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Adding morphine in ultrasound-guided thoracic paravertebral block for lung surgery: A prospective, randomized, controlled trial

Qian Liu[1], Pengpeng Wang[2], Hongguang Song[2], Yonggang Xie[2]*

[1]Binzhou medical university

[2]Department of Anesthesiology, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, China

Abstract: Objectives: This study aimed to compare the efficacy and the safety of ultrasound-guided thoracic paravertebral block (TPB) using ropivacaine to TPB using ropivacaine - morphine for pain relief in patients undergoing lung surgery.

Material and methods: Our study included 100 patients after lung surgery at Yantai Yuhuangding Hospital from 09/2020 to 09/2022. Patients were divided into 2 groups: ropivacaine group (R group) (n=50) and ropivacaine-(morphine 4mg) group (RM group) (n=50). The primary outcomes were the Visual Analogue Scale (VAS) scores when patients were at rest (VR) and movement (VM). The secondary outcomes were postoperative complications (nausea, respiratory depression, lethargy, constipation, itching). The study was approved by the Ethics Committee of Yantai Yuhuangding Hospital. All participants provided their informed consent.

Results: Compared with R group, the VR and the VM was lower than RM group ($p<0.05$). Postoperative nausea, respiratory depression and lethargy did not have significant different between the two groups ($p> 0.05$). The percent of patients in the RM group undergoing constipation and itching postoperative was higher than in the R group but without statistic difference.

Conclusion: Ultrasound-guided TPB using ropivacaine - morphine is an effective intervention of pain relief after lung surgery. Its analgesic efficacy is more stronger that using ropivacaine only. Meanwhile, this method does not have more adverse reactions compared to TPB using ropivacaine.

Keywords: Paravertebral block; analgesia; lung surgery; morphine; ropivacaine

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*Corresponding Author: Yonggang Xie

1. Introduction

Thoracotomy pain is one of the most common complications after thoracic surgery[1]. Although video-assisted thoracoscopic surgery (VATS) has been expanded worldwide. Postoperative pain still causes shallow breathing and limited cough resulting in the impairments of respiratory functions, the stagnation of secretions, collapsed lung, hypoxemia and hypercapnia. They increase the risk of the reintubation of the endotracheal tube and seriously affect the patients' mental health. Taken them together, pain relief for patients after thoracic surgery is essential for their recovery of regular movements and their satisfaction[2]. There is a variety of studied treatments to reduce pain after thoracic surgery including pain prophylaxis before surgery, additional treatments of morphine analogues or non-steroids anti-inflammatory drugs (NSAIDs), or nerve block[3]. Recently, thoracic paravertebral block (TPVB) is likely to be accepted for the replacement of TEB which is commonly a "golden standard" for pain management after cardiothoracic surgeries and ultrasound-guided TPVB is attracting anesthesiologists and is increasingly applied[4].

In order to provide a stronger effective of analgesia, a number of adjuvants, such as non-steroidal anti-inflammatory drugs, alpha 2-agonists and opioids have been used in conjunction with local anesthetics for neuraxial blocks, including TPVB[5, 6]. This study aimed to explore the effect of ultrasound guided TPVB using ropivacaine combined with morphine on postoperative analgesia followed by VATS. In order to be able to enhance the analgesic effect of TPVB, achieve an ideal analgesic state and reduce postoperative complications .

2.Patients and Methods

2.1 Study Design

This is a prospective, parallel randomized, controlled clinical trial. This study report followed CONSORT guideline. The sample size of each group was calculated by the following formula previously reported[7], for the continuous variables and two controlled equivalent groups as follows: determined from α and β (the probability that a test statistic giving $p <0.05$). $\alpha = 0.05$ was chosen for the null hypothesis, and $\beta = 0.1$ was chosen for the alternative hypothesis. The constant C corresponding to the α and β values retrieved from a standard table was = 10.5. We chose the significant difference of Visual Analogue Scale (VAS) at rest between two

groups by 0.59 (p= 0.104) with standard deviation = 0.91, followed the report of Tamura et al.[8]. Therefore, we had ES = 0.648. The sample size of each group was estimated at 49. Finally, we recruited 50 patients in each group.

After being provided a written informed consent, the participants were included. The random allocation sequence was conducted by author doctor who did not participate in the experiment. Followed by the inclusion, the patients were randomly divided into two groups by the author doctor who did not participate in the experiment, by the simple random sampling method. Patients were randomly divided into two groups, ultrasound-guided TPVB receiving postoperative analgesic regimen of 0.375% ropivacaine 20ml (n= 50) and 0.375% ropivacaine combined morphine 4mg mixture solution 20ml (n= 50). The anesthesiologist, sawbones and the follow-up doctors were blined to the experiment.

