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ORIGINAL RESEARCH

Effects of Subanesthetic Esketamine on Postoperative Sleep Quality Through EEG Analysis in Breast Cancer Patients: A Randomized Clinical Trial

Yuening Zhan[1,*], Yanmei Zhang[1,*], Zhaohui Liu[1], Zheng Yin[2], Dan Wang[1], Xin Xie[1,*], Lingfei Wang[1,*]

[1]Department of Anesthesiology, Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital & Institute, Shenyang, Liaoning, People's Republic of China; [2]Department of Orthopedics, Anshan Hospital, The First Hospital of China Medical University, Anshan, Liaoning, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lingfei Wang; Xin Xie, Anesthesiology, Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital & Institute, Xiaoheyan Road, Shenyang, Liaoning, 110042, People's Republic of China, Tel +86 18900918433; +86 18940236751, Email wanglingfei.good@163.com; xiexin@cancerhosp-ln-cmu.com

Background: Postoperative sleep disturbance (POSD) is prevalent following breast cancer surgery, impairing postoperative recovery. However, effective interventions and underlying mechanisms remain unclear. This study aims to evaluate whether intravenous subanesthetic esketamine improves postoperative sleep quality and its association with electroencephalogram (EEG) frequency band changes in breast cancer patients.

Methods: In this randomized, double-blind, placebo-controlled trial, patients undergoing breast cancer surgery received either intravenous esketamine (0.2 mg/kg induction, 0.4 mg/kg/h maintenance) or placebo during anesthesia. Both groups received intraoperative EEG monitoring. The primary outcome was POSD incidence at 24 hours assessed by the Pittsburgh Sleep Quality Index (PSQI). Secondary outcomes included PSQI scores at 72 hours, Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) scores, Visual Analog Scale (VAS) pain scores, and intraoperative EEG parameters.

Results: POSD incidence was significantly reduced in the esketamine group compared with the control group (27.3% [16/58] vs 51.7% [30/58]; odds ratio, 0.36; 95% CI, 0.16–0.77; $P = 0.014$). Moreover, the esketamine group demonstrated significantly lower PSQI scores at both 24 hours (median [IQR], 2 [1–5] vs 4 [4–8]; $P < 0.001$) and 72 hours (1 [0–2.5] vs 3.5 [2.75–5]; $P < 0.001$). The esketamine group exhibited significantly higher intraoperative gamma-band relative power spectral density (mean [SD], 0.74 [0.25] vs 0.52 [0.18]; $P < 0.001$), which was independently associated with reduced POSD risk in multivariate analysis (odds ratio, 0.63; 95% CI, 0.40–0.97; $P = 0.039$).

Conclusion: Subanesthetic esketamine significantly reduced the incidence of POSD and lowered PSQI scores. Importantly, esketamine was associated with enhanced intraoperative gamma-band EEG activity, which was independently associated with reduced POSD risk, suggesting that modulation of specific cortical oscillations may underlie its sleep-enhancing effects.

Trial Registration: Chinese Clinical Trial Registry Identifier: ChiCTR2400092257.

Keywords: subanesthetic esketamine, electroencephalogram, gamma oscillations, postoperative sleep disturbance, breast cancer surgery

Introduction

Breast cancer is one of the most prevalent malignancies among women worldwide, with an increasing incidence and the number of breast cancer surgeries performed annually continuing to rise.[1,2] However, studies have shown that up to 50% of patients undergoing general anesthesia (GA) for breast cancer surgery experience postoperative sleep disturbance (POSD), making it one of the most common postoperative complications affecting mental health.[3] Moreover, nearly 30% of patients exhibit significant depressive and anxiety symptoms seven days postoperatively.[4] POSD is associated with a range of adverse effects, including delayed recovery, increased pain sensitivity, impaired immune function, and prolonged hospital stays.[5]

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These disturbances can exacerbate emotional distress, leading to a vicious cycle of poor sleep and heightened anxiety or depression. Furthermore, POSD is linked to a higher risk of developing chronic sleep disorders, impacting the long-term quality of life for patients. Various interventions have been explored to alleviate POSD, such as melatonin, dexmedetomidine, and zolpidem. Melatonin, though commonly used for regulating the circadian rhythm, is more effective for short-term relief and may cause dependency if used long-term.[6] Dexmedetomidine offers sedation and anxiolysis, but it is limited by potential side effects like hypotension and bradycardia, as well as its high cost.[7] Zolpidem, while effective for sleep induction, fails to address the underlying neurophysiological changes induced by anesthesia and may cause mood disturbances, such as anxiety and depression, with prolonged use.[8] Recent studies[9–12] have explored the use of esketamine in various surgical settings. Research indicates that esketamine not only improves mood symptoms but also enhances postoperative sleep quality and supports neurocognitive recovery. These findings further highlight its promising therapeutic potential in the perioperative management of patients.

Esketamine, the (S)-enantiomer of ketamine, has a similar pharmacological mechanism to ketamine but demonstrates higher potency. Research has demonstrated that esketamine, as a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, exerts its therapeutic effects through multifaceted interactions with glutamatergic receptors, monoamine receptors, opioid receptors, and brain-derived neurotrophic factor (BDNF) signaling pathways.[13] In 2019, the US Food and Drug Administration (FDA) approved esketamine for the treatment of treatment-resistant depression (TRD). Given the significant correlation between POSD and depression, both conditions share common neurobiological pathways, esketamine may not only alleviate depressive symptoms but also significantly improve POSD in breast cancer patients. Several studies have explored the efficacy of esketamine in improving POSD and alleviating depressive symptoms. For instance, a clinical trial demonstrated that esketamine significantly reduced POSD in elderly patients undergoing abdominal surgery,[14] with marked improvements in depressive and anxiety symptoms observed by the second postoperative day. Furthermore, a study assessing esketamine in the treatment of TRD reported its effectiveness in alleviating sleep disturbances associated with chronic depression, further supporting its potential therapeutic role in the management of POSD.[15]

