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ORIGINAL INVESTIGATION

Analgesic effect of intercostal nerve block given preventively or at the end of operation in video-assisted thoracic surgery: a randomized clinical trial

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Abstract
Objective: To compare the analgesic effect of intercostal nerve block (INB) with ropivacaine when given preventively or at the end of the operation in patients undergoing video-assisted thoracic surgery (VATS).
Methods: A total of 50 patients undergoing VATS were randomly divided into two groups. The patients in the preventive analgesia group (PR group) were given INB with ropivacaine before the intrathoracic manipulation combined with patient-controlled analgesia (PCA). The patients in the post-procedural block group (PO group) were administered INB with ropivacaine at the end of the operation combined with PCA. To evaluate the analgesic effect, postoperative pain was assessed with the visual analogue scale (VAS) at rest and Prince Henry Pain Scale (PHPS) scale at 6, 12, 24, 48, and 72 hours after surgery.
Results: At 6 h and 12 h post-surgery, the VAS at rest and PHPS scores in the PR group were significantly lower than those in the PO group. There were no significant differences in pain scores between two groups at 24, 48, and 72 hours post-surgery.
Conclusion: In patients undergoing VATS, preventive INB with ropivacaine provided a significantly better analgesic effect in the early postoperative period (at least through 12 h post-surgery) than did INB given at the end of surgery.
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Introduction

Video-assisted thoracic surgery (VATS) has largely replaced open thoracic operations because it causes minimal trauma, and has enhanced postoperative recovery.[1] The postoperative pain, however, can still be severe, and this impairs postoperative recovery. In these cases, postoperative INB under thoracoscopic vision is now accepted and used by thoracic surgeons and anesthesiologists.[2−4] It is easy to perform, provides a precise analgesic effect and few complications. While postoperative INB in combination with patient-controlled analgesia (PCA) is effective, postoperative pain is still common. To date, no study has examined the analgesic effect of INB at different timepoints during the operation. Since the trauma and pain fiber stimulation starts at the time of the initial surgical incisions, INB, for example with ropivacaine, after the initial incision but before the intrathoracic operation might be expected to decrease the central nervous system stimulation[5] and achieve a better analgesic effect. Thus, we designed this study to compare the analgesic effects of INB with ropivacaine when given preventively or at the end of the operation in patients undergoing VATS.

Methods

Patient selection

This study was a single-blind, prospective, randomized clinical trial, which was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR1900024877) and approved by the Ethics Committee of Affiliated Hospital of Nantong University (Approval number: 2019-K036). All participants provided signed informed consent before recruitment into the study. Subjects eligible for the study were patients admitted to the hospital from August 2019 to December 2019, aged 35−75 years, American Society of Anesthesiologists (ASA) physical status I−II, and scheduled for elective VATS including pulmonary lobectomy, pulmonary segmentectomy, pulmonary wedge resection, and mediastinal tumor resection. Preoperative exclusion criteria were previous history of thoracotomy, history of alcoholism, and cardiac, lung, liver or kidney dysfunction. Intraoperative and postoperative exclusion criteria included intraoperative conversion from minimally invasive surgery to open thoracotomy, operation time > 3 hours, intraoperative bleeding > 1000 mL, reintubation, or reoperation due to various complications, and incision infection. Patients were randomly divided into two groups via a random number generator. The preventive analgesia group (PR group) received INB with ropivacaine at the start of surgery combined with PCA postoperatively. The post-procedural block group (PO group) received INB with ropivacaine at the end of surgery combined with PCA. PCA was removed 24 h after surgery for all patients.

Anesthesia management

All operations were performed by the same surgical team. On arriving at the operating room, patients were monitored via electrocardiography (ECG), and noninvasive measurement of blood pressure and oxygen saturation. After anesthesia induction with intravenous injection of propofol 2 mg.kg^{-1}, midazolam 0.1 mg.kg^{-1}, vecuronium 0.1 mg.kg^{-1}, and fentanyl 4 μg.kg^{-1}, patients were intubated with a double-lumen endotracheal tube and ventilated at the following settings: tidal volume (VT) 8−12 mL.kg^{-1}, breathing rate (RR) 12−18 times/min, I: E 1:1.5, positive end expiratory pressure (PEEP) 5 cm H_2O. Anesthesia was maintained with propofol and remifentanil. The PR group received INB with 20 mL 1% ropivacaine in three intercostal spaces around every incision and the site where the thoracic drainage tube was placed (generally the observation hole). This was done under the guidance of a thoracoscope after the initial incision and before the intrathoracic manipulation. The specific puncture point was at the posterior adjacent to the spine. The PO group underwent the same injection procedure but at the end of operation. After surgery, a patient was moved to the postanesthesia care unit, and after complete recovery of breathing and muscle tension the endotracheal tube was removed. Postoperative analgesia was administered via a PCA pump with 0.8 mg fentanyl/100 mL 0.9% normal saline at a continuous rate of 2 mL/h (the patient-controlled analgesia dose was 2 mL/time, and the locking time was 15 min). An intramuscular injection of 8−10 mg morphine was given to patients with intolerable postoperative pain (a score of 9−10 on the 10-point visual analogue scale).