2.2 Patients Selection

The study was performed at Yantai Yuhuangding Hospital, from 09/2020 to 09/2022, for patients who received video-assisted thoracoscopic surgery.

The inclusion criteria were patients who underwent VATS and agreed to cooperate with the anesthesiologists for the analgesic regimen. The American Society of Anesthesiologist (ASA) class of the included patients was I, II and III. Exclusion criteria were patient with history of local anesthetic allergy, age younger than 18 years, vegetative nerve functional disturbance, serious cardiovascular disease, hepatorenal insufficiency, history of malignant disease, daily use of any type of analgesics, previous chest surgery, pregnancy, breast feeding, previous chemotherapy, radiation therapy, or both.

2.3 Procedures

Under aseptic condition and using local anesthesia, a linear ultrasound probe was placed between the sixth to eighth thoracic spinous process. A 10-cm 22-G sonovisible needle was inserted using in-plane technique and guided to the paravertebral space. After ascertaining that the tip of the needle was in the target site, anesthetic solution was administered. The injectate in the R group consisted of 20 mL of ropivacaine 0.375%; meanwhile, 20 mL of bupivacaine 0.375% plus morphine 4mg was administered in group RM.

Multiportal VATS was performed with a 3-4 cm incision at the mid-axillary line in the 4th intercostal space, a 1.5 cm incision at the anterior axillary line in the 6th intercostal space, and a 1.5 cm at the posterior axillary line in the 7th intercostal space. An Alexis® Wound Retractor XS was inserted into the 3-4 cm incision, while

Table 1 The demographic characteristics of enrolled patients

	R	RM	*P*
Number	50	50	
Gender (Male/Female)	18/32	24/26	0.224
Age	54.75±15.35	55.54±13.98	0.789
BMI	23.16±3.53	23.25±4.86	0.914
ASA			
I	14	10	0.148
II	28	30	0.685
III	8	10	0.603
Surgical procedure			
Pulmonary wedge resection	16	14	0.663
Lobectomy	21	14	0.539
Segmentectomy	13	18	0.280

ASA: American Society of Anesthesiologist, BMI: Body mass index. The data were expressed as mean ± SD.

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ports were inserted into the other incisions. The thoracoscopic port site was the anterior axillary line in the 6th intercostal space on the right side, and the posterior axillary line in the 7th intercostal space on the left side. The thoracoscope used was a 10 mm rigid device. The drainage tube was inserted through the incision at the 6th intercostal space.

2.4 Study Outcomes and Measurements

Our primary outcomes included the VAS score at the rest (VR) and VAS score at the movement (VM), at postoperative 2h、4h、6h、12h、24h and 48h. VAS score at rest was defined as the VAS score measured when patients relaxed. VAS score at the movement was defined as the VAS score measured when the patients coughed. VAS score was assessed to measure the pain degrees of patients. Patients chose the best suitable images for their pain which were concordant with numeric pain degrees, where 0 = no pain, 1 - 3 = mild pain, 4 - 6 = moderate pain, 7 - 8 = severe pain, 9 - 10 = worst pain. The second outcome was the undesirable effects relating to the anesthetic technique, anesthetic medicines, and morphine analogues which including nausea, respiratory depression, lethargy, constipation, itching.

2.5 Statistical Analysis

The collected data was analyzed using SPSS software (version 19, SPSS Inc., USA). The quantitative variables are expressed as mean ± SD. The categorical variables were expressed as percent (%). The differences of categorical variables by groups were assessed by $\chi 2$. The means of quantitative variables between before and after the intervention across each group were compared by paired student's t-test. The differences in means between the two groups were analyzed by independent student's t-test. The differences were statistical significance if $p < 0.05$.

3.Results

The study was performed from 09/2020 to 09/2022. 105 patients participated in the trail, while 5 patients dropped out of our study. Data of the rest 100 patients were included in the analysis. The characteristics of the included patients relating to gender, average ages, body mass index (BMI), ASA score and surgical procedure types were shown in Table 1. There was no significant different between the two groups ($p > 0.05$).

At postoperative 2, 4, 6, 12 and 24h, patients in both groups mainly suffered from minor pain at rest in the R group and RM group. When they had any movement, the pain level was severe at these time point in the R group and RM group. At postoperative 48h, the pain level increased from minor pain to moderate pain at rest and at movement in both groups. At postoperative 6, 12 and 24h, VAS scores were lower in the RM group than in the R group at rest ($P<0.05$). At postoperative 2, 4, 6, 12 and 24h, VAS scores were significant lower in the RM group than in the R group at movement ($P<0.05$). At postoperative 48h, the pain level increased from minor pain to moderate pain both at rest and movement in the two groups without statistical differences ($P > 0.05$) (Table 2).

