Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

CLINICAL TRIAL REPORT

Intraoperative Dexmedetomidine Infusion Improved Postoperative Sleep Quality and Melatonin Secretion in Patients Undergoing Elective Thoracoscopic Lung Surgery: A Prospective, Randomized Study

Bin Mei*, Xiao Yang*, Yue-yue Yang, Jun-tao Weng, San-dong Cao, Rui Yang, Guanghong Xu

Department of Anesthesiology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guanghong Xu; Rui Yang, Email xuguanghong2004@163.com; yangruianaes@163.com

Nature and Science of Sleep downloaded from https://www.dovepress.com/
For personal use only.

Background: Dexmedetomidine has been reported to improve postoperative sleep quality. However, the underlying mechanism remains unclear. This study aimed to investigate the effect of intraoperative dexmedetomidine infusion on postoperative sleep quality and changes in melatonin secretion in older patients undergoing elective thoracoscopic lung surgery.

Methods: A total of 126 older patients were randomly divided into two groups: dexmedetomidine group (Group D), which received continuous dexmedetomidine infusion at 0.3–0.5 μg/(kg·h) combined with propofol during surgery, and propofol group (Group P), which received propofol alone. The primary outcome was the postoperative sleep quality on the first postoperative night, assessed by the Richards-Campbell Sleep Questionnaire (RCSQ). Secondary outcomes included sleep quality scores on the second and third postoperative nights, melatonin concentrations postoperatively, and the incidence of delirium on the first and seventh postoperative days (discharge day).

Results: On the first postoperative night, Group D had a higher sleep quality score compared to Group P (57±11.4 vs 53±10.3; [95% CI, 1.1 to 8.7];P = 0.012), with no difference between the groups on the second and third postoperative nights. There was no statistically significant difference in the preoperative and postoperative night 3 urine 6-SMT concentrations between the two groups (P > 0.05); however, Group D had significantly higher urine 6-SMT concentrations on postoperative nights 1 and 2 compared to Group P (27 (24, 30) vs 21 (17, 24); [95% CI, −8.56 to −4.73]; P = 0.000. 28 (25, 30) vs 26 (21, 27); [95% CI, −4.37 to −1.65]; P = 0.000). There was no significant difference in the incidence of postoperative delirium between the two groups (P=0.65).

Conclusion: Continuous intraoperative infusion of dexmedetomidine can effectively improve sleep quality during the first postoperative night by promoting melatonin secretion over the first two postoperative nights.

Keywords: dexmedetomidine, postoperative sleep quality, melatonin

Background

Postoperative sleep disturbance is a common complication, with a prevalence rate of 15%–72% in patients undergoing surgery under general anesthesia.[1] Several studies have demonstrated that postoperative sleep disturbance is associated with postoperative delirium (POD), and even delayed postoperative functional rehabilitation in surgical patients.[2–5] Postoperative sleep disturbance also has a negative effect on the postoperative recovery of patients, resulting in prolonged hospital stay and increased medical costs.[6] The potential mechanism of postoperative sleep disturbance involves a perioperative change in the melatonin level.[7,8] The secretion of melatonin exhibits an obvious circadian rhythm.[9] Previous studies have indicated that anesthesia and surgery could interfere with the secretion rhythm of melatonin.[10] Our previous study also showed that the time of the day when the surgery is performed influences the postoperative sleep quality of older patients undergoing hip surgery and that a short-term change in the melatonin level after surgery was the potential cause of this phenomenon.[11]

Received: 12 August 2024
Accepted: 3 December 2024
Published: 10 December 2024

© 2024 Mei et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

To reduce the incidence of postoperative sleep disturbance, non-pharmacological interventions have been attempted, such as eye masks and earplugs to reduce noise and light stimulation.[12,13] Studies have indicated that the modulation of melatonin secretion could be the reason for the sleep improvement induced by these non-pharmacological interventions.[10,14] Among the pharmacological methods, dexmedetomidine, an α2-adrenoceptor agonist that is routinely used in the perioperative period for its sedative effect in surgical patients, was reported to improve postoperative sleep quality.[6,15,16] However, there are still insufficient studies to observe both sleep quality and melatonin secretion level in patients receiving dexmedetomidine infusion, so our study is meaningful for understanding the potential mechanism of dexmedetomidine improving sleep quality. Patients who undergo thoracic surgery have a higher incidence of post-operative sleep disorders due to perioperative surgical anxiety, surgical interventions, anesthesia, pain, introduction of new medications, and potential alterations in physio logical functions.[17] The number of elderly patients undergoing thoracoscopic lung resection is increasing with the advancement of thoracoscopic technology. As age increases, the sleep quality of elderly patients themselves is also constantly declining. Therefore, we believe that selecting this population as research subjects has clinical significance, as it reflects the advantage of dexmedetomidine in patients with fragile sleep structures. Similarly, delirium occurs in approximately 18.8% of thoracic surgery patients.[18] Therefore, it is valuable to observe the preventive effect of dexmedetomidine on delirium in this population. We hypothesized that dexmedetomidine could improve the postoperative sleep quality in thoracic patients by modulation of melatonin secretion.

This study aimed to investigate the effect of intraoperative dexmedetomidine on the postoperative sleep quality in older patients undergoing elective video-assisted thoracoscopic lung surgery, in addition to analyzing the relationship with the change in melatonin secretion.

Methods

Study Design

This prospective, randomized, controlled study was conducted after obtaining approval from the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (registration no.: Anhui Medical University First Affiliated Hospital Ethics Review - Quick - PJ2023-07-20). The study was also registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2300072824).

Study Population

Inclusion Criteria

Patients aged 65 years and above, who were scheduled for elective thoracoscopic lung surgery, and classified as American Society of Anesthesiologists (ASA) physical status II to III were included in the study.

Exclusion Criteria

Patients with ASA > III; patients with contraindications to regional block (allergy to local anesthetic agents, infection around the puncture site, and coagulation disorders); Patients who took prescription sedating medications at home; those with a history of analgesic drug dependence; patients with dementia or cognitive dysfunction (positive CAM scale); those who had any cerebrovascular accident within 3 months, such as stroke or transient ischemic attack (TIA); patients with preoperative sleep disorders breathing (When patients were included, they were first asked if they had symptoms of nighttime snoring. Patients with nighttime snoring symptoms would be required to undergo a polysomnography examination to further rule out sleep-disordered breathing); and those with any communication difficulties.

