

Effects of Intravenous Anesthetics vs Inhaled Anesthetics on Early Postoperative Sleep Quality and Complications of Patients After Laparoscopic Surgery Under General Anesthesia

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Objective: Decreased postoperative sleep quality remains a serious problem in surgical settings at present. The purpose of our study was to compare the effect of propofol vs sevoflurane on early postoperative sleep quality and complications of patients receiving laparoscopic surgery after general anesthesia.

Methods: Seventy-four patients undergoing selective laparoscopic surgery under general anesthesia were randomly assigned to the propofol group or sevoflurane group. The wireless portable sleep monitor (WPSM) is used to collect sleep quality on the night before surgery (sleep preop 1), the first night after surgery (sleep POD 1), and the third night after surgery (sleep POD 3). Record the subjective sleep quality and dreaming state during the operation. The perioperative hemodynamics, postoperative sleep and complications were also evaluated.

Results: Compared with Sleep preop 1, patients showed lower sleep efficiency, Stable sleep and Unstable sleep during Sleep POD 1 and Sleep POD 3. In addition, compared with the propofol group, the proportion of REM sleep in the sevoflurane group was much higher during Sleep POD 1 and Sleep POD 3, and the incidence of dreaming was also higher in the sevoflurane group. Patients in the propofol group had better pain relief at 2, 4, and 6 hours after surgery. And the incidence of postoperative nausea and vomiting and dizziness in the sevoflurane group was significantly higher than that in the propofol group.

Conclusion: The degree of postoperative sleep efficiency was better on Sleep POD1 and Sleep POD3; the incidence of postoperative nausea and vomiting, and dizziness was lower; and postoperative pain was slighter when the operation was performed under propofol anesthesia compared with patients in the sevoflurane group. Propofol should be considered a better choice during the operation to promote the patient's postoperative sleep quality, relieve postoperative pain and improve the incidence of postoperative dizziness and nausea and vomiting.

Keywords: postoperative sleep quality, general anesthesia, propofol, sevoflurane

Introduction

Adequate sleep is necessary for physical and mental health of human beings. Although surgery and anesthesia techniques have improved in recent years, postoperative sleep disturbance remains a challenging problem in surgical procedures.¹ Postoperative sleep fragmentation and poor sleep quality can not only result in hyperalgesia and a delay in postoperative recovery,² lack of sleep

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after surgery can also bring many potential adverse effects, such as cognitive disorders (such as delusions, delirium), chronic pain, mood disorders, metabolic disorders, and pro-inflammatory changes. Moreover, postoperative delirium may also influence postoperative sleep disturbances.^{3–5} Previous studies have reported that age, preoperative comorbidity and severity of surgical trauma were independent factors associated with postoperative sleep disturbance.^{6,7} Our prior studies have also found that patients are more likely to experience decreased sleep quality after receiving general anesthesia, which was characterized by a decrease in each sleep stage.⁸ Propofol and sevoflurane are commonly used general anesthetics in clinical practice. The choice of anesthetic may also affect the cognitive outcome after surgery, but the results of clinical studies have been contradictory. Some studies have reported that the cognitive results after inhalation are worse than those after intravenous anesthesia.^{9–11} Another study conducted among infants proved that compared with propofol-remifentanyl, sevoflurane appears to be associated with less sleep disturbances in the first weeks after surgery.¹² Based on these conflicts, the aim of the current study was to compare the effect of propofol vs sevoflurane on early postoperative sleep quality and complications of patients receiving laparoscopic surgery after general anesthesia.

Materials and Methods

The study was approved by the Human Research Ethics Committee of Shengjing Hospital, Shenyang, Liaoning Province, China (IRB registration number 2017PS29K) and complied with the Declaration of Helsinki. Written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at Clinicaltrials.gov (NCT04123249).

Sample Size

Based on the primary outcome between the two groups in our preliminary study and according to the calculation of the sample size ($n_1=n_2=2*[(1.96+0.842)*\delta/\sigma]^2$), we chose 0.56 as the estimated variability between the two groups, and 0.8 as the standard deviation. Therefore, 32 patients for each group were required, assuming a two-sided Type I error (α) of 0.05 and a power of 80%. The potential loss was expected during follow-up or due to drop out; therefore, a total of 74 patients were enrolled in this study.

