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Effect of a single low-dose esketamine administration during surgical abortion on postoperative sleep disturbance: a randomized controlled trial

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Women with pre-existing sleep disturbance frequently experience postoperative sleep disturbance after surgery. This randomized, double-blind, placebo-controlled, parallel-group trial was conducted to investigate the efficacy of intraoperative adjunctive esketamine administration in the reduction of postoperative sleep disturbance following surgical abortion for women with pre-existing sleep disturbance. 204 women who had sleep disturbance and were scheduled for elective surgical abortion were randomized in a one-to-one allocation ratio to receive either a single intravenous injection of 0.2 mg/kg of esketamine or placebo (saline) immediately after the beginning of surgery (102 women allocated to each group). This trial has now completed. The primary outcome, incidence of sleep disturbance on the first night after surgery, is significantly lower in the esketamine group than in the placebo group (47.1% [48 of 102] vs 71.6% [73 of 102]; odds ratio, 0.35; 95%CI, 0.20–0.64; $P = 0.0004$). No treatment-related serious adverse events were observed. Here we show that a single low dose of esketamine during surgical abortion improves postoperative sleep quality for women with pre-existing sleep disturbance. ClinicalTrials.gov identifier: NCT06388824.

Approximately 9.6–19.4% of adults experience sleep disturbance, which might manifest as sleep deprivation (lack of adequate sleep), aberrant architecture, or disorder of circadian rhythm[1–3]. Postoperative sleep disturbance is common among patients following surgery, which may cause an increased risk of delirium, a worse recovery, and more cardiovascular events[4,5]. Preoperative sleep disorder, female sex, and preoperative anxiety are main predictors of postoperative sleep disturbance[4,6]. Furthermore, intraoperative administration of general anesthetics (propofol, sevoflurane, isoflurane) and analgesics (morphine, remifentanil) has been identified to negatively impact postoperative sleep quality and sleep architecture[7–9]. Accordingly, female patients with pre-existing sleeping issues who require surgery under general anesthesia are at high risk of postoperative sleep disturbance.

An estimated 77.3 million abortions occur worldwide annually[10]. While surgical abortion is a viable option for terminating a pregnancy under 12 weeks gestation among women with missed miscarriage or unwanted pregnancy[11], it can be frightening, painful and uncomfortable for patients. These may aggravate sleep disturbance after surgeries among women. Given that propofol is a desired anesthetic with a quick onset and brief duration of action, it has become a most

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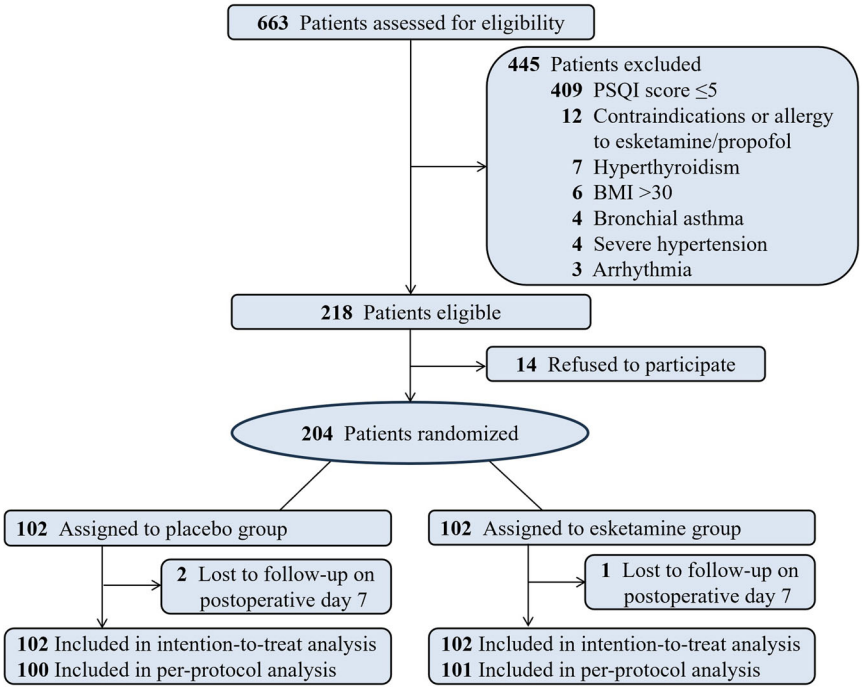

Fig. 1 | Consolidated standards of reporting trials (CONSORT) flow diagram. BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PSQI Pittsburgh Sleep Quality Index.

common component of balanced anesthesia in the overwhelming majority of outpatient surgery-induced abortions[12,13]. However, recent clinical literatures report that intraoperative usage of propofol is capable of impairing postoperative sleep quality of patients undergoing gastrointestinal endoscopy, especially in patients with preoperative sleep disorder[7,8]. These discoveries have prompted researchers to look for potential therapeutic strategies for enhancing postoperative sleep quality in women with pre-existing sleep disorders who require surgical abortion under propofol anesthesia.

Esketamine is characterized as an S-enantiomer of racemic ketamine and a novel N-methyl-D-aspartate receptor (NMDAR) antagonist with a greater affinity as compared to ketamine, simultaneously, esketamine has been identified to exhibit stronger anesthetic and analgesic properties with fewer side-effects than ketamine[14,15]. Intriguingly, subanesthetic doses of esketamine exhibit excellent antidepressant actions and therapeutic potential in major depressive disorder, postpartum depression, bipolar depression and treatment-resistant depression[16–18]. Moreover, accumulating evidence emphasizes the efficacy of esketamine/ketamine in improving sleep quality in patients with depression and sleep disturbance[19,20], although the mechanism for this remains unclarified. Consistently, intraoperative administration of esketamine is demonstrated to have a prophylactic effect against postoperative sleep disturbance in patients without preoperative sleep disorders[4,21]. Nevertheless, esketamine has never been investigated for the alleviation of sleep disturbance in women undergoing surgical abortion in the clinical setting. We therefore evaluated the effects of perioperative adjunctive esketamine administration during surgical abortion on patients with pre-existing sleep disturbance.