Data Collection

Paper case report forms (CRFs) were used to record the clinical data and study outcomes. Data were stored in password-protected computers to protect participant confidentiality. Good clinical practice (GCP) guidelines were strictly followed during the study period. A designated researcher was assigned to track participants throughout the study process, from the preoperative setup to discharge, and was responsible for data collection, archiving, and transmission, while another researcher was in charge of verifying the accuracy and safety of the stored data.

Randomization and Blinding

Randomization was performed in a 1:1 ratio before the start of the study using a computer-generated random table (SPSS).

Blinding and drug preparation: Group allocation was concealed using sequentially numbered, opaque, sealed envelopes, which were maintained by an independent researcher. All study drugs (dexmedetomidine) and normal saline were prepared by an independent pharmacist. Dexmedetomidine (200 μg) was dissolved in saline to achieve a concentration of 4 μg/mL. The study drugs and saline were indistinguishable in color and syringe size and were distributed in identical containers to ensure blinding. During maintenance, participants in each group received the study drug or saline at a rate of 0.3–0.5 μg/(kg·h). Additionally, dexmedetomidine or placebo administration was stopped 30 minutes before the end of the surgery. Both the study participants and observers were blinded to the group assignments and the study drugs used, adhering to the principles of blinding.

Study Protocol

Demographic information, complications, and test results were recorded for each participant. Preoperative assessments included the Richards-Campbell Sleep Questionnaire (RCSQ), and Confusion Assessment Method (CAM) to evaluate the preoperative sleep quality and cognitive level. A total of 126 participants were randomly assigned to one of the following groups: the dexmedetomidine group (D group), which received a combination of dexmedetomidine and propofol infusion during surgery; and the control group (P group), who received only propofol infusion during surgery. Randomization was performed by resident physicians who were unaware of the study details.

Participants were required to fast for 8 hours and refrain from drinking for 4 hours before the surgery. Upon entering the operating room, a peripheral vein was accessed, and heart rate (HR), oxygen saturation (SpO2), and electrocardiography (ECG) were routinely monitored. Radial artery cannulation was performed for invasive blood pressure (IBP) monitoring. All participants were monitored for the anesthesia depth using the Bispectral Index (BIS). To reduce opioid consumption and provide adequate postoperative analgesia, ultrasound-guided serratus anterior plane block was administered to all participants. In all participants, general anesthesia induction was performed using intravenous midazolam (0.02–0.05 mg/kg), etomidate (0.2–0.3 mg/kg), sufentanil (0.3–0.5 μg/kg), and cisatracurium (0.2–0.3 mg/kg). After induction, double-lumen tracheal intubation was performed using a fiberoptic bronchoscope. In the control group (Group P), intravenous propofol was injected to maintain BIS between 40 and 60, remifentanil was injected at a rate of 0.05–0.15 μg/(kg·min) to provide intraoperative analgesia, and cisatracurium was injected intravenously intermittently to maintain muscle relaxation. Participants in Group D received a continuous infusion of dexmedetomidine 10 min before anesthesia induction. Continuous infusion of propofol combined with dexmedetomidine 0.3–0.5 μg/ (kg·h) to maintain BIS between 40–60 during surgery. Remifentanil was injected at a rate of 0.05–0.15 μg/(kg·min) to provide intraoperative analgesia, and cisatracurium was intermittently injected intravenously to maintain muscle relaxation. Subsequently, 0.1 μg/kg sufentanil was administered intravenously 5 minutes before the procedure began and 30 minutes before the procedure ended. Additionally, the dexmedetomidine pump was stopped 30 minutes before the end of surgery. Intraoperative hypotension was treated immediately and was defined as a decrease of more than 30% in the systolic blood pressure from the pre-operative value and/or a systolic blood pressure of less than 90 mmHg. It was managed by intravenous fluids or ephedrine injection.

Postoperative patient-controlled intravenous analgesia (PCIA) consisted of sufentanil 4 μg/kg + flurbiprofen axetil 150 mg, with an infusion rate of 2 mL/h, bolus dose of 2 mL, lockout period of 15 minutes, and total volume of 150 mL. All participants recovered in the post-anesthesia care unit (PACU) after anesthesia and were transferred to the inpatient ward when their Steward score was greater than 6. Postoperative pain was considered absent when the Visual Analog Scale (VAS score) ≤3; if VAS>3, participants received either patient-controlled analgesia or non-steroidal anti-inflammatory drugs for pain relief.

Ward care: There was only one caregiver per participant in the ward after 9 PM. The volume of mobile phones of participants and caregivers and call bells were turned down. The bed curtains were drawn. The light intensity at night was adjusted to soft light. Turned off all lights except the bedside lamp in the ward after 9 PM, and turned off the bedside lamp after 10 PM.

Outcome Measures

Postoperative Sleep Quality and POD Assessment

The RCSQ was used to assess the sleep quality the night before the surgery and for three nights postoperatively, with the score on the first postoperative night considered the primary outcome indicator in this study. The questionnaire includes five items: sleep depth, sleep latency, awakenings, returning to sleep, and overall sleep quality. Each item is rated on a 100-mm VAS. Scores range from 0 (indicating the worst possible sleep) to 100 (indicating the best possible sleep). The total RCSQ sleep score is calculated by summing the individual scores of the five items and dividing by 5. The higher the score of participants, the better the quality of their sleep. Additionally, the incidence of POD within three days post-surgery was recorded using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

Nocturnal Urine Collection and 6-Sulfatoxymelatonin (6-SMT) Measurement

Nocturnal urine was collected by resident physicians involved in the study from 8:00 PM to 8:00 AM the night before the surgery and for three nights postoperatively. A 2 mL urine sample was frozen at −80°C and analyzed in batches once the collection was complete. The concentration of 6-SMT, a stable metabolite of melatonin, was measured using enzyme-linked immunosorbent assay (ELISA) kits and corrected for creatinine levels to account for individual variations in the urine concentration.

