

Original Article

Effects of epidural block anesthesia combined with general anesthesia on inflammatory factors, cognitive function and postoperative pain in patients with lung cancer after thoracoscopic surgery

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Received April 19, 2021; Accepted August 19, 2021; Epub November 15, 2021; Published November 30, 2021

Abstract: Objective: To investigate the effects of epidural block anesthesia combined with general anesthesia on inflammatory factors, cognitive function and postoperative pain in patients with lung cancer after thoracoscopic surgery. Methods: A total of 144 lung cancer patients admitted to the Department of Cardiothoracic Surgery of Ganzi Tibetan Autonomous Prefecture People's Hospital from October 2017 to October 2019 were included in this retrospective cohort study. The patients were divided into an observation group and a control group, with 72 cases in each group. Observation group was treated with epidural block anesthesia plus general anesthesia under thoracoscopic surgery, while control group was treated with general anesthesia alone. General information of both groups was compared. Tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) levels were measured by enzyme-linked immunosorbent assay before anesthesia (T0), before the end of operation (T1), 12 h after operation (T2) and 24 h after operation (T3). Calcium-binding protein (S-100 β) content, mini-mental state examination (MMSE) and Montreal cognitive assessment (MoCA) at T0, T3, the 3rd day after operation (T4), and the 5th day after operation (T5) were measured. And postoperative pain was recorded. Results: There were no significant differences in TNF- α , IL-6, MMSE and MoCA between the two groups at T0, and no significant differences were seen in S-100 β between the two groups at T0 and T1 (all $P > 0.05$). Compared with control group, observation group had lower TNF- α and IL-6 at T1, T2, T3, T4 and T5, and lower S-100 β at T3, T4 and T5 (all $P < 0.001$). Lower pain scores and higher MMSE and MoCA were found in the observation group at T3, T4 and T5 (all $P < 0.05$). Conclusion: Epidural block anesthesia combined with general anesthesia can effectively reduce levels of inflammatory factors, cognitive disorder and postoperative pain in patients with lung cancer after thoracoscopic surgery.

Keywords: Epidural block anesthesia, general anesthesia, thoracoscopic surgery, S-100 β , inflammatory factor, postoperative cognition

Introduction

Lung cancer, characterized by high incidence, is a disease that endangers human health [1]. In China, lung cancer has the highest incidence and mortality among all malignant tumors [2]. Non-small cell lung cancer is the most common type of lung cancer, followed by squamous cell carcinoma [3]. Generally, advanced lung cancer is often accompanied by metastases [4, 5]. Therefore, early detection and treatment are important for the prognosis of lung cancer patients. Surgery is still the main clinical treat-

ment for early and middle stages of lung cancer, but with the development of science and technology and minimally invasive technology, the surgical methods have gradually transformed from thoracotomy to thoracoscopic surgery [6, 7]. Thoracoscopic surgery has the advantages of small trauma and quick recovery [8]. Although thoracoscopic surgery is becoming more and more mature in clinic, complications such as postoperative pain and infection are still inevitable [9]. In addition, there is still strong oxidative stress that leads to inflammation in the body after thoracoscopic surgery, and the

occurrence of inflammation is not conducive to the recovery of postoperative pain. Therefore, although thoracoscopic surgery produces less trauma, the postoperative pain cannot be significantly improved [10]. Surgical stimulation, the use of general anesthesia, and the patient's own characteristics of chronic disease and poor surgical tolerance can increase the risk of postoperative cognitive impairment [11, 12]. Therefore, how to effectively control postoperative inflammation and prevent the occurrence of cognitive impairment has become the research focus of thoracoscopic surgery.

Anesthesia is an essential process before surgery. General anesthesia is usually used in thoracoscopic surgery. Although general anesthesia alone has good sedative and analgesic effects, the excessive use of propofol and opioids may lead to significant inhibition of central nervous system and respiratory system, and intraoperative hemodynamic instability [13]. It is reported that the occurrence of postoperative cognitive dysfunction has nothing to do with the way of surgery and anesthesia [14]. However, in recent years, different anesthesia methods and the use of anesthetic drugs can cause postoperative cognitive impairment, and postoperative cognitive impairment can occur within 1 week after surgery [15]. General anesthesia alone mainly inhibits the cerebral cortex and hypothalamus activity, but does not inhibit the transmission of the local stimulation of the surgical area to brain, so, some researchers believed that general anesthesia cannot effectively inhibit the traumatic stress and the release of inflammatory factors caused by surgery [16]. The incidence of postoperative cognitive impairment has reached 9-26% due to the aging trend of patients [17]. Inflammatory factors can cause damage to memory function [18]. Surgical trauma can cause neuroinflammation by destroying the blood-brain barrier, and then develop functional destruction of nerve activity, leading to postoperative cognitive impairments. Generally, the blood-brain barrier consists of tight junctions of transmembrane proteins between neurovascular endothelial cells. It allows only passive diffusion of water, gas, and small fat-soluble molecules. Aseptic surgical trauma causes inflammation at the surgical site, which is amplified by peripheral pro-inflammatory cytokines. Damaged cells at the site of injury passively release small