Participants

Seventy-four patients undergoing elective laparoscopic surgery after general anesthesia in Shengjing Hospital of China Medical University were selected. The inclusion criteria were as follows: (1) patients aged 18–75 years; (2) patients with American Society of Anesthesiology (ASA) physical fitness classification grade I–II; (3) the duration of surgery in the range of 1–2 hours. The exclusion criteria included the following: (1) Patients with a history of sleep apnea syndrome and/or preoperative sleep disorders; (2) Patients requiring the long-term use of hypnotics and sedatives; (3) Patients with a history of mental disorders and psychological disorders and the recent use of antipsychotic drugs and anti-depression drugs; (4) Patients were unwilling to the participant or were unable to communicate.

Study Protocol and Standardized Anesthesia

The 74 patients were randomly assigned either to the sevoflurane anesthesia group (Group S, $n=37$) or the propofol anesthesia group (Group P, $n=37$) in a 1:1 ratio using a computer-generated randomization number sequence. The group assignment was sealed in sequentially numbered opaque envelopes. Of all patients, 60 minutes before being transferred to the operating room, the patients were prescribed intramuscular midazolam (0.05 mg/kg). After entering the operating room, standard monitoring is performed, such as electrocardiogram, heart rate (HR), non-invasive blood pressure (NIBP) and peripheral blood oxygen saturation (SpO₂). General anesthesia was induced with penehyclidine hydrochloride (0.5 mg), sufentanil citrate (0.2 μ g/kg), etomidate (2.5 mg/kg), and intravenously bolus-injected with cisatracurium besilate (0.2 mg/kg) following the disappearance of the speech reflex, and then an ID7.0 endotracheal tube was inserted under video laryngoscopy after the patients' muscles were fully relaxed and the blood circulation was stable. Mechanical ventilation was provided using the following parameters: tidal volume (TV) 7 mL/kg, respiration rate (RR) 12 times/min, inspiration and expiration ratio (I/E) 1:2, positive end-expiratory pressure (PEEP) 0, oxygen/air mixture (50%/50%). Thereafter, the minute ventilation volume (MV) was adjusted to keep end-tidal CO₂ (EtCO₂) at 35–40 mmHg. In Group P, propofol 4–6 mg/kg/h and remifentanyl 0.2 μ g/kg/min were infused by intravenous pump separately for assisted sedation and assisted analgesia. In Group S, sevoflurane (concentration: 2%–3%, mixed with

50% air and 50% oxygen to keep the minimum alveolar concentration (MAC) at 1.0–1.1) was inhaled to maintain assisted sedation, and remifentanyl 0.2 µg/kg/min was infused by intravenous pump for assisted analgesia. Ten minutes before the end of the surgery, all patients were intravenously infused with sufentanil 5 µg and ketorolac tromethamine 5 mg/kg to assist postoperative analgesia, and administered with ramosetron 0.3 mg to prevent postoperative vomiting. Before closing the abdominal cavity, 0.1% ropivacaine solution (7 mL each) was made to locally block at the incisions. After the operation, all the patients were transferred to the PACU for continuous monitoring.

Data Collection

Primary Observation Indicators

In the hospital, the gold standard for measuring sleep stage is polysomnography, however, it is difficult to conduct polysomnography for patients perioperatively. The Wireless Portable Sleep Monitor (WPSM) is convenient for patients to wear, as recording only requires a single-lead electrocardiogram or photoplethysmography and an accelerometer to produce an output. It relies on cardio-pulmonary coupling (CPC) technology that establishes sleep quality from the analysis of the coupling between heart rate variability and respiratory volume variability: this coupling will be high or low depending on their relative stability.¹³ The application of WPSM was as follows: a) Stick two electrodes, respectively, to the 3rd intercostal space of the right midclavicular line and the V5 point on the left anterior axillary line. b) Put the WPSM on the left anterior axillary line close to the left clavicle. c) Press the power button for 3 seconds to start recording d) After use, press the power button for 3 second again to stop recording.^{8,14} The WPSM was performed on the following three nights from 23 PM to 7 AM: the first night before surgery (Sleep-preop 1), the first night after surgery (Sleep POD1) and the third night after surgery (Sleep POD 3). The following sleep variables were evaluated by physicians in the sleep laboratory without knowing the patient information: sleep efficiency (sleep time/recording time) and the percentage of REM sleep, Stable sleep and Unstable sleep. Collect detailed information about whether the patient reports dreaming during the operation after general anesthesia or not and record whether the dreams had influence on patients' satisfaction with care.

