

Minimum Alveolar Concentration-Awake of Sevoflurane is Decreased in Patients with Parkinson's Disease: An Up-and-Down Sequential Allocation Trial

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Background: An increasing number of patients with Parkinson's disease (PD) will have surgery under general anesthesia. A previous study demonstrated that propofol requirement for inducing unconsciousness in PD patients was lower than that in non-PD (NPD) patients. However, the requirement of inhaled anesthetics in PD patients has not been clarified. The aim of this study was to investigate the minimum alveolar concentration-awake (MAC_{awake}) of sevoflurane in patients with PD compared to NPD patients.

Patients and Methods: The current study is an up-and-down sequential allocation trial. The initial end-tidal concentration of sevoflurane (CET_{sevo}) was estimated by the response of the previous patient to verbal command using the Dixon's up-and-down method. The first patient in each group received CET_{sevo} at 1%, and the step size between patients was 0.2%.

Results: Forty-one patients including 20 PD patients and 21 NPD patients were enrolled. Patients' characteristics and arterial blood gas parameters (except blood sodium) were comparable between two groups. The MAC_{awake} of sevoflurane estimated by the Dixon's up-and-down method in PD patients ($0.47\% \pm 0.08\%$ [Mean \pm S.D.]) was significantly lower than that in NPD patients ($0.64\% \pm 0.10\%$) ($P=0.003$). The estimated difference in means was 0.17% (95% CI, 0.10–0.24%). Probit analysis showed that the MAC_{awake} of sevoflurane in PD and NPD patients was 0.49% (95% CI, 0.42–0.57%) and 0.67% (95% CI, 0.59–0.76%), respectively. The relative median potency was 0.73 (95% CI, 0.38–0.94).

Conclusion: Patients with PD exhibit a significantly lower MAC_{awake} of sevoflurane compared with NPD patients. Clinicians should avoid an overdose of sevoflurane in patients with PD.

Trial Registration: Registered at ChiCTR1900026956.

Keywords: Parkinson's disease, sevoflurane, the minimum alveolar concentration-awake

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Introduction

Parkinson's disease (PD) is the second common neurodegenerative disorder at present.¹ It was reported that the prevalence of PD is about 0.3% in the general population and 1% in the people older than 60 years.² Moreover, the incidence of PD is growing quickly over the last 20 years.³ Symptoms of PD mainly include bradykinesia, rigidity, and resting tremor, which affect the quality of life of patients significantly.

An increasing number of patients with PD will have surgery under general anesthesia as the society is aging rapidly. We have noticed that patients with PD were slower to emerge from anesthesia compared with non-PD (NPD) patients in clinical practice. However, very little is known about the requirements of PD patients for anesthetic agents. Xu et al found that propofol requirement to induce unconsciousness in PD patients was lower than NPD patients due to the degenerative brain.⁴ The reasons for this decreased requirement might include the reduced dopamine production and anti-PD medications in PD patients. Their team also demonstrated that patients with PD have lower remifentanyl requirements to suppress the response to tracheal intubation and skin incision.⁵ Sevoflurane is one of the most commonly used anesthetic agents in clinic anesthesia. However, the requirement of sevoflurane in PD patients is unknown. Proper dose of sevoflurane avoids deep general anesthesia, which may affect the practice of the enhanced recovery after surgery (ERAS) of PD patients.^{6,7}

The minimum alveolar concentration (MAC) to achieve a 50% probability of no response to a verbal command (MAC_{awake}) can be used to measure the hypnotic potency of inhaled anesthetics.⁸ We hypothesized that the MAC_{awake} of sevoflurane was decreased in patients with PD compared with those with normal neurological function.

