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ORIGINAL RESEARCH

Thoracoscopic Intercostal Nerve Block with Cocktail Analgesics for Pain Control After Video-Assisted Thoracoscopic Surgery: A Prospective Cohort Study

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Objective: To evaluate whether using a cocktail of intercostal nerve blocks (TINB) during thoracoscopic surgery results in better clinical outcomes than patient-controlled analgesia (PCIA).

Methods: Patients in two medical groups undergoing video-assisted thoracoscopic surgery (VATS) for pulmonary nodules in West China Hospital of Sichuan University were collected consecutively between March 2022 and December 2022. The groups were divided into two subgroups based on their analgesic program, which were TINB group and PCIA group. The primary outcome was the visual analogue scale (VAS) of the two groups at different stage after surgery and after discharge. Any analgesic related adverse events (ARAEs) were also recorded.

Results: A total of 230 patients who underwent VATS were enrolled, in which 113 patients (49.1%) received a cocktail TINB after surgery, and 117 patients (50.9%) received a PCIA. After PSM, 62 patients in each group were selected. The difference of resting VAS (RVAS) and active VAS (AVAS) at different stage during hospitalization was only related to the change of period ($p < 0.05$, $p < 0.05$), and the two groups showed no significant differences in RVAS or AVAS during hospitalization ($p = 0.271$, $p = 0.915$). However, the rates of dizziness (4.84% vs 25.81%, $p = 0.002$), nausea and vomiting (0 vs 22.58%, $p < 0.05$), fatigue (14.52% vs 34.87%, $p = 0.012$), and insomnia (0 vs 58.06%, $p < 0.05$) in TINB group were lower than that in PCIA group. Besides, AVAS and RVAS at 7, 14, and 30 days after discharge in TINB group were both significantly lower than that in PCIA group ($p < 0.05$, $p < 0.05$).

Conclusion: Cocktail TINB provided better analgesia after discharge and reduced the incidence of ARAEs in patients undergoing VATS.

Keywords: analgesia, thoracoscopic intercostal nerve block, cocktail analgesia, video-assisted thoracoscopic surgery

Introduction

Over the past 20 years, video-assisted thoracoscopic surgery (VATS) has become widely used as a minimally invasive alternative to thoracotomy for thoracic surgery.[1] Although the postoperative pain associated with VATS is significantly reduced compared to thoracotomy, a considerable number of patients still experience moderate to severe postoperative pain.[2] Inadequate postoperative analgesia after thoracic surgery can lead to a range of respiratory complications, such as atelectasis and pneumonia, resulting in prolonged hospitalization, reduced quality of life, and increased medical burden.[3,4]

With the development of enhanced recovery after surgery (ERAS), multimodal analgesia has become an important component of perioperative analgesia management in ERAS. Regional analgesia is a key technology for multimode analgesia because of its desired pain relief and reduced opioid use.[5–7] Regional analgesia mainly includes thoracic epidural analgesia (TEA), paravertebral nerve block (PVB), intercostal nerve block (ICNB), intrathecal blockade, incision infiltration, serratus anterior plane block (SAPB), and erector spinal plane block (ESPB).[8–11] Although TEA and PVB has long been the gold standard of procedural multimodal analgesia for thoracotomy, its application as part of ERAS may be limited due to common

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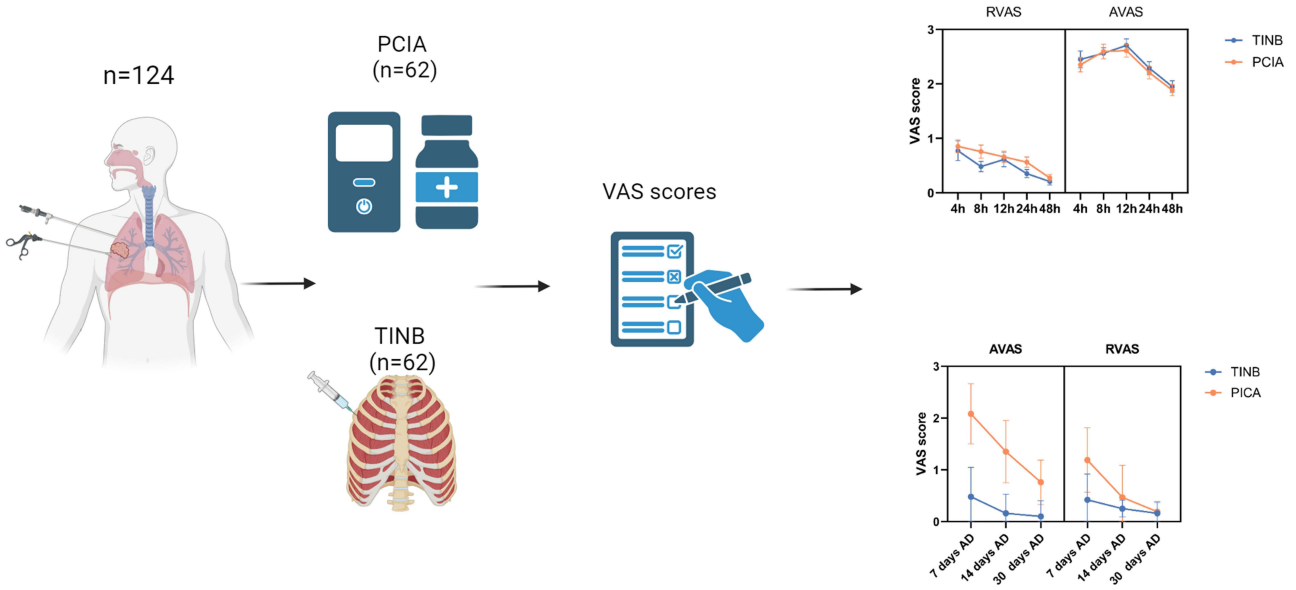
Graphical Abstract



