Am J Transl Res 2021;13(10):11797-11805
www.ajtr.org /ISSN:1943-8141/AJTR0132579

Original Article

The effect of different depths of anesthesia monitored using Narcotrend on cognitive function in elderly patients after VATS lobectomy

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Received February 27, 2021; Accepted May 11, 2021; Epub October 15, 2021; Published October 30, 2021

Abstract: Objective: The purpose of this study was to examine the effects of various depths of anesthesia monitored using Narcotrend on cognitive function in elderly patients after video-assisted thoracic surgery (VATS) lobectomy. Methods: A total of 73 elderly patients who underwent VATS lobectomy were selected and divided into a control group (n=36) and an observation group (n=37) using a random number table. Both groups received general anesthesia. The Narcotrend index (NTI) of the control group was maintained at 50-59 and that of the observation group was maintained at 30-39. Results: The heart period (HP) and mean arterial pressure (MAP) from both groups were decreased first, and then were increased during T_1-T_5; the MAP levels at T_2, T_3, and T_4 were lower in the observation group than in the control group ($P < 0.05$). The propofol dosage was higher and the awake to extubation time was greater in the observation group than in the control group ($P < 0.05$). The visual analogue scale (VAS) score was lower in the observation group than in the control group at 6 h and 12 h after surgery ($P < 0.05$). The left and right regional cerebral oxygen saturation (rSO_2) at T_3-T_4 was higher in the observation group and the cerebral oxygen extraction ratio ($CERO_2$) was lower in the observation group than in the control group ($P < 0.05$). Conclusion: The anesthetic depth that maintained an NTI of 30-39 as monitored using Narcotrend could improve cerebral oxygen metabolism, inhibit the inflammatory reaction, and reduce the incidence of postoperative cognitive dysfunction (POCD) in patients after VATS lobectomy.

Keywords: Narcotrend monitoring, depth of anesthesia, elderly, video-assisted thoracic surgery lobectomy, postoperative cognitive function, hemodynamic

Introduction

Postoperative cognitive dysfunction (POCD) is a common complication associated with anesthesia, and the underlying mechanism remains unclear. Clinical studies have indicated that advanced age is one of the high-risk factors for POCD [1, 2]. In addition, POCD is closely related to cerebral hypoperfusion caused by the depth of anesthesia, intraoperative hypoxemia, and perioperative pain [3]. Elderly patients are more prone to POCD due to their decreased physical capacity and low tolerance of surgery and anesthesia [4]. Studies have indicated that the incidence rates of POCD in elderly patients can be as high as 25.8% at 1 week after non-cardiac surgery [5]. One-lung ventilation is required during video-assisted thoracic surgery (VATS) lobectomy. This may interfere with respiratory physiology, cause ventilation-perfusion mismatch, increase intrapulmonary shunt, affect cerebral oxygen balance, lead to a change in cerebral oxygen metabolism, and thus affect postoperative cognitive function [6]. Surgical trauma can cause traumatic stimulation to the body, and induce a large amount of acute response factors such as C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor (TNF) to be released into the blood, and then act on the vital organs of the body, which can easily lead to the occurrence of systemic inflammatory response syndrome, and can also further induce or aggravate the occurrence of postoperative cognitive function impairment [7]. The main purpose of Narcotrend monitoring is to avoid over- or underdosing of anesthesia and improve the quality management of anesthesia. The Narcotrend index (NTI) ranges from 0 to 100, with a lower index value indicating deeper anesthesia, and vice versa. NTI < 40 indicates a state of deep anesthesia [8]. This study assessed the effect of two depths of anesthesia as monitored using Narcotrend, *i.e.*, NTI of 50-59 and 30-39, on POCD in patients after VATS lobectomy.