Secondary Observation Indicators

The systolic, diastolic blood pressure, mean arterial pressure (MAP), and heart rate (HR) of each patient were recorded 5 minutes after entering the operation room (T0), at the moment of induction (T1), at the moment after intubation (T2), at the moment the surgery began (T3), at the moment the surgery ended (T4), and at the moment after extubation (T5). The postoperative pain score was evaluated by a visual analog scale (VAS) score, where 0 means no pain and 10 means severe pain.¹⁵ VAS scores were measured at 2, 4, 6, and 24 hours after surgery. The adverse reactions, such as respiratory depression, bradycardia, nausea, vomiting and dizziness within 24 hours after surgery and surgery complications, were also recorded and treated accordingly.

Statistical Analysis

SPSS 23.0 (IBM Corp, Armonk, NY, United States) and GraphPad Prism8.0 statistical software were used for data processing and statistical analysis. The quantitative data of normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and intergroup comparison was performed with an independent sample *t*-test. The qualitative data were expressed as number (n) and percentage (%), and compared with the χ^2 test. $P < 0.05$ (two-sided) suggested that a difference was statistically significant.

Results

As shown in Figure 1, we initially assessed the eligibility of 105 patients to participate in the study (Figure 1), of which 20 did not meet the inclusion criteria, and 11 patients refused to participate. In the end, 74 patients participated in the study. Four patients in Group S were excluded from analysis with three of them were converted to laparotomy during the operation and one of them was transferred to the intensive care unit (ICU) after the operation. Two patients in Group P were excluded from analysis with the one who was allergic to electrode paste and the other who was transferred to ICU after the operation. Finally, 68 patients with 33 patients in Group S and 35 patients in Group P were analyzed in this study.

The Comparison of Demographic Characteristics of the Two Groups

There were no statistical differences between the two groups including patients age ($P = 0.624$), sex ($P = 0.234$), ASA ($P = 0.446$), BMI (Body Mass Index) ($P = 0.623$),

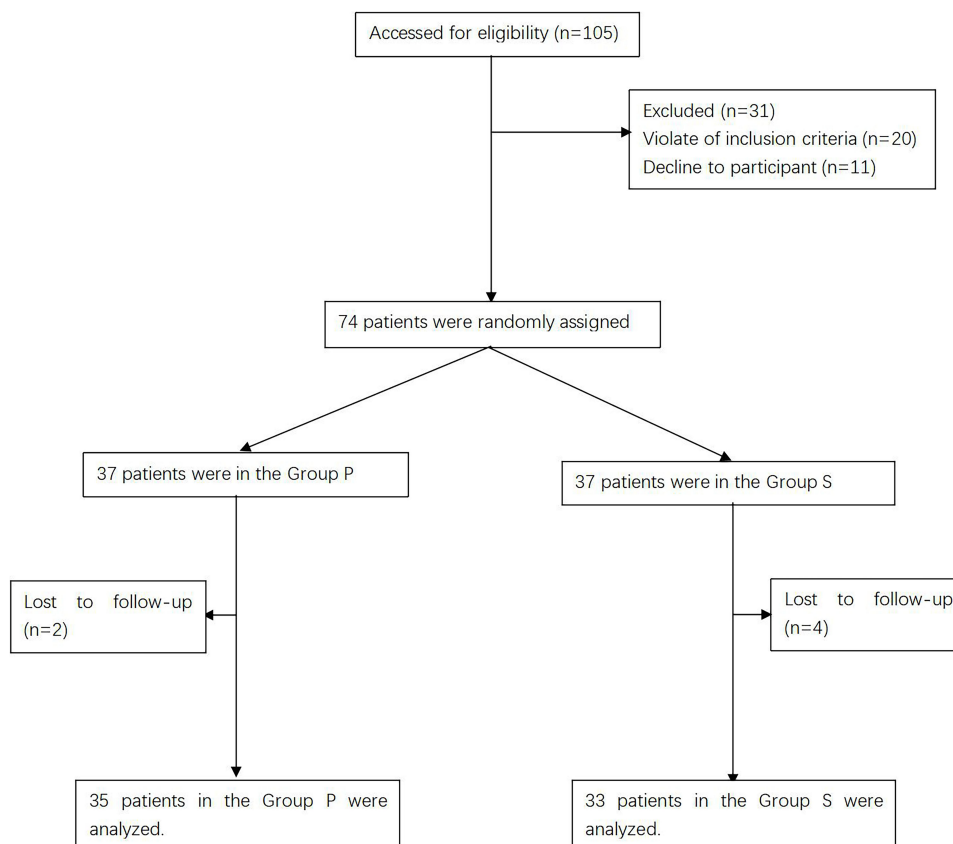


Figure 1 Flow diagram showing the patients that were included and excluded in this study.