side effects including hypotension, lightheadedness, and pruritus.[12,13] Alternatives to TEA, such as ICNB, SAPB, and ESPB, may provide adequate early pain control, but none of these approaches provides durable relief of pain after thoracic surgery due to the relatively short half-life of local anesthetics. Therefore, ideal nerve block analgesia - a single injection that can last up to 72 hours or even longer after surgery - has always been the goal of clinicians. Long-duration ICNB with liposomal bupivacaine may make 72-hour analgesia possible. A few small studies have shown similar, and even better analgesia in some instances than TEA up to 72 hours after long-duration ICNB placement.[14,15] However, previous attempts at intercostal nerve block were performed with ultrasound-guided injection, which not only has puncture risks but may also lead to different analgesic effects due to differences in proficiency. Additionally, the use of a single anesthetic agent may affect the duration of anesthetic effectiveness. Postoperative analgesia with ICNB is relatively short, which has led to numerous but largely unsuccessful efforts to prolong it. These efforts include adding adjuvants such as epinephrine, clonidine, morphine, nonsteroidal anti-inflammatory drugs, and corticosteroids.[16–19] Our experience suggests that ropivacaine with sodium bicarbonate, magnesium sulfate, methylprednisolone, dexamethasone, and dexmedetomidine can significantly prolong the duration of analgesia.[20] This approach safely and effectively treats pain after VATS, with less opioid use and better recovery after surgery. However, this novel approach has not been proven.

Our hypothesis is that surgeon-administered thoracoscopic intercostal nerve block (TINB) with cocktail analgesics would provide at least equivalent analgesia to opioid-based continuous patient–controlled intravenous analgesia (PCIA), which was is widely used for its effective postoperative analgesia,[21,22] but without common side effects such as dizziness, nausea, drowsiness, and vomiting associated with opioids. The purpose of this study was to investigate the effects of PCIA and TINB with cocktail analgesics on the postoperative pain scores of patients; and to compare the occurrence of postoperative adverse reactions in patients with different anesthesia methods.

Patients and Methods

Ethical Review

Prior to submission, this study was licensed with the Chinese Clinical Trial Registry (ChiCTR2100046774). In addition, in accordance with the Declaration of Helsinki, Ethics Committee on Biomedical Research, West China Hospital of Sichuan University and the Chinese Ethics Committee of Registering Clinical Trials approved our clinical research

protocol (#357) in April 2021. The participants signed a formal informed consent form. The research was presented by strengthening the reporting of cohort studies in surgery criteria.[23]

Inclusion and Exclusion Criteria

Patients in two medical groups undergoing surgical treatment for pulmonary nodules in West China Hospital of Sichuan University were collected consecutively. Patients were enrolled if they met the following inclusion criteria: (1) aged 18–65 years old; (2) undergoing VATS; (3) American Society of Anesthesiologists (ASA) score of 3 or fewer points; and (3) no history of allergy to analgesics. The exclusion criteria were as follows: (1) patients with a thoracic operation history; (2) patients with chronic pain on long-term narcotic medication; or (3) converted from VATS to thoracotomy.

Study Design

This was a prospective cohort study conducted between March 2022 and December 2022. All data, including follow-up data, were completed by February 2023. The study included patients from two medical groups in our hospital in which the medical teams have similar surgical habits. It should also be noted that, with the exception of PCIA and TINB, other intravenous regiments were similar in both groups during and after surgery. Patients were divided into two cohorts based on their respective medical groups. One group's patients were treated with TINB for pain control (TINB group), while the other group's patients were treated with PCIA (PCIA group) due to differences in surgeon preferences. As the analgesia protocol was selected based on the two medical groups, the randomization cannot be made, propensity score matching (PSM) was used to reduce the offset due to selection bias after all data, including follow-up data, were collected.

Analgesia Methods

General anesthesia was typically induced with intravenous fentanyl or sufentanil and propofol or etomidate. Muscle relaxation was facilitated by the administrating succinylcholine, cisatracurium, or rocuronium. Desflurane or sevoflurane, balanced with air, was used to maintain anesthesia in most patients, with 50% to 100% oxygen. Mechanical ventilation was adjusted to maintain an end-tidal pCO2 between 35 mm Hg and 40 mm Hg. Following surgery, the muscle relaxation was reversed, and all patients were extubated. No commercial sponsors were involved in the study.

Surgical Approach

The VATS procedure was mainly performed using the three-portal thoracoscopic technique in two groups. The thoracoscopy entrance was selected to be 1.5 cm in the 7th intercostal space anterior to the midaxillary line. The main operation port was in the 3rd or 4th intercostal space, while the auxiliary operation port was placed at the 9th intercostal space behind the axillary line.

Cocktail Medications

The cocktail analgesics were composed of sodium bicarbonate, magnesium sulfate, methylprednisolone, 0.5% ropivacaine, dexamethasone, and dexmedetomidine. The solubility and concentration of these medications in cocktail analgesics were shown in Table 1. These pharmaceutical agents exhibit excellent compatibility and do not induce detrimental chemical interactions according to our previous study.[20]

TINB group After completing thoracic surgery while the patient was still intubated under general anesthesia, a cocktail of analgesics was administered to the intercostal nerves surrounding the incision and two adjacent nerves using TINB. Under thoracoscopic guidance, the surgeon used a cocktail analgesic to infiltrate the intercostals of the minimally invasive approach and the adjacent intercostals (Figure 1). Each intercostal space was infiltrated with 3 to 5 mL of the cocktail analgesic, and a total of 24 to 40 mL of cocktail analgesic was used for TINB. The parietal pleura was not disrupted to ensure that the local anesthetic remained within the intercostal space and did not enter the pleural space (Supplementary Video). After the procedure, an additional 10 to 15 mL of cocktail analgesics was injected into the surgical wounds for local infiltration analgesia.

Table 1 Cocktail Medications

Component	Solubility in 100 mL H_2O	Quality in 40 mL Saline	Concentration
Sodium bicarbonate	7.8 g	0.6g	1.5%
Magnesium sulfate	54 g	0.1mg	2.5 ug mL^{-1}
Methylprednisolone	5 g	8mg	0.2 mg mL^{-1}
Ropivacaine (0.5%)	500 mg	4mg	2 mg mL^{-1}
Dexamethasone	10 mg	2mg	0.05 mg mL^{-1}
Dexmedetomidine	100 mg	0.2ug kg^{-1}	5 ng kg^{-1} mL^{-1}

PCIA group Patients in PCIA group were managed with continuous PCIA using granisetron hydrochloride (12 mg) and hydromorphone hydrochloride (10 mg) diluted to 200 mL with normal saline. The basal dose was 1 mL/h, and the additional dose was 2mL. The locking time was set at 10 minutes.

