中国临床研究 Chin J Clin Res, December 2024, Vol.37, No.12
Cite as: Wu MC, Yang FF, Cai N, Ma XJ. Affects for stress reaction and hemodynamics by multimodal opioid free anesthesia on patients with video-assisted thoracoscopic surgery [J]. Chin J Clin Res, 2024, 37(12): 1839-1844.
DOI: 10.13429/j.cnki.cjcr.2024.12.005

Affects for stress reaction and hemodynamics by multimodal opioid free anesthesia on patients with video-assisted thoracoscopic surgery

WU Meichao, YANG Fangfang, CAI Ning, MA Xingjun

Department of Anesthesia, Fuyang People's Hospital, Fuyang, Anhui 236000, China

Corresponding author: MA Xingjun, E-mail: maxj1234@163.com

Abstract: Objective To compare the hemodynamics and stress reaction of opioid free anesthesia (OFA) and opioid anesthesia (OA) in patients undergoing video-assisted thoracoscopic surgery. **Methods** A total of 110 patients who underwent thoracoscopic bullectomy or lobectomy under general anesthesia at Fuyang People's Hospital from January to October 2023 were randomly divided into OA group (n=55) and OFA group (n=55). Patients in OA group received opioid anesthesia combined with thoracic paravertebral nerve block during surgery, while the patients in OFA group used esketamine instead of opioids. Hemodynamic indicators [mean arterial pressure (MAP), heart rate (HR)] and stress response indicators [blood glucose (Glu), plasma cortisol(Cor) and plasma 8- isoprostaglandin F2α(8-iso)] at different time points and the dosage of propofol used during surgery were observed. Postoperative recovery time, VAS score and adverse reactions (nausea, vomiting, skin itching and mental symptoms) within 48 h after surgery were recorded. **Results** At the beginning of the study, 110 patients were included, of which 4 patients were excluded (1 patient was converted to open chest surgery, 1 patient experienced allergic reactions during surgery, and 2 patients were lost to follow-up). Finally, 53 cases were included in each of OA group and OFA group. Compared with the OA group, MAP and HR are significantly higher during induction, intubation and skin incision, while MAP and HR were significantly lower during extubation in OFA group (P<0.05). And the dosage of propofol used during surgery was lower in the OFA group than that in the OA group [(428.4±147.5)mg vs(499.5±171.1)mg, t=2.291, P<0.05]. Besides, the incidence of postoperative nausea and vomiting was lower in the OFA group (2% *vs* 15%, F=4.371, P<0.05). There was no statistically significant difference in the stress response indicators (Glu, Cor, 8-iso), postoperative recovery time, incidence of skin itching and mental symptoms, and VAS score between two groups (P>0.05). **Conclusion** Multimodal OFA using esketamine combined with thoracic paravertebral nerve block can effectively control surgical stress response, reduce intraoperative propofol dosage, maintain the circulatory system steady during anesthesia.

Keywords: Opioid free anesthesia; Esketamine; Stress response; Thoracic paravertebral nerve block; Thoracoscopic surgery
Fund program: Research Project of Anhui Provincial Health Commission (AHWJ2023BAc20120); Research Project of Fuyang Municipal Health Commission (FY2021-013)

Thoracic surgery can cause damage to muscle, pleura, and lung tissues, and such injury, along with severe pain, may trigger a stress response in the body. An excessive stress response can significantly affect the patient's prognosis.[1] Currently, opioids dominate perioperative pain management [2], but they have numerous side effects, including addiction, abuse, and a potential to promote tumor recurrence and metastasis [3]. Thus, opioid-free anesthesia (OFA) has gradually become a clinical research focus, but most studies have mainly focused on post-operative recovery quality [4-5]. There is little research on whether OFA effectively controls surgical nociceptive stimuli and reduces intraoperative stress responses. This study replaces opioids with esketamine as the primary analgesic in general anesthesia for thoracoscopic surgery, combined with paravertebral block, to implement multimodal opioid-free anesthesia and compare it with the traditional opioid-based anesthesia method (opioid anesthesia, OA). The aim is to explore whether multimodal opioid-free anesthesia can be safely and effectively applied in thoracoscopic surgery by observing the impact of both methods on patient hemodynamics and stress response.

1 Material and methods

1.1 Sample size calculation

The sample size for this study was calculated based on the post-operative plasma 8-iso-PGF2α levels, with α = 0.05 and β = 0.10. Based on preliminary results, σ = 81 ng/mL and δ = 52.6 ng/mL, the sample size was calculated to be 100 cases, with 50 cases per group. Considering a 10% dropout rate, exclusion criteria, and safety monitoring, 110 patients were enrolled.

1.2 General information

This study was a randomized, single-blind, single-center clinical trial approved by the Ethics Committee of Fuyang People's Hospital ([2022] No. 96). The trial was registered with the Chinese Clinical Trial Registry (Registration No. CHiCTR2200064281), and all patients or their families signed informed consent forms. The study

included 110 patients scheduled for thoracoscopic surgery (e.g., pulmonary bullae or lobectomy) under general anesthesia at Fuyang People's Hospital from January to October 2023. Patients were randomly assigned to the opioid anesthesia group (OA group, n = 55) or opioid-free anesthesia group (OFA group, n = 55). There were no significant differences in the general characteristics of the two groups (age, sex, BMI) (P > 0.05). See **Table 1.**

Tab.1 Comparison of general information between the two groups (n=55)

Group	Age (years, $\bar{x}\pm s$)	BMI (kg/m^2, $\bar{x}\pm s$)	Male/female (case)
OA group	53.8±11.9	23.6±2.5	2（2, 2）
OFA group	55.1±11.5	23.7±2.6	2（2, 2）
***t*/χ^2 value**	0.554	0.160	0.572
***P* value**	0.581	0.873	0.567

1.3 Inclusion and exclusion criteria

Inclusion criteria: Patients scheduled for elective thoracoscopic surgery; aged 25-70 years; body mass index (BMI) between 18 and 28 kg/m^2 ; American Society of Anesthesiologists (ASA) class I or II; basic cognitive function with the ability to cooperate in anesthesia; no severe organ dysfunction.

Exclusion criteria: Patients with coronary heart disease, severe hypertension, or neurological/psychiatric disorders; patients allergic to the study drugs; patients with a history of drug dependence; patients with coagulopathy or thoracic/spinal deformities.

Exclusion criteria for dropout: Conversion to open thoracotomy; occurrence of anesthesia or surgical complications; incomplete nerve block effect; lost to follow-up.

1.4 Grouping and blinding

This trial was a randomized, single-blind, controlled, single-center study. The anesthesiologists were aware of the group allocations, while the observers and data collectors were blinded to the groupings. All patients and their families were also blinded. Anesthesiologists were attending physicians with experience in thoracic surgery anesthesia, and surgeons were at least associate chief physicians skilled in performing thoracoscopic surgery to minimize operator influence on the results.

1.5 Anesthesia methods

Patients were instructed to fast (8 hours for solids and 2-4 hours for liquids) before surgery. Informed consent for anesthesia was obtained prior to the procedure. In the operating room, invasive blood pressure, electrocardiogram (ECG), pulse oximetry, and bispectral index (BIS) monitoring were applied, and an intravenous line was established with Ringer's lactate solution. A pre-anesthetic dose of 0.5 mg of intravenous pentazocine was administered. After 2 minutes of mask oxygenation, anesthesia was induced with a combination of propofol (2 mg/kg), rocuronium (0.2 mg/kg), and esketamine (0.5 mg/kg for the OFA group) or sufentanil (0.4 μg/kg for the OA group). After 5 minutes of nitrogen washout, a double-lumen endotracheal tube was inserted under bronchoscopy. Mechanical ventilation was initiated with tidal volume (VT) of 8-10 mL/kg, respiratory rate (RR) of 12 breaths/min, inhaled oxygen at 80%, and end-tidal CO_2 ($PETCO_2$) maintained between 30-45 mmHg.

