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Comparison of Target-Controlled Infusion with Etomidate versus Propofol Combined with Intravenous Esketamine for Ultrasound-Guided Segmental Mastectomy in Benign Breast Tumors: A Single-Center, Randomized, Controlled Study

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Abstract

Objective

To investigate the clinical efficacy and safety of two different anesthesia protocols (etomidate-esketamine vs. propofol-esketamine) in ultrasound-guided segmental resection of benign breast tumors.

Patients and Methods:

Ninety-five patients who were scheduled for segmental resection of benign breast tumors under nonintubated general anesthesia were randomly assigned via a random number table to either the etomidate-esketamine combination group (Group E) or the propofol-esketamine combination group (Group P). The primary outcome assessed was the incidence of respiratory depression (defined as a respiratory rate ≤ 8 breaths/min, apnea ≥ 15 s, or SpO_2 ≤ 95% for > 10 s). The secondary outcomes included the number of airway interventions, recovery time, surgeon satisfaction scores, hemodynamic parameters (pulse oximetry, blood pressure, heart rate), and perioperative adverse reactions or events.

Results

Ultimately, 47 patients composed Group E and 48 Group P. The incidence of respiratory depression was markedly lower in Group E than in Group P (10.6% vs 35.4%; P < 0.05). While Group P required more airway interventions than Group E did (10.42% vs 2.13%, P = 0.204), this difference was not statistically significant. Injection pain occurred significantly more frequently in Group P than in Group E (20.8% vs. 6.4%, P = 0.040). The incidence of Myoclonus in Group E was 10.6% (5/47). Hemodynamic parameters demonstrated greater stability in Group E than in Group P. No significant differences emerged between the groups concerning recovery time, surgeon satisfaction scores, or the incidence of adverse events within 24 hours.

Conclusion

In patients who underwent breast segmentectomy under nonintubated general anesthesia with esketamine analgesia, the etomidate-esketamine protocol yielded a significantly lower incidence of respiratory depression than did the propofol-esketamine protocol while maintaining superior hemodynamic stability.

Introduction

Benign breast lesions, such as fibroadenoma, fat necrosis, and hyperplasia, represent the most frequent conditions encountered in breast clinics, accounting for nearly 90% of all breast-related diseases. These lesions predominantly affect women of childbearing age between 30 and 50 years of age[1]. Although

only 3% to 6% of women presenting with clinical symptoms receive a breast cancer diagnosis, benign lesions can still significantly impact patients' mental well-being, even inducing anxiety. Consequently, timely and precise diagnosis and treatment of breast lesions are particularly vital[2, 3]. Segmental mastectomy serves as the primary method for diagnosing and managing benign breast tumors. This procedure offers distinct advantages, including comprehensive resection, operational simplicity, and cost-effectiveness, contributing to its widespread clinical use. Nevertheless, debate persists regarding the optimal anesthesia approach for such surgeries.

Traditional local infiltration anesthesia frequently suffers from issues such as inadequate dosing, drug accumulation, and tissue swelling that can obscure the lesion. These problems result in suboptimal anesthetic efficacy, increased patient discomfort, and increased surgical complexity[4]. In contrast, nonintubated general anesthesia with intravenous analgesia and sedation provides a straightforward, economical, and safe protocol. This ensures patient comfort while effectively meeting surgical demands without increasing procedural intricacy. However, conventional nonintubated general anesthesia via intravenous administration is associated with significant respiratory depression[5]. Moreover, during segmental resection of benign breast tumors, patients' heads are often covered with sterile drapes, complicating respiratory management. Therefore, minimizing respiratory depression risk and enhancing overall anesthesia safety remain critical research priorities. Currently, no intravenous anesthetic exists that simultaneously delivers sufficient analgesia and sedation with minimal side effects[6, 7].

Propofol is a traditional sedative that has been the dominant standard for anesthesia induction since its market launch because of its safe and controllable sedative effects[8]. Propofol has even revolutionized the practice of outpatient surgery worldwide and is widely used in general anesthesia; however, its use remains controversial[8]. It is often combined with analgesics such as sufentanil during surgery to achieve optimal anesthesia effects because of a lack of analgesic properties[9]. Propofol, however, is associated with significant respiratory depression, with studies indicating a respiratory depression rate of 40.4%[10]. This rate increases to 45% when combined with opioids[11]. Additionally, propofol injection is associated with considerable injection pain[12]. Therefore, propofol may not be the ideal sedative for general anesthesia requiring maintenance of spontaneous breathing.

Emulsified etomidate represents a relatively novel sedative that acts as an imidazole-based γ-aminobutyric acid A-type (GABAA) receptor agonist[13]. It is characterized by rapid onset and swift recovery, making it uniquely suited for general anesthesia induction and sedation[14]. Compared with propofol and other anesthetics, it provides exceptional stability in cardiopulmonary function, avoiding cardiovascular or respiratory depression. Remarkably, it maintains hemodynamic and respiratory stability even in high-risk patient populations[15]. This distinct profile makes it particularly ideal for patients with unstable hemodynamics or poor cardiopulmonary reserve, a unique advantage among anesthetic agents[16]. Previous studies have consistently demonstrated that etomidate is associated with a reduced incidence of respiratory depression events and exhibits superior sedative efficacy compared to propofol[16, 17], suggesting that emulsified etomidate may be an ideal sedative for such anesthesia.

However, no published reports exist on combining esketamine with emulsified etomidate to further minimize respiratory depression in nonintubated patients under general anesthesia.

Consequently, we hypothesized that the utilization of etomidate target-controlled infusion (TCI) in combination with esketamine for anesthesia during segmental resection of benign breast tumors, as compared to propofol TCI combined with esketamine, would significantly mitigate the risk of intraoperative respiratory depression and hypoxemia.