molecular biomolecules which is called damage-related molecular patterns. Especially, the release of high-mobility group box 1 (HMGB1) in response to surgical trauma is observed. HMGB1 activates the nuclear factor- κ B (NF- κ B) signaling pathway in bone marrow-derived monocytes, causing nuclear translocation of NF- κ B, upregulating the expression of cyclooxygenase-2, and promoting the inflammatory expression of interleukin-1 β , interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α). These pro-inflammatory cytokines can positively promote further release of HMGB1, thereby amplifying the inflammatory response [19]. The increase of calcium-binding protein (S-100 β) can lead to cell dysfunction and play a role in the pathophysiology of nerve cell degeneration, deterioration of inflammatory response and neurodegenerative changes [20]. Meanwhile, epidural block anesthesia combined with general anesthesia can reduce the dosage of propofol and opioid in the process of general anesthesia, and the nerve impulse uploaded through the spinal cord due to surgical trauma, thereby reducing the excitation of the sympathetic nerve-adrenal medulla axis and the occurrence of traumatic stress, which ultimately reduce the occurrence of inflammatory factors [21, 22]. However, there are rare studies on the effect of epidural block anesthesia combined with general anesthesia on cognitive function in thoracoscopic surgery. Therefore, this study aimed to investigate the effect of epidural block anesthesia combined with general anesthesia on inflammatory factors, cognitive function, and postoperative pain in lung cancer patients after thoracoscopic surgery.

Materials and methods

Clinical data

A retrospective cohort study was conducted on 144 lung cancer patients admitted to the Department of Cardiothoracic Surgery of Ganzi Tibetan Autonomous Prefecture People's Hospital from October 2017 to October 2019. The patients were divided into an observation group and a control group, with 72 cases in each group. Observation group was treated with epidural block anesthesia plus general anesthesia under thoracoscopic surgery, and control group was treated with general anesthesia alone. All patients were 30-68 years old,

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with an average age of 63.3 ± 8.3 years. This study was approved by the ethics committee of our hospital (Approval No. GZZYY-2017-10). All the patients signed the informed consent.

Inclusion criteria

(1) Patients with lung cancer confirmed by preoperative laboratory examination, fiberoptic bronchoscopy pathological biopsy and postoperative pathology, and who underwent thoracoscopic surgery [3]; (2) patients with tumor size ≤ 6 cm; (3) patients without mediastinal lymph node enlargement and tumor invasion of chest wall; (4) patients with TNM staging of I-III; (5) patients with normal blood coagulation and bone marrow function; (6) patients whose clinical data were complete.

Exclusion criteria

(1) Patients with cardiac insufficiency; (2) patients with other primary malignant tumors; (3) patients with abnormal blood coagulation or bone marrow function; (4) patients with liver or kidney insufficiency; (5) patients who could not cooperate with the medical staff; (6) patients who changed to thoracotomy from thoracoscopic surgery due to massive hemorrhage; (7) patients with incomplete clinical data.

Anesthesia methods

Patients in the two groups completed the laboratory examinations of electrocardiogram, blood routine, liver and kidney functions, and blood coagulation before the surgery and were informed of the risks associated with anesthesia. To reduce the risk of aspiration, patients were fasted for 6-8 h and forbidden to drink for 2-4 h before surgery. All patients signed informed consent for anesthesia. Before the patients were admitted, the following things were prepared to ensure the perioperative safety of patients: checking of the anesthesia machine, connection of the respiratory pipeline, preparation of the vasoactive drugs such as epinephrine and norepinephrine, and preparation of the visual laryngoscope, double-lumen tube, fiberoptic bronchoscope and tape.

Patients in the control group were given general anesthesia. Patients were given oxygen by mask at 6-8 L/min. Then the patients were intravenously injected with midazolam (0.05-

0.10 mg/kg, Jiangsu Enhua Pharmaceutical Co., Ltd., China), long chain fat milk in propofol (1-1.5 mg/kg, Yangtze River Pharmaceutical Co., Ltd., China), remifentanyl (0.1 μ g/kg, Yichang Renfu Pharmaceutical Co., Ltd., China), and rocuronium bromide (0.1 mg/kg, Zhejiang Xianju Pharmaceutical Co., Ltd., China) for induction according to their body weight (kg). Tracheal intubation and controlled ventilation were performed 3 min after assisted respiration. After anesthesia, vecuronium bromide (0.1 μ g/(kg·min)) and propofol (6 mg/(kg·h)) were used to maintain the anesthesia depth. The anesthetic was stopped about 10 min before the surgery was completed.