Material and methods

General information

A total of 73 elderly patients who underwent VATS lobectomy in our hospital during the period of January 2019 to January 2020 were included. Inclusion criteria: (1) elective VATS lobectomy; (2) general anesthesia; (3) age ≥ 65 years; (4) American Society of Anesthesiologists (ASA) 1 or 2; and (5) informed consent was provided by the patients and family members. Exclusion criteria: (1) recent use of sedatives; (2) long-term alcohol consumption; (3) previous history of mental illness; (4) pulmonary ventilatory reserve < 75%; (5) patients with visual or hearing impairment; (6) patients with severe metabolic disease; (7) patients with a primary school education or below; or (8) preoperative Mini-Mental State Examination (MMSE) score < 23 points. The patients were divided into a control group (n=36) and an observation group (n=37). This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

Methods

Venous access was established, and a surgical display was connected monitor variables such as blood pressure, heart rate (HR), and blood oxygen saturation in the operating room. A Narcotrend electroencephalogram (EEG) monitor, which was developed by Monitor Technik in Germany, was connected. The regional cerebral oxygen saturation (rSO_2) level was measured using a monitor of regional cerebral oxygen saturation. Anesthesia induction was performed using an intravenous (bolus) injection of midazolam 0.05 mg/kg + sufentanil 0.4 μg/kg, etomidate 0.3 mg/kg, and rocuronium 0.6 mg/kg. Double-lumen endotracheal intubation was performed, and a Dräger anesthesia machine was attached for volume-control ventilation. The tidal volume for lung ventilation was 9 mL/kg while that for one-lung ventilation was 6 mL/kg. The oxygen concentration was 100%, oxygen flow was 2 L/min, respiratory rate was 12-16/min, respiratory ratio was 1:1.5-2, and partial pressure of end-tidal carbon dioxide was 35-45 mmHg. Intraoperative continuous infusion with 1.5-2.5 mg/(kg·h) propofol, 0.15 μg/(kg·min) remifentanil, and 2 μg/(kg·min) cis-atracurium was performed. The variation of arterial pressure and HR during the surgery was maintained at ±30%. Ephedrine, esmolol, atropine, and other cardio-active drugs were administered during the surgery when necessary. The infusion of cis-atracurium was discontinued 30 minutes before the end of surgery. Postoperative analgesia comprised 2 μg/kg sufentanil, 10 mg tropisetron diluted with 100 mL normal saline infused intravenously at 2 mL/h. The NTI of the control group was maintained at 50-59, whereas that of the observation group was maintained at 30-39 during the surgery.

Evaluation criteria

The following were compared between the two groups: (1) the general characteristics of the surgery including operation time, anesthesia time, intraoperative blood loss, one-lung ventilation duration, urine output, and infusion quantity; (2) the heart period (HP) and mean arterial pressure (MAP) at the preoperative stage (T_1), the one-lung ventilation stage (T_2), 1 hour into the surgery (T_3), the end of one-lung ventilation (T_4), and 2 hours after the surgery (T_5); (3) the propofol dosage, remifentanil dosage, use of vasoactive drugs, sufentanil dosage, and awake to extubation time; (4) the visual analogue scale (VAS) for pain at 6 h, 12 h, 24 h, 36 h, and 48 h, with 0 indicating no pain and 10 indicating unbearable pain; (5) rSO_2 and cerebral oxygen extraction ratio ($CERO_2$, $CERO_2$ = [Arterial oxygen content - venous oxygen content]/arterial oxygen content × 100%) at T_1, T_2, T_3, T_4, and T_5; (6) serum IL-6 and TNF-α levels measured using enzyme-linked immunosorbent assay of 3 mL samples of venous blood that were centrifuged at 3000 rpm for 10 min at T_5, T_6, and T_7; (7) MMSE scores at the preoperative stage and 1 d, 2 d, 3 d, 5 d, and 7 d after surgery; and (8) incidence rates of POCD at 1 d, 2 d, 3 d, 5 d,

Table 1. Comparison of general data from the two groups ($\bar{x}\pm s$, n)

Groups	n	Gender		Average age (years old)	ASA classification		Weight (kg)	Body mass index (kg/m^2)	Surgical side	
		Male	Female		Grade I	Grade II			Left side	Right side
Observation group	37	20	17	70.82±5.11	16	21	65.39±7.22	23.99±1.06	22	15
Control group	36	21	15	71.03±5.96	16	20	66.02±7.68	24.13±1.15	20	16
χ^2/t		0.137		0.162	0.011		0.361	0.541	0.114	
P		0.713		0.872	0.918		0.719	0.590	0.736	