Paravertebral Block: Both groups received ultrasound-guided paravertebral nerve blocks before anesthesia induction. The procedure involved placing the ultrasound probe at the T5-6 interspace, performing local anesthesia with 1% lidocaine, and injecting 20 mL of 0.375% ropivacaine after confirming no blood or air return. After 20 minutes, a fine needle was used to assess the effectiveness of the block, excluding cases of incomplete nerve blockade.

Intraoperative Maintenance: During the surgery, propofol was continuously infused at a rate of 3-6 mg/(kg • h) to maintain BIS between 40 and 60. Rocuronium was administered as needed in 1/4 to 1/3 of the initial dose. In the OFA group, esketamine was continuously infused at 0.5-1 mg/(kg • h) until chest drainage tube placement, after which esketamine was discontinued. In the OA group, remifentanil was infused at a rate of 0.05-0.2 μg/(kg • h) until skin closure. Propofol and remifentanil were discontinued after skin suturing.

Postoperative Analgesia: After the surgery, when the BIS value was above 80 and ventilation parameters normalized, the double-lumen tube was removed, and an intravenous analgesia pump was connected. The analgesia pump contained butorphanol (10 mg), dexamethasone (10 mg), and saline (100 mL), with a background dose of 2 mL/h and a bolus dose of 1 mL every 30 minutes. Patients were transferred to the post-anesthesia recovery room after waking up.

1.6 Observation indicators

Baseline Indicators: Age, sex, BMI, surgical method, surgery duration.

Primary Outcome: Plasma 8-isoprostaglandin F2α (8-iso-PGF2α, 8-iso).

Secondary Outcomes:

(1) Average arterial pressure (MAP) and heart rate (HR) at the following time points: pre-induction, 3 minutes after induction, during intubation, skin incision, and extubation.

(2) Blood glucose (Glu) measurements at induction, intubation, skin incision, and at the end of surgery, and 2 mL of arterial blood was collected to analyze cortisol (Cor) and 8-iso using ELISA after centrifugation.

(3) Intraoperative propofol usage.

(4) Extubation time and recovery time post-surgery.

(5) Visual Analog Scale (VAS) scores for resting and coughing pain at 1-, 4-, 24-, and 48-hours post-surgery.

(6) Incidence of postoperative adverse effects such as nausea, vomiting, pruritus, and mental symptoms within 48 hours.

1.7 *Statistical methods*

Data were analyzed using SPSS 22.0 software. Normally distributed continuous variables were expressed as means ± standard deviation ($\bar{x}\pm s$) and compared using the t-test. Non-normally distributed continuous variables were expressed as median (interquartile range, IQR) and compared using the Mann-Whitney U test. Repeated measures data were analyzed using analysis of variance (ANOVA), with Bonferroni post-hoc tests. Categorical data were presented as numbers (percentages) and compared using the χ^2 test. P<0.05 was considered statistically significant.

2 Results

2.1 Comparison of surgery outcomes, adverse reactions, and intraoperative propofol usage

A total of 110 patients were initially enrolled in this study, of which 1 case underwent conversion to a thoracotomy, 1 experienced an allergic reaction during surgery, and 2 were excluded due to missing data or loss to follow-up. Ultimately, 106 patients were included and randomly divided into the opioid anesthesia group (OA group, n=53) and the non-opioid anesthesia group (OFA group, n=53).

There were no statistically significant differences between the two groups in terms of surgical method, operation time, extubation time, or recovery time (P>0.05). **See Table 2.**

When comparing adverse reactions, the incidence of nausea and vomiting in the OFA group was significantly lower than in the OA group [1 (1.89%) vs. 8 (15.09%), χ^2=4.371, P<0.05]. The incidence of pruritus and mental symptoms did not differ significantly between the two groups (P>0.05).

Regarding intraoperative propofol usage, the OFA group used significantly less propofol than the OA group [(428.4 ± 147.5) mg *vs.* (499.5 ± 171.1) mg, t=2.291, P<0.05].

Tab.2 Comparison of surgical outcomes between two groups (n=53, $\bar{x}\pm s$)

Group	Surgical method (case)[a]	Operation time (min)	Extubation time (min)	Recovery time (min)
OA group	6/47	91.4±29.3	9.8±6.5	18.5±6.7
OFA group	4/49	99.7±29.1	9.5±3.7	17.3±4.4
***t*/χ^2 value**	0.442	1.468	0.239	1.131
***P* value**	0.506	0.145	0.811	0.261

Note: The operation method was thoracoscopic bullectomy / thoracoscopic lobectomy.

2.2 Comparison of MAP and HR at various time points

The baseline values of MAP and HR upon admission were not significantly different between the two groups (P>0.05). During induction, intubation, and skin incision, both MAP and HR were higher in the OFA group compared to the OA group (P<0.05). However, at extubation, MAP and HR were significantly lower in the OFA group (P<0.05), with MAP fluctuations remaining within 20% of baseline values (**Figures 1 and 2**).

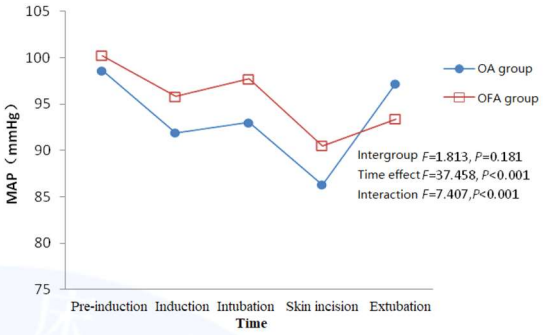

Fig.1 Comparison of MAP at different time points between the two groups

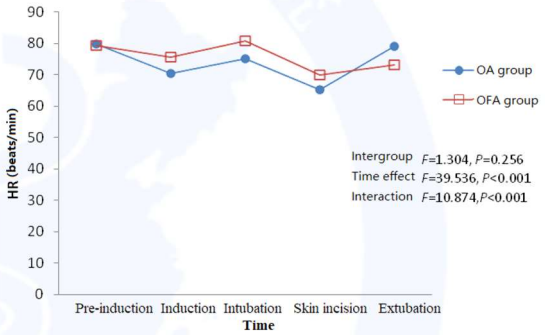

Fig.2 Comparison of HR at different time points between the two groups

2.3 Comparison of Glu, Cor, and 8-iso at various time points

There were no significant differences in Glu, Cor, or 8-iso levels between the two groups at admission, intubation, skin incision, and at the end of surgery (P>0.05). **See Figures 3-5**.