After surgery, both groups of patients received oral celecoxib (200 mg) and intravenous parecoxib (40 mg) twice a day to relieve postsurgical pain. If postoperative pain scores were rated 4 out of 10 or greater, 10 mg of morphine hydrochloride was injected subcutaneously for rescue analgesia. Otherwise, the same chest drainage tube was used in both groups.

Pain Assessment

All participants received uniform training before the study began to reduce researcher bias. A nurse assigned to each patient's care regularly assessed their pain using a visual analog scale (VAS). Patients were asked to rate their pain on a scale from 0 (no pain) to 10 (disabling pain) at rest (resting VAS, RVAS) or during motion (active VAS, AVAS). Pain assessments were made at 4, 8, 12, 24, and 48 hours after surgery, and pain scores were obtained by reviewing daily nursing records.

Before discharge, patients were trained to assess their pain using the VAS, and a special VAS card was given to help with pain assessment. After discharge, patients were followed up via telephone or outpatient service, and their pain scores

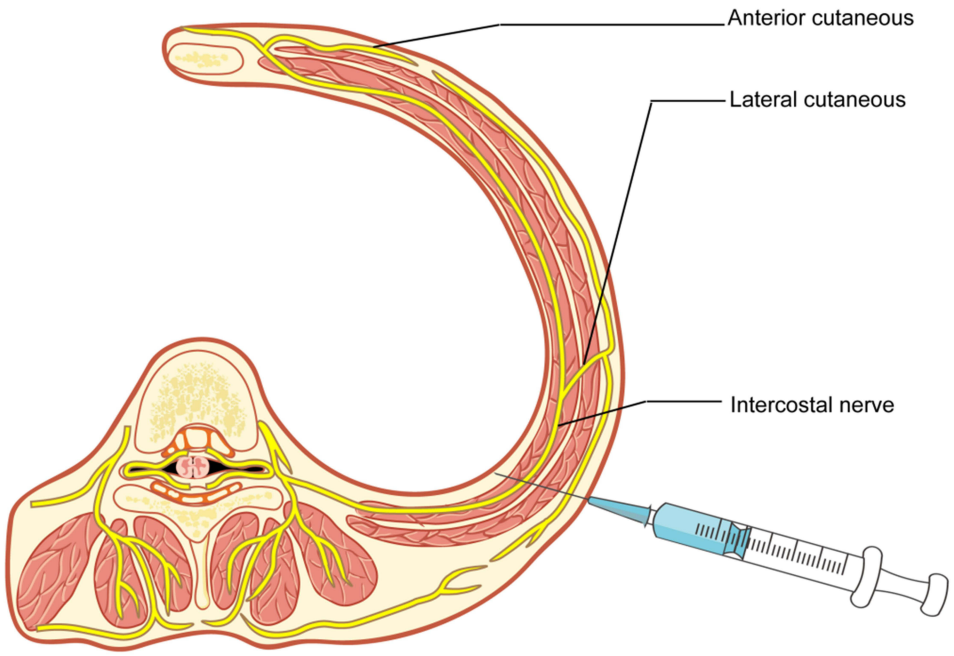


Figure 1 Thoracoscopic intercostal nerve block (TINB) schematic diagram. TINB was administered by infiltration of intercostal nerves by cocktail analgesics from the space between parietal pleura and intercostal muscle.

were recorded at 7, 14, and 30 days post-discharge. Celecoxib capsules were prescribed for pain control at discharge. In cases of breakthrough pain, the patients were referred to the pain department for further treatment.

Endpoints for the Study

The primary outcome was the VAS of the two groups at different stage after surgery and after discharge. The VAS was assessed at 4, 8, 12, 24, and 48 hours after surgery, and at 7, 14, and 30 days after discharge. The secondary outcome was the analgesic-related adverse events (ARAEs) during hospitalization, including dizziness, nausea and vomiting, cough, dyspnea, fatigue, insomnia, urinary retention, constipation, disturbance of consciousness, flatulence, and venous thrombotic events. The Apfel score was used for postoperative nausea and vomiting (PONV) risk assessments to evaluate the preoperative PONV risk difference between the two groups.[24] Vital signs, including heart rate, mean arterial pressure (MAP), body temperature and oxygen saturation, were also recorded at different stages after surgery in two groups.

Statistical Analysis

PSM was used to compare characteristics between the two distinct cohorts by using observational data from the hospital information system. The regression model used the dependent variable of analgesic mode (TINB or PCIA), and the independent variables of preoperative patient factors (sex, age, pulmonary function, smoking history, and body mass index (BMI) and hospital characteristics [operation method, surgery duration and length of stay (LOS) after surgery] to calculate the PSM value for every patient. PSM for discharges was also conducted using the regression model. Within the two study cohorts, discharges were randomly sorted. Then, using the closest PSM value, each discharge in the TINB group was matched 1:1 to a discharge in the PCIA group. The balance of measured covariates was assessed using the p value, with a value of < 0.05 indicating a significant difference between the study groups.

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 23.0, IBM Corporation, Armonk, New York, USA). The Kolmogorov–Smirnov test was used to test continuous variables for normal distribution, and analysis of variance (ANOVA) was used to compare parametric data. Between-group comparisons at different time intervals were assessed using ANOVA for repeated measurement. All categorical data were compared using X^2 test. Continuous data are represented herein by means and standard deviations (SDs), nonnormally distributed data are represented by medians and ranges, and binary variables are represented by proportions. A two-tailed p value of < 0.05 was considered statistically significant in all analyses.

Results

Study Population

A total of 230 patient records were enrolled. The TINB group included 113 patients who received TINB with cocktail analgesics. The PCIA group included 117 patients who were managed with continuous opioid–based PCIA. Table 2 presents the characteristics of patients in the TINB group and PCIA group before and after PSM. After PSM, 124 patients were enrolled in this study, including 62 patients in the TINB group and 62 patients in the PCIA group (Figure 2). The PSM was shown in Figure S1. The clinical characteristics, pulmonary function, surgical information, Apfel score, and ASA score, which were matched and comparable, are listed in Table 2.

