CLINICAL TRIAL REPORT

Subanesthetic Dose of Esketamine Improves the Sedative and Analgesic Effects of Dexmedetomidine and Remifentanil in Liposuction Anesthesia: A Prospective, Double-Blinded, Randomized Controlled Trial

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Purpose: Esketamine have anesthetic and analgesic properties. This study aimed to observe the enhancing effect of subanesthetic doses of esketamine (0.15–0.3 mg/kg/h) with dexmedetomidine and remifentanil during anesthesia for liposuction surgery.

Patients and Methods: A total of 155 subjects were randomized with a 1:1 ratio to Group E (esketamine-dexmedetomidine/remifentanil, n=78) or Group C (saline-dexmedetomidine/remifentanil group, n=77). The primary outcome was satisfaction of patient and surgical team with the procedure. The secondary outcomes were the postoperative Athens Insomnia Scale (AIS) and Hospital Anxiety and Depression Scale (HADS) scores, hemodynamic and respiratory changes, drug consumption, adverse event rates, and predictors associated with patient satisfaction.

Results: Patient and surgical team satisfaction with the procedure was significantly higher in Group E than in Group C (4.7 ± 0.6 vs 4.2 ± 0.7, P < 0.001; 4.7 ± 0.5 vs 4.4 ± 0.7, P = 0.005). The postoperative AIS (4 [1, 6] vs 5 [2, 9], P = 0.012) and HADS-A (1 [0, 3] vs 2 [0, 6], P = 0.012) scores were significantly lower in Group E than in Group C. Hemodynamic and respiratory parameters were more stable in Group E than in Group C, with the lower opioids consumption of sufentanil (0 [0, 4] vs 5 [2.5, 7.7], P < 0.001) and remifentanil (700 [480, 900] vs 800 [500, 1200], P = 0.023) in Group E compared to Group C. On ordinal logistics regression, postoperative sleep quality (OR, 0.70; 95% CI, 0.62–0.79), anxiety level (OR, 0.77; 95% CI, 0.62–0.95) and recovery time in post-anesthesia care unit (PACU) (OR, 0.69; 95% CI, 0.56–0.98) were identified as significant predictors associated with patient satisfaction.

Conclusion: A subanesthetic dose of esketamine (0.15–0.3 mg/kg/h) as an adjuvant can improves the sedative and analgesic effects of dexmedetomidine and remifentanil during anesthesia for liposuction surgery.

Clinical Trial Registration: ChiCTR2400080363.

Keywords: esketamine, sedation, analgesia, satisfaction, liposuction

Introduction

Liposuction, a frequently performed plastic surgical procedure, primarily aims to improve body contour and aesthetics by eliminating excess fat from specific areas of the body.[1] Currently, liposuction procedures primarily employ three well-recognized anesthesia techniques. The traditional approach, tumescent local anesthesia (TLA), carries the risk of toxicity from local anesthetic.[2] Additionally, it may offer inadequate pain control, which can lead to involuntary patient

movement during the operation, thereby potentially affecting the quality and satisfaction of surgical results.[3] On the other hand, general anesthesia often leads to an extended recovery time and is associated with a higher likelihood of experiencing nausea, vomiting, and sore throat due to the use of intubation.[4,5]

Typically, the most intense discomfort experienced during liposuction surgery arises during the administration of tumescent fluid or TLA.[6] Therefore, sedation anesthesia combined with TLA allows for flexible adjustment of anesthesia depth according to surgical progress, but also helps prevent complications associated with prolonged periods in a passive position.[7] Achieving ideal sedation and analgesia for liposuction necessitates high-quality anesthesia, which must maintain moderate sedation depth while ensuring respiratory and circulatory stability. However, an optimal sedation regimen for plastic surgeries, such as liposuction, has yet to be established.

Sedation and analgesia have been achieved with dexmedetomidine combined with different adjuncts like remifentanil or sufentanil in liposuction.[8] A significant challenge during sedation and analgesia with dexmedetomidine and remifentanil is to maintain a delicate balance between the depth of anesthesia and spontaneous breathing.[9,10] Dexmedetomidine exerts sedative and hypnotic effects by acting on α2 receptors in locus coeruleus and activating endogenous sleep-promoting pathways.[11] Remifentanil, as a short-acting opioid analgesic, is associated with a higher risk of respiratory depression.[12] While esketamine can effectively antagonize remifentanil-induced respiratory depression.[13] Therefore, esketamine combined with dexmedetomidine and remifentanil may have more desirable effect of sedation and analgesia.

Ketamine is a racemic mixture of two enantiomers, S-ketamine (esketamine) and R-ketamine.[14] Perioperative anxiety, which can worsen postoperative pain, depression, and sleep after surgery, may be alleviated by esketamine due to its potent action on the N-methyl-D-aspartate receptor (NMDAR), with benefits extending to various aspects of postoperative recovery, such as treatment-resistant depression and anxiety.[15,16] Studies indicate that operative intravenous 0.25 or 0.5 mg/kg ketamine can reduce immediate post-surgical pain and the risk of postpartum depression,[17–19] while intraoperative 0.3 mg/kg/h esketamine infusion improves sleep quality following gynecological laparoscopic surgery.[20] Moreover, its 1 mg/kg intranasal use in pediatric dental procedures shows significant anxiety reduction.[21] All the above studies demonstrate the role of esketamine in maintaining stable hemodynamics and improving the comfort of patients during the perioperative period.[22]

Currently, there are limited data on the efficacy and safety of a subanesthetic dose of esketamine (0.15–0.30 mg/kg/h), used as an adjuvant to dexmedetomidine and remifentanil, in sedation anesthesia for patients undergoing liposuction surgery. Therefore, this study aimed to observe the effect of a subanesthetic dose of esketamine on the satisfaction of both the patient and the surgical team when used with dexmedetomidine and remifentanil during anesthesia for liposuction surgery, and to provide a clinical basis and selection for the optimization of sedation and analgesia in plastic surgical procedures.

Material and Methods
Ethics and Trial Registration
The study protocol was approved by the Ethics Committee of the Plastic Surgery Hospital, Chinese Academy of Medical Sciences (Ethics Number: (2023) Registration No. (226), Head: Prof. Dr. Wei), and the study was registered in the Chinese Clinical Trials Registry (Registration number: ChiCTR2400080363. Principal Investigator: Wei Lingxin). All the participants provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice.