Observation index

For pain assessment, both the visual analogue scale (VAS) score at rest and the Prince Henry Pain Scale (PHPS) score were recorded at 6, 12, 24, 48, and 72 hours after surgery. The VAS score ranged from 0 (pain free) to 10 (intolerable pain), and the PHPS score ranged from 0 (no pain when coughing) to 4 (severe pain when quiet). The end point of the study was 72 hours post-surgery. If the patient was discharged within 72 h, the discharge time was used as the end point. The total additional amount of morphine, and adverse reactions such as nausea, vomiting and atelectasis before the end point of the study were recorded.

Statistical analysis

A power analysis was performed on preliminary data with postoperative VAS pain scores at rest as the primary outcome variable. The analysis showed a minimal sample size of 21 subjects in each group would be required to detect a significant between-group difference of 30%, at 5% α and 20% β. In this study, 25 patients were enrolled in each group. Continuous data are presented as mean $\pm$ standard deviation. The Student's t-test and Chi-squared test were used to analyze continuous variables and categorical variables, respectively. Statistical analysis was performed with SPSS 20.0 software (SPSS, Inc, Chicago, Ill, USA). Differences were considered statistically significant at $p < 0.05$.

Table 1 Clinical data of two groups.

Index	PA group	PO group	p-value
Gender (male/female)	9/16	10/15	0.776
Age (years)	56.2 ± 9.3	57.8 ± 9.7	0.555
BMI (kg/m^2)	24.2 ± 2.3	25.3 ± 2.2	0.090
ASA (I/II)	16/9	15/10	0.776
Time of operation (minutes)	98.4 ± 39.0	92.8 ± 40.1	0.622
Number of thoracic drainage tube	0.68	0.6	0.565
Time of thoracic drainage tube removal (hours)	31.7	29.6	0.768

PA group, preventive analgesia group; PO group, post-procedural block group; BMI, Body Mass Index; ASA, American Society of Anesthesiologists (ASA) physical status.

Table 2 The visual analogue scales at rest of two groups.

Timepoint (hour)	PA group	PO group	p-value
6	0.72 ± 0.68[a]	1.52 ± 1.00	0.0020
12	1.72 ± 0.61[a]	2.56 ± 0.87	0.0003
24	2.32 ± 1.03	2.4 ± 1.08	0.7898
48	1.20 ± 0.82	1.48 ± 0.87	0.2470
72	0.60 ± 0.50	0.76 ± 0.66	0.3407

PA group, preventive analgesia group; PO group, post-procedural block group.

[a] p < 0.05 vs PO group.

Table 3 The Prince Henry Pain Scales of two groups.

Timepoint (hour)	PA group	PO group	p-value
6	0.60 ± 0.50[a]	1.40 ± 0.58	< 0.0001
12	1.36 ± 0.57[a]	2.00 ± 0.65	0.0005
24	1.72 ± 0.74	1.88 ± 0.67	0.4246
48	1.20 ± 0.41	1.24 ± 0.44	0.7392
72	0.92 ± 0.28	0.96 ± 0.20	0.5612

PA group, preventive analgesia group; PO group, post-procedural block group.

[a] p < 0.05 vs PO group.

Results

Comparison of clinical data between the two groups

Sixty-two patients were enrolled in the study. Nine patients were excluded as a result of not meeting preoperative inclusion criteria. Three patients were excluded because of conversion to open thoracotomy. Finally, twenty-five patients in each group were analyzed (Fig. 1). The demographic and operation characteristics of the patients are summarized in Table 1. There were no statistically significant differences between the two groups in gender, age, Body Mass Index, ASA physical status, operation time, number of the thoracic drainage tube and time of thoracic tube removal (Table 1).

