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Effects of spinal-epidural anesthesia combined with intravenous etomidate on adrenocortical and immune stress in elderly patients undergoing anorectal surgery: A retrospective analysis

Yangyi Li[1*], Jiangyan Wu[1], Chengbo Chen[2], Changsheng Su[1]

[1]Department of Anesthesiology, Quanzhou First Hospital Affiliated to Fujian Medical University, Fujian, China;

[2]Department of Cardiology, Quanzhou First Hospital Affiliated to Fujian Medical University, Fujian, China.

[*]**Corresponding author:** Yangyi Li, Email: angie-1978@fjmu.edu.cn

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ABSTRACT

The management of anesthesia in elderly patients undergoing surgery presents unique challenges, particularly in mitigating stress responses and ensuring stability. Etomidate may alleviate adrenocortical and immune stress. This study aims to investigate the anesthetic effects of combined spinal-epidural anesthesia (CSEA) supplemented with etomidate during anorectal surgery in elderly patients. The medical records of forty-nine cases treated with CSEA and etomidate (ETO group) and forty-eight cases treated with CSEA alone (control group) were reviewed and analyzed. All patients received ropivacaine hydrochloride for anesthesia, with the ETO group additionally receiving an infusion of etomidate for sedation. Parameters such as arterial blood gas, visual analog scale (VAS), Ramsay sedation scale (RSS), serum cortisol and norepinephrine levels, pro-inflammatory cytokines, and lymphocyte ratios were assessed at different time points. Compared to the control group, the ETO group showed increased mean arterial pressure, decreased heart rate, and elevated arterial SpO_2 30 minutes after anesthesia. The ETO group also had higher RSS scores, lower VAS scores, and reduced serum cortisol and norepinephrine levels. Additionally, decreased levels of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-8, were observed, along with an increase in the regulatory cytokine IL-10. An increased proportion of CD4+ T cells and a higher CD4/CD8 ratio were also noted. This study demonstrates the benefits of using etomidate to mitigate adrenocortical and immune stress in elderly patients undergoing anorectal

surgery.

Keywords: Combined spinal-epidural anesthesia (CSEA), etomidate, anorectal surgery.

INTRODUCTION

Anorectal surgery is recommended for proctologic disorders affecting the anus, rectum, and pelvic floor [1, 2]. Proctologic disorders are highly prevalent (4-5%) and cause significant morbidity and mortality [3, 4]. Elderly patients are more likely to have concomitant diseases, such as pulmonary and cardiovascular comorbidities, diabetes mellitus, and hyperlipidemia, which can increase the perioperative risk and the higher requirements for anesthesia. Combined spinal-epidural anesthesia (CSEA) is recommended for elderly patients during anorectal surgery to alleviate the stress induced by the operation. CSEA is a relatively new regional anesthesia technique, that includes an initial subarachnoid injection, following epidural catheter placement, and subsequent epidural administration to achieve a controlled anesthesia level and selective segmental block [5-7].

Etomidate has the unique characteristics of hemodynamic stability and minimal respiratory depression among the rapid-onset induction agents and provides a wider margin of safety than barbiturates or propofol [8]. In general anesthetic induction, etomidate has been utilized for patients undergoing cardiac surgery or with poor cardiac function [9]. On the other hand, etomidate anesthesia shows little influence on the immune functions of infectious shock patients with a low incidence of adverse reactions [10]. Theoretically, etomidate can interact with adrenal steroidogenesis enzymes of steroid 11-beta-hydroxylase, which converts 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. A meta-analysis suggests that intensivists should anticipate the need for glucocorticoid supplementation after etomidate in those with severe critical illness and in those with acute deterioration of vital signs [11]. These findings indicate that supplementary utilization of etomidate might have the potential to alleviate adrenocortical stress and immune stress during anorectal surgery in elderly patients.

The current study aims to evaluate the anesthetic effects of CSEA supplemented with etomidate during anorectal surgery in elderly patients.