Results

patient characteristics

A total of 204 female patients (median [IQR] age, 31 [25–34] years; median [IQR] body mass index, 21.75 [20.30–23.65]) were enrolled and randomly assigned among 663 women who had their eligibility evaluated. Three women declined follow-up on day 7 following the surgery during the research period. Consequently, the intention-to-treat analysis included all 204 women (n = 102 in each group), but the per-protocol analysis included 201 women (Fig. 1). The demographic information, such as age, body mass index, ASA classification, reason for surgery, history of pregnancy and abortion, previous medical disorders, and preoperative hemoglobin and HCG level, was well balanced between the two groups (Table 1). Moreover, no significant differences were detected between the 2 groups in terms of PSQI scores for sleep disorders during one month before surgery, preoperative AIS scores for sleep quality, as well as HADS scores for anxiety and depression (Table 1).

Duration of operation and anesthesia, intraoperative mean arterial pressure and HR, the percentage of patients who received atropine and phenylephrine, post-anesthetic recovery time were comparable between the two groups (Table 2, Supplementary Table 1). Nonetheless, the esketamine group consumed a considerably lower median (IQR) of intraoperative propofol than the placebo group (86 [80–95] vs 117 [105.8-135] mg; median difference, −30; 95%CI, −34 to −25; $P < 0.0001$). Also, patients receiving esketamine exhibited lower frequency of intraoperative body movement than placebo-treated patients (2.9% vs 11.8%; odds ratio [OR], 0.23 [95%CI, 0.07-0.75]; $P = 0.0158$) (Table 2).

Efficacy assessment

The esketamine group experienced less sleep disturbance on postoperative night 1 (47.1% vs 71.6%; OR, 0.35 [95%CI, 0.20–0.64]; $P = 0.0004$) and postoperative night 2 (42.2% vs 60.8%; OR, 0.47 [95% CI, 0.27–0.82]; $P = 0.0078$) when compared with the placebo group (Table 3 and Fig. 2). However, we did not detect any differences between two groups for the incidence of sleep disturbance on postoperative night 3 (placebo vs esketamine, 49.0% vs 39.2%; OR, 0.67 [95%CI, 0.38–1.17]; $P = 0.1585$) and 7 (placebo vs esketamine, 39.0% vs 33.7%; OR, 0.79 [95%CI, 0.45–1.39]; $P = 0.4315$). For primary outcome, per-protocol analysis produced comparable results (Table 3). Moreover, the median (IQR) AIS scores were dramatically lower in the esketamine group vs placebo group at the first night (5 [5–8] vs 6.5

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Table 1 | Patient demographic and baseline characteristics[a]

Variable	Placebo group (n = 102)	Esketamine group (n = 102)	*P* value
Age, median (IQR), y	32 (25–34)	30.5 (25–34.25)	0.7439
Height, median (IQR), cm	160 (158–165)	162 (160–165)	0.2492
BMI, median (IQR)	22.0 (20.5–24.1)	21.5 (20.3–23.4)	0.2008
ASA classification, No. (%)			0.3295
I	86 (84.3)	82 (80.4)	
II	13 (12.8)	19 (18.6)	
III	3 (2.9)	1 (1.0)	
Education degree, No. (%)			0.6559
Primary school	3 (2.9)	3 (2.9)	
High school	8 (7.8)	8 (7.8)	
College	81 (79.4)	75 (73.5)	
Master's degree or above	10 (9.8)	16 (15.7)	
Full time employment, No. (%)	68 (66.7)	76 (74.5)	0.2190
Family income (Chinese Yuan/month), No. (%)			0.9354
<10,000	37 (36.3)	36 (35.3)	
10,000–20,000	53 (52.0)	52 (51.0)	
20,000–40,000	8 (7.8)	8 (7.8)	
>40,000	4 (3.9)	6 (5.9)	
Covered by health insurance	54 (52.9)	56 (54.9)	0.7788
Pregestational comorbidities, No. (%)			
Heart disease	2 (2.0)	2 (2.0)	>0.9999
Diabetes	2 (2.0)	2 (2.0)	>0.9999
Hypertension	2 (2.0)	3 (2.9)	>0.9999
Thyroid disease	0	2 (2.0)	0.4975
Liver disease	0	0	>0.9999
Kidney disease	1 (1.0)	0	>0.9999
Drinking status, No. (%)	4 (3.9)	2 (2.0)	0.6828
Smoking status, No. (%)	2 (2.0)	3 (2.9)	>0.9999
Dysmenorrhea status, No. (%)			0.7408
No	33 (32.4)	29 (28.4)	
Occasionally	57 (55.9)	58 (56.9)	
Frequently	12 (11.8)	15 (14.7)	
Number of pregnancies, No. (%)			0.8726
0	17 (16.7)	14 (13.7)	
1	42 (41.2)	41 (40.2)	
2	18 (17.7)	22 (21.6)	
≥3	25 (24.5)	25 (24.5)	
Number of abortions, No. (%)			0.6268
0	39 (38.2)	35 (34.3)	
1	37 (36.3)	38 (37.3)	
2	13 (12.8)	19 (18.6)	
≥3	13 (12.8)	10 (9.8)	
Childlessness, No. (%)	48 (47.1)	57 (55.9)	0.2074
Cause of elective surgical abortion, No. (%)			0.6916
Unplanned pregnancy	62 (60.8)	65 (63.7)	
Health reasons	23 (22.6)	21 (20.6)	
Existing children	9 (8.8)	7 (6.9)	
Socioeconomic factors	3 (2.9)	4 (3.9)	
Age factor	3 (2.9)	5 (4.9)	
Unknown reasons	2 (2.0)	0	
HCG level (mIU/mL), median (IQR)	60,502 (36,028–81,456)	54616 (22,455–77,266)	0.2534
Hemoglobin level (g/L), median (IQR)	125.5 (112.8–134.3)	132.0 (115.0–137.3)	0.1068
PSQI, median (IQR)[b]	9 (8–11)	9 (7–11)	0.6128
AIS score, median (IQR)[c]	8 (5–10)	8.5 (5–11)	0.6505
HADS-A score, median (IQR)[d]	10 (8–11.25)	10 (8–11)	0.3524
HADS-D score, median (IQR)[e]	3 (2–3)	3 (2–3)	0.6185