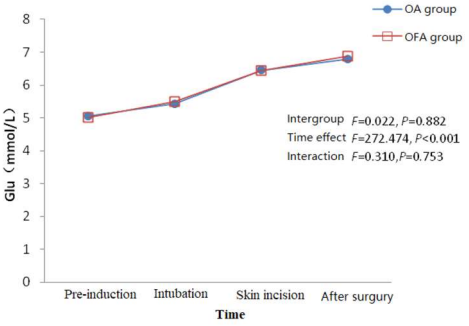

Fig.3 Comparison of Glu at different time points between the two groups

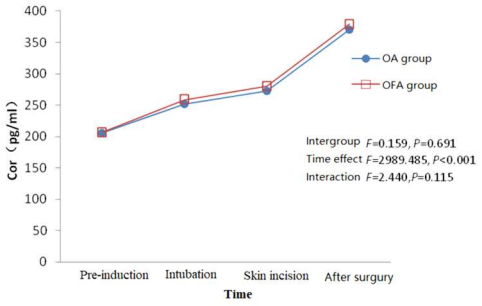

Fig.4 Comparison of Cor at different time points between the two groups

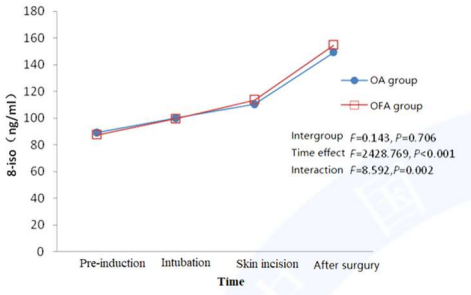

Fig.5 Comparison of 8-iso at different time points between the two groups

2.4 Comparison of VAS Scores at rest and during coughing at various time points

There were no significant differences in VAS scores at rest or during coughing between the two groups at 1 hour, 4 hours, 24 hours, and 48 hours postoperatively (P>0.05). **See Figures 6 and 7.**

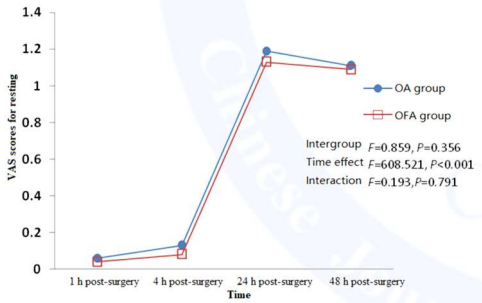

Fig.6 Comparison of postoperative VAS at rest between the two groups at different time points

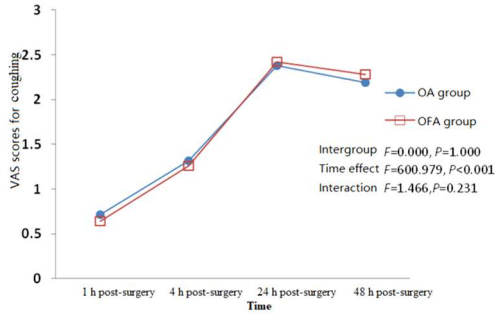

Fig.7 Comparison of postoperative VAS during coughing between the two groups at different time points

3 Discussion

Among all types of surgical pain, pain from thoracotomy is a significant challenge for clinicians. Although thoracoscopic minimally invasive techniques are commonly used, postoperative pain remains severe. Poor management of acute pain may lead to chronic pain, affecting postoperative recovery quality [1, 6]. For most common surgeries, opioids are indispensable in pain management regimens, but they can cause excessive sedation, respiratory depression, nausea, vomiting, and even potentially promote tumor recurrence and metastasis [2-3]. This has led to the promotion of OFA in clinical practice.

Currently, commonly used OFA protocols combine analgesics with different mechanisms of action (e.g., NMDA antagonists, sodium channel blockers, anti-inflammatory drugs, and α -2 agonists) and multiple analgesic techniques (e.g., epidural anesthesia, nerve blocks, and local anesthetic injection at the surgical site) to block different phases of pain pathophysiology [7-9]. Studies have shown that OFA can reduce postoperative complication rates [10]. However, some recent studies have indicated that OFA may not reduce anesthesia-related side effects [11-12]. These studies suggest that the effectiveness and safety of various OFA protocols in different types of surgeries remain controversial, and most current studies focus on postoperative recovery quality rather than whether OFA effectively controls surgical nociceptive stimulation or reduces intraoperative stress responses.

Esketamine is a novel intravenous anesthetic with both sedative and analgesic properties, fast elimination, quick recovery, and minimal side effects [13-14]. It holds significant value in OFA protocols [15-17]. Paravertebral blockade can block peripheral nociceptive stimulation at the nerve root level, reducing the body's stress response [18]. Therefore, in this study, we replaced opioids with esketamine and combined it with thoracic paravertebral blockade to implement a multimodal opioid-free anesthesia approach, comparing it with traditional opioid-based anesthesia methods. The effects of both methods on patient hemodynamics and stress responses were observed to explore whether multimodal opioid-free anesthesia can be safely and effectively used in thoracoscopic surgery.

Thoracic surgery may damage muscles, pleura, and lung tissue, and the resulting nociceptive stimulation and intense pain can place the body in a stress state [1]. (1) Pain and injury stimuli can activate the sympathetic nervous system and stimulate the hypothalamic-pituitary-adrenal axis to release large amounts of cortisol (Cor), which increases blood pressure, heart rate, and blood glucose levels. Because Cor is metabolically stable in the bloodstream, it is often used clinically as an indicator of the severity of surgical injury [19]. (2) Severe stress can lead to elevated blood glucose levels, inducing intracellular oxidative stress, which increases the production of 8-iso. 8-iso is a stable chemical compound and is one of the most sensitive markers for detecting

oxidative stress, and can also serve as a quantitative indicator of the strength of surgical-induced stress responses [20]. A reasonable and effective anesthesia technique can alleviate pain and injury stimuli, thereby reducing the stress response. Therefore, in this study, Clu, Cor, and 8-iso were used to assess whether the OFA protocol could effectively counteract the nociceptive stimuli induced by thoracoscopic surgery. In this study, there were no significant differences in Clu, Cor, and 8-iso levels at various time points between the two groups, indicating that the stress response levels were similar in both groups during the surgery. These data confirm that the multimodal OFA protocol can effectively control perioperative stress responses.

The study found that MAP and HR in the OFA group were slightly higher than those in the OA group during induction, intubation, and skin incision, but they were similar to preoperative baseline values, with MAP fluctuations remaining within 20% of baseline. Furthermore, the OFA group used less propofol intraoperatively than the OA group. This may be attributed to the sympathomimetic effect of esketamine [21], which increases heart rate and blood pressure, partly offsetting the depressant effects of propofol on the circulatory system. Additionally, because esketamine has sedative effects, it reduced the need for propofol, helping to maintain stable circulation during anesthesia.

Moreover, in this study, at extubation, the MAP and HR in the OFA group were lower than in the OA group. This may be related to the different durations of action of esketamine and remifentanil. Remifentanil is an ultra-short-acting drug, and its effects dissipate rapidly after discontinuation, while the analgesic effect of esketamine lasts 30-40 minutes [22]. Furthermore, the blood concentration of esketamine required to achieve analgesia is much lower than that required to induce loss of consciousness. Therefore, even after the patient awakens, there is still some analgesic effect, which helps to reduce the stimulation during extubation and results in more stable circulation. Thus, replacing opioids with esketamine reduces the intraoperative propofol dosage and helps maintain stable circulation during anesthesia.

In this study, there was no statistically significant difference in recovery time between the two groups, indicating that the use of esketamine in the OFA protocol does not increase the time to awakening. Regarding adverse reactions, the incidence of nausea and vomiting was lower in the OFA group than in the OA group, while the incidence of pruritus and mental symptoms was similar between the two groups. These results confirm that the OFA protocol can reduce opioid-related adverse effects, and no esketamine-related adverse effects were observed.

There were no significant differences in VAS pain scores at various time points within 48 hours postoperatively between the two groups, indicating that the OFA protocol did not significantly affect the incidence of acute postoperative pain in patients undergoing thoracoscopic surgery. This contrasts with the findings of Yan et al., who reported that, when comparing esketamine with morphine, the 24-hour incidence of acute pain was higher in the OFA group than in the OA group, although no significant differences were observed at 48 hours [5]. Yan et al. suggested that morphine may be more effective than esketamine in epidural blocks at the same concentration of local anesthetic. In contrast, our study used intravenous esketamine throughout the entire anesthesia period, which may explain the differing results between the two studies.

Limitations of the study: This study was a single-center trial with a small sample size. Further multi-center studies with larger sample sizes are needed to validate these findings. Additionally, the study only observed short-term adverse reactions and pain scores. Further research is needed to explore whether the OFA protocol can improve long-term outcomes such as postoperative complications and the incidence of chronic pain in patients undergoing thoracoscopic surgery.

