Effects of Total Intravenous Anesthesia With Etomidate and Propofol on Postoperative Cognitive Dysfunction

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Received October 5, 2022
Accepted February 9, 2023

Summary

Increased incidence of postoperative cognitive dysfunction (POCD) is observed in elderly patients underwent intravenous anesthesia (TIVA) with endotracheal intubation. Modulation of anesthetics compatibility may reduce the severity of POCD. Elderly patients scheduled for TIVA with endotracheal intubation were randomly divided into the control group (1.00-2.00 mg/kg propofol) and the etomidate and propofol combination group (1.00-2.00 mg/kg propofol and 0.30 mg/kg etomidate). Serum cortisol, S100β, and neuron-specific enolase (NSE), interleukin (IL)-6, and IL-10 were monitored during or after the operation. Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were utilized to assess the severity of POCD. 63 elderly patients in the etomidate and propofol combination group and 60 patients in the control group were enrolled, and there was no significant difference in gender, American Society of Anesthesiologists (ASA) physical status, surgical specialty, intraoperative blood loss, and operation time between the two groups. Significantly increased serum cortisol, S100β, NSE, IL-6, and reduced MMSE and MoCA scores were detected in the control group at different time points after the operation (0-72 h post operation) when compared to those before the operation. Similar trends for these observed factors were found in the etomidate and propofol combination group. In addition, the etomidate and propofol combination group showed better effects in reducing the serum levels of cortisol, S100β, NSE, IL-6, and increasing the MMSE and MoCA scores when compared to the control group. The present study demonstrates that the combination of propofol with etomidate could alleviate POCD in elderly patients underwent TIVA with endotracheal intubation anesthesia.

Key words

Etomidate • Propofol • Postoperative cognitive dysfunction • Total intravenous anesthesia

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Introduction

Total intravenous anesthesia (TIVA), with a combination of propofol and remifentanil, has attractive advantages over traditional inhalation anesthesia with regard to rapid onset, short duration of action, fast recovery, anticonvulsive potential, minimum hemodynamic fluctuation, and improved postoperative cognitive dysfunction (POCD) [1,2]. TIVA with endotracheal intubation is advocated for elderly patients to maintain optimum mechanical ventilation [3]. In comparison, endotracheal intubation can augment hemodynamic fluctuation and induce strong systemic stress response and neuroinflammation, which can increase the incidence of POCD [4]. The progressive hypomnesia, deteriorating cognitive function, and personality change will significantly affect the quality of life and increase morbidity and mortality [5].

Although the mechanisms underlying POCD remain elusive, the anesthetics utilized will greatly affect the incidence of POCD in elderly patients [6]. It is necessary to modulate the compatibility of anesthetics to reduce the impact of POCD in elderly patients. Etomidate is an intravenous induction agent typically used for rapid sequence intubation and induction of general anesthesia, especially for patients with marginal blood pressure, with the advantage of maintenance of hemodynamic and cardiovascular stability [7-9], which is also indicated for anesthesia maintenance in short operative procedures [10].

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Whether etomidate could be combined with propofol for sedation and maintenance anesthesia in elderly patients underwent TIVA with tracheal intubation to diminish the severity of POCD is investigated in this study.

Methods and Materials

Patient samples

The physical status classification system of American Society of Anesthesiologists (ASA) was utilized to classify the elderly patients, and patients with ASA I classification (normal healthy), ASA II classification (mild systemic disease), and ASA III classification (severe systemic disease, no constant threat to life) were included in this investigation. Anesthesia induction was performed in the course of surgery for TIVA with intravenous injection of remifentanil (0.05-1.00 μg/kg), midazolam (0.04 mg/kg), propofol (1.00-2.00 mg/kg), and cisatracurium (0.10-0.15 mg/kg). After the onset of muscle relaxation, endotracheal intubation was performed, and an anesthesia machine (IntelliSave AX700, Philips) was connected to control breathing (tidal volume 6-8 ml/kg, inspiratory-to-expiratory ratio of 2:1, respiratory rate 12-15 times/min). The participants were further divided into the control group (1.00-2.00 mg/kg propofol) and the ETO group (the etomidate and propofol combination group, 1.00-2.00 mg/kg propofol, followed by 0.30 mg/kg etomidate) according to the random number table method. During the maintenance period of general anesthesia, the dosage of anesthetics was adjusted according to heart rate (HR), blood pressure, and surgical stimulation intensity. The HR and mean arterial pressure (MAP) were kept stable (within ± 20 % deviation before operation), bispectral index (BIS) indicating the depth of anesthesia was maintained between 40-60, and postapneic end-tidal carbon dioxide pressure (PETCO2) was maintained between 35-45 mmHg. After the patients' consciousness and spontaneous breathing recovered and pulse oximetry (SpO_2) remained more than 95 %, the tracheal tube was removed.