Sample Size

A pilot study was conducted with 20 patients randomly assigned to either Group D or Group P. The mean RCSQ score on the first postoperative night was 57.2 in the D group and 52.0 in the P group, with a standard deviation of 10.0. It was determined that a sample size of 54 participants per group would provide 85% power, with a two-sided α of 5%, to detect a difference in mean scores between the groups, as assessed by PASS11.0 software. Therefore, the sample size was increased to 63 participants per group to account for potential dropouts.

Statistical Methods

Data analysis was performed using SPSS version 16.0 for Windows. The Shapiro–Wilk test was used to test the normality of distribution for continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), while non-normally distributed continuous variables were expressed as median (interquartile range). The normality of variables and homogeneity of variances were tested beforehand. Based on the test results, either the independent samples *t*-test or the Mann–Whitney *U*-test was chosen for comparing continuous data. Categorical variables were described using frequencies and percentages. The Pearson chi-square test or Fisher's exact test was used for comparison, as appropriate. The statistical results showed that the RCSQ scores followed a normal distribution; therefore, the independent samples *t*-test was used to compare RCSQ scores within and between groups, and the Mann–Whitney *U*-test was used to compare the five components of the RCSQ. The Mann–Whitney *U*-test was also used to compare the urine 6-SMT concentrations within and between groups. The correlation between the urine 6-SMT concentrations and the RCSQ scores was analyzed using the Pearson correlation. A two-tailed probability of $P < 0.05$ was considered statistically significant.

Results

From October 2023 to April 2024, 135 patients were screened for this study. Among them, four were excluded and five refused to participate. There were no dropouts during the postoperative follow-up period. A total of 126 participants were included in the final analysis (Figure 1). There were no differences in the demographic characteristics between the two groups (Table 1).

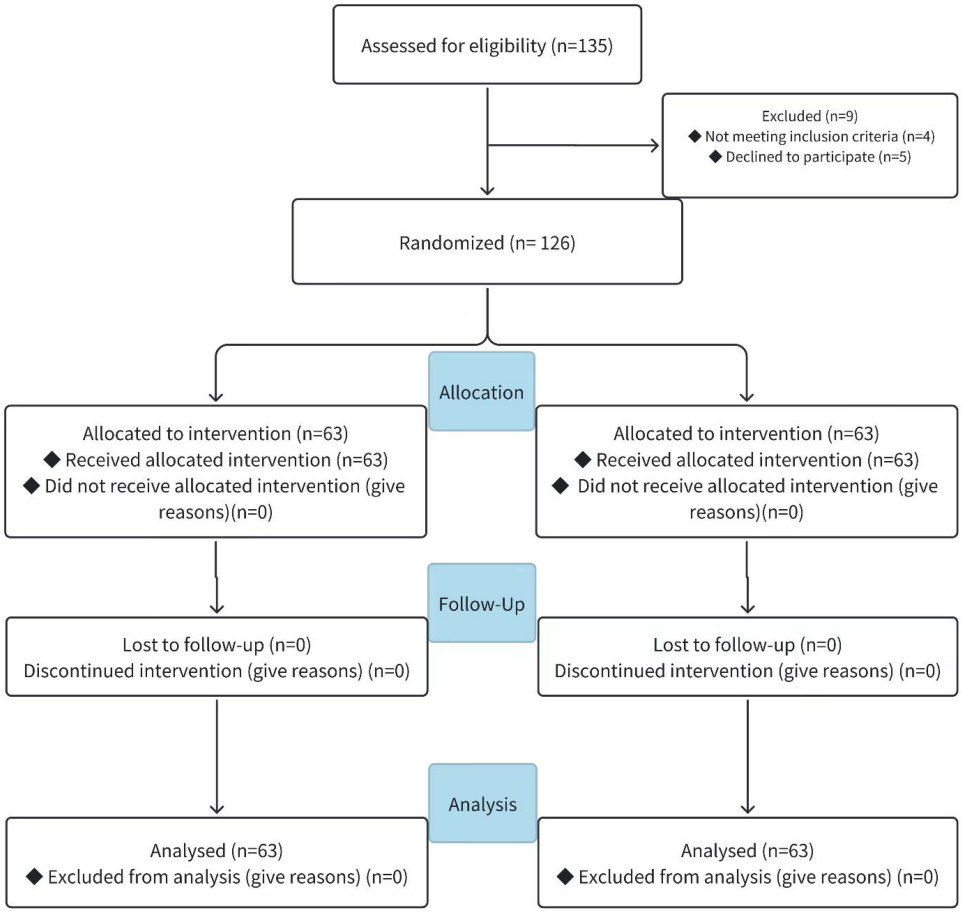

Figure 1 Consort flow diagram.

As shown in Table 2, there were no differences between the groups in terms of intraoperative propofol or remifentanil use, duration of surgery, or anesthesia (all $P > 0.05$). There were also no differences between the groups in the eye-opening time, extubation time, or time spent in the PACU following surgery (all

Table 1 Demographic Characteristics of the Patients

	Group D	Group P	P value
ASA grade	3(2, 3)	3(2, 3)	0.183
Age (year)	69(67,74)	69(67,72)	0.504
BMI (kg/m^2)	23.62±2.41	22.93±2.53	0.120
Cardiac function grade	2(1, 2)	1(1,2)	0.154
Gender, male/female (n)	40/23	35/28	0.364
Comorbidities (n)			
Hypertension (%)	31(49)	28(44)	0.592
Diabetes (%)	8(13)	9(14)	0.794
COPD (%)	5(8)	2(3)	0.243
Coronary Heart Disease (%)	3(5)	1(2)	0.310
MAP (mmHg)	96.8±9.3	97.4±11.3	0.752
Preoperative RCSQ	64(56,68)	62(58,68)	0.893

Notes: Values are expressed as mean ± SD, median (interquartile range [IQR]), and frequency (%).

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; MAP, Mean Arterial Pressure; RCSQ, Richards-Campbell Sleep Questionnaire; Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone.