AIS Athens Insomnia Scale, *ASA* American Society of Anesthesiologists, *BMI* body mass index (calculated as weight in kilograms divided by height in meters squared), *HADS-A* Hospital Anxiety and Depression Scale-Anxiety, *HADS-D* Hospital Anxiety and Depression Scale-Depression, *HCG* Human Chorionic Gonadotropin, *PSQI* Pittsburgh Sleep Quality Index.
[a]Data presented as median (IQR) were compared using the Mann-Whitney test. Data reported as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test. All statistical tests used were two-sided.
[b]Scores ranges from 0 to 21 points, with a total score greater than 5 indicating poor sleep quality.
[c]Scores ranges from 0 to 24 points, with a total score of 6 or above indicating sleep disturbance.
[d]Scores ranges from 0 to 21 points, with a total score of 8 or above indicating anxiety.
[e]Scores ranges from 0 to 21 points, with a total score of 8 or above indicating depression.

[5–8.25]; $P = 0.0046$), second night (5 [4–7.25] vs 7 [5–9]; $P = 0.0378$), and third night (5 [4–9] vs 5 [5–9]; $P = 0.045$) after surgical abortion (Table 3).

Among other secondary outcomes, the NRS score at rest at postoperative hour 1 was lower in the esketamine group (median [IQR], 3 [2–4]) than in the placebo group (median [IQR], 4 [2.75–5]; median difference, 0; 95%CI, −1 to 1; $P = 0.0151$; Table 3). However, there were no differences in HADS-A, HADS-D, and NRS scores on postoperative days 1, 2, 3, and 7 between the two groups (Table 3). Likewise, the percentage of patients who took oral acetaminophen during the first three days after surgery was not different between groups (placebo vs esketamine, 12.8% vs 5.9%; $P = 0.0917$). No change of QoR15 scores on seven days after surgery was noted across groups ($P = 0.2542$; Table 3). In addition, The Ramsay sedation scores during or within 30 min after surgery did not differ between groups (Supplementary Table 2).

Safety assessment

With respect to surgery-related adverse events, including cervical laceration, uterine perforation, hemorrhage and incomplete, no differences were seen between groups (Supplementary Table 3). Similarly, the median (IQR) HCG level on postoperative day 7 did not differ between placebo and esketamine groups (134.6 [66.27-234.1] vs 123.3 [55.26-324.6] mIU/mL; $P = 0.6066$). Among anesthesia-related adverse events, the incidence of intraoperative respiratory depression in placebo group were higher than that in esketamine group (15.7% vs 3.9%; OR, 0.22 [95%CI, 0.08–0.64]; $P = 0.0047$), whereas postoperative nausea, vomiting, and respiratory depression were equally prevalent in both groups (Table 4). Additionally, as compared to patients with placebo administration, patients receiving esketamine did not exhibit any notable neuropsychiatric symptoms during the three days following surgery, including delirium, somnolence, dizziness, agitation, hallucination, diplopia and memory impairment (Table 4). There were no serious side effects during the trial period.

Table 2 | Intraoperative and anesthetic data of the patients[a]

Variable	Placebo group (n = 102)	Esketamine group (n = 102)	*P* value
Duration of surgery, median (IQR), min	8 (7–9)	8.5 (7–9)	0.7075
Duration of anesthesia, median (IQR), min	13 (13–14)	14 (13–15)	0.0759
Incidence of body movement, No. (%)	12 (11.8)	3 (2.9)	0.0158
Time to fully alert, median (IQR), min	4 (3–5)	4.5 (3–7)	0.0831
Total amount of propofol, median (IQR), min	117 (105.8–135)	86 (80–95)	<0.0001
Intraoperative use of atropine, No. (%)	10 (9.8)	5 (4.9)	0.1798
Intraoperative use of phenylephrine, No. (%)	6 (5.9)	2 (2.0)	0.2792

[a]Data presented as median (IQR) were compared using the Mann-Whitney test. Data reported as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test. All statistical tests used were two-sided.

Discussion

The primary findings of this randomized clinical trial are that incidence of sleep disturbances on the first two postoperative nights in the esketamine group were significantly lower compared with the control group. Moreover, patients receiving single esketamine injection exhibited the decreased AIS scores on the first three postoperative nights. These results imply that intravenous administration of esketamine with subanesthetic dose during surgical abortion can provide significant and temporary improvements in sleep quality for patients who already had sleep disturbances. Additionally, esketamine-treated patients consumed less propofol, as well as exhibited less respiratory depression and body movement during the intraoperative phase than placebo group. Overall, esketamine may be as a useful component of general anesthesia and analgesia therapy during surgical abortion for women with pre-existing sleep issues.

