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Original Article

Neurophysiological comparisons of subthalamic deep-brain stimulation for Parkinson's disease between patients receiving general and local anesthesia

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ABSTRACT

Objectives: Subthalamic nucleus deep-brain stimulation (STN-DBS) is suggested as a standard treatment for patients with Parkinson's disease (PD) and drug-related side effects. Most centers perform the operation under local anesthesia (LA) to ensure better microelectrode recording (MER). Given the advances in imaging and MER, general anesthesia (GA) is perceived as an alternative choice for PD patients undergoing STN-DBS. However, the outcomes in terms of clinical symptoms and MER after GA have rarely been reported. In this report, we compared the outcomes after STN-DBS for PD between patients receiving LA and GA.

Materials and Methods: We included 16 patients with comparable severity of PD undergoing either GA ($n = 8$) or LA ($n = 8$) for STN-DBS. MER was performed in all patients for STN localization, and surgical outcomes were evaluated using the Unified PD Rating Scales, and Mini-mental status examination. All adverse effects were documented.

Results: Both groups (GA and LA) acquired similar benefits from STN-DBS, and there were no significant differences in neuropsychiatric outcome analysis between groups. There were no significant differences in stimulation parameters and adverse effects from STN-DBS between groups. The GA group had a trend toward a lower frequency rate of STN firing on MER.

Conclusion: Although the GA group has a lower neuronal firing frequency in the STN during surgery, STN-DBS under GA showed comparable and non-inferior outcomes as compared with STN-DBS under LA.

1. Introduction

The efficacy of subthalamic nucleus deep-brain stimulation (STN-DBS) for Parkinson's disease (PD) has been well documented in long-term follow-up studies. It offers patients with medication-related side effects a better quality of life as compared with using medication alone [1,2]. Given the imperative role of the electrode position within the target nucleus for DBS, delineation of the “intraventricular” nuclei with imaging and detailed electrophysiological mapping with microelectrode recording (MER) are the most powerful tools available to improve surgical outcomes [3]. Adverse effects from STN-DBS are rare and most can be improved with adjustment of the DBS parameters.

DBS for neuropsychiatric diseases is usually performed in awake patients under local anesthesia (LA) to provide the most accurate neural characteristics of the target nucleus. However, intraoperative safety risks and postoperative psychosis, although rare, increase in awake patients undergoing long cranial surgeries [4]. It is still debated whether neuromodulation surgery with intraoperative electrophysiological localization could be performed under general anesthesia (GA). There is a paucity of reports directly comparing PD symptoms after STN-DBS between patients who had GA or LA.

Conflicts of interest: none.

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Previous reports demonstrated that intravenous sedation with propofol led to significant damping of MER during STN-DBS for PD [5]. In our previous study, we showed that inhalation anesthetics could ensure adequate recording of neural firing during STN-DBS. We therefore analyzed clinical and electrophysiological outcomes between PD patients who had GA or LA [6].

2. Materials and methods

2.1. Patient selection

From January 2010 to December 2014, 16 PD patients who underwent bilateral STN-DBS at Tzu Chi General Hospital, Hualien, Taiwan were enrolled in this comparison study. Eight were assigned to the GA group and received desflurane GA with endotracheal intubation during bilateral STN-electrode implantation, and eight patients were assigned to the LA group and received regional anesthesia in the scalp. The type of anesthesia was determined by patient preference after comprehensive explanation of the pros and cons of different anesthetic strategies. Considerations in choosing the anesthetic method generally included ability of the patient to stay alert and cooperate during the entire DBS procedure and risks of GA in terms of medical status. The inclusion criteria for PD patients included: (1) significant positive response on a levodopa test [United PD Rating Scale (UPDRS) part III > 30% improvement in score]; (2) preoperative brain magnetic resonance imaging (MRI) ruling out structural abnormalities (i.e., stroke, traumatic brain injury, encephalopathy, etc.) and showing cerebral vasculature; and (3) no active psychiatric or severe medical diseases. This study was approved by the Institutional Review Board of Tzu Chi General Hospital (No. 103-09-B).

