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ORIGINAL RESEARCH

Effect of Intraoperative Intravenous Infusion of Esketamine Combined with Dexmedetomidine on Postoperative Sleep Disturbance in Patients Undergoing Radical Mastectomy

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Objective: Postoperative sleep disturbance(POSD) is a problem in breast cancer patients after surgery. Little is known about the differences in the treatment of POSD with esketamine combined with dexmedetomidine under the same circumstances. We investigated the effects of intraoperative esketamine combined with intravenous dexmedetomidine on the incidence of POSD and postoperative sleep architecture.

Methods: A single-center, randomized, double-blind controlled trial was conducted. A total of 100 participants were randomly assigned to four groups: the esketamine group (Group E), the dexmedetomidine group (Group D), the esketamine combined with dexmedetomidine group (Group ED), and the control group (Group S) (n=25 each). The intervention drugs were continuously infused until the placement of the drainage tube. The primary outcome measure was the incidence of POSD, defined as an Athens Insomnia Scale (AIS) score >6 on at least one of the first three postoperative days. The secondary outcome measure was the duration of sleep structure, which was collected using the Fitbit Charge 2® smartwatch (Fitbit, Inc. San Francisco, California, USA).

Results: In the first three postoperative days, the incidence of POSD was similar across the four groups (P=0.947). However, on postoperative day 3 (POD3), there was a significant interaction between esketamine and dexmedetomidine (P=0.004). Further simple effect analysis revealed that, in the absence of esketamine, dexmedetomidine had a significant effect on POSD on POD3 (OR=0.196, [0.056–0.691]; P=0.019). In the absence of dexmedetomidine, esketamine had a significant effect on POSD on POD3 (OR=0.248, [0.074–0.833]; P=0.042). Dexmedetomidine reduced rapid eye movement (REM) sleep on postoperative day 1 (P=0.042). Esketamine reduced nighttime awakening time on POD1 (P=0.036) and POD3 (P=0.020).

Conclusion: Intraoperative infusion of esketamine combined with dexmedetomidine had no significant effect on POSD, but dexmedetomidine reduced REM sleep, and esketamine reduced the nocturnal awakening time.

Keywords: breast cancer, sleep disturbance, esketamine, dexmedetomidine

Introduction

Breast cancer is currently the second leading cause of cancer-related deaths among women, with an increasing incidence rate year by year, and the increase is even greater among younger women.[1] Modified radical mastectomy is an effective clinical treatment for breast cancer patients, but POSD are a common complication. This disorder may be caused by various factors, including surgical trauma, postoperative pain, side effects of anesthetic drugs, anxiety, and environmental

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factors. Research shows that the incidence of POSD in patients undergoing general anesthesia on the first postoperative day (ranging from approximately 23% to 80%) is significantly higher than that in patients undergoing neuraxial anesthesia. This difference is mainly influenced by the dosage of opioid drugs.[2,3] Among breast cancer patients, this proportion is even higher, reaching 42%-69%, which is significantly higher than in other cancer types. This may be due to changes in hormone levels and the effects of chemotherapy drugs.[4] Many women even experience POSD for an extended period, increasing their risk of developing heart disease, obesity, diabetes, cognitive disorders, mental illnesses, and even death. It is necessary to explore appropriate anesthesia methods for this population to prevent and improve postoperative sleep disorders.

General anesthesia (GA) has many of the same neurophysiological features as the natural sleep process does, and given the similarity between sleep and GA states, the shared circuit hypothesis that different types of GA drugs may exert their hypnotic effects through overlapping neural networks has become a hot topic of research.[5] Ketamine is an N-methyl-D-aspartate receptor (NMDAR) antagonist, a racemic mixture of equal amounts of (R)-ketamine (arketamine) and (S)-ketamine (esketamine), with esketamine having a greater affinity for NMDARs.[6,7] For patients with refractory depression, esketamine offers new therapeutic potential.[8,9] Sleep disorders often cooccur with depression, and in patients with major depression, the rapid antidepressant effects of ketamine are associated with reduced arousal and increased total sleep, slow wave sleep (SWS), slow wave activity (SWA) and REM sleep.[10] Ketamine also increases brain-derived neurotrophic factor (BDNF) levels, and cortical BDNF, a modulator of neuroplasticity, has been shown to induce stage N3 of sleep, suggesting a beneficial effect of ketamine on sleep.[11] Dexmedetomidine, an α2-adrenoceptor agonist with both sedative and analgesic properties, induces the neurophysiological closest approximation to nonrapid eye movement(NREM) sleep through the activation of endogenous sleep-promoting pathways.[12,13] Prophylactic low-dose dexmedetomidine infusion increased the percentage of N2-stage sleep in elderly patients admitted to the ICU after noncardiac surgery and not requiring mechanical ventilation. It also prolongs the duration of total sleep time, increases sleep efficiency, decreases the percentage of stage N1 sleep, and ultimately improves the subjective sleep quality of patients.[14,15]

Traditionally, polysomnography (PSG) is the gold standard for sleep studies. However, the environment and instrumentation for routine PSG can be uncomfortable, create anxiety, and even disrupt sleep.[16] In recent years, the accuracy and reliability of the wearable portable device Fitbit Charge 2® (Fitbit, Inc., San Francisco, CA, USA) smart bracelet for sleep studies have been demonstrated by validating its device according to PSG and portable single-channel EEG sleep monitoring devices.[17–19] In our study, the AIS was used to collect perioperative sleep parameters.