The normal sleep cycle consists of two distinct stages: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep.[16] REM sleep is characterized by low-amplitude, high-frequency beta and gamma waves, while NREM sleep consists of three stages dominated by low-frequency, high-amplitude theta and delta waves.[17,18] Evidence suggests that esketamine alters the thalamocortical loop by antagonizing NMDA receptors and reducing the release of the excitatory neurotransmitter glutamate.[19,20] This alteration in neurotransmission leads to changes in the sleep cycle, particularly by reducing REM sleep and enhancing NREM sleep.[21] Furthermore, esketamine has been shown to enhance the function of both the locus coeruleus and the suprachiasmatic nucleus (SCN).[22] Subanesthetic esketamine can modulate the locus coeruleus in a more controlled manner, potentially mitigating postoperative circadian rhythm disturbances,[23,24] which are commonly associated with irregularities in REM sleep patterns. These disturbances often lead to REM rebound, characterized by excessive REM sleep, which subsequently impairs overall sleep quality and disrupts the normal sleep cycle.[25,26] Dysregulation of the sleep cycle, particularly the imbalance between REM and NREM sleep, can compromise postoperative recovery, contributing to fatigue and cognitive dysfunction.[27] Esketamine may help restore normal sleep architecture by stabilizing the locus coeruleus and SCN, thereby preventing REM rebound and promoting optimal balance between NREM and REM sleep.[28,29]

Additionally, studies have demonstrated that subanesthetic esketamine has significant effects on brain wave oscillations.[30,31] A study in animals demonstrated that subanesthetic esketamine activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which enhance slow-wave (theta) activity in the EEG.[32,33] Additional studies have shown that subanesthetic esketamine also increases gamma wave activity.[34,35] These findings suggest that esketamine may simultaneously modulate two distinct and seemingly opposing frequency bands of brain activity. While gamma waves are associated with wakefulness and cognitive attention, theta waves are linked to deeper stages of sleep.[34,36] Given its effects on brain wave oscillations, we hypothesize that subanesthetic esketamine may alleviate POSD by modulating intraoperative EEG changes in breast cancer patients. Therefore, we conducted a randomized, controlled, double-blind clinical trial to examine the effects of subanesthetic esketamine on both POSD and intraoperative EEG changes.

Methods

Study Design

This single-center, double-blind, placebo-controlled randomized clinical trial was approved by the Institutional Ethics Committee of Liaoning Cancer Hospital & Institute and prospectively registered in the Chinese Clinical Trials Registry (registration number: ChiCTR2400092257). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and the Declaration of Helsinki.

We recruited female breast cancer patients aged 35–55 years who were scheduled for elective breast surgery. Eligible participants met the following inclusion criteria: (1) patients scheduled for elective breast cancer surgery, including mastectomy, breast-conserving surgery, or reconstructive procedures; (2) American Society of Anesthesiologists (ASA) physical status I–II; (3) no use of central nervous system (CNS)-affecting medications or history of substance abuse; and (4) no history of chronic sleep disorders (such as insomnia or sleep apnea) within the preceding 30 days. Exclusion criteria included: (1) severe cardiovascular, hepatic or renal dysfunction; (2) known allergy to esketamine; (3) pregnancy or lactation; (4) history of major surgery within the preceding 6 months; (5) unwillingness to provide informed consent or inability to comply with study procedures; and (6) any conditions deemed inappropriate for study participation by the investigator.

Randomization and Blinding

Patients were randomly assigned in a 1:1 ratio to the esketamine or control group using a computerized randomization table Prior to anesthesia, the study coordinator opened sequential sealed envelopes, and the anesthesia nurse, who was aware of group allocation, prepared esketamine or saline in identical syringes. The anesthesiologist, blinded to group allocation, first adjusted the anesthetic depth using opioids or sedative medications as required. Esketamine was then administered as a fixed infusion at subanesthetic doses. Throughout the study, all patients, anesthesiologists, surgeons, outcome assessors, and investigators involved in data collection and analysis remained blinded to the group assignments. The randomization sequence was accessible only to the anesthesia nurse, ensuring proper allocation concealment.

Perioperative Anesthesia and Management of Analgesia

All patients received total intravenous anesthesia (TIVA) according to a standardized protocol. (Supplementary Figure 1). For the control (CON) group, standard anesthesia consisted of induction with sufentanil (0.3 μg/kg), propofol (1–1.5 mg/kg), and rocuronium (0.6–0.9 mg/kg), followed by maintenance with propofol (4–12 mg/kg/h) and remifentanil (0.05–0.2 μg/kg/min). The esketamine (ESK) group received the identical anesthesia protocol with adjunctive esketamine administered at 0.2 mg/kg during induction and 0.4 mg/kg/h during the maintenance phase. Esketamine infusion was maintained throughout the entire surgical procedure until the end of surgery. Before the completion of surgery, patients were given 40 mg parecoxib by intravenous injection and 100 mg acetaminophen through a 30-minute intravenous infusion. At the conclusion of the procedure, 10 mg azasetron was administered to reduce the risk of postoperative nausea and vomiting. Upon arrival in the operating room, standard monitoring was established, including noninvasive blood pressure (BP), pulse oximetry (SpO_2), and ECG. Additionally, EEG monitoring was performed using an EEG-832 monitor (Delica, China) with a sampling rate of 1000 Hz. EEG electrodes were positioned according to the International 10–20 system at FP1, FP2, T1, T2, O1, and O2, with earlobe electrodes (A1, A2) serving as reference electrodes. Electrode impedance was maintained below 5 kΩ, and data were recorded in European Data Format (EDF) for subsequent analysis.

Outcome Measurements

Baseline characteristics included demographic data, ASA physical status classification, and history of preoperative radiotherapy or chemotherapy. Intraoperative physiological parameters, including mean arterial pressure (MAP), end-tidal carbon dioxide ($ETCO_2$), bispectral index (BIS), heart rate (HR), and SpO_2, were recorded at five predefined time points: T0 (before induction), T1 (5 minutes after intubation), T2 (20 minutes after surgical incision), T3 (40 minutes after surgical incision), and T4 (at surgical conclusion). Continuous EEG data were acquired throughout the surgical

procedure. EEG analysis focused on two primary measures: absolute power spectral density (aPSD), representing the total power (expressed in microvolts squared, μV^2) within specific frequency bands, and relative power spectral density (rPSD), calculated as the percentage of power in each frequency band relative to total spectral power.

The primary outcome was the incidence of POSD, assessed with the Pittsburgh Sleep Quality Index (PSQI), which ranges from 0 to 21 points. POSD was defined as a PSQI score ≥5, assessed 24 hours postoperatively (morning of the first postoperative day). Secondary outcomes included PSQI, Self-Rating Anxiety Scale (SAS), Self-Rating Depression Scale (SDS), and Visual Analog Scale (VAS) pain scores at both 24 and 72 hours postoperatively.