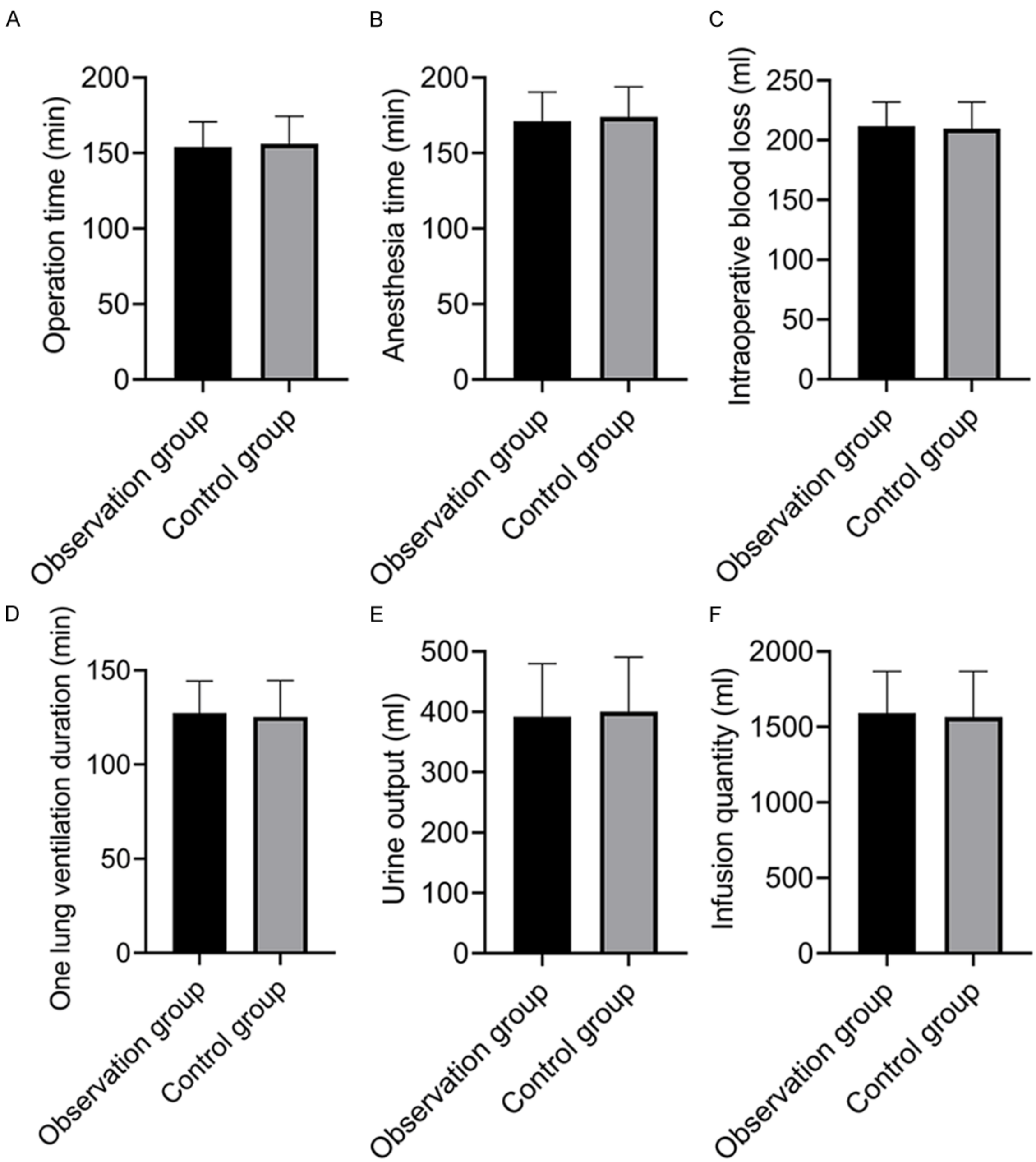

Figure 1. Different depths of anesthesia had little effect on the general characteristics of the surgery. The differences in the operation time (A), anesthesia time (B), intraoperative blood loss (C), one-lung ventilation duration (D), urine output (E), and infusion quantity (F) were not statistically significant between the two groups ($P > 0.05$).