Table 2 Intraoperative and Postoperative Data of the Two Anesthetic Groups

	Group D	Group P	P value
Propofol dose(mg)	570.1±240.0	517.9±229.8	0.063
Remifentanil dose(ug)	1059.6±488.4	1008.4±522.1	0.308
Vasoactive drug use, n (%)	43(68)	34(54)	0.100
Inotropes, n (%)	31(49)	24(38)	0.209
Pressors, n (%)	22(35)	18(29)	0.444
Dexmedetomidine dose(ug)	52.5±22.9	0	0.000*
Duration of surgery(min)	120.4±57.1	102.9±50.3	0.074
Duration of anesthesia(min)	156.3±60.5	136.4±53.4	0.055
Recovery time(min)	28(19,38)	24(16,34)	0.085
Extubation time(min)	30(22,40)	26(18,35)	0.065
Duration of PACU stay(min)	45(35,60)	40(32,55)	0.105
Crystal infusion(mL)	850(600,1100)	800(600,950)	0.502
Colloid infusion(mL)	0(0450)	0(0350)	0.082
Surgical Start Time, morning/ afternoon (n)	38/25	28/35	0.074
Postoperative delirium, n (%)	11 (17)	13 (21)	0.650

Notes: Values are expressed as mean ± SD, frequency (%), and median (interquartile range [IQR]). *P < 0.05.
Abbreviations: Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone, PACU, postanesthesia care unit.

P > 0.05). Furthermore, there was no statistically significant difference in POD incidence between the two groups (P > 0.05).

Sleep Quality Scores

As shown in Figure 2 and Table 3, the sleep quality score of Group D was higher than that of Group P on the first postoperative night (57±11.4 versus 53±10.3; [95% CI, 1.1 to 8.7];P = 0.012), but there were no differences in the sleep quality scores between the two groups on the second and third postoperative nights.

The five components of the RCSQ were calculated separately. As shown in Table 4, on the first postoperative night, group D had higher scores for sleep latency and returning to sleep compared to group P, with no differences between the groups in the other three components (P=0.009 and P=0.001). On the second postoperative night, group D had higher scores for sleep latency and sleep restoration compared to group P, with no differences between the groups in the other three components (P=0.019 and P=0.037). On the third postoperative night, there were no differences between the two groups in all five components.

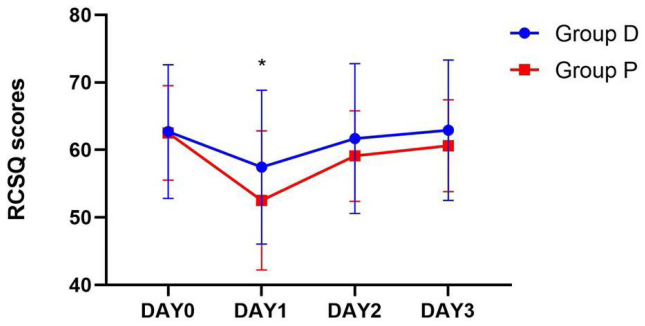

Figure 2 Comparison of the RCSQ scores before surgery and on the three days after surgery between the two groups.
Notes: *Significant difference (P<0.05) between Group D and Group P. Data are presented as mean plus/minus standard deviation.
Abbreviations: DAY0, before surgery; DAY1, first day after surgery; DAY2, second day after surgery; DAY3, third day after surgery; RCSQ, Richards-Campbell Sleep Questionnaire; Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone.

Table 3 Scores of RCSQ Before and Three Days After Surgery for the Two Anesthetic Groups

RCSQ	Group D	Group P	Mean difference(95% CI)	P value
D0	62.73±9.9	62.52±7.0	0.2 (−2.8,3.2)	0.893
D1	57.44±11.4	52.52±10.3	4.9 (1.1,8.7)	0.012*
D2	61.67±11.1	59.10±6.7	2.6 (−0.7,5.8)	0.119
D3	62.92±10.4	60.62±6.8	2.3 (−0.8,5.4)	0.144

Note: Data are presented as mean ± SD, *P < 0.05.
Abbreviations: RCSQ, Richards-Campbell Sleep Questionnaire; D0, before surgery; D1, first day after surgery; D2, second day after surgery; D3, third day after surgery Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone; 95% CI, 95% confidence interval.

Table 4 Comparison of the Five Components of the RCSQ in the First Two Days Post-Surgery

	Group D	Group P	P value
D1 sleep depth	60 (40,70)	60 (40,70)	0.214
D1 latency to sleep	60 (50,70)	50 (40,70)	0.009*
D1 awakenings during sleep	50 (40,60)	50 (40,60)	0.951
D1 return to sleep	60 (50,70)	50 (40,60)	0.001*
D1 sleep quality	60 (50,70)	60 (50,60)	0.098
D2 sleep depth	70 (60,70)	60 (60,70)	0.059
D2 latency to sleep	70 (60,70)	60 (50,70)	0.019*
D2 awakenings during sleep	50 (40,60)	60 (50,60)	0.659
D2 return to sleep	60 (50,70)	60 (50,60)	0.037*
D2 sleep quality	70 (60,75)	60 (60,70)	0.060

Note: Values are expressed as median (interquartile range [IQR]) *P < 0.05.
Abbreviations: RCSQ, Richards-Campbell Sleep Questionnaire; D1, first day after surgery; D2, second day after surgery; Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone.

Nighttime Urine 6-SMT Concentrations

The concentrations of 6-SMT in the urine of participants before and after surgery during the night are shown in Figure 3 and Table 5. A comparison of 6-SMT concentrations in the urine between the two groups on the preoperative night and third

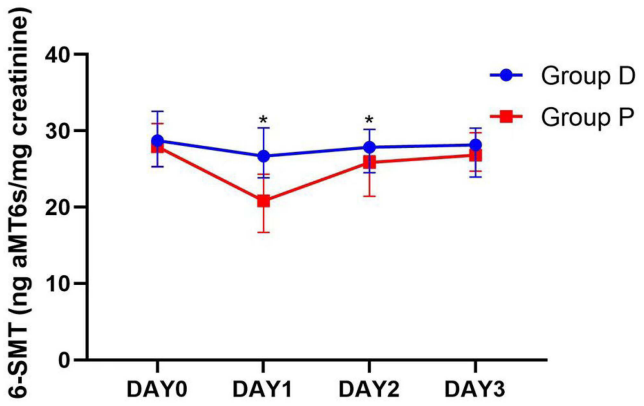

Figure 3 Comparison of the urinary excretion of 6-SMT during the night before the surgery, and the first, second, and third postoperative nights in the two groups.
Notes: *Significant difference (P<0.05) between Group D and Group P. Data are expressed as the median and interquartile range.
Abbreviations: DAY0, before surgery; DAY1, first day after surgery; DAY2, second day after surgery. DAY3, third day after surgery.6-SMT, 6-sulphatoxymelatonin; Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone.