2.2. Preoperative imaging planning

Before the date of operation, cranial images were obtained with a 1.5-tesla magnetic resonance (MR) unit (General Electric, Rahway, NJ, USA). The standard settings comprised T1-weighted axial images at 0.75-mm thickness, T2-weighted axial images at 2-mm thickness, and T1-weighted images with contrast (delineation of vasculature in cases of inadvertent injury). Each of these sequences was performed in contiguous axial slices. The images were transferred to the Stealth neuronavigation workstation (Medtronic, Minneapolis, MN, USA). The image fusion software fused all three sets of MR images. The tentative surgical target coordinates for the tip of the permanent implantable electrode were set at the central lowest border of the STN by direct visualization from brain MRI (direct targeting) and adjusted according to the relative position of the anterior commissure–posterior commissure (AC-PC) line and red nucleus (indirect targeting).

2.3. Stereotactic and anesthetic procedure

On the morning of the operation, a Leksell G-frame (Elekta Instrument Inc., Norcross, GA, USA) was applied under LA with the patient sitting in a chair. Both groups of patients (GA and LA) were then given computed tomography (CT) examinations. The CT images were fused on preoperative MRI to determine target coordinates. Patients in the LA group were placed in the supine position with the head of the bed elevated at 30°. GA was induced in the other group of patients by administration of regular narcotic agents and a muscle relaxant. After intubation, patients were maintained by desflurane inhalation during the entire surgical course. The depth of anesthesia was maintained at 0.5–1.0 minimal alveolar concentration, so the patient would not experience a cough reflex or any change in heart rate or blood pressure during the MER procedure [6].

Table 1
Pre-operative status between GA and LA.

Clinical demographics	GA ($n = 8$)	LA ($n = 8$)
Age of onset, y	49.6 ± 7.1	41.1 ± 10.2
Disease duration, y	9.3 ± 2.4	12.4 ± 9.2
Pre-op Levodopa response (%)		
Part I	39.9 ± 27.7	30.0 ± 13.9
Part II	54.3 ± 30.1	49.0 ± 27.1
Part III	41.7 ± 29.4	39.9 ± 16.3
Brady	41.5 ± 21.0	32.3 ± 17.3
Tremor	33.8 ± 67.4	39.3 ± 44.4
Rigidity	49.2 ± 43.3	54.3 ± 23.4
Posture & Gait	41.9 ± 29.4	43.1 ± 27
Axial	35.7 ± 25.6	34.4 ± 22.3
Total	41.1 ± 25.9	35.2 ± 13.2
Part IV score	6.1 ± 3.1	4.6 ± 3.5
H&Y stage[a]	3.0 ± 0.5	2.9 ± 0.6
SEADL score[a] (%)	68.8 ± 18.9	66.3 ± 17.7

Data are presented as mean ± standard deviation.
GA = general anesthesia; H&Y = Hohen and Yahr; LA = local anesthesia; SEADL = Schwab and England activity of daily living score; STN-DBS = subthalamic nucleus deep-brain stimulation; UPDRS = unified Parkinson's Disease rating scale.
[a] H&Y stage and SEADL were expressed in Med off status.

2.4. MER procedure

Neural firings obtained from the tip of the microelectrode (FHC, Bowdoin, ME, USA) were sent to the intraoperative MER system (Leadpoint; Medtronic) where they were magnified and displayed. The sampling rate was 24 kHz. For both groups of patients, passive movement of the contralateral limb was tested during MER in the STN to observe whether there were any movement-related neuronal firing changes. The selection of the final trajectory for electrode implantation depended on adequate length of STN hyperactivity neuronal firing and the presence of movement-related firing-pattern changes. In the LA group, stimulation of up to ~4–5 V was done to test for adverse effects and the immediate effectiveness of each individual electrode. We did not perform any intraoperative test stimulation in the GA group.

Table 2
STN-DBS effectiveness (%) between preoperative and postoperative status in both groups.