Materials and methods

Ethics and Clinical Trial Registration

This study was conducted at the Third Affiliated Hospital of Southern Medical University, a major tertiary care medical center located in Guangzhou, China, spanning the period from February 2024 to December 2025. The study protocol received ethical approval from the Institutional Ethics Committee of the aforementioned hospital (Approval No. 2023-Ethics Review-094) and was registered in the Chinese Clinical Trial Registry (ChiCTR 2600131912). We strictly adhered to the Declaration of Helsinki guidelines. All participants provided written informed consent before enrollment. The trial protocol was conducted in strict accordance with the applicable CONSORT (Consensus on Standards for Reporting Trials) guidelines (Figure 1), and all procedures were described in detail.No modifications occurred to key methodologies after trial initiation.

Inclusion and Exclusion Criteria

Patients aged 18–65 years and scheduled for breast tumor resection between January 2024 and December 2025, with American Society of Anesthesiologists physical status (ASA PS) I–II and a BMI of 18–28 kg/m^2, were eligible. The exclusion criteria included comorbid cardiovascular or respiratory diseases, epilepsy or psychiatric disorders, hypersensitivity or contraindications to study drugs (e.g., esketamine, etomidate, or propofol), a history of general anesthesia within 7 days, or other conditions deemed unsuitable by the investigator.

Randomization and Blinding

An independent investigator from our research team used SPSS 26.0 statistical software to generate a random number table with a seed value of 2,000,000. Each patient was assigned a unique random number based on their enrollment sequence, after which participants were grouped randomly according to these numbers. We designed a 1:1 randomization scheme for 96 subjects, who were divided into Group E and Group P, with the allocation scheme concealed in sequentially numbered, opaque envelopes. A unique identifier was assigned to each patient according to the order of enrollment. All participants, surgical staff, outcome assessors, and researchers responsible for data collection and analysis remained blinded to the allocation.Only the anesthesiologists and nursing assistants

administering the anesthetic agents, who did not participate in patient assessment or follow-up procedures, were aware of the group allocations.

Intervention Protocol

Prior to anesthesia induction, both groups received identical preanesthetic medications: 8 mg ondansetron for nausea/vomiting prophylaxis and 0.5 mg penehyclidine hydrochloride to suppress secretions. Pretreatment included 0.02 mg/kg midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., China) and 0.1 mg/kg esketamine (Jiangsu Hengrui Pharmaceutical Co., Ltd., China; 50 mg/ampoule, 25 mg/mL concentration) to alleviate anxiety. The operating room temperature was maintained at 24°C to prevent shivering. Peripheral venous access was established via the antecubital vein for fluid and medication infusion; a compound electrolyte solution was administered at 10 mL/kg/h. Routine monitoring included mean arterial pressure (MAP), pulse oximetry (SpO_2), heart rate (HR), and respiratory rate (RR). Continuous oxygen was supplied via a simple mask at 4 L/min. Patients were placed in a supine position without pillows.

The study drugs were prepared by the assistants of the anesthesiologist as follows: In both groups, esketamine was diluted with normal saline to 10 mL to prepare a 5 mg/mL solution. For Group E, a 50 mL syringe was used to draw 80 mg of etomidate (Jiangsu Nhwa Pharmaceutical Co., Ltd., 2 mg/mL, total 40 mL). In Group P, a 50 mL syringe was similarly prepared to draw 400 mg of propofol (10 mg/mL, total 40 mL; JiaBo, Guangzhou, China). Sedation levels were assessed in both groups via the Modified Observer Alertness/Sedation Scale (MOAA/S)[18, 19]. We used a target-controlled infusion pump (Beijing SLGO Medical Technology Co., Ltd.) preprogrammed for etomidate TCI in the Schnider model and propofol TCI in the Marsh model with a targeted plasma drug concentration (Cpt), which determined the pump infusion rate and calculated the effect concentration (Ce). Patients in group E were treated with a target-controlled infusion of etomidate (Schnider model with pharmacokinetic parameters, Cpt 0.5 μg/mL), with a gradually increasing or decreasing amplitude from 0.1 μg/mL until the MOAA/S was less than 2[20]. Patients in group P were treated with propofol TCI (Marsh model with pharmacokinetic parameters, Cpt 2 μg/mL), with a gradual increase or decrease in steps of 0.5 μg/mL[19]. The infusion speed was adjusted according to the MOAA/S score of the patient. When the Ce of etomidate reached 0.5 μg/mL or the Ce of propofol reached 2 μg/mL, 0.2 mg/kg esketamine was administered. Two minutes after esketamine administration, the level of patient sedation was assessed via the MOAA/S scale. The target MOAA/S score for sedation was less than 2, with the patient responding only after a painful trapezius squeezes. When the MOAA/S score was 1, the current Ce of etomidate or propofol was maintained. When the MOAA/S score was less than 1 or airway obstruction symptoms occurred, TCI etomidate or propofol was paused or decreased. At the start of surgery, the Ce of etomidate or propofol was maintained at 0.5 μg/mL or 2 μg/mL, and the MOAA/S score was reassessed again. If the MOAA/S score did not exceed 1, and the patient's vital signs remained stable with no body movement observed during the procedure, the infusion rates of etomidate or propofol were maintained at their current levels. When the MOAA/S ratio was ≥2 or the patient exhibited a bodymovement response, the etomidate TCI target (Cpt) was increased from 0.1 μg/mL to 0.4 μg/mL, or the propofol TCI target (Cpt) was increased

from 0.5 μg/mL to 2.5 μg/mL, while 50 μg/kg esketamine was administered. If the MOAA/S was above 2, for example, if the patient was still too responsive to tolerate the procedure, additional sedation was provided with increments of 0.1 μg/mL etomidate or 0.5 μg/mL propofol at the plasma target level (Cpt) every 3 min. This titration continued until MOAA/S ≤1 was achieved. For every step of etomidate or propofol, 50 μg/kg of esketamine was added. Fifteen minutes before the end of surgery, 50 mg of flurbiprofenester was administered. The maximum dose of esketamine in both groups did not exceed 0.5 mg/kg.