Patients and Methods

The current study is an up-and-down sequential allocation trial. Ethical approval for this study (2019KY111) was provided by the Medical Research Ethic Committee of Anhui Provincial Hospital, Hefei, China (Chairperson Prof Zuojun Shen) on 14 October 2019. Written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at ChiCTR1900026956, Principal investigator: Chengwei Yang, Date of registration: October 14, 2019. We performed this study from October 15, 2019 to May 26, 2020. Written informed consents were obtained from all participants. Thirty patients with PD undergoing bilateral deep brain stimulation (DBS) electrode insertion and pulse generator placement were included in this study. Thirty patients with normal neurological function scheduled for supratentorial brain tumor (less than 30 mm in diameter) resection (NPD) served as controls. All patients were 40 to 64 years old. Exclusionary criteria were as follows: an American Society of Anesthesiologists (ASA) score higher

than class III, a body mass index (BMI) more than 30 kg·m⁻², a history of respiratory, hepatic, renal, or psychiatric diseases, cardiac ejection fraction less than 40%, a history of alcohol or drug abuse, contraindication to inhalational drugs, history of emergence delirium with sevoflurane induction, medications known to affect MAC_{awake} , known family history of malignant hyperthermia, a history of auditory impairment, acid-base or electrolyte abnormalities, diabetes, sepsis, or obvious weight loss caused by carcinoma.

After DBS electrodes were inserted under local anesthesia, we conducted general anesthesia to place the pulse generator in PD patients. All patients were fasted for 8 hours and took no premedication. PD patients stopped taking anti-PD drugs at the night before surgery. After arriving in the operation room, a 20 G vena catheterization was established. Patients received 10 kg·mL⁻¹ lactated Ringer's solution and maintained at a rate of 10 mL·kg⁻¹·h⁻¹. The temperature in the operation was controlled between 24°C and 26°C. Electrocardiograms, pulse oxygen saturation and invasive arterial pressures were routinely monitored. Inspired and expired concentrations of sevoflurane and oxygen and end-tidal carbon dioxide (ETCO₂) were continuously monitored using a Dräger Primus machine (Drägerwerk AG & Co. KGaA, Lübeck, Germany) calibrated by a standard gas mixture before induction of anesthesia. An arterial blood gas analysis was conducted in each patient. PD patients received a DBS electrode insertion under local anesthesia using 30 mL 1% lidocaine and 0.375% ropivacaine mixture. Then, we performed general anesthesia to place the pulse generator. NPD patients received local anesthetics of the same volume before induction of anesthesia.

The MAC_{awake} of sevoflurane (HengRui, Pharmaceutical Co, Ltd., Shanghai, China) was estimated using the Dixon's up and down method according to previous studies.^{8,9} A mixed gas with 8% sevoflurane and 100% oxygen at a flow rate of 6 L/min primed the circuit for 1 minute. Then, we asked patients to take deep breaths via a tight-fitting facemask attached to a semi-closed circuit system (Vapor 2000, Draegerwerk AG & Co. KGaA, Lübeck, Germany). If the ETCO₂ greater than 45 mmHg or tidal volume less than 500 mL, mechanical ventilation was applied. After the patient lost responsiveness, the concentration of sevoflurane was adjusted to a predetermined level. The first patient in each group received an end-tidal concentration of sevoflurane (CETsevo) at 1%. After the CETsevo was

maintained for 15 minutes, an anesthesiologist blinded to the study design asked the patient to open eyes in a normal tone for no more than 3 times. If the patient made a response appropriately, the CETsevo for the next patient was increased by a step of 0.2%. In contrast, if the patient made no response, the CETsevo for the next patient was decreased by 0.2%. The study was continued until 7 “no response/response” crossover pairs had occurred.

Another anesthesiologist blinded to the study design recorded the data. A bolus of 6–10 mg ephedrine was injected intravenously if the mean arterial pressure (MAP) was less than 60 mmHg or reduced by more than 20% of baseline values. Atropine 0.5 mg was administered intravenously if the heart rate (HR) was less than 50 beats per minute. After finishing this study, we deepened the anesthesia to perform tracheal intubation and surgical procedure.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL). Data are expressed as the means \pm standard deviations for continuous variables or the number (percentage) for categorical variables. The MAC_{awake} of sevoflurane was estimated by calculating the mean of 7 independent crossover pairs of CETsevo. The MAC_{awake} of sevoflurane, patients' age, weight, and arterial blood gas values between two groups were compared by the independent-samples *t*-test. Patients' sex was compared by Pearson's chi-square test. The up and down data were also analyzed using the probit analysis,^{9,10} deriving the MAC_{awake} with 95% confidence interval (CI). The relative median potency estimated from the probit analysis, which is the ratio of CETsevo needed to obtain a 50% probability of being awake in each group, was used to compare the calculated MAC_{awake} between two groups. Finally, we assessed the association between MAC_{awake} and PD (vs non-PD) while controlling for sevoflurane by a binary logistic regression analysis.