Table 5 Concentration of 6-SMT Before and Three Days After Surgery in the Two Anesthetic Groups

6-SMT	Group D	Group P	Median Difference (95% CI)	P value
D0	28.72 (25.31,32.56)	27.91 (25.29,30.95)	0.76 (−1.13,2.65)	0.381
D1	26.68 (23.85,30.39)	20.82 (16.68,24.33)	6.64 (4.73,8.56)	0.000*
D2	27.86 (24.52,30.18)	25.86 (21.41,26.73)	2.84 (1.65,4.37)	0.000*
D3	28.16 (23.94,30.35)	26.81 (24.72,29.76)	0.52 (−1.16,2.09)	0.578

Note: Values are expressed as median (interquartile range [IQR]), *P < 0.05.
Abbreviations: 6-SMT, 6-sulphatoxymelatonin; D0, before surgery; D1, first day after surgery; D2, second day after surgery; D3, third day after surgery; Group D, Group dexmedetomidine plus propofol; Group P, Group propofol alone; 95% CI, 95% confidence interval.

Table 6 6-SMT Concentrations of Patients in Both Groups Change Over Time

	D0-D1	D0-D1	D1-D2	D1-D2	D2-D3	D2-D3
Group	D	P	D	P	D	P
ES	−0.17	−1.3	0.08	0.66	0.02	0.60
6-SMT 95% CI	(−0.52,0.18)	(−1.68, −0.92)	(−0.27,0.43)	(0.30,1.02)	(−0.33,0.37)	(0.24,0.95)

Abbreviations: 6-SMT, 6-sulphatoxymelatonin; D0, before surgery; D1, first day after surgery; D2, second day after surgery; D3, third day after surgery; Group D, Group dexmedetomidine plus propofol; Group P, Group Propofol alone; ES, effect size; 95% CI, 95% confidence interval.

postoperative night showed no statistically significant difference (P > 0.05); however, the 6-SMT concentrations in group D on the first and second postoperative nights were significantly higher than those in group P (27 (24, 30) vs 21 (17, 24); [95% CI, −8.56 to −4.73]; P = 0.000. 28 (25, 30) vs 26 (21, 27); [95% CI, −4.37 to −1.65]; P = 0.000). On the first night after surgery, a positive correlation was found between the 6-SMT concentrations and RCSQ scores (Pearson correlation, r=0.204, P=0.022). At other time points, no significant correlation was found between the 6-SMT concentrations and RCSQ scores.

The effect size (ES) calculation shows that the decrease in 6-SMT concentration on the first postoperative night in Group P was more significant compared to Group D (ES: −1.3 vs ES: −0.17). On the second and third postoperative nights, there was an increase in the 6-SMT concentration (ES>0). In group D, there was a slight decrease in the 6-SMT concentration on the first postoperative night, and a slight increase on the second postoperative night, while the concentration was relatively stable on the third postoperative night (Table 6).

Discussion

After major surgery, patients can experience sleep disturbance, which mainly manifests as severe sleep deprivation, sleep fragmentation, and decrease or loss of slow-wave sleep (SWS) and rapid eye movement (REM) sleep.[19] The leading cause of postoperative sleep disturbance in surgical patients is pain. Pain is often accompanied by an increase in opioid consumption. Higher opioid consumption was associated with an elevated risk of postoperative sleep disturbance.[20] Age is a known risk factor for perioperative neurocognitive disorders, and aging has been shown to increase sleep fragmentation and the difficulty of falling asleep.[21] In the current study, participants who underwent thoracoscopic lobectomy were enrolled with less trauma than open surgery. Preoperative anterior serratus plane block combined with postoperative multimodal analgesics was used for perioperative pain management to ensure that postoperative acute pain was controlled with minimal opioid use. Nevertheless, postoperative sleep disturbance was observed in patients in both groups. Our study findings show that surgery and anesthesia may contribute to the development of sleep disorders in older patients.

Although there is still insufficient evidence regarding which pharmacological measure plays a definite role in the prevention and treatment of postoperative sleep disturbance, several studies have indicated that dexmedetomidine may potentially reduce the incidence of postoperative sleep disturbance.[6,15,16] Dexmedetomidine is a potent and highly selective alpha-2 adrenergic receptor agonist, considered a unique sedative with analgesic, sympatholytic, and respiratory

protective properties.[22] In non-mechanically ventilated patients admitted to the intensive care unit after surgery, dexmedetomidine infusion at night can help patients maintain a normal circadian rhythm and improve their sleep structure and quality.[23] Another study demonstrated that for patients with non-mechanical ventilation in the intensive care unit, a low-dose dexmedetomidine (0.1μg/kg/h) infusion after surgery can improve postoperative sleep quality.[24] These results suggest that the postoperative use of dexmedetomidine can effectively prevent and treat postoperative sleep disturbance. In addition to being used in the intensive care unit, dexmedetomidine is also commonly used during surgery and its primary role is to confer extra sedation in surgical patients.[25] However, there is still controversy regarding whether the intraoperative use of dexmedetomidine can affect the postoperative sleep quality of patients. A recent study showed that the intraoperative use of dexmedetomidine did not improve the postoperative sleep quality in patients undergoing breast cancer surgery.[26] However, for patients undergoing gastrointestinal surgery, intraoperative dexmedetomidine can significantly improve postoperative sleep quality.[27] It is worth noting that for surgical patients, the use of dexmedetomidine during the day or night has different effects on the postoperative sleep quality, and the use of dexmedetomidine during the day (8:00–12:00) is more conducive to improving the postoperative sleep quality of patients,[28] which may be the potential reason for the above-mentioned differences. In our previous study, patients who underwent surgery under general anesthesia in the afternoon had better short-term sleep quality after surgery than those who underwent surgery under general anesthesia in the morning.[11] In our study, there was an imbalance between the number of patients in the two groups who had surgery in the morning and those who had surgery in the afternoon. More patients in Group P (35) than in Group D (25) underwent surgery in the afternoon. In theory, patients in Group P should have better sleep quality than those in Group D. Such an imbalance in population distribution in the two groups might have weakened the advantage of dexmedetomidine. It was found that intraoperative dexmedetomidine improved the sleep quality in older patients undergoing thoracoscopic lung surgery, as these patients may feel more relaxed while falling asleep and falling back asleep after waking up.