METHODS AND MATERIALS

Patient samples

Elderly patients who underwent anorectal surgery in Quanzhou First Hospital Affiliated with Fujian Medical University from February 1st, 2019 to February 1st, 2020 were reviewed and retrospectively analyzed in this study. Two groups of patients were analyzed. One group was the patients with traditional CSEA treatment (control group), and another group was the patients with the treatment of etomidate combined with CSEA (ETO group). The sample size was calculated using established statistical power analysis. Age matching and disease type matching were utilized as baseline information between different groups. Visual Analog Scale (VAS) and Ramsay sedation scale (RSS) were utilized as the primary outcome indicators. Secondary outcome indicators included arterial pressure, heart rate, blood oxygen saturation, stress indicators, and immune function indicators. Differences in VAS between the two groups were divided by the standard deviation to determine the standardized effect size, and 5% was used as the significance level in the Mann-Whitney test and 90% power.

Inclusion criteria: age > 60 years old; who met the diagnostic criteria of anorectal diseases and surgical indications; who met the American Society of Anesthesiologists (ASA) physical status classification (I-III).

Exclusion criteria: having contraindications to anesthesia; abnormal coagulation function; severe cardiovascular and cerebrovascular diseases; abnormal immune function; organ dysfunction or malignant tumor; the cumulative time of blood pressure < 90 / 60 mmHg during the operation was greater than 15 min, or the cumulative time of blood pressure > 160 /110 mmHg was greater than 15 min; shock and bradycardia during operation; with missing statistics data. The research was designed according to the Specification for Reporting Observational Studies (STROBE), which was also approved by the Ethical Committee of Quanzhou First Hospital affiliated to Fujian Medical University.

Anesthesia procedure

In the central operating room, the Datex-Ohmeda S/5 Monitor was used to monitor the SpO2, non-invasive blood pressure, and electrocardiogram. Oxygen inhalation (oxygen flow rate of 2 l/min) was performed for 5 min, epidural puncturing was performed in L2 to L4 intervertebral space, and then lumbar puncture was carried out with puncture needles.

After confirming cerebrospinal fluid flow, 1 ml of ropivacaine hydrochloride (100 mg/10 mL, Zhuhai Rundu Pharmaceutical Co., Ltd., China) and 1 ml of glucose (10 g/100 mL) was infused for 10 s. After withdrawing the needles, tubes were inserted in the epidural space to facilitate further injection. The lateral decubitus position was adopted to adjust the anesthesia level.

In the ETO group, 0.3 mg/kg/h etomidate (Guangzhou Baiyunshan Mingxing Pharmaceutical Co., Ltd., China) was slowly intravenously injected before the skin incision. After the conjunctival reflex disappeared, the patients were given 0.1 mg/kg/h etomidate intravenously. Time course (before the anesthesia, T0; 30 min after the anesthesia, T1; after the operation, T2; 1 hour after the operation, T3; 12 hours after the operation, T4; 24 hours after the operation, T5; 72 hours after the operation, T6) analysis of mean arterial pressure (MAP), heart rate (HR), and arterial SpO2 were monitored. The effectiveness of spinal anesthesia for anorectal surgery: the surgical pain completely disappeared, the abdominal muscles showed good relaxation, and the surgery was successfully completed.

Postoperatively, a patient-controlled analgesia pump was connected to the epidural catheter. The medication dosage was controlled according to the patients' pain condition. The loading dose was 5 mL. Background infusion rate was 2 mL/h. Patient-controlled bolus dose was 0.5 mL per activation, with a lockout interval of 15 minutes. The analgesic mixture consisted of morphine 4 mg + ropivacaine 100 mg diluted with saline to 100 mL. Both groups used identical postoperative analgesia pump conditions.

Sedative and analgesic effects

VAS with 100 mm horizontal lines to indicate the severity of pain (0 to 10 points) and RSS (1, anxious and agitated or restless, or both; 2, co-operative, oriented, and tranquil; 3, responds to commands only; 4, brisk response to a light glabellar tap or loud auditory stimulus; 5, sluggish response; 6, no response) were utilized to assess analgesic and sedative effects as indicated in previous reports [12, 13]. The evaluation of sedative and analgesic effects were performed 1 h after the operation, 24 h after the operation, and 72 h after the operation.