The sample size was calculated according to a previous study.⁹ We hypothesized that the MAC_{awake} of sevoflurane in PD and NPD patients were 0.5% and 0.7%, respectively. The standard deviation was 0.2%. Thus, in order to achieve a power of 80% and a type I error of 0.05 to detect a difference of 0.2% with a possible dropout rate of 15%, 19 patients per group were required.

Results

As shown in Figure 1, 41 patients including 20 PD patients and 21 NPD patients were enrolled in the final analysis. Patients' characteristics and arterial blood gas parameters (except blood sodium) were comparable between two groups (Table 1). The anti-Parkinson medications taken by PD patients are shown in Table 2.

The sequences for response to verbal command in two groups are shown in Figure 2. The MAC_{awake} of sevoflurane estimated by the Dixon's up-and-down method in PD patients ($0.47\% \pm 0.08\%$ [Mean \pm S.D.]) was significantly lower than that in NDP patients ($0.64\% \pm 0.10\%$) ($P=0.003$). The estimated difference in means was 0.17% (95% CI, 0.10–0.24%). From the probit analysis, the MAC_{awake} of sevoflurane in PD and NPD patients were 0.49% (95% CI, 0.42–0.57%) and 0.67% (95% CI, 0.59–0.76%), respectively. The relative median potency was 0.73 (95% CI, 0.38–0.94), the CI of which did not include one, indicating a difference in the median potency between two groups (Table 3). Figure 3 showed the dose–response curve of the probability of being awake in two groups from the probit analysis. The age, weight, and sex were not significantly different between “awake” and “not awake” patients (Table 4). Table 3 demonstrated that PD patients had a significant lower risk of being awake compared with NPD patients when controlling for age, weight, and sex (OR=0.041667, 95% CI, 0.003441–0.504522, $P=0.0125$) (Table 5).

One PD patient' HR was less than 50 beats per minute, which was successfully treated with 0.5 mg atropine.

Discussion

The current study demonstrated that the MAC_{awake} of sevoflurane in patients with Parkinson's disease was significantly lower than that in NPD patients. We derived the MAC_{awake} of NPD patients as 0.64%, which is similar to those in previous studies.^{9,11}

The Dixon's up-and-down method is widely used to estimate the MAC of inhaled anesthetics.^{9,12–14} At least 6 crossover pairs are required when using the Dixon's method.¹⁵ Based on the calculated sample size, this study was continued until 7 no response/response crossover pairs had occurred. In the current study, a high concentration of sevoflurane was firstly used to make patients lose responsiveness. Then, we adjusted the concentration of sevoflurane to a predetermined level to test the responsiveness of