The presence of any one of the following three conditions constituted respiratory depression: oxygen saturation (SpO_2) ≤95%, a respiratory rate ≤8 breaths per minute, or apnea lasting ≥15 seconds. If SpO_2 remains below 95% for more than 10 seconds or exhibits a continuous downward trajectory, we immediately implement interventions such as adjusting the patient's head position (tilting it to one side), elevating the jaw, or applying a pressure mask to assist ventilation. If these measures fail to reverse respiratory depression, as evidenced by a persistent decrease in SpO_2 within 10 seconds, then we initiate the next interventions, such as inserting an oropharyngeal or nasopharyngeal airway and providing artificial assisted ventilation.

Hypotension was defined as a mean arterial pressure (MAP) falling below 60 mmHg or decreasing by 20% from baseline; this condition was managed with intravenous administration of 5–10 mg ephedrine. Hypertension, defined as a 20% increase from baseline, was addressed with intravenous administration of 12.5 mg urapidil. Bradycardia was identified as a decrease in heart rate (HR) to less than 60 beats per minute. If the HR ranged between 50 and 60 beats per minute, close monitoring was sufficient without specific intervention; however, if the HR fell below 50 beats per minute, intravenous administration of 0.5 mg of atropine was needed. All the medication dosages were meticulously recorded.

All surgical procedures were performed by a highly experienced general surgeon, while anesthesia was administered by the same dedicated anesthesiologist. Patient data were gathered and documented by another trained physician.

Outcomes and definitions

The primary outcome of the study was the incidence of intraoperative respiratory depression during the procedure, which was defined as a respiratory rate ≤8 breaths/min, apnea ≥15 seconds, or SpO_2 ≤95%. Other secondary outcomes included the duration of anesthesia and surgical procedures, the amount of body reactive movements, the amount of each airway intervention, and the awaken time, which was defined as the interval between cessation of anesthetic pump infusion and the patient's ability to respond to verbal commands immediately and a MOAA/S score ≥4. Multiple vital signs, including heart rate, SpO_2, blood pressure (SBP, DBP, MAP), and respiratory rate, were recorded at multiple time points: the patient entered the operating room and rested for 5 minutes later, the baseline value (T_0), 1 minute after induction (T_1), 1 minute before skin incision (T_2), 3 minutes after skin incision (T_3), at the end of the operation (T_4), and 3 minutes after the patient entered the postanaesthesia care unit (PACU, T_5).

Intraoperative hypotension (defined as a decrease in intraoperative SBP exceeding 20% of the baseline value), hypertension (defined as an increase in intraoperative SBP exceeding 20% of the baseline value), bradycardia (HR <60 beats/min), and tachycardia (HR>100 beats/min) were also recorded. Surgeon satisfaction with anesthesia was assessed via a five-point Likert scale (1= "very dissatisfied," 2= "dissatisfied," 3= "neutral," 4= "satisfied," 5= "very satisfied")[18]. The modified Aldrete score[21] was used to evaluate the patient's condition upon entering the PACU and at 15 min, 30 min, and 45 min after entering the PACU, with the Visual Analogue Scale(VAS) pain score recorded at the time of admission to the PACU. Additionally, perioperative adverse events, including injection pain, myoclonus, nausea or vomiting, dizziness, and psychiatric symptoms (e.g., nightmares, delirium hallucinations), were documented.

Sample size calculation

On the basis of previous research data, this study primarily evaluated respiratory depression as the main assessment metric. Compared with etomidate, propofol-based intravenous anesthesia in target-controlled infusion induces significant respiratory depression, and the incidence of respiratory depression-related complications is approximately 23%[17], whereas the incidence in etomidate is only 4%[22]. We hypothesized that there would be a difference in respiratory depression rates of 20% (d=20%) between the two groups, with a lower rate of P1=5%. The α level for Type I error is set at 0.05 (P<0.05), and the β level for Type II error is 0.2 (power of 1--β=80%). According to the table of sample sizes required for comparing two sample rates (two-sided), each group will require n=44 patients. We plan to recruit 49 patients per group to compensate for a 10% dropout rate.

Statistical analysis

All the statistical analyses were conducted via SPSS ver. 26.0 for Windows (SPSS Inc., IL, USA) .The Shapiro–Wilk test was used to assess the normality of the measurement data. When the data followed a normal distribution, the results are presented as the mean ± standard deviation, and the two independent-samples *t* test was used for intergroup comparisons. For nonnormally distributed data, the median and interquartile range (M (IQR)) were reported, with the Mann–Whitney U test used for intergroup comparisons. Categorical variables are described as frequencies (percentages) and were analyzed between groups via the chi-square test or Fisher's exact test.

Linear mixed-effects models analyze repeated measures data, incorporating fixed effects for group, time point, and their interaction, alongside random intercepts for individual subjects. Further analysis compared group differences in HR, SBP, DBP, and MAP at each time point and examined dynamic changes within groups across time points, applying Bonferroni correction to adjust significance levels. The primary analyses utilized the lme4, lmerTest, and emmeans packages. All the statistical tests were two-sided, with a P value <0.05 considered statistically significant.

Results

Inclusion and Exclusion Criteria for Patients

The CONSORT flow diagram is presented in Figure 1. Between January 2024 and December 2025, a total of 98 patients were assessed for eligibility. One patient failed to satisfy the inclusion criteria, and one declined participation, resulting in 96 patients being randomly allocated to receive either etomidate or propofol in combination with esketamine. One patient in Group E was converted to general anesthesia owing to procedural changes. Consequently, the final statistical analysis comprised 47 patients in Group E and 48 patients in Group P.

