Ropivacaine for Intercostal Nerve Block Improves Early Postoperative Cognitive Dysfunction in Patients Following Thoracotomy for Esophageal Cancer

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Background: Ropivacaine is commonly used as an intercostal nerve block, but its effects on postoperative cognitive dysfunction (POCD) have not previously been investigated. This study aimed to examine the effects of the use of ropivacaine as an intercostal nerve block on early POCD, postoperative analgesia, and inflammation in patients following thoracotomy for esophageal cancer.

Material/Methods: One hundred patients with esophageal cancer undergoing thoracotomy were randomly divided into a group with intercostal nerve block (group A) (n=50) and a control group (group B) (n=50). The cognitive function score and visual analog scale (VAS) scores for pain were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). Blood samples were collected at each time point, and plasma levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-10, and S100-β were measured using an enzyme-linked immunosorbent assay (ELISA). Cognitive function was determined using the Mini-Mental State Examination (MMSE) scale.

Results: The VAS scores in group A were significantly lower compared with group B ($p<0.05$). In the T2, T3, and T4 time points, group A had significantly increased MMSE scores compared with group B ($p<0.05$). Compared with group B, the levels of IL-6 and TNF-α were significantly decreased in group A at T3 and T4 ($p<0.05$), while the levels of IL-10 were significantly increased ($p<0.05$) when compared with group A.

Conclusions: The use of the intercostal nerve block, ropivacaine, improved early PCOD in patients following thoracotomy for esophageal cancer.

MeSH Keywords: Analgesia • Inflammation • Intercostal Nerves • Thoracotomy

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Background

Thoracic surgical procedures can involve large incisions involving the chest wall, which can lead to restricted breathing and persistent postoperative pain that may limit recovery and rehabilitation. Also, postoperative pain may limit sputum production, while increasing the respiratory rate [1–3]. A history of respiratory disease can make the patient more prone to postoperative shortness of breath, and severe pain may prevent the patient to regain spontaneous breathing, which can result in lung injury [4,5]. Previous studies have shown that severe pain associated with thoracic surgery can be associated with the occurrence of inflammation, which is one of the important mechanisms of lung injury [6]. Inflammatory mediators, including the cytokines, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), IL-10, and S100-β are released into the plasma following thoracic surgery and can be associated with a systemic inflammatory response [7].

Pain after thoracotomy has been shown to originate from both the somatic and visceral afferent nervous system leading to a cascade of neural activity, which contributes to chronic pain and post-thoracotomy pain syndrome (PTPS) [8,9]. Previously published studies have shown a close association between chronic pain and cognitive dysfunction, and chronic pain is associated with cognitive deficits in the areas of attention, memory, and executive function [10–12] and occur with different types of pain, including migraine, fibromyalgia, and diabetic neuropathy [13–15]. Postoperative cognitive dysfunction (POCD) associated with chronic pain may be a consequence of diverse and persistent nociceptive input associated with chronic pain that may compete with other forms of sensory input, resulting in reduced cognitive performance [16]. Neuroplasticity in the brain allows neurons to compensate for injury and to adjust neuronal activity in response to pain, resulting in neural rewiring or reorganization that interferes with normal cognitive function [17]. Therefore, neurochemical mediators released during chronic pain may have an adverse effect on cognitive processing.

In thoracic surgery, the use of analgesia with a regional block and systemic administration are the two main approaches to pain control following thoracotomy. Ropivacaine is commonly used as an intercostal nerve block, but its effects on postoperative cognitive dysfunction (POCD) have not previously been investigated. Therefore, this study aimed to examine the effects of the use of ropivacaine as an intercostal nerve block on early POCD, postoperative analgesia, and inflammation in patients following thoracotomy for esophageal cancer.

Material and Methods

Ethical approval, patient consent, and patient inclusion criteria

This study was approved by the Ethical Committee of Bishan District Peoples' Hospital. All study participants signed informed consent forms before recruitment into the study.

