributed close to the roots of intercostal nerves, splanchnic nerves, and the sympathetic chain (using computed tomography) [25]. In this study, ice and pinprick were used to measure the sensory plane of the chest wall bilaterally. Neither the sense of temperature nor the sense of pain changed. We consider that our intrapleural analgesia at these doses cannot result in paravertebral block, intercostal nerve block, splanchnic nerve block, or sympathetic chain block. Considering the time of onset and duration of intrapleural analgesia, it was mainly showed an infiltration affect. Clamping of the chest drain before injection assisted in avoiding leakage of the anesthetic from the chest drain, thereby allowing a local anesthetic “smear” of the pleura as much as possible.

Silva et al. [17] reported that intrapleural analgesia with 20 ml of 0.5% ropivacaine resulted in less pain than analgesia with 20 ml of 0.375% ropivacaine in the late postoperative period of endoscopic thoracic sympathectomies, thereby suggesting the analgesic affect was related to the dosage of the local anesthetic. Elman et al. [26] administered 20 ml of 0.5% bupivacaine or 40 ml of 0.25% bupivacaine in two groups after posterolateral thoracotomy. Their results showed that the percentage of pain variation did not show difference between the groups, suggesting that concentration does not influence pain relief when the volume varies. The study did not report the time of onset or the duration of intrapleural analgesia. Ishikawa et al. [27] reported that the analgesic duration of 40 ml of 0.375% ropivacaine ranged from 120 to 450 min (median 180 min). In our study, the average duration of analgesia was 320 min (140, 630). We report an analgesic duration greater than that reported by Ishikawa et al. (which may be related to the use of 0.75% ropivacaine). Therefore, we conclude that the concentration of local anesthesia is an important influential factor in the duration of analgesia. In our study, an intrapleural injection of 15 ml or 20 ml of 0.75% ropivacaine significantly relieved postoperative pain

due to coughing without causing serious adverse reactions.

Our study had the following limitations: 1) In our preliminary study, the C-NRS scores of the 20 ml group and the 15 ml group after intrapleural administration were very similar. The calculated sample size was suitable for the 20 ml and 15 ml groups, which was better than that of the 10 ml group, as we showed in our preliminary study. However, it can not prove the difference between the 20 ml group and the 15 ml group, which is the flaw of this experiment. Assuming there is a statistical difference between the 20 ml and 15 ml groups, the power analysis was based on the result of our preliminary study calculated using Power Analysis and Sample Size (PASS11.0) software; the mean and SD of the C-NRS 30 min after intrapleural injection in the 20 ml group and 15 ml group was 2.73 ± 1.41 and 2.6 ± 1.67, respectively. We assumed a type I error of 0.05 and a power of 0.90, and the t-test was used, and 4750 patients were required per group. The sample size is so large that we think there may be no difference between the 20 ml group and the 15 ml group. 2) Only a single injection of 0.75% ropivacaine for intrapleural analgesia at different dosages had been observed in our study; further research is needed to demonstrate whether different concentrations at the same dose produce different results. 3) A single injection of ropivacaine for intrapleural analgesia can last for approximately 2–10 h; therefore, further research is needed to demonstrate whether the effects of a longer duration of analgesia with the use of intermittent injection or continuous injection are more effective.

5. Conclusion

Our study demonstrated that intrapleural analgesia with 15 ml or 20 ml of 0.75% ropivacaine effectively relieved pain due to coughing following thoracoscopic lobectomy.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

Sisi Chen, Xuzhong Xu were responsible for study design, conduct of the study, data collection and manuscript preparation. Xiaona Zhu, Lvdan Huang, Wei Chen and Sainan Zhang were participated in conduct of the study. Hongying Shi and Yun Xia were responsible for study design and data analysis. Thomas J. Papadimos was Participated in revising manuscript. Xuzhong Xu, design the study and critically revise the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.All authors read and approved the final manuscript.

Trial registry number

The trial was registered prior to patient enrollment in the Chinese Clinical Trial Registry (ChiCTR1800017515, Principal investigator: Xuzhong Xu, Date of registration: 2018-08-02).

Guarantor

Sisi Chen, Xuzhong Xu.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data statement

No additional data are available.

CRediT authorship contribution statement

Sisi Chen: Writing - original draft. **Xiaona Zhu:** Investigation. **Lvdan Huang:** Methodology. **Wei Chen:** Data curation. **Sainan Zhang:** Supervision. **Hongying Shi:** Formal analysis. **Yun Xia:** Writing - review & editing. **Thomas J. Papadimos:** Writing - review & editing. **Xuzhong Xu:** Project administration.

Acknowledgments

The authors thank the nurses and the thoracic surgeons involved in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.05.013.

Ethical approval

This trial was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (Ethical number 2018-090) and written informed consent was obtained from all subjects participating in the trial.

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