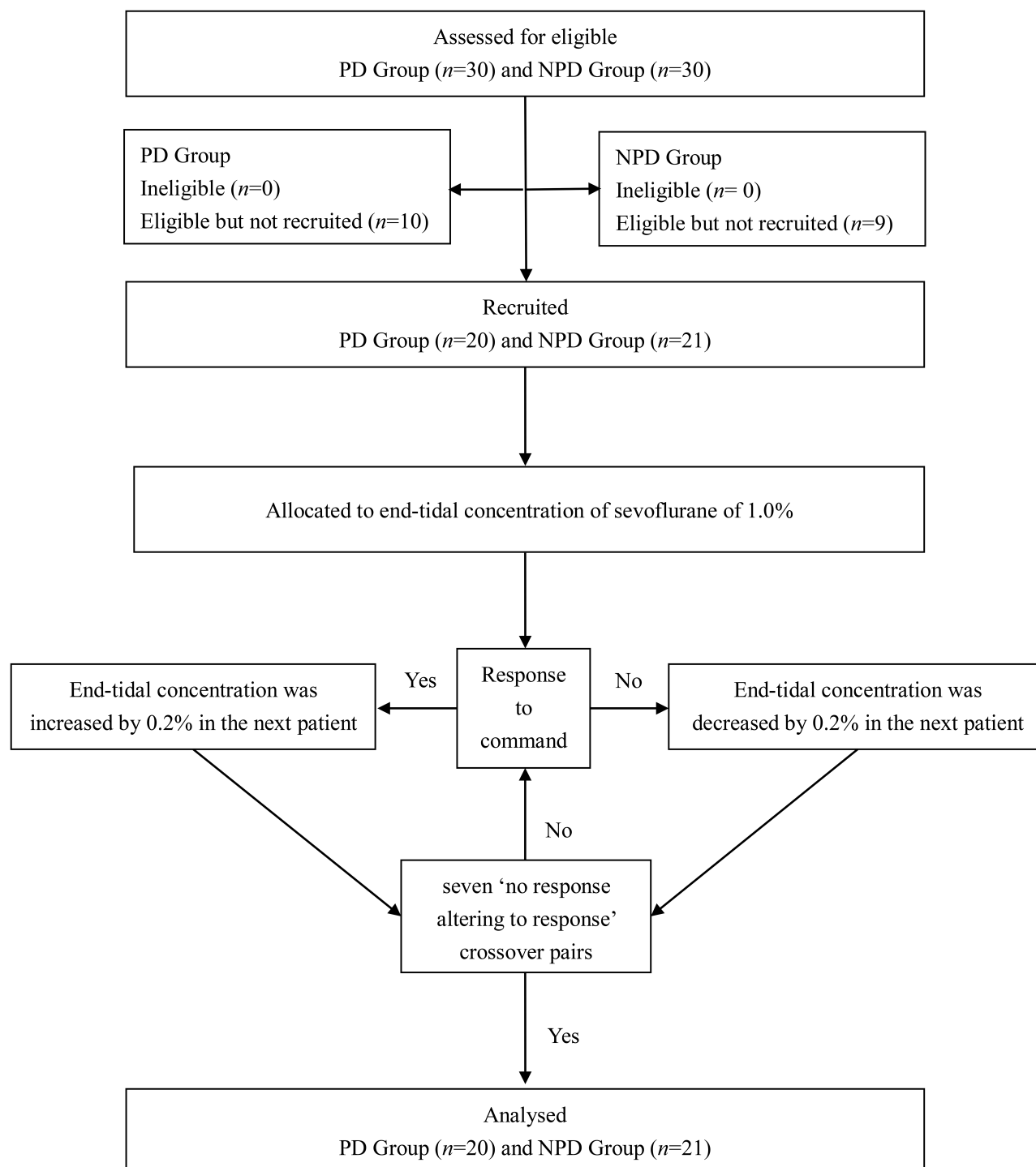


Figure 1 Flow diagram for the Dixon's up-and-down method.
Abbreviations: PD, Parkinson's disease; NPD, non-Parkinson's disease

patients. This method is widely used to investigate the MAC_{awake} of sevoflurane.^{9,14,16}

To our best knowledge, this is the first trial to explore the MAC of inhaled anesthetic in patients with PD. In our hospital, more than 70% PD patients undergoing DBS

surgery are younger than 65 yr. Thus, we chose middle-aged (40–64 yr) patients in our study. The PD patients' average age was 57.2 yr, which is similar to that in a previous study (57.4 yr) by Wang et al in China.⁵ The time required to reach an equilibrium between alveolar and

