Inhibitory concentration of propofol in combination with dexmedetomidine during microelectrode recording for deep brain stimulator insertion surgeries under general anesthesia

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Abstract

Background: Microelectrode recording (MER) for target refinement is widely used in deep brain stimulator insertion for Parkinson disease. Signals may be influenced by anesthetics when patients receive general anesthesia (GA). This study determined the inhibitory concentration (IC) of propofol on MER signals when it was coadministered with dexmedetomidine.

Methods: Patients were anesthetized with dexmedetomidine (0.5 μg·kg^{-1} loading, followed by infusion at 0.4 μg·kg^{-1}h^{-1}) and propofol through target-controlled infusion for GA with tracheal intubation. The surgeon conducted the online scoring of the background signals, spiking frequency, amplitude, and pattern of single-unit activities by using a 0–10 verbal numerical rating scale (NRS; 0, maximal suppression; 10, minimal suppression), and responses were grouped into suppression (NRS ≤ 6) and nonsuppression (NRS > 6). The median inhibitory concentration (IC_{50}) of propofol (as target effect-site concentrations: Ce_{prop}) was determined using modified Dixon's up-and-down method. Probit regression analysis was further used to obtain the dose–response relationship, and IC_{05} and IC_{95} were calculated.

Results: Twenty-three adult patients participated in this study. Under the concomitant infusion of dexmedetomidine, the predicted IC_{50} value (95% CI) of Ce_{prop} for neuronal suppression during MER was 1.29 (1.24–1.34) μg·mL^{-1} as calculated using modified Dixon's up-and-down method. Using probit analysis, the estimated IC_{05}, IC_{50}, and IC_{95} values (95% CIs) were 1.17 (0.87–1.23), 1.28 (1.21–1.34), and 1.40 (1.33–1.85) μg·mL^{-1}, respectively.

Conclusion: Our data provided reference values of propofol for dosage adjustment to avoid interference on MER under GA when anesthetics have to be continuously infused during recording.

Keywords: Dexmedetomidine; Inhibitory concentration 50; Microelectrode recording; Parkinson disease; Propofol

1. INTRODUCTION

Microelectrode recording (MER) is a well-established means of functional verification of target refinement for deep brain stimulator (DBS) insertion into the subthalamic nucleus (STN).[1,2] Currently, the most common anesthetic technique used for DBS procedures is local anesthesia or conscious sedation using propofol or dexmedetomidine.[3] The anesthetic infusion is stopped for at least 15–30 minutes to allow the drug concentration to decrease to avoid the anesthetic interfering with neurophysiology when the MER process begins. However, general anesthesia (GA) with endotracheal intubation is occasionally requested by surgeons for fear of intermittent cessation of surgical procedure when patients presented with extremely reduced cooperativity, possible coughing attacks, and spells of respiratory depression or hypoxemia. Therefore, GA represents a viable option when awake surgery or sedation may be risky,[4] but it requires more anesthetics for the maintenance of anesthetic depth, which may suppress MER neuronal signals and render the process of target location more complex for surgeons. Therefore, determining how to maintain GA and avoid impeding the online evaluation of MER can be a challenge to anesthesiologists with respect to certain populations.

According to the literature, dexmedetomidine has the least interference on MER signals.[5,6] No difference in neuronal signals was observed before and after the infusion of dexmedetomidine at a dose of 0.2 μg·kg^{-1}h^{-1}.[7] By contrast, propofol produced a dose-dependent reduction in basal ganglion neuronal activity.[7,8] However, dexmedetomidine alone may not be sufficiently potent to maintain GA for a long time during DBS surgery. Using a higher dose of dexmedetomidine would also induce side effects, such as bradycardia and hypotension. A combined use of

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dexmedetomidine with other anesthetics, such as propofol, can provide adequate anesthetic depth but carries the risk of suppression of neuronal signals. To date, no reference dosage has been suggested in the literature concerning the performance of MER under GA maintained with the combination of dexmedetomidine and propofol.