Patients in the observation group received epidural block anesthesia combined with general anesthesia. The patients underwent epidural block anesthesia in the lateral position. The anesthesia position was chosen between 5-7 of thoracic vertebrae for thoracic puncture. After successful thoracic puncture, 3 mL of 2% lidocaine injection (Hebei Tiancheng Pharmaceutical Co., Ltd., China) was injected into the epidural space, and observed for about 5 min. If there was no special situation, 5 mL of 0.5% ropivacaine hydrochloride (Yichang Humanwell Pharmaceutical Co., Ltd., China) was added, and the block level was observed after 20 min. If no extensive block and local anesthetic poisoning were observed, and no catheter entered the subarachnoid space by mistake, the anesthesia level was controlled at thoracic vertebra 1-8, and general anesthesia induction was performed 5 min after the level was determined. The right internal jugular vein was punctured and placed into the central venous catheter. The induction drugs of general anesthesia were propofol (1-1.5 mg/kg), remifentanyl (0.1 μ g/kg) and vecuronium bromide (0.1 mg/kg). After anesthesia, double-lumen endobronchial tube was selected according to the patient's height, weight and surgical site. After intravenous induction, double-lumen endobronchial tube was inserted (after auscultation and fiberoptic bronchoscopy were used to determine the rationality of catheter position, and the lungs were well separated, the anesthesia machine was connected to control the breathing). During the period of anesthesia maintenance, propofol (3.6-6.6 mg/(kg·h), Xi'an Libang Pharmaceutical Co., Ltd., China) was pumped by micropump for sedation, and propofol dosage was adjusted based on blood pressure and

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heart rate. When necessary, single intravenous injection of vecuronium bromide (0.05 mg/kg) and remifentanyl (0.1 µg/kg) was given to maintain muscle relaxation.

Both groups of patients were anesthetized by the same group of anesthetic medical staff.

Outcome measures

(1) Length of hospital stay after surgery: Length from the day after surgery to discharge.

(2) Postoperative exhaust time: Time from the completion of surgery to first anal exhaust.

(3) Time of free movement after surgery: After surgery, the time patients took to freely get out of bed and move in the ward for more than 30 minutes without any discomfort, which was recorded in hours.

(4) Time of the removal of thoracic drainage tube and drainage volume: The time from the completion of surgery to the removal of the thoracic drainage tube was recorded, and the amount of drainage at the time of removal was recorded.

(5) Determination of serum TNF-α and IL-6 at different time points: For each patient, 5 mL of elbow vein blood was collected before anesthesia (T0), before the end of surgery (T1), 12 h after surgery (T2), 24 h after surgery (T3), the 3rd day after surgery (T4), and the 5th day after surgery (T5), respectively. The collected blood samples were stored in the ethylenediamine-tetraacetic acid sterile tube (Shanghai Jierui Biology Co., Ltd., China). After being stored at 4°C for 15 min, the serum and plasma were separated by centrifuge at 3300 rpm. The isolated plasma was added with 40 µL phosphate buffer solution of protease inhibitor (Lianyungang Duanfeng Biotechnology Co., Ltd., China) and stored at -80°C. ELISA Kit (Shanghai Jierui Bioengineering Co., Ltd., China) was used to determine the level of TNF-α and IL-6.

(6) Determination of S-100β, mini-mental state examination (MMSE) and the Montreal cognitive assessment (MoCA) at different time points: Serum levels of S-100β were determined at T0, T1, T2, T3, T4 and T5, respectively. The cognitive function before and after treatment was evaluated by MMSE and MoCA at T0, T3, T4 and T5, among which, the total score of

19-item MMSE scoring system was 30, and that of MoCA scoring system was 30. Lower score indicates worse cognitive function [23].

(7) Postoperative pain: The subjective sensation of pain was quantified by visual analogue scale (VAS). A 10 cm long scale was used, with two stop-points of 0 and 10, in which 0 represented the absence of any pain, while 10 represented the most severe pain experienced by the patients. The patients chose a point between 0 and 10 depending on the degree of pain. The scale value was measured at T3, T4 and T5, respectively, and the scale value was the VAS score of patients [24].

Statistical analysis

The data obtained in this study was processed and analyzed using SPSS 17.0 software. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm sd$). The enumeration data was expressed as % or percentage and compared using chi-square test. Comparison between two groups was conducted by independent sample t test, and before-after comparison within the same group was performed using the paired t-test. Repeated measurement data were analyzed by repeated measures one-way ANOVA and expressed by F. There was a significant difference at $P < 0.05$.

Results

Comparison of general data

All the 144 patients completed anesthesia and surgery without withdrawal. There were no significant differences between the two groups in gender, age, cancer type, cTMN stage, differentiation degree, operation time, amount of intraoperative fluid replacement, amount of intraoperative blood loss, body mass index, number of postoperative analgesia cases and amount of intraoperative anesthetics ($P > 0.05$). See **Table 1**.