A total of 100 patients with esophageal cancer aged between 20–60 years of age were enrolled in this study. Patients were randomly divided into the intercostal nerve block group (group A) (n=50) and the control group (group B) (n=50), with 25 men and 25 women in each group. Inclusion criteria for the study included the absence of abnormal hepatic, renal, cardiac, or pulmonary function, with no chronic pain, hyperthyroidism, diabetes mellitus, or heart disease, and no severe diseases of the central nervous system or respiratory system. All patients were required to be able to communicate well with clinicians and to understand the scoring standards of patient-controlled intravenous analgesia (PCIA) and the visual analog scale (VAS).

Anesthetic methods

In clinical practice, the patients were prepared for thoracic surgery 45 minutes before thoracotomy, and 0.5 mg of phencyclidine hydrochloride was administered intravenously to patients in both group A and group B. Noninvasive blood pressure (BP), an electrocardiogram (ECG), heart rate (HR), and mean oxygen saturation (SpO$_2$) were routinely monitored. Analgesic drugs given to all the patients included fentanyl (3–4 μg/kg), midazolam (0.1–0.4 mg/kg), propofol (1.0–2.0 mg/kg), and cisatracurium (0.15 mg/kg). Three minutes later, intubation of all the patients in group A and group B was performed and hospital anesthetic equipment was used to ventilate both groups of patients. The respiratory rate was controlled at 13–15 times/min, the partial pressure of the end-tidal carbon dioxide (PeTCO$_2$) was maintained at 35–45 mmHg and tidal volume was maintained at 7–10 mL/kg. To maintain anesthesia, sevoflurane was inhaled, with a minimum alveolar concentration (MAC) maintained at 1.5–1.8 ng/mL, and remifentanil was given by target controlled infusion (TCI) with a concentration of 2.5 ng/mL.

After intubation, all the patients in group A received induction of general anesthesia, and 0.5% ropivacaine hydrochloride (Naropin) was injected from one intercostal space superior to and two intercostal spaces inferior to the incision performed during thoracic surgery, with an injection volume of 5 mL at each site. Patients in group B were controls with no injection of ropivacaine into the intercostal spaces.

Table 1. Demographic and clinical data of patients in group A and group B.

Group	Gender (Male/Female)	Mean age (years)	Mean weight (kg)	Mean operation time (min)
Group A (n=50)	25/25	45.26±1.36	68.49±1.68	213.11±14.86
Group B (n=50)	25/25	44.87±1.87	67.99±2.66	226.11±16.47

Evaluation of cognitive function and pain in the two study groups at four time intervals post-thoracotomy

The test items included in the Mini-Mental State Examination (MMSE) scale for the scoring of cognitive function included scores for verbal fluency, orientation, number recall, counting, memory and association, dexterity, and digit and symbol recognition. There were 30 items in total, with 1 point for each item in the case of a right answer. If the item was incorrectly or not answered, the patients were assigned 0 points. The maximum score was 30 points. The cognitive function score and visual analog scale (VAS) scores for pain were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4).

The relationship between the score and cognitive function was determined in accordance with the following standards. If the score was less than or equal to 25 points, or if more than 2 points reduced the MMSE score after surgery compared with that before surgery, cognitive dysfunction was identified. If the score was between 25–30 points, the cognitive function of the patients was identified as normal. The degree of pain at each time point (T1–T4) was expressed using the VAS score: 10 points (severe pain), ≥5 points (poor analgesia), 3–4 points (satisfactory analgesia), <3 points (good analgesia), and 0 points (no pain).

Measurement of inflammatory cytokines in peripheral blood

A total of 6 mL of venous blood was collected from each patient in both group A and group B at T1, T2, T3, and T4, respectively. A standard enzyme-linked immunosorbent assay (ELISA) method was used to analyze the concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and IL-10 in the plasma using commercial ELISA kits, according to manufacturer's instructions. Plasma levels of S100-β protein were also measured.