The efficacy of the combination of esketamine and dexmedetomidine for the prevention of sleep disorders after breast cancer surgery has not been reported. We conducted this placebo-controlled, double-blind clinical trial with a four-group design. We hypothesized that an anesthetic regimen of esketamine combined with dexmedetomidine would reduce the incidence of POSD and improve postoperative sleep architecture.

Methods

Study Design

This study was approved by the Clinical Trial Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2024-KL063-01) and registered with the China Clinical Trial Registry (ChiCTR2400086026). This single-center, prospective, double-blind, randomized controlled trial was conducted from July to September 2024 with written informed consent signed by all participants, and all procedures followed the principles of the Declaration of Helsinki and conformed to the harmonized standards of the guidelines for reporting trials. We maintained the principle of randomization and stopped recruitment until target collection was complete.

Participants

We included women who underwent modified radical mastectomy for breast cancer under general anesthesia, aged 18–65 years, with an American Society of Anesthesiologists (ASA) physical status classification of I--III, a body mass index between 15 and 30 kg/m^2, and signed written informed consent. Patients who met any of the following criteria were excluded: preoperative sleep disorders; AIS score >6 or Pittsburgh Sleep Quality Index (PSQI) score ≥10 points; long-

term use of sedative-hypnotic medications to aid in sleep; communication comprehension disorders (language disorders, psychiatric abnormalities) who were unable to complete the scale test; sick sinus node syndrome; severe sinus bradycardia (HR <50 beats/min); atrioventricular block of degree II or greater without a pacemaker; obstructive sleep apnea syndrome with a STOP-Bang score ≥3; severe hepatic or renal dysfunction; serious blood pressure or intracranial pressure; untreated or undertreated hyperthyroidism; and allergy to the drugs involved in this trial. Using a computer-generated randomization table, patients were randomly assigned to receive esketamine, dexmedetomidine, esketamine combined with dexmedetomidine, or an equal volume of saline at a 1:1:1:1 ratio. Group E received an intraoperative infusion of 0.3 mg/kg/h esketamine, group D received an intraoperative infusion of 0.4 μg/kg/h dexmedetomidine, group ED received an intraoperative infusion of 0.3 mg/kg/h esketamine combined with 0.4 μg/kg/h dexmedetomidine, and an equal volume of placebo (0.9% saline) was infused intraoperatively in group S. The intervention medications were continuously infused intraoperatively until placement of the surgical drain. Esketamine, dexmedetomidine, and saline preparations were prepared in identical 20 mL syringes by the same anesthesia specialist who was not responsible for patient follow-up. Randomized sequences were generated by a specific researcher via blocks of size 4 or 8, which were then placed in the form of cards in sealed and opaque envelopes. The grouping was communicated to the anesthesiologist before surgery by a nurse who was unaware of the purpose of our study. The researcher responsible for preoperative follow-up and intervention was the same person, while another person was unaware of the grouping for postoperative data collection. All surgeons were blinded to the grouping and purpose of our study.

Anesthesia Procedure

Each subject fasted for 6 hours and then was dehydrated for 2 hours. After the patients entered the operating room, routine intraoperative monitoring was established with pulse oximetry, electrocardiogram, noninvasive blood pressure measurement, and depth of anesthesia monitoring, venous access was opened, and if necessary, an action vein puncture was performed for catheterization, and the anesthesiologist recorded the baseline values. After preoxygenation for 3 min, 0.02–0.04 mg/kg midazolam, 0.3–0.5 μg/kg sufentanil, 0.15–0.30 mg/kg etomidate, and 0.08–0.1 mg/kg vecuronium bromide were administered for anesthesia induction. The laryngeal mask was placed after the patient's consciousness disappeared and the jaw muscles relaxed. The ventilator parameters were set as follows: respiratory rate, 12–16 breaths/min; tidal volume, 6–8 mL/kg; inspiratory-expiratory ratio, 1:1.5; and end-expiratory carbon dioxide partial pressure, 35–45 mmHg. During the period of anesthesia maintenance, remifentanil was intravenously infused in all groups at 0.1–0.3 μg/kg/min, propofol at 4–6 mg/kg/h, and vecuronium bromide was given according to the requirements of the surgery at 0.02–0.03 mg/kg. The anesthesiologist in charge of the intervention maintained the BIS between 40 and 60, the arterial blood pressure between 70% and 130% of the basal value, and the HR between 50 and 110 beats/min. Dexmedetomidine and esketamine infusions were stopped at the time of drain placement, while 50 mg flurbiprofen axetil was injected to control postoperative pain. Propofol and remifentanil were discontinued at the end of skin suturing. Tropisetron (2 mg) was administered intravenously to prevent postoperative nausea and vomiting. The laryngeal mask should be in place and transferred to the postanesthesia care unit (PACU) for recovery. Anesthesia was reversed with sugammadex, and the laryngeal mask was removed once the patient was awake and muscle strength was fully restored. In this study, the Fitbit Charge 2® smart bracelet was used for perioperative sleep monitoring. The sleep monitoring bracelet was administered by the ward nurse and worn on the participant's wrist on the surgical side at an appropriate level of elasticity. All Fitbit Charge 2® smart bracelets were retrieved on the third postoperative day by group-blinded nurses.