Statistical Analysis

Based on previously reported literature, the incidence of POSD in breast cancer patients ranges from 40% to 65%.[37,38] This was consistent with our pilot study (n=20 per group), which observed POSD rates of 50% (10/20) in the control group and 25% (5/20) in the esketamine group. Sample size calculations were performed using G*Power 3.1.9.7 with a 2-tailed two-proportion Z test. Assuming a clinically meaningful reduction in POSD incidence from 50% to 25% (50% relative risk reduction), with $\alpha = 0.05$ and power $(1-\beta) = 80\%$, the required sample size was 46 patients per group. To account for an anticipated 20% attrition rate due to loss to follow-up and withdrawals, a total of 116 patients were enrolled, with 58 patients randomly allocated to each group.

Statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp, Armonk, NY, USA) and R software version 4.0 (R Foundation for Statistical Computing, Vienna, Austria). EEG data processing was conducted using MATLAB R2022a (MathWorks, Natick, MA, USA). Data normality was assessed using the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean (SD) and compared using independent *t*-tests, while non-normally distributed variables are presented as median (interquartile range [IQR]) and compared using the Mann–Whitney *U*-test. Categorical variables are expressed as frequencies and percentages, with between group comparisons performed using the χ^2-test or Fisher's exact test as appropriate. The primary analysis was conducted using the per-protocol approach, including patients who completed the study without major protocol violations. All randomized patients were included in the safety analysis.

Risk factor analysis for POSD employed a three-step approach: initial univariate screening ($P < 0.10$), LASSO regularization for variable selection, and multivariable logistic regression for final modeling. Results are reported as odds ratios (ORs) and 95% confidence intervals (CIs) for significant predictors. Model stability was assessed through sensitivity analyses.

EEG data processing and analysis were performed using MATLAB R2022a (MathWorks, Natick, MA, USA). For exploratory EEG analyses across multiple regions and time points, we report both uncorrected P-values and indicate FDR-corrected significant findings. Detailed regression model statistical parameters and EEG data statistical analysis are provided in Supplementary Methods 1 and 2.

Results

Between November 2024 and April 2025, 352 patients were screened, of whom 186 were excluded for not meeting inclusion criteria and 21 declined to participate. Among the 145 randomized patients, 29 were excluded from analysis due to the following reasons: in the ESK group, 6 had electrode detachments, 4 were lost to follow-up, and 4 had benign histology; in the CON group, 9 had electrode detachments, 3 were lost to follow-up, and 3 had benign histology. The per-protocol analysis included 116 patients (58 per group; Figure 1). All 145 randomized patients were included in the safety analysis. Baseline demographic and clinical characteristics were well balanced between groups (Table 1). Preoperative PSQI scores were comparable between groups, with median (IQR) values of 3 (2–5) in the ESK group and 4 (2–5) in the CON group ($P = 0.940$). Similarly, no significant between-group differences were observed in preoperative SAS scores ($P = 0.158$) or SDS scores ($P = 0.620$).

Efficacy Outcomes

For the primary endpoint, POSD incidence was significantly lower in the ESK group compared with the CON group (27.6% vs 51.7%; odds ratio, 0.36; 95% CI, 0.16–0.77; $P = 0.014$) (Table 2). For secondary outcomes, the ESK group

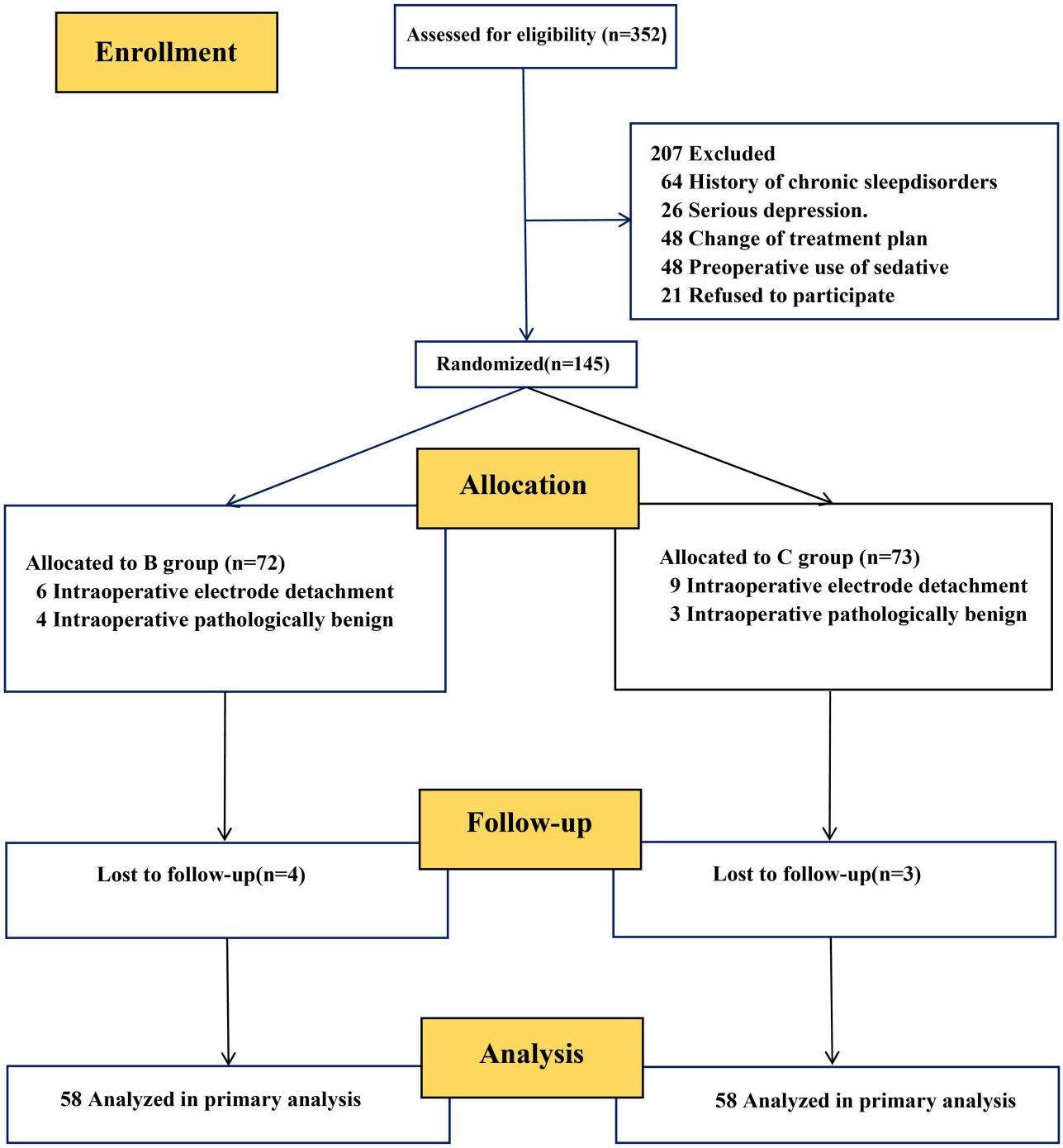

Figure 1 CONSORT Diagram of Patient Flow Through the Study.
Abbreviations: ESK, esketamine; CON, control. Numbers represent patients at each stage of the study.