Adrenocortical stress assessment

The blood sample was collected in BD Vacutainer® SST™ Venous Blood Collection Tube from the antecubital vein, aseptically through venipuncture, at the time course of T0, T1, and T5. The levels of norepinephrine were detected with high-performance liquid chromatography (3H-NE, Tiangen Corp., Beijing, China). The levels of cortisol were measured by radioimmunoassay as indicated by previous reports [14, 15].

Immune stress assessment

The interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-8, and IL-10 levels were measured at the time course of T0, T1, and T5 in the serum of the patients. PBMCs EasySep Direct Human PBMC Isolation Kit (StemCell) was utilized to isolate peripheral blood mononuclear cells (PBMCs), which were further incubated with anti-CD4-Pacific Blue antibody and anti-CD8-APC-Cy7 antibody (Invitrogen, Karlsruhe, Germany) for 20 min at 4°C in the dark. The staining cells were measured with an LSR-II flow cytometer (Becton Dickinson).

Ethical statement

The study was approved by the Ethical Committee of Quanzhou First Hospital affiliated to Fujian Medical University. The study was performed in strict accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

Statistical analysis

The sample size was calculated using established statistical power analysis. Differences between each compared treatment group were divided by the standard deviation to determine the standardized effect size and 5% was used as significance level. Then the minimum required sample size was calculated. The Shapiro-Wilk test and Kolmogorov-Smirnov test were used to test the normality of data before analysis. When at least one of these tests indicates that both groups of data followed a normal distribution, they were considered to meet the normality assumption. Values were expressed as mean ± standard deviation (SD). p values were derived from the Mann-Whitney test. The chi-square test or Fisher's exact test was used for assessing the distribution of observations or phenomena between different groups. The significance level was set as a P value less than 0.05. All statistical analyses were performed using GraphPad Prism (GraphPad Software, Inc.).

RESULTS

Comparison of baseline data

A total of 49 cases in the ETO group and 48 cases in the control group were included in this study. The control group was matched for gender, age, ASA scale, surgical specialty, and complicating disease with the ETO group (Table 1). The postoperative time of recovery in the ETO group was 6.8 ± 2.1 min, and the postoperative time of recovery in the control group was 7.2 ± 2.6 min. There was no significant difference between the two groups in the postoperative time of recovery ($P = 0.105$). It was worth noting that there was no significant difference between postoperative nausea and vomiting (PONV), inflammation, and hospital length of stay (LOS) between the two groups.

Etomidate maintains hemodynamic stability

Abnormal MAP, HR, and SpO2 were observed during the operation procedure in both groups, consistent with the previous observation that the operation will affect patients' normal oxygenation and hemodynamics [16]. A significant difference in MAP, HR, and SpO2 was observed 30 minutes after anesthesia in the ETO group compared with the control group (Table 2). In other words, ETO could induce decreased heart rate, higher blood oxygen saturation, and higher mean arterial pressure when compared with CSEA at T1 time. In contrast, no significant difference in heart rate, higher blood oxygen saturation, and higher mean arterial pressure was observed in T2 and T5 times. All of these indicated that an early stage of hemodynamic stability could be attributed to the supplementary administration of etomidate.

Etomidate induces sedative and analgesic effect

Increased RSS score was observed in the ETO group at the time of T3 and T4 when compared with the control group (Figure 1A), which indicated the anesthesia advantage of post-operation sedation. On the other hand, ETO showed the anesthesia advantage of post-operation analgesia at T3 and T5 when compared with the control group (Figure 1B). All of these data demonstrated that supplementary administration of etomidate could benefit sedative and analgesic effects.

Etomidate alleviates adrenocortical stress

As expected, cortisol and norepinephrine were significantly up-regulated at the time of T1 and T5 after the operation when compared with T0. On the other hand, diminished cortisol (Figure 2A) and norepinephrine (Figure 2B) at the time of T1 and T5 were observed in the ETO group compared with the control group.