Primary and Secondary Endings

Postoperative sleep quality was assessed via the AIS, and postoperative pain was assessed via the visual analog scale (VAS). Anxiety and depression were assessed via the Hospital Anxiety and Depression Scale (HADS) on preoperative day 1 and postoperative days 1 and 3. Postoperative sleep disturbance was defined as an AIS score greater than 6, characterized by difficulty falling asleep, difficulty sleeping, early morning awakenings, and clinical distress or impairment in daily activities. The primary outcome was the incidence of sleep disturbance during the first three postoperative nights (an AIS score greater than 6 on any 1 night was sufficient to determine the occurrence of sleep disturbance). Secondary outcomes included the duration of different sleep structures (including arousal, light sleep, deep sleep, and rapid eye movement sleep) during the first three postoperative

nights, obtained from the Fitbit Charge 2® smart bracelet; anxiety–depression scores on postoperative days 1 and 3 (using the HADS); pain scores at rest and during exercise at 24 and 48 hours postoperatively (using the VAS); and postoperative adverse event incidence (postoperative nausea and vomiting, dry mouth, dizziness, rescue analgesia, etc.) The AIS is a self-assessed psychometric questionnaire that quantifies sleep difficulties according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems criteria. The AIS consists of 8 items: nocturnal awakening, sleep induction, final awakening, total sleep duration, sleep quality, well-being, functional ability, and daytime sleepiness. AIS scores range from 0 to 24, with a total score of more than 6 indicating a diagnosis of insomnia. The VAS score ranges from 0 (indicating no pain) to 10 (indicating intolerable pain). The HADS consists of 14 questions, with 7 items each on the Anxiety and Depression subscales, each having 7 items. The scores for each item ranged from 0 to 3, and the scores were summed to produce separate scores for anxiety (HADS-A) and depression (HADS-D). A score of 8 or higher was considered indicative of depression or anxiety. In addition, the duration of surgery and anesthesia, intraoperative consumption of maintenance anesthesia medications such as propofol, estimated volume of fluids infused, blood and urine loss, vital signs at important intraoperative time points (after induction of anesthesia, after intubation, at the time of skin incision, 1 h into surgery, at the end of surgery, and at the time of extubation), time to removal of the laryngeal mask (from the end of the surgery until the time of removal of the laryngeal mask airway), and duration of the stay in the anesthesia recovery room were also recorded.

Sample Size Calculation

This study was a 2×2 analytic factorial design experiment with four groups: the esketamine group (E), the dexmedetomidine group (D), the esketamine combined with dexmedetomidine group (ED), and the normal saline group (S). On the basis of a review of the literature, the overall incidence of POSD in the blank control group was expected to be approximately 68%.[20] The sample size of the analytic design was calculated under the assumption that there was no interaction between the two interventions to test the main effect of the two interventions. According to Cai's study (dexmedetomidine reduced the incidence of POSD to 34.4%-70.3% of the placebo group),[21] we hypothesized that dexmedetomidine would reduce the incidence of POSD to approximately 50% of the placebo group. Two-sided α=0.05 and 1-β=0.9 were set. Using PASS 2021 software, we calculated a sample size of N=82 cases (41 assigned to the intervention group and 41 to the relevant control group), and taking into account missed visits as well as refusals of visits by 20%, we calculated that we would eventually need at least 100 study participants, of which at least 25 study participants would be needed in each group.

Statistical Methods

Statistical analysis was performed via SPSS version 26.0 (IBM SPSS). The normal distribution of variables was tested via the Kolmogorov–Smirnov test. If the data were normally distributed, comparisons were made via one-way analysis of variance (ANOVA), and the results are expressed as the means ± standard deviations (SDs). Nonnormally distributed data were analyzed via the Kruskal–Wallis test or Mann–Whitney test and are expressed as medians (interquartile ranges, IQRs). Categorical variables are reported as numbers (%) and were compared via the χ^2 test or Fisher's exact test, as appropriate. Logistic regression modeling was used to assess potential risk factors associated with POSD. A two-sided $P<0.05$ was considered statistically significant. For the baseline characteristics of the four groups, one-way ANOVA was used for normally distributed quantitative data, the Kruskal–Wallis test was used for nonnormally distributed data, and the chi–square test or Fisher's exact test (as appropriate) was used for qualitative data. For the main outcomes of the four groups, the chi-square test or Fisher's exact test was used to analyze the data. For outcomes with significant differences, binary logistic regression was used to analyze whether there was any interaction effect. If there was no interaction effect, the independent effects could be analyzed. If there is an interactive effect, the Cochran–Mantel–Haenszel test is continued to explore its simple effect. The nonparametric rank sum test was used for postoperative sleep structure (provided by Fitbit Charge 2®). One-way and multifactorial logistic regression models were used to explore the risk factors for POSD within 3 days after surgery. One-way logistic regression model analysis was first performed to screen out the independent variables with $P<0.1$, and then the screened independent variables were included in the multifactorial logistic regression model. For blood pressure and heart rate data at different time points during the operation, repeated-measures ANOVA was used. All analyses were two-tailed and used a 5% level of significance.