70 cases were included in each group, and 7 cases in the etomidate and propofol combination group and 10 cases in the control group were respectively terminated during the study. All participants provided demographic and clinical characteristics and written consent. This study was approved by the Ethical Committee of Wuxi No.2 People's Hospital, Nanjing Medical University, in compliance with the principles of the Helsinki Declaration II, the approval number is 2012XD/WS.

Inclusion criteria were as follows: Age 60-85 years; Preoperative blood coagulation and platelet examination were normal; No analgesic or sedative drugs were used one day before the operation; No allergy to the narcotic drugs used in this study; Meet the requirements of TIVA with endotracheal intubation; Junior high school degree or above, able to complete questionnaire investigation.

Exclusion criteria were as follows: Participants with central nervous system diseases or mental diseases; Participants who take drugs that affect the nervous and psychiatric system for a long time; Participants with severe impairment of vision, hearing, and language expression; Participants with severe brain tumor or brain surgery; Participants complicated with severe liver, kidney, and metabolic dysfunction.

Termination (exclusion) criteria were as follows: Participants who request to withdraw; Participants with severe adverse reactions; The cumulative time of blood pressure < 90 / 60 mmHg during operation is greater than 15 min, or the cumulative time of blood pressure > 160 / 110 mmHg is greater than 15 min; Participants unable to complete or refuse to complete the test; Shock and bradycardia during operation.

Cognitive function assessment

Mini-Mental State Examination (MMSE) [11] and Montreal Cognitive Assessment (MoCA) [12] were measured during an in-center health assessment. On completing the assessment, participants were given a score from 0 to 30, with higher scores representing better cognitive performance.

Enzyme-linked immunosorbent assay

Peripheral blood serum was taken from the antecubital vein during the operation. The serum S100β, neuron-specific enolase (NSE), interleukin (IL)-6, and IL-10 were measured with ELISA kits (eBioscience, San Diego, CA, USA) before the operation (T0), at the end of the operation (T1), 24 hours after the operation (T2), 48 hours after the operation (T3), and 72 hours after the operation (T4). Cortisol Competitive Human ELISA Kit (Thermo Scientific, Waltham, MA) was utilized to detect cortisol according to the manufacturer's instructions. All samples and standards were measured with a SpectraMax M5 microplate reader (Molecular Devices, Sunnyvale, CA) at a wavelength of 450 nm.

Statistical analysis

Anderson-Darling test, D'Agostino & Pearson test, Shapiro-Wilk test, Kolmogorov-Smirnov test were used for test the normality of the data before analysis, and it was shown that the data was in accordance with the normal distribution. Chi-square test or Fisher's exact test was utilized to assess the difference between groups. Two-way ANOVA followed by Tukey's multiple comparisons tests. Significance level was set as p-value < 0.05. All statistical analyses were performed with GraphPad Prism (GraphPad Software, Inc., SanDiego, CA, USA).

Results

Demographic and clinical characteristics

63 patients in the etomidate and propofol combination group (age, 70.1±6.2 years old) and 60 patients in the control group (age, 68.8±6.7 years old) were recruited. Through comparison, we found that there was no significant difference in gender, ASA scale, surgical specialty, intraoperative blood loss, and operation time between the two groups (Table 1).

Table 1. Demographic and clinical characteristics of the study participants.

Characteristics		**Study group**		
		ETO (n=63)	**Control (n=60)**	**p**
Gender	Male	34 (53.9 %)	35 (58.3 %)	0.717
	Female	29 (46.1 %)	25 (41.7 %)	
Age (years)		70.1±6.2	68.8±6.7	0.216
ASA scale	I	19 (30.2 %)	20 (33.3 %)	0.699
	II	35 (55.5 %)	29 (48.3 %)	
	III	9 (14.3 %)	11 (18.4 %)	
Surgical specialty	Orthopedics	16 (25.4 %)	14 (23.3 %)	0.822
	Cardiovascular	13 (20.6 %)	16 (26.7 %)	
	Gastrointestinal	19 (30.2 %)	15 (25 %)	
	Urology	10 (15.9 %)	12 (20 %)	
	Gynecology	5 (7.9 %)	3 (5 %)	
Operation time (min)		168.4±21.3	173.6±22.7	0.418
Blood loss ml)		196.2±44.9	204.7±48.3	0.275

Values were expressed as n (percentage, %) or mean ± SD. p values were derived from Mann–Whitney test. Chi-square test or Fisher's exact test was used for assessing distribution of observations or phenomena between different groups. ASA: American Society of Anesthesiologists; ETO: etomidate.