VAS Scores and Vital Signs After Surgery

Data for VAS scores and vital signs at different stages between two groups are given in Table 3 and Figure S2. All variables showed no significant time and group interactions. However, the main effect of time was significant, which means that the difference in VAS scores and vital signs at different stages was only related to the change in period, and the two groups showed no significant differences in pain scores (Figure 3) and vital signs at all time points. Postoperative pain VAS at different stages during hospitalization between two unmatched groups was shown in Table S1 and Figure S3.

Table 2 Population Characteristics in Two Groups Before and After Propensity Score Matching

Index		Overall Cohort			Matched Cohort		
		TINB (n=113)	PCIA(n=117)	P value	TINB (n=62)	PCIA(n=62)	P value
Gender	Male	40	43	0.831	21	22	0.998
	Female	73	74		41	40	
Age(year)		49.65±12.10	56.29±14.54	<0.001	50.77±14.44	52.45±11.76	0.480
BMI		22.85±3.22	22.99±2.81	0.727	22.59±2.93	22.92±3.40	0.565
Smoking history	Yes	20	30	0.144	13	15	0.830
	No	93	87		49	47	
Pulmonary function	FEV1%pred	105.46±13.84	104.83±17.97	0.766	105.21±15.31	105.23±16.15	0.828
	FEV1/FVC, %	81.75±7.61	78.28±9.19	0.002	0.80±0.09	0.81±0.08	0.632
Comorbidities	COPD	0	0	0.253	0	0	0.643
	Hypertension	15	25		7	9	
	Diabetes	3	3		1	1	
Operation approach	Lobectomy	28	49	0.008	17	18	0.721
	Segmentectomy	55	44		30	31	
	Wedge resection	30	24		15	13	
Duration(min)	Surgery	79.28±27.76	106.15±48.08	<0.001	84.40±30.20	86.06±29.96	0.759
	Anesthesia	123.17±33.18	165.31±58.71	<0.001	137.61±40.81	128.66±33.77	0.186
Apfel score	0	3	3	0.540	1	1	0.782
	1	6	4		1	2	
	2	80	76		40	42	
	3	24	34		20	17	
ASA score	I	2	2	0.420	0	0	1.000
	II	91	109		59	60	
	III	10	6		3	2	
Histology	Adenocarcinoma	80	78	0.570	45	42	0.695
	Squamous carcinoma	0	0		0	0	
	Benign	33	39		17	20	
TNM stage (2017 UICC)	I	78	75	0.629	44	42	0.331
	II	2	3		1	0	
	III or IV	0	0		0	0	
LOS		3.90±2.15	5.21±3.16	<0.001	4.24±1.63	4.06±2.24	0.615

Abbreviations: TINB, thoracoscopic intercostal nerve blocks; PCIA, patient controlled intravenous analgesia; BMI, body mass index; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease, ASA, American society of anesthesiologists; LOS, length of stay.

VAS Scores and Analgesic Drug Usage After Discharge

To better understand the analgesic effects of the two methods, patients were followed up by telephone and their pain scores were recorded at 7, 14, and 30 days after discharge. Details can be seen in Table 4 and Figure 4. VAS scores showed a significant time and group interaction. Significant differences in VAS scores were found between 7 days and 14 days, 7 days and 30 days, and 14 days and 30 days after discharge in the two groups. In addition, the AVAS and RVAS scores at 7, 14, and 30 days after discharge in the TINB group were both significantly lower than those in the PCIA group. Regarding the usage of analgesic drugs after discharge, no significant time and group interactions were found. However, the main effect of time was significant. Postoperative pain VAS at different stages after discharge between two unmatched groups was shown in Table S2 and Figure S4.

Analgesic Related Adverse Events

Table 5 and Figure 5 show the differences in ARAEs between the two groups. The rates of dizziness, nausea and vomiting, fatigue, and insomnia in the TINB group were significantly lower than that in the PCIA group. No differences were found in cough, dyspnea, urinary retention, constipation, and flatulence. No patients experienced disturbance of

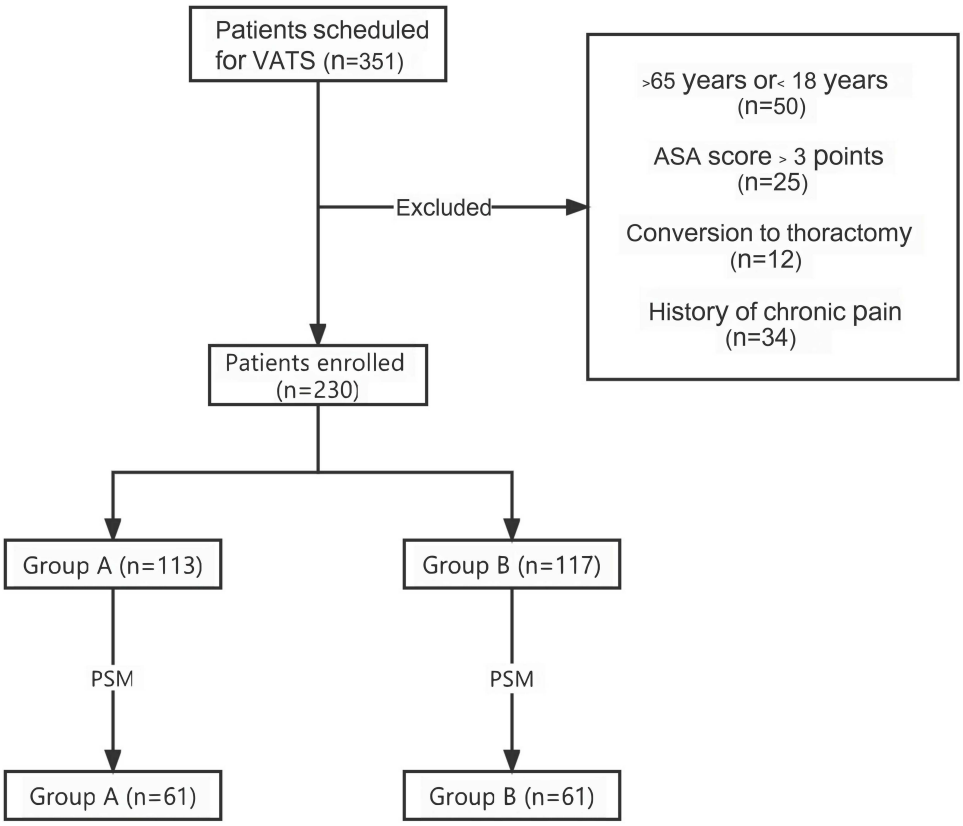


Figure 2 Study flow diagram of sample selection.
Abbreviations: TINB, Thoracoscopic intercostal nerve block; PCIA, Patient-controlled intravenous analgesia.

consciousness or venous thrombotic events. Analgesic related adverse events between two unmatched groups were shown in Table S3 and Figure S5.