Table 1 Patients' Characteristics and Arterial Blood Gas Results

Parameters	PD Group (n=20)	NPD Group (n=21)	P
Age, yr	57.2±6.7	54.8±6.0	0.236
Sex, male/female	9/11	10/11	0.867
Height, cm	161.8±8.0	163.4±5.8	0.463
Weight, kg	60.1±6.9	62.8±6.9	0.215
Temperature, °C	36.4±0.2	36.4±0.2	0.600
pH	7.41±0.03	7.41±0.02	0.577
PaO ₂ (mmHg)	85.2±4.2	86.6±3.3	0.216
PaCO ₂ (mmHg)	37.7±1.5	37.8±2.6	0.882
Na ⁺ (mmol/L)	139.7±2.5	138.2±1.7	0.033*
K ⁺ (mmol/L)	3.9±0.4	3.8±0.2	0.285
Ca ²⁺ (mmol/L)	1.10±0.03	1.09±0.03	0.512
Glucose (mmol/L)	5.5±0.6	5.8±0.5	0.081
Lactic acid (mmol/L)	1.55±0.26	1.60±0.31	0.474
Hemoglobin (g/L)	119.3±11.0	117.7±10.7	0.643
Hematocrit (%)	0.35±0.03	0.34±0.03	0.373

Notes: Data are presented as mean ± S.D. or number of subjects. *The P value for significance tested by t test is set at < 0.05.

Abbreviations: PD, Parkinson's disease; NPD, non-Parkinson's disease.

target organ concentrations is 9–12 minutes.^{9,17} Thus, we maintained the end-tidal sevoflurane concentration for 15 minutes before we assessed the response of subjects. Many factors influence the efficacy of inhaled anesthetics, including age,^{18,19} temperature,²⁰ hypotension, acid-base status,²¹ diabetes,²² and sepsis.²³ We excluded the patients with these pathophysiologic conditions. Moreover, patients' characteristics and blood gas values were

Table 2 The Anti-Parkinson Medications Taken by Patients with Parkinson's Disease

Medications	Number of Uses (%)
Levodopa/benserazide	20 (100%)
Amantadine	11 (55%)
Piribedil	5 (25%)
Trihexyphenidyl	3 (15%)
Selegiline	2 (10%)
Levodopa/carbidopa	1 (5%)
Pramipexole	1 (5%)

Note: Data are presented as number (percentages).

generally comparable, making our results more reliable in measuring the effects of PD on MAC_{awake}.

There may be several reasons why PD patients have a lower MAC_{awake} value of sevoflurane compared with NPD patients. Previous studies have demonstrated that PD patients show increased γ -aminobutyric acid (GABA) in several brain regions^{24–26} and decreased cortical glutamate²⁷ by using the magnetic resonance spectroscopy. GABA and glutamate are major inhibitory and excitatory neurotransmitters in the brain. Sevoflurane at amnestic concentrations suppressed synaptic plasticity by enhancing GABA-mediated inhibition and reducing glutamate release.²⁸ Intrathecal injection of a GABA_A agonist or a glutamate antagonist induced a significant reduction of sevoflurane MAC in rats.²⁹ Xu et al found that propofol requirement to induce