Table 2 Postoperative VAS score

	R (rest)	RM (rest)	R (move)	RM (move)	P (rest)	P (move)
2h	3.63±0.90	3.50±1.18	4.12±1.05	3.75±1.23#	0.564	0.032
4h	3.75±0.42	3.34±0.88	4.32±1.27	3.82±1.17#	0.599	0.015
6h	3.39±0.98	2.96±0.73*	4.45±1.31	3.79±1.15#	0.013	0.003
12h	3.82±1.06	3.20±1.00*	4.56±1.53	3.82±1.32#	0.003	<0.001
24h	4.52±1.48	3.78±1.26*	4.96±2.21	4.43±1.76#	0.008	0.034
48h	5.01±1.35	4.68±1.40	5.42±2.41	5.34±2.24	0.231	0.345

The percentage of postoperative complications to morphine analogues such as nausea, respiratory depression and lethargy was not statistically different between both groups ($P > 0.05$). Although there were lower frequencies in the R group compared to the RM group on postoperative astriction and pruritus, there was no statistic

Table 3 Postoperative complication of the two groups

	R	RM	*P*
Nausea	8/42	6/44	0.564
Respiratory depression	2/48	4/46	0.674
Lethargy	5/45	4/46	0.727
Astriction	0/50	4/46	0.117
Pruritus	0/50	3/47	0.242

difference between the two groups (Table 3).

4.Discussion

Application of multiple analgesics is welcome in the management of postoperative pain. The synergy of different analgesics can achieve a satisfactory analgesic effect and decrease drug dosage, which reduces the incidence of postoperative complications. Previous study showed that perioperative transverse abdominal muscle plane block (TAP) using morphine combined bupivacaine significantly alleviated postoperative pain and reduced the demand for opioids with dose dependent[9]. El Sherif et al. also investigated the effect of adding morphine during TAP on postoperative pain in patients undergoing abdominal malignant tumor surgery. The results demonstrated that an effective analgesia without serious postoperative complications[10]. Kumari et al. showed that compared with ropivacaine alone, intraperitoneal perfusion of ropivacaine combined with tramadol could alleviate postoperative pain and reduce the requirement of opioids in patients undergoing laparoscopic cholecystectomy[11].

Recently, the peripheral effects of opioids has been an focus in postoperative analgesia. It has been found that opioid receptors existed not only in the brain, the spinal cord, the medulla oblongata and the sympathetic preganglionic fibers, but also in immune cells and peripheral nerves, which regulated inflammatory pain[12]. The analgesic mechanisms of morphine in peripheral nerve block may be as follows: firstly, it directly binds to opioid receptors in peripheral nerve tissues; secondly, morphine binds to opioid receptors on the peripheral nerve membrane and the binding protein is transported to the dorsal horn of the spinal cord which regulates inflammatory response[13]; thirdly, it crosses peripheral blood vessels over and stimulates the release of endogenous opioid peptides which produces anti-noxious stimulation[14]. Tesfaye et al. found that morphine could effectively relieve pain hypersensitivity and hyperalgesia, and had a significant effect on neuropathic pain [15]. Morphine binds opioid receptors of inflammatory tissues and primary afferent neurons to provide analgesia. Another study demonstrated that morphine can effectively attenuate neuropathic pain through the activation of the peripheral nitric oxide-cGMP-PKG-KATP signaling pathway and the decreased expression of MOR after sciatic nerve injury is regulated by nitric oxide. We believe this may be one of the mechanisms of morphine for nerve block.

Our findings showed that patients in the R and the RM group had a significant reduction of pain level postoperatively. There was minor pain in the two groups in the first day postoperatively, which meant two kinds of treatment regimen were effective to relieve pain. The pain levels of patients in both groups were comparable in all time-points indicating that these procedures had comparable efficacy in the reduction of pain. This means that a certain dose of morphine plus ropivacaine for TPB can provide sufficient analgesia for VATS especially in the moving condition. Our study demonstrated that no significant postoperative complications related to opioids occurred during postoperative 48h. Considering that the adverse complications caused by opioids may be related to the drug dose, administration of 4mg morphine in TPB may be safe and effective for postoperative analgesia.

Overall, morphine combined with ropivacaine for TPB can prolong the duration of regional anesthetic, reduce VAS at different time points after surgery for lung cancer patients and did not increase adverse complications related to opioids. Moreover, 4 mg of morphine is an appropriate dose for analgesia, which is worthy of clinical promotion and application.

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