demonstrated significantly lower PSQI scores at both 24 hours (median [IQR], 2 [1–5] vs 4 [4–8]; P < 0.001) and 72 hours (median [IQR], 1 [0–2.5] vs 3.5 [2.75–5]; P < 0.001). Analysis of individual PSQI components revealed that the ESK group had significantly better outcomes across multiple sleep parameters: sleep duration (0 [0, 1] vs 1 [1, 2]; P = 0.016), sleep latency (0 [0, 1] vs 1 [1, 2]; P = 0.032), sleep efficiency (0 [0, 1] vs 1 [1, 2]; P = 0.027), and sleep quality (0 [0, 1] vs 1 [1, 2]; P = 0.002). Similarly, SAS scores were significantly lower in the ESK group at both 24 hours and 72 hours (P = 0.001 and P < 0.001, respectively). SDS scores were significantly lower in the ESK group at 24 hours

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Table 1 Baseline Demographic and Clinical Characteristics of Patients by Treatment Group

	ESK Group (n = 58)	**CON Group (n = 58)**	***P*-value**
Age, (y)	48 (43, 55)	50 (43, 52)	0.676
Height, cm	159.62 (2.59)	159.41 (3.67)	0.726
Weight, kg	61.63 (10.48)	63.48 (8.35)	0.294
Preoperative hemoglobin, g/dL	130.66 (11.51)	130.03 (10.80)	0.763
Preoperative SAS score	24 (21, 25)	23 (21, 24)	0.158
Preoperative SDS score	21 (21, 25)	22 (21, 25)	0.620
Preoperative PSQI score	3 (2, 5)	4 (2, 5)	0.940
Thoracic surgery division, No. (%)			
I	21 (36.2)	16 (27.6)	0.161
II	4 (6.9)	12 (20.7)	
III	8 (13.8)	3 (5.2)	
IV	12 (20.7)	10 (17.2)	
V	5 (8.6)	5 (8.6)	
VI	8 (13.8)	12 (20.7)	
Location, No. (%)			
Offsite	27 (46.6)	26 (44.8)	0.852
Local	31 (53.4)	32 (55.2)	
ASA, No. (%)			
I	51 (87.9)	50 (86.2)	0.782
II	7 (12.1)	8 (13.8)	
Education, No. (%)			
Primary school	6 (10.2)	3 (5.2)	0.084
Junior high school	23 (39.7)	27 (46.6)	
High school	15 (25.9)	8 (13.8)	
College	3 (5.2)	11 (19.0)	
Undergraduate and above	11 (19.0)	9 (15.5)	
Smoking history, No. (%)	0 (0)	1 (1.7)	0.315
Drinking history, No. (%)	4 (6.9)	5 (8.6)	0.729
Chronic respiratory disease, No. (%)	0 (0)	0 (0)	> 0.99
Cardiovascular disease, No. (%)	4 (6.9)	2 (3.4)	0.402
Diabetes, No. (%)	8 (13.8)	4 (6.9)	0.223
Hypertension, No. (%)	5 (8.6)	9 (15.5)	0.254

(*Continued*)

Table 1 (Continued).

	ESK Group (n = 58)	CON Group (n = 58)	*P*-value
Surgery history, No. (%)	16 (27.6)	18 (31.0)	0.683
Pre-radiotherapy/chemotherapy, No. (%)	22 (37.9)	16 (27.6)	0.235
Care situation, No. (%)	56 (96.6)	54 (93.1)	0.402
Fertility status, No. (%)	53 (91.4)	54 (93.1)	0.729
Pre-tumour classification, No. (%)	39 (67.2)	33 (56.9)	0.251
Menopausal status, No. (%)	12 (20.7)	14 (24.1)	0.656
Marital status, No. (%)			
Unmarried	2 (3.4)	4 (6.9)	0.221
Married	48 (82.8)	51 (87.9)	
Divorced	8 (13.8)	3 (5.2)	
Widowed	0 (0)	0 (0)	
Employment status, No. (%)	34 (58.6)	36 (62.1)	0.704
Economic status, No. (%)			
Low	5 (8.6)	3 (5.2)	0.765
Medium	27 (46.6)	28 (48.3)	
High	26 (44.8)	27 (46.6)	
Lesion location, No. (%)			
Left	34 (58.6)	24 (41.4)	0.091
Right	19 (32.8)	22 (37.9)	
Bilateral	5 (8.6)	12 (20.7)	
Implant status, No. (%)	3 (5.2)	5 (8.6)	0.464

Notes: SI conversion factor: To convert hemoglobin from g/L to g/dL, multiply by 0.1. Data are presented as median (IQR) for non-normally distributed continuous variables, mean (SD) for normally distributed continuous variables, and No. (%) for categorical variables. P values were calculated using independent t-tests for normally distributed continuous variables, Mann–Whitney *U*-test for non-normally distributed continuous variables, and χ^2-test or Fisher's exact test for categorical variables. P < 0.05 was considered statistically significant. Thoracic surgery divisions (I–VI) represent different specialized teams within the thoracic surgery department. Location refers to the tumor site within the breast. Education level represents the highest educational achievement attained by the patient. Care situation indicates whether the patient had adequate home support for postoperative care. Fertility status indicates whether the patient was physiologically capable of conception. Pre-tumor classification was performed according to the American Joint Committee on Cancer (AJCC) TNM staging system, 8th edition. Economic status was self-reported by patients based on household income relative to local standards.

Abbreviations: ASA, American Society of Anesthesiologists; CON, control; ESK, esketamine; IQR, interquartile range; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

(P = 0.003) but not at 72 hours (P = 0.122). No significant between-group differences were observed in VAS pain scores. Additional perioperative data are presented in Supplementary Table 1.