Multimodal OFA protocols using esketamine to replace opioids, in combination with thoracic paravertebral blockade, can effectively control surgical stress responses, reduce intraoperative propofol use, maintain stable circulatory function during anesthesia.

Conflict of interest None

Reference

[1] Umari M, Carpanese V, Moro V, et al. Erratum to ‘Postoperative analgesia after pulmonary resection with a focus on video-assisted thoracoscopic surgery [J]. Eur J Cardiothorac Surg, 2017, 53(5): 932–938.

[2] Ning XL, Liu W, Li J, et al. Effects of esketamine combined with erector spinae block on the quality of early postoperative recovery in patients undergoing thoracoscopic surgery[J]. J Clin Anesthesiol, 2024, 40(5): 473-477. **[In Chinese]**

[3] Nguyen J, Luk K, Vang D, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer[J]. Br J Anaesth, 2014, 113 Suppl 1: i4-i13.

[4] Tripathy S, Mandal I, Rao PB, et al. Opioid-free anesthesia for breast cancer surgery: a comparison of ultrasound guided paravertebral and pectoral nerve blocks. A randomized controlled trial[J]. J Anaesthesiol Clin Pharmacol, 2019, 35(4): 475-480.

[5] Yan H, Chen WN, Chen YW, et al. Opioid-free versus opioid-based anesthesia on postoperative pain after thoracoscopic surgery: the use of intravenous and epidural esketamine[J]. Anesth Analg, 2023, 137(2): 399-408.

[6] Zhao RL, Liang LL, Wang DM, et al. Efficacy of low-dose esketamine on postoperative analgesia in patients undergoing thoracoscopic radical resection of lung cancer[J]. J Chin Pract Diagn Ther, 2023, 37(3): 269-272. **[In Chinese]**

[7] Wang ZY, Li J, Wang AQ, et al. Effects of esketamines at subanesthetic dose on hemodynamics and stress response during anesthesia induction in elderly patients undergoing knee arthroplasty[J]. J Chin Pract Diagn Ther, 2022, 36(1): 88-92. **[In Chinese]**

[8] McCullough IL, Shteamer JW, Erwood AM, et al. Opioid-free anesthesia for craniotomy[J]. J Neurosurg Anesthesiol, 2023, 35(1): 80-85.

[9] Toleska M, Dimitrovski A, Dimitrovska NT. Postoperative nausea and vomiting in opioid-free anesthesia versus opioid based anesthesia in laparoscopic cholecystectomy[J]. Pril (Makedon Akad Nauk Umet Odd Med Nauki), 2022, 43(3): 101-108.

[10] Selim J, Jarlier X, Clavier T, et al. Impact of opioid-free anesthesia after video-assisted thoracic surgery: a propensity score study[J]. Ann Thorac Surg, 2022, 114(1): 218-224.

[11] Massoth C, Schwellenbach J, Saadat-Gilani K, et al. Impact of opioid-free anaesthesia on postoperative nausea, vomiting and pain after gynaecological laparoscopy - A randomised controlled trial[J]. J Clin Anesth, 2021, 75: 110437.

[12] Beloeil H, Garot M, Lebuffe G, et al. Balanced opioid-free anesthesia

with DexmedetomidineversusBalanced anesthesia with remifentanil for major or intermediate noncardiac surgery[J]. Anesthesiology, 2021, 134(4): 541-551. [LinkOut]

[13] Eberl S, Koers L, van Hooft J, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: a randomised controlled multicentre trial[J]. Eur J Anaesthesiol, 2020, 37(5): 394-401.

[14] Wang L, Yan WJ. Progress in clinical application of esketamine in pediatric anesthesia[J]. Chin J Clin Res, 2024, 37(4): 506-509, 518. **[In Chinese]**

[15] Weng LY, Yang YC, Mao G, et al. Esketamine combined with remimazolam in painless gastroscopy in obese patients[J]. Chin J Clin Res, 2024, 37(4): 540-543. **[In Chinese]**

[16] Chen L, He WS, Liu X, et al. Application of opioid-free general anesthesia for gynecological laparoscopic surgery under ERAS protocol: a non-inferiority randomized controlled trial[J]. BMC Anesthesiol, 2023, 23(1): 34.

[17] Hublet S, Galland M, Navez J, et al. Opioid-free versus opioid-based anesthesia in pancreatic surgery[J]. BMC Anesthesiol, 2022, 22(1): 9.

[18] Iwasaki M, Edmondson M, Sakamoto A, et al. Anesthesia, surgical stress, and "long-term" outcomes[J]. Acta Anaesthesiol, 2015, 53(3): 99-104.

[19] Asteriou C, Lazopoulos A, Rallis T, et al. Video-assisted thoracic surgery reduces early postoperative stress. A single-institutional prospective randomized study[J]. Ther Clin Risk Manag, 2016, 12: 59-65.

[20] Wang YY, Yan S, Xiao B, et al. Prostaglandin F2α facilitates hepatic glucose production through CaMKIIγ/p38/FOXO1 signaling pathway in fasting and obesity[J]. Diabetes, 2018, 67(9): 1748-1760.

[21] Eberl S, Koers L, van Hooft J, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: a randomised controlled multicentre trial[J]. Eur J Anaesthesiol, 2020, 37(5): 394-401.

[22] Peltoniemi MA, Hagelberg NM, Olkkola KT, et al. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy[J]. Clin Pharmacokinet, 2016, 55(9): 1059-1077.

Submission received: 2024-06-05/ **Revised:** 2024-08-13

·论　著·

多模式无阿片药物麻醉对胸腔镜手术患者应激反应及血流动力学的影响

吴美潮，杨芳芳，蔡宁，马行军

安徽医科大学附属阜阳人民医院麻醉科，安徽 阜阳 236000

摘要：目的　比较无阿片药物麻醉（OFA）和阿片药物麻醉（OA）对胸腔镜手术患者血流动力学和应激反应的影响。**方法**　选择阜阳市人民医院 2023 年 1 月至 10 月拟全麻下行胸腔镜肺大疱或肺叶切除手术的患者 110 例，随机分为阿片类药物麻醉组（OA 组，$n=55$）和无阿片类药物麻醉组（OFA 组，$n=55$），OA 组术中使用常规阿片类药物全麻联合胸椎旁间隙阻滞进行麻醉，OFA 组使用艾司氯胺酮全麻联合胸椎旁间隙阻滞进行麻醉，观察患者术中不同时间点的血流动力学指标［平均动脉压（MAP）、心率（HR）］，应激反应指标［血糖、血浆皮质醇（Cor）、血浆 8-异前列腺素 F2α（8-iso）］和术中丙泊酚用量，术后复苏时间、视觉模拟疼痛评分（VAS）和不良反应（恶心呕吐、皮肤瘙痒、精神症状）发生情况。**结果**　研究初始纳入患者 110 例，其中 4 例被剔除（1 例中转开胸手术，1 例术中发生过敏反应，2 例失访），最终 OA 组和 OFA 组各 53 例。OFA 组在诱导、插管、切皮时 MAP 和 HR 均高于 OA 组（$P<0.05$），在拔管时，MAP 及 HR 均低于 OA 组（$P<0.05$），术中丙泊酚用量低于 OA 组［（428.4±147.5）mg *vs*（499.5±171.1）mg，$t=2.291$，$P=0.024$］，术后恶心呕吐发生率低于 OA 组（1.89% *vs* 15.09%，$\chi^2=4.371$，$P=0.037$）；两组患者术中各时点血糖、Cor、8-iso，术后复苏时间、皮肤瘙痒与精神症状发生率及 VAS 疼痛评分对比，差异无统计学意义（$P>0.05$）。**结论**　艾司氯胺酮全麻联合胸椎旁间隙阻滞的多模式 OFA 方案用于胸腔镜手术麻醉可以有效控制手术应激反应，减少术中丙泊酚用量，有利于维持患者麻醉期间循环稳定。