The median inhibitory concentration (IC_{50}) refers to the concentration of a drug, which induces a response halfway between the minimal and maximal inhibition. Determining the IC_{50} of anesthetics that causes the suppression of neuronal activity during MER provides important reference dosages when complete discontinuation of anesthetic infusion is unsuitable in the course of GA. Thus, we hypothesized the combination of dexmedetomidine and propofol may inhibit the neuronal signals during MER and impede the neurosurgeon's interpretation. Our primary endpoint is to determine the IC_{50} of propofol (as target effect-site concentrations; Ce_{prop}) that might reduce the spiking frequency or amplitude of single-cell recording signals and interfere with surgeon's online interpretation of MER under GA. The secondary endpoint was to obtain values of IC_{05} and IC_{95} derived the dose–response relationship curve.

2. METHODS

2.1. Patients and ethical consideration

This was a prospective observational study. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (approval number *2015-12-004B*) and registered in ClinicalTrial.gov (registration number *NCT03213912*). All patients signed an informed consent form before participating in the investigation. We enrolled patients who were aged between 20 and 85 years, had American Society of Anesthesiologists class 1–3 physical status, were diagnosed with Parkinson disease, and were scheduled for DBS of STN under GA after a preoperative visit and assessment by the surgeon. The exclusion criteria included a history of allergy to dexmedetomidine or propofol, taking the aforementioned medication or analgesic within 24 hours before the operation, a history of congestive heart failure, heart block on electrocardiography, abnormal liver function tests or liver cirrhosis, or unwillingness to sign the informed consent form. This study was conducted according to the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. This article adheres to the TREND guidelines.[9]

2.2. Anesthetic and surgical management

On the day of surgery, after placing a rigid stereotactic head frame under local anesthesia and MRI, the patient was sent to the operating room for DBS surgery. Standard monitoring systems were setup (Infinity Kappa, Draeger Medical Systems, PA, USA). The depth of anesthesia was monitored using the bispectral index (BIS; Loc 2 Channel, COVIDIEN, Singapore). After the setup, dexmedetomidine (Precedex; Hospira, IL) was infused at a loading dose of 0.5 $\mu g \cdot kg^{-1}$ over 10 minutes, followed by a continuous infusion of a dose of 0.4 $\mu g\ kg^{-1}h^{-1}$. Subsequently, anesthesia was induced through TCI of propofol (Fresofol 1% MCT/LCT; Fresenius Kabi, Austria GmbH) by using a model for propofol introduced by Schnider et al.[10] The target concentration (Ce_{prop}) of propofol was set at 3.5 $\mu g \cdot mL^{-1}$,[11,12] and then was titrated incrementally until the BIS value was <50.[13] Tracheal intubation was facilitated with the administration of 0.2 $mg \cdot kg^{-1}$ cisatracurium. After tracheal intubation, Ce_{prop} was adjusted decrementally to the predetermined concentration for the up-and-down determination. In the meantime, a burr hole was then made in the cranium for electrode insertion. After the electrode was inserted, signals of individual neuronal cells on recording were detected and amplified. The permanent quadripolar electrode was inserted 10–15 mm above the target site and was advanced 0.5–1 mm along its trajectory toward the STN, while spontaneous neuronal discharges were recorded. Subsequently, the same procedure was performed on the other side of the STN. Macrostimulation was performed, but clinical testing of patients' movements and side effects was omitted. In this study, the DBS surgery under GA was a two-staged procedure, with the internalization of the electrodes and generator conducted on a different day, usually 2 days later. Postoperative computed tomography (CT) scanning was performed to examine the position of DBS leads and rule out hemorrhage and pneumocephalus. Patients were asked after surgery if they had any recall of event and other adverse effects.