Intraoperative Anesthesia and Postoperative Rescue Analgesia

According to the data in Table 6, there was no significant difference in the anesthetic maintenance drugs, intraoperative anesthesia, and rate of postoperative rescue analgesia between the TINB and PCIA groups. However, the TINB group used significantly less morphine than the PCIA group.

Table 3 VAS and Vital Sign at Different Stage During Hospitalization Between Two Groups

Variables	Baseline (Mean ± SD)	4 Hours AS (Mean ± SD)	8 Hours AS (Mean ± SD)	12 Hours AS (Mean ± SD)	24 Hours AS (Mean ± SD)	48 Hours AS (Mean ± SD)	Time† (p value)	Interaction* (p value)
AVAS							<0.001	0.915
PCIA	0	2.45±1.22	2.56±0.80	2.71±0.93	2.29±0.93	1.95±0.84	<0.001	
TINB	0	2.35±1.06	2.60±1.06	2.61±0.93	2.21±0.91	1.89±0.79	<0.001	
RVAS							<0.001	0.271
PCIA	0	0.77±0.18	0.48±0.74	0.61±1.03	0.35±0.58	0.21±0.52	<0.001	
TINB	0	0.85±0.94	0.76±0.95	0.66±0.83	0.56±0.74	0.27±0.49	<0.001	
Body temperature							<0.001	0.164
PCIA	36.35±0.21	36.40±0.20	36.51±0.25	36.65±0.38	36.58±0.29	36.46±0.22	<0.001	
TINB	36.38±0.21	36.40±0.18	36.60±0.36	36.57±0.34	36.49±0.32	36.44±0.24	<0.001	

(*Continued*)

Table 3 (Continued).

Variables	Baseline (Mean ± SD)	4 Hours AS (Mean ± SD)	8 Hours AS (Mean ± SD)	12 Hours AS (Mean ± SD)	24 Hours AS (Mean ± SD)	48 Hours AS (Mean ± SD)	Time† (p value)	Interaction* (p value)
Heart rate							0.119	0.460
PCIA	74.69±10.96	75.45±11.53	77.92±10.96	78.73±11.54	79.19±10.90	77.68±8.90	0.121	
TINB	75.26±10.05	77.35±11.97	78.23±9.75	79.69±11.91	76.95±9.04	78.26±9.98	0.214	
MAP							<0.001	0.824
PCIA	92.06±11.06	90.52±13.15	81.18±10.12	83.36±12.39	86.26±10.40	86.60±9.00	<0.001	
TINB	90.85±12.20	93.05±12.59	82.33±11.76	84.99±11.68	86.77±11.39	86.67±11.26	<0.001	
Oxygen saturation							<0.001	0.933
PCIA	97.24±1.60	98.00±1.72	97.90±1.59	97.73±1.68	96.98±2.20	96.85±1.61	<0.001	
TINB	97.13±1.87	97.89±1.58	97.40±4.04	97.34±2.00	96.94±2.22	96.84±1.55	<0.001	

Note: †Intragroup and *intergroup interactions were evaluated by repeated measures ANOVA.
Abbreviations: AS, after surgery; AVAS, active visual analogue scale; RVAS, resting visual analogue scale; MAP, mean arterial pressure; PCIA patient controlled intravenous analgesia; TINB thoracoscopic intercostal nerve blocks.

Discussion

Patients undergoing VATS have several analgesic options available, including systemic and regional analgesia.[25] Currently, there is no consensus on the optimal analgesic regimen for VATS. However, the regimen should aim to reduce patients' pain, minimize the side effects related to analgesic drugs, and simplify the analgesic procedure. Operative TINB with cocktail analgesics has been shown to provide satisfactory analgesic effects for short-term and long-term pain without incurring higher rates of adverse reactions to analgesic drugs or making the analgesic procedure more difficult.

According to our results we found that the two groups showed no significant differences in pain scores after surgery. However, as shown in Figure 3, the proportion of patients who had AVAS scores of 0–2 within 48 hours after surgery was higher in the TINB group than in the PCIA group. TINB may show better pain control when patients are active in this respect. Good early postoperative pain control can help patients recover better and achieve enhanced recovery after surgery. Firstly, a good AVAS allows the patient to breathe deeply and cough more effectively. This is particularly important in thoracic surgery patients, as the incision and associated pain can lead to reduced respiratory effort. This can cause atelectasis (collapse of the lung), which in turn can lead to pneumonia, a serious postoperative complication. With better AVAS in early stage after surgery, patients are more likely to engage in necessary respiratory exercises and thus reduce the risk of pulmonary complications. Proper pain control at early stage enables early mobilization. Patients who with less AVAS are more likely to get out of bed, walk, and perform physical therapy exercises sooner. Early mobilization is associated with decreased rates of deep vein thrombosis (DVT), improved gastrointestinal function, and shorter hospital stays. This active engagement in recovery can also reduce the incidence of muscle atrophy and improve overall functional outcomes. In addition, analgesic–related adverse events were significantly lower in the TINB groups. Lighter analgesic-related adverse events contribute to a better postoperative recovery by enabling more effective respiratory function, quicker return to normal gastrointestinal function, increased patient alertness and participation in rehabilitation, reduced risk of complications such as urinary retention and DVT, and improved psychological well-being. It's obvious that patients in the TINB group had better adverse reaction control after surgery due to less opioid usage than patients in the PCIA group.