Recently, the prophylactic effects of esketamine on postoperative sleep disorders have been validated in surgical patients without pre-existing sleep problems[4,22–24]. In particular, following gynecological laparoscopic surgery, the incidence of sleep disorders was reduced from 44.0% to 22.8% on postoperative day 1 and from 19.8% to 7.6% on postoperative day 3 by intraoperative infusion of esketamine (0.3 mg/kg/h, intravenous)[4]. Another clinical literature reported that a single dosage of esketamine (0.5 mg/kg, intravenous) during anesthesia induction produced better sleep quality among patients after laparoscopic resection of gastric carcinoma[22]. Furthermore, patients undergoing liposuction surgery were able to avoid postoperative sleep disorders with a subanesthetic dose (0.15–0.3 mg/kg/h) of esketamine during anesthesia[23]. Also, esketamine as a supplement in patient-controlled intravenous analgesia reduced postoperative sleep disturbance in the elderly after total hip or knee arthroplasty[24]. Nevertheless, these previous studies were largely restricted to patients who were healthy and excluded those with pre-existing sleep disorders who were thus at high risk of postoperative sleep disturbance. Notably, a trial evaluating the prophylactic effect of esketamine on postoperative sleep disorder for elderly patients undergoing laparoscopic abdominal surgery did not exclude patients with preoperative sleep disorders[25]. But in this study, preoperative sleep quality and disorder were not evaluated and mentioned, thus it is difficult to demonstrate if patients selected in this trial had preoperative sleep disorder. This study could not conclude that esketamine is effective in patients with preoperative sleep disorder. It is unknown whether esketamine is protective against sleep disturbance after surgical abortion in women with pre-existing sleeping issues. Our present study, for the first time, illustrated that a single low dose (0.2 mg/kg, intravenous) of esketamine administered immediately after the start of operation reduced the incidence of sleep disturbance from 71.6% to 47.1% on postoperative night 1 and from 60.8% to 42.2% on postoperative night 2 following surgical abortion in patients with preoperative sleep disturbances. The selection of participants with pre-existing sleep issues led to a low number needed to treat, which is dependent on baseline incidence. By focusing on patients who are most likely to benefit, side effects were reduced to those who would benefit, resulting in a positive risk-benefit ratio.

We only observed that there was a significant difference between two groups in postoperative pain within one hour after surgery, whereas intraoperative exposure to adjunctive esketamine was ineffective in improving post-surgical pain phenotypes during postoperative day 1 to day 7. It seems likely that surgical abortion is associated with minimal surgical trauma and low postoperative pain intensity. Therefore, it was assumed that the beneficial impact of esketamine on postoperative sleep disorders might not be correlated with its analgesic qualities in this patient population. Although postoperative pain has been implicated in the development of postoperative sleep disturbance[4,6], the high prevalence of postoperative sleep disturbance in our selected population is mainly due to these female patients with pre-existing sleep disturbance.

We discovered the lower percentage of somatic motor reactions during surgical procedures in patients receiving esketamine, which may be due to the rapid and short-term anesthetic and analgesic properties of esketamine. Consistent with earlier research[26,27], we also detected that patients receiving esketamine consumed less propofol, which may be the reason for low frequency of intraoperative respiratory depression in esketamine group. Given the detrimental roles of propofol in postoperative sleep quality[7,8,28,29], the lower prevalence of postoperative sleep disorders in esketamine group may be, at least in part, explained by the reduction of propofol consumption in patients who underwent surgical abortion. Sure, it is more likely that the pharmacological effect of esketamine on sleep disorders is associated with inflammation inhibition and circadian rhythm system modification[20,29–33]. Collectively, our findings elucidate that a single low dose of esketamine occupies a clear advantage in surgical abortion and is worth popularizing if patients have pre-existing sleep disturbances. Further investigations are, however, warranted to confirm specific mechanistic links between esketamine, circadian rhythms, and inflammation in sleep disturbance.

Two meta-analyses of randomized controlled trials support the potential for perioperative administration of esketamine to attenuate postoperative anxiety and depression, although the effect was transient[34,35]. In contrast, a recent study involving 129 adult patients undergoing elective non-cardiac thoracic surgery under general anesthesia revealed that a single intraoperative dose of 0.2 mg/kg esketamine failed to reduce postoperative anxiety and depression[36]. Another clinical trial involving 426 elderly patients demonstrated that a single injection of 0.2 mg/kg esketamine before the induction of general anesthesia could not help in preventing postoperative anxiety and depression following elective non-cardiac surgery[37]. Likewise, our current results also manifested that a single intravenous injection of low-dose esketamine (0.2 mg/kg) was unable to reduce the prevalence of anxiety and depression within the initial postoperative 7 days. These controversial results imply that discrepancies in anti-depressant and anxiolytic characteristics of esketamine throughout the perioperative

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Table 3 | Efficacy outcomes[a]

