Propofol Reduces Microelectrode-Recording Artefacts caused by Parkinsonian Tremor during Deep Brain Stimulation

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Abstract

A 51-year-old male with medically refractory Parkinson's disease was scheduled for bilateral deep brain stimulation (DBS). During microelectrode recordings (MERs) of right side DBS, the patient developed severe sustained whole-body tremors causing severe artefacts in MER. The right side DBS electrode was inserted with suboptimal MER. For the creation of left burr hole, propofol infusion at a rate of 20 µg/kg/min, was used and soon after, all tremor activity ceased. Propofol infusion was continued during left side MER. With the absence of tremors, left subthalamic nucleus spike activity was better identified and neurological testing could take place. At 6 months after DBS, the patient's symptoms had improved significantly without the need for levodopa.

Keywords
- a tremor effect
- deep brain stimulation
- Parkinson's disease
- propofol

Introduction

The anesthetic goals for deep brain stimulation (DBS) are to ensure patient comfort for insertion of electrodes through burr holes while avoiding all drugs that interfere with microelectrode recordings (MERs) and macrostimulation. There are few studies which examine the effects of anesthetic drugs on MER during deep brain nucleus (DBN) localisation. This has led some neurosurgical teams to totally avoid sedation, especially propofol, during DBS. We would like to report a case, however, where the anti tremor effect of propofol was used to facilitate MER.

The patient gave written permission for the authors to publish the report.

Case Report

A 51-year-old male with medically refractory Parkinson's disease (PD) was scheduled for bilateral DBS under conscious sedation. Despite taking levodopa of 125 mg and amantadine of 100 mg twice daily, he suffered severe resting tremor in all limbs affecting his daily activities. The parkinsonian drugs were withheld on the day of surgery. He had no other significant medical history.

A Leksell stereotactic frame was placed on the patient using a local anesthetic to pin sites before computed tomography scan of the head and transferred to the operation room. No premedication was given. The standard monitoring, including electrocardiogram, pulse oximetry, and non invasive blood pressure monitoring were used. Propofol infusion (30-50 µg/kg/min) was used for sedation during the creation of first burr hole on the right side. Twenty minutes before MER, propofol was stopped in accordance with our institution's protocol, to avoid possible interference with MER. During MER, the patient developed severe sustained whole-body tremors leading to violent shaking of the Leksell head frame and operating table. The tremors caused so many artefacts in the MER that they prevented identification of the inferior border of the right subthalamic nucleus (STN) (►**Fig. 1**). MER was suboptimal despite 45 min of mapping with repeated trajectories. The final placement of the right

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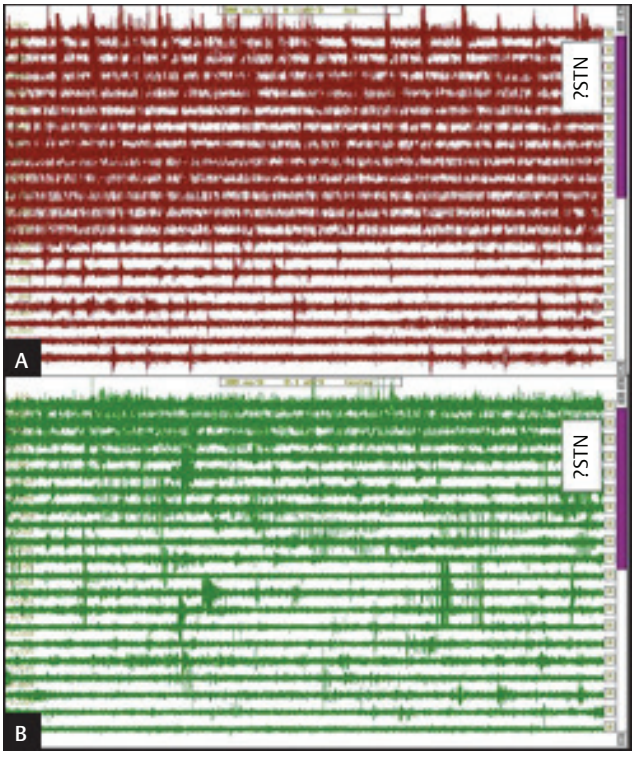