Opioid-based PCIA is widely used due to its effective analgesic properties. However, opioids have a narrow therapeutic window, and their use can lead to harmful side effects such as respiratory depression, sputum retention, drowsiness, constipation, nausea, vomiting, and addiction. As a result, opioids have been replaced with rescue drugs as the main analgesics.[25] To reduce opioid prescribing, physicians have turned to multimodal analgesia options. In this study, cocktail analgesics were used, including sodium bicarbonate, magnesium sulfate, methylprednisolone, ropivacaine hydrochloride, dexamethasone, and dexmedetomidine, which is an opioid-free formula. Compared to opioid based PCIA, TINB with cocktail analgesics provided similar analgesic effects while at rest and during motion. Therefore, TINB with cocktail analgesics is an effective and opioid-free analgesic option for thoracic surgery. Our study found that TINB in

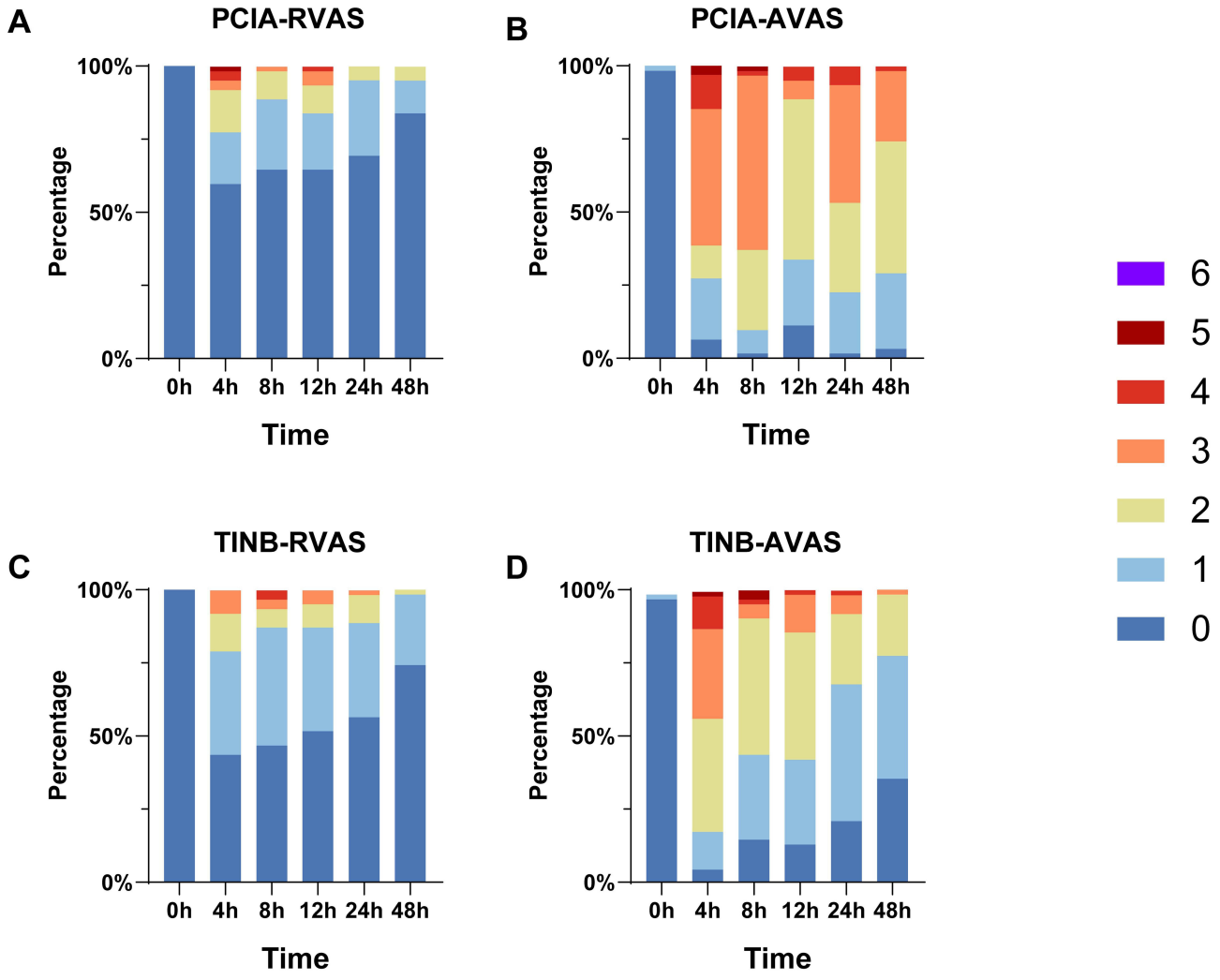


Figure 3 Postoperative pain VAS at different stages during hospitalization between two groups.
Notes: (**A**). RVAS of patients in PCIA group. (**B**). AVAS of patients in PCIA group. (**C**). RVAS scores of patients in TINB group. (**D**). AVAS scores of TINB group patients.
Abbreviations: PCIA, patient controlled intravenous analgesia; TINB, thoracoscopic intercostal nerve blocks; AVAS, active visual analogue scale; RVAS, resting visual analogue scale.

a cocktail formulation had analgesic effects superior to those of PCIA. Furthermore, the incidence of adverse reactions to anesthesia was significantly reduced in the experimental group due to the significant reduction in opioid use.

Intercostal nerve block (ICNB) is an alternative to TEA for procedural multimodal analgesia in thoracotomy, with fewer severe complications and side effects.[26] Although early pain control with ICNB is adequate, it used to be unable to provide durable pain relief after thoracic surgery due to the relatively short half-life of local anesthetics (approximately 5 hours).[27] Theoretically, liposome formulations of bupivacaine can improve the bioavailability of the drug and prolong its half-life, but the formulation still has a complex preparation process, resulting in a high price, unstable drug load, and the possibility of introducing other allergens. In some recent clinical studies, liposome bupivacaine has not shown a clear advantage.[28–31] In our study, TINB with cocktail analgesics provided long-acting analgesia for up to one month, which was superior to PCIA patients in terms of pain control at 7, 14, and 30 days after discharge, according to our follow-up records. It is interesting to note that in our cocktail analgesics, magnesium sulfate and sodium bicarbonate may contribute to long-acting analgesia. Magnesium sulfate enhances and prolongs analgesic effects by inhibiting N-methyl-D-aspartate (NMDA) receptors. This prevents hypersensitization by blocking the activation of dorsal horn NMDA receptors induced by excitatory amino acid transmitters.[32–36] Sodium bicarbonate converts ropivacaine from its nonionized form to its