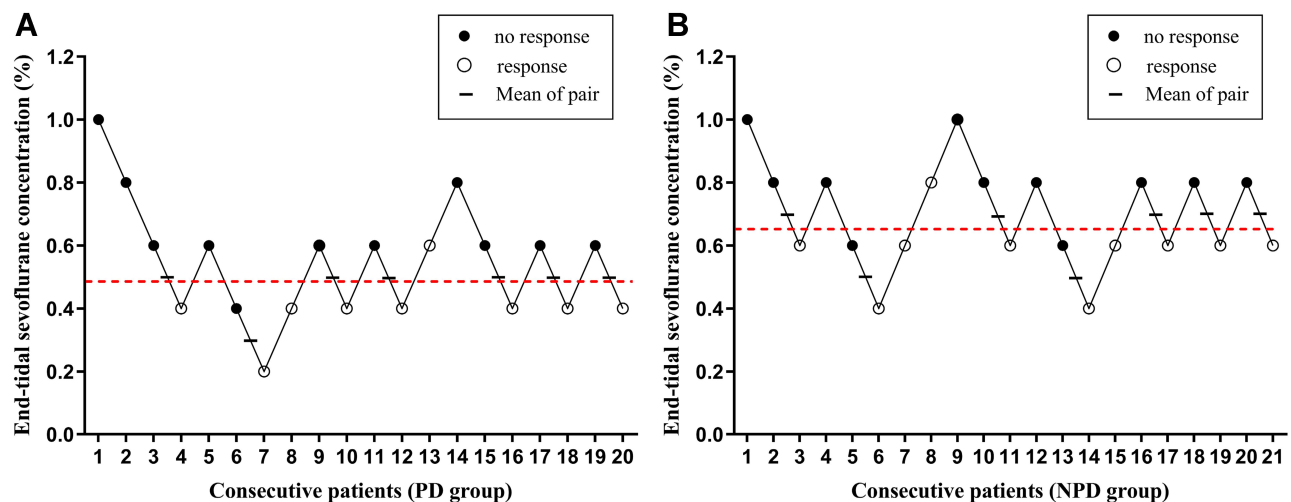


Figure 2 Assessment of responses to verbal command under a predetermined end-tidal concentration of sevoflurane using the Dixon's up-and-down method in 20 consecutive PD patients (A) and 21 consecutive NPD patients (B). A "no response" concentration is denoted by a solid circle; a "response" concentration is denoted by an open circle; horizontal bars represent crossover midpoints ("no response" to "response"). The MAC_{awake} values are indicated with red dashed line.

Abbreviations: PD, Parkinson's disease; NPD, non-Parkinson's disease.

Table 3 Minimum Alveolar Concentration-Awake of Sevoflurane

Methods	PD Group (n=20) (%)	NPD Group (n=21) (%)	Differences (95% CI) (%)	p	Relative Median Potency
Dixon's method	0.47±0.08	0.64±0.10	0.17 (0.10–0.24)	0.003*	–
Probit analysis (95% CI)	0.49 (0.42–0.57)	0.67 (0.59–0.76)	–	–	0.73 (0.38–0.94)

Notes: Data from the Dixon's up-and-down method are presented as mean ± S.D. Data from the probit analysis are EC₅₀ with (95% confidence interval). *The P value for significance tested by t test is set at 0.05.

Abbreviations: PD, Parkinson's disease; NPD, non-Parkinson's disease; CI, confidence interval; EC₅₀, median effective concentration.

unconsciousness was reduced in patients with PD.⁴ Thus, the widely used intravenous and inhaled anesthetics were both reduced in PD patients. Propofol is known to potentiate activity of the inhibitory neurotransmitter GABA.³⁰ Thus, the altered neurotransmitters, especially GABA, may play important roles in the reduction of anesthetics in PD patients. In addition, dopamine levels in the brain might indirectly affect the inhaled anesthetic requirements. A previous study reported that a dopamine antagonist led to a decreased halothane MAC.³¹ The mice with high dopamine levels in the mesencephalon exhibited an increased enflurane requirement.³² Therefore, depletion of central nervous system dopamine in PD patients might decrease the MAC_{awake} of

sevoflurane. Moreover, some anti-Parkinson medications may decrease sevoflurane MAC_{awake}. Segal and his colleagues found that levodopa dose-dependently decreased halothane MAC to a maximum of 49% of control.³³ Preoperative oral amantadine, a non-competitive NMDA antagonist, reduced the inspired isoflurane concentration during maintenance of anesthesia in female patients undergoing abdominoplasty.³⁴ In addition, piri-bedil and pramipexole may lead to somnolence, which might also contribute to the lower MAC_{awake} of sevoflurane in PD patients.

There are limitations in our study. First, our sample size is relatively small. Thus, we cannot investigate the influence of some confounding factors, including patients'