Etomidate alleviates immune stress

The percentage of $CD4^+$ T cells or the ratio of CD4/CD8 in the two groups was significantly reduced at the time of T2 and T5 compared with the T0 stage, which indicated that surgery and anesthesia could induce immune stress. As expected, an up-regulated percentage of

CD4^{+} T cells (Figure 3A) or the ratio of CD4/CD8 (Figure 3B) was observed in the ETO group compared with the control group at the time of T2 and T5.

The increased release of pro-inflammatory factors caused by the operation and analgesia was observed at the time of T2 and T5 compared with the T0 stage. Decreased IL-6 (Figure 4A), TNF-α (Figure 4B), and IL-8 (Figure 4C), and increased IL-10 (Figure 4D) were observed in the ETO group compared with the control group at the time of T2 and T5. All of these data indicated that the supplementary etomidate could be utilized to alleviate the hormone stress and immune stress induced by surgery.

DISCUSSION

Anesthesia may affect adrenocortical and immune stress for elderly patients during anorectal surgery [17]. In this study, combined spinal-epidural anesthesia supplementary with etomidate shows more sedative and analgesic benefits than traditional combined spinal-epidural anesthesia with diminished expression of stress hormones and CD4/CD8 ratio. Hence, the application of etomidate in elderly patients undergoing anorectal surgery should be utilized in clinical practice.

Our results reveal that the application of CSEA supplemented with intravenous etomidate shows significant advantages in managing adrenocortical stress in elderly patients undergoing surgery. Etomidate's unique pharmacological profile, particularly its ability to inhibit adrenal steroidogenesis, results in reduced cortisol production [18]. This suppression is crucial in elderly patients who are more susceptible to the adverse effects of elevated cortisol levels during the perioperative period. Elevated cortisol, a common response to surgical stress, can lead to various complications, including impaired wound healing, hyperglycemia, and increased susceptibility to infections [19]. By maintaining cortisol at lower, more stable levels, etomidate minimizes these risks, promoting a more favorable postoperative course.

Moreover, CSEA with etomidate provides comprehensive analgesia and anesthesia, which further attenuates the stress response. Spinal-epidural anesthesia effectively blocks the afferent pain pathways, thereby reducing the central nervous system's perception of pain and subsequent stress response [20]. When combined with etomidate, this anesthetic approach ensures minimal hemodynamic fluctuations and reduces the overall stress burden on the patient's body.

The anal canal and perianal skin are rich with nerves and sensitive to pain and damage. Anorectal surgery-associated tissue damage inevitably leads to inflammation. Uncontrolled inflammation may lead to systemic inflammatory syndrome or multiple organ dysfunction [21]. Inflammation or surgical stimulation of perianal skin can cause spasms and contraction of the external anal sphincter and levator ani muscle to affect postoperative recovery [22, 23]. Etomidate acts on the central nervous system by stimulating γ-aminobutyric acid receptors and depressing the reticular activating system, demonstrating a more negligible effect on hemodynamics and stress reaction during intravenous anesthesia. Etomidate can inhibit adrenocortical stress by prohibiting cortisol biosynthesis. Thus, cortisol plasma levels can maintain a normal level and do not increase in response to surgery as would ordinarily occur [19, 24, 25].

Surgical stress and anesthesia can significantly impact the immune system, often leading to a pro-inflammatory state that can complicate recovery [26]. In this study, it was found that the use of etomidate in conjunction with CSEA has been shown to modulate this immune response favorably. Etomidate's ability to suppress the inflammatory response is particularly beneficial in elderly patients, who typically have a diminished immune reserve and a higher propensity for postoperative complications. Etomidate is testified to alleviate the surgery and anesthesia-induced inflammatory response during lung adenocarcinoma resection compared with propofol [27]. During surgery for lower limb fracture, etomidate can maintain serum superoxide dismutase activity and inhibit inflammatory factors released to reduce sedation and the occurrence of anesthesia complications [28, 29]. In elderly patients with rheumatic heart valve disease undergoing heart valve replacement, combined etomidate-ketamine anesthesia can stabilize the perioperative electrocardiogram indicators, improve postoperative cognitive function, and reducer pain sensation compared with the ketamine group [30]. All of these data indicate that etomidate utilization should be promoted and applied in practice with more precise analysis.