Table 4 VAS and Analgesic Drugs After Discharge

Variables	7 Days AD (Mean ± SD)	14 Days AD (Mean ± SD)	30 Days AD (Mean ± SD)	Time† (p value)	Interaction* (p value)
AVAS				<0.001	<0.001
PCIA	2.08±0.58	1.35±0.60	0.76±0.43	<0.001	
TINB	0.48±0.57	0.16±0.37	0.10±0.30	<0.001	
RVAS				<0.001	<0.001
PCIA	1.19±0.62	0.47±0.62	0.19±0.40	<0.001	
TINB	0.42±0.50	0.06±0.25	0	<0.001	
Celecoxib (g)				<0.001	0.801
PCIA	2.75±0.29	3.10±0.41	3.10±0.41	<0.001	
TINB	2.42±0.31	2.75±0.34	2.75±0.34	<0.001	

Note: †Intragroup and *intergroup interactions were evaluated by repeated measures ANOVA.
Abbreviations: AD, after discharge; AVAS, active visual analogue scale; RVAS, resting visual analogue scale; PCIA, patient controlled intravenous analgesia; TINB, thoracoscopic intercostal nerve blocks.

ionized form, which has a stronger interaction with the sodium channel receptor.[37] The ionized form of ropivacaine shuts down the sodium channel receptor, blocking nerve impulse conduction and establishing an enhanced and prolonged anesthesia block. Furthermore, the addition of sodium bicarbonate may cause precipitation, which can prolong the absorption of analgesic drugs. However, further study is required to determine the relative efficacy of magnesium sulfate and sodium bicarbonate independently. Therefore, TINB with cocktail analgesics is an easy-to-operate and long-acting analgesia that compensates for the shortcomings of conventional ICNB.

In addition, each subsequent injection carries the risk of pneumothorax, nerve injury, and vascular damage if not performed under direct visualization.[38] Typically, ultrasound guidance is required during ICNB to avoid blood vessels and lung tissue and prevent bleeding and pneumothorax. This requires technical skills from the operator and may result in different analgesic effects depending on their proficiency. However, in thoracoscopic surgery, these concerns do not exist, and the affected lung collapses without causing pneumothorax. The surgeon performed TINB under direct visualization, which can be achieved easily without the use of ultrasonic equipment.[39] Additionally, thoracoscopic direct injection can prevent significant structural damage, and the operator can easily perform intercostal nerve block.

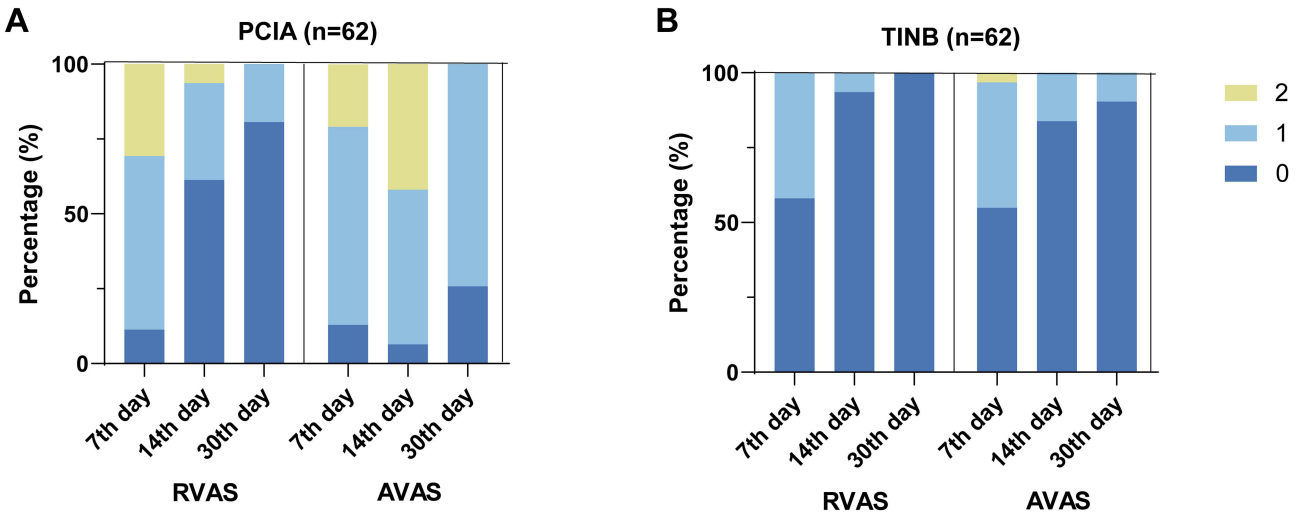


Figure 4 Postoperative pain VAS at different stages after discharge between two groups.
Notes: (**A**). VAS of patients in PCIA group. (**B**). VAS scores of patients in TINB group.
Abbreviations: PCIA, patient controlled intravenous analgesia; TINB, thoracoscopic intercostal nerve blocks;AVAS, active visual analogue scale; RVAS, resting visual analogue scale.

Table 5 Analgesic Related Adverse Events

Events	TINB (n=62)	PICA (n=62)	P value
Dizziness	3 (4.84%)	16 (25.81%)	0.002
Nausea and vomiting	0	14 (22.58%)	<0.001
Cough	4 (6.45%)	3 (4.84%)	0.697
Dyspnea	5 (8.06%)	5 (8.06%)	1.000
Fatigue	9 (14.52%)	21 (33.87%)	0.012
Insomnia	0	36 (58.06%)	<0.001
Urinary retention	0	2 (3.23%)	0.154
Constipation	0	1 (1.61%)	0.315
Disturbance of consciousness	0	0	NA
Flatulence	3 (4.84%)	1(1.61%)	0.309
Venous thrombotic event	0	0	NA

Abbreviations: PCIA, patient controlled intravenous analgesia; TINB, thoracoscopic intercostal nerve blocks.

However, it is important to acknowledge that infiltrating the intercostal of the surgical incision and the adjacent intercostal requires multiple injections. Each injection can increase the blood concentration of local anesthetics and pose a higher risk of local anesthetic toxicity. Although none of the 113 patients who underwent TINB experienced local anesthetic toxicity events, it is still necessary to take precautions to prevent such events from occurring.