Postoperative pain by VAS at rest

The postoperative VAS pain scores in both groups were low at 6 hours, reached a peak at 12–24 hours, and then gradually decreased at 48 and 72 hours. At 6 and 12 hours postoperative, the VAS scores in the PR group were significantly lower than those in the PO group (p < 0.05). There were no statistically significant differences between the two groups in VAS scores at 24, 48 and 72 hours (Table 2).

Postoperative pain by PHPS

The changes and differences in postoperative PHPS pain scores were similar to those for the VAS scores, reaching a peak at 12–24 hours and then gradually decreasing at 48 and 72 hours. At 6 and 12 hours postoperative, the PHPS scores

in the PR group were significantly lower than those in the PO group (p < 0.05). There were no statistically significant differences between the two groups in PHPS scores at 24, 48 and 72 hours (Table 3).

Postoperative complications

No postoperative complications, including nausea, vomiting and atelectasis, were observed in either of the two groups. No patients experienced severe postoperative pain that required additional morphine.

Discussion

Due to the high degree of trauma with thoracic surgery, patients often experience severe pain at the incision site after surgery especially in the early postoperative period. This pain and anticipation of this pain has some serious consequences. It often prevents patients from coughing, causing retention of respiratory secretions, which in turn leads to pulmonary infection, atelectasis, hypoxemia, and other complications.[6] It increases postoperative bed rest, which increases the risk of deep vein thrombosis and pulmonary embolism,[7] and slows the recovery of pulmonary function. Overall, severe postoperative pain is considered the fifth vital sign that significantly impairs postoperative recovery, and this is also true even for patients after VATS. Enhanced recovery after surgery (ERAS)/fast track surgery (FTS) is a recent evidence-based medicine approach to surgical treatment that integrates and optimizes perioperative management that includes anesthesia, medical treatments, and nursing. The goal is to reduce the stress of surgical trauma and to improve the speed of recovery.[8,9] ERAS has
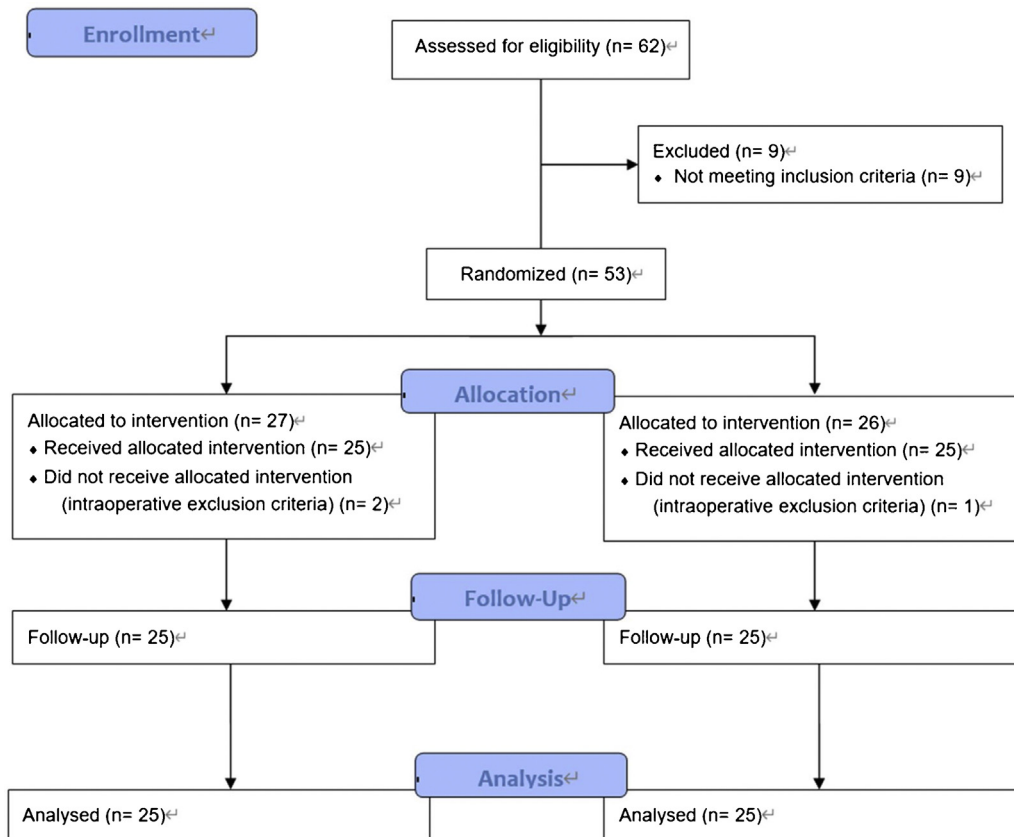
Figure 1 Flowchart showing the progress of participants.

greatly increased awareness of the management of post-operative pain,[10] and thoracic surgeons and nurses should consider this approach to help reduce the pain after VATS, especially in the early postoperative period.