EEG power spectral analysis revealed significant between-group differences across multiple frequency bands (Figure 2). The aPSD was consistently higher in the ESK group compared with the CON group for theta waves (P < 0.001, except P = 0.028 for temporal region at T1, P = 0.001 for occipital region at T2) and gamma waves (P < 0.001 for all region-time combinations). Similar patterns were observed for alpha, beta, and delta bands, with

Table 2 Comparison of Postoperative Sleep and Psychological Outcomes Between Patients Receiving Subanesthetic Esketamine and the Control Group

	ESK Group (n = 58)	CON Group (n = 58)	*P-value*
POSD, n (%)	16 (27.6)	30 (51.7)	0.014
PSQI 24 hours	2 (1, 5)	4 (4, 8)	< 0.001
Duration of sleep score	0 (0, 1)	1 (1, 2)	0.016
Sleep latency	0 (0, 1)	1 (1, 2)	0.032
Sleep efficiency	0 (0, 1)	1 (1, 2)	0.027
Sleep disturbance score	0 (0, 1)	1 (1, 2)	0.058
Use of sleep medication	0 (0, 0)	0 (0, 0)	> 0.99
Daytime dysfunction due to sleepiness	0 (0, 1)	1 (1, 2)	0.112
Sleep quality	0 (0, 1)	1 (1, 2)	0.002
PSQI 72 hours	1 (0, 2.5)	3.5 (2.75, 5)	< 0.001
SAS 24 hours	21 (20, 23)	23 (21, 24)	0.001
SAS 72 hours	20 (20, 21.25)	22 (20, 23)	< 0.001
SDS 24 hours	21 (20, 23)	22 (21, 24)	0.003
SDS 72 hours	20 (20, 21)	20 (20, 21)	0.122
VAS 24 hours	1 (1, 3)	2 (1, 4)	0.491
VAS 72 hours	1 (1, 1)	1 (1, 2.5)	0.147

Notes: P-values were calculated using the Mann–Whitney *U*-test for continuous variables and χ^2-test for categorical variables. Postoperative sleep disturbance was defined as a PSQI score ≥5 at 24 hours after surgery. Values for SAS, SDS, PSQI, and VAS scores are presented as median (IQR).

Abbreviations: CON, control; ESK, esketamine; IQR, interquartile range; POSD, postoperative sleep disturbance, PSQI, Pittsburgh Sleep Quality Index; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale; VAS, Visual Analog Scale.

generally higher aPSD values in the ESK group (P < 0.05), with notable exceptions at specific time-region combinations: alpha waves in the central region at T2 (P = 0.117), beta waves in the prefrontal region at T2 (P = 0.584), delta waves in the temporal region at T2 (P = 0.288), and alpha waves in the prefrontal region at T3 (P = 0.011).

Analysis of rPSD in the prefrontal channels throughout the surgical procedure is presented in Figure 3A. The ESK group demonstrated significantly higher rPSD values compared with the CON group for beta (mean [SD], 11.42 [4.82] vs 9.69 [4.25]; P = 0.043), theta (mean [SD], 16.36 [4.08] vs 14.25 [3.74]; P = 0.004), and gamma bands (mean [SD], 0.74 [0.25] vs 0.52 [0.18]; P < 0.001) (Supplementary Table 2).

Time-frequency analysis demonstrated distinct cortical activity patterns between groups 30 minutes after EEG monitoring initiation. The ESK group exhibited intermittent bursts of low- and mid-frequency activity with progressively increasing high-frequency power, whereas the CON group showed more stable and suppressed activity across all frequency bands (Figure 3B).

In multivariable logistic regression analysis, 24 hours VAS pain scores were associated with increased POSD risk (OR, 1.75; 95% CI, 1.04–3.06; P = 0.040), while gamma-band rPSD was protective against POSD (OR, 0.63; 95% CI, 0.40–0.97; P = 0.039). In the first sensitivity analysis, both associations remained significant: 24-hour VAS scores (adjusted OR, 1.79; 95% CI, 1.05–3.19; P = 0.038) and gamma-band rPSD (adjusted OR, 0.60; 95% CI, 0.38–0.94; P = 0.029). In the second sensitivity analysis, only 24 hours VAS scores maintained significance (adjusted OR, 1.81; 95% CI, 1.07–3.20; P = 0.032), while gamma-band rPSD showed a trend toward significance (adjusted OR, 0.65; 95% CI,