Inclusion and Exclusion Criteria
A prospective, single-center, double-blind, randomized clinical trial was performed in the Plastic Surgery Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China between December 30, 2023, and March 30, 2024, were eligible for this trial. The inclusion criteria were: (1) patients aged 18–60 years, undergoing liposuction; (2) American Society of Anesthesiologists (ASA) physical status I to II (with I indicating a healthy patient and II a patient with mild systemic disease); and (3) voluntary participation and signed an informed consent form.

The exclusion criteria were as follows: (1) acute and/or chronic pain before surgery; (2) administration of analgesic drugs within 48 h of surgery; (3) history of congenital heart disease, arrhythmia, or hypertension; (4) severe lung disease in the past month; (5) contraindications or allergy to esketamine; (6) history of severe mental or neurological diseases, drug or psychotropic drug abuse; and (7) cognitive dysfunction or inability to communicate.

Randomization and Blinding

In this study, all patients with informed consent were assigned sequential inclusion numbers and randomly assigned in a 1:1 ratio to two groups: Group E received intravenous esketamine infusion 0.15–0.3 mg/kg/h, Group C received an equivalent volume of saline. Assignment was achieved using sealed envelopes with an allocation result generated by a computerized random number generator and permuted block randomization strategy. The corresponding serial number envelope was opened on the day of the procedure to reveal allocation. A nurse anesthetist who was not involved in the liposuction procedure prepared the drugs in identical syringes labeled with the study drug numbers only. The anesthesiologist performed anesthesia according to the instructions in the envelope. The patients, surgical team, anesthesiologists, nurses, data collectors, and statistical analysts were blinded to the group allocation.

Study Interventions

This study was designed as a prospective, single-center, double-blind, randomized controlled trial. All patients underwent TLA combined with intravenous sedation by anesthesiologists from the same research team, and all data were collected by another anesthesiologist, both of whom were blinded to the patient allocation group. All procedures were performed by the same team.

Preoperatively, all the patients were instructed to fast, water intake was restricted, and drug use was prohibited. An anesthesia nurse who was unaware of the group assignments dispensed the medications. On admission, routine monitoring included electrocardiography (ECG), oxygen saturation (SpO_2), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), end-tidal CO_2 pressure ($PetCO_2$), bispectral index (BIS), and modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) score. All patients were provided with oxygen at 5 L/min via a nasal oxygen catheter with a carbon dioxide capture capability.

For the induction of anesthesia, esketamine was diluted to 50mL at a concentration of 1 mg/mL, labeled as Drug 1, and the control Drug 1 was 50mL of saline. Both remifentanil and dexmedetomidine were diluted to 20mL at concentrations of 50ug/mL and 10ug/mL, labeled Drugs 2 and 3, respectively. After establishing peripheral venous access, midazolam 0.03 mg/kg, dexamethasone 5 mg and tropisetron 0.1 mg/kg were administered. Anesthesia was induced with an intravenous infusion of Drug 1 (esketamine or saline) 0.3 mg/kg/h, Drug 2 (remifentanil) 6 ug/kg/h and Drug 3 (dexmedetomidine) 3 ug/kg/h. When patient's MOAA/S score was between 2–3, TLA was started, and after the injection, esketamine and dexmedetomidine were reduced to 0.15 mg/kg/h and 1ug/kg/h, respectively. Because of the influence of esketamine on the BIS value, the BIS value was only used as a reference index for the depth of anesthesia.[23] The level of sedation was targeted to an MOAA/S score of approximately 3 points and a BIS value of 60–80 throughout the surgery. If the MOAA/S score was >3 or BIS value was > 80, midazolam was increased in increments of 0.02 mg/kg. If the patients made physical or verbal expressions of pain, according to the anesthesiologist personal habits, the doses of remifentanil or sufentanil were increased in increments of 0.02 ug/kg/min or 0.1 ug/kg. When the BIS value was < 60, the injection rate of the three drugs reduced by 50% from the original level. Opioids were discontinued at the end of surgery. Drug 1 (esketamine or saline) was discontinued, and intravenous ketorolac tromethamine 30 mg was administered 30 minutes before the end of surgery.

Surgery was initiated by administration of 0.25–0.50% lidocaine 1:400,000 adrenaline and tumescent fluid (saline 1000mL + adrenaline 1 mg + lidocaine 400 mg) to the incision line as a local anesthetic to induce swelling and firmness of the surgical area. If a patient developed sinus bradycardia (HR < 50 beats/min), intravenous atropine was administered at increments of 0.5 mg. If a patient experienced hypotension (SBP < 90 mmHg or a reduction > of > 20% from the baseline blood pressure), intravenous ephedrine was administered in increments of 6 mg. If respiratory depression (respiratory rate dropping < 8 breaths/min or absence of breathing for > 10s), or hypoxemia (SpO_2 < 90%) occurred, jaw

thrust was used to improve ventilation. Other perioperative adverse events were recorded and managed in accordance with clinical operation standards.

Upon completion of liposuction surgery, the patients were transferred to the recovery room for at least 60 min. The patients were able to leave the operating room when they were fully awake and had stable vital signs, with an Aldrete score of ≥ 9.

Observed Parameters

The primary outcome was the satisfaction of the patient and surgical team with the procedure, which was quantified using a five-point Likert scale.[24,25] Overall satisfaction with body appearance after liposuction surgery was rated on a 5-point Likert scale of 1–5, where 1 is "poor", 2 is "fair", 3 is "good", 4 is "very good", and 5 is "excellent". The evaluation was made on the discharge date, within 1–3 days after surgery. Secondary outcomes included patients' AIS scores on postoperative day 1 (POD 1) and HADS scores on postoperative day 3 (POD 3). Hemodynamic and respiratory parameters, including SBP, DBP, HR, RR, $PetCO_2$, and SpO_2, along with MOAA/S scores and BIS values, were recorded at various time points: baseline (T0), 15 min after anesthesia administration (T1), at the start of surgery (T2), 1 h into surgery (T3), and at the end of surgery (T4). Intraoperative complications included respiratory depression, hypoxemia, sinus bradycardia, hypertension, hypotension, and body movement. Postoperative complications included hypersomnia, xerostomia, sinus bradycardia, nausea and vomiting, headache, shivering, and nightmares.