2.3. Outcome assessment

The modified Dixon's up-and-down method (UDM) was used to determine the IC_{50}.[14,15] It is a sequential analysis using binary responses to establish the drug concentration that caused neuronal suppression, which is displayed on MER. Binary responses were suppression or nonsuppression of MER signals. The predetermined Ce_{prop} for MER was chosen based on the response of the previous patient. A dose interval of 0.1 $\mu g \cdot mL^{-1}$ was used. The first patient received 1.6 $\mu g \cdot mL^{-1}$. Suppression or nonsuppression was determined according to the surgeon's instant online scoring of neuronal activity (Fig. 1) for a single-cell recording (Leadpoint Workstation V5.12, Medtronic, Denmark). The surgeon conducted scoring on the basis of the global assessment of the background signals, spiking frequency, amplitude, and pattern of neuronal activity by using a 0–10 verbal numerical rating scale (NRS), with 0 denoting the maximal interference of MER interpretation and 10 denoting the minimal effect. In this study, if NRS ≤ 6, we defined it as suppression; if NRS > 6, we defined it as nonsuppression. Scoring was conducted during the first side of MER and performed by a single neurosurgeon. The neurosurgeon was blinded to Ce_{prop} and intraoperative physiological parameters. If the response for the first patient revealed nonsuppression, then the Ce_{prop} administered to the next patient was increased to one dose-spacing above. In the case of suppression, Ce_{prop} for the next patient was decreased to one dose-spacing below. If in the beginning of MER, the surgeon's interpretation was significantly suppressive, confusing, or doubtful, the response would be suppression, and Ce_{prop} would be immediately adjusted to avoid delaying the procedure. The scoring was made within 10 minutes after the surgeon determining the typical STN spiking activity. If the BIS level exceeded 70 and lasted >30 seconds, Ce_{prop} was adjusted to achieve a lower BIS value for an adequate anesthetic level and the determination was abandoned. The primary outcome was the IC_{50} of Ce_{prop} determined using the modified Dixon UPM. The secondary outcome was IC_{05}, IC_{50}, and IC_{95} determined using probit regression analysis from a dose–response curve.

BIS, heart rate, and blood pressure were recorded and analyzed at the following time points: baseline (T1), after administering dexmedetomidine loading dose (T2), after tracheal intubation (T3), after surgical incision (T4), in the beginning (T5) and end (T6) of MER, and discontinuation of anesthetics (T7). By recording the track of the typical electrophysiological pattern of the STN, a track length was obtained. A track length of ≥ 5 mm was considered an ideal tract for the placement of the final lead with four contact points. The track length and number of tracks passed were also recorded. After concentration determination, patients were grouped into suppression and nonsuppression groups according to their responses, and their characteristics and perioperative data were compared.

2.4. Statistical analysis and sample size

The modified Dixon's UDM[14,15] was used to calculate the IC_{50} of Ce_{prop} for the neuronal suppression on MER. The IC_{50} was

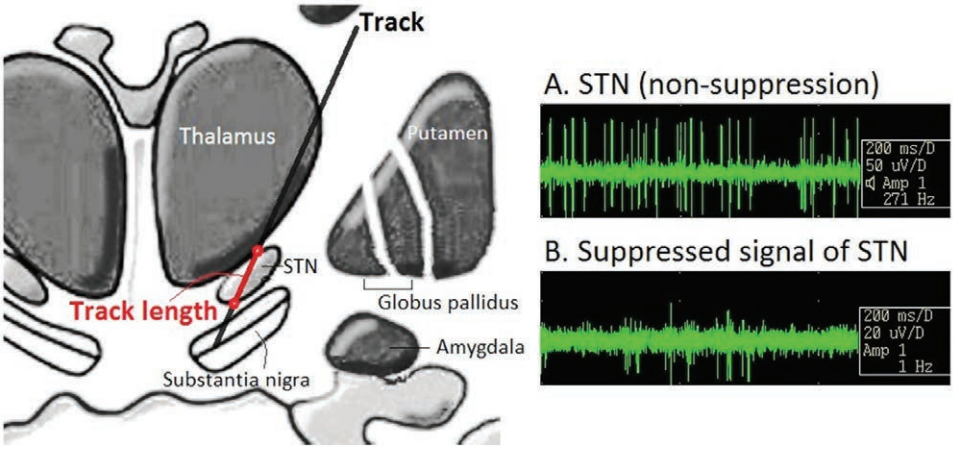

Fig. 1. Examples from a single trajectory during on-line microelectrode recording during deep brain stimulation for subthalamic nucleus in our study design. A, Inside the STN, scored as nonsuppression. B. Inside the STN, scored as suppression.

determined by calculating the mean of the midpoint dose of all independent pairs of patients who manifested crossover from a negative response (nonsuppression), followed by a positive response (suppression) after seven crossover points. Thus, 20–40 patients would be required to provide stable estimates of the target dose for our study.[16] Probit regression analysis was used to calculate the dose–response curve to determine the Ce_{prop} in 5%, 50%, and 95% of patients (IC_{05}, IC_{50}, and IC_{95}, respectively) with suppression signals on MER. Data are expressed as the mean and 95% CI. For numerical data, Student's *t* test was used for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data between the groups. For nominal data, statistical analysis was performed using Fisher's exact test. Data were analyzed using SPSS software (IBM corp, version 22.0, Armonk, NY). Results were considered statistically significant when $p < 0.05$.