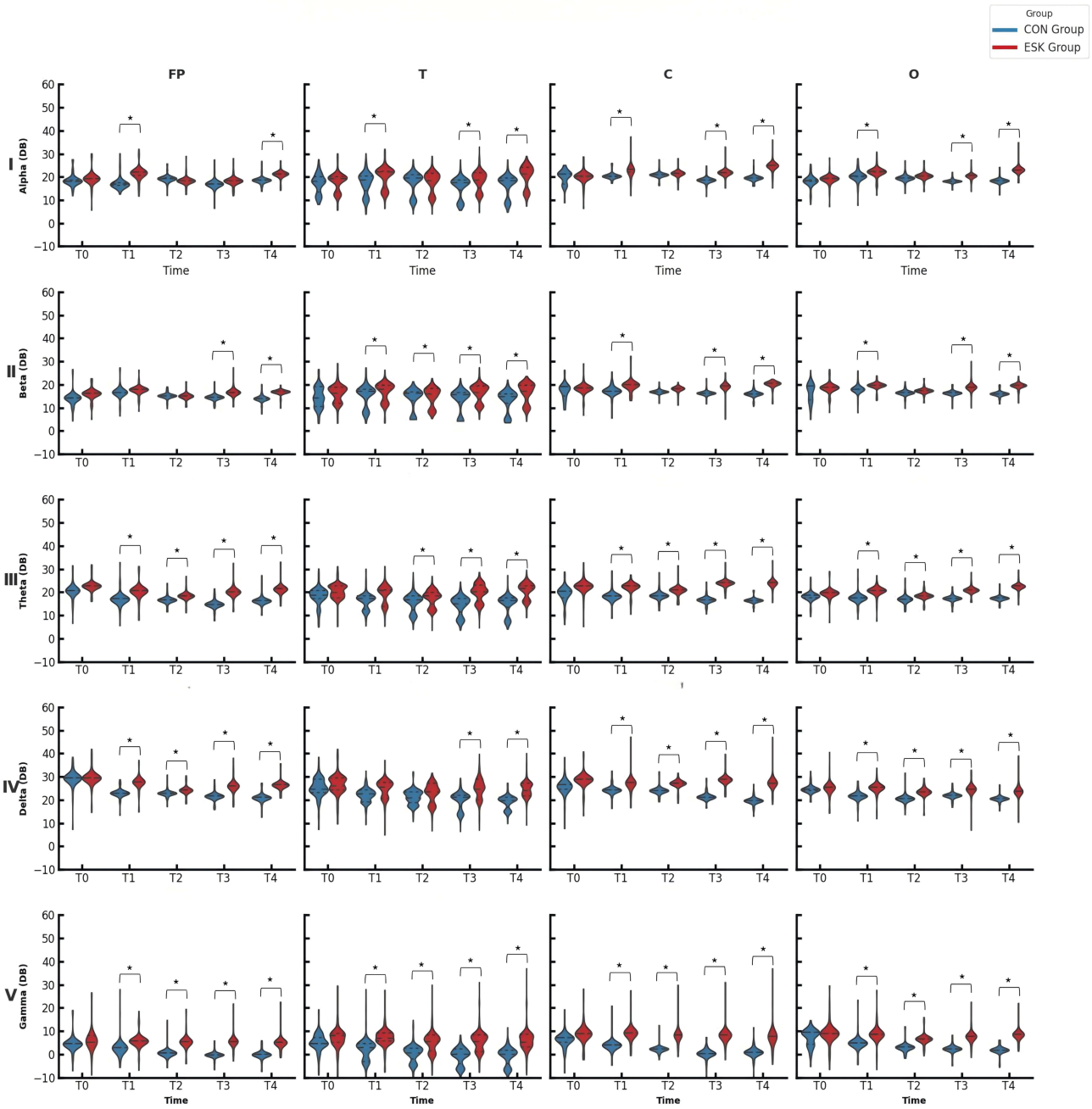

Figure 2 Absolute Power Spectral Density Across Brain Regions and Frequency Bands in Patients.
Notes: Violin plots display the absolute power spectral density (aPSD, measured in μV^2) distribution across 4 brain regions and 5 frequency bands at 5 time points during surgery. Rows represent frequency bands: (**I**) Alpha (8–13 Hz), II. Beta (13–30 Hz), III. Theta (4–8 Hz), IV. Delta (0.5–4 Hz), and V. Gamma (30–45 Hz). Columns represent brain regions: FP (prefrontal), T (temporal), C (central), and O (occipital). The horizontal line within each violin plot indicates the median value, and the vertical lines extend to the interquartile range. Time points: T0 (before induction), T1 (5 minutes after intubation), T2 (20 minutes after the start of surgery), T3 (40 minutes after the start of surgery), and T4 (end of surgery). Statistical significance: *FDR-corrected $q < 0.05$.

0.40–1.01; P = 0.060) (Figure 4). Other variables were not significantly associated with POSD across all models. The results of the variable selection process and the model parameters are detailed in Supplementary Tables 3, 4, and Supplementary Figures 2, 3.

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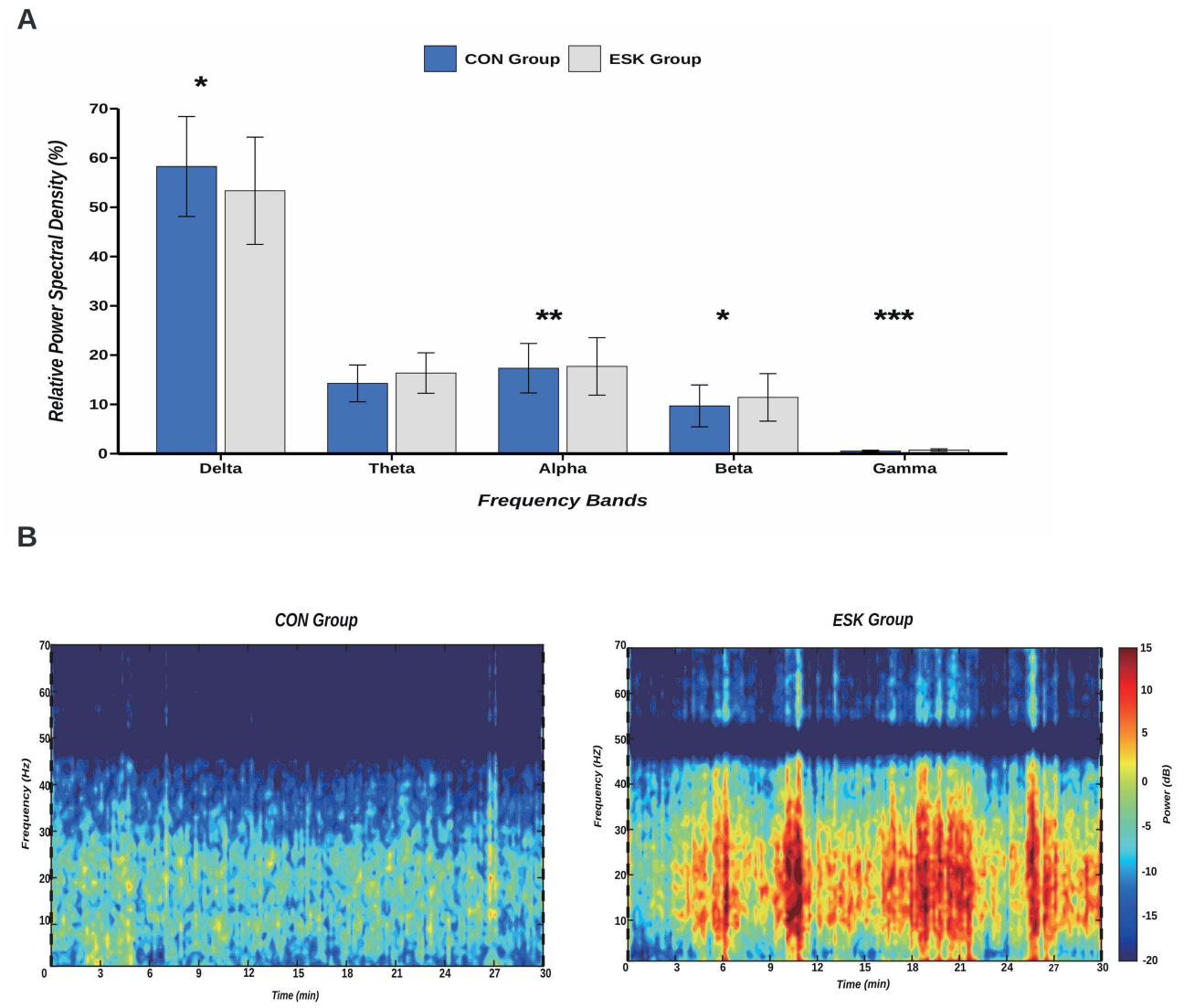

Figure 3 Electroencephalographic Analysis of Relative Power Spectral Density in Patients Receiving Subanesthetic Esketamine vs Control.
Notes: (**A**) Comparison of relative power spectral density between the CON and ESK groups across different frequency bands: alpha (8–13 Hz); beta (13–30 Hz); theta (4–8 Hz); delta (0.5–4 Hz); gamma (30–45 Hz). Data are presented as mean ± standard error of the mean. $p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. (**B**) Time-frequency spectrograms for both groups. Blue indicates lower power density, and red indicates higher power density.
Abbreviations: CON, control; ESK, esketamine.