The collection of all the data was performed by the same physician who unaware of the patients' details and grouping, but who was familiar with the assessment methods and indices used in the study.

Statistical analysis

Statistical analysis of the data was performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, USA). Data were presented as the mean ± standard deviation (SD). The Student's t-test was performed for comparison of the difference between the two groups, and two-way analysis of variance (ANOVA) was conducted to evaluate the difference between the two groups at different time points. A p-value <0.05 indicated statistical significance.

Results

Comparison of clinical and demographic data between the two study groups

The clinical and demographic data in group A and group B were compared and analyzed, and there were no statistically significant differences between the two groups (p>0.05) (Table 1).

The Mini-Mental State Examination (MMSE) scores and the incidence of postoperative cognitive dysfunction (POCD)

The MMSE score for postoperative cognitive function in group A was significantly higher compared with group B (p<0.05) (Figure 1). Group B had a significantly increased incidence of postoperative cognitive dysfunction (POCD) compared with group A.

Postoperative visual analog scale (VAS) scores in group A and group B

As shown in Figure 2, in both group A and group B, the VAS scores of the patients at T2, T3 and T4 were significantly increased when compared with those at T1 (p<0.05). Compared with group B, the VAS scores in group A were significantly decreased at T2, T3, and T4 (p<0.05). The plasma level of S100-β protein was one of the most important indices associated with the VAS score. The plasma levels of S100-β protein at T2, T3, and T4 in patients in group A were significantly lower when compared with the same time points in group B (p<0.05) (Table 2). The plasma levels of S100-β protein at T2, T3, and T4 in both group A and group B were increased compared with the plasma levels of S100-β protein at T1.
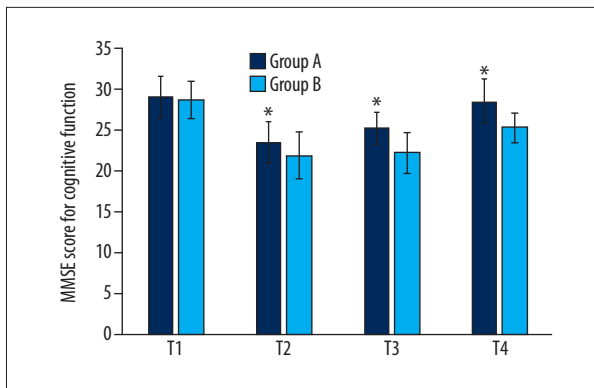
Figure 1. The Mini-Mental State Examination (MMSE) scores for cognitive function in group A and group B at four time points after thoracotomy. The Mini-Mental State Examination (MMSE) scale scores were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). The patient group with intercostal nerve block using ropivacaine (group A) (n=50) and the control group (group B) (n=50).

Figure 2. The visual analog scale (VAS) scores for pain in group A and group B at four time points after thoracotomy. The visual analog scale (VAS) scores for pain were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). The patient group with intercostal nerve block using ropivacaine (group A) (n=50) and the control group (group B) (n=50).
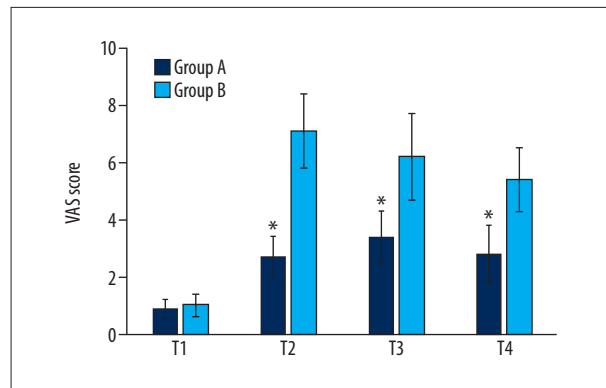
Table 2. Comparison of plasma levels of S100-β protein (pg/L) in group A and group B at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4).