The AIS consists of 8 items: waking up at night, sleep induction, final awakening, total sleep duration, sleep quality, well-being, functional ability, and daytime sleepiness. AIS was scored on a 24-point scale, which was recorded on POD 1, where 0–3 points indicated no sleep disorder; 4–6 points defined as suspected insomnia; and 7–24 points defined as insomnia.

The HADS consists of 14 questions, with 7 items each for the anxiety and depression subscales. The score for each item ranged from 0 to 3 points, and the scores were summed to yield separate scores for anxiety (HADS-A) and depression (HADS-D). Scores of ≥ 8 points were considered indicative of depression or anxiety.

The MOAA/S scale[26] was scored on a 5-point scale where 5 points indicated that the patient was fully awake and readily responded to their name spoken in a normal tone; 4 points indicated that the patient was slow to respond to their name spoken in a normal tone; 3 points indicated that the patient did not respond to their name spoken in a normal tone, and only responded after their name was called loudly and repeatedly; 2 points indicated that the patient did not respond to their name called loudly and repeatedly, and only responded to prodding and shaking; and 1 point indicated that the patient did not respond to prodding and shaking but responded to a noxious stimulus.

Sample Size Calculation

The sample size calculation was based on the results of our preliminary study in 60 patients, in which the mean $\pm$ standard deviation of patient satisfaction score was 4.7 ± 0.6 in Group E and 4.4 ± 0.7 in Group C. Using G-power software (v.3.1.9.7), we calculated a sample size of 152 to achieve a power of 0.8 and an alpha error of 0.05. Assuming a dropout rate of 10%, 169 patients were recruited for the trial.

Statistical Analysis

Statistical analysis was performed using the SPSS software 29.0 (SPSS Inc., Chicago, IL, United States) and GraphPad Prism (version 10.0.0). The normality of the data distribution was examined using the Shapiro–Wilk test. Continuous variables with normal distribution are presented as mean $\pm$ SD, and continuous variables with non-normal distribution are represented by median (interquartile range) and 25th and 75th percentiles (p25, p75). Categorical variables were expressed as frequencies (%). Normally distributed data between the two groups were assessed using two independent sample t-tests, and variables at different time points within each group were compared using repeated measures ANOVA. Continuous variables with non-normal distributions were compared between the two groups using the Mann–Whitney U-test. Categorical data were compared using the $\chi2$ test or Fisher's exact test as appropriate. An ordinal logistic regression model was used to assess the predictors associated with patient satisfaction. Statistical significance was set at $P < 0.05$.

Results

## Patient Inclusion and Demographic Characteristics

Between December 31, 2023, and March 31, 2024, 169 patients were assessed for eligibility, and 11 were excluded before randomization. Overall, 158 patients were randomly allocated: 79 in Group E and 79 in Group C. Among these, 3 patients were excluded from the analysis for changing to general anesthesia. Thus, 155 patients were finally analyzed in our study, with 78 in Group E and 77 in Group C, respectively (Figure 1). The distribution of procedures among the 155 patients by body site was: 72 cases for abdomen, 28 cases for bilateral thighs, 18 cases for bilateral gynecomastia in males, 11 cases for bilateral accessory breasts, 9 cases for bilateral upper arms, 8 cases for the face and neck, 5 cases for the back, and 4 cases for bilateral lower legs. The demographic data in terms of age, gender, height, weight, body mass index (BMI), ASA classification, anesthesia time, operative time, recovery time in PACU, preoperative AIS scores and HADS scores for anxiety and depression were no significant differences in both groups (Table 1).

Patient and Surgical Team Satisfaction Scores

Patient satisfaction with the procedure was significantly higher in Group E compared to Group C (4.7 ± 0.6 vs 4.2 ± 0.7, $P < 0.001$). Surgical team with the procedure was also higher in Group E compared to Group C (4.7 ± 0.5 vs 4.4 ± 0.7, $P = 0.005$) (Figure 2 and Table 2). Ordinal logistic regression identified postoperative sleep quality (OR, 0.70; 95% CI, 0.62–0.79), anxiety level (OR, 0.77; 95% CI, 0.62–0.95) and recovery time in the PACU (OR, 0.69; 95% CI, 0.56–0.98) were identified as significant predictors associated with patient satisfaction. (Figure 3).

Postoperative Sleep Quality, Anxiety and Depression Level

The AIS scores (4 [1, 6] vs 5 [2, 9], $P = 0.012$) in Group E were significantly lower than those in Group C on POD 1. The HADS-A scores (1 [0, 3] vs 2 [0, 6], $P = 0.012$) were significantly lower in Group E than in Group C on POD 3. There were no differences in HADS-D scores on POD 3.
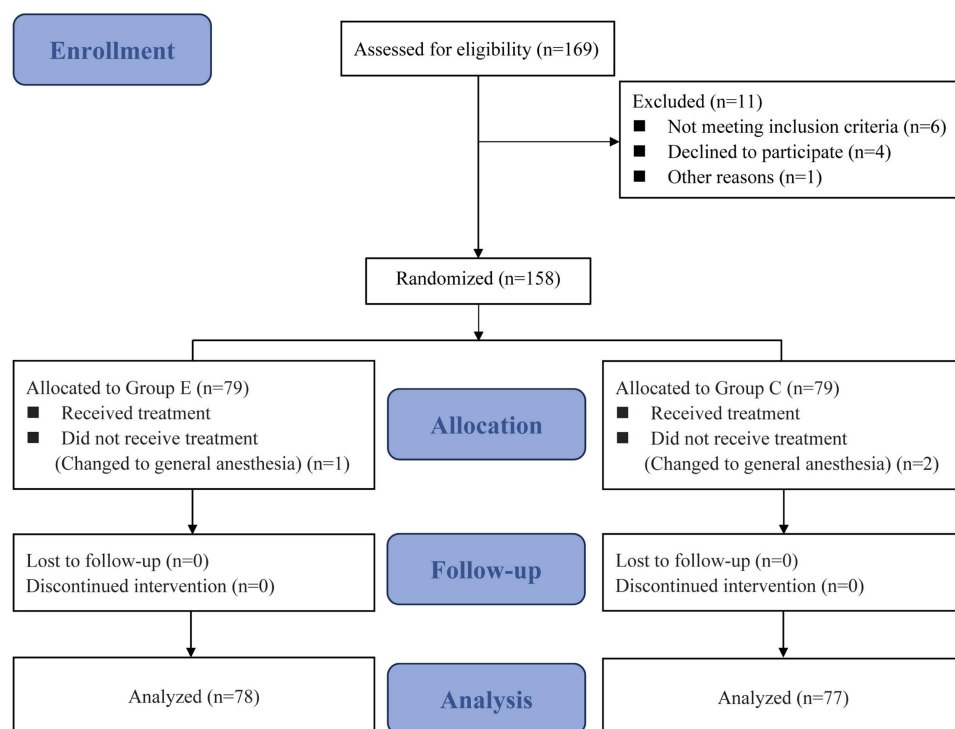
Figure 1 Participant flowchart.
Abbreviations: E, esketamine; C, control.