	GA	p[a]	LA	p[a]
Part I	36.2 ± 31.7	0.0127 *	35.7 ± 15.9	0.0053 **
Part II	41.8 ± 51.0	0.0102 *	49.2 ± 26.6	0.0028 **
Part III	41.5 ± 35.8	0.0008 **	45.8 ± 26.2	0.0003 **
Brady	31.0 ± 10.1	0.0013 **	33.5 ± 25.8	0.0016 **
Tremor	69.8 ± 38.5	0.0082 **	76.2 ± 38.1	0.0085 **
Rigidity	59.0 ± 1.9	0.0028 **	61.3 ± 38.2	0.0056 **
Posture & Gait	29.7 ± 32.8	0.0080 **	33.3 ± 33.2	0.0199 *
Axial	34.0 ± 35.0	0.0109 *	31.9 ± 40.3	0.0094 **
Part IV	43.3 ± 0.6	0.0050 **	39.5 ± 4.9	0.0100 *
Total	38.5 ± 41.7	0.0013 **	46.0 ± 30.9	0.0006 **
Hoehn & Yahr Stage	28.1 ± 23.7	0.0050 **	32.2 ± 20.2	0.0479 *
SEADL Score	73.8 ± 11.9	0.0038 **	86.3 ± 10.6	0.0035 **

Data are presented as mean ± standard deviation.
* $p < 0.05$.
** $p < 0.01$.
GA = general anesthesia; H&Y = Hohen and Yahr; LA = local anesthesia; SEADL = Schwab and England activity of daily living score; STN-DBS = subthalamic nucleus deep-brain stimulation.
[a] The p–value represents a comparison to preoperative status.

Table 3
Stimulation parameters between GA and LA.

	LA							
	Amp Ch1	Amp Ch2	PW Ch1	PW Ch2	Rate Ch1	Rate Ch2	Ch1	Ch2
1	3.3	3.3	60	60	130	130	1-C+	1-C+
2	3.7	3.8	60	60	130	130	1-C+	1-C+
3	2.1	3.6	60	60	130	130	1-C+	2-C+
4	3.3	3.8	60	60	145	145	1-C+	1-C+
5	3.4	4.2	60	60	130	130	1-C+	1-C+
6	2.9	4	60	60	130	130	1-C+	1-C+
7	2.1	3.8	60	60	130	130	1-C+	2-C+
8	3.9	3.5	60	60	130	130	1-C+	1-C+
Mean	3.1	3.8	60.0	60.0	131.9	131.9		
SD	0.7	0.3	0.0	0.0	5.3	5.3		
	GA							
1	3.1	3.3	60	60	100	100	1-C+	0-C+
2	3.3	1.8	60	60	130	130	2-C+	1-C+
3	3.5	3.7	60	60	100	100	1-C+	2-C+
4	3.5	3.2	60	60	130	100	1-C+	1-C+
5	3.4	3.7	60	60	130	130	1-C+	1-C+
6	3.5	3	60	60	130	130	0-C+	1-C+
7	3.5	3.9	60	60	130	130	1-C+	2-C+
8	2.8	2.8	60	60	130	130	1-C+	1-C+
Mean	3.3	3.2	60.0	60.0	122.5	118.8		
SD	0.3	0.7	0	0	13.9	15.5		

Amp = amplitude (voltage); Ch1 = channel 1 (left electrode); Ch2 = channel 2 (right electrode); GA = general anesthesia; LA = local anesthesia; PW = pulse wide (microseconds); Rate = hertz; SD = standard deviation.

2.5. Postoperative care and localization of stimulation electrode

Brain CT imaging was obtained immediately after the operation in both groups to exclude intracranial hemorrhage and to verify the initial postoperative electrode coordinates. A pulse generator was usually implanted 1 week after electrode implantation. A postoperative active-stimulation test was performed to identify the maximal effectiveness of contact and related adverse effects.

2.6. Clinical outcome analysis

We conducted visits with all patients at the last follow-up after implanting the DBS electrodes. Each patient was evaluated with the UPDRS under four different conditions. The medication off condition (Med-off) was defined as when a patient had not taken antiparkinsonian medication for at least 12 hours. The DBS off condition (DBS-off) was defined as when a patient had not received DBS for 4 hours or for the time of tolerance of the patient (sometimes < 4 hours due to intolerable symptoms).