Comparison of postoperative related indexes

There were no differences in length of hospital stay, postoperative exhaust time, time of getting out of bed, and time of the removal of thoracic drainage tube between the two groups (all $P > 0.05$). See **Table 2**.

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Table 1. Comparison of general data and baseline data

Items	Observation group (n=72)	Control group (n=72)	χ^2/t	P
Gender (n)			0.113	0.736
Male	42	40		
Female	30	32		
Age (year)	63.1±8.3	63.5±8.3	0.261	0.795
Cancer type (n)			0.123	0.726
Adenocarcinoma	46	48		
Squamous cell carcinoma	26	24		
cTMN stage (n)			0.052	0.820
I-II	61	60		
III	11	12		
Differentiation degree (n)			0.123	0.940
High	42	41		
Middle	26	26		
Low	4	5		
Operation time (h)	2.93±0.22	2.92±0.21	0.353	0.752
Amount of intraoperative fluid replacement (L)	1.20±0.19	1.20±0.19	0.082	0.935
Amount of intraoperative blood loss (mL)	321.43±42.82	324.02±32.83	0.272	0.787
BMI (kg/m ²)	25.21±3.62	24.82±3.54	0.412	0.684
Number of postoperative analgesia cases (n)	44	47	0.269	0.604
Amount of intraoperative anesthetics				
Propofol (mg)	110.26±24.36	107.24±22.78	0.444	0.768
Remifentanyl (μg)	7.25±1.05	7.21±1.03	0.818	0.231
Vecuronium bromide (mg)	7.34±1.09	7.30±1.08	0.825	0.221

Note: BMI: body mass index.

Table 2. Comparison of postoperative indexes

Item	Observation group (n=72)	Control group (n=72)	t	P
Length of hospital stay (d)	8.94±2.38	9.04±2.65	0.238	0.812
Postoperative exhaust time (h)	21.14±2.72	21.62±3.15	0.979	0.329
Thoracic drainage (mL)	132.13±30.22	139.22±40.24	1.195	0.234
Time of getting out of bed (h)	24.63±2.20	24.54±2.29	0.241	0.810
Time of the removal of thoracic drainage tube (d)	2.91±0.33	3.02±0.35	1.940	0.054

Comparison of inflammatory factors and S-100β before and after surgery at different time points

In terms of TNF-α and IL-6, there were no significant differences between the two groups at T0 (P>0.05); no significant differences were seen in S-100β between the two groups at T0 and T1. TNF-α and IL-6 levels in the observation group were lower than those in the control group at T1, T2, T3, T4 and T5, and S-100β levels in the observation group were lower than

those in the control group at T3, T4 and T5 (P<0.001). See **Tables 3-5**.

Comparisons of MMSE and MoCA before and after surgery

In terms of MMSE and MoCA, there were no significant differences between the two groups at T0 (P>0.05). MMSE and MoCA in the observation group were higher than those in the control group at T3, T4 and T5 (P<0.05). See **Tables 6, 7**.

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Table 3. Comparison of TNF- α at different time points (pg/mL)

Group	T0	T1	T2	T3	T4	T5
Observation group (n=72)	4.92 \pm 1.07	10.29 \pm 1.52	21.87 \pm 4.35	30.51 \pm 5.07	25.82 \pm 4.98	19.81 \pm 3.88
Control group (n=72)	5.02 \pm 1.33	15.27 \pm 2.22	39.87 \pm 7.95	44.25 \pm 6.15	35.82 \pm 6.33	24.72 \pm 4.86
t	0.349	11.478	12.081	10.489	10.542	6.699
P	0.728	<0.001	<0.001	<0.001	<0.001	<0.001

Note: TNF- α : tumor necrosis factor- α ; T0: before anesthesia; T1: before the end of surgery; T2: 12 h after surgery; T3: 24 h after surgery; T4: the 3rd day after surgery; T5: the 5th day after surgery.

Table 4. Comparison of IL-6 at different time points (pg/mL)

Group	T0	T1	T2	T3	T4	T5
Observation group (n=72)	11.48 \pm 1.58	18.58 \pm 5.42	33.58 \pm 8.49	41.62 \pm 5.23	35.92 \pm 5.12	30.92 \pm 4.62
Control group (n=72)	10.95 \pm 1.72	29.51 \pm 7.31	42.95 \pm 9.17	54.31 \pm 7.15	46.23 \pm 6.21	40.28 \pm 5.82
t	1.380	7.036	4.385	8.713	8.912	7.723
P	0.172	<0.001	<0.001	<0.001	<0.001	<0.001

Note: IL-6: interleukin-6; T0: before anesthesia; T1: before the end of surgery; T2: 12 h after surgery; T3: 24 h after surgery; T4: the 3rd day after surgery; T5: the 5th day after surgery.