Studies have indicated that etomidate can reduce the release of pro-inflammatory cytokines and maintain a more balanced immune response during and after surgery [31-33]. This immunomodulatory effect helps prevent the excessive inflammatory reaction that can lead to conditions such as systemic inflammatory response syndrome or multiple organ dysfunction syndrome. By mitigating these inflammatory responses, etomidate contributes to a smoother recovery process and reduces the incidence of postoperative complications related to immune stress. Our results were consistent with these results, as etomidate further decreased the inflammatory activities when compared to CSEA alone.

Nevertheless, there are some limitations to this study. Dosage and speed of etomidate injection will greatly affect the incidence of myoclonus [34, 35], which will affect the patient's breathing, leading to hypoxemia. In this study, several patients in this study suffered from myoclonus, which indicates a more precise clinical design should be performed to testify the extensive utilization of CSEA supplementary with etomidate to minimize the incidence of myoclonus. Secondly, the specific mechanism related to CSEA supplementary with etomidate-induced adrenocortical stress and immune stress alleviation is not deciphered in this study. Thirdly, whether CSEA supplementary with etomidate could be utilized in the general population beyond the elderly patients needs further analysis.

CONCLUSION

Our investigation indicates the possibility of utilizing etomidate for elderly patients undergoing anorectal surgery to minimize adrenocortical stress and immune response.

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TABLES AND FIGURES

Table 1. Demographic and clinical characteristics of the study participants

Characteristics	Study group Control (n=48)	 ETO (n=49)	*P*
Gender			
Male	22 (45.8%)	25 (51.1%)	0.686
Female	26 (54.2%)	24 (48.9%)	
Age (years)	69.4±4.8	71.2±5.1	0.193
ASA scale			
I	15 (31.3%)	13 (26.5%)	0.542
II	23 (47.9%)	21 (42.9%)	
III	10 (20.8%)	15 (30.6%)	
Surgical specialty			
Mixed hemorrhoid	16 (33.3%)	14 (28.6%)	0.909
Internal hemorrhoids	9 (18.8%)	11 (22.4%)	
External hemorrhoid	6 (12.5%)	5 (10.2%)	
Low anal fistula	7 (14.6%)	10 (20.4%)	
High anal fistula	5 (10.4%)	6 (12.3%)	
Perianal abscess	5 (10.4%)	3 (6.1%)	

Complicating disease			
Hypertension	15 (31.3%)	13 (26.5%)	0.659
Diabetes mellitus	8 (16.7%)	5 (10.2%)	0.387
Hyperlipidaemia	11 (22.9%)	14 (28.6%)	0.644
COPD	6 (12.5%)	3 (6.1%)	0.317
PONV	3 (6.25%)	2 (4.08%)	0.678
Infections	0 (0.0 %)	0 (0.0%)	1.000
LOS (days)	8.4±1.9	7.9±1.7	0.133

Values were expressed as n (percentage, %) or mean ± SD. *P* values were derived from the Mann–Whitney test. The chi-square test or Fisher's exact test was used for assessing the distribution of observations or phenomena between different groups. ASA: American Society of Anesthesiologists; ETO: etomidate; COPD: chronic obstructive pulmonary disease; PONV, postoperative nausea and vomiting; LOS, hospital length of stay.

Table 2. Comparisons of MAP, HR, and arterial SpO_2 between the two groups

		T0	T1	T2	T5
MAP (mmHg)	Control (n=48)	96.3±6.4	79.5±6.9	85.3±6.8	93.9±7.2
	ETO (n=49)	95.9±7.0	84.7±6.5*	88.2±7.1	94.7±5.9
HR (/min)	Control (n=48)	76.2±8.1	85.3±7.6	80.2±9.1	78.5±7.8
	ETO (n=49)	77.4±7.8	79.1±8.6*	78.7±8.4	77.1±8.4
Arterial SpO_2 (%)	Control (n=48)	97.8±3.5	91.5±4.2	94.3±3.8	96.9±3.7
	ETO (n=49)	97.4±2.9	94.6±3.3*	96.1±3.4	97.5±3.1

Values were expressed as mean ± SD. *$P < 0.05$ compared to control at the same time point. Mann-Whitney test. MAP: mean artery pressure; HR: heart rate.