Outcome	Placebo group (n = 102)	Esketamine group (n = 102)	Estimated effects (95% CI)[b]	*P* value
Primary outcome				
Incidence of sleep disturbance on the first night after surgery, No. (%)	73 (71.6)	48 (47.1)	OR, 0.35 (0.20–0.64)	0.0004
Incidence of sleep disturbance on the first night after surgery (per-protocol analysis), No. (%)	73 (73) (n = 100)	48 (47.5) (n = 101)	OR, 0.34 (0.19–0.62)	0.0002
Secondary outcomes				
AIS score, median (IQR)[c]				
First night after surgery	6.5 (5–8.25)	5 (5–8)	Median difference, −1 (−1 to 0)	0.0046
Second night after surgery	7 (5–9)	5 (4–7.25)	Median difference, −1 (−1 to 0)	0.0378
Third night after surgery	5 (5–9)	5 (4–9)	Median difference, 0 (−1 to 0)	0.0450
Seventh night after surgery	5 (4–9) (2)[h]	5 (4–7) (1)[h]	Median difference, 0 (−1 to 0)	0.1097
HADS-A score, median (IQR)[d]				
Postoperative day 1	9.5 (8–11)	9 (7–11)	Median difference, 0 (−1 to 1)	0.5864
Postoperative day 2	9.5 (7.75–11)	9 (8–11)	Median difference, 0 (−1 to 0)	0.5046
Postoperative day 3	10 (8–12)	9.5 (7.75–11)	Median difference, 0 (−1 to 0)	0.2879
Postoperative day 7	10 (8–11.75)(2)[h]	10 (7–11)(1)[h]	Median difference, 0 (−1 to 0)	0.3418
HADS-D score, median (IQR)[e]				
Postoperative day 1	3 (2–3)	3 (2–3)	Median difference, 0(0 to 0)	0.6073
Postoperative day 2	2.5 (2–3)	3 (2–3)	Median difference, 0(0 to 0)	0.2558
Postoperative day 3	3 (2–3)	3 (2–3)	Median difference, 0(0 to 0)	0.4363
Postoperative day 7	3 (2–3)(2)[h]	3 (2–3)(1)[h]	Median difference, 0(0 to 0)	0.3008
NRS score[f]				
At rest, median (IQR)				
Postoperative hour 1	4 (2.75–5)	3 (2–4)	Median difference, 0 (−1 to 0)	0.0151
Postoperative day 1	4 (3–4)	3 (2–4)	Median difference, 0 (−1 to 0)	0.0676
Postoperative day 2	3 (2–3)	2 (2–3)	Median difference, 0 (−1 to 0)	0.0999
Postoperative day 3	2 (1–2)	2 (1–2)	Median difference, 0 (0 to 0)	0.3328
Postoperative day 7	1 (0–1)(2)[h]	1 (0–1)(1)[h]	Median difference, 0 (0 to 0)	0.53
After movement, median (IQR)				
Postoperative hour 1	5 (4–6)	5 (4–5)	Median difference, 0 (−1 to 0)	0.0661
Postoperative day 1	4 (3–4)	3 (3–4)	Median difference, 0 (−1 to 0)	0.0750
Postoperative day 2	3 (2–3)	2 (1–3)	Median difference, 0 (−1 to 0)	0.1219
Postoperative day 3	2 (1.75–2)	2 (1–2)	Median difference, 0 (0 to 0)	0.4332
Postoperative day 7	1 (0.25–1)(2)[h]	1 (0–1)(1)[h]	Median difference, 0 (0 to 0)	0.4121
Postoperative use of acetaminophen, No. (%)	13 (12.8)	6 (5.9)	OR, 2.34 (0.89 to 6.31)	0.0917
QoR15 score on postoperative day 7, median (IQR)[g]	118 (106–126) (2)[h]	121 (112–127) (1)[h]	Median difference, 2 (−1 to 5)	0.2542

AIS Athens Insomnia Scale, *ASA* American Society of Anesthesiologists, *HADS-A* Hospital Anxiety and Depression Scale-Anxiety, *HADS-D* Hospital Anxiety and Depression Scale-Depression, *NRS* numerical rating scale, *OR* odds ratio, *QoR-15* 15-item quality of recovery.

[a]Data presented as median (IQR) were compared using the Mann-Whitney test. Data reported as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test. All statistical tests used were two-sided.

[b]Calculated as the esketamine group minus or vs the placebo group.

[c]Scores ranges from 0 to 24 points, with a total score of 6 or above indicating sleep disturbance.

[d]Scores ranges from 0 to 21 points, with a total score of 8 or above indicating anxiety.

[e]Scores ranges from 0 to 21 points, with a total score of 8 or above indicating depression.

[f]Scores ranges from 0 to 10 points, with 0 indicating no pain and 10 indicating the worst pain.

[g]Scores ranges from 0 to 150 points, with 118 or greater points indicating a good postoperative recovery.

[h]Patients with missing data owing to refused assessment.

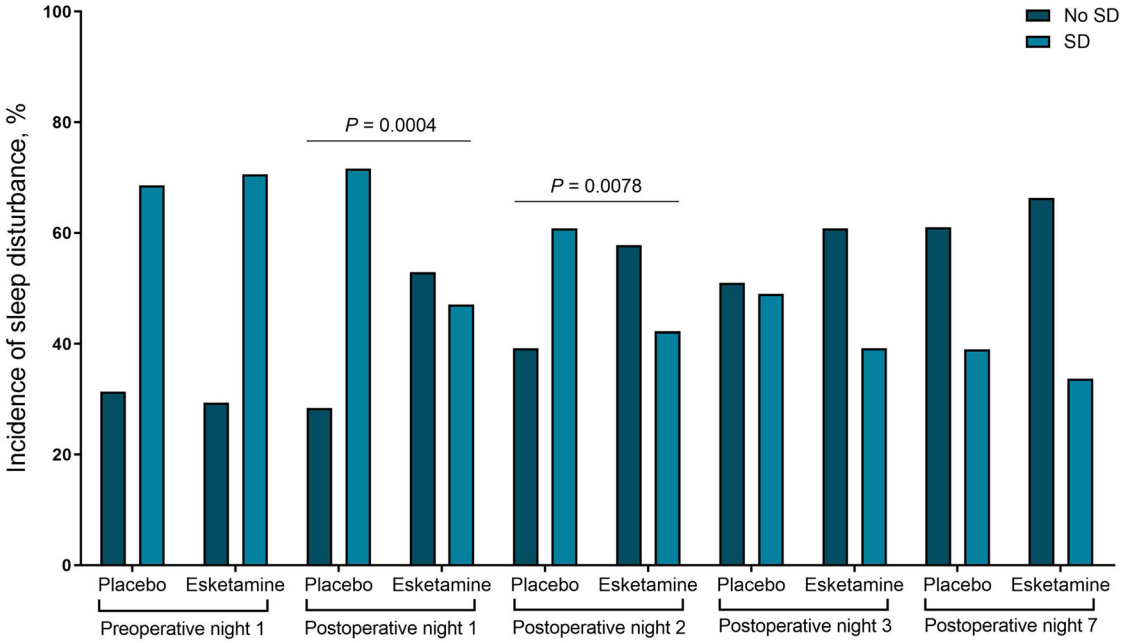

Fig. 2 | Incidence of preoperative and postoperative sleep disturbance (SD). Compared with the placebo group, the esketamine group showed a significant decrease in the incidence of SD on postoperative night 1 and postoperative night 2, with no significant differences observed at the rest of the time points. Data reported as the percentage of patients with/without sleep disturbance were compared using the Pearson χ^2 test or Fisher exact test. All statistical tests used were two-sided. Source data are provided as a Source Data file.

phase might be attributed to variations in the dosage, mode, and timing of therapeutic administration.