**Table 1** Patient Demographic and Baseline Characteristics

Characteristic	Group E (n=78)	Group C (n=77)	P value
Age (years)	33.3±10.1	33.1±10.9	0.904
Gender (n%)			0.603
Male	20 (25.6%)	17 (22.1%)	
Female	58 (74.4%)	60 (77.9%)	
Height (cm)	165 (160, 172)	165 (160, 172)	0.583
Weight (kg)	61.5 (55, 73)	58 (52, 70)	0.112
BMI (kg/m2)	22.3 (20.6, 25.5)	21.7(19.7, 23.3)	0.066
ASA Physical Status Classification (n%)			0.719
I	73 (93.6%)	74 (96.1%)	
II	5 (6.4%)	3 (3.9%)	
Anesthesia time (min)	180 (122, 233)	195 (138, 270)	0.117
Operative time (min)	150 (110, 211)	160 (110, 240)	0.342
Preoperative AIS scores	4 (3, 6)	4 (2, 7)	0.727
Preoperative HADS-A scores	2 (1, 4)	3 (1, 5)	0.413
Preoperative HADS-D scores	1 (0, 3)	2 (0, 4)	0.619

Notes: Data are presented as the mean ± standard deviation and were compared using two independent sample t-tests. Data presented as median (interquartile range) and the 25th and 75th percentiles (p25, p75) were compared using the Mann–Whitney U-test. Data reported as the number of patients (%) were compared using the Pearson's χ^2 test or Fisher's exact test. Statistical significance was set at P <0.05.
Abbreviations: E, esketamine; C, control; ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); AIS, Athens Insomnia Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

Hemodynamic and Respiratory Results

Hemodynamic changes in the two groups during surgery are shown in Table 3 and Figure 4. There were no significant differences in SBP, DBP, MAP, HR, SpO_2, RR, $PetCO_2$, BIS, or MOAA/S scores at T0 (P > 0.05). SBP were significantly lower at T2 in Group C than in Group E (107.8 ± 12.2 vs 103.7 ± 13.3, P < 0.05). RR were significantly
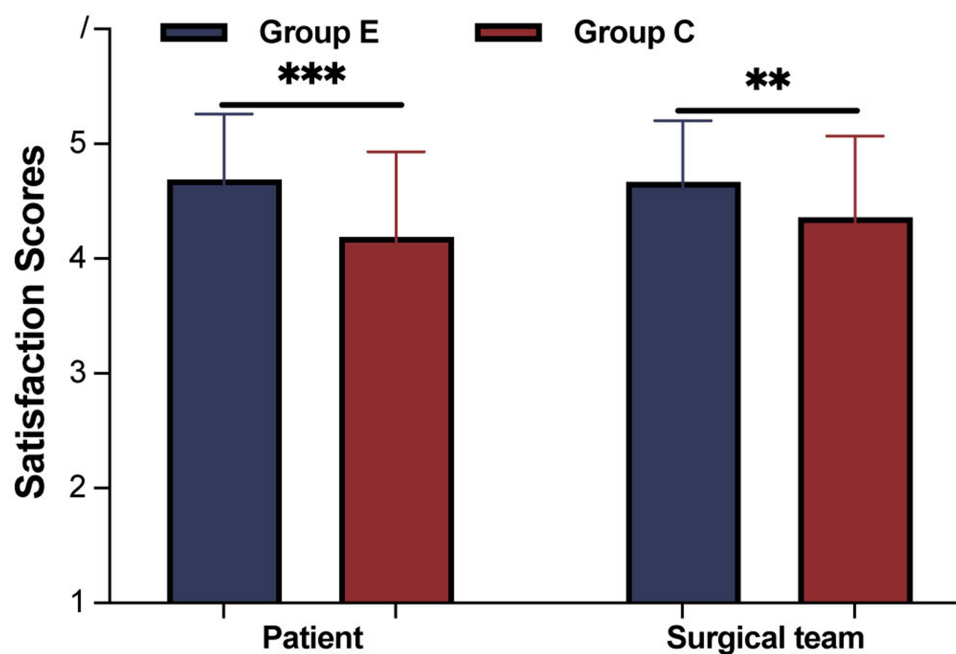
Figure 2 The satisfaction scores of patient and surgical team. Statistical significance was set at **P<0.05, ***P<0. 001.
Abbreviations: E, esketamine; C, control.