关键词：无阿片药物麻醉；艾司氯胺酮；应激反应；胸椎旁间隙阻滞；胸腔镜手术；丙泊酚

中图分类号：R614.2　**文献标识码：**A　**文章编号：**1674-8182(2024)12-1839-06

Affects for stress reaction and hemodynamics by multimodal opioid free anesthesia on patients with video-assisted thoracoscopic surgery

WU Meichao, YANG Fangfang, CAI Ning, MA Xingjun

Department of Anesthesia, Fuyang People's Hospital Affiliated to Anhui Medical University, Fuyang, Anhui 236000, China

Corresponding author: MA Xingjun, E-mail: maxj1234@163.com

Abstract: Objective　To compare the hemodynamics and stress reaction of opioid free anesthesia (OFA) and opioid anesthesia (OA) in patients undergoing video-assisted thoracoscopic surgery. **Methods**　A total of 110 patients who underwent thoracoscopic bullectomy or lobectomy under general anesthesia at Fuyang People's Hospital from January to October 2023 were randomly divided into OA group ($n=55$) and OFA group ($n=55$). Patients in OA group received OA combined with thoracic paravertebral nerve block during surgery, while the patients in OFA group used esketamine instead of opioids. Hemodynamic indicators [mean arterial pressure (MAP) and heart rate (HR)] and stress response indicators [blood glucose (Glu), cortisol (Cor), 8-isoprostaglandin F2α (8-iso)] at different time points and the dosage of propofol used during surgery were observed. Postoperative recovery time, Visual Analogue Scale (VAS) score and adverse reactions (nausea, vomiting, skin itching and mental symptoms) within 48 h after surgery were recorded. **Results**　At the beginning of the study, 110 patients were included, of which 4 patients were excluded (1 patient was

DOI: 10.13429/j.cnki.cjcr.2024.12.005

基金项目：安徽省卫健委科研项目（AHWJ2023BAc20120）；阜阳市卫健委科研项目（FY2021-013）

通信作者：马行军，E-mail：maxj1234@163.com

出版日期：2024-12-20

QR code for English version

converted to open chest surgery, 1 patient experienced allergic reactions during surgery, and 2 patients were lost to follow-up). Finally, 53 cases were included in each of OA group and OFA group. Compared with the OA group, MAP and HR were significantly higher during induction, intubation and skin incision, while MAP and HR were significantly lower during extubation in OFA group ($P<0.05$). And the dosage of propofol used during surgery was lower in the OFA group than that in the OA group [(428.4±147.5) mg *vs* (499.5±171.1) mg, $t=2.291$, $P=0.024$]. Besides, the incidence of postoperative nausea and vomiting was lower in the OFA group (1.89% *vs* 15.09%, $\chi^2=4.371$, $P=0.037$). There was no statistically significant difference in the stress response indicators (Glu, Cor, 8-iso), postoperative recovery time, incidence of skin itching and mental symptoms, and VAS score between two groups ($P>0.05$). **Conclusion** Multimodal OFA using esketamine combined with thoracic paravertebral nerve block can effectively control surgical stress response, reduce intraoperative propofol dosage, maintain the circulatory system steady during anesthesia.

Keywords: Opioid free anesthesia; Esketamine; Stress response; Thoracic paravertebral nerve block; Thoracoscopic surgery; Propofol

Fund program: Research Project of Anhui Provincial Health Commission (AHWJ2023BAc20120); Research Project of Fuyang Municipal Health Commission (FY2021-013)

胸外科手术可使肌肉、胸膜和肺组织等受到损伤,损伤刺激及剧烈疼痛可使机体产生应激反应,而过度的应激反应会影响患者预后[1]。目前阿片类药物在围术期疼痛治疗中占有主导地位[2],但有成瘾及滥用问题,且存在促进肿瘤复发与转移可能[3]。因此无阿片药物麻醉(opioid-free anesthesia, OFA)逐渐成为临床研究的热点,但目前研究多聚焦在患者术后恢复质量的观察[4-5]。本研究在胸腔镜手术中将艾司氯胺酮作为全麻主要镇痛药物代替阿片类药物,联合胸椎旁间隙阻滞,进行多模式 OFA,并与传统的阿片药物麻醉(opioid anesthesia, OA)进行对比,通过观察两种方法对患者血流动力学及应激反应的影响,来探究多模式 OFA 是否能安全有效的用于胸腔镜手术。

1　资料与方法

1.1　*样本量计算*　本研究以术毕血浆 8-iso 值为主要指标计算样本量,该研究 $\alpha=0.05$,$\beta=0.10$,根据预试验结果,$\sigma=81$ ng/mL,$\delta=52.6$ ng/mL,计算得样本量 100 例,每组 50 例,考虑 10%脱落、剔除因素和安全性观察的需要,拟纳入 110 例患者。

1.2　*一般资料*　本研究为临床随机对照单盲单中心试验研究,经过阜阳市人民医院伦理委员会批准([2022]第 96 号),中国临床试验中心注册(注册号:CHiCTR2200064218),所有患者家属均签署知情同意书。选择阜阳市人民医院 2023 年 1 月至 10 月拟全麻下行胸腔镜肺大疱或肺叶切除手术的患者 110 例。随机分为 OA 组($n=55$)和 OFA 组($n=55$)。两组患者一般资料[年龄、性别、身体质量指数(body mass index, BMI)]对比,差异无统计学意义($P>0.05$)。见表 1。

表 1　两组患者一般资料对比　($n=55$)

Tab. 1　Comparison of general information between the two groups　($n=55$)

组别	年龄(岁, $\bar{x}\pm s$)	性别(男/女,例)	BMI(kg/m^2, $\bar{x}\pm s$)
OA 组	53.8±11.9	24/31	23.6±2.5
OFA 组	55.1±11.5	21/34	23.7±2.6
t/χ^2 值	0.554	0.338	0.160
P 值	0.581	0.561	0.873

1.3　*纳入和排除标准*　纳入标准:需择期行胸腔镜手术的患者;年龄 25~70 岁;BMI 18~28 kg/m^2;美国麻醉医师协会(American Society of Anesthesiologists, ASA)健康状况分级Ⅰ~Ⅱ级;具备基本的认知意识,能够配合相关的麻醉治疗;无严重器官功能障碍的患者。排除标准:冠状动脉粥样硬化性心脏病、严重高血压;有精神神经系统疾病病史;对研究所使用药物过敏;有药物依赖或者药物依赖史;凝血功能障碍;胸廓及脊柱畸形。剔除标准:中途转开胸手术;发生麻醉、手术意外;神经阻滞效果不全;失访。

1.4　*分组方法及盲法*　本试验为随机、单盲、对照、单中心研究。麻醉医师为分组知情者,观察及数据采集者对分组不知情,所有患者及家属对分组情况不知情。麻醉医师均为熟悉胸外科手术麻醉的主治医师及以上级别医生,手术医生均为能熟练操作胸腔镜手术的副主任医师及以上级别医生。

1.5　*麻醉方法*　患者术前常规禁饮禁食(禁食 8 h,禁饮 2~4 h)。入室后行有创血压、心电监护及脉搏血氧饱和度及脑电双频指数(bispectral index, BIS)监测,并开放上肢静脉,输入乳酸钠林格注射液。静脉注射盐酸戊乙奎醚注射液 0.5 mg。平卧面罩吸氧 2 min 待患者情绪平复后开始麻醉,两组均行双腔支气管插管全麻复合胸椎旁神经阻滞麻醉。