All current commonly used analgesia methods after thoracic surgery have disadvantages and limitations.[11] Epidural anesthesia is effective and easy to control, but has complications such as respiratory inhibition, nausea and vomiting, urinary retention, hypotension, delayed muscular function, epidural hematoma and infection.[12] For PCA plus opioid, the difficulty lies in producing a precise analgesic effect at the incision site. In addition, it has several systemic adverse effects including drowsiness, respiratory depression, gastrointestinal dysfunction, and nausea and vomiting.[13] Oral NSAIDs are well accepted by patients, but can cause gastric ulcers, acute renal insufficiency, platelet dysfunction and other adverse reactions.[14] Compared with these regimens, INB under thoracoscopic vision, is easy to perform without additional discomfort to the patient. It is associated with significantly reduced incidence of postoperative pulmonary complications, urinary retention, and nausea and vomiting, all of which help postoperative recovery.[15]

Ropivacaine is a long-acting local anesthetic. The main pharmacological effect is to block the transport of sodium ions across the nerve fiber membrane, which increases the threshold level of the nerve action potential, reduces the speed of the ascending action potential, and blocks nerve impulse conduction.[16] Clinically ropivacaine is often used as

an intercostal nerve blocker given postoperatively because of its definite analgesic effect, long duration of action, and few adverse reactions.[17] Compared with other long-acting local anesthetics such as bupivacaine and levobupivacaine, ropivacaine is less lipophilic, which results in less cardio-depression and less central nervous system inhibition seen as less of a decrease in motor function.[16,18,19] Providing analgesia at the moment of a pain-causing action has been reported to attenuate the sensitization within the central nervous system.[5,20] Based on this, we proposed that intercostal block with ropivacaine just after making the initial incision but before the intrathoracic manipulation would block the stimulation of pain fibers at the beginning of operation, and so decrease the excitatory effect on the central nervous system providing a better analgesic effect.

The results of this study support this hypothesis for the early postoperative period. The pain scores (VAS at rest and PHPS) after VATS were low at 6 hours post-surgery, peaked at 12 to 24 hours, and gradually declined at 48 and 72 hours. In the early postoperative period (6 and 12 h), the pain scores in the PR group were lower than those in the PO group. Although the pain scores in the PR group were numerically lower than in the PO group in the middle and late postoperative period (24−72 h), the differences were not significant. The absorption half-life of ropivacaine from the epidural space is biphasic with a 14-minute fast phase and a 4-h slow phase, and a terminal half-life of > 4 hours.[21] It is also absorbed rapidly from the intercostal space.[22] Due to the short operation time of VATS (in this

study an average of < 100 minutes), intercostal ropivacaine in the PR group would exert an analgesic effect throughout the operation and into the early postoperative period. With the metabolism and elimination of ropivacaine, its analgesic effect gradually disappeared and the lack of significant differences in pain scores between two groups after 24 hours would be expected. In order to try and prevent this, continuous wound infiltration with ropivacaine for postoperative pain management has been tested.[23] This technique, however, required the insertion of a separate catheter into the intercostal space, which increases the difficulty and risk of the operation. One additional observation that might be relevant is that the peak pain score was delayed in the PR group (24 h) vs. the PO group (12 h) and was lower (VAS 2.32 vs. 2.56 and PHPS 1.72 vs. 2.00). These differences were not significant and more data are needed to determine if this is a real effect or not. In addition, our data suggest the elimination rate of ropivacaine may not be an issue since no postoperative complications (such as nausea, vomiting, and atelectasis) occurred in either of the two groups, and no morphine was added for severe pain in any of the patients.

Overall, our data confirm the efficacy and safety of INB with ropivacaine, but the study has some limitations. First, it was not double-blind because the surgeon carried out the analgesia process. Second, 25 subjects per group may be too few to detect differences between groups and to show all potential adverse effects. A double-blind or triple-blind design study with a larger sample size will provide more supportive data for this procedure.

Conclusion

In this study, in patients undergoing VATS, preventive INB with ropivacaine provided significantly better analgesia in the early postoperative period than did INB at the end of surgery. Preventive INB with ropivacaine provided an accurate analgesic effect with few complications and low risk, and is worthy of further study as an effective and safe clinical application.

Conflicts of interest

The authors declare no conflicts of interest.

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