Table 5. Comparison of S-100 β at different time points (pg/mL)

Group	T0	T1	T2	T3	T4	T5
Observation group (n=72)	17.23 \pm 10.23	35.23 \pm 14.29	73.92 \pm 41.82	161.32 \pm 122.12	74.12 \pm 20.92	21.02 \pm 13.76
Control group (n=72)	16.89 \pm 9.30	39.92 \pm 14.78	152.33 \pm 100.95	328.21 \pm 162.29	131.43 \pm 35.92	64.31 \pm 29.01
t	0.789	1.936	11.823	14.923	10.902	8.613
P	0.493	0.055	<0.001	<0.001	<0.001	<0.001

Note: S-100 β : calcium-binding protein; T0: before anesthesia; T1: before the end of surgery; T2: 12 h after surgery; T3: 24 h after surgery; T4: the 3rd day after surgery; T5: the 5th day after surgery.

Table 6. Comparison of MMSE at different time points (score)

Group	T0	T3	T4	T5
Observation group (n=72)	28.42 \pm 1.22	26.83 \pm 0.91	28.28 \pm 1.54	28.36 \pm 1.76
Control group (n=72)	28.37 \pm 1.16	22.70 \pm 1.80*	24.23 \pm 1.04*	26.43 \pm 1.54
t	0.108	14.923	12.902	2.893
P	0.914	<0.001	<0.001	0.003

Note: Compared with T0, *P<0.05. MMSE: mini-mental state examination; T0: before anesthesia; T3: 24 h after surgery; T4: the 3rd day after surgery; T5: the 5th day after surgery.

Table 7. Comparison of MoCA at different time points (score)

Group	T0	T3	T4	T5
Observation group (n=72)	28.50 \pm 1.44	27.73 \pm 1.03	27.82 \pm 1.28	28.24 \pm 1.45
Control group (n=72)	28.20 \pm 1.56	24.23 \pm 1.23*	25.39 \pm 1.65*	26.22 \pm 1.58
t	0.538	2.759	2.583	2.352
P	0.592	0.008	0.029	0.041

Note: Compared with T0, *P<0.05. MoCA: Montreal cognitive assessment; T0: before anesthesia; T3: 24 h after surgery; T4: the 3rd day after surgery; T5: the 5th day after surgery.

Comparison of postoperative pain score

After one-way ANOVA analysis for postoperative pain score, there was a significant difference

among T3, T4 and T5 in both groups (P<0.001). Further comparison found that postoperative pain scores in both groups at T4 were lower than those at T3, and those at T5 were lower

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Table 8. Comparison of postoperative pain score (score)

VAS pain score	Observation group (n=72)	Control group (n=72)	F	P
T3	2.65±0.52 ^a	4.85±0.65	344.893	<0.001
T4	1.04±0.27 ^{a,*}	2.07±0.27 [*]		
T5	0.37±0.36 ^{a,*,#}	1.25±0.38 ^{*,#}		
F	1087.347	321.895		
P	<0.001	<0.001		

Note: Compared with T3, *P<0.05; compared with T4, *P<0.05; compared with control group, #P<0.05. VAS: visual analogue scale; T3: 24 h after surgery; T4: the 3rd day after surgery; T5: the 5th day after surgery.

than those at T3 and T4. The postoperative pain scores in the observation group were lower than those in the control group at T3, T4 and T5 (P<0.05). See **Table 8**.

Discussion

With the acceleration of aging, more and more elderly patients need surgery because of diseases. Anesthesia is an indispensable part of the process of surgery, and it is also closely related to the success or failure of the surgery. In recent years, the occurrence of perioperative cognitive impairment has become a new research focus in anesthesia complications, and it has been found that the incidence of perioperative cognitive impairment increases with the increase of patients' age [25]. For lung cancer patients, the technology of thoracoscopic surgery is increasingly mature, and the anesthesia method has also improved with the development of technology. In recent years, epidural block anesthesia has been widely applied in thoracoscopic surgery. Epidural block anesthesia can reduce postoperative pain in patients, and it is considered as the "gold standard" for postoperative analgesia [26]. However, for epidural block anesthesia combined with general anesthesia and general anesthesia alone, which one has better effect on cognitive function has not been determined [27]. Both TNF- α and IL-6 are important factors involved in inflammatory response [28]. The aggregation of inflammatory factors can damage the learning and memory functions mediated by hippocampus [18]. Proinflammatory factors can induce central nervous system inflammation in a variety of ways, thereby affecting cognitive function [29]. Moreover, when proinflammatory factors enter the nervous system, they can cause mitochondrial damage, which can lead to neuroinflammatory damage to nerve cells [30]. The periph-

eral immune regulation of rats after surgery can make them secrete anti-inflammatory factors and regulate the expression of T cell markers, which can prevent the cognitive impairment and neuroinflammation of rats after surgery [31]. In this study, it was found that TNF- α and IL-6 levels in patients undergoing epidural block anesthesia combined with general anesthesia were lower than those in patients receiving general anesthesia alone.