Etomidate combing with propofol anesthesia alleviates the stress response

Endotracheal intubation can dramatically produce a strong stress response on patients under general anesthesia with alteration in hemodynamics, which can be indicated by up-regulated cortisol [13]. We found that the concentration of cortisol in the control group increased significantly at the end of the operation (T1) when compared with that before the operation (T0) ($p < 0.001$), indicating that the patients had a strong stress response during the operation. It was worth noting that the concentration of cortisol 24 hours after the operation (T2) was still higher than that before the operation (T0) ($p<0.01$) and returned to normal level 48 hours after the operation (T3). While in the propofol and etomidate combined anesthesia group, the serum cortisol concentration returned to the preoperative level 24 hours after the operation (T2) (Fig. 1). Importantly, the serum cortisol concentrations were significantly lower in the propofol and etomidate combined anesthesia group when compared to those in control group at T1 and T2. All of these indicated that the additional combination of etomidate with propofol would decrease endotracheal intubation-induced stress response, as shown with diminished cortisol levels.

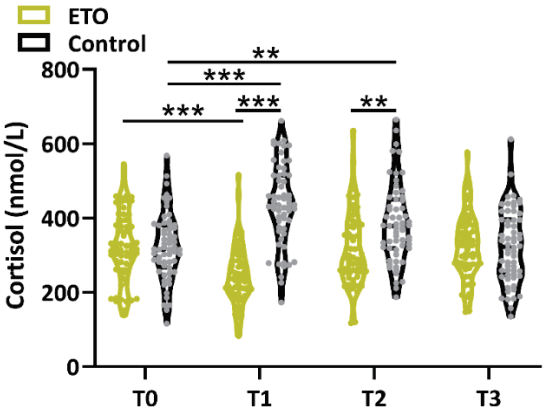

Fig. 1. Comparisons of serum cortisol between the two groups before (T0), at the end of the operation (T1), 24 hours after the operation (T2), and 48 hours after the operation (T3). Violin plots showing all the data. n = 63 for the etomidate and propofol combination group (ETO group) and n = 60 for the propofol group (control group). $^{**}p < 0.01$, $^{***}p < 0.001$. Two-way ANOVA followed by Tukey's multiple comparisons tests.

Etomidate combing with propofol anesthesia improves postoperative cognitive dysfunction

MMSE and MoCA screening tests for postoperative cognitive impairment were performed in elderly patients. In both control group and propofol and etomidate combined anesthesia group, MMSE and MoCA scores were significantly reduced after the operation (T2 and T4) when compared to those before operation. Compared with the control group, propofol and etomidate combined anesthesia has advantages in reducing postoperative cognitive impairment 24 hours after the operation (T2) and 72 hours after the operation (T4), as indicated by the increase of MMSE (Fig. 2A) and MoCA scores (Fig. 2B).

S100β and NSE are related to cognitive impairment, especially early cognitive dysfunction [14,15]. Up-regulated serum S100 β (Fig. 3A) and NSE (Fig. 3B) could be detected 24 hours after the operation (T2) and 72 hours after the operation (T4) when compared with those before the operation (T0) in both groups. Compared with propofol anesthesia, diminished S100β (Fig. 3A) and NSE (Fig. 3B) expression in the serum could be detected 24 hours after the operation (T2) and 72 hours after the operation (T4) in the propofol and etomidate combined anesthesia. These results demonstrated that etomidate combing with propofol anesthesia could improve the impaired cognitive function.

Etomidate combing with propofol anesthesia diminishes the inflammation

Inflammatory cytokines, including tumor necrosis factor (TNF) α, IL-6, and IL-10 in the blood, are associated with cognitive impairment [16]. IL-6 was significantly up-regulated at the end of the operation (T1) and down-regulated 72 hours after the operation (T4) in both groups (Fig. 4A) when compared to those before the operation. At the same time, IL-10 was significantly up-regulated at the end of the operation (T1) and maintained until 72 hours after the operation (T4) in the the propofol and etomidate combined anesthesia group (Fig. 4B). Diminished IL-6 (Fig. 4A) and up-regulated IL-10 (Fig. 4B) expression in the serum could be detected at the end of the operation (T1) and 72 hours after the operation (T4) in the propofol and etomidate combined anesthesia group compared with those the propofol anesthesia group.