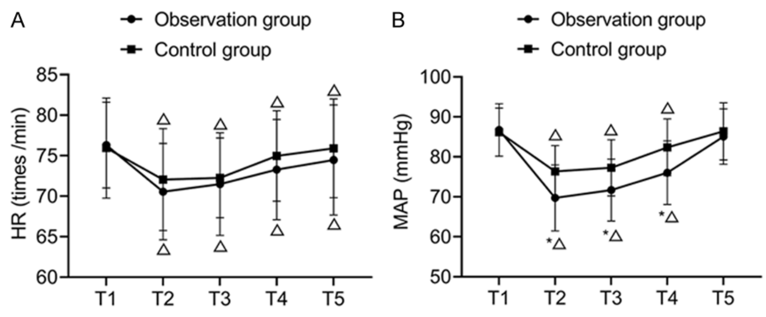

Figure 2. The MAP level in patients was more stable when the NTI was 30-39 as monitored using Narcotrend. The difference in HR (A) at T_1-T_5 between the two groups was not statistically significant (P > 0.05). The levels of MAP (B) at T_2, T_3, and T_4 were higher in the observation group than in the control group (P < 0.05). Note: Compared with the value at same time point in the control group $^*P$ < 0.05; compared with the value at T_1, $^{\Delta}P$ < 0.05.

and 7 d after surgery. The criteria for the diagnosis of POCD were MMSE ≤ 23 points and ≥ 2-point decrease in MMSE scores.

Statistical analysis

The statistical analysis was performed using SPSS 19.0 statistical software. The statistical charts were made using Graphpad Prism 8.2 graphic software. The measurement data were expressed as $\bar{x}$±s and were assessed using the *t*-test. Count data were expressed as % and were assessed using the chi-square test. P < 0.05 indicates statistical significance.

Results

Comparison of general conditions

The differences in baseline data such as sex, age, ASA classification, weight, body mass index, and operative side between the two groups were not statistically significant (P > 0.05) (**Table 1**). The differences in the operation time, anesthesia time, intraoperative blood loss, one-lung ventilation duration, urine output, and infusion quantity were not statistically significant between the two groups (P > 0.05), which suggested little difference between the effects of the two depths of anesthesia at an NTI of 50-59 and 30-39 on general perioperative conditions (**Figure 1**).

The MAP levels in patients were more stable when the NTI was 30-39 as monitored using Narcotrend

The levels of HR and MAP were decreased first, and then were increased during T_1-T_5 in both groups. The levels of MAP at T_2, T_3, and T_4 were higher in the observation group than in the control group (P < 0.05). The difference in HR at T_1-T_5 between the two groups was not statistically significant (P > 0.05). This indicated that the levels of MAP in patients were more stable when the NTI was 30-39 as monitored using Narcotrend (**Figure 2**).

The effect of different depths of anesthesia on the dosage of propofol, remifentanil, vasoactive drugs, sufentanil, and the time from awake to extubation

The propofol dosage was higher and awake to extubation time was longer in the observation group than in the control group (P < 0.05), which suggested that patients with an NTI of 30-39 required a higher dosage of propofol and longer awake to extubation time (**Figure 3**).

Better postoperative pain management at an NTI of 30-39 as monitored using Narcotrend

The VAS scores were increased at 6 h, 12 h, and 24 h after surgery, and were decreased at 36 h and 48 h after surgery. The VAS scores at 6 h and 12 h were lower in the observation group than in the control group (P < 0.05). This suggested that the postoperative pain management in patients after VATS lobectomy was better when NTI was 30-39 as monitored using Narcotrend (**Figure 4**).

Better cerebral oxygen supply at NTI of 30-39 as monitored using Narcotrend

The left and right rSO_2 at T_3-T_4 was higher and the $CERO_2$ was lower in the observation group than in the control group (P < 0.05), which indicated that the cerebral oxygen supply was improved when the NTI was 30-39 as monitored using Narcotrend (**Figure 5**).