To evaluate the effectiveness of STN-DBS or medications, we compared postoperative UPDRS scores between patients with DBS on/Med off and those with DBS off/Med off. The extent to which a patient benefitted from the operation was defined as the percentage of change in the difference between UPDRS scores. Neuropsychiatric function was evaluated using the Mini-Mental Status Examination (MMSE), Cognitive Abilities Screening Instrument (CASI), and Beck Depression Inventory (BDI).

Table 4
MER characteristics between GA and LA.

	GA	LA	*p*
Firing frequency	34.40 ± 26.16	40.5 ± 20.33	0.09
CV of ISI	1.22 ± 0.33	1.12 ± 0.23	0.56
AI of ISI	0.25 ± 0.15	0.30 ± 0.12	0.21

AI = asymmetric index; CV = coefficient of variance; GA = general anesthesia; ISI = interspike interval; LA = local anesthesia; MER = microelectrode recording.

2.7. MER outcome analysis

The raw data from MER from the 16 PD patients were exported from the LeadPoint software (Medtronic). Only those recording tracts utilized as the final electrode-implantation site were harvested for off-line analysis. We used Spike2 software (version 5.0; Cambridge Electronic Design, Cambridge, UK) to perform spike sorting, and firing frequencies of individual STN neurons, as well as correlation variance and interspike intervals, were calculated from Neuroexplorer (version 4; Nex Technologies, Boston, MA, USA).

2.8. Statistical analysis

Paired Student *t* test was used for comparing characteristics between the two groups and preoperative and versus postoperative outcomes. Significance was set at $p < 0.05$ for all tests.

3. Results

Although there were no differences in demographic characteristics, preoperative patients in the LA group seemed to be younger than those in the GA group (Table 1). The two groups had comparable preoperative disease severity (disease duration, scores for UPDRS parts I–IV, and Hoehn and Yahr staging).

At the last follow-up after the operation, both groups showed significant improvement from bilateral STN-DBS in UPDRS total scores and scores for parts I–IV (Table 2). There were also significant reductions in the Levodopa equivalent daily dose (LEDD) and a reduction in motor complications (UPDRS part IV) in both groups. Analysis did not reveal a significant difference in the effectiveness of STN-DBS between groups. Postoperative neuropsychological evaluation (GA vs. LA) showed similar results for the MMSE (25.8 ± 4.0 vs. 27.7 ± 1.4), CASI-II (84.7 ± 14.6 vs. 91.3 ± 10.0), and BDI (12.0 ± 8.2 vs. 16.7 ± 14.6).

Stimulation parameters of STN-DBS showed nearly the same results in both groups for amplitude, pulse width, and rate ($p > 0.05$; Table 3). The mean coordinates for the postoperative-stimulation electrodes were similar in the two groups, as well.