Results

As shown in the study flow chart (Figure 1), 114 female patients scheduled to undergo elective modified radical mastectomy for breast cancer under general anesthesia were invited to participate in this study. Among them, nine patients were ineligible for inclusion, and five refused to participate in the study. A total of 100 participants were randomized into 4 groups.

Baseline Characteristics

There were no differences in age, body mass index (BMI), education, underlying disease (eg, hypotension, diabetes mellitus), duration of surgery, or duration of anesthesia (all $P>0.05$) (Table 1).

Primary Outcome Indicator

There was no significant difference in the incidence of POSD among the 4 groups within the first 3 postoperative nights (including nights 1 and 3) ($P=0.947$). However, at POD3, there were significant differences among the four groups ($P=0.025$) (Table 2). Binary logistic regression was used for further analysis, and the interaction term was significant in the dexmedetomidine and esketamine groups ($P=0.004$), suggesting a significant interaction effect between dexmedetomidine and esketamine at POD3 (Table 3), which was further explored as a simple effect via a stratified chi-square test. When the stratification factor was esketamine, in the absence of esketamine, there was a significant effect of dexmedetomidine on sleep disturbance on POD3 ($P=0.019$), with an OR=0.196<1, indicating that dexmedetomidine had an ameliorating effect on sleep disturbance on POD3. However, in the presence of esketamine, there was no significant effect of dexmedetomidine on POD3 sleep disturbance ($P=0.232$); when the stratification factor was dexmedetomidine, there was a significant effect of esketamine on POD3 sleep disturbance in the absence of dexmedetomidine ($P=0.042$), with an OR value of 0.248, which is less than 1, suggesting that esketamine had a significant effect on POD3 sleep disorder. However, in the presence of dexmedetomidine, there was no significant effect of esketamine on postoperative night-3 sleep disturbance ($P=0.128$) (Table 4).

Multivariate Logistic Regression regression analysis revealed that preoperative depressive status and the PSQI score were factors for POSD during the first three postoperative days. We included preoperative depressive status and PSQI score, as well as other variables (including age, BMI, literacy, length of anesthesia, length of surgery, dexmedetomidine dosage, esketamine dosage, and preoperative anxiety status), in the multivariate logistic regression model. The preoperative depressive state (adjusted OR 2.74, $P=0.023$) and PSQI score (adjusted OR=4.24, $P=0.035$) were still independent risk factors for POSD.

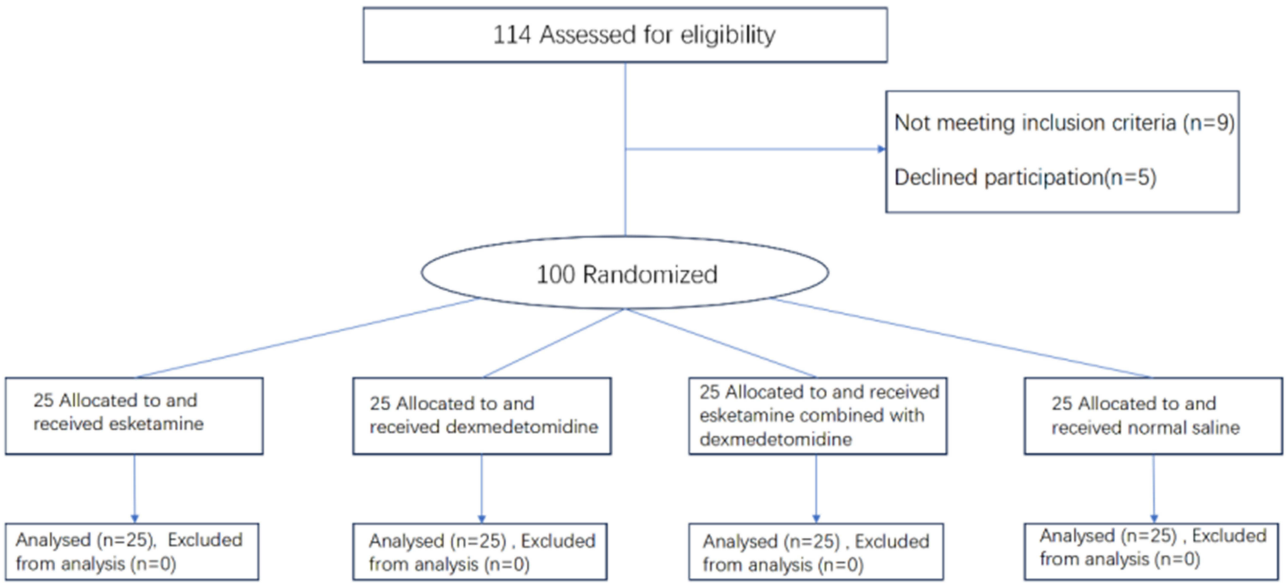

Figure 1 CONSORT flow diagram of the study.