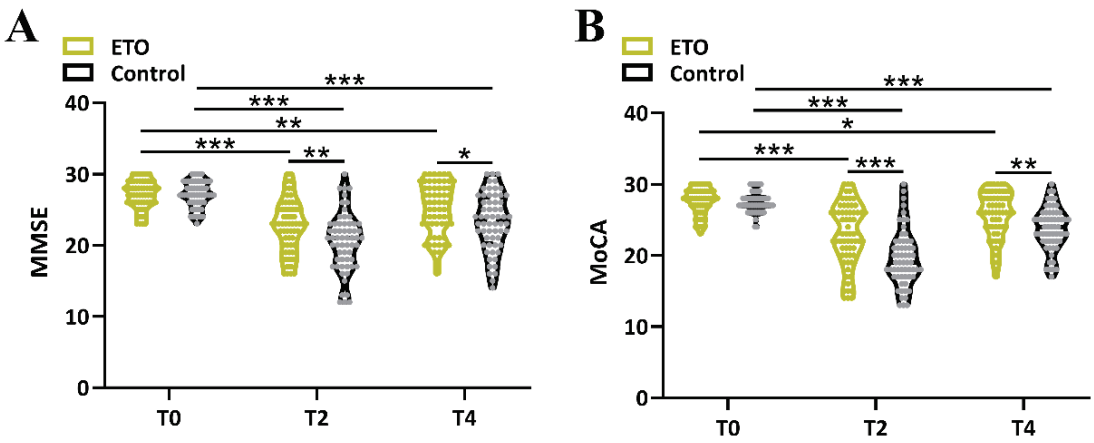

Fig. 2. Comparisons of mini-mental state examination (MMSE, **A**) and montreal cognitive assessment (MoCA, **B**) between the two groups before (T0), 24 hours after the operation (T2), and 72 hours after the operation (T4). Violin plots showing all the data. n = 63 for the etomidate and propofol combination group (ETO group) and n = 60 for the propofol group (control group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Two-way ANOVA followed by Tukey's multiple comparisons tests.

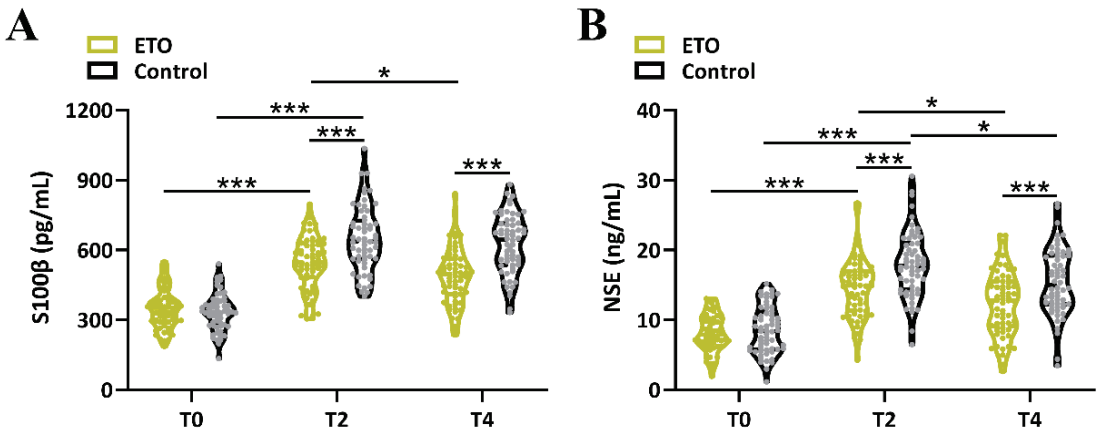

Fig. 3. Comparisons of serum S100β (**A**) and NSE (**B**) between the two groups before (T0), 24 hours after the operation (T2), and 72 hours after the operation (T4). Violin plots showing all the data. n = 63 for the etomidate and propofol combination group (ETO group) and n = 60 for the propofol group (control group). *p < 0.05, **p < 0.01, ***p < 0.001. Two-way ANOVA followed by Tukey's multiple comparisons tests.