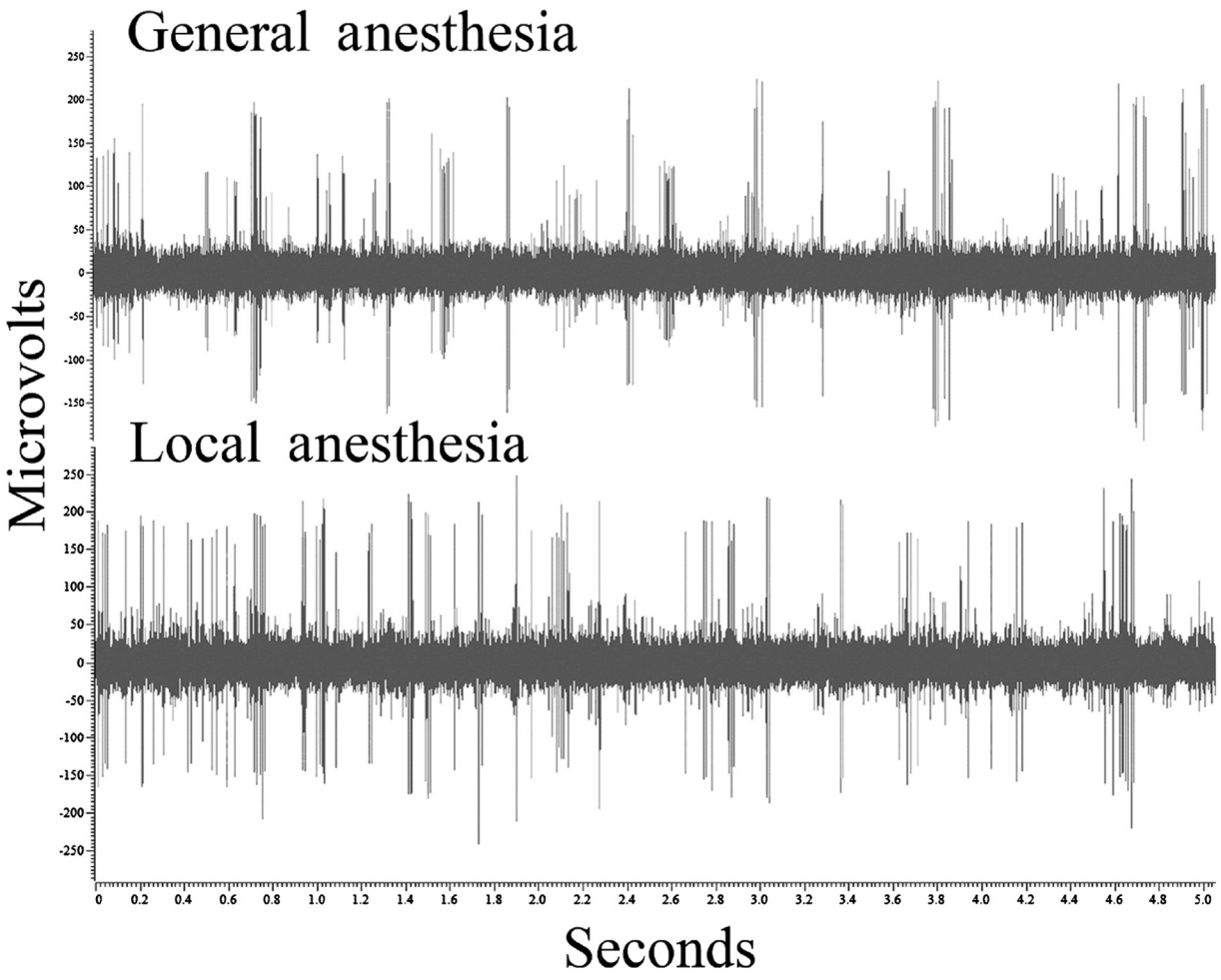

Fig. 1. Representative raw neuronal firings from the subthalamic nucleus in patients with Parkinson's disease under general and local anesthesia.

Coordinates according to the AC-PC line in the GA group were X = 10.96 ± 0.69, Y = −2.46 ± 0.52, and Z = −5.96 ± 0, and in the LA group were X = 10.69 ± 0.39, Y = −2.33 ± 0.42, and Z = −5.06 ± 0.63.

Firing frequencies in the STN tended to be higher in the LA group as compared with those in the GA group ($p < 0.1$); however, both the coefficients of variance and interspike intervals were not much different between groups (Table 4, Fig. 1). Postoperative adverse effects were similar.

4. Discussion

Our results first showed that PD patients can have significant improvement in motor disability under conditioned-inhalation GA, and that this benefit was similar compared with patients under LA STN-DBS. Although the GA group seemed to have lower firing frequencies in STN neurons during MER, other signatures of neural firing did not obviate justification of the STN position to ensure the optimal position of electrodes. Based on our knowledge, our reports are the first to provide direct comparison of clinical and electrophysiological outcomes between GA and LA methods for STN-DBS in a PD patient cohort in a single center.