In line with other studies[27,38], the results of our present trial did not indicate clinically significant increase in time to fully alert after surgery in patients receiving esketamine. Simultaneously, in our study, the median Ramsay sedation scores did not differ between the two groups and were identical with the first 30 min postoperative period. This finding might be attributable to the rapid metabolism of esketamine and the low dose of esketamine injected. In parallel, the application of tropisetron before the completion of surgery may account for the lack of significant variation in postoperative nausea and vomiting seen in both groups. Emergence delirium is characterized by non-purposeful movements, inattention and disorientation that typically occurs within 45 minutes from general anesthesia[39]. Anesthetic agents used and depth of anesthesia are gradually recognized as leading contributors of emergence delirium[39]. In our current study, we detected that esketamine caused a tendence of an increased incidence of delirium from 1% to 3.9% within one hour of surgery. It might be attributed to the increased depth of anesthesia after the combination of esketamine and propofol in esketamine group. Also, esketamine itself is one risk factor for emergence delirium[40]. However, we did not observe any delirium during 1 hour to 72 hours after surgery, suggesting that emergency delirium in esketamine group is transient. Additionally, as previously documented[4,17,26,27,41], intraoperative esketamine did not notably cause any other neuropsychiatric symptoms throughout the postoperative phase. As a result, our dosing regimen is safe for this patient population. Additionally, a clinical trial evaluating the efficacy of epidural esketamine on postoperative sleep quality after laparoscopic and robotic lower abdominal surgeries is in progress[42]. Although epidural esketamine is not suitable for patients undergoing outpatient surgical abortion with low postoperative pain, it will be of great interest to explore alternative administration routes for esketamine for our patient population.

This study has several limitations. First, all experiments were carried out at a single hospital and might not be indicative of perioperative practice at other facilities, thus necessitating multicenter studies. Second, we failed to collect biological samples, which might be useful to identify the potential mechanism of esketamine's beneficial influence on sleep disruptions. Third, because of the difficulty of monitoring, especially in a large-scale experiment, electroencephalography and polysomnography were not utilized to assess patients' sleep quality. Fourth, further trials are required to determine whether similar encouraging outcomes are generalizable to other surgical populations with a history of sleeping issues. Fifth, we were unable to distinguish if sleep disturbance in patients was pre-pregnant or gestational due to the PSQI scores, which mostly evaluated sleep quality during the month before surgery, however, this may help include individuals in greatest need of care. Sixth, we only evaluated primary and secondary outcomes during and within the first postoperative 7 days, the long-term effects of esketamine on AIS and HADS scores in these patients warrants further exploration.

Overall, the results of this placebo-controlled randomized clinical trial recapitulated that an intraoperative injection of esketamine reduced sleep disturbances after surgical abortion in women who had pre-existing sleeping issues. Furthermore, esketamine administration to the patients showed a satisfactory degree of tolerability and safety. Additional research with a larger sample size is required to ascertain these characteristics of esketamine in this patient population.

Methods

Study design

This prospective, double-blind, placebo-controlled randomized clinical trial was approved by the Tianjin Medical University General Hospital Ethic Committee and registered at ClinicalTrials.gov (NCT06388824). The study was conducted in accordance with the principles of the Declaration of Helsinki. The trial protocol is provided in Supplementary Note 1. Written informed consent was obtained from all patients in this study, which followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline (Supplementary Note 2).

Potential participants were screened with Pittsburgh Sleep Quality Index (PSQI) scale on the day before surgery. The PSQI measured

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Table 4 | Anesthesia-related adverse events in the study participants[a]

Adverse Event	Placebo group, No. (%) (n = 102)	Esketamine group, No. (%) (n = 102)	*P* value
Intraoperative period			
Hypotension[b]	8 (7.8)	4 (3.9)	0.2340
Hypertension[c]	6 (5.9)	9 (8.8)	0.4210
Bradycardia[d]	11 (10.8)	5 (4.9)	0.1182
Tachycardia[e]	5 (4.9)	9 (8.8)	0.2680
Respiratory depression	16 (15.7)	4 (3.9)	0.0047
Postoperative period			
Within 1 h after surgery			
Hypotension	4 (3.9)	4 (3.9)	>0.9999
Hypertension	8 (7.8)	6 (5.9)	0.5797
Bradycardia	7 (6.9)	6 (5.9)	0.7744
Tachycardia	5 (4.9)	7 (6.9)	0.5518
Respiratory depression	2 (2.0)	3 (2.9)	>0.9999
Nausea and vomiting	7 (6.9)	13 (12.8)	0.1578
Delirium	1 (1.0)	4 (3.9)	0.3688
Somnolence	5 (4.9)	11 (10.8)	0.1182
Dizziness	19 (18.6)	25 (24.5)	0.3071
Agitation	0	2 (2.0)	0.4975
Hallucination	0	0	NA
Diplopia	0	0	NA
Memory impairment	1 (1.0)	4 (3.9)	0.3688
1–24 h after surgery			
Respiratory depression	0	0	NA
Nausea and vomiting	4 (3.9)	8 (7.8)	0.2340
Delirium	0	0	NA
Somnolence	2 (2.0)	4 (3.9)	0.6828
Dizziness	11 (10.8)	14 (13.7)	0.5218
Agitation	0	0	NA
Hallucination	0	0	NA
Diplopia	0	0	NA
Memory impairment	1 (1.0)	1 (1.0)	>0.9999
24–72 h after surgery			
Respiratory depression	0	0	NA
Nausea and vomiting	1 (1.0)	3 (2.9)	0.6213
Delirium	0	0	NA
Somnolence	0	2 (2.0)	0.4975
Dizziness	6 (5.9)	9 (8.8)	0.4210
Agitation	0	0	NA
Hallucination	0	0	NA
Diplopia	0	0	NA
Memory impairment	1 (1.0)	1 (1.0)	>0.9999