Group	T1	T2	T3	T4
Group A (n=50)	1.04±0.11	1.17±0.09*	1.28±0.12*	1.35±2.7*
Group B (n=50)	1.12±0.09	1.23±0.13	1.38±0.09	1.48±0.13

* $p < 0.05$ *vs.* group B.

Table 3. Comparisons of serum levels of inflammatory factors (pg/L) in group A and group B at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4).

Group	Time point	IL-6	IL-10	TNF-α
Group A	T1	14.3±2.8	22.4±4.3	15.6±1.6
	T2	19.5±3.2*	25.9±5.3*	21.3±3.1*
	T3	26.8±4.7*	45.8±7.6*	25.3±4.8*
	T4	28.7±5.9*	59.8±7.1*	27.9±4.5*
Group B	T1	13.8±2.9	21.9±3.1	14.9±2.8
	T2	22.5±4.0	26.8±3.9	25.9±4.7
	T3	33.4±4.5	34.5±5.1	33.8±5.3
	T4	37.2±3.9	46.9±6.3	34.3±4.9

* $p < 0.05$ *vs.* group B. IL – interleukin; TNF-α – tumor necrosis factor-α.

Comparisons between the plasma levels of interleukin-6 (IL-6), IL-10, and tumor necrosis factor-α (TNF-α) in group A and group B

As shown in Table 3 and Figures 3–5, the plasma levels of interleukin-6 (IL-6), IL-10, and tumor necrosis factor-α (TNF-α) of all the patients participating in this study at T2, T3, and T4 were increased, compared with those at T1. Comparisons of data between the two groups at T2, T3 and T4 showed that patients in group A had lower plasma levels of IL-6 and TNF-α compared with group B. At T3 and T4, the plasma levels of IL-10 of patients in group A were significantly increased compared with those in group B ($p < 0.05$).
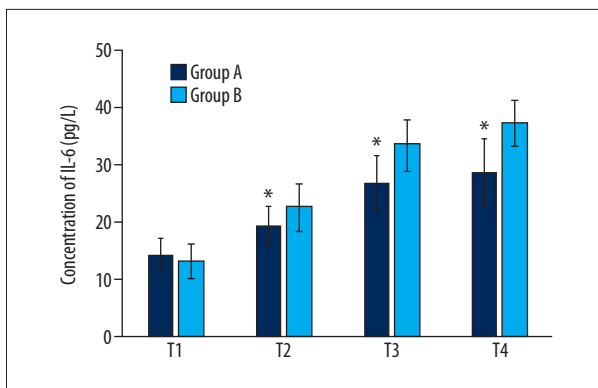
Figure 3. Plasma levels of interleukin-6 (IL-6) in group A and group B at four time points after thoracotomy. The plasma levels of interleukin-6 (IL-6) were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). The patient group with intercostal nerve block using ropivacaine (group A) (n=50) and the control group (group B) (n=50).

Figure 5. Plasma levels of tumor necrosis factor-α (TNF-α) in group A and group B at four time points after thoracotomy. The plasma levels of tumor necrosis factor-α (TNF-α) were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). The patient group with intercostal nerve block using ropivacaine (group A) (n=50) and the control group (group B) (n=50).
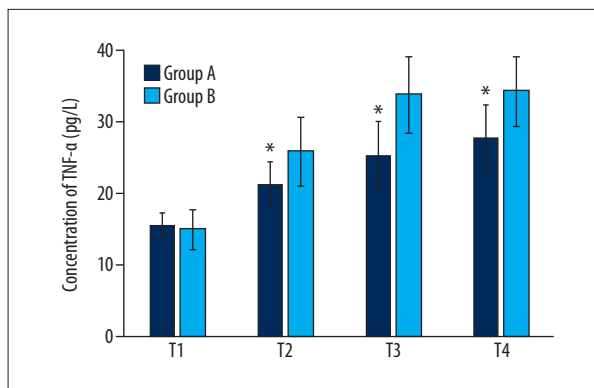