Patient demographic characteristics and baseline values

The demographic characteristics and baseline values of the patients are presented in Table 1.Analysis revealed no statistically significant differences between the two groups regarding baseline characteristics, including age, body mass index (BMI), and American Society of Anesthesiologists (ASA) classification (P>0.05), demonstrating excellent comparability and baseline balance in the general data. Similarly, no significant differences emerged in surgical duration, anesthesia induction time, or intraoperative use of rescue analgesics (P>0.05). All the data met the predefined statistical assumptions, further bolstering the robustness of the subsequent efficacy and safety analyses.

Table 1 Baseline Patient Characteristics

Variable	Group E（n=47）	Group E（n=48）	$t/Z/c^2$	P value
Age,Median (IQR）	37.00(26.00, 46.00)	35.50(26.75,45.50)	0.000	1.000
Weight(kg),Median(IQR）	53.00(48.00, 58.00)	55.00(49.00, 62.00)	-1.551	0.121
Height(cm),Mean±SD	158.32±4.42	159.83±4.63	-1.630	0.107
BMI(kg/m2),Median (IQR）	20.70(19.05,22.90)	22.45(19.50,23.85)	-1.262	0.207
HR,Mean±SD	77.28±12.69	76.96±10.93	0.131	0.896
MAP,Mean±SD	93.21±11.21	91.31±11.15	0.828	0.410
SPO2,Median(IQR）	100.00(100.00,100.00)	100.00(100.00,100.00)	0.095	0.924
ASA physical status, n（%）			0.731	0.393
Ⅱ	5（10.6）	8（16.7）		
Ⅲ	42（89.4）	40（83.3）		
Mallampati score, n (%)			1.665	0.197
Ⅰ	41 (87.2)	37 (77.1)		
Ⅱ	6 (12.8)	11 (22.9)		

Notes: BMI: Body Mass Index, MAP:Mean Arterial Pressure, ASA: American Society of Anesthesiologists, IQR: Interquartile Range, SD: Standard Deviation.

Perioperative outcomes

Table 2 shows the perioperative outcomes. No significant difference emerged in the awakening time between the two groups [Group E vs. Group P: 14 (10,20.8) vs. 12 (10,17), P=0.545]. Although one patient in group P moved during surgery, disrupted the surgical procedure and resulted in dissatisfaction with the anesthetic effect, overall surgeon satisfaction was not significantly different between the groups (P>0.05). Similarly, the VAS pain scores in the postanaesthesia recovery room were not significantly different (P=0.089).

Table 2 Perioperative Outcomes

Variable	Group E（n=47）	Group E（n=48）	$t/Z/c^2$	P value
Awaken time,Median (IQR）	14.0(10,20.8)	12(10,17)	0.238	0.545
Surgeon satisfaction, n (%)	25 (57.4)	28 (58.3)		1
Likert grade: 5	22 (42.6)	19 (39.6)		
Likert grade: 4	0	1 (2.1)		
Likert grade: 2				
VAS score in the PACU, n (%)	38（80.9）	40（83.3）		0.089
VAS:0-2	8 （17.1）	5 (10.4)		
VAS:3-4				

Notes: VAS :Visual Analogue Scale,PACU:Postanesthesia care unit

Incidence of respiratory depression and the need for airway intervention

Table 3 lists the primary outcome measures. The incidence of respiratory depression was 10.6% (5/47) in Group E, which was significantly lower than the 27.1% (13/48) reported in Group P (P=0.041). Compared with Group E, Group P required more frequent hypoxic airway interventions due to respiratory depression (10.4% vs 2.1%, P=0.204), and Group P had a greater proportion of patients requiring jaw lift (6.3% vs 0.0%) and mask-assisted ventilation (2.1% vs 0.0%), although the difference was not statistically significant.

Table 3 Primary and Secondary Outcomes

Variable	Group E（n=47）	Group P（n=48）	$t/Z/c^2$	P-value
Primary outcome				
Respiratory suppression*, n (%)	5(10.6)	13(27.1)	4.18	0.041
RR≤8 breaths/min, n (%)	3(6.4)	9(18.7)		
Apnea ≥15s, n (%)	0	1(2.1)		
SpO2 ≤95%(≥15s), n (%)	2(4.2%)	3(6.3)		
Need for airway intervention, n (%)	1(2.1)	5(10.4)		0.204
Methods of airway intervention, n (%)				
Adjust head position	1(2.1)	1(2.1)		
Jaw-lift	0	3(6.3)		
Mask-assisted ventilation	0	1(2.1)		
Body movement, n (%)	18(38.3)	15(31.3)	0.520	0.471

Notes: RR: respiratory rate; SpO2: pulse oximetry.Data are presented as numbers (%). *P<0.05 between groups.

Adverse Events

Injection pain occurred in three patients (6.4%) in Group E and in ten patients (20.8%) in Group P (P=0.040) (Table 4). Bradycardia manifested in 3 patients (6.4%) in Group E and 8 patients (16.7%) in Group P (P=0.117). Only a single case (2.13%) of tachycardia was recorded, occurring in Group E. One case in each group exhibited a delirium-like state (P=1.000). Additionally, dizziness was reported in five Group E patients (10.64%) and three Group P patients (6.25%), with no significant difference between the groups (P=0.486). Nausea and vomiting affected three patients in Group E (6.4%) and one patient in Group P (2.08%). Furthermore, the incidences of hypotension, hypertension, and body movement were not significantly different between the two groups.