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Table 1 Clinical Data of Patients

Variables	Group E (n=25)	Group D (n=25)	Group ED (n=25)	Group S (n=25)	*P* value
Age, year	50.44±1.538	54.00±1.745	50.92±1.527	50.80±1.294	0.329
BMI,kg/m2	23.288±0.477	24.492±0.709	23.880±0.569	24.528±0.678	0.439
Educational level, n(%)					0.591
Illiteracy	2 (8%)	2 (8%)	2 (8%)	1 (4%)	
Primary school	6 (24%)	5 (20%)	10 (40%)	5 (20%)	
Middle school	7 (28%)	8 (32%)	5 (20%)	9 (36%)	
High school	4 (16%)	6 (24%)	2 (8%)	4 (16%)	
Vocational education	4 (16%)	2 (8%)	3 (12%)	3 (12%)	
Undergraduate and above	2 (8%)	2 (8%)	3 (12%)	3 (12%)	
Neoadjuvant chemotherapy, n(%)	2 (8%)	3 (12%)	2 (8%)	2 (8%)	0.947
Surgical history, n(%)	6 (24%)	7 (28%)	5 (20%)	6 (24%)	0.932
Hypertension, n(%)	6 (24%)	10 (40%)	4 (16%)	5 (20%)	0.219
Diabetes, n(%)	4 (16%)	6 (24%)	4 (16%)	4 (16%)	0.846
Preoperative anxiety state (feminine/mildly/moderately/severe), n	4/6/11/4	8/6/8/3	5/9/8/3	5/8/9/3	0.615
Preoperative depressive state (feminine/mildly/moderately/severe), n	2/13/8/2	3/12/7/3	3/14/6/2	2/12/9/2	0.871
Surgical site(left/right), n	10/15	12/13	14/11	11/14	0.704
Length of anesthesia, min	108 (70.5,145.5)	108 (91,147)	102 (90,128)	102 (89,165.5)	0.964
Length of surgery, min	80 (60,120)	85 (65,130.5)	80 (67,106.5)	83 (69.5,144.5)	0.743
Time out of PACU,min	40 (33.5,46.5)	45 (40,50)	40 (40,45)	45 (40,50)	0.188
Influenced by ward environment, n(%)	3 (12%)	4 (16%)	2 (8%)	3 (12%)	0.860
Elastic restraint tape, n(%)	3 (12%)	3 (12%)	2 (8%)	3 (12%)	0.959
Wound pain, n(%)	2 (8%)	6 (24%)	4 (16%)	5 (20%)	0.479
Postural discomfort, n(%)	1 (4%)	3 (12%)	2 (8%)	5 (20%)	0.311
Length of postoperative hospitalization,h	91.84±4.93	98.12±7.59	94.36±4.38	87.04±5.93	0.595

Notes: Data are present as the mean ± standard deviation or number.
Abbreviations: Group E, esketamine group; Group D, dexmedetomidine group; Group ED, dexmedetomidine combined with esketamine group; Group S, normal saline group; BMI, Body mass index.

Table 2 Peri-Operative Sleep Outcomes

Variables	Group E (n=25)	Group D (n=25)	Group ED (n=25)	Group S (n=25)	*P* value
Primary outcome					
POSD (within 3 days)	17(68%)	16 (64%)	17 (68%)	18 (72%)	0.947
POD1 Sleep quality					
AIS score	8 (4,9)	9 (5,11)	8 (4.5,10)	9 (5.5,10.5)	0.541
POSD, NO. n(%)	17 (68%)	16 (64%)	17 (68%)	18 (72%)	0.947
POD3 Sleep quality					
AIS score	5 (4,7)	5 (4,5)	5 (4,8)	8 (4.5,9.5)	0.064
POSD, NO. n(%)	6 (24%)	5 (20%)	11 (44%)	14 (56%)	**0.025***

Notes: *Bold values indicate statistically significant values ($P<0.05$).
Abbreviation: AIS, Athens Insomnia Scale.

Secondary Ending Indicator

The sleep structure after surgery was compared with that before surgery via the Mann–Whitney test on PODs 1 and 3. In the absence of dexmedetomidine, the wake time on POD1 was significantly lower than that in the absence of esketamine (P=0.036), and in the presence of dexmedetomidine, the wake time on POD3 was significantly lower than that in the absence of esketamine (P=0.020). In the absence of esketamine, the first postoperative REM time in patients treated with

Table 3 POD3 Analysis of Influencing Factors of Sleep Disorders

Variables	Regression Coefficient	Standard Error	Wald χ^2	*P* value	OR value	95% CI
Dexmedetomidine	−1.627	0.642	6.423	**0.011***	0.196	0.056 ~ 0.691
Esketamine	−1.394	0.618	5.091	**0.024***	0.248	0.074 ~ 0.833
Interactive	2.539	0.891	8.119	**0.004***	12.667	2.209 ~ 72.632

Notes: *Bold values indicate statistically significant values (*P*<0.05).
Abbreviation: POD3, The third day after surgery.