Safety Outcomes

Subanesthetic esketamine was well tolerated throughout the perioperative period, with no serious adverse events attributable to the study medication observed in the ESK group. Postoperative adverse reactions, including vomiting, agitation, and other adverse reactions, did not show significant differences between the two groups (Supplementary Table 1). Among the 145 randomized patients included in the safety analysis, no participants in either group experienced severe bradycardia (requiring treatment), clinically significant respiratory depression, or other serious anesthesia-related complications. Intraoperative hemodynamic parameters, including heart rate, blood pressure, and oxygen saturation, remained relatively stable throughout the surgical procedure in both groups, though transient mild hypotension occurred in some patients from both groups and was managed with routine vasopressor support (Supplementary Figure 4 and Supplementary Table 5).

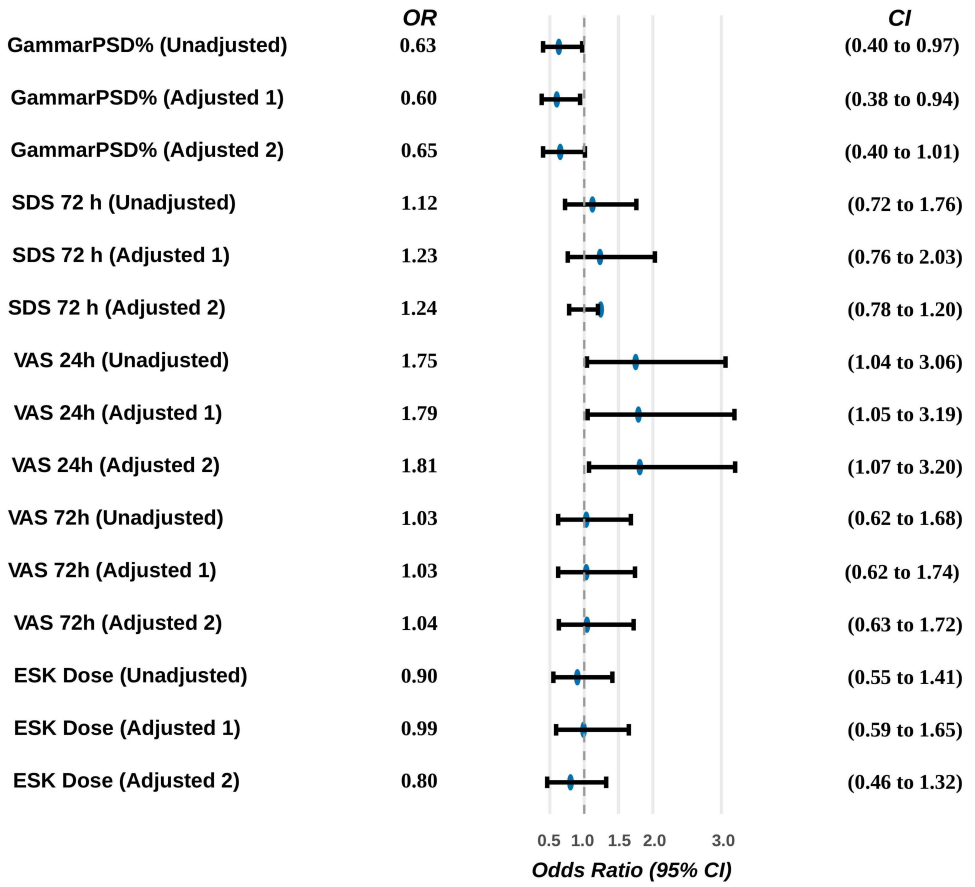

Figure 4 Association of Risk Factors with Postoperative Sleep Disturbance.
Notes: Forest plot displays odds ratios (ORs) and 95% confidence intervals (CIs) from three logistic regression models examining risk factors for postoperative sleep disturbance. For each variable, three estimates are shown: "Unadjusted" represents the crude model without covariates; "Adjusted 1" represents the baseline-adjusted model (adjusted for age, preoperative Self-Rating Anxiety Scale and Self-Rating Depression Scale scores); "Adjusted 2" represents the surgery-adjusted model (additionally adjusted for blood loss, surgery duration, and propofol dose). Horizontal lines represent 95% CIs. The vertical reference line indicates OR = 1.0. Points to the left of the reference line indicate protective associations (OR <1.0); points to the right indicate increased risk (OR >1.0).
Abbreviations: ESK, esketamine; rPSD, relative power spectral density percentage; SDS, Self-Rating Depression Scale; VAS, Visual Analog Scale.

Discussion

In our study, the incidence of POSD in patients with breast cancer was 51.7% in the CON group, consistent with previously reported rates of approximately 50%.[7,39] In contrast, the ESK group showed a significantly lower incidence of 27.6% (P = 0.014). The number of POSD cases in the ESK group was 16 (16/58), which was lower than that in the CON group 30 (30/58). Moreover, PSQI scores at both 24 and 72 hours postoperatively were significantly lower in the ESK group. Multivariable regression analysis demonstrated that intraoperative gamma rPSD and postoperative pain (VAS scores) were associated with the incidence of POSD.

Component-level analysis of PSQI revealed that esketamine was particularly effective in reducing nighttime awakenings and improving sleep efficiency, but had minimal impact on snoring or sleep medication use, as these are not direct targets of NMDA receptor antagonism. NMDA receptors are predominantly distributed in brain regions involved in sleep-wake regulation, including the hippocampus and cortex, where esketamine modulates cortical excitability and arousal states through receptor blockade.[40] However, its effects are limited against sleep disturbances mediated by peripheral or non-glutamatergic mechanisms, such as airway obstruction-induced snoring or medication-dependent sleep problems. The sleep-improving effects of different pharmacological agents appear to be selective. For instance, Sun et al[41] found that low-dose dexmedetomidine primarily enhanced subjective sleep quality. Similarly, Grima et al[42] demonstrated that perioperative melatonin administration effectively shortened sleep latency. Zhu et al[43] also reported that intraoperative intravenous infusion of 2 μg/kg/h and 4 μg/kg/h of esketamine significantly improved postoperative sleep quality in patients undergoing radical mastectomy, which is consistent

with the findings of our study. Moreover, a recent study[44] demonstrated that subanesthetic ketamine (0.5–0.75 mg/kg) in the ICU significantly improved sleep quality, which is consistent with our results.