椎旁神经阻滞：麻醉诱导前，两组均接受超声引导下胸椎旁间隙神经阻滞。方法：患者取侧卧位术侧在上，标记 $T_{5\sim6}$间隙，消毒铺巾，使用 HL35 低频超声探头置于预穿刺间隙旁，探头长轴与脊柱垂直，调整超声探头至最佳显示位置，1%利多卡因局部麻醉后进行平面内技术穿刺，针尖抵达椎旁间隙，回抽无血无气后注入 0.375%罗哌卡因 20 mL。20 min 后使用细针检测麻醉效果，剔除神经阻滞效果不全病例。

麻醉诱导：诱导前 10 min 静脉滴注 0.5 μg/kg 右美托咪定，静脉依次注入丙泊酚 2 mg/kg、顺阿曲库铵 0.2 mg/kg，OFA 组静脉注射艾司氯胺酮 0.5 mg/kg，OA 组静脉注射舒芬太尼 0.4 μg/kg，给氧去氮 5 min 开始插入双腔支气管导管，并用纤维支气管镜确定导管位置。机控呼吸，调整呼吸机参数，潮气量（tidal volume，V_T）8～10 mL/kg，呼吸频率（respiratory rate，RR）12 次/分，吸呼比 1∶2，呼吸末二氧化碳分压（end-tidal carbon dioxide partial pressure，$PETCO_2$）维持在 30～45 mmHg。

术中维持：术中以丙泊酚 3～6 mg/（kg·h）速度持续泵注，调整泵注速度使 BIS 维持 40～60 之间，按需给予顺阿曲库铵首剂量的 1/4～1/3。OFA 组以 0.5～1.0 mg/（kg·h）速度持续泵注艾司氯胺酮，术毕手术医生置入胸腔引流管时停用艾司氯胺酮，至缝皮结束停用丙泊酚。OA 组以 0.05～0.2 μg/（kg·h）速度持续泵注瑞芬太尼，缝皮结束停用丙泊酚和瑞芬太尼。

手术开始后单肺通气：V_T 6～8 mL/kg，RR 15 次/分，吸入气氧浓度为 80%，维持血氧饱和度在 95%以上。术中根据需要调整药物浓度及使用血管活性药物（阿托品、去甲肾上腺素和艾司洛尔）。手术结束前予氟比洛芬酯 50 mg 静脉滴注。

术后镇痛：术毕，当患者 BIS 值大于 80，V_T和每分通气量达到正常时拔除双腔管，静脉连接镇痛泵。镇痛泵药物为布托啡诺 10 mg+地塞米松 10 mg，生理盐水稀释到 100 mL，设置背景剂量 2 mL/h，追加剂量 1 mL，锁定时间间隔 30 min。患者清醒后转移到术后麻醉恢复室。

1.6　观察指标　基线指标：年龄、性别、BMI、术式、手术时间等。主要观察指标：血浆 8-异前列腺素 F2α（8-iso-PGF2α，8-iso）。次要观察指标：（1）记录入室、诱导后 3 min、插管时、切皮及拔管时的平均动脉压（mean arterial pressure，MAP）、心率；（2）测定入室、插管、切皮、术毕时血糖，并从桡动脉处抽取动脉血2 mL，静置 1 h 后，1 000 r/min 离心 10 min，取上清液置入-80 ℃冰箱保存，使用 ELISA 法检测血浆中皮质醇（Cor）、8-iso；（3）记录术中丙泊酚用量；（4）记录术毕患者拔管时间和清醒时间；（5）随访记录患者术后 1、4、24、48 h 静息和咳嗽时的视觉模拟疼痛评分（Visual Analogue Scale，VAS）；（6）记录术后 48 h 内恶心、呕吐、皮肤瘙痒、精神症状等不良反应发生情况。

1.7　统计学方法　采用 SPSS 22.0 软件进行统计分析。正态分布计量资料以 $\bar{x}\pm s$ 表示，组间比较采用 t 检验。重复测量数据比较采用方差分析，事后检验采用 Bonferroni 多重比较；计数资料以例（%）表示，组间比较采用χ^2 检验。P<0.05 为差异有统计学意义。

2　结　果

2.1　两组手术情况、不良反应及术中丙泊酚用量对比　本研究初始纳入患者 110 例，其中 1 例中转开胸手术，1 例术中发生过敏反应，2 例数据缺失或失访被剔除，最终纳入患者 106 例，OA 组和 OFA 组各 53 例。两组患者手术方式、手术时间、拔管时间、苏醒时间对比，差异无统计学意义（P>0.05）。见表 2。两组不良反应相比，OFA 组恶心呕吐发生率低于 OA 组[1.89%（1/53）*vs* 15.09%（8/53），χ^2=4.371，P=0.037]，两组皮肤瘙痒及精神症状发生率差异无统计学意义（P>0.05）；术中 OFA 组丙泊酚用量低于 OA 组[（428.4±147.5）mg *vs*（499.5±171.1）mg，t=2.291，P=0.024]。

2.2　各时点 MAP、心率对比　两组患者 MAP、心率入室时基础值对比，差异无统计学意义（P>0.05）。OFA 组在诱导、插管、切皮时 MAP 和心率均高于 OA 组（P<0.05），在拔管时，MAP 及心率均低于 OA 组（P<0.05），其 MAP 波动范围均在基础血压 20%范围内（图 1、图 2）。

2.3　各时点血糖、Cor、8-iso 对比　两组患者在入室、插管、切皮和术毕时血糖、Cor、8-iso 对比，差异无统计学意义（P>0.05）。见图 3～5。

2.4　各时点静息、咳嗽时 VAS 评分对比　两组患者在术毕 1 h、4 h、24 h 和 48 h 静息、咳嗽时 VAS 评分对比，差异无统计学意义（P>0.05）。见图 6、图 7。

表 2　两组手术情况对比　（n=53，$\bar{x}\pm s$）
Tab. 2　Comparison of surgical outcomes between two groups　（n=53，$\bar{x}\pm s$）

组别	手术方式（①/②，例）	手术时间（min）	拔管时间（min）	清醒时间（min）
OA 组	6/47	91.4±29.3	9.8±6.5	18.5±6.7
OFA 组	4/49	99.7±29.1	9.5±3.7	17.3±4.4
t/χ^2 值	0.442	1.468	0.239	1.131
P 值	0.506	0.145	0.811	0.261

注：① 为胸腔镜下肺大疱切除术；② 为胸腔镜下肺叶切除术。

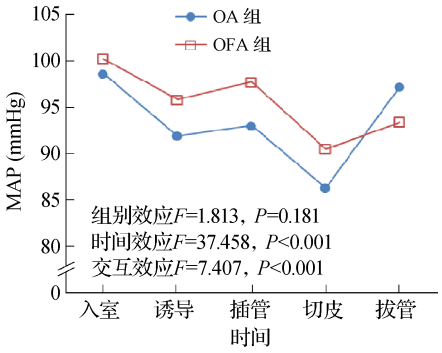

图 1　两组患者各时点 MAP 对比

Fig. 1　Comparison of MAP at different time points between the two groups

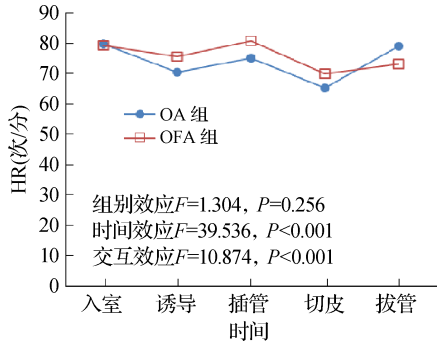

图 2　两组患者各时点心率对比

Fig. 2　Comparison of heart rate at different time points between the two groups

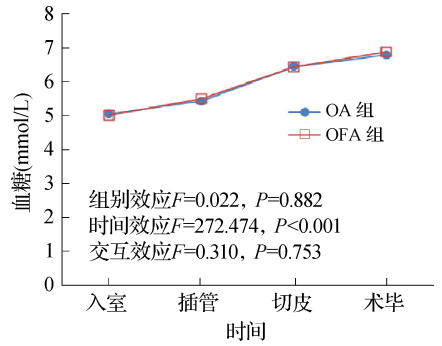

图 3　两组患者各时点血糖对比

Fig. 3　Comparison of blood glucose at different time points between the two groups