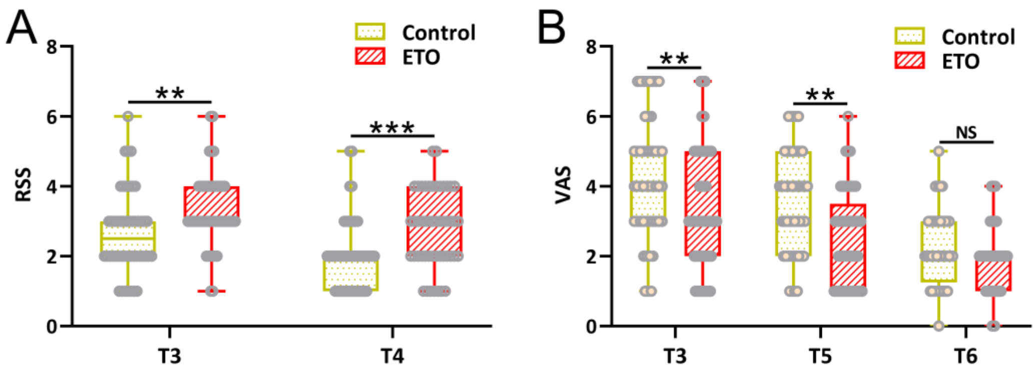

Figure 1. A) Comparison of RSS score between the two groups 1 h after the operation (T3) and 12 h after the operation (T4). B) Comparison of VAS score between the two groups 1 h after the operation (T3), 24 h after the operation (T5), and 72 h after the operation (T6). n = 48 for control and n = 49 for ETO. Box plot. $^{**}P < 0.01$, $^{***}P < 0.001$, and ns means no significance. Mann-Whitney test.

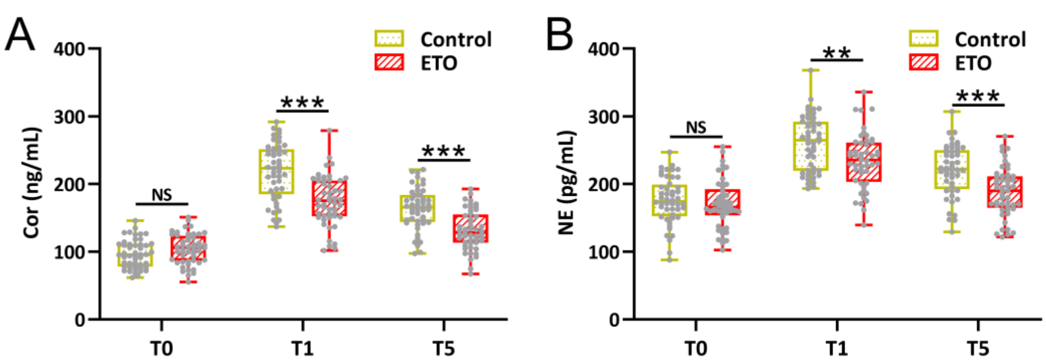

Figure 2. Comparison of stress indexes including serum cortisol (A) and norepinephrine (B) between the two groups before (T0), 30 min after anesthesia beginning (T1), and 24 h after the operation (T5). n = 48 for control and n = 49 for ETO. Box plot. $^{**}P < 0.01$, $^{***}P < 0.001$, and ns means no significance. Mann-Whitney test.