Table 2 Satisfaction Scores, Sleep Quality, Anxiety and Depression Scores on Postoperative Days

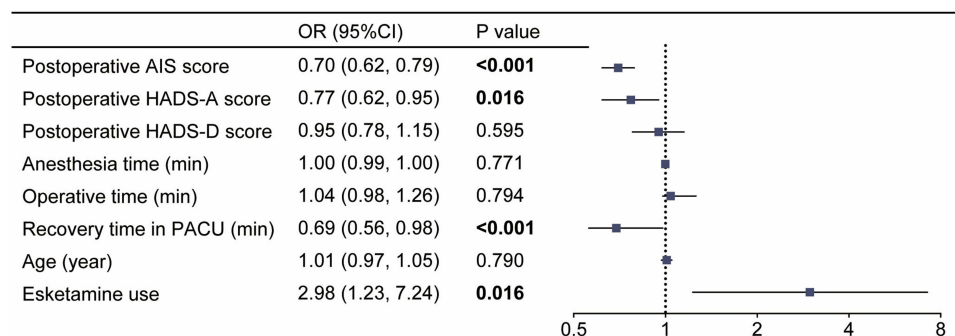|	Group E (n=78)	Group C (n=77)	P value
Patient satisfaction scores	4.7 ± 0.6	4.2 ± 0.7	**<0.001**
Surgical team satisfaction scores	4.7 ± 0.5	4.4 ± 0.7	**0.005**
POD 1 AIS scores	4 (1, 6)	5 (2, 9)	**0.012**
POD 3 HADS-A scores	1 (0, 3)	2 (0, 6)	**0.012**
POD 3 HADS-D scores	1 (0, 4)	1 (0, 3)	0.868

Notes: Data are presented as the mean ± standard deviation and were compared using two independent sample t-tests. Data presented as median (interquartile range) and the 25th and 75th percentiles (p25, p75) were compared using the Mann–Whitney *U*-test. Statistical significance was set at P<0.05. Significant results are in bold.
Abbreviations: E, esketamine; C, control; POD, postoperative day; AIS, Athens Insomnia Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

higher in Group E than in Group C at T1 (10.2 ± 2.7 vs 9.2 ± 2.6, P = 0.026), T1 (10.9 ± 2.4 vs 9.4 ± 2.8, P < 0.001) and T3 (10.4 ± 2.2 vs 9.5 ± 2.3, P = 0.012). And PetCO$_2$ in Group E than in Group C were significantly lower at T1 (43.9 ± 4.7 vs 46.0 ± 5.1, P = 0.008), T2 (45.1± 5.4 vs 48.6 ± 6.0, P = 0.002), T3 (46.0 ± 5.7 vs 49.0 ± 6.1, P = 0.002) and T4 (43.9 ± 4.7 vs 45.9 ± 6.0, P = 0.022). There were also differences between the two groups in the monitoring indicators of the depth of anesthesia and sedation. Including BIS value at T1 (Group E vs Group C:78.9 ± 7.0 vs 74.9 ± 8.3, P = 0.012), T2 (Group E vs Group C:75.0 ± 11.7 vs 67.8 ± 12.1, P = 0.004) and T3 (Group E vs Group C:72.3 ± 10.0 vs 66.8 ± 9.2, P = 0.006). And MOAA/S score at T1 (Group E vs Group C:4.2 ± 0.5 vs 4.0 ± 0.3, P = 0.010) and T2 (Group E vs Group C:3.5 ± 0.5 vs 3.8 ± 0.4, P = 0.002).

The Duration of Procedure and Drug Consumption

The Duration of Procedure, intraoperative drug dosage, and clinical complications in the two groups are shown in Table 4. First, there were no significant differences in the induction time between the two groups. Second, Group E had a significantly lower total consumption of opioids, such as remifentanil (700 [480, 900] vs 800 [500, 1200], P = 0.023) and sufentanil (0 [0, 4] vs 5 [2.5, 7.7], P < 0.001) than Group C. The induction consumption of dexmedetomidine in Group E was significantly higher than that in Group C (40 [26, 50] vs 30 [20, 42], P = 0.007). The consumption of midazolam in Group E was significantly lower than that in Group C during induction (1.1 [1.0, 1.3] vs 1.5 [1.0, 2.0], P = 0.004) and during the entire surgery (3.6 [2.0, 5.0] vs 4.5 [3.0, 6.5], P = 0.007).

	OR (95%CI)	P value
Postoperative AIS score	0.70 (0.62, 0.79)	**<0.001**
Postoperative HADS-A score	0.77 (0.62, 0.95)	**0.016**
Postoperative HADS-D score	0.95 (0.78, 1.15)	0.595
Anesthesia time (min)	1.00 (0.99, 1.00)	0.771
Operative time (min)	1.04 (0.98, 1.26)	0.794
Recovery time in PACU (min)	0.69 (0.56, 0.98)	**<0.001**
Age (year)	1.01 (0.97, 1.05)	0.790
Esketamine use	2.98 (1.23, 7.24)	**0.016**

Figure 3 Forest plot of factors analyzed for association with satisfaction scores of patient in multivariable ordinal logistic regression. Statistical significance was set at P <0.05. Significant results are in bold.
Abbreviations: AIS, Athens Insomnia Scale; Hads-A, Hospital Anxiety and Depression Scale for Anxiety; HADS-D, Hospital Anxiety and Depression Scale for Depression; PACU, post-anesthesia care unit.