Melatonin, a hormone released from the pineal gland is crucial in maintaining the normal sleep rhythm.[29] Studies have shown that disordered melatonin metabolism due to surgery and anesthesia may be an important cause of postoperative sleep disturbance.[30–32] In our study, 6-SMT, a metabolite of melatonin, was found to be a reliable humoral index for reflecting the change in the endogenous melatonin.[10] In patients without intraoperative dexmedetomidine infusion, the 6-SMT concentrations were significantly decreased on postoperative nights 1 and 2, suggesting that surgery and anesthesia affected melatonin secretion, which may be the potential cause of postoperative sleep disturbance in these surgical patients.

Our study results revealed that intraoperative dexmedetomidine infusion elevated the reduced postoperative 6-SMT concentrations induced by surgery and anesthesia, suggesting that dexmedetomidine potentially modulated melatonin secretion, which improved the postoperative sleep quality. Unfortunately, there is still a lack of definite evidence to clarify the mechanism by which dexmedetomidine modulates melatonin secretion. However, the results of previous studies can help us to understand the specific mechanism of this regulation. Studies have shown that in addition to pineal cells, astrocytes in the cerebral cortex also participate in the synthesis of melatonin, and astrocyte dysregulation was associated with decreased melatonin production.[33–35] Notably, preclinical studies have demonstrated that dexmedetomidine has a direct regulatory effect on the function of astrocytes in the central nervous system.[36,37] Dexmedetomidine was reported to have a neuroprotective effect against neuroinflammation induced by surgery, anesthesia, sepsis, and other nervous system diseases.[38–40] Studies have shown that direct regulation of the central nervous system is an important mechanism underlying the neuroprotective effect of dexmedetomidine. Animal studies have revealed that mice astrocytes abundantly express α2A adrenoceptors, and the α2A adrenoceptor in astrocytes is a key target for the protective effect of dexmedetomidine on neurocognitive function.[39,41] Consequently, the regulatory effect of dexmedetomidine on astrocyte function may be an important mechanism by which dexmedetomidine promotes melatonin synthesis. However, preclinical and clinical studies are needed to confirm this hypothesis.

A large number of studies have shown that postoperative sleep disturbance was closely associated with neurocognitive dysfunction in surgical patients.[42,43] However, in our study, dexmedetomidine was found to improve sleep quality in the early postoperative period, without having a significant effect on postoperative neurocognitive function. At present, there still exist controversies regarding the postoperative neurocognitive protective effect of dexmedetomidine. In a study on older patients undergoing non-cardiac surgery, postoperative dexmedetomidine infusion significantly decreased the occurrence of delirium during the first 7 days after surgery.[44] However, in another study that evaluated patients who had

undergone cardiac surgery with cardiopulmonary bypass, the results indicated that intraoperative dexmedetomidine infusion did not decrease POD, which is consistent with the results of our study.[43] One hypothetical explanation for the contradictory findings is the potential influence of the different timings of dexmedetomidine administration, as a recent study has demonstrated that dexmedetomidine infusion at different times during the day has different effects on sleep and pain in surgical patients in the early postoperative period.[28]

In the current study, the RCSQ scores were reduced in patients who received intraoperative dexmedetomidine infusion, without a decrease in the 6-SMT concentration on postoperative night 1. The main reason for this result may be the close monitoring on the first postoperative night, such as the use of a discontinuous inflatable cuff which may interfere with the sleep quality.

The findings of the current study have considerable implications. Dexmedetomidine is routinely used for perioperative sedation and potentially confers neuroprotection. We found that dexmedetomidine improved the postoperative sleep quality and corrected melatonin metabolic disorder induced by surgery and anesthesia in older patients who underwent elective video-assisted thoracoscopic lung surgery. This study provides clinical and biologic evidence supporting the use of a pharmacological method to improve the postoperative sleep quality in surgical patients.

There are some limitations of our study. Firstly, Due to the high incidence of postoperative sleep disturbances and delirium in elderly patients undergoing lobectomy, we aimed to observe the improvement of dexmedetomidine in this population. The older patients were included in our study as aging is associated with sleep structure changes, and the sleep quality of older patients is also more susceptible to environmental changes. Generalizations of the findings of the current study to other surgical populations and age groups need to be cautious. Secondly, Consider the difference in the effect of surgery under general anesthesia in the morning and afternoon on postoperative sleep quality. Balancing the timing of surgery between the two groups may help avoid bias in drawing conclusions. Thirdly, oral melatonin has also been reported to improve the sleep quality of surgical patients.[45] Vij et al reported that exogenous melatonin improved sleep quality on the first day after laparoscopic cholecystectomy.[46] In our study, we did not compare the postoperative sleep improvement induced by oral melatonin and intraoperative dexmedetomidine infusion. Further studies are needed to determine the most effective and safe pharmacological method to treat postoperative sleep disturbance.

In conclusion, older patients undergoing thoracoscopic lung surgery experienced a significant decline in sleep quality and melatonin concentrations on the first two postoperative nights. Continuous intraoperative infusion of dexmedetomidine can effectively improve sleep quality during the first postoperative night by promoting melatonin secretion over the first two postoperative nights.

Data Sharing Statement

Data on individual deidentified participants can be obtained from the corresponding author with approval within three years of publication, as can the published study protocol and main results.

Ethical Adherence

All patients provided informed consent and all procedures were conducted according to the Declaration of Helsinki.