The cognitive function-related S-100 β was further detected in this study. It was found that S-100 β was significantly increased at T3, and significantly decreased at T4 and T5, but the observation group had the lower S-100 β level compared with the control group. S-100 β exists in nerve cells. When the serum content is less than 0.2 ng/mL, it can protect nerve cells, but it can exude from cells to cerebrospinal fluid after nerve cell injury. When the concentration is higher than 0.5 ng/mL, it can damage neurons, thus causing abnormal blood-brain barrier and entering human blood, which increases the content of S-100 β in blood. Therefore, the content of S-100 β in blood is positively correlated with the degree of nerve injury [32, 33]. The content of S-100 β in the blood was significantly increased after surgery, and the incidence of cognitive impairment was increased with the increase of the content of S-100 β in the blood [34]. The release of plenty of inflammatory factors after surgery led to brain edema and blood-brain barrier leakage, while systemic inflammatory response caused endothelial cell damage which resulted in neutrophils gathering in the microvascular bed, increased endothelial cell permeability, and a large amount of S-100 β released into the blood [35]. MMSE and MOCA are common evaluation tools reflecting patients' cognitive function [19]. In this study, it was found that in terms of postoperative cognitive impairment, the observation group (epidural block anesthesia combined with general anesthesia) had worse cognition compared with that of the control group (general anesthesia). It is possible that general anesthesia combined with epidural block anesthesia can reduce the secretion of adrenaline and noradrenaline during perioperative period, and reduce the stress response after surgery, thereby reducing inflammatory factors release, S-100 β content in blood, and the cognitive

damage after surgery [36]. Previous studies have shown that compared with general anesthesia, epidural block anesthesia can effectively reduce the possibility of cognitive dysfunction in elderly patients after surgery, and this anesthesia method has less impact on cognitive function in elderly patients after surgery. This may be because the central nervous system is affected by general anesthesia, which leads to the imbalance of the brain memory protein level, increases the serum S-100 β protein, and eventually causes cognitive dysfunction [37]. A Chinese study also indicates that epidural block anesthesia mainly plays a role in the spinal cord, which can significantly reduce the adverse effects of anesthesia drugs on the central nervous system of elderly patients, reduce the serum S-100 β protein concentration, and further reduce the possibility of postoperative cognitive function decline in elderly patients [38]. The above results were consistent with the results of this study.

In terms of postoperative pain, epidural block anesthesia can effectively block sympathetic nerve and the stimulation conduction to the center after physical injury, while general anesthesia can inhibit the afferent stimulation of vagus nerve and phrenic nerve, so the combination of the two can effectively block nerve, and reduce postoperative stress and pain [39, 40]. In this study, epidural block anesthesia combined with general anesthesia can effectively reduce postoperative pain, which is consistent with the above studies.

This study still has some limitations. It was a single-center study with a small sample size, which required further expansion of the sample size and a combined multi-center study. Moreover, since the observation time was short, it should be further increased in the future to investigate the postoperative recovery status of the two groups. In this study, due to the differences in the use of anesthetics between the two groups, the effects of different anesthetics on postoperative cognitive impairment were not further studied.

In conclusion, epidural block anesthesia combined with general anesthesia can effectively reduce the levels of inflammatory factors and S-100 β , postoperative cognitive impairment and postoperative pain in lung cancer patients after thoracoscopic surgery.

Disclosure of conflict of interest

None.

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References

- [1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; 68: 7-30.
- [2] Yamauchi Y, Isaka M, Ando K, Mori K, Kojima H, Maniwa T, Takahashi S, Ando E and Ohde Y. Continuous paravertebral block using a thoracoscopic catheter-insertion technique for postoperative pain after thoracotomy: a retrospective case-control study. *J Cardiothorac Surg* 2017; 12: 5.
- [3] Reck M and Rabe KF. Precision diagnosis and treatment for advanced non-small-cell lung cancer. *N Engl J Med* 2017; 377: 849-861.
- [4] Ulahannan D, Khalifa J, Faivre-Finn C and Lee SM. Emerging treatment paradigms for brain metastasis in non-small-cell lung cancer: an overview of the current landscape and challenges ahead. *Ann Oncol* 2017; 28: 2923-2931.
- [5] Yousefi M, Bahrami T, Salmaninejad A, Nosrati R, Ghaffari P and Ghaffari SH. Lung cancer-associated brain metastasis: molecular mechanisms and therapeutic options. *Cell Oncol (Dordr)* 2017; 40: 419-441.
- [6] Tamura T, Mori S, Mori A, Ando M, Yokota S, Shibata Y and Nishiwaki K. A randomized controlled trial comparing paravertebral block via the surgical field with thoracic epidural block using ropivacaine for post-thoracotomy pain relief. *J Anesth* 2017; 31: 263-270.
- [7] Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR, D'Amico TA, DeCamp MM, Dilling TJ, Dobelbower M, Doebele RC, Govindan R, Gubens MA, Hennon M, Horn L, Komaki R, Lackner RP, Lanuti M, Leal TA, Leisch LJ, Lilenbaum R, Lin J, Loo BW Jr, Martins R, Otterson GA, Reckamp K, Riely GJ, Schild SE, Shapiro TA, Stevenson J, Swanson SJ, Tauer K, Yang SC, Gregory K and Hughes M. Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2017; 15: 504-535.
- [8] Zuo T, Gong FY, Chen BJ, Ni ZY and Zhang DY. Video-assisted thoracoscopic surgery for the treatment of mediastinal lymph node tuberculous abscesses. *J Huazhong Univ Sci Technol Med Sci* 2017; 37: 849-854.