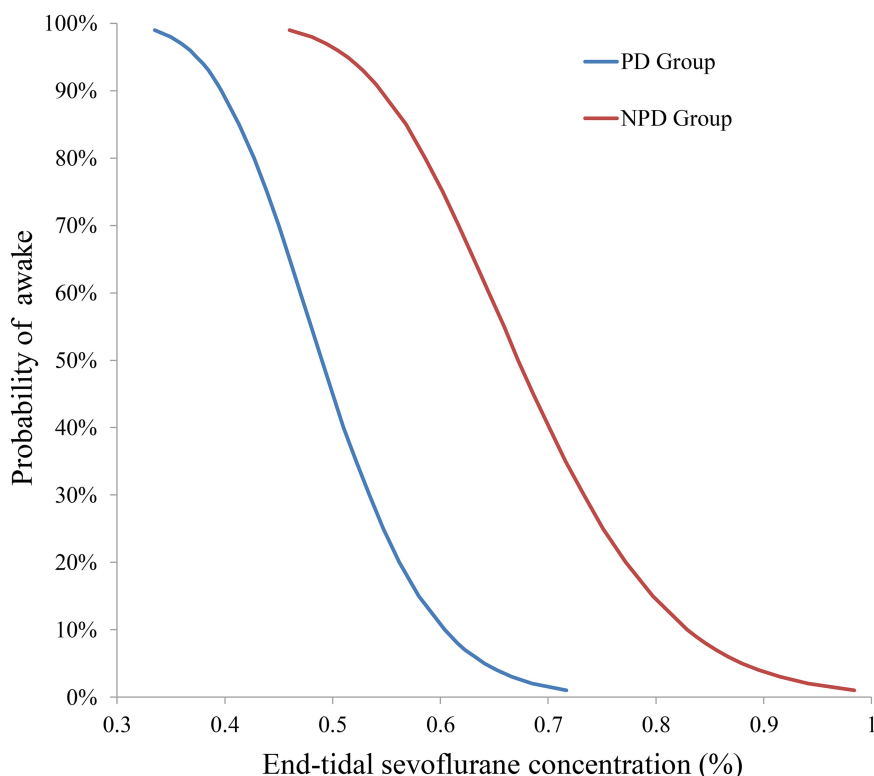


Figure 3 Dose-response curve from the probit analysis. The minimum alveolar concentration-awake (MAC_{awake}) of sevoflurane in PD patients was 0.49% (95% CI, 0.42–0.57%). MAC_{awake} of sevoflurane in the NPD patients was 0.67% (95% CI, 0.59–0.76%).

Abbreviations: PD, Parkinson's disease; NPD, non-Parkinson's disease.

Table 4 The Age, Weight, and Sex Between “awake” and “Not Awake” Patients

Parameters	Awake Group (n=20)	Not Awake Group (n=21)	P
Age, yr	56.7±6.3	55.2±6.5	0.457
Sex, male/female	8/11	11/11	0.613
Weight, kg	61.6±5.9	61.4±7.9	0.904

Note: Data are presented as mean ± S.D. or number of subjects.

Table 5 Binary Logistic Regression Analysis for Being Awake

Covariates (n=41)	OR	95% CI for OR		P
		Lower	Upper	
Sevoflurane concentration (%)	1.714×10 ⁻⁸	1.187×10 ⁻¹²	0.000247	0.0003*
PD group	0.041667	0.003441	0.504522	0.0125*
NPD group (as reference)	–	–	–	–

Notes: *The P value for significance tested by binary logistic regression analysis is set at < 0.05.

Abbreviations: PD, Parkinson's disease; NPD, non-Parkinson's disease.

comorbidities and medications. Second, two groups of patients had taken different types of surgery. As DBS implantation is not performed in NPD patients, we chose patients with brain tumors as control. Thus, we cannot exclude the effect of difference in surgical procedures on the MAC_{awake} of sevoflurane. Third, the plasma concentrations of local anesthetics in the two study groups were not measured in our study. However, the similar MAC_{awake} of sevoflurane in NPD patients with previous studies indicates that the local anesthesia may have a minimal effect on the results.

Conclusion

Our study demonstrated that patients with Parkinson's disease exhibit a significant lower MAC_{awake} of sevoflurane compared with NPD patients. This result suggests that the sevoflurane requirement is decreased in patients with PD. Clinicians should avoid an overdose of sevoflurane in patients with PD. It may affect the practice of ERAS of these patients. More animal and clinical studies are needed to explore the underlying mechanisms of the MAC_{awake} reduction in these patients.

Data Sharing Statement

The data supporting this study are available from the corresponding author for a reasonable request.

Ethics Approval

The current study was conducted in accordance with the Declaration of Helsinki and approved by the Medical

Research Ethic Committee of Anhui Provincial Hospital (2019KY111).

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Disclosure

The authors declare that they have no conflicts of interest.

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