Table 4 Adverse Events

Event	Group E（n=47）	Group P（n=48）	c^2	P-value
Hypotension, n (%)	4/47 (8.5%)	9/48 (18.8%)	2.108	0.147
Hypertension, n (%)	0/47 (0.0%)	0/48 (0.0%)	-	-
Bradycardia, n (%)	3/47 (6.4%)	8/48 (16.7%)	2.453	0.117
Tachycardia, n(%)	1/47（2.13%）	0/48 (0.0%)	-	0.495
Delirium, n (%)	1/47（2.13%）	1/48（2.08%）	-	1.000
Dizziness, n (%)	5/47（10.64%）	3/48（6.25%）	-	0.486
Nausea or vomiting, n (%)	3/47 (6.4%)	1/48（2.08%）	-	0.362
Injection pain, n (%)*	3/47 (6.4%)	10/48（20.8%）	4.198	0.040
Myoclonus*	5/47（10.64%）	0/48 (0.0%)	-	0.026
Body movement, n (%)	18/47（38.30%）	15/48（31.25%）	0.520	0.471

Notes: *P<0.05 between groups.

Hemodynamic results

Figure 2 depicts the changes in vital signs. No significant differences emerged in HR, MAP, SBP, or DBP between the two groups at T_0 (P>0.05). SBP, DBP, and MAP were significantly lower in Group P than in Group E at all time points from T_1 to T_5 (all P<0.05). HR was significantly lower in Group P than in Group E only at T_5 (P=0.005), with no significant differences observed at other time points. Within groups, SBP, DBP, and MAP in Group P decreased significantly below the baseline values at all time points from T_1 to T_5 (all P<0.05); HR decreased significantly below the baseline values at T_1, T_4, and T_5 (all P<0.05). Conversely, SBP, DBP, MAP, and HR in Group E did not significantly differ from baseline at any time point; however, there was a slight decrease in SBP at T1 (-6.11 mmHg, P=0.009). Furthermore, the linear mixed-effects model revealed statistically significant group-by-time interactions for SBP, DBP, MAP, and HR (all P<0.05), as detailed in Tables 5-8. Tables 9-10 list comparisons of each time point to baseline within each group.

Table 5 Linear mixed-effects model for HR

Source	Numerator df	Denominator df	F	P
Group	1	93	1.65	0.202
Time point	5	465.00	2.64	0.023
Group × Time point	5	465.00	3.48	0.004

Table 6 Linear mixed-effects model for MAP

Source	Numerator df	Denominator df	F	P
Group	1	93	21.90	<0.001
Time point	5	465.00	20.80	<0.001
Group × Time point	5	465.00	8.23	<0.001

Table 7 Linear mixed-effects model for DBP

Source	Numerator df	Denominator df	F	P
Group	1	93	24.69	<0.001
Time point	5	465.00	14.71	<0.001
Group × Time point	5	465.00	7.06	<0.001

Table 8 Linear mixed-effects model for SBP

Source	Numerator df	Denominator df	F	P
Group	1	93	14.12	<0.001
Time point	5	465.00	17.77	<0.001
Group × Time point	5	465.00	5.54	<0.001

Table 9 The comparison of each time point to the baseline(Group E)

Indicator	T1	T2	T3	T4	T5
HR (bpm)	-1.26 (1.000)	-2.06 (0.941)	-2.94 (0.307)	-1.21 (1.000)	2.47 (0.579)
SBP (mmHg)	**-6.11 (0.009)**	-5.00 (0.054)	-3.30 (0.461)	-4.83 (0.069)	-1.00 (1.000)
DBP (mmHg)	-2.13 (0.902)	-1.64 (1.000)	-1.32 (1.000)	-2.89 (0.343)	0.13 (1.000)
MAP (mmHg)	-3.53 (0.146)	-2.96 (0.338)	-2.38 (0.703)	-3.79 (0.097)	-0.30 (1.000)

Table 10 The comparison of each time point to the baseline(Group P)

Indicator	T1	T2	T3	T4	T5
HR (bpm)	**-4.33 (0.027)**	-3.35 (0.155)	-1.58 (1.000)	**-5.25 (0.004)**	**-4.19 (0.036)**
SBP (mmHg)	**-10.79 (<0.001)**	**-15.58 (<0.001)**	**-14.33 (<0.001)**	**-16.62 (<0.001)**	**-8.54 (<0.001)**
DBP (mmHg)	**-7.21 (<0.001)**	**-12.38 (<0.001)**	**-11.25 (<0.001)**	**-12.31 (<0.001)**	**-4.06 (0.050)**
MAP (mmHg)	**-8.71 (<0.001)**	**-14.21 (<0.001)**	**-13.25 (<0.001)**	**-15.00 (<0.001)**	**-5.44 (0.004)**

Notes for Table 9-10:Values represent differences from the baseline (T_0) (negative values indicate below baseline). P-values in parentheses are Bonferroni-corrected. Bold indicates corrected P <0.05, statistically significant.

Discussion

This randomized clinical trial evaluated the efficacy and safety of esketamine-etomidate anesthesia for breast segmentectomy. The results revealed a significantly lower incidence of respiratory depression in Group E than in Group P. Previous studies have not explored the impact of esketamine combined with etomidate in nonintubated intravenous general anesthesia for benign breast tumor segmentectomy. Our findings provide the first compelling evidence that esketamine combined with etomidate may offer a more effective and safer anesthetic option for this procedure, thereby potentially promoting its promising application across diverse types of daytime superficial tumor resection surgeries.

For superficial surgical procedures, such as segmental resection of benign breast tumors, the anesthesia protocol generally requires a moderate depth of anesthesia while maintaining stable respiratory and circulatory conditions throughout the operation. Accordingly, anesthesiologists preferentially employ anesthetic agents and techniques associated with a reduced risk of respiratory depression to optimize patient safety. Propofol in combination with short-acting opioids is commonly utilized as a conventional total intravenous anesthesia (TIVA) regimen for brief interventions, including gastroscopy[23], hysteroscopy[24], and abortion or curettage procedures[11]. Although this combination affords sufficient analgesia and sedation, the synergistic pharmacodynamic effects of these agents may result in considerable airway obstruction, respiratory depression, and cardiovascular instability. Studies indicate that target-controlled infusion (TCI) of propofol via a syringe pump offers advantages over manual bolus administration, including a reduced impact on cardiorespiratory function, faster recovery profiles, and enhanced hemodynamic and respiratory stability[25, 26]. Therefore, in the present study, both etomidate and propofol were administered via TCI to ensure accurate dosing and minimize adverse effects on the respiratory and circulatory systems.