NA not applicable.
[a]Data reported as the number of patients (%) were compared using the Pearson χ^2 test or Fisher exact test. All statistical tests used were two-sided.
[b]Defined as systolic arterial pressure ≤90 mmHg or systolic blood pressure lower than 20% of the baseline.
[c]Defined as systolic arterial pressure ≥160 mmHg, or an increase of greater than 20% of the baseline.
[d]Defined as heart rate less than 50 beats per minute.
[e]Defined as heart rate greater than 100 beats per minute.

subjective sleep quality and sleep interruptions over the past month[43]. Subjective sleep quality, sleep length, sleep latency, habitual sleep efficiency, use of sleep drugs, sleep disruptions, and daytime dysfunction were among the seven domains in which the 19 items were assessed. A scale of 0 to 3 was utilized to grade the domains, with 3 denoting serious impairment. The seven subscale scores were then added together to generate a global PSQI score, which ranged from 0 to 21 points, with a total score greater than 5 indicating poor sleep quality.

This trial enrolled pregnant individuals who were aged 18 years or older with American Society of Anesthesiologists physical status I to III classification, had sleep disturbance (PSQI score >5), had intrauterine pregnancy with gestational age below 12 weeks and were scheduled for elective surgical abortion from May 2024 to October 2024 in Tianjin Medical University General Hospital in China. Dates of first and last enrollments were May 5, 2024, and October 31, 2024, respectively. The exclusion criteria included the following: (1) contraindications or allergy to ketamine, esketamine, general anesthesia drugs, opioid drugs, or non-steroidal drugs; (2) body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) lower than 19 or higher than 30; (3) previous illness history, such as respiratory insufficiency, bronchial asthma, severe hypertension, abnormal hepatic and renal function, severe cardiovascular disease, or hyperthyroidism; (4) inability or unwillingness to complete the experiment according to the study plan; (5) participants who have participated in clinical trials of other drugs within the last 4 weeks; (6) any circumstances deemed unsuitable for inclusion by the researcher for any reason.

Randomization and blinding

Patients were randomized in a 1:1 ratio to receive either an injection of 0.2 mg/kg esketamine (Jiangsu Hengrui Pharmaceutical Co Ltd), or an equivalent volume of saline immediately after the beginning of surgery (Fig. 1). Before anesthesia, 50 mg of esketamine was diluted with saline solution to a total of 20 mL. The study coordinators (G.W., F.H.), who did not participate in the intraoperative management or data collecting, prepared both esketamine and saline in identical 20 mL syringes. A computer-generated random number scheme and individually sealed envelopes served as the guidelines for all patient assignments. The study coordinators distributed the study medicines to the attending anesthesiologists (W.C., Y.Y.) after opening the envelopes consecutively in accordance with the recruiting order. The group allocation was concealed from all patients, anesthesiologists, and outcome assessors (Z.S., C.W., L.H., X.Y., L.Z.) who were involved in data collection and analysis.

Anesthesia management and interventions

An experienced gynecologist (M.M.) performed all surgical procedures. Patients fasted prior to surgery. Upon arrival in the operating room, a peripheral intravenous channel was established following standard monitoring with non-invasive blood pressure, pulse oximetry, electrocardiography, heart rate (HR), and bispectral index (BIS). The patient was in the lithotomy position. A nasal cannula was then utilized to deliver oxygen at a flow rate of 4 L/min. After three minutes of oxygen inhalation, anesthesia induction was initiated.

Anesthesia was induced with intravenous administration of 1 μg/kg fentanyl and 1.5 mg/kg propofol. Sedation level was evaluated using Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score scale: 0 = no response to painful stimuli; 1 = a response to painful stimuli only (squeezing at the Trapezius site); 2 = a response to light pushing and vibration; 3 = a response to loud or repeated name calling; 4 = a delayed response to name calling with normal tone; 5 = a sensitive response to name calling with normal tone[44]. The anesthesiologist determined the necessary extra dose of propofol required to reach a MOAA/S score ≤2, BIS (45–60) and no body movement. The depth of anesthesia was adjusted by intravenous titration of propofol (0.25 mg/kg each time) at intervals of one minute when patients did not achieve adequate sedation (MOAA/S score >3, BIS > 60 or any body movement) at 2 minutes after the initial dose of propofol or during the surgery. Before the surgical procedure was completed, tropisetron (2 mg) was intravenously injected for the prophylaxis of postoperative

nausea and vomiting (PONV). Any anesthesia-related adverse events during the surgery were documented and handled in accordance with our hospital's treatment standards. If continuous bradycardia (HR < 50 beats/min) and hypotension (systolic arterial pressure ≤90 mmHg or systolic arterial pressure lower than 20% of the baseline) persisted, additional fluid infusion, atropine (0.5 mg), and phenylephrine (0.1 mg) were administered. When respiratory depression (defined as SpO_2 < 90%) persisted, inhaled oxygen concentration was elevated, and assisted manual ventilation using a face mask or oropharyngeal airway was provided if necessary.

Outcome measurements

Baseline data included demographic characteristics, ASA classification, number of pregnancies and abortions, socioeconomic status, pregestational comorbidities, and preoperative hemoglobin and HCG (human chorionic gonadotropin) level. Intraoperative data included intraoperative HR and mean arterial blood (MAP), operation time, anesthesia time, total propofol consumption, the incidence of body movement, as well as time to be fully alert (the time from completing surgical procedure to the time when MOAA/S score >4).