3. RESULTS

A total of 23 patients participated in our study from May 2016 to October 2017 (Fig. 2), comprising 14 men and nine women with a mean age of 68.8 years. All patients underwent bilateral

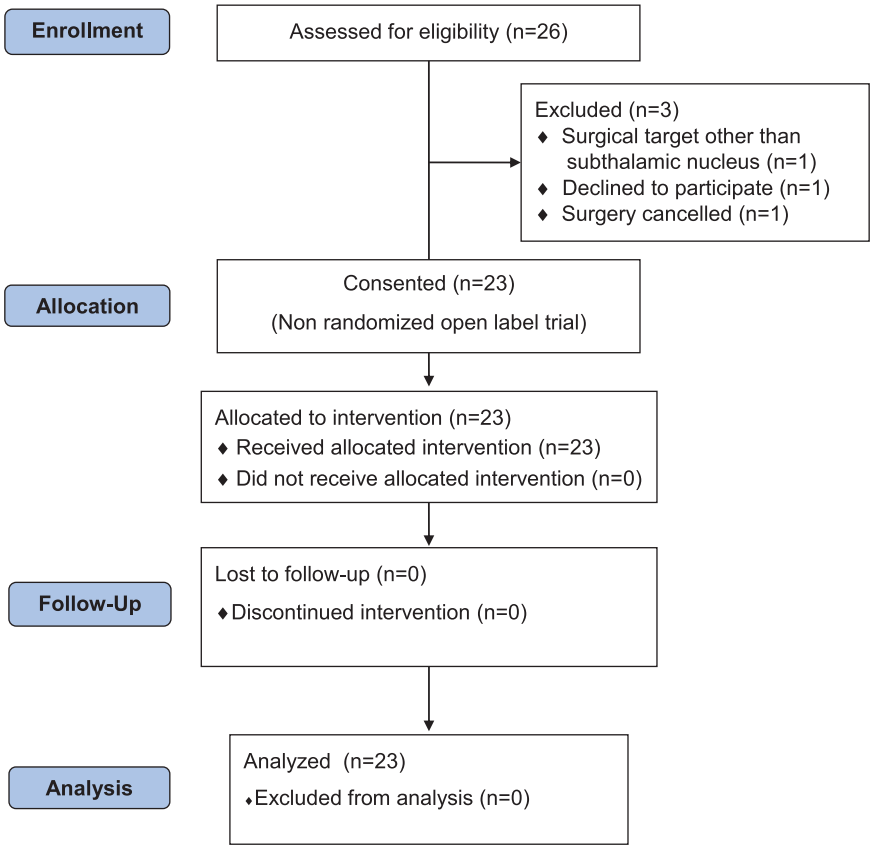

Fig. 2. Patient selection flowchart.

DBS surgery. The median number of trajectories (track) used was 2 (range 2–2), and the mean length of STN typical signals (track length) was 5.3 mm (range 4.4–6.0 mm). The STN was identified using MER in all cases. In one patient, the neurosurgeon became uncertain, and the NRS was scored <5, indicating the suppression of neuronal activity. We immediately lowered the Ce_{prop} to avoid delaying the recording. The patients were grouped into suppression and nonsuppression groups according to the surgeon's NRS score. No difference of the demographic and anesthesia data of individual groups (Table 1).

Sequential dose–response data obtained using modified Dixon's UDM method is shown in Figure 3A. The predicted IC_{50} required to achieve a suppression response (NRS ≤ 6) during MER was 1.29 (95% CI, 1.24–1.34) μg·mL^{-1}. The estimated IC_{05}, IC_{50}, and IC_{95} of propofol using probit analysis were 1.17 (95% CI, 0.87–1.23), 1.28 (95% CI, 1.21–1.34), and 1.40 (95% CI, 1.33–1.85) μg·mL^{-1}, respectively (Fig. 3B). Surgical data are listed in Table 2. The duration of MER, number of tracks, and length of tracks were all similar between the groups, except for the subjective NRS on neuronal activity scored during the first side of MER. BIS values at various time points are depicted in Figure 4. The BIS was significantly higher in the nonsuppression group at the beginning of MER. The BIS values at other time points were not different. Blood pressure and heart rate of the suppression and nonsuppression groups were similar at every time points ($p > 0.05$, data not shown).