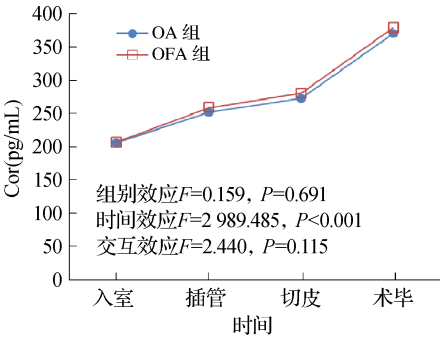

图 4　两组患者各时点 Cor 对比

Fig. 4　Comparison of Cor at different time points between the two groups

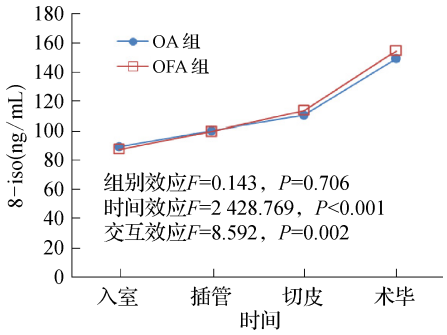

图 5　两组患者各时点 8-iso 对比

Fig. 5　Comparison of 8-iso at different time points between the two groups

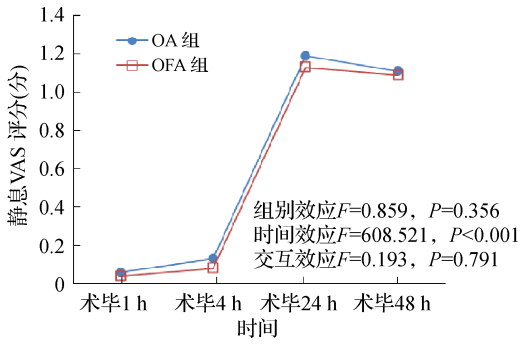

图 6　两组患者术后各时点静息时 VAS 评分对比

Fig. 6　Comparison of postoperative VAS at rest between the two groups at different time points

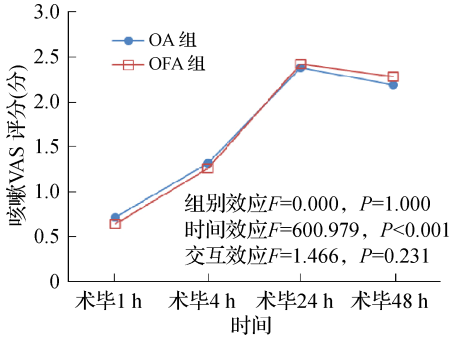

图 7　两组患者各时点咳嗽时 VAS 评分变化趋势

Fig. 7　Comparison of postoperative VAS during coughing between the two groups at different time points

3　讨　论

开胸手术疼痛是临床医生面临的巨大挑战，尽管目前临床上多采用胸腔镜微创技术，但其术后疼痛仍然较为剧烈，急性疼痛控制不佳可能转为慢性疼痛，从而影响患者术后恢复质量[1,6]。阿片类药物是手术镇痛方案中不可替代的药物，但其可导致患者出现过度镇静、呼吸抑制、恶心呕吐，甚至存在促进肿瘤复发与转移可能[2-3]。因此临床开始提倡 OFA。

目前临床上常用的 OFA 方案多联合不同作用机

制的镇痛药物(NMDA 拮抗剂、钠通道阻滞剂和 α2 激动剂等)和多种镇痛方法(椎管内麻醉、神经阻滞及切口局部麻醉)来阻断疼痛病理生理的不同时相靶位[7-9]。有研究证实 OFA 可以降低术后并发症发生率[10]。然而,也有研究显示 OFA 并不能减少麻醉副作用[11-12]。这些研究表明,不同类型手术中不同 OFA 方案的有效性和安全性仍然存在争议,且当前研究多针对患者术后恢复质量进行观察,而对于 OFA 是否能有效控制手术伤害性刺激,减轻术中应激反应的研究目前尚未明确。

艾司氯胺酮是一种新型的同时兼具镇静、镇痛作用的静脉麻醉药,其药物消除快、苏醒快、不良反应少[13-14],在 OFA 中具有重要的应用价值[15-17]。胸椎旁间隙阻滞可以在神经根水平阻断外周损伤性刺激向中枢的传导,降低机体应激反应[18]。因此,本研究在胸腔镜手术中用艾司氯胺酮替代阿片类药物,联合胸椎旁间隙阻滞,进行多模式 OFA,并与传统的 OA 进行对比,通过观察两种方法对患者血流动力学及应激反应的影响,来探究多模式 OFA 是否能安全有效的用于胸腔镜手术。

胸外科手术可损伤肌肉、胸膜和肺组织,损伤刺激及剧烈疼痛可使机体处于应激状态[1]:(1) 疼痛和损伤刺激可兴奋交感神经,刺激垂体-肾上腺皮质系统分泌大量 Cor 等,使患者血压增高、心率加快及血糖升高。Cor 性质稳定,常被临床作为检测机体损伤刺激强弱的指标[19];(2) 严重的应激状态可导致机体血糖增高,从而诱发细胞内氧化应激反应,使其产物 8-iso 增多,8-iso 化学性质稳定,是检测机体氧化应激反应的敏感指标之一,也可作为评估手术导致应激反应强弱的量化指标[20]。合理有效的麻醉方式可减轻手术导致的疼痛和损伤刺激,减轻应激反应,因此本研究采用血糖、Cor 和 8-iso 三个指标来评估 OFA 方案能否有效对抗胸腔镜手术所致伤害性刺激。本次研究中,两组患者各个时点血糖、Cor 和 8-iso水平相当,差异无统计学意义,表明两组患者术中应激反应水平相当,该多模式 OFA 方案可以有效控制围手术期应激反应。

本研究发现,OFA 组患者 MAP、HR 在诱导、插管、切皮时略高于 OA 组,但其与术前基础值相似,MAP 波动范围在基础值的 20%之内,且 OFA 组术中丙泊酚用量低于 OA 组。分析其原因,可能与艾司氯胺酮中枢拟交感神经作用使患者心率增快[18],血压升高有关,该特点也部分抵消了丙泊酚对循环系统的抑制作用,又因其具有镇静作用,可减少术中丙泊酚用量,有利于维持患者麻醉期间循环的平稳。在本研究中,OFA 组拔管时 MAP、心率低于 OA 组,其原因可能与艾司氯胺酮和瑞芬太尼作用时间不同有关。瑞芬太尼为超短效药物,停药后药效很快消失,而艾司氯胺酮镇痛有效时间可维持 30~40 min[21],且其达到镇痛效果时的血药浓度远远小于意识丧失时所需要的浓度[22],因此在患者苏醒后,仍有一定的镇痛效应,可减少拔管刺激,从而使拔管时循环更加平稳。艾司氯胺酮代替阿片类药物可减少术中丙泊酚用量,有利于维持患者麻醉期间循环系统的稳定。