The primary outcome was the prevalence of sleep disturbance on the first night after surgery, diagnosed using the Athens Insomnia Scale (AIS)[4]. The AIS includes eight components: waking up at night, sleep induction, ultimate awakening, total sleep duration, sleep quality, well-being, functional ability, and daytime drowsiness. A cumulative score of 6 points or above on the AIS scale, which goes from 0 to 24 points, denotes a diagnosis of sleep disturbance.

Secondary outcomes included the incidence of sleep disturbance on the second, third, and seventh postoperative nights, postoperative anxiety and depression scores on postoperative days 1, 2, 3, and 7, postoperative pain at rest and after movement at postoperative hour 1 and on postoperative days 1, 2, 3, and 7, postoperative quality of recovery, as well as postoperative adverse events. The Hospital Anxiety and Depression Scale (HADS) was utilized to assess anxiety and depression[4,36]. Each anxiety and depression subscales of the HADS have seven items, totaling 14 questions. A distinct score for anxiety (HADS-A) and depression (HADS-D) is generated by adding the scores for each item, which vary from 0 to 3 points. Anxiety or depression are identified with scores of 8 or above. An 11-points numerical rating scale (NRS) was employed for evaluating postoperative pain intensity, with 0 representing no pain and 10 being the worst suffering conceivable pain[17]. During the postoperative period, oral acetaminophen (500 mg) was administered as needed. The number of patients taking acetaminophen was recorded during the initial three postoperative days. Sedation scores were recorded at 5, 15, and 30 min following surgical abortion, using the Ramsay scale (a 6-point scale, with 1 indicating anxious and agitated or restless, 2 indicating completely cooperative, awake, and tranquil, and 6 indicating asleep, unarousable)[41]. Postoperative anesthesia-related complications, including nausea and vomiting, respiratory depression, dizziness, delirium, somnolence, agitation, hallucination, diplopia, and memory impairment, were documented and managed according to routine practice. Oral metoclopramide (10 mg) was supplied when necessary for PONV treatment. Surgical complications were also recorded, such as cervical laceration, uterine perforation, bleeding (>200 mL) and incomplete abortion. Postoperative recovery for 7 days after surgery was assessed using 15-item quality of recovery (QoR-15) scale, which ranges from 0 (extremely poor QoR) to 150 (excellent QoR), with 118 or greater points indicating a good postoperative recovery)[34].

Statistical analyses

The estimated sample size was determined using PASS software, version 15.0 (NCSS). Based on our preliminary investigation, 67% of women with pre-operative sleep disruption experienced sleep disturbance on the first night following surgical abortion. The expected effect size was then computed to identify that therapy with low dosage of esketamine would reduce the incidence of sleep disturbance by around one-third, with a two-sided $\alpha = 5\%$ and 90% power. We determined that 93 patients per group would be needed to find such a difference. Assuming a 10% dropout rate, we planned to increase the sample size of each group to 102 patients.

The intention-to-treat population was used for primary and secondary outcomes analysis, which means that every patient was analyzed within the group to which they were allocated. We also conducted analysis in the per-protocol principle for the primary outcome, removing participants who withdrawn consent or had protocol deviations.

For the primary outcome, incidence of sleep disturbance on the first night after surgery was compared with a χ^2 test, with differences between groups expressed as odds ratio and 95% confidence interval (CI). A similar analysis was conducted for the per-protocol population.

Amongst secondary outcomes, the Kolmogorov-Smirnov test was used to determine the normality of distribution for continuous variables. The unpaired, 2-tailed t test was used to compare normally distributed variables that were reported as mean (SD). The Mann-Whitney test was employed for assessing data with non-normal distribution, which were reported as median (IQR). Median differences (and 95% CIs) were calculated with Hodges-Lehmann estimators. Categorical variables were expressed as number (percentage) and compared using χ^2 or Fisher exact tests, where applicable. Odds ratios and 95% CIs were calculated. Missing data were not replaced. No imputation was performed for missing data in all analyses.

For each hypothesis testing, a 2-sided P value < 0.05 indicated statistical significance. All data were statistically analyzed with GraphPad Prism, version 8.0 (GraphPad Software Inc).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All relevant data are within the main manuscript, supplementary information or source data file. Due to patient privacy concerns, the clinical raw data are not publicly available; however, they are available upon request from the corresponding author. A specific explanation of study protocol should be included with any request directed to the corresponding author, L.Z., by email at linlinzhang@tmu.edu.cn. Individual de-identified participant data will be shared and accessible for a year after access is granted. Please give a month to respond to inquiries. The corresponding author and Tianjin Medical University General Hospital will assess the reasonableness of the request for our data and reserve the right to share it or not. Additionally, the data is exclusively utilized for research purposes. The Study Protocol is available as Supplementary Note 1 in the Supplementary Information. CONSORT Checklist is available as Supplementary Note 2 in the Supplementary Information. Source data are provided with this paper.

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Conceptualization: Z.S., M.M., C.W., and L.Z. Data curation: Z.S., L.H., X.Y., Y.Y., C.W., and L.Z. Formal analysis: Z.S., L.H., Y.Y., and L.Z. Investigation: Z.S., L.H., X.Y., C.W., and L.Z. Methodology: Z.S., L.H., X.Y., C.W., and L.Z. Project administration: Z.S., M.M., F.H., L.H., X.Y., G.W., C.W., and L.Z. Supervision: W.C., and G.W. Funding acquisition: L.Z. Writing-original draft: Z.S., M.M., F.H., and L.Z. Writing-review & editing: Z.S., M.M., F.H., W.C., C.W., and L.Z.

Competing interests

The authors declare no competing interests.

Additional information

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