While STN-DBS performed under LA has been the mainstream for PD to ensure accurate MER recording and intraoperative-test stimulation, several reports demonstrated the sustained long-term effectiveness of STN-DBS under GA [7–10]. UPDRS part III scores could be improved significantly by STN-DBS under LA, and the extent of improvement has ranged from 45% to 50% [9,11]. However, Fluchere et al [12] demonstrated significant sustained benefits after 5 years of STN-DBS (improvement of UPDRS III score in Med off/DBS on was 61% at 1 year and 37% at 5 years) in a large cohort of PD patients under controlled GA STN-DBS. If we included those outcomes of GA STN-DBS at other centers, the UPDRS part III outcome improved from 32% to 63% [13]. These achievements are similar to those observed from STN-DBS performed under LA. Our single-institution report not only showed direct comparison of consecutive PD patients under standard surgical procedures (except anesthetic modality), but also confirmed non-inferiority of the efficacy of the GA method (improvement of UPDRS III score in Med off/DBS on at 5 years was 43.2% in GA vs. 46.8% in LA). Between-groups analysis also revealed a similar percentage improvement in LEDD reduction. Both groups had similar stimulation parameters postoperatively.

In addition to the general risks of cranial surgery, most adverse effects after STN-DBS are attributed to misplacement of DBS or current diffusion from stimulating contact [14]. Misplacement or deviation of DBS electrodes is difficult to identify under GA. To achieve a maximal clinical outcome, the STN-DBS operation involves implantation of electrodes with electrophysiological refinement and an intraoperative macrostimulation test with immediate patient feedback [15]. Both have been claimed as caveats for DBS under sedatives. Our results of stimulation parameters, active-contact coordinates, and similar adverse effects all indicated similar surgical outcomes for the LA and GA groups. Misplaced

trajectory of MER may lead to more recording time and associated risks. Additionally, suboptimal placement of DBS electrodes usually leads to adverse effects from stimulation due to current diffusion or higher power consumption [16]. Given the advances in imaging modalities and neurophysiological recording, controlled anesthesia may provide patients a safe, comfortable operation without compromising surgical benefits [17–19].

In our previous report, we found that MER can be accurately recorded in PD patients under inhalation GA with clinical outcomes similar to those in STN-DBS performed under LA [6]. Although propofol can be safely used for STN-DBS, it was shown to dramatically decrease neural activity in the STN [5,17]. The effectiveness of postoperative outcomes in patients given a combination of ketamine and remifentanil for GA STN-DBS were similar to those under LA, and there were also no significant differences in neurophysiological parameters [20]. However, ketamine has been associated with increased intracranial pressure, which is dose-responsive. Therefore, ketamine must be carefully titrated in intracranial operations, and it is usually combined with other inhalation anesthetics [21]. We only administered inhalation anesthetics (desflurane) as maintenance anesthesia during STN-DBS. Although the firing frequency of STN neurons was lower in the GA group, other neurophysiological outcomes did not show much difference from the LA group. This further highlighted the reliability of using inhalation anesthetics for DBS without compromising electrophysiological recording [18].

Advances in brain-imaging techniques (especially intraoperative ones) have been claimed to preclude use of MER and its rare associated risks [22]. Deciphering the neural underpinning of PD neurophysiology could provide a clearer picture for optimized stimulation adjustment. Several centers have tried performing off-line analysis of neural recording to predict or start individualized stimulation-parameter combinations before adjusting them based on clinician experience and patient-trial responses [23]. However, STN-DBS under GA enables neuroscientists or clinicians to record the detailed neurophysiology of the STN while the patient is unconscious. This provides an opportunity to better understand how inhalation anesthetics influence single-neuron recording analysis [24].

Limitations of this study include its non-randomized nature. We tried to include patients with similar disease severity in the two groups. Additionally, patients all underwent stringent, blinded preoperative evaluation by other movement specialists, which should eliminate some selection bias. Also, the number of patients in both groups was small.

We believe that the STN-DBS operation using LA allows successful MER and a convincing intraoperative-macrostimulation test. Our study provided direct evidence of the similar effectiveness of STN DBS using GA (with inhalation anesthetics) as compared with LA for PD patients in a single-hospital experience. We can provide more options in surgical methods for PD patients to facilitate widespread benefits from neuromodulation operations.

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