duration of the operation (min) ($P = 0.051$), type of surgery ($P = 0.342$), co-morbidities ($P = 0.842$), intraoperative anesthetics ($P = 0.576$, $P = 0.292$, $P = 0.057$ and $P = 0.056$, respectively) and bleeding volume (mL) ($P = 0.060$) (Table 1).

The Comparison of Perioperative Hemodynamics and Sleep Quality Between the Two Groups

As shown in Figure 2, there were no significant differences in HR, the systolic, diastolic blood pressure and MAP at each time point between the two groups ($P > 0.05$, respectively). The incidence of dreaming differed significantly between the two groups ($P < 0.05$). The proportion of dreamers in the sevoflurane group was 60.6%, while the proportion of dreamers in the propofol group was 31.4% ($P < 0.001$). Overall, dreams had no influence on patients' satisfaction with care ($P > 0.05$) (Figure 3B and C). There was no significant difference in the sleep efficiency of patients in the two groups at Sleep-preop 1 ($P = 0.816$). Compared to Sleep-preop 1, patients in both groups presented with a lower sleep efficiency during Sleep POD 1 and Sleep POD 3 ($P < 0.001$, respectively). Patients in

Group P reported a better sleep efficiency than patients in the Group S at the same time point ($P < 0.001$, respectively) (Figure 3A). Patients in the two groups presented with a lower proportion of Stable sleep and Unstable sleep during Sleep POD 1 and Sleep POD 3 when compared to Sleep-preop 1 ($P < 0.001$, respectively). Patients in Group S showed a significantly higher proportion of REM sleep at Sleep POD 1 and Sleep POD 3 than that in Group P ($P < 0.001$, respectively) (Figure 4A–C).

The Comparison of Postoperative Pain, Adverse Effects and Surgery Complications Between the Two Groups

Patients in Group P had significantly lower VAS scores compared to the Group S at 2, 4, and 6 hours after the surgery ($P = 0.004$, $P = 0.005$, $P = 0.008$, respectively). The incidences of nausea and vomiting and dizziness were also significantly higher in Group S than those in Group P ($P = 0.031$, $P = 0.029$, respectively). There were no significant differences in surgery complications between the two groups ($P = 0.459$) (Table 2).

Table 1 The Comparison of Demographic Characteristics Between the Two Groups

	Group P (n=35)	Group S (n=33)	P
Age (year)	42.03±11.8	40.67±11.0	0.624
Gender (Male/Female) (n)	12/23	16/17	0.234
BMI (kg/m ²)	23.32±1.9	23.12±1.4	0.623
ASA (I/II) (n)	17/18	13/20	0.446
Duration of surgery (min)	103.94±10.1	97.61±15.4	0.051
Intraoperative bleeding volume (mL)	22.14±9.6	17.42±10.7	0.060
Co-morbidities (n %)			0.842
Hypertension	4 (11.4)	3 (9.1)	
Diabetes	2 (5.7)	2 (6.1)	
Cardiovascular disease	2 (5.7)	3 (9.1)	
Intraoperative anesthetics			
Total dose of etomidate (mg)	13.60±2.7	14.00±3.2	0.576
Total dose of sufentanil (µg)	21.14±3.2	20.30±3.3	0.292
Total dose of cisatracurium (mg)	13.03±1.9	13.94±2.0	0.057
Total dose of remifentanyl (mg)	0.63±0.1	0.57±0.1	0.056
Type of Surgery (n %)			0.342
Laparoscopic cholecystectomy	11 (31.4)	12 (36.4)	
Laparoscopic appendectomy	11 (31.4)	14 (42.4)	
Laparoscopic gynecological surgery	13 (37.1)	7 (21.2)	

Note: Variables were presented as Mean±SD.

Abbreviations: ASA, American Society of Anesthesiology; BMI, body mass index.