在本研究中,两组患者复苏时间对比,差异无统计学意义,表明 OFA 方案中使用艾司氯胺酮并不增加患者苏醒时间。不良反应对比,OFA 组恶心呕吐发生率低于 OA 组,两组皮肤瘙痒及精神症状发生率相当,其结果证实该 OFA 方案可降低阿片类药物相关不良反应,且未发现艾司氯胺酮相关不良反应。两组患者术后 48 h 内各时点 VAS 疼痛评分对比,差异无统计学意义,尚未发现该 OFA 方案对胸腔镜手术患者术后急性疼痛发生率的显著影响。与 Yan 等[5]的研究结果不同,其发现艾司氯胺酮与吗啡对比,术中静脉注射和硬膜外输注以及术后硬膜外输注,OFA 组 24 h 急性疼痛发生率高于 OA 组,48 h 的急性疼痛发生率在两组之间没有显著差异,造成这种现象的一个原因可能是在相同浓度的局麻药下,吗啡在硬膜外阻滞中的效果优于艾司氯胺酮。而本研究麻醉期间全程采用静脉注射艾司氯胺酮,这可能是导致两个研究结果不同的一个原因。

本研究不足之处:研究是单中心研究,样本量不大,后续可进行多中心研究,扩大样本量来进一步验证该结果;仅对近期不良反应及疼痛评分进行了观察,对于该 OFA 方案是否能改善胸腔镜手术患者远期不良反应和慢性疼痛的发生还需进一步探索。

综上所述,以艾司氯胺酮代替阿片类药物联合胸椎旁间隙阻滞的多模式 OFA 方案用于胸腔镜手术麻醉可以有效控制手术应激反应,减少术中丙泊酚用量,有利于维持患者麻醉期间循环稳定。

利益冲突　无

参考文献

[1] Umari M, Carpanese V, Moro V, et al. Postoperative analgesia after pulmonary resection with a focus on video-assisted thoracoscopic surgery[J]. Eur J Cardiothorac Surg, 2018, 53(5): 932-938.

[2] 宁晓丽,刘伟,李娟,等.艾司氯胺酮联合竖脊肌平面阻滞对胸腔镜手术患者术后早期恢复质量的影响[J].临床麻醉学杂志,2024,40(5):473-477.

Ning XL, Liu W, Li J, et al. Effects of esketamine combined with erector spinae block on the quality of early postoperative recovery in patients undergoing thoracoscopic surgery[J]. J Clin Anesthesiol, 2024, 40(5): 473-477.

[3] Nguyen J, Luk K, Vang D, et al. Morphine stimulates cancer progression and mast cell activation and impairs survival in transgenic mice with breast cancer[J]. Br J Anaesth, 2014, 113 Suppl 1: i4-i13.

[4] Tripathy S, Mandal I, Rao PB, et al. Opioid-free anesthesia for breast cancer surgery: a comparison of ultrasound guided paravertebral and pectoral nerve blocks. A randomized controlled trial[J]. J Anaesthesiol Clin Pharmacol, 2019, 35(4): 475-480.

[5] Yan H, Chen WN, Chen YW, et al. Opioid-free versus opioid-based anesthesia on postoperative pain after thoracoscopic surgery: the use of intravenous and epidural esketamine[J]. Anesth Analg, 2023, 137(2): 399-408.

[6] 赵若林,梁丽丽,王冬梅,等.围手术期应用小剂量艾司氯胺酮对胸腔镜肺癌根治术患者术后镇痛的影响[J].中华实用诊断与治疗杂志,2023,37(3):269-272.
Zhao RL, Liang LL, Wang DM, et al. Efficacy of low-dose esketamine on postoperative analgesia in patients undergoing thoracoscopic radical resection of lung cancer[J]. J Chin Pract Diagn Ther, 2023, 37(3): 269-272.

[7] 王中玉,李娟,王安琪,等.亚麻醉剂量艾司氯胺酮对行膝关节置换术老年患者麻醉诱导期间血流动力学和应激反应的影响[J].中华实用诊断与治疗杂志,2022,36(1):88-92.
Wang ZY, Li J, Wang AQ, et al. Effects of esketamines at subanesthetic dose on hemodynamics and stress response during anesthesia induction in elderly patients undergoing knee arthroplasty[J]. J Chin Pract Diagn Ther, 2022, 36(1): 88-92.

[8] McCullough IL, Shteamer JW, Erwood AM, et al. Opioid-free anesthesia for craniotomy[J]. J Neurosurg Anesthesiol, 2023, 35(1): 80-85.

[9] Toleska M, Dimitrovski A, Dimitrovska NT. Postoperative nausea and vomiting in opioid-free anesthesia versus opioid based anesthesia in laparoscopic cholecystectomy[J]. Pril (Makedon Akad Nauk Umet Odd Med Nauki), 2022, 43(3): 101-108.

[10] Selim J, Jarlier X, Clavier T, et al. Impact of opioid-free anesthesia after video-assisted thoracic surgery: a propensity score study[J]. Ann Thorac Surg, 2022, 114(1): 218-224.

[11] Massoth C, Schwellenbach J, Saadat-Gilani K, et al. Impact of opioid-free anaesthesia on postoperative nausea, vomiting and pain after gynaecological laparoscopy-A randomised controlled trial[J]. J Clin Anesth, 2021, 75: 110437.

[12] Beloeil H, Garot M, Lebuffe G, et al. Balanced opioid-free anesthesia with Dexmedetomidine *versus* Balanced anesthesia with remifentanil for major or intermediate noncardiac surgery[J]. Anesthesiology, 2021, 134(4): 541-551.

[13] Eberl S, Koers L, van Hooft J, et al. The effectiveness of a low-dose esketamine versus an alfentanil adjunct to propofol sedation during endoscopic retrograde cholangiopancreatography: a randomised controlled multicentre trial[J]. Eur J Anaesthesiol, 2020, 37(5): 394-401.

[14] 王璐,阎文军.艾司氯胺酮在儿童麻醉中的临床应用进展[J].中国临床研究,2024,37(4):506-509,518.
Wang L, Yan WJ. Progress in clinical application of esketamine in pediatric anesthesia[J]. Chin J Clin Res, 2024, 37(4): 506-509, 518.

[15] 翁立阳,杨玉春,毛菇,等.艾司氯胺酮复合瑞马唑仑在肥胖患者无痛胃镜中的应用[J].中国临床研究,2024,37(4):540-543.
Weng LY, Yang YC, Mao G, et al. Esketamine combined with remimazolam in painless gastroscopy in obese patients[J]. Chin J Clin Res, 2024, 37(4): 540-543.

[16] Chen L, He WS, Liu X, et al. Application of opioid-free general anesthesia for gynecological laparoscopic surgery under ERAS protocol: a non-inferiority randomized controlled trial[J]. BMC Anesthesiol, 2023, 23(1): 34.

[17] Hublet S, Galland M, Navez J, et al. Opioid-free versus opioid-based anesthesia in pancreatic surgery[J]. BMC Anesthesiol, 2022, 22(1): 9.

[18] Iwasaki M, Edmondson M, Sakamoto A, et al. Anesthesia, surgical stress, and "long-term" outcomes[J]. Acta Anaesthesiol, 2015, 53(3): 99-104.

[19] Asteriou C, Lazopoulos A, Rallis T, et al. Video-assisted thoracic surgery reduces early postoperative stress. A single-institutional prospective randomized study[J]. Ther Clin Risk Manag, 2016, 12: 59-65.

[20] Wang YY, Yan S, Xiao B, et al. Prostaglandin $F_{2\alpha}$ facilitates hepatic glucose production through CaMKIIγ/p38/FOXO1 signaling pathway in fasting and obesity[J]. Diabetes, 2018, 67(9): 1748-1760.

[21] Peltoniemi MA, Hagelberg NM, Olkkola KT, et al. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy[J]. Clin Pharmacokinet, 2016, 55(9): 1059-1077.

[22] White MC, Karsli C. Long-term use of an intravenous ketamine infusion in a child with significant burns[J]. Paediatr Anaesth, 2007, 17(11): 1102-1104.

收稿日期:2024-06-05 **修回日期**:2024-08-13 **编辑**:王海琴