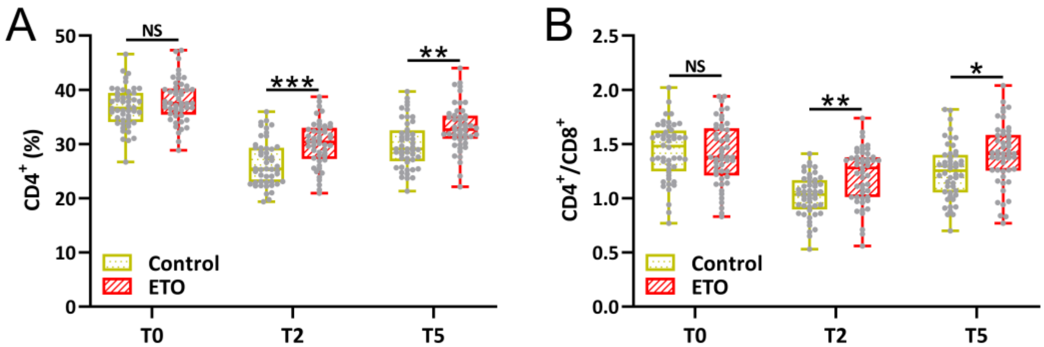

Figure 3. Comparison of immune indexes including CD4 positive T cells (A) and CD4 positive to CD8 positive T cell ratio (B) in peripheral blood between the two groups before anesthesia (T0), at the end of the operation (T2), and 24 h after the operation (T5). n = 48 for control and n = 49 for ETO. Box plot. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, and ns means no significance. Mann-Whitney test.

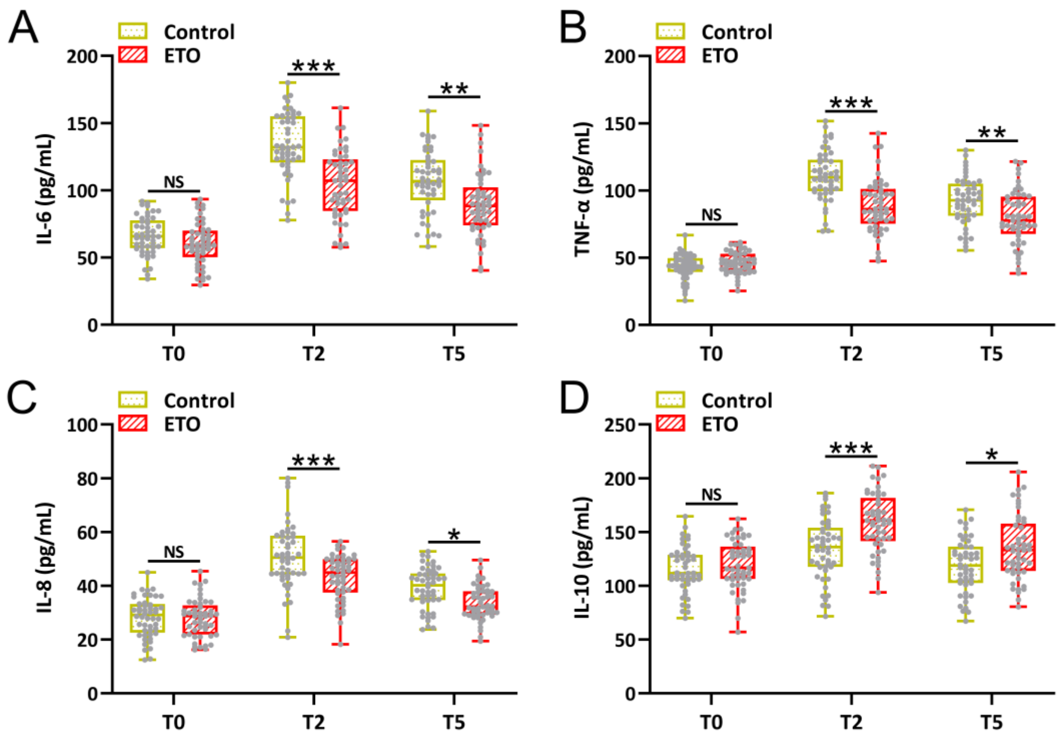

Figure 4. Comparison of serum IL-6 (A), TNF-α (B), IL-8 (C), and IL-10 (D) between the two groups before anesthesia (T0), at the end of the operation (T2), and 24 h after the operation (T5). n = 48 for control and n = 49 for ETO. Box plot. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ and ns means no significance. Mann-Whitney test.