Discussion

Our study demonstrated that in the general population, decreased postoperative sleep quality was found after both propofol and sevoflurane anesthesia. The proportion of patients who reported dreaming during general anesthesia was significantly higher in the sevoflurane anesthesia group compared to the propofol group. And the proportion of postoperative REM sleep was also higher in the sevoflurane anesthesia group than that in the propofol group. The postoperative pain intensity and sleep efficiency were better after propofol anesthesia than sevoflurane anesthesia. And the incidence of postoperative dizziness, and nausea and vomiting was also lower after propofol anesthesia than sevoflurane anesthesia.

General anesthesia is a medically hyporesponsive state of consciousness, which is considered to be an independent risk factor that causes dysregulation of the circadian rhythm time structure and cause postoperative sleep disturbances.¹⁶ Although the function of sleep is still unclear, “sleep quality” is an important clinical indicator, for example: complaining about the deterioration of quality of life caused by impaired sleep quality is a common

reason for patients to seek medical attention.¹⁷ In our study, we found that the sleep stages, such as Stable sleep and Unstable sleep, were both decreased after general anesthesia in the two groups. And the postoperative sleep efficiency was also reduced when compared to that before surgery. Moreover, an animal study conducted by Pick et al demonstrated that exposure to volatile anesthetic for six hours resulted in insufficient REM sleep in mice and then followed by a significant REM rebound time after the anesthetic is stopped.¹⁸ Similar to the previous study, we also found that the proportion of REM sleep on the first night after surgery was significantly higher than that on the night before surgery in the sevoflurane anesthesia group. And the proportion of postoperative REM sleep in the sevoflurane anesthesia group was higher than that in the propofol group at the same time point. The potential mechanism may be due to the propofol may regulate sleep homeostasis by satisfying the need for non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, however, volatile anesthetic anesthetized brain is prevented from accessing the neuronal circuits driving REM sleep but the REM homeostat continues to register the accruing deficit and rebound after general anesthesia.¹⁸ Kaw et al confirmed that REM rebound was associated with hemodynamic instability, myocardial infarction, stroke and postoperative delirium.¹⁹ In addition, in our study, 60.6% of patients in the sevoflurane anesthesia group reported dreaming during the operation, which was more than that in the propofol anesthesia group. The reason for this phenomenon may be that patients anesthetized with sevoflurane had higher BIS values during the operation than patients anesthetized with propofol, which was consistent with a prior study's finding that dreamers have higher BIS values compared to non-dreamers.²⁰

Besides surgery trauma, type of anesthesia and different anesthetics may change sleep function and sleep cycle perioperatively, the postoperative complications, such as pain, nausea and vomiting after general anesthesia, may also reduce postoperative sleep quality.^{21,22} In our study, we found that the pain intensity was less severe after propofol anaesthesia than after sevoflurane anaesthesia. The possible mechanisms may as follows: 1) Propofol has anti-inflammatory and antioxidant effects on cytokine biosynthesis, which is important in pain signal transduction;²³ 2) The ability of propofol to scavenge free radicals is both useful and important. It has antioxidant properties and can also dynamically protect the body;²⁴ 3) Propofol can regulate NMDA receptors in