Table 4 Stratified Chi-Square Test Results

Variables						*P* value	OR value	95% CI
Esketamine	POSD	**Yes**		**No**				
	Dexmedetomidine	Yes	No	Yes	No			
No		5	14	20	11	**0.019***	0.196	0.056 ~ 0.691
Yes		11	6	14	19	0.232	2.488	0.741 ~ 8.350
Dexmedetomidine	POSD	**Yes**		**No**				
	Esketamine	Yes	No	Yes	No			
No		19	11	6	14	**0.042***	0.248	0.074 ~ 0.833
Yes		14	20	11	5	0.128	3.143	0.893 ~ 11.064

Notes: *Bold values indicate statistically significant values (*P*<0.05).
Abbreviation: POSD, Postoperative sleep disturbance.

dexmedetomidine was significantly lower than that in patients without dexmedetomidine (*P*=0.042) (Table 5) (Figure 2). In Group E, the use of remifentanil intraoperatively was reduced (P<0.001). There were no significant differences in postoperative pain score or postoperative nausea and vomiting among the four groups (Table 6).

Table 5 Comparison of Sleep in the Four Groups After Surgery

Variables	Group E (n=25)	Group D (n=25)	Group ED (n=25)	Group S (n=25)	P^a	P^b	P^c	P^d
Duration of wakefulness, min								
POD1	5(–10.5,29.5)	16(–16,58.5)	26(–7.5,41)	32(11,44.5)	**0.036***	0.831	0.509	0.290
POD3	–3(–17,10)	8(–13,21.5)	–14(–26.5,1.5)	7(–12,11.5)	0.273	**0.020***	0.593	0.145
Light sleep time, min								
POD1	84(50,146)	86(–3.5,134)	78(40,154.5)	77(26.5,130)	0.614	0.786	0.861	0.727
POD3	44(8.5,70.5)	43(17,66.5)	63(17.5,80)	50(20.5,78)	0.764	0.455	0.655	0.473
Deep sleep time, min								
POD1	–20(–31, –2)	–24(–34.5, –7.5)	–23(–37.5, –5.5)	–17(–33,7)	0.662	0.884	0.367	0.528
POD3	–1(–16,12)	–6(–14.5,2.5)	–7(–20,10)	–3(–11.5,10.5)	0.786	0.719	0.252	0.684
REM sleep, min								
POD1	–10(–31.5,33)	–19(–48,7.5)	–13.00(–34,0)	–7(–31,36.5)	0.398	0.547	**0.042***	0.154
POD3	11(–4.5,39)	9(–11.5,39)	24(11.5,37.5)	22(3,49)	0.421	0.130	0.244	0.294

Notes: a indicates E vs S, b indicates ED vs D, c indicates D vs S, d indicates ED vs E, *Bold values indicate statistically significant values(*P*<0.05). The change was defined as the difference (rather than the ratio) between preoperative sleep duration and postoperative sleep duration on postoperative first and third days.As seen from the above table, in the presence of dexmedetomidine, the time of awakening on the first postoperative day was significantly lower in patients with esketamine than in patients without esketamine (*P*=0.036), and in the presence of dexmedetomidine, the time of awakening on the third postoperative day was significantly lower in patients with esketamine than in patients without esketamine (*P*=0.020). In the absence of esketamine, the time to REM on the first postoperative day was significantly lower in patients with dexmedetomidine than in patients without dexmedetomidine (*P*=0.042).

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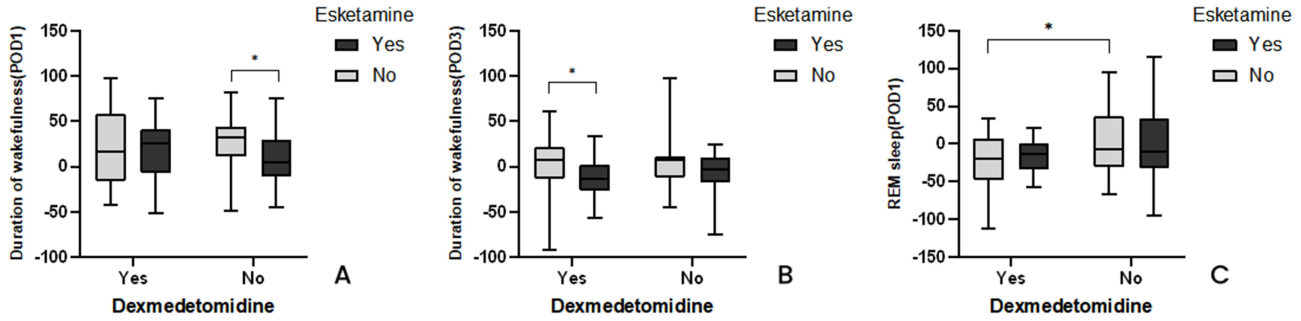

Figure 2 The difference in sleep structure between POD1 and POD3 and the preoperative sleep structure. (**A**) Difference on POD1. (**B**) Differences on POD3. (**C**) Difference on POD1.

Notes: Data are presented as the median (IQR). *Indicates statistically significant values ($P<0.05$).

Discussion

The main findings of this study are as follows. First, during the first three postoperative nights, there was no significant difference in the incidence of sleep disturbances between the esketamine group and the dexmedetomidine group or between the two drugs combined. However, on POD3, esketamine alone or dexmedetomidine alone improved nighttime sleep quality. Second, on POD1, the use of dexmedetomidine reduced postoperative rapid eye movement sleep; on POD1 and POD3, the use of esketamine reduced nocturnal awakening. Third, multivariate logistic regression revealed that both preoperative depressive status and the PSQI score were risk factors for POSD and that esketamine reduced remifentanil use. Esketamine or dexmedetomidine improved postoperative sleep quality and POSD in postoperative patients.