Lower levels of serum IL-6 and TNF-α at an NTI of 30-39 as monitored using Narcotrend

The levels of IL-6 and TNF-α were increased at T_3 and were decreased at T_5 in both groups. The levels of serum IL-6 and TNF-α at T_3 and T_5 were lower in the observation group than in the

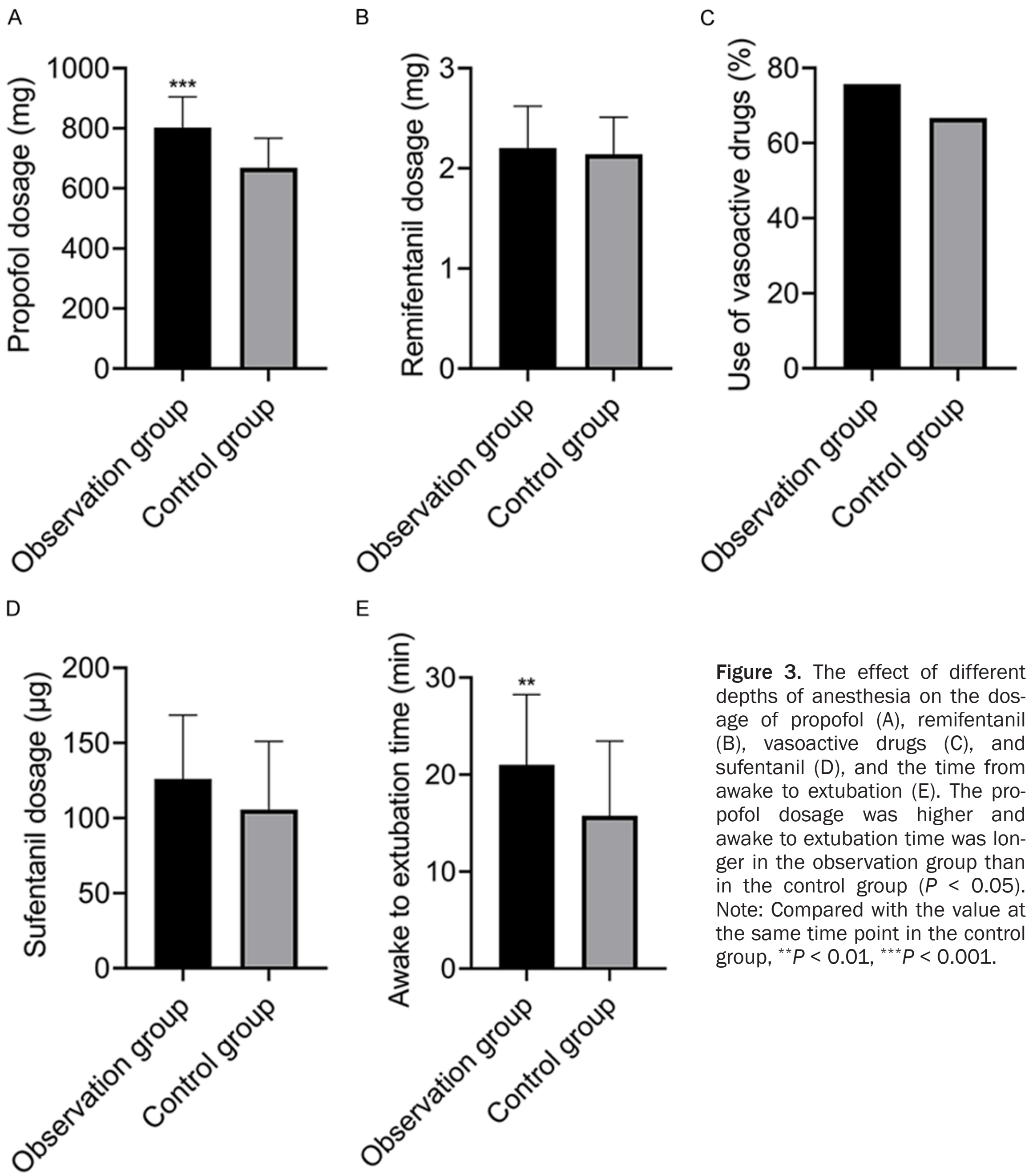

Figure 3. The effect of different depths of anesthesia on the dosage of propofol (A), remifentanil (B), vasoactive drugs (C), and sufentanil (D), and the time from awake to extubation (E). The propofol dosage was higher and awake to extubation time was longer in the observation group than in the control group ($P < 0.05$). Note: Compared with the value at the same time point in the control group, $^{**}P < 0.01$, $^{***}P < 0.001$.

control group ($P < 0.05$). This suggested that the postoperative levels of inflammatory factors were improved when the NTI was 30-39 as monitored using Narcotrend (**Figure 6**).