As a high-affinity noncompetitive N-methyl-D-aspartate(NMDA) receptor antagonist, esketamine has approximately twofold greater anesthetic potency than ketamine does, accompanied by fewer psychiatric adverse effects[27]. This agent has several advantages, such as a low incidence of nausea and vomiting, coupled with rapid recovery, making it a preferred choice among anesthesiologists[28]. Previous investigations have confirmed the significant analgesic efficacy of esketamine within opioid-free anesthetic protocols[29–31]. Propofol, a conventional sedative, is associated with inducible hypotension, bradycardia, respiratory depression, and pronounced injection pain[32]. Accumulating evidence indicates that intraoperative hypotension is correlated with increased risks of injury to vital organs, including the heart, kidneys, and brain, as well as increased mortality among high-risk patients[9, 33]. These adverse consequences constrain the clinical utility of propofol. Consequently, a growing body of recent research has utilized esketamine as an alternative to opioids,combined with propofol for providing sedation and analgesia under non-intubated general anesthesia[18, 19, 34]. This approach significantly decreases the required dosage of propofol and reduces the incidence of adverse events,

including respiratory and circulatory depression.Nevertheless, the incidence of respiratory depression remains considerable[6, 11, 23, 35], and its associated risks mandate thorough clinical assessment. Anesthesiologists must therefore explore alternative pharmacologic agents to deliver a safer and more comfortable anesthetic experience. In the present study, esketamine was employed as an analgesic alternative to opioids, while etomidate was substituted for propofol. The results demonstrated that, compared to the esketamine-propofol regimen, the proposed protocol was associated with a reduced incidence of respiratory depressive events and enhanced hemodynamic stability, while no statistically significant differences were observed in awaken time and surgeon satisfaction. These findings indicate that the combination of etomidate and esketamine may confer benefits by mitigating respiratory depression and promoting hemodynamic stability.

Etomidate is a positive allosteric modulator (PAM) featuring an imidazole backbone that primarily potentiates the activity of γ-aminobutyric acid type A (GABAA) receptors at elevated concentrations[36]. It exhibits a rapid onset of action and minimal hemodynamic suppression, thereby facilitating its widespread application in both the induction and maintenance of anesthesia.[13]. However, its clinical utility is limited by several adverse effects, including adrenal cortex suppression, postoperative nausea and vomiting, and myoclonus[37]. In recent years, the global research community has intensified its focus on structural modifications of the etomidate molecule, with the dual objectives of mitigating its adverse effects and improving hemodynamic stability[38].

Compared with propofol, etomidate elicits a lower incidence of respiratory depression and offers enhanced sedative efficacy, however, its predominant adverse effect is myoclonus[39]. Pretreatment with midazolam or esketamine has been demonstrated to markedly reduce both the incidence and severity of myoclonus induced by etomidate.[40–43]. In the present study, a pretreatment regimen comprising 0.02 mg/kg midazolam and 0.1 mg/kg esketamine was administered prior to anesthetic induction. Among the 95 patients across both groups, only 5 in Group E (10.64%) exhibited myoclonus, a rate significantly lower than that reported in previous studies.

The coadministration of dexmedetomidine and etomidate has been shown to effectively mitigate adrenocortical suppression in elderly patients, while concurrently preserving intraoperative hemodynamic stability[44]. These findings offer significant implications for future investigations aimed at further mitigating etomidate-associated adverse effects. Furthermore, evidence indicates that etomidate substantially reduces the risk of cerebral ischemia–reperfusion injury, suggesting distinct neuroprotective benefits[45]. Therefore, the concomitant administration of etomidate and esketamine may exert synergistic effects in enhancing neuroprotective efficacy, while concurrently maintaining cardiopulmonary stability. This combination holds promise for improving perioperative safety profiles, and its potential application in high-risk patient populations warrants further rigorous evaluation.

Although previous investigations have established the advantages of combining esketamine and propofol under local anesthesia in minimally invasive breast surgery,including procedural simplicity, favorable cost-efficacy, a satisfactory safety profile, and a low incidence of adverse effects,the rate of

respiratory depression remains substantially elevated, reaching as high as 32.5%, accompanied by hypoxemia in 17.5% of cases[19]. Moreover, the administration of local anesthetics within such protocols may compromise the accuracy of intraoperative frozen section analysis. During the excision of small benign breast tumors, tissue edema resulting from local anesthetic infiltration can obscure the precise delineation of the lesion, thereby elevating the complexity of the surgical procedure[4, 46]. In the present study, the adoption of nonintubated general anesthesia alone circumvented the interference with lesion localization inherent to local anesthetic use. Surgeons reported a high degree of satisfaction with the anesthetic outcome. Our findings demonstrated that the incidence of respiratory depression in Group E was merely 10.6%, significantly lower than the 27.1% observed in Group P ($P < 0.05$), with no concomitant increase in the risk of adverse reactions such as delirium, dizziness, nausea, or vomiting. These outcomes indicate that the combination of esketamine and propofol not only enhances intraoperative hemodynamic stability but also promotes more favorable early postoperative respiratory recovery.

Notably, to increase patient safety, we defined respiratory depression as $SpO_2 \leq 95\%$ accompanied by apnea lasting ≥ 15 seconds or a respiratory rate ≤ 8 breaths per minute. This threshold is more stringent than those employed in earlier studies, which conventionally defined hypoxemia as $SpO_2 \leq 92\%$ for ≥ 10 seconds[11, 19]. Nevertheless, the observed rate of respiratory depression remained lower than that reported in prior studies, an outcome potentially attributable to the utilization of target-controlled infusion (TCI). Evidence suggests that propofol administration via TCI microinfusion pumps exerts a less pronounced influence on respiratory and circulatory function compared with intermittent manual bolus administration, thereby facilitating a more rapid recovery[25, 47]. These findings yield novel clinical insights that inform the optimization of anesthetic protocols and delivery techniques in ambulatory surgical settings.