POSD refers to a series of brain dysfunctions and autonomic hyperactivity in the sleep–wake process of postoperative patients, manifested by difficulty falling asleep, sleep deprivation, and decreased sleep quantity and quality, characterized by decreased total sleep time and NREM sleep stage 3 (N3) sleep, followed by decreased REM sleep fragmentation and cycle disruption. NREM sleep stage 3 (N3) sleep reduction and REM sleep reduction are particularly prominent,

Table 6 Use of Anesthesia Drugs During Operation and Score of Postoperative VAS and PONV

Variables	Group E (n=25)	Group D (n=25)	Group ED (n=25)	Group S (n=25)	*P* value
Midazolam, mg	2 (2,2.3)	2 (2,3)	2 (2,3)	2	0.823
Sufentanil, μg	30 (25,30)	30	30 (22.5,30)	30	0.192
Remifentanil, mg	1.5 (1.1,1.9)	1.7 (1.4,2.5)	1.4 (1,1.5)	2 (1.5,2.5)	**0.001***
Propofol, mg	0.45 (0.3,0.6)	0.35 (0.3,0.5)	0.4 (0.3,0.4)	0.43 (0.4,0.7)	0.113
Esketamine, mg	32.5 (22.5,40)	0	35 (25,47.5)	0	0.690
Dexmedetomidine, μg	0	50 (42.5,60)	50 (35,50)	0	0.175
Postoperative VAS scores					
24 h(at rest)	2 (2,3.5)	3 (2,4)	3 (2,3.5)	3 (2.5,4)	0.349
48 h(at rest)	1 (1,2)	2 (1,3)	2.000 (1.0,2.5)	2 (1.5,3)	0.128
24 h(on movement)	5 (4,6.5)	5 (5,7)	6 (5,7)	6 (4.5,7)	0.408
48 h(on movement)	3 (3,4.5)	4 (3,5.5)	4 (3,5)	4 (3,6)	0.224
24 h postoperative PONV, n(%)					0.501
0	10 (40.00%)	12 (48%)	17 (68%)	14 (56%)	
1	1 (4%)	2 (8%)	1 (4%)	1 (4%)	
2	7 (28%)	3 (12%)	2 (8%)	2 (8%)	
3	7 (28%)	8 (32%)	5 (20%)	8 (32%)	
48 h postoperative PONV, n(%)					0.387
0	24 (96%)	25 (100%)	25 (100%)	25 (100%)	
1	1 (4%)	0	0	0	

Notes: *Bold values indicate statistically significant values ($P<0.05$). 0 level: No symptoms such as nausea or dry heaves; 1 level: Mild nausea and abdominal discomfort; 2 level: Severe nausea that is unbearable but without vomiting; 3 level: Vomiting with gastric contents being vomited out.

Abbreviations: VAS, Visual Analog Scale; PONV, postoperative nausea and vomiting.

followed by sleep fragmentation and cycle disruption.[22–25] Breast cancer patients tend to experience significant postoperative sleep disturbances due to pain, discomfort, and psychological and physiological changes,[4] which is similar to the results of this trial (80.0% in the POD 1 control group). Postoperative sleep problems in the vast majority of patients do not receive adequate attention or appropriate treatment. Appropriate sleep can promote the secretion of growth hormone, accelerate tissue repair and collagen synthesis, and promote the healing of surgical incisions; it can enhance the activity of immune cells and reduce the risk of postoperative infection; sleep deprivation can lead to an increase in the levels of pro-inflammatory cytokines (IL-6, TNF-α).[26] In this study, we found that esketamine combined with dexmedetomidine did not reduce the incidence of postoperative sleep disorders, which is inconsistent with the findings of Qiu and Shi et al.[27,28] Psychological conditions such as anxiety, depression, and stress can affect an individual's perception of sleep, and this disorder may cause patients to overestimate sleep latency and underestimate total sleep time.[29–31] Environmental disturbances such as noise and light may also affect patients' perception of sleep,[32] leading to inconsistencies between subjective perceptions and objective sleep data. In our study, the effect of esketamine or dexmedetomidine on postoperative sleep architecture rather than POSD incidence can be explained by this phenomenon.

Ketamine, a fast-acting antidepressant, has been shown to significantly affect the treatment of major depression and other related mood disorders.[33] There is a strong bidirectional relationship between depression and sleep disorders,[34] and the rapid antidepressant effects of ketamine are associated with its ability to increase neurotrophic activity and synaptic strength, normalize sleep, and enhance the circadian rhythm system.[35,36] Ketamine improves sleep problems in patients with major depression. However, even low doses of ketamine may produce side effects, including psychiatric system symptoms.[37,38] Esketamine is twice as potent as racemic ketamine and is less likely to produce side effects.[39] A randomized trial showed that intraoperative infusion of esketamine improved the incidence of POSD in patients undergoing gynecologic laparoscopic surgery.[27] In our study, intraoperative infusion of esketamine (0.3 mg/kg/h) reduced the nocturnal awakening time on POD3. These findings suggest that esketamine has a positive effect on postoperative nocturnal sleep.