Table 3 Changes in Vital Signs of Patients During Liposuction

Characteristic	Group E (n=78)	Group C (n=77)	P value
SBP, mmHg			
Baseline (T0)	120.2±15.3	120.8±19.5	0.826
15 min after anesthesia administration (T1)	110.6±12.6	107.6±14.2	0.176
Surgery onset (T2)	107.8±12.2	103.7±13.3	**0.045**
1 h of surgery (T3)	106.1±11.0	104.2±13.7	0.338
End of surgery (T4)	110.3±12.5	110.2±15.1	0.936
DBP, mmHg			
Baseline (T0)	73.5±9.9	73.7±9.9	0.899
15 min after anesthesia administration (T1)	66.3±9.4	65.5±9.7	0.615
Surgery onset (T2)	63.4±10.2	62.1±10.1	0.401
1 h of surgery (T3)	60.8±8.1	61.6±9.7	0.577
End of surgery (T4)	63.6±9.4	66.0±11.3	0.142
MAP, mmHg			
Baseline (T0)	89.0±10.7	89.4±12.0	0.852
15 min after anesthesia administration (T1)	81.1±9.5	79.5±9.8	0.327
Surgery onset (T2)	78.2±9.6	75.9±10.1	0.149
1 h of surgery (T3)	75.9±7.7	75.8±10.0	0.620
End of surgery (T4)	79.2±9.1	80.8±11.7	0.222
HR, bpm			
Baseline (T0)	72.1±10.4	75.4±10.9	0.053
15 min after anesthesia administration (T1)	64.9±9.3	66.2±9.7	0.359
Surgery onset (T2)	67.5±8.9	67.7±9.3	0.845
1 h of surgery (T3)	65.5±8.3	67.7±8.9	0.110
End of surgery (T4)	68.6±9.6	69.7±10.1	0.496
SpO$_2$, %			
Baseline (T0)	99.8±0.7	99.6±0.6	0.163
15 min after anesthesia administration (T1)	99.3±1.9	99.3±1.5	0.896
Surgery onset (T2)	99.4±1.5	99.5±0.8	0.518
1 h of surgery (T3)	99.5±1.4	99.4±0.7	0.974
End of surgery (T4)	99.5±1.1	99.5±0.7	0.990
RR, bpm			
Baseline (T0)	15.3±2.1	15.3±2.7	0.938
15 min after anesthesia administration (T1)	10.2±2.7	9.2±2.6	**0.026**
Surgery onset (T2)	10.9±2.4	9.4±2.8	**<0.001**
1 h of surgery (T3)	10.4±2.2	9.5±2.3	**0.012**
End of surgery (T4)	12.4±2.4	11.7±2.3	0.055
PetCO$_2$, mmHg			
Baseline (T0)	38.7±2.9	39.5±3.8	0.333
15 min after anesthesia administration (T1)	43.9±4.7	46.0±5.1	**0.008**
Surgery onset (T2)	45.1±5.4	48.6±6.0	**0.002**
1 h of surgery (T3)	46.0±5.7	49.0±6.1	**0.002**
End of surgery (T4)	43.9±4.7	45.9±6.0	**0.022**
BIS			
Baseline (T0)	97.3±2.6	97.1±2.9	0.634
15 min after anesthesia administration (T1)	78.9±7.0	74.9±8.3	**0.012**
Surgery onset (T2)	75.0±11.7	67.8±12.1	**0.004**
1 h of surgery (T3)	72.3±10.0	66.8±9.2	**0.006**
End of surgery (T4)	83.0±7.8	82.2±7.2	0.613

(Continued)

Table 3 (Continued).

Characteristic	Group E (n=78)	Group C (n=77)	P value
MOAA/S			
Baseline (T0)	5.0±0.0	5.0±0.0	1.000
15 min after anesthesia administration (T1)	4.2±0.5	4.0±0.3	**0.010**
Surgery onset (T2)	3.5±0.5	3.8±0.4	**0.002**
1 h of surgery (T3)	3.1±0.8	3.0±0.7	0.409
End of surgery (T4)	4.3±0.7	4.6±0.5	0.155

Notes: Data are presented as mean ± standard deviation. Normally distributed data between the two groups were assessed using the Student's t-test, and variables at different time points within each group were compared using repeated measures ANOVA. Continuous variables with non-normal distributions were compared between the two groups using the Mann–Whitney U-test. Statistical significance was set at P <0.05. Significant results are in bold.
Abbreviations: E, esketamine; C, control; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; SpO_2, oxygen saturation; RR, respiratory rate; $PetCO_2$, end-tidal CO_2 pressure; BIS, bispectral index; MOAA/S, modified Observer's Assessment of Alertness/Sedation Scale.

Incidence of Adverse Events

As for clinical complications, the incidence of intraoperative bradycardia (0 (0%) vs 11 (14.3%), P < 0.001) and body movement (17 (21.8%) vs 32 (41.6%), P = 0.008) were significantly lower in Group E compared with Group C, and 2 patients in the Group E experienced nightmare. Intraoperative hypoxemia and hypertension were not observed in either group. There were no significant differences in intraoperative respiratory depression, hypotension, postoperative hypersomnia, xerostomia, bradycardia, nausea, vomiting, headache, shivering, and nightmares.

Discussion

The results of our study indicated that a subanesthetic dose of esketamine (0.15–0.3 mg/kg/h) improved the sedative and analgesic effects of dexmedetomidine and remifentanil during anesthesia in liposuction surgery. It could enhance the satisfaction scores of the patient and surgical team, improve sleep quality and anxiety levels, maintain hemodynamic and respiratory stability, decrease the consumption of opioids, thus optimizing the perioperative experience.

Sedation anesthesia is rapidly becoming a preferred choice in the realm of plastic surgery, particularly for procedures such as abdominoplasty.[27] This shift is propelled by accumulated expertise alongside incremental enhancements in local anesthesia and intravenous sedation anesthesia. In our study, the sedation protocol incorporating esketamine received higher satisfaction scores from both the patient and the surgical team. This has several clinical implications. For patients, satisfaction improvement is about their direct feedback about the surgical outcome and perioperative experience. Through ordinal logistic regression, we have identified several non-surgical predictors of procedure outcome satisfaction, including postoperative sleep quality, anxiety levels, recovery time in PACU, and the use of esketamine, which may indicate the importance of patient's perioperative experience including emotional distress and dysfunction in the perioperative period. For the surgical team, surgeon satisfaction scores can reflect the efficacy and efficiency of the surgical and anesthesia techniques, which may be associated with the best perioperative protocols. In conclusion, patient-reported outcome measures (PROMs) of procedure outcome satisfaction can provide meaningful clinical data to help doctors choose appropriate surgical methods and provide more valuable and meaningful individualized medical services for patients.[28]