Figure 4. Plasma levels of interleukin-10 (IL-10) in group A and group B at four time points after thoracotomy. The plasma levels of interleukin-10 (IL-10) were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). The patient group with intercostal nerve block using ropivacaine (group A) (n=50) and the control group (group B) (n=50).
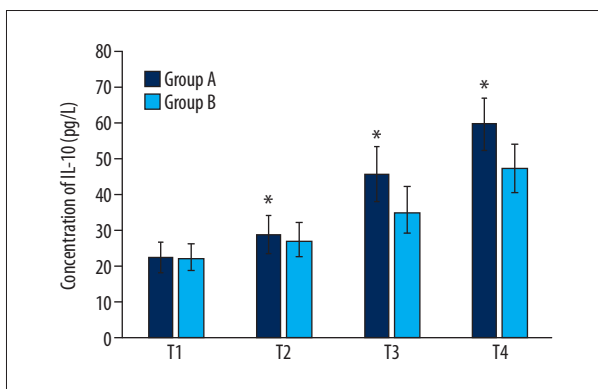
Discussion

Cognitive dysfunction generally occurs in patients over a period after thoracotomy, and are associated with different degrees of cognitive dysfunction [18]. Previously published studies have identified high-risk postoperative states and factors cognitive dysfunction, which in thoracotomy cases is usually associated with large incisions and surgical trauma as well as severe postoperative pain [19].

In this study, 100 patients with esophageal cancer undergoing thoracotomy for esophageal cancer were divided into a group with intercostal nerve block (group A) (n=50) and a control group (group B) (n=50). The cognitive function score and visual analog scale (VAS) scores for pain were measured at one hour before surgery (T1), two hours after surgery (T2), 12 hours after surgery (T3), and 24 hours after surgery (T4). The findings of the present study showed that that the incidences of postoperative cognitive dysfunction (POCD) in group A and group B were (21.0±1.3) and (38.7±2.1), respectively. The Mini-Mental State Examination (MMSE) score obtained at any time point in group A was significantly increased compared with that in group B, indicating that ropivacaine could improve cognitive function post-thoracotomy by blocking the intercostal nerves.

The intercostal nerves damaged in the process of thoracotomy can trigger pain after surgery, and such pain can restrict respiratory movement, coughing, and sputum production of the patients [3]. Also, respiratory secretions can be more difficult to remove and can block the bronchus, cause pneumonia, atelectasis, chest tightness, chest pain, and other pulmonary complications. Also, the inflammatory mediators that are increased and released into the circulation were increased after thoracotomy, and were associated with an increase in heart rate, in blood pressure, and can increase the risk of myocardial ischemia [20,21]. According to the results and data analysis from the present study, ropivacaine for intercostal nerve block improves cognitive dysfunction, possibly through the alleviation of pain.

For patients undergoing thoracotomy, an increase in pro-inflammatory cytokines is often released into the body, thus breaking

the balance between the pro-inflammatory cytokines and anti-inflammatory cytokines [22]. The pro-inflammatory cytokines in the blood are capable of triggering systemic inflammatory responses in the body [23]. As inducible factors, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are closely associated with the degree of surgical trauma and are associated with the degree of chronic pain after surgery [24]. IL-6 and TNF-α are two crucial inflammatory mediators that are indices for the level of systemic inflammatory response. To maintain homeostasis in the body, the increased levels of pro-inflammatory cytokines will inevitably lead to a corresponding increase in the level of anti-inflammatory cytokines, but this process may be slow, resulting in prolonged pain and resulting POCD.

Conclusions

The use of the intercostal nerve block, ropivacaine, improved early postoperative cognitive dysfunction (POCD) in patients following thoracotomy for esophageal cancer, possibly through inhibition of the inflammatory response. These beneficial effects of ropivacaine may result in improving and accelerating postoperative rehabilitation of patients following thoracotomy.

Conflict of interest

None.

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