Normal adult sleep cycles are characterized by alternating stages of NREM and REM sleep. NREM can be further subdivided into N1, N2, and N3 stages, with N3 (slow-wave sleep) characterized by high-amplitude, low-frequency delta and theta waves, while REM sleep is characterized by low-amplitude, high-frequency beta and gamma waves.[45–47] Regular alternation between NREM and REM sleep, together with dynamic multi-band oscillatory modulation, is essential for maintaining normal sleep architecture and brain function recovery.[48] Studies have shown that subanesthetic esketamine increases BDNF secretion, which is crucial for synaptic plasticity and slow-wave activity on EEG.[49,50] Other studies[34] have also shown that intravenous esketamine at 0.5 mg/kg for 40 minutes significantly improved total sleep time, slow-wave sleep (SWS), and NREM. Based on these findings, one would expect that improved sleep quality after esketamine administration would be associated with enhanced slow-wave activity. However, contrary to this expectation, our EEG analysis revealed a distinct pattern: the ESK group exhibited increased aPSD across all frequency bands, not limited to slow waves. Orchestrated alternation between slow and fast wave oscillations is essential for optimal sleep quality and memory consolidation. Pham et al[51] demonstrated that esketamine increased excitability in the medial prefrontal cortex and subcortical regions of rodents across all frequency bands. Bernat et al[52,53] observed in both human and rodent anesthesia models that administration of NMDA receptor antagonists (such as ketamine/esketamine) preserved gamma oscillatory rhythms during anesthesia.

Gamma oscillations are critical for cortical information processing, synaptic plasticity, and transitions between wakefulness and sleep.[54] Similarly, de la Salle et al[55] found that esketamine increased subcortical gamma activity, rather than simply enhancing slow wave activity, consistent with our findings. This observation challenges the traditional hypothesis that postoperative sleep improvement primarily depends on enhanced slow-wave activity.

Moreover, beyond the significant increase in rPSD of theta and delta waves in the prefrontal region of the ESK group, we also observed a significant increase in gamma rPSD, which is traditionally associated with wakefulness. Time frequency analysis revealed that EEG activity in the ESK group exhibited patterns reminiscent of the rhythmic alternation between NREM and REM sleep, closely resembling EEG activity seen during natural stage N3 sleep.[56] This pattern is similar to the cyclic alternating pattern (CAP) observed in physiological sleep, which is characterized by transient slow-wave oscillations interspersed with high-frequency gamma-band oscillations.[57,58] This suggests that esketamine may induce EEG activity during anesthesia that closely approximates physiological sleep architecture, potentially explaining its beneficial effects on postoperative sleep continuity. Previous studies[59] have shown that esketamine suppresses thalamo-cortical loop activity while preserving high frequency cortical network activity. In this dissociated state, deep suppression of theta waves may coexist with localized high-frequency gamma activity, consistent with our findings. Thus, this unique EEG pattern suggests that esketamine may provide a neurophysiological basis for improved sleep quality and restoration of circadian rhythms in the postoperative period.

Multivariable regression analysis demonstrated that intraoperative gamma rPSD and postoperative pain (VAS scores) were independent risk factors for POSD. However, notably, there was no significant difference in postoperative VAS scores between groups, thus, pain was not a confounding variable for between-group differences in sleep quality. Additionally, both groups showed significant postoperative improvement in SAS and SDS scores, consistent with the known antidepressant and anxiolytic effects of esketamine. However, postoperative anxiety and depression were not independent risk factors for POSD in regression analysis, emphasizing the central role of gamma oscillations and sleep rhythm changes in postoperative sleep preservation. This further supports the hypothesis that subanesthetic esketamine improves postoperative sleep primarily through direct modulation of intraoperative EEG rather than indirect analgesic or mood effects. After adjusting for surgical-related variables, the gamma protective effect was attenuated, suggesting that multiple intraoperative factors (such as surgical stress and anesthetic depth) may affect the relationship between EEG activity and sleep outcomes,and may be targets for enhancing postoperative sleep continuity and reducing sleep fragmentation.

In summary, subanesthetic esketamine reduces the incidence of early POSD by preserving and augmenting gamma synchrony and inducing CAP like EEG oscillations. Our findings suggest that integrating detailed EEG analysis with component-level clinical evaluation of the PSQI reveals the critical role of multi-band dynamic balance and rhythmic switching in perioperative sleep preservation. Intraoperative modulation of gamma rhythms provides a novel target for POSD prevention and offers new avenues for perioperative neurophysiological management and targeted frequency specific interventions.

Limitations

This study has several limitations. First, our study population was restricted to middle-aged women (35–55 years), limiting generalizability to older patients who may have different responses to subanesthetic esketamine. Second, we assessed POSD outcomes only at 24 and 72 hours postoperatively; the long-term persistence of esketamine's effects remains uncertain. Additionally, although the PSQI is a widely used tool, its design for chronic sleep disorders may limit its ability to fully assess acute POSD. Third, as a single centre study, external validity may be limited, and multicentre trials are needed to confirm these findings. Future studies with more diverse patient populations and surgical types could incorporate subgroup analyses to explore treatment effect heterogeneity. Fourth, our analysis was limited to the per-protocol population. Future studies should include intention-to-treat analyses to enhance generalizability. Finally, while our sample size was adequate for the primary analysis, it was insufficient for robust predictive modeling.

Conclusions

This randomized clinical trial demonstrated that intravenous subanesthetic esketamine during elective breast cancer surgery significantly reduced POSD incidence. Moreover, esketamine significantly improved postoperative sleep quality, as evidenced by lower PSQI scores at both 24 and 72 hours. Importantly, our findings suggest that these sleep enhancing effects may be mediated through modulation of intraoperative gamma band EEG activity, which was independently associated with reduced POSD risk. These results provide preliminary evidence that intraoperative subanesthetic esketamine may offer a novel therapeutic approach for improving postoperative sleep quality in breast cancer patients.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its Supplementary Information files.

Ethics Approval and Consent to Participate

This single-center, double-blind, placebo-controlled randomized clinical trial was approved by the Institutional Ethics Committee of Liaoning Cancer Hospital & Institute (KY20240907-2) and prospectively registered in the Chinese Clinical Trials Registry (registration number: ChiCTR2400092257). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines and the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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