The pursuit of aesthetic improvement often leads young women, a key demographic for liposuction, to experience heightened anxiety, depression, and sleep disturbances perioperatively. Subanesthetic doses of esketamine may mitigate these issues. Chen MH et al reported a single low-dose (0.5 mg/kg, intravenous infusion) ketamine can quickly lift depression.[29] Similarly, Gan SL et al reported perioperative administration of esketamine (0.1 mg/kg intravenous infusion before surgery, followed by 0.1 mg/kg/h during surgery) has been linked to fewer depressive symptoms post-thoracoscopic lung cancer surgery.[30] Qiu D et al reported intraoperative esketamine (0.3 mg/kg/h) has been shown to reduce postoperative sleep disturbances following gynecological laparoscopic surgery.[20] Our research suggests that
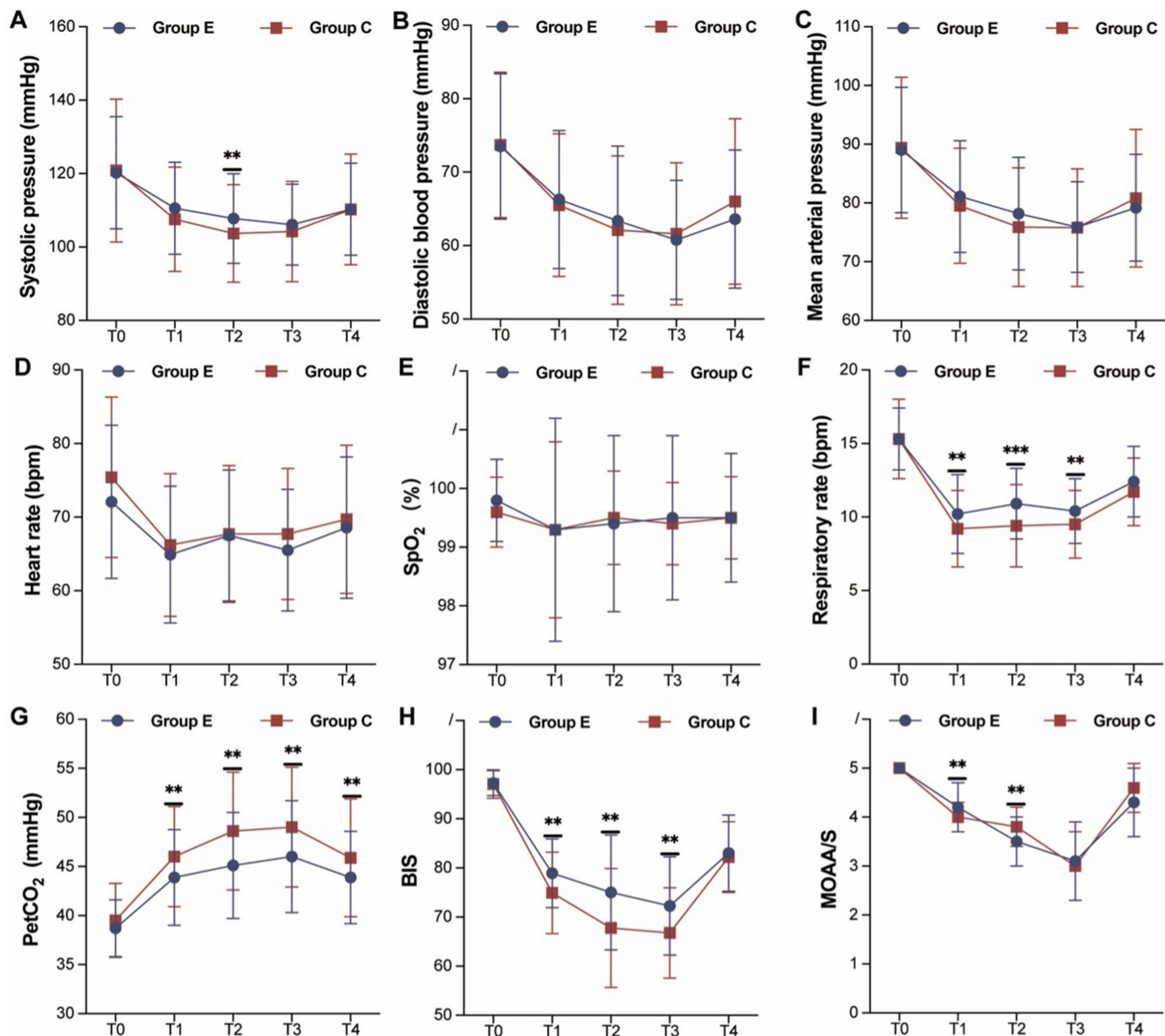
Figure 4 The results of repeated measurements of hemodynamic parameters. Systolic blood pressure (**A**), Diastolic blood pressure (**B**), Mean blood pressure (**C**), Heart rate (**D**), SpO₂ (**E**), Respiratory rate (**F**), PetCO₂ (**G**), BIS (**H**) and MOAA/S (**I**) of patient treated with dexmedetomidine and remifentanil or in combination with esketamine during liposuction. Statistical significance was set at **P<0.05, ***P<0.001.
Abbreviations: E, esketamine; C, control; SpO₂, Oxygen saturation; PetCO₂, End-tidal partial pressure of carbon dioxide; BIS, bispectral index; MOAA/S, modified Observer's Assessment of Alertness/Sedation Scale.

intravenous esketamine during liposuction surgery improves the postoperative sleep quality and relieve anxiety level for patients, though its effect on depression is less clear. The complexity of postoperative anxiety is shaped by factors such as sleep quality, pain management, and the overall postoperative experience. The intricate interplay between these variables requires extensive research to decipher the precise effect of esketamine on postsurgical emotional states.

Opioid-induced respiratory depression (OIRD) presents a significant concern in surgery; however, subanesthetic doses of esketamine may reduce opioid requirements and related preoperative complications.[31] Jonkman K et al reported that subanesthetic doses of esketamine counteract respiratory depression from opioids, such as remifentanil, by enhancing ventilatory CO_2 chemosensitivity.[13] Additionally, esketamine has been shown to increase cardiac output dose-dependently.[32] Zheng L et al demonstrated that combining propofol with esketamine not only improves safety but also decreases the likelihood of complications such as hypoxemia and hypotension in patients undergoing painless gastroscopy.[33] In our study also indicated that Group E required fewer opioids and experienced reduced intraoperative

Table 4 The Duration of Procedure, Drug Consumption and Complications During Perioperative Period

	Group E (n=78)	Group C (n=77)	P value
Induction time (from start to MOAA/S score 2–3, min)	17 (15, 20)	15 (12, 20)	0.058
Recovery time in PACU (min)	90 (90, 120)	120 (90, 120)	0.499
Induction dose			
Dexmedetomidine (ug)	40 (26, 50)	30 (20, 42)	**0.007**
Midazolam (mg)	1.1 (1.0, 1.3)	1.5 (1.0, 2.0)	**0.004**
Remifentanil (ug)	82 (70, 105)	83 (60, 127)	0.990
Total dose			
Dexmedetomidine (ug)	160 (114, 203)	170 (120, 220)	0.353
Midazolam (mg)	3.6 (2.0, 5.0)	4.5 (3.0, 6.5)	**0.007**
Remifentanil (ug)	700 (480, 900)	800 (500, 1200)	**0.023**
Sufentanil (ug)	0 (0, 4)	5 (2.5, 7.7)	**<0.001**
Intraoperative complications			
Respiratory depression	2 (2.6%)	6 (7.8%)	0.167
Body movement	17 (21.8%)	32 (41.6%)	**0.008**
Hypoxemia	0 (0%)	0 (0%)	1.000
Sinus bradycardia	0 (0%)	11 (14.3%)	**<0.001**
Nausea and vomiting	1 (1.3%)	0 (0%)	1.000
Headache	1 (1.3%)	1 (1.3%)	1.000
Shivering	1 (1.3%)	0 (0%)	1.000
Nightmare	2 (2.6%)	0 (0%)	0.497