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- [9] Yu Z, Xie Q, Guo L, Chen X, Ni C, Luo W, Li W and Ma L. Perioperative outcomes of robotic surgery for the treatment of lung cancer compared to a conventional video-assisted thoracoscopic surgery (VATS) technique. *Oncotarget* 2017; 8: 91076-91084.
- [10] Lee SJ and Lee DG. Distribution of atherosclerotic stenosis determining early neurologic deterioration in acute ischemic stroke. *PLoS One* 2017; 12: 185314.
- [11] Needham MJ, Webb CE and Bryden DC. Post-operative cognitive dysfunction and dementia: what we need to know and do. *Br J Anaesth* 2017; 119 Suppl 1: i115-i125.
- [12] Ghaffary S, Ghaeli P, Talasaz AH, Karimi A, Noroozian M, Salehiomran A and Jalali A. Effect of memantine on post-operative cognitive dysfunction after cardiac surgeries: a randomized clinical trial. *Daru* 2017; 25: 24.
- [13] Schroy PC 3rd, Coe AM, Mylvaganam SR, Ahn LB, Lydotes MA, Robinson PA, Davis JT, Chen CA, Ashba J, Atkinson ML, Colditz GA and Heeren TC. The Your Disease Risk Index for colorectal cancer is an inaccurate risk stratification tool for advanced colorectal neoplasia at screening colonoscopy. *Cancer Prev Res (Phila)* 2012; 5: 1044-1052.
- [14] Evered L, Scott DA, Silbert B and Maruff P. Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. *Anesth Analg* 2011; 112: 1179-1185.
- [15] Goswami U, Babbar S and Tiwari S. Comparative evaluation of the effects of propofol and sevoflurane on cognitive function and memory in patients undergoing laparoscopic cholecystectomy: a randomised prospective study. *Indian J Anaesth* 2015; 59: 150-155.
- [16] Milanovic D, Pesic V, Loncarevic-Vasiljkovic N, Pavkovic Z, Popic J, Kanazir S, Jevtovic-Todorovic V and Ruzdijic S. The Fas Ligand/Fas Death receptor pathways contribute to propofol-induced apoptosis and neuroinflammation in the brain of neonatal rats. *Neurotox Res* 2016; 30: 434-452.
- [17] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauen PM, Kristensen PA, Biedler A, van Beem H, Fradakis O, Silverstein JH, Beneken JE and Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. *International Study of Post-Operative Cognitive Dysfunction. Lancet* 1998; 351: 857-861.
- [18] Huang C, Irwin MG, Wong GTC and Chang RCC. Evidence of the impact of systemic inflammation on neuroinflammation from a non-bacterial endotoxin animal model. *J Neuroinflammation* 2018; 15: 147.
- [19] Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, Lewis M, Marriott A, Moore EM, Morris G, Page RS and Gray L. Post-operative cognitive dysfunction: an exploration of the inflammatory hypothesis and novel therapies. *Neurosci Biobehav Rev* 2018; 84: 116-133.
- [20] Donato R, Sorci G, Riuzzi F, Arcuri C, Bianchi R, Brozzi F, Tubaro C and Giambanco I. S100B's double life: intracellular regulator and extracellular signal. *Biochim Biophys Acta* 2009; 1793: 1008-1022.
- [21] Mineo TC, Tamburrini A, Perroni G and Ambrogio V. 1000 cases of tubeless video-assisted thoracic surgery at the Rome Tor Vergata University. *Future Oncol* 2016; 12: 13-18.
- [22] Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF and Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. *Anesthesiology* 2018; 129: 829-851.
- [23] Ciesielska N, Sokołowski R, Mazur E, Podhorecka M, Polak-Szabela A and Kędziora-Kornatowska K. Is the montreal cognitive assessment (MoCA) test better suited than the mini-mental state examination (MMSE) in mild cognitive impairment (MCI) detection among people aged over 60? Meta-analysis. *Psychiatr Pol* 2016; 50: 1039-1052.
- [24] Dahlstrand U, Sandblom G, Nordin P, Wollert S and Gunnarsson U. Chronic pain after femoral hernia repair: a cross-sectional study. *Ann Surg* 2011; 254: 1017-1021.
- [25] Whitaker D and Motallebzadeh R. Intraoperative cerebral high-intensity transient signals and postoperative cognitive function: a systematic review. *Am J Surg* 2009; 198: 295-297; author reply 254-5.
- [26] Seners P, Turc G, Oppenheim C and Baron JC. Incidence, causes and predictors of neurological deterioration occurring within 24 h following acute ischaemic stroke: a systematic review with pathophysiological implications. *J Neurol Neurosurg Psychiatry* 2015; 86: 87-94.
- [27] The elderly anesthesiology group of Anesthesiology branch of Chinese Medical Association, National Clinical Research Center for geriatric diseases, psychiatric branch of Chinese Medical Association, National Sleep Research Center, national geriatric anesthesia alliance and perioperative organ protection branch of Chinese society of cardiothoracic anesthesia. Multidisciplinary expert consensus on perioperative brain health of Chinese elderly patients (2). *Natl Med J China* 2019; 99: 2252-2269.
- [28] Cheng C, Xu JM and Yu T. Neutralizing IL-6 reduces heart injury by decreasing nerve growth factor precursor in the heart and hypothalamus during rat cardiopulmonary bypass. *Life Sci* 2017; 178: 61-69.