Pain is an important disruptor of sleep in the postoperative period, and pain as well as opioid use can interfere with sleep.[40] Sleep deprivation can lower the pain threshold and intensify the perception of postoperative pain. Similarly, postoperative pain can disrupt the sleep structure, increase cortisol secretion by 2–3 times, inhibit the ability to maintain sleep, and reduce sleep drive. There is a significant bidirectional vicious cycle relationship between postoperative pain and postoperative sleep.[41] Opioids interact with the central nervous system and may affect the balance of neurotransmitters that regulate sleep, such as dopamine and norepinephrine.[42] Studies have shown that opioid use is associated with a decrease in the percentage of slow-wave sleep.[43] In our study, there was no significant difference in postoperative pain scores (either at rest or with exercise) among the four groups. However, remifentanil use was reduced in Group E. Given the analgesic effect of esketamine, the effect of esketamine on postoperative sleep quality may be related to reduced opioid consumption.

Dexmedetomidine may act through several mechanisms. Its ability to modulate the central nervous system, especially the inhibition of noradrenergic neurons in the nucleus accumbens, may help to stabilize the sleep–wake cycle and reduce postoperative sleep disturbances due to factors such as stress and pain.[44–46] A real-world cohort study demonstrated that the intraoperative use of low-dose dexmedetomidine (0.2–0.4 μg/kg/h) significantly reduced the incidence of severe sleep disturbances on the day of surgery in patients who underwent major noncardiac surgery.[47] Oral dexmedetomidine increased the duration of non-REM stage 2 sleep and decreased the duration of REM sleep,[14] suggesting the potential of dexmedetomidine to effectively improve sleep architecture, which is consistent with our study.[48,49] However, the side effects caused by the perioperative use of dexmedetomidine are still controversial, and some studies have shown that dexmedetomidine increases the incidence of hypotension or bradycardia. In our study, there were no significant differences in the dexmedetomidine group, despite having a lower heart rate and lower mean arterial pressure than the other 3 groups did.

Multivariate logistic analysis revealed that preoperative depression and PSQI scores were associated with the development of POSD. This finding is consistent with those of previous studies.[50] Anxiety and depression can lead to hyperfunction of the hypothalamic–pituitary–adrenal axis, increased sympathetic excitability, and elevated circulating levels of norepinephrine and cortisol, resulting in an increased state of arousal in patients.[30] Patients with preoperative sleep problems are at significantly increased risk of developing sleep problems postoperatively, and future studies need to explore the mechanisms of interaction between the two in greater depth.

The perioperative application of dexmedetomidine increases the incidence of hypotension and bradycardia, and dexmedetomidine has negative chronotropic and metamorphic effects on the heart. An overdose of dexmedetomidine may increase the incidence of perioperative adverse cardiovascular events (eg, hypotension, bradycardia) and even lead to cardiac arrest.[51] Ketamine can cause catecholamine release, inhibit norepinephrine reuptake, and activate the sympathetic nervous system, resulting in indirect cardiovascular stimulation.[52] The combination of the two can compensate for the side effects of dexmedetomidine and, at the same time, can reduce the need for opioids, which can help to avoid the problem of opioid-induced addiction. In our study, the combination group did not reduce the incidence of postoperative sleep disorders, and given that both drugs have a positive effect on postoperative sleep disorders, more large-sample multicenter trials can be designed in the future to investigate their effects on sleep in terms of the route of administration and drug dosage. Our follow-up observations revealed that postoperative monitoring instruments, poor holding positions, and compression bandages adversely affect nocturnal sleep, and related issues need to be optimized. The results of several studies suggest that hope and social support, as positive factors, have great potential to improve the quality of sleep in patients.[4] By mobilizing multiple sources of social support, such as family, friends, communities, and hospitals, the sleep problems faced by patients can be effectively addressed. Future studies could explore the variable effects of different sources of social support on patients' sleep quality.

Limitations

This study has several limitations. First, our findings are based on data from a single center with a relatively small sample size. Future research with larger sample sizes and a multicenter design is needed. Second, this study only monitored sleep during the first three nights after surgery and did not investigate patients' sleep conditions after discharge. Third, biological samples such as blood were not collected, which could have been helpful in analyzing the mechanisms by which esketamine and dexmedetomidine affect postoperative sleep. Additionally, the specific effects of different drug combinations on MAC were not quantified, nor was a pharmacokinetic model used to dynamically predict drug interactions. Due to the complexity of monitoring, we did not use polysomnography (the gold standard for sleep monitoring) but instead collected patients' sleep data using the Fitbit Charge 2® smartwatch, which may introduce certain errors.

Conclusions

In the context of our study, intraoperative infusion of esketamine combined with dexmedetomidine did not have a significant effect on POSD, in which the preoperative depressive state and PSQI score play a more critical role. However, the effects of esketamine and dexmedetomidine on sleep architecture (eg, reduction in nocturnal awakening time) are still of concern to clinicians, and further studies with larger samples are needed to explore the mechanisms of the effects of both drugs on postoperative sleep.

Data Sharing Statement

The data generated during the current study are available from the corresponding author (Xing-Yu Geng) upon reasonable request. The study protocol, statistical analysis plan, and clinical study report will also be available.

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Disclosure

The authors report no conflicts of interest related to this work.

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