Time to regain consciousness was comparable in the suppression and nonsuppression group. Three patients in the suppression group and one in the nonsuppression group required intraoperative atropine for bradycardia (Table 1, $p > 0.05$). Four patients received ephedrine, and three patients received nicardipine for the control of intraoperative blood pressure in the suppression group, whereas one patient received nicardipine in the nonsuppression group (Table 1, $p = 0.07$). No patients had any recall of the events. Postoperative CT scans confirmed the location of contact leads, and the existence of hemorrhage and pneumocephalus was ruled out in all patients.

Table 1

Demographic and anesthetic data

	Non-suppression (n = 10)	Suppression (n = 13)	*p*
Age (year)	69.5 ± 6.1	68.2 ± 7.2	0.784
Gender (M/F)	7/3	7/6	0.669
Height (cm)	158.5 ± 8.6	157.9 ± 8.5	0.738
Weight (kg)	60.8 ± 8.4	55.5 ± 10.8	0.088
BMI (kgm^{-2})	24.2 ± 2.3	22.3 ± 4.8	0.131
ASA physical status (I/II/III/IV)	0/9/1/0	0/11/2/0	1.000
Total anesthetic duration (min)	351.0 ± 29.3	355.0 ± 43.3	1.000
Input (mL)	1604.0 ± 471.6	1684.6 ± 412.0	0.605
Urine (mL)	980.0 ± 388.2	770.8 ± 303.1	0.166
Blood loss (mL)	74.0 ± 38.6	60.0 ± 31.1	0.410
Use of atropine (no/yes)	9/1	10/3	0.604
Use of ephedrine (no/yes)	10/0	9/4	0.104
Use of perdipine (no/yes)	9/1	10/3	0.604

Data are expressed as mean ± SD or count.

ASA = American Society of Anesthesiologists; BMI = body mass index.

4. DISCUSSION

In this study, we combined dexmedetomidine and propofol to maintain GA for DBS surgery. When dexmedetomidine was infused at a dose of 0.4 μg·kg^{-1}h^{-1}, the IC_{50} of the Ce_{prop} was 1.29 μg·mL^{-1} using the modified Dixon's UDM. Through probit analysis, the estimated IC_{05}, IC_{50}, and IC_{95} values were 1.17, 1.28, and 1.40 μg·mL^{-1}, respectively. These values suggest that these doses (or above) may suppress neuronal activities and interfere with the proceeding of MER. Doses below EC_{05} might have the least degree of interference.

In a previous report, dexmedetomidine administered to the dose of 0.48 ± 0.15 μg·kg^{-1}h^{-1} by the first hour and 0.52 ± 0.17 μg·kg^{-1}·h^{-1} by the second hour resulted in adequate sedation for DBS surgery and surgical satisfaction with mapping.[17] However, a higher dose of dexmedetomidine causes a significant decrease in the signals of STN neurons.[18] Therefore, after discussion with the neurosurgeon, we adopted a 0.5 μg·kg^{-1} dose of dexmedetomidine for the loading and 0.4 μg·kg^{-1}h^{-1} dose for maintenance,[17] The suppressive effect of neuronal activity when dexmedetomidine was infused in combination with another anesthetic remained uncertain. Trivial changes in STN activity were reported before and after dexmedetomidine was added to