Acknowledgment

This work was supported by the National Nature Science Foundation of China (Grant No. 82172136).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Qiu D, Wang XM, Yang JJ, et al. Effect of intraoperative esketamine infusion on postoperative sleep disturbance after gynecological laparoscopy: a randomized clinical trial. *JAMA Network Open*. 2022;5(12):e2244514. doi:10.1001/jamanetworkopen.2022.44514
2. Ou-Yang CL, Ma LB, Wu XD, et al. Association of sleep quality on the night of operative day with postoperative delirium in elderly patients: a prospective cohort study. *Eur J Anaesthesiol*. 2024;41(3):226–233. doi:10.1097/EJA.0000000000001952

3. Song Y, Liu Y, Yuan Y, et al. Effects of general versus subarachnoid anaesthesia on circadian melatonin rhythm and postoperative delirium in elderly patients undergoing Hip fracture surgery: a prospective cohort clinical trial. *EBioMedicine*. 2021;70:103490. doi:10.1016/j.ebiom.2021.103490
4. Kjølhede P, Langström P, Nilsson P, et al. The impact of quality of sleep on recovery from fast-track abdominal hysterectomy. *J Clin Sleep Med*. 2012;8(4):395–402. doi:10.5664/jcsm.2032
5. Fernandes NM, Nield LE, Popel N, et al. Symptoms of disturbed sleep predict major adverse cardiac events after percutaneous coronary intervention. *Can J Cardiol*. 2014;30(1):118–124. doi:10.1016/j.cjca.2013.07.009
6. Su X, W DX. Improve postoperative sleep: what can we do? *Curr Opin Anaesthesiol*. 2018;31(1):83–88. doi:10.1097/ACO.0000000000000538
7. Jia X, Song Y, Li Z, et al. Melatonin regulates the circadian rhythm to ameliorate postoperative sleep disorder and neurobehavioral abnormalities in aged mice. *CNS Neurosci Ther*. 2024;30(3):e14436. doi:10.1111/cns.14436
8. Bourne RS, M GH. Melatonin: possible implications for the postoperative and critically ill patient. *Intensive Care Med*. 2006;32(3):371–379. doi:10.1007/s00134-005-0061-x
9. Amaral FGD, J C-N. A brief review about melatonin, a pineal hormone. *Arch Endocrinol Metab*. 2018;62(4):472–479. doi:10.20945/2359-3997000000066
10. Hu RF, Jiang XY, Hegadoren KM, et al. Effects of earplugs and eye masks combined with relaxing music on sleep, melatonin and cortisol levels in ICU patients: a randomized controlled trial. *Crit Care*. 2015;19(1):115. doi:10.1186/s13054-015-0855-3
11. Yang R, Xu XX, Liu H, et al. The impact of morning surgery or afternoon surgery on postoperative sleep quality and melatonin levels of elderly patients: a prospective, randomized study. *Nat Sci Sleep*. 2022;14:1677–1686. doi:10.2147/NSS.S377209
12. Soh PQP, Wong WHT, Roy T, et al. Effectiveness of non-pharmacological interventions in improving sleep quality after cardiac surgery: a systematic review and meta-analysis. *J Clin Nurs*. 2024;33(6):2084–2098. doi:10.1111/jocn.17115
13. Acharya R, Blackwell S, Simoes J, et al. Non-pharmacological interventions to improve sleep quality and quantity for hospitalized adult patients-co-produced study with surgical patient partners: systematic review. *BJS Open*. 2024;8(2):zrae018. doi:10.1093/bjsopen/zrae018
14. Huang HW, Zheng BL, Jiang L, et al. Effect of oral melatonin and wearing earplugs and eye masks on nocturnal sleep in healthy subjects in a simulated intensive care unit environment: which might be a more promising strategy for ICU sleep deprivation? *Crit Care*. 2015;19(1):124. doi:10.1186/s13054-015-0842-8
15. Li S, Li R, Li M, et al. Dexmedetomidine administration during brain tumour resection for prevention of postoperative delirium: a randomised trial. *Br J Anaesth*. 2023;130(2):e307–e16. doi:10.1016/j.bja.2022.10.041
16. Niu JY, Yang N, Tao QY, et al. Effect of different administration routes of dexmedetomidine on postoperative delirium in elderly patients undergoing elective spinal surgery: a prospective randomized double-blinded controlled trial. *Anesth Analg*. 2023;136(6):1075–1083. doi:10.1213/ANE.0000000000006464
17. Lin J, Wang B, Zeng W, Zhuang S, Liu M, Yang J. Evidence-based interventions to improve sleep quality after thoracic surgery:A retrospective analysis of clinical studies. *Sleep Med*. 2024;121:85–93. doi:10.1016/j.sleep.2024.06.006
18. Tong C, Huang C, Wu J, Xu M, Cao H. The prevalence and impact of undiagnosed mild cognitive impairment in elderly patients undergoing thoracic surgery: a prospective cohort study. *J Cardiothorac Vasc Anesth*. 2020;34(9):2413–2418. doi:10.1053/j.jvca.2020.03.011
19. Rosenberg-Adamsen S, Kehlet H, Dodds C, et al. Postoperative sleep disturbances: mechanisms and clinical implications. *Br J Anaesth*. 1996;76(4):552–559. doi:10.1093/bja/76.4.552
20. Knill RL, Moote CA, Skinner MI, et al. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology*. 1990;73(1):52–61. doi:10.1097/00000542-199007000-00009
21. Boulos MI, Jairam T, Kendzerska T, et al. Normal polysomnography parameters in healthy adults: a systematic review and metaanalysis. *Lancet Respir Med*. 2019;7(6):533e43. doi:10.1016/S2213-2600(19)30057-8
22. Carollo DS, Nossaman BD, R U. Dexmedetomidine: a review of clinical applications. *Curr Opin Anaesthesiol*. 2008;21(4):457–461. doi:10.1097/ACO.0b013e328305e3ef
23. Sun YM, Zhu SN, Zhang C, et al. Effect of low-dose dexmedetomidine on sleep quality in postoperative patients with mechanical ventilation in the intensive care unit: a pilot randomized trial. *Front Med Lausanne*. 2022;9:931084. doi:10.3389/fmed.2022.931084
24. Wu XH, Cui F, Zhang C, et al. Low-dose Dexmedetomidine Improves Sleep Quality Pattern in Elderly Patients after Noncardiac Surgery in the Intensive Care Unit: a Pilot Randomized Controlled Trial. *Anesthesiology*. 2016;125(5):979–991. doi:10.1097/ALN.0000000000001325
25. Kim H, Kim Y, Bae J, et al. Comparison of remimazolam and dexmedetomidine for intraoperative sedation in patients undergoing lower extremity surgery under spinal anesthesia: a randomized clinical trial. *Reg Anesth Pain Med*. 2024;49(2):110–116. doi:10.1136/rapm-2023-104415
26. Dong Y, Wang M, Li W, et al. Effect of dexmedetomidine infusion on postoperative sleep disturbances in women with breast cancer: a monocentric randomized-controlled double-blind trial. *Anaesth Crit Care Pain Med*. 2024;43(3):101358. doi:10.1016/j.accpm.2024.101358
27. Lu Y, Fang PP, Yu YQ, et al. Effect of intraoperative dexmedetomidine on recovery of gastrointestinal function after abdominal surgery in older adults: a randomized clinical trial. *JAMA Network Open*. 2021;4(10):e2128886. doi:10.1001/jamanetworkopen.2021.28886
28. Song B, Li Y, Teng X, et al. The effect of intraoperative use of dexmedetomidine during the daytime operation vs the nighttime operation on postoperative sleep quality and pain under general anesthesia. *Nat Sci Sleep*. 2019;11:207–215. doi:10.2147/NSS.S225041
29. RJ R. Pineal melatonin: cell biology of its synthesis and of its physiological interactions. *Endocr Rev*. 1991;12(2):151–180. doi:10.1210/edrv-12-2-151
30. Nishi T, Saeki K, Miyata K, et al. Effects of cataract surgery on melatonin secretion in adults 60 years and older: a randomized clinical trial. *JAMA Ophthalmol*. 2020;138(4):405–411. doi:10.1001/jamaophthalmol.2020.0206
31. Dispersyn G, Pain L, T Y. Propofol anesthesia significantly alters plasma blood levels of melatonin in rats. *Anesthesiology*. 2010;112(2):333–337. doi:10.1097/ALN.0b013e3181c920e2
32. Scholtens RM, van Munster BC, van Faassen M, et al. Plasma melatonin levels in Hip fracture patients with and without delirium: a confirmation study. *Mech Ageing Dev*. 2017;167:1–4. doi:10.1016/j.mad.2017.08.016
33. Anderson G, R M. Multiple sclerosis: the role of melatonin and N-acetylserotonin. *Mult Scler Relat Disord*. 2015;4(2):112–123. doi:10.1016/j.msard.2014.12.001
34. Liu YJ, Zhuang J, Zhu HY, et al. Cultured rat cortical astrocytes synthesize melatonin: absence of a diurnal rhythm. *J Pineal Res*. 2007;43(3):232–238. doi:10.1111/j.1600-079X.2007.00466.x