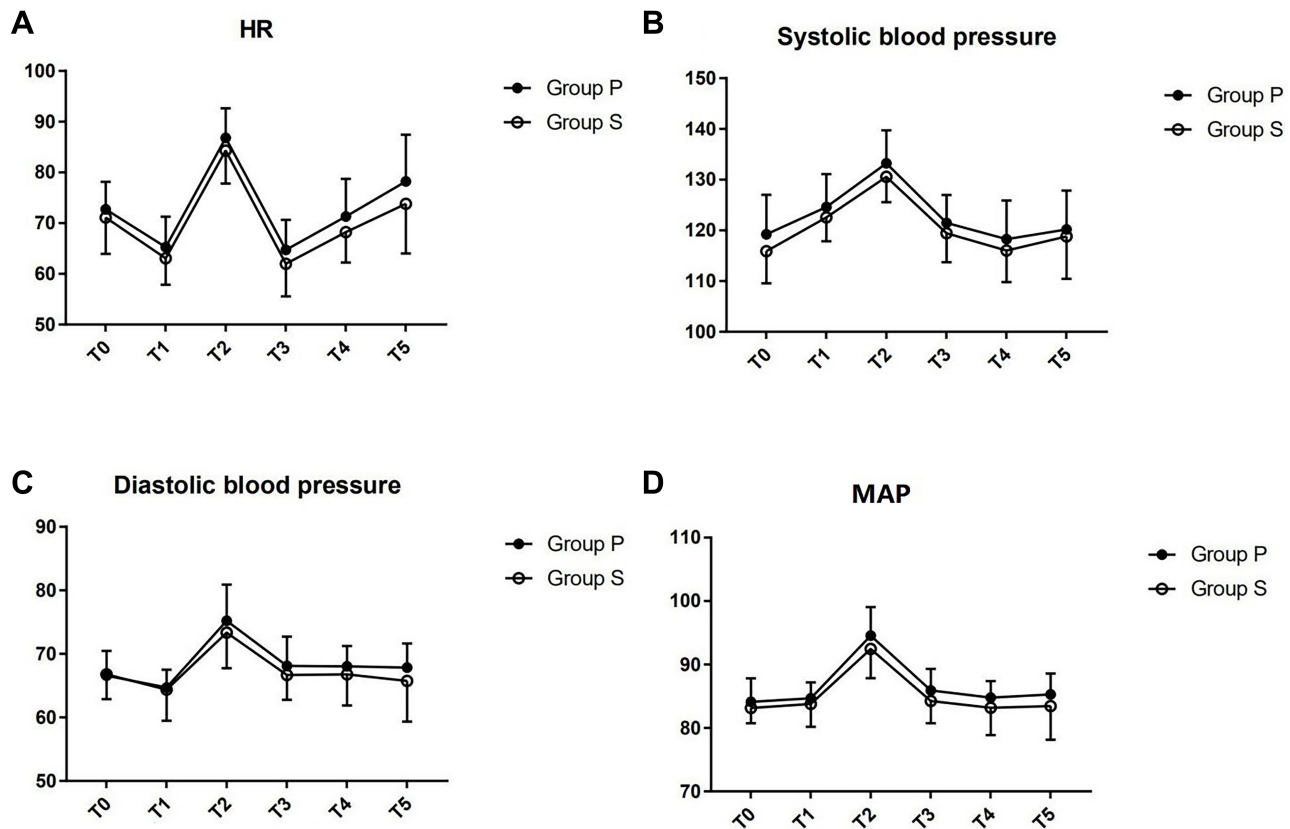


Figure 2 The comparison of perioperative hemodynamics between the two groups. (A) HR: Heart rate; (B)systolic blood pressure; (C) diastolic blood pressure; (D) MAP: mean arterial pressure.

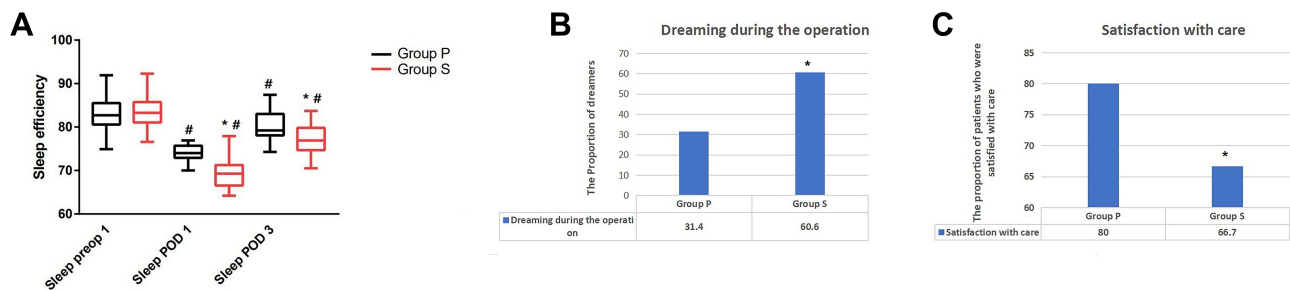


Figure 3 The comparison of sleep efficiency, dreaming during the operation and satisfaction with care between the Group P and the Group S. (A) Sleep efficiency; (B) dreaming during the operation. (C) Satisfaction with care. Sleep efficiency: the ratio of total sleep time/total recording time. Sleep-preop 1: the first night before surgery; Sleep POD 1: the first night after surgery; Sleep POD 3: the third night after surgery. In the same group, #vs the previous time point: P < 0.001. At the same point, *vs the Group P: P < 0.001.

neurons in the body, which plays an important role in the transmission and maintenance of pain signal pathways.²⁵ These anti-inflammatory, free radical scavenging and NMDA receptor antagonistic properties of propofol suggest that it may have perioperative analgesic effects. Meanwhile, the incidence of post-operative nausea and vomiting, and dizziness was obviously lower in the propofol anesthesia group than that in the sevoflurane anesthesia group. Thus, the

postoperative sleep efficiency presented better in the propofol anesthesia group than that in the sevoflurane anesthesia group.