This study acknowledges several limitations. First, as a single-center trial with a relatively small sample size, the reliability and generalizability of the findings may be constrained. Furthermore, the investigation may not adequately capture other infrequent drug-related adverse events. Second, the absence of a control group receiving different dosages of esketamine precludes definitive conclusions regarding the optimal preoperative dose and the maximum safe intraoperative administration threshold. Third, since the majority of patients undergoing breast segmentectomy at this institution are generally free of significant comorbidities, caution is warranted when extrapolating these results to high-risk populations. Finally, the study focused solely on the short-term safety and efficacy of etomidate combined with esketamine for the resection of benign breast tumors, without evaluating long-term outcomes such as postoperative recovery quality, pain management, adrenocortical function, or patient satisfaction. Future studies should be designed as multicenter, large-sample randomized controlled trials that include elderly individuals and patients with chronic comorbidities. Extending the follow-up period would also facilitate a comprehensive assessment of long-term effects, particularly with respect to postoperative cognitive function, chronic pain incidence, and psychological status.

Conclusion

In conclusion, for elective segmental mastectomy, nonintubated general anesthesia employing esketamine-etomidate demonstrates a significant reduction in the incidence of respiratory depression compared to esketamine-propofol, without adversely affecting recovery time, surgical satisfaction, or the frequency of other adverse events. Moreover, the esketamine-etomidate group exhibited more stable hemodynamic profiles, suggesting its particular suitability for patients with underlying cardiopulmonary comorbidities or those at increased risk of respiratory depression. This combination also presents a promising alternative for broader use in anesthesia for other outpatient and minor day-case procedures.

Abbreviations

GABAA:g-aminobutyric acid A-type; TCI:target-controlled infusion; ASA PS:American Society of Anesthesiologists physical status; MOAA/S:Modified Observer Alertness/Sedation Scale ; SBP:systolic pressure;DBP:diastolic pressure;MAP: Mean arterial pressure;Cpt:targeted plasma drug concentration;Ce:effect concentration;HR:heart rate; SpO_2:pulse oximetry;RR:respiratory rate;PACU: Post-anesthesia care unit;VAS:Visual Analogue Scale; NMDA:N-methyl-D-aspartate; TIVA:total intravenous anesthesia.

Declarations

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Not applicable

Authors' contributions

All authors reviewed and approved the final manuscript. HL assisted in the supervision of data collection, contributed to designed,drafted and reviewed the manuscript. JHJ contributed to the supervision of data collection, conducted literature review, and assisted in manuscript preparation. KYX was responsible for the methodological design of the study, provided specialized expertise in surgical content, supervised data collection, and performed data analysis. GDW provided supervisory support during data collection and contributed to the editing of the final manuscript. FHS assisted in supervising data collection and participated in the editing of the final manuscript. XJD analyzed the data and edited the final manuscript; LC designed the manuscript, provided anesthesiologic content expertise, supervised the data collection analyzed the data, drafted, and reviewed the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of The Third Affiliated Hospital of Southern Medical University on December 28, 2023, under the reference No. 2023-Ethics Review-094, in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to enrollment.