Lower postoperative MMSE scores at NTI of 30-39 as monitored using Narcotrend and incidence rates of POCD

The MMSE scores at 1 d, 2 d, 3 d, and 5 d after surgery were higher in the observation group than in the control group ($P < 0.05$) (**Figure 7**). The incidence rates of POCD at 1 d, 2 d, and 3 d after surgery were lower in the observation group than in the control group ($P < 0.05$). The difference in incidence rate of POCD at 5 d and 7 d after surgery was not statistically significant ($P > 0.05$) (**Table 2**). These suggested that postoperative MMSE scores and incidence rates of POCD were lower in patients when the NTI was 30-39 as monitored using Narcotrend.

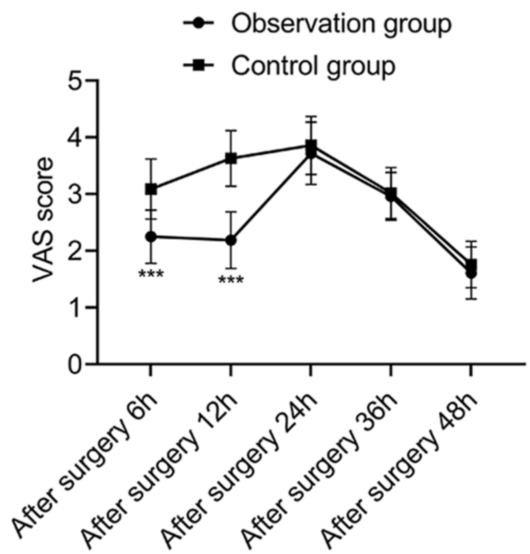

Figure 4. Better postoperative pain management at an NTI of 30-39 as monitored using Narcotrend. The VAS scores at 6 h and 12 h were lower in the observation group than in the control group ($P < 0.05$). Note: Compared with the value at the same time point in the control group, $^{***}P < 0.001$.

Discussion

Previous studies have shown that POCD is common in patients after major cardiac, orthopedic, thoracic, and abdominal operations. POCD is characterized by confusion, anxiety, personality changes, and memory impairment, which affect the postoperative recovery of patients [9, 10]. In VATS lobectomy among elderly patients, one-lung ventilation interferes with respiratory physiology and intraoperative blood loss leads to a reduction of blood volume and hemoglobin, which results in cerebral hypoxia and further increases the risk of POCD [11-13].

Narcotrend monitoring can maintain the depth of anesthesia within a desired range to avoid over- or underdosing of anesthesia [14]. This study showed that the difference in operation time, anesthesia time, intraoperative blood loss, one-lung ventilation duration, urine output, infusion quantity, remifentanil dosage, use of vasoactive drugs, and sufentanil dosage between anesthetic depths of an NTI of 50-59 and an NTI of 30-39 was not statistically significant, whereas patients anesthetized at an NTI of 30-39 had a higher propofol dosage and longer awake to extubation time. A higher dosage was used in the surgery to maintain