There were several limitations in our study. Firstly, we only collect data on sleep quality in the short-term perioperative period after surgery. The effect of different anesthetics on long-term sleep quality after surgery still needs further study. Secondly, there are many confounding factors that may affect the quality of postoperative

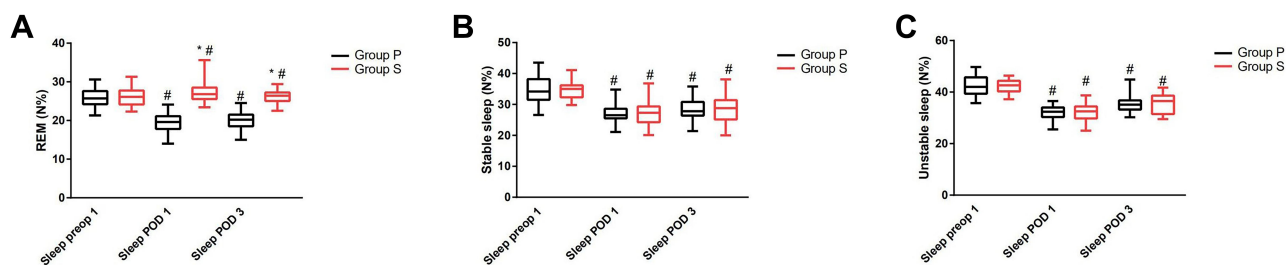


Figure 4 The comparison of the distribution of different sleep stages between the Group P and the Group S. (A) REM, (B) stable sleep, (C) unstable sleep. REM: rapid eye movement; Sleep-preop 1: the first night before surgery; Sleep POD 1: the first night after surgery; Sleep POD 3: the third night after surgery. In the same group, #vs the previous time point: P < 0.001. At the same point, *vs the Group P: P < 0.001.

sleep. Although we are trying to reduce the interference factors of postoperative sleep quality, such as light, noise or interference caused by night care, there may also be other unavoidable factors. Thirdly, we only conduct the research in a single center. The effect of different anesthetics on postoperative sleep quality in multicenter studies of large scale and more types of surgeries under general anesthesia are still needed to study in the future.

Conclusion

In conclusion, we demonstrated that patients undergoing laparoscopic surgery after general anesthesia who were randomized to the propofol group perceived a better

postoperative sleep efficiency on Sleep POD1 and Sleep POD3 and less postoperative pain and adverse effects compared with patients in the sevoflurane group. Propofol should be considered a better choice during the operation to promote the patient’s postoperative sleep quality, relieve postoperative pain and improve the incidence of postoperative dizziness, and nausea and vomiting.

Data Sharing Statement

The individual deidentified participant data in our study could be shared with the readers. Readers can obtain the data by emailing the corresponding author (zhujunchao1@hotmail.com). We did not include specific data and documents from other studies in our study. All the data in our study are available for 10 years.

Table 2 The Comparison of Postoperative Pain and Adverse Effects Between the Group P and the Group S

	Group P (n=35)	Group S (n=33)	P
VAS scores			
2 h	4.34±1.2	5.21±1.1	0.004
4 h	3.06±0.9	3.70±1.0	0.005
6 h	1.97±0.9	2.55±0.9	0.008
24 h	1.57±0.5	1.82±0.7	0.093
Adverse effects			
Nauseated and vomiting, n (%)	2 (5.7)	8 (21.2)	0.031
Dizziness, n (%)	4 (5.7)	11 (12.1)	0.029
Respiratory depression, n (%)	0 (0)	0 (0)	–
Bradycardia, n (%)	1 (2.8)	4 (12.1)	0.144
Surgery complications			0.459
Intra-abdominal abscess (n/%)	1 (2.9)	2 (6.1)	
Reoperation (n/%)	2 (5.7)	1 (3.0)	
Bleeding (n/%)	1 (2.9)	0 (0)	
Cardiac complications (n/%)	0 (0)	0 (0)	

Note: Variables are presented as mean (±SD) or as frequency (percentage).

Abbreviation: VAS, visual analogue scale.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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