Epidural block anesthesia and general anesthesia for thoracoscopic surgery

- [29] Kohman RA and Rhodes JS. Neurogenesis, inflammation and behavior. *Brain Behav Immun* 2013; 27: 22-32.
- [30] Gubellini P, Picconi B, Di Filippo M and Calabresi P. Downstream mechanisms triggered by mitochondrial dysfunction in the basal ganglia: from experimental models to neurodegenerative diseases. *Biochim Biophys Acta* 2010; 1802: 151-161.
- [31] Fonken LK, Frank MG, D'Angelo HM, Heinze JD, Watkins LR, Lowry CA and Maier SF. *Mycobacterium vaccae* immunization protects aged rats from surgery-elicited neuroinflammation and cognitive dysfunction. *Neurobiol Aging* 2018; 71: 105-114.
- [32] Erikson K, Ala-Kokko TI, Koskenkari J, Liisanantti JH, Kamakura R, Herzig KH and Syrjälä H. Elevated serum S-100 β in patients with septic shock is associated with delirium. *Acta Anaesthesiol Scand* 2019; 63: 69-73.
- [33] Petzold A, Jenkins R, Watt HC, Green AJ, Thompson EJ, Keir G, Fox NC and Rossor MN. Cerebrospinal fluid S100B correlates with brain atrophy in Alzheimer's disease. *Neurosci Lett* 2003; 336: 167-170.
- [34] Al Tmimi L, Van de Velde M, Meyns B, Meuris B, Sergeant P, Milisen K, Pottel H, Poesen K and Rex S. Serum protein S100 as marker of postoperative delirium after off-pump coronary artery bypass surgery: secondary analysis of two prospective randomized controlled trials. *Clin Chem Lab Med* 2016; 54: 1671-1680.
- [35] Zou R, Shi W, Tao J, Li H, Lin X, Yang S and Hua P. Neurocardiology: cardiovascular changes and specific brain region infarcts. *Biomed Res Int* 2017; 2017: 5646348.
- [36] Donmez T, Erdem VM, Uzman S, Yildirim D, Av-aroglu H, Ferahman S and Sunamak O. Laparoscopic cholecystectomy under spinal-epidural anesthesia vs. general anaesthesia: a prospective randomised study. *Ann Surg Treat Res* 2017; 92: 136-142.
- [37] Xie H, Zhou J, Du W, Zhang S, Huang R, Han Q and Guo Q. Impact of thoracic paravertebral block combined with general anesthesia on postoperative cognitive function and serum adiponectin levels in elderly patients undergoing lobectomy. *Wideochir Inne Tech Maloinwazyjne* 2019; 14: 538-544.
- [38] Guo HL, Zhang XJ, Zhou YK and Zhou J. Effect and mechanism of different anesthetics on postoperative cognitive functions in elderly patients after orthopedic surgery. *Zhong Guo Yi Yuan Yao Xue Za Zhi* 2017; 37: 643-646.
- [39] Mehta N, Gupta S, Sharma A and Dar MR. Thoracic combined spinal epidural anesthesia for laparoscopic cholecystectomy in a geriatric patient with ischemic heart disease and renal insufficiency. *Local Reg Anesth* 2015; 8: 101-104.
- [40] Bardia A, Sood A, Mahmood F, Orhurhu V, Mueller A, Montealegre-Gallegos M, Shnider MR, Ultee KH, Schermerhorn ML and Matyal R. Combined epidural-general anesthesia vs. general anesthesia alone for elective abdominal aortic aneurysm repair. *JAMA Surg* 2016; 151: 1116-1123.