35. Tsai YL, Yen CT, W YF. Astrocyte dysregulation and calcium ion imbalance may link the development of osteoporosis and Alzheimer's disease. *J Alzheimers Dis*. 2022;88(2):439–445. doi:10.3233/JAD-220218
36. Perioperative Neurocognitive Disorders (PND) Study Group, Mei B, Xu G, Han W, et al. The benefit of dexmedetomidine on postoperative cognitive function is unrelated to the modulation on peripheral inflammation: a single-center, prospective, randomized study. *Clin J Pain*. 2020;36 (2):88–95. doi:10.1097/AJP.0000000000000779.
37. Qiu G, Wang P, Rao J, et al. Dexmedetomidine inhibits paraventricular corticotropin-releasing hormone neurons that attenuate acute stress-induced anxiety-like behavior in mice. *Anesthesiology*. 2024;140(6):1134–1152. doi:10.1097/ALN.0000000000004982
38. Fu S, Zhao X, Li Y, et al. Dexmedetomidine alleviates hippocampal neuronal loss and cognitive decline in rats undergoing open surgery under sevoflurane anaesthesia by suppressing CCAAT/enhancer-binding protein beta. *Eur J Neurosci*. 2024;59(1):36–53. doi:10.1111/ejn.16193
39. Mei B, Li J, Z Z. Dexmedetomidine attenuates sepsis-associated inflammation and encephalopathy via central α2A adrenoceptor. *Brain Behav Immun*. 2021;91:296–314. doi:10.1016/j.bbi.2020.10.008
40. Gao J, Sun Z, Xiao Z, et al. Dexmedetomidine modulates neuroinflammation and improves outcome via alpha2-adrenergic receptor signaling after rat spinal cord injury. *Br J Anaesth*. 2019;123(6):827–838. doi:10.1016/j.bja.2019.08.026
41. Mei B, Xu X, Weng J, et al. Activating astrocytic α2A adrenoceptors in hippocampus reduces glutamate toxicity to attenuate sepsis-associated encephalopathy in mice. *Brain Behav Immun*. 2024;117:376–398. doi:10.1016/j.bbi.2024.02.005
42. Wang X, Hua D, Tang X, et al. The role of perioperative sleep disturbance in postoperative neurocognitive disorders. *Nat Sci Sleep*. 2021;13:1395–1410. doi:10.2147/NSS.S320745
43. Devinney MJ, VanDusen KW, Kfouri JM, et al. The potential link between obstructive sleep apnea and postoperative neurocognitive disorders: current knowledge and possible mechanisms. *Can J Anaesth*. 2022;69(10):1272–1287. doi:10.1007/s12630-022-02302-4
44. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388(10054):1893–1902. doi:10.1016/S0140-6736(16)30580-3
45. Deiner S, Luo X, Lin HM, et al. Intraoperative infusion of dexmedetomidine for prevention of postoperative delirium and cognitive dysfunction in elderly patients undergoing major elective noncardiac surgery: a randomized clinical trial. *JAMA Surg*. 2017;152(8):e171505. doi:10.1001/jamasurg.2017.1505
46. Vij V, Dahiya D, Kaman L, et al. Efficacy of melatonin on sleep quality after laparoscopic cholecystectomy. *Indian J Pharmacol*. 2018;50 (5):236–241. doi:10.4103/ijp.IJP_250_18

Nature and Science of Sleep Dovepress

Publish your work in this journal

Nature and Science of Sleep is an international, peer-reviewed, open access journal covering all aspects of sleep science and sleep medicine, including the neurophysiology and functions of sleep, the genetics of sleep, sleep and society, biological rhythms, dreaming, sleep disorders and therapy, and strategies to optimize healthy sleep. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/nature-and-science-of-sleep-journal