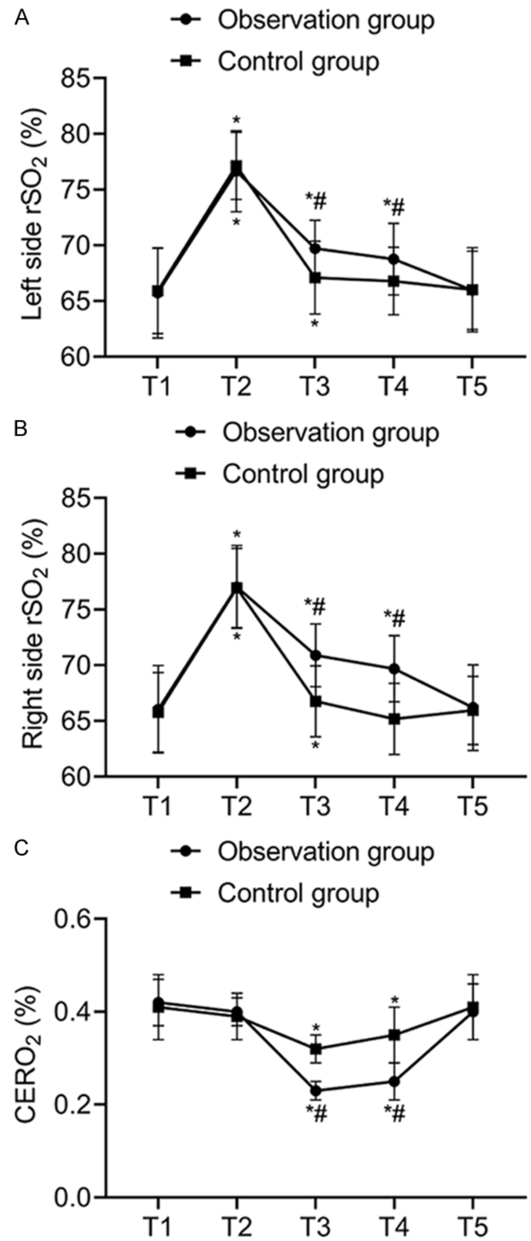

Figure 5. Better cerebral oxygen supply at NTI of 30-39 as monitored via Narcotrend. The left (A) and right (B) rSO_2 at T_3-T_4 was higher and the $CERO_2$ (C) was lower in the observation group than in the control group ($P < 0.05$). Note: Compared with value at T_1, $^{*}P < 0.05$; compared with the value at the same time point in the control group, $^{\#}P < 0.05$.

deeper anesthesia, which further affected the duration of postoperative recovery. Moreover, from the hemodynamic perspective, the levels of HR and MAP were decreased first and then were increased at each time point after the end of surgery to 24 hours after surgery. The difference in HR between the two groups was not

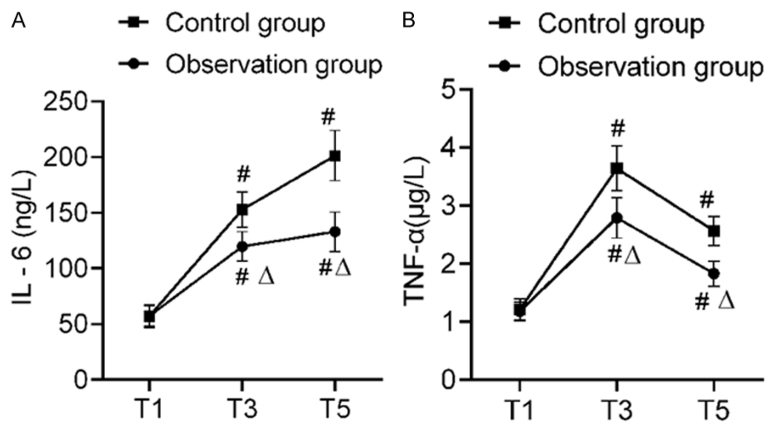

Figure 6. Lower levels of serum IL-6 and TNF-α at NTI of 30-39 as monitored via Narcotrend. The levels of serum IL-6 (A) and TNF-α (B) at T_3 and T_5 were lower in the observation group than in the control group ($P < 0.05$). Note: Compared with value at T_1, $^{*}P < 0.05$; compared with value at the same time point in the control group, $^{\#}P < 0.05$.

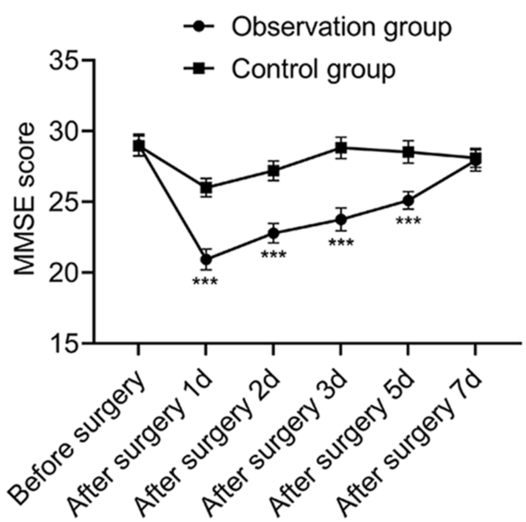

Figure 7. Lower postoperative MMSE scores at an NTI of 30-39 as monitored using Narcotrend. The MMSE scores at 1 d, 2 d, 3 d, and 5 d after surgery were higher in the observation group than in the control group ($P < 0.05$). Note: Compared with the value at the same time point in the control group, $^{***}P < 0.001$.