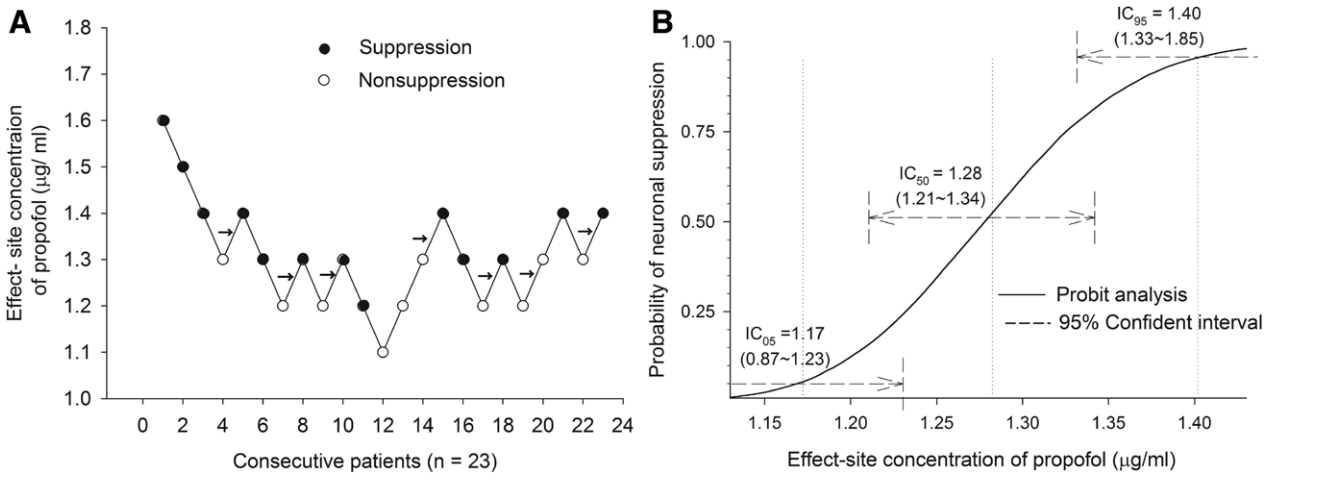

Fig. 3. Median Inhibitory concentration determination. (A) Consecutive effect-site concentration of propofol (Ce_{prop}) administered in combination with dexmedetomidine infusion, as determined using modified Dixon's Up and Down Method. Arrow represents the mean concentration of propofol when crossing from "nonsuppression" (white circles) to "suppression" (black circles). (B) Probability of neuronal suppression as a function of effect-site concentration of propofol in combination with dexmedetomidine infusion. Horizontal dashed lines represent the 95% CI for inhibitory concentration (IC) of propofol at 5%, 50%, and 95% probabilities for neuronal suppression (IC_{05}, IC_{50}, and IC_{95}, respectively).

Table 2

Surgical characteristics

	Non-suppression (n = 10)	Suppression (n = 13)	*p*
NRS for MER signals	8.60 ± 52	5.92 ± 2.08	0.000
Right MER duration (min)	56.3 ± 28.5	42.6 ± 17.5	0.376
Left MER duration (min)	36.7 ± 27.9	56.1 ± 33.4	0.148
Total MER duration (min)	93.0 ± 45.7	98.7 ± 46.4	0.605
Track length (mm)	5.3 ± 0.4	5.2 ± 0.4	0.832
Number of tracks	2 (2–3)	2 (2–2)	0.281
Total surgical duration (min)	243.9 ± 29.0	244.2 ± 40.8	0.738
Time to regain consciousness (min)[a]	40.6 ± 18.0	37.5 ± 12.1	0.927

Data are expressed as mean ± SD, count, or median (25%–75% interquartile range).
NRS = numerical rating scale; MER = microelectrode recording.
[a]Time to regain consciousness, time of discontinuation of all drugs to the time when the modified Observer Assessment of Alertness and Sedation score was ≥4.

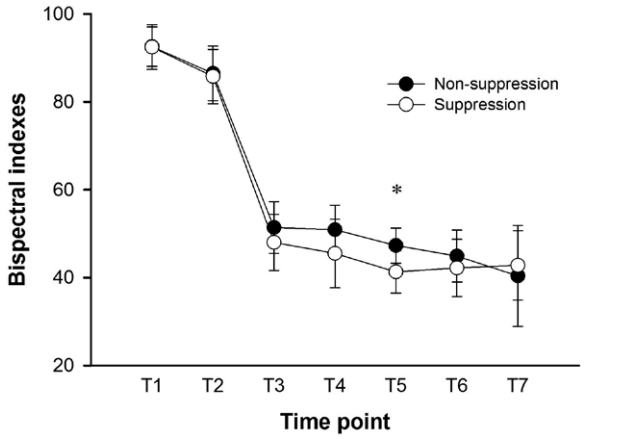

Fig. 4. Intraoperative values of BIS at specific time points. Data were mean ± SD. *$p < 0.05$ suppression group vs nonsuppression group. T1 = baseline, T2 = after loading dexmedetomidine dose, T3 = after tracheal intubation, T4 = after surgical incision, T5 = at the beginning of MER, T6 = at the end of MER, T7 = discontinuation of anesthetics.

remifentanil infusion during MER,[19] but the combination may not provide sufficient hypnosis for GA. The combined use of propofol and an opioid for sedation may significantly reduce STN neuronal activity when the propofol dose is increased to 50 μg·kg^{-1}min^{-1}.[8,20] If anesthetics must constantly be infused throughout the recording period when a patient is under GA, the combination of dexmedetomidine and propofol offers both adequate hypnosis and moderate analgesia. The propofol-sparing effect of dexmedetomidine can also reduce the dose of propofol required for maintenance and minimize its effect on MER signals.