Notes: Data are presented as median (interquartile range) and the 25th and 75th percentiles (p25, p75) were compared using the Mann–Whitney test. Data reported as the number of patients (%) were compared using the Pearson's χ^2 test or Fisher's exact test. Statistical significance was set at P <0.05. Significant results are in bold.
Abbreviations: E, esketamine; C, control; MOAA/S, modified Observer's Assessment of Alertness/Sedation Scale; PACU, post-anesthesia care unit.

bradycardia and patient movement, suggesting more stable hemodynamics without significantly affecting respiratory rate or end-tidal CO_2 pressure. It's recognized that ketamine can elevate the Bispectral Index (BIS) in anesthetized patients, potentially confounding its usefulness in gauging hypnotic administration.[23] Our findings also showed an increase in BIS values following a 0.3 mg/kg/h dose of esketamine dose. Therefore, we predominantly relied on the MOOA/S to assess sedation depth between the groups.

Administration of esketamine is known to potentially cause nausea and psychiatric symptoms such as prolonged sedation, nightmares, and dissociation in a dose-dependent manner, with psychic reactions observed in 5–30% of patients.[34,35] To mitigate such reactions, benzodiazepines such as midazolam are often recommended.[36] In our study, 2 of the 78 patients (less than 3%) in Group E, who had no prior depression, experienced nightmares during the surgery. Follow-up evaluations indicated that the patients' sleep quality was favorable on both the first and second nights following surgery, with no nightmares reported. To enhance the depth of sedation for all participants and mitigate potential psychological side effects, midazolam was administered, which also served to counter any mental disturbances potentially induced by esketamine. Subanesthetic esketamine doses (0.15–0.30 mg/kg/h) throughout the surgical procedure and the structurally higher selectivity of esketamine compared to ketamine, which may also explain the lack of significant differences in psychiatric side effects between the two groups observed in our research.[37,38] The nuances of esketamine's structural selectivity and its implications on side effects merit further investigation and reference to pertinent literature.

Research has shown that age related inverse dose relation of sedatives and analgesics.[39] Yeo H et al reported that precise dose adjustments of sedatives, accounting for not only weight but also age, sex, and alcohol consumption, are required to achieve safe, effective, and predictable conscious sedation.[40] Zhi D et al reported the shift from conscious sedation to general anesthesia during endovascular therapy because severe agitation, respiratory insufficiency or loss of

airway and so on.[41] Other factors like sex, hypertension, diabetes, smoking status, atrial fibrillation, blood pressure were not significantly associated with conversion to general anesthesia.

In our study, 3 of the 165 patients required a transition from sedation anesthesia to general anesthesia. Specifically, a 49-year-old individual in Group E exhibited body movement during administration of the swelling solution to the face and neck. Due to unconsciousness and inability to cooperate, the decision was made to switch to general anesthesia. Within the Group C, two patients, aged 55 and 50, experienced respiratory depression following the administration of 0.01ug/kg sufentanil to manage pain associated with the swelling solution injection, necessitating a change to general anesthesia for safety. However, 98% of the participants effectively underwent sedation and anesthesia. The mean age of participants in our study was 33 years. As age advances, there tends to be a decline in patient tolerance to sedative and analgesic medications, accompanied by an increase in the variability of individual responses.

The reticular activating system (RAS), a key player in modulating consciousness and arousal within the anesthesia context, may be indirectly influenced by esketamine due to its NMDA receptor antagonism, potentially altering the arousal state.[42] Existing research thoroughly examines anesthetic pharmacokinetics and dynamics across ages, yet the interaction of anesthetics with the RAS among different age groups remains less understood.[43] Therefore, further investigation into how sedation depth monitoring correlates with the RAS's role in anxiety arousal is warranted to enhance our understanding and management of anesthesia across diverse patient profiles.

Liposuction is becoming more common as an outpatient procedure performed concomitantly with other procedures.[44] As comfortable medical care and accelerated postoperative recovery become more prevalent, there's a rising demand for sedation and analgesia in many kinds of surgeries. The ideal sedation protocol must be safe and effective while considering patient comfort. This study showed that esketamine can effectively improve the analgesic and sedative effects of dexmedetomidine combined with remifentanil during anesthesia for liposuction surgery and enhance the satisfaction of the patient and surgical team.

However, this study has some limitations. Firstly, the main surgical procedure included was abdominal liposuction, and the enrolled subjects were not subdivided according to specific liposuction sites such as abdominal, thighs, upper arms, and so on, which may cause confounding bias. Secondly, no specific established or validated PROMs were used in liposuction surgery. Furthermore, due to the nature of liposuction surgery predominantly attracting female participants, the study observed a gender imbalance in its results, with a higher representation of women than men. Finally, patients aged > 60 years were excluded from this study. In the future, multicenter prospective randomized controlled trial studies with a larger sample capacity should be performed to verify the results of this study.

Conclusion

Our findings suggest that a subanesthetic dose of esketamine (0.15–0.30 mg/kg/h), when used as an adjunct to dexmedetomidine and remifentanil for sedation and analgesia in liposuction anesthesia, can improve the satisfaction of both patients and the surgical team, as well as postoperative sleep and anxiety levels. It can also maintain more stable intraoperative hemodynamics and respiratory parameters, lower opioid consumption, and a lower incidence of intraoperative respiratory depression, sinus bradycardia, and body movement. Our findings provide a reference for clinical sedation anesthesia during plastic surgical procedures.

Data Sharing Statement

All data generated or analyzed during this study have been included in the published article. Further inquiries regarding the datasets can be directed to the corresponding author, Professor Lingxin Wei, upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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