statistically significant, which suggested that the different depths of anesthesia had similar effects on the HR of patients. The MAP at T_2, T_3, and T_4 was lower in the observation group, which suggested that deeper anesthesia could lead to lower intraoperative levels of MAP. The study outcomes indicated that the VAS scores at 6 h and 12 h after surgery were lower in the observation group, whereas the difference in VAS scores at 24 h, 36 h, and 48 h after surgery between the two groups was not statistically significant. The reasons could be that higher doses of anesthesia were used in the observation group and the effects of anesthesia did not completely disappear, thus reducing the pain in the early postoperative stages. As the effects of anesthesia subsided over time, reported pain was no longer significantly different between the two groups [15, 16].

Relevant studies showed that the incidence rate of POCD was closely correlated with intraoperative abnormalities in cerebral oxygen metabolism [17, 18]. The rSO_2 and $CERO_2$ are important indicators of cerebral oxygen metabolism; a decrease in the rSO_2 level suggests an imbalance between regional cerebral O_2 supply and consumption and cerebral hypoxia, whereas an increase in $CERO_2$ suggests an increase in cerebral O_2 consumption but a decrease in cerebral O_2 supply, and vice versa [19, 20]. The differences in rSO_2 and $CERO_2$ between the two groups were not statistically significant; the rSO_2 in the left and right sides at T_3-T_4 was higher and the $CERO_2$ was lower in the observation group. Possible reasons for this include that deeper anesthesia during VATS lobectomy reduced the cerebral metabolic rate in patients, thereby reducing cerebral oxygen consumption, improving intraoperative rSO_2, and decreasing $CERO_2$. Operation, anesthesia, pain, and other stimuli could disrupt the balance of pro- and anti-inflammatory cytokines, causing the system to release a large amount of IL-6 and TNF-α [21]. Il-6 is a pro-inflammatory cytokine that can activate the immune system, increase expression in endothelial cells, and inhibit the differentiation and apoptosis of regulatory T cells, thereby promoting inflammation [22]. TNF-α is an important mediator during the early stages of inflammation, which can promote the release of inflammatory mediators and other inflammatory cytokines, triggering an inflammatory cascade [23]. In this study, the levels of IL-6 and TNF-α were increased at T_3 and were decreased at T_5 in both groups, and

Table 2. Comparison of the incidence rates of POCD in two groups [n (%)]

Groups	n	1 day after surgery	2 day after surgery	3 day after surgery	5 day after surgery	7 day after surgery
Observation group	37	7 (18.92)	2 (5.41)	0 (0.00)	0 (0.00)	0 (0.00)
Control group	36	17 (47.22)	12 (33.33)	7 (19.44)	2 (5.56)	0 (0.00)
χ^2		6.234	9.182	5.873	2.114	0.000
P		0.010	0.002	0.005	0.146	1.000

the levels of serum IL-6 and TNF-α were higher in the observation group. One reason for this could be that multiple factors, including VATS lobectomy, anesthesia, and one-lung ventilation, stimulated the body to release large amounts of inflammatory cytokines. Deeper anesthesia could reduce the inflammatory cascade triggered by noxious stimuli and the release of IL-6 and TNF-α triggered by external pain stimuli, thereby decreasing the level of inflammatory cytokines in patients during the perioperative period [24]. MMSE scores at 1 d, 2 d, 3 d, and 5 d after surgery were higher in the observation group and the incidence rate of POCD at 1 d, 2 d, and 3 d after surgery was lower in the observation group. This may be because deeper anesthesia could improve rSO_2 and $CERO_2$, decrease cerebral oxygen consumption, and improve cerebral oxygen metabolism, thereby reducing the risk of postoperative POCD [25].

In conclusion, an anesthetic depth of an NTI of 30-39 as monitored using Narcotrend could improve cerebral oxygen metabolism, inhibit inflammatory reactions, and reduce the incidence of POCD in patients after VATS lobectomy. However, due to limitations including the small sample from a single center, further studies should be conducted with larger sample sizes and scope of indications to detect the optimal anesthetic depth for elderly patients undergoing VATS lobectomy.

Disclosure of conflict of interest

None.

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