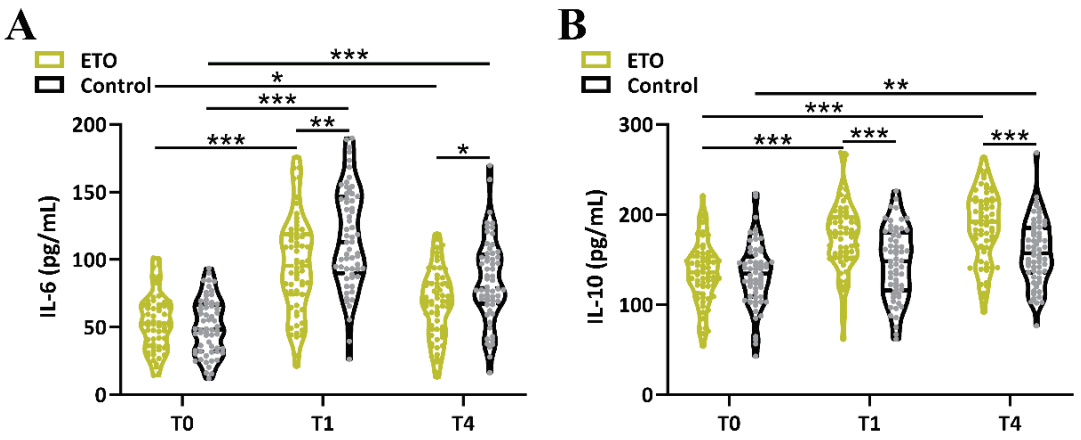

Fig. 4. Comparisons of serum IL-6 (**A**) and IL-10 (**B**) between the two groups before (T0), at the end of the operation (T1), and 72 hours after the operation (T4). Violin plots showing all the data. n = 63 for the etomidate and propofol combination group (ETO group) and n = 60 for the propofol group (control group). *p < 0.05, **p < 0.01, ***p < 0.001. Two-way ANOVA followed by Tukey's multiple comparisons tests.

Discussion

Many factors, such as age, type of surgery, and intraoperative anesthesia, may contribute to the development of POCD [17, 18]. In this investigation, only participants with ASA I, II, III stage without severe comorbidity are included, and comparable demographic and clinical characteristics are observed in the enrolled participants. The combined propofol and etomidate anesthesia has unique characteristics to improve impaired cognitive function as indicated by up-regulated MMSE and MoCA score and diminished serum S100β and NSE release. At the same time, tracheal intubation induced systemic stress and inflammation indicated by the up-regulated cortisol, IL-6, and down-regulated IL-10, which could be reversed by the combined propofol and etomidate anesthesia. All of these results demonstrate the possibility of utilizing propofol and etomidate in elderly patients underwent TIVA with tracheal intubation to improve POCD.

Anesthesia and surgery may induce central nervous system inflammation and neuronal apoptosis with increased pro-inflammatory cytokines, such as IL-6 and TNF α, and down-regulated regulatory cytokine IL-10, which plays a vital role in the development and pathogenesis of POCD [19, 20]. As an acidic calcium-binding protein, S-100 proteins are damage-associated molecular pattern molecules to induce the following inflammation process [21], which can be considered as biomarkers of acute brain injury and pro-inflammation [6]. NSE can function as an intracytoplasmic enzyme, and the elevated concentration in the serum can indicate

neuron damage [22]. The elevated release of S100β, NSE, and IL-6 may lead to the severity of POCD.

The anesthesia effect of etomidate may be attributed to the interaction with γ-aminobutyric acid type A receptor, which can inhibit adrenocortical function through the suppression of 11β-hydroxylase to produce corticosterone, cortisol, and aldosterone [23]. In addition, etomidate can activate the central α2-receptors as an agonist to maintain vascular tone and myocardial contractility [24]. It is worth noting that etomidate can decrease oxidative stress and inflammation in rats with myocardial ischemic reperfusion injury with diminished IL-10 in both serum and myocardial tissues [25]. These reports indicate that the alleviation of POCD may be attributed to the combination of etomidate.

There are some limitations that should be noted here. The sample sizes investigated are relatively small in a single center, which might introduce bias that obfuscates the clinical meaning of the combined use of propofol and etomidate, further multi-center investigations on a large scale of elderly patients underwent TIVA with tracheal intubation are needed to confirm the present results. The short-term POCD assessment is deciphered in this investigation, and the long-term outcomes should be investigated in the future.

All in all, TIVA with tracheal intubation will induce postoperative cognitive dysfunction in the elderly patients, which could be alleviated by the anesthesia of etomidate combing with propofol.

Conclusions

Our work systematically studied the protective effect of etomidate combing with propofol anesthesia on postoperative early cognitive impairment in elderly patients underwent TIVA with tracheal intubation, and revealed its possible mechanism from the comprehensive analysis of stress levels, serum S100β and NSE concentrations, and serum inflammation levels. These findings could provide guildance for the anesthesia for the elderly patients underwent TIVA with tracheal intubation.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This study was approved by the Ethical Committee of Jiangnan University Medical Center, JUMC, in compliance with the principles of the Helsinki Declaration II, the approval number is 2012XD/WS.

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