Consent for publication

Not Applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

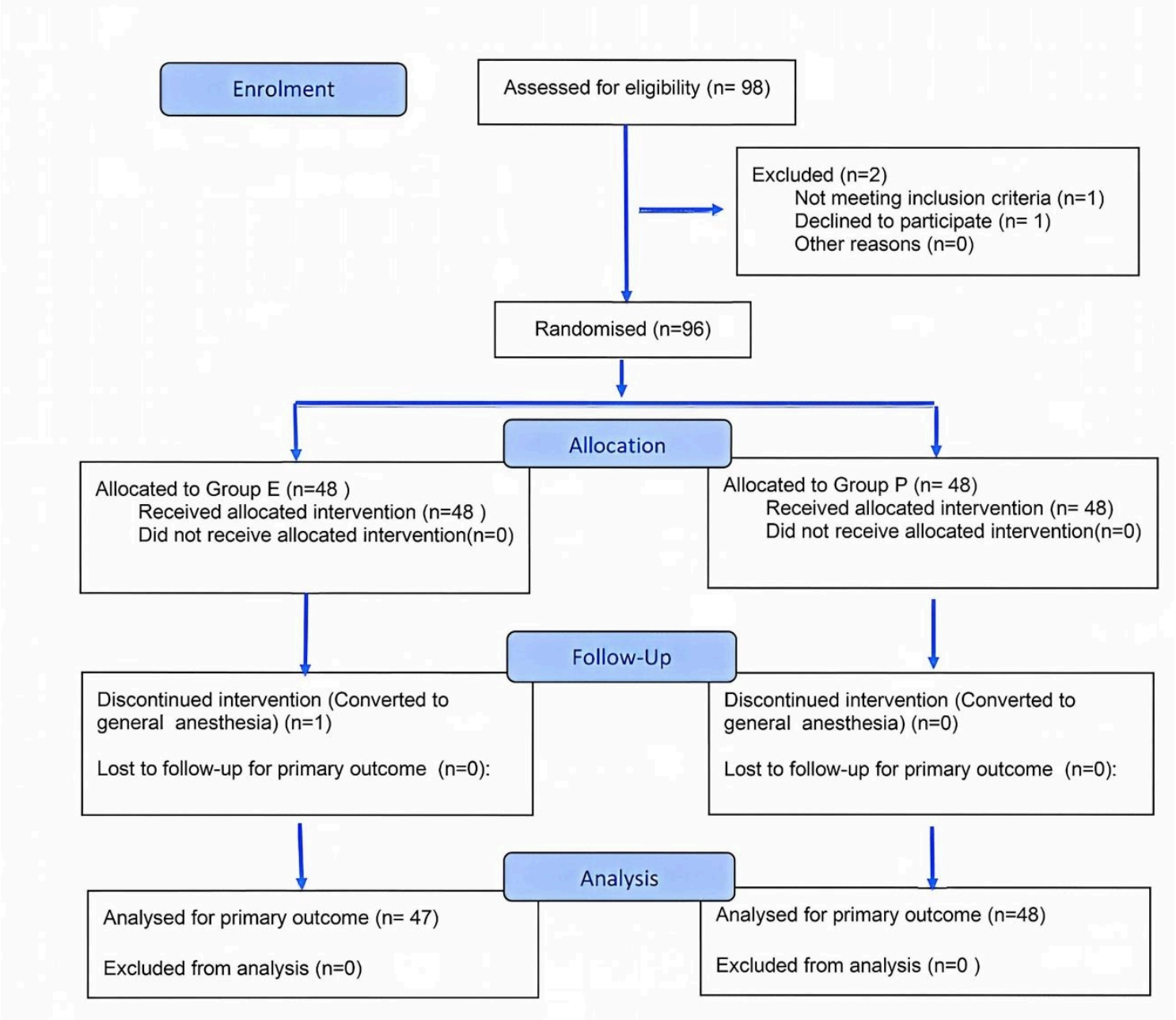


Figure 1

Flow chart of patients throughout the randomized trial

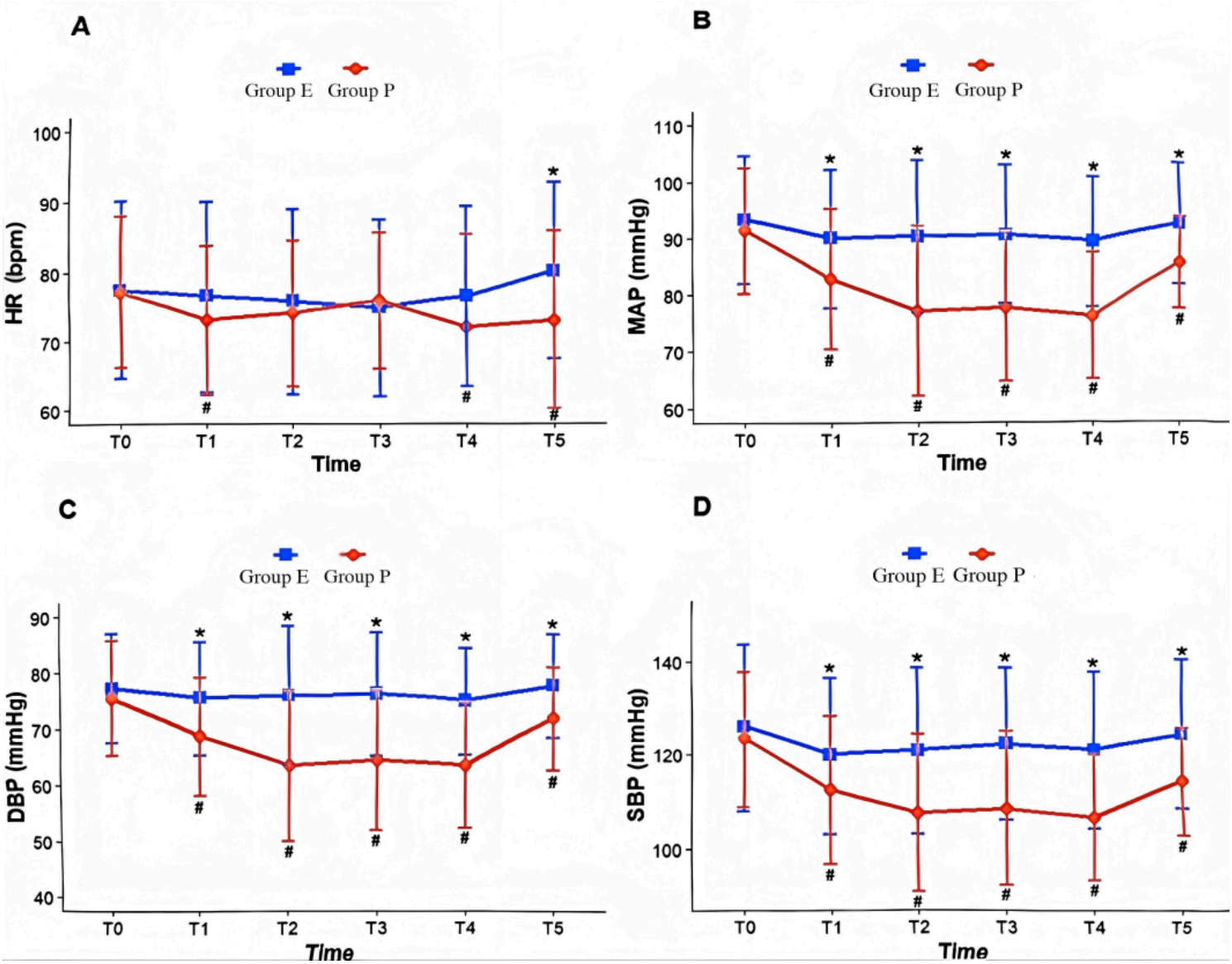


Figure 2

Changes in vital signs over the duration of anesthesia. HR: heart rate (A), bpm: beat per minute, MAP: mean arterial pressure (B),DBP:diastolic blood pressure(C),SBP:systolic blood pressure(D). T0, the baseline; T_1, 1 min after induction; T_2, 1 min before skin incision; T_3, 3 min after skin incision; T_4, the end of the operation;T_5,3 min after the patient enters the PACU. (*P< 0.05 between groups; $^{\#}$P< 0.05 compared with T_0 within group).