We adopted an online interpretation of MER, which is the immediate feedback from the surgeon, to instantly identify the relationship of dosage, neuronal signal, and anesthetic depth. Previous studies have adopted detailed electrophysiological signals, such as local field potentials,[7] firing rate,[20] and spiking activity as normalized root mean square.[8] Most studies investigating the effect of anesthetics on MER have been neurophysiology oriented, addressing the change of the firing characteristics of STN neurons. Because objective data require offline analysis and the use of special software to sort and compute neuronal signals, the objective data were analyzed after the MER-based surgery was finished. Our study sought to determine the appropriate dose of anesthetic to administer to avoid interrupted surgeries when GA is used; this was intended to benefit the practice of anesthesiologists and neurosurgeons. Surgeons' global assessment of the background signals, spiking frequency, amplitude, and pattern of the neuronal activity is subjective; however, it represents the confidence and satisfaction of real-time judgments from MER. The binary outcome of suppression or nonsuppression is an artificial and simplified grouping for the execution of the modified Dixon's UDM. To avoid possible delay of the MER process, we conservatively adopted NRS ≤ 6 to represent suppression. Because we lacked baseline awake MER data for comparison, the derived concentration is suggestive of decreased MER signals rather than the suppression threshold of electrophysiological signals relative to the baseline signals.

The IC_{50} value determined in our study was 1.29 μg·mL^{-1}, which entails some risk of intraoperative recall because many patients will wake up below a target effect-site concentration of propofol of 1.5 μg·mL^{-1}.[21,22] We used the BIS monitor to guide intraoperative anesthetic depth, and no patients exhibited high values of BIS. None of our patients had recall at postoperative follow-ups. One explanation for this result is the combined use of dexmedetomidine. Dexmedetomidine has a propofol-sparing effect in combination with anesthesia, in terms of induction (23%~48% lower in dosage requirement), and maintenance (29%~61% lower in maintenance dosage).[23–25] Additionally, compared with propofol, dexmedetomidine was reported to achieve a lower BIS value when used as a sole agent for maintaining anesthesia during cardiopulmonary bypass during cardiac surgery, and it achieved a low BIS when used as an adjuvant to propofol to decrease the incidence of recall during cardioversion.[26] However, our derived dose was limited to patients with Parkinson disease undergoing DBS surgery. The patient number was too low in our study to draw a conclusion regarding the adequacy of the dosage of the combination of dexmedetomidine and propofol administered to maintain GA in the general population. Patients in the suppression group had a significantly lower BIS value than those in the nonsuppression group. This indicates that patients presented with more suppressed neural signals on MER had a more inhibited level of consciousness. The three inhibitory concentrations (IC_{05}, IC_{50}, and IC_{95}) were derived from a regression analysis, and their clinical implementation warrants investigation. For example, IC_{05} was least likely to inhibit neuronal signals; however, it carries a risk of intraoperative awareness. Nevertheless, our findings still establish a dosage suggestion that balances considerations of GA and the interpretation of MER.

This study has limitations. First, we did not perform an offline analysis of signals for details of drug effect on neuronal signals. This was because our aim was to determine an appropriate dose instead of determining the specific effect of an anesthetic on the firing characteristic of STN neurons. Second, we used modified Dixon's UDM and minimized the number of patients required for analysis. A small sample size (~20) may be adequate for a sequential trial in our investigation.[14] Furthermore, the clinical implementation of derived doses, especially IC_{05}, warrants clinical investigation. Despite these limitations, the modified Dixon's UDM has remained a popular approach in anesthesiology research because a relatively low number of patients are required, and the method is relatively simple to handle.

In conclusion, considering the possible suppression of MER, we determined the IC_{50} of propofol to be 1.29 μg·mL^{-1} (95% CI, 1.24–1.34) when dexmedetomidine (0.4 μg·kg^{-1}·h^{-1}) was concomitantly infused. The data can be a reference concentration for maintaining adequate anesthetic depth for GA in patients during MER.

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