Cocktail analgesics compositions consist of sodium bicarbonate, magnesium sulfate, methylprednisolone, ropivacaine hydrochloride, dexamethasone, and dexmedetomidine, each with its own effect. Ropivacaine was preferred over bupivacaine due to its milder toxicity to the central nervous and cardiovascular systems.[40] No ropivacaine-related adverse events occurred according to our records. Methylprednisone, dexamethasone, and dexmedetomidine were chosen for their ability to potentiate the analgesic effects of ropivacaine.[41,42] Magnesium sulfate and sodium bicarbonate enhance and prolong analgesic effects, as mentioned above. However, the addition of sodium bicarbonate may cause precipitation.[43,44] Bicarbonate is known to cause formulation changes and has many contraindications for coadministration. When combined with other drugs, the injection site can easily become blocked. Additionally, it is thought that if bicarbonate leaks into subcutaneous or soft tissue, it can cause tissue necrosis. However, precipitation of ropivacaine has been observed to occur even without alkalinization in rats.[38] In another study in our hospital, it was shown that the turbidity of the solution caused by the addition of sodium bicarbonate to ropivacaine did not cause muscle and nerve necrosis in rats, and the precipitation could be absorbed over time. At the same time, no tissue necrosis was observed in the TINB group patients.[38] The animal study preliminarily indicated that the precipitates were absorbable and safe, and no related side effects were observed in the current and previous clinical trials. According to our follow-up records, no

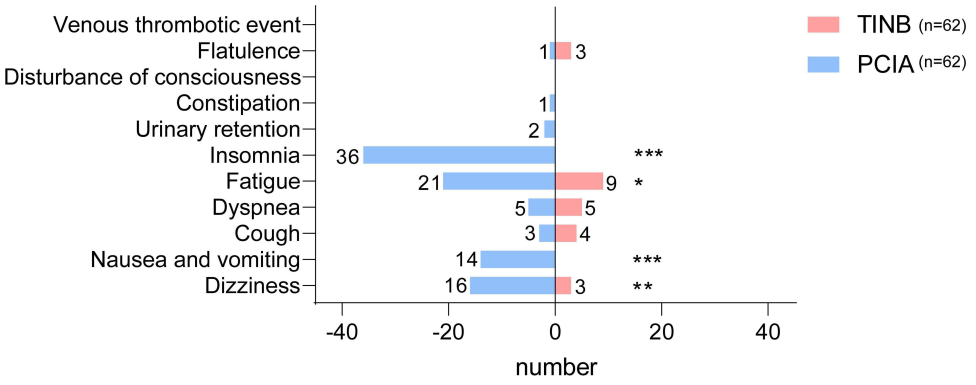


Figure 5 Analgesic related adverse events between two groups.
Notes: *p value < 0.05; **p value < 0.01; ***p value < 0.001.

Table 6 Intraoperative Anesthetic Information and Postoperative Rescue Analgesia

Index		TINB (n=62)	PCIA (n=62)	P value
Anesthetic maintenance drugs (Mean ± SD)	Sevoflurane (mL)	26.69±9.61	25.52±8.10	0.539
	Desflurane (mL)	22.28±13.63	24.65±13.30	0.267
	Propofol (mg)	176.50±78.86	169.95±90.36	0.844
Intraoperative anesthesia (Mean ± SD)	Sufentanil (ug)	26.15±4.59	24.96±6.18	0.227
	Remifentanil (ug)	802.24±366.38	783.27±353.77	0.771
	Flurbiprofen (mg)	74.52±43.77	74.05±41.44	0.951
Total rescue analgesia		6 (9.84%)	7 (11.29%)	0.187
No rescue analgesia during hospitalization		56 (90.16%)	55 (83.87%)	0.187
Postoperative morphine consumption (mg) (Mean ± SD)		0.48	6.45±2.90	<0.001

Abbreviations: PCIA, patient controlled intravenous analgesia; TINB, thoracoscopic intercostal nerve blocks.

patients complained of tissue necrosis around the incision. However, further study is needed to assess its potential harm in humans and more accurate and simplified formulas needs to be exploited.

Limitations

This investigation was subject to several limitations. Firstly, the absence of randomization in this non-randomized controlled trial, despite our implementation of propensity score matching (PSM) to mitigate selection bias, leaves room for unaccounted variables to influence the outcomes. Secondly, the analgesic protocol for the control group relied on opioid-based patient-controlled intravenous analgesia (PCIA), as opposed to the standardized intercostal nerve block (ICNB), which may constrain the extrapolation of our conclusions. Thirdly, the independent analgesic contributions of magnesium sulfate and sodium bicarbonate were not examined, although they hold promise as adjuncts for pain relief. Besides, the general anesthetics are different for maintaining the anesthesia, in which different general anesthetics, sevoflurane, desflurane may affect differently the results of the study. Lastly, the dosing of the combined medications warrants further refinement to align with drug administration standards and to enhance patient safety. Subsequent research should direct attention to these emerging analgesic adjuncts and adopt more robust methodologies.

Conclusion

The utilization of TINB with cocktail analgesics can deliver effective pain relief across both acute and chronic pain management scenarios. The combination has been shown to markedly extend the duration of analgesia and diminish the need for opioid analgesics, a substantial advantage considering the opioid crisis and the quest for opioid-sparing alternatives. Furthermore, the adoption of this analgesic strategy did not correlate with an uptick in adverse reaction rates, suggesting a favorable safety profile. Future studies, harnessing more sophisticated and refined research methodologies, are imperative to delve deeper into these innovative analgesic adjuncts. Such research endeavors are necessary to fully elucidate their mechanisms of action, optimize their clinical application, and confirm their safety and efficacy through more extensive and carefully controlled trials. Enhanced study designs will provide the high-quality evidence needed to potentially integrate these novel analgesic options into standard pain management protocols.

Data Sharing Statement

Clinical trial data that underlie the results reported in this article (text, tables, figures, and Supplementary Materials) and other study documents like Study Protocol, Informed Consent Form, Clinical Study Report are available to regulators, researchers, and trial participants upon request. And these data will be made available beginning 3 months and ending 5 years following article publication. Contact details: cheguoweixw@126.com.

Consent for Publishing

All the authors consent to publish the paper.

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Disclosure

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