Fig. 1 (**A**) Right hemispheric anterior microelectrode shows excessive tremor artefacts throughout the entire length of the recording. The superior subthalamic nucleus is detected 1.5 mm above target. Inferior border of subthalamic nucleus is not detected, (**B**) Right hemispheric center microelectrode shows excessive tremor artefacts throughout the entire length of the recording. The superior subthalamic nucleus is detected 1 mm above target. Inferior border of subthalamic nucleus is not detected.

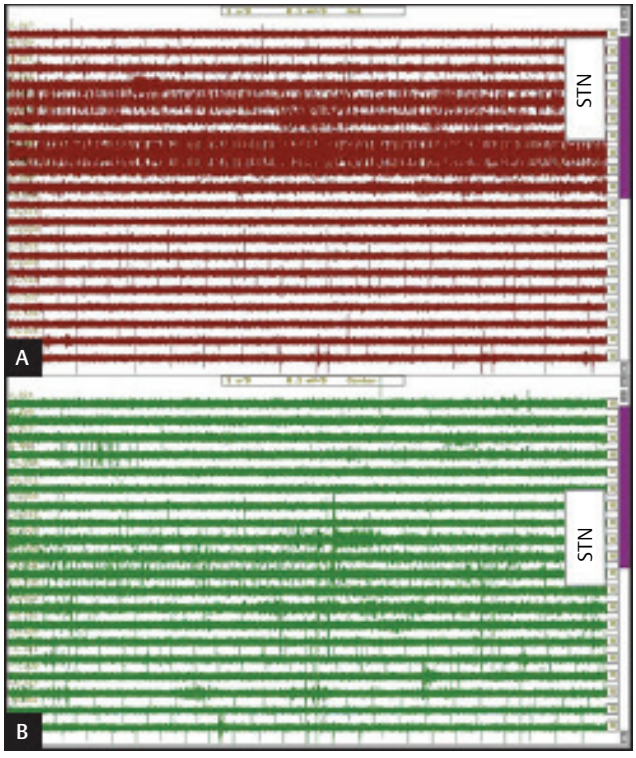

Fig. 2 (**A**) Left hemispheric anterior microelectrode shows fewer tremor artefacts throughout the entire length of the recording. The superior subthalamic nucleus is detected 4 mm above target. Inferior border of subthalamic nucleus is 2 mm above target. (**B**) Left hemispheric center microelectrode shows very few tremor artefacts throughout the entire length of the recording. The superior subthalamic nucleus is detected 0.5 mm below target. Inferior border of subthalamic nucleus is 3.5 mm below target.

DBS electrode was based on the neurological examination with macrostimulation of the electrode.

Propofol infusion at a rate of 30 to 50 µg/kg/min was recommenced for the creation of the left burr hole, and soon after, all tremor activity ceased. A decision was made to continue propofol during MER. With propofol infusion at a rate of 20 µg/kg/min, there was no recurrence of tremor activity, and the patient obeyed verbal commands and spoke fluently. With the absence of tremor artefact in MER, left STN spike activity was better identified (►**Fig. 2**). Then, propofol was stopped to allow the tremor resurface-which it did within 7 min after cessation of propofol. Macrostimulation and neurological testing took place for the final placement of the left DBS electrode. Following this, general anesthesia was instituted for stage 2-tunneling and insertion of the generator.

At 6-months post-DBS, the patient's symptoms had improved significantly, and he was weaned off levodopa.

His simplified Movement Disorders Societies-Unified Parkinson's Disease Rating Scale III, a rating score used by our neurologists, was markedly reduced from 18.5 to 6.5 (stimulation-on; medication off state), equivalent to 65% reduction in symptoms (►**Table 1**).

Discussion

In this case, we observed a reversible anti-Parkinsonian tremor effect associated with the administration of low dose propofol, facilitating MER, which might be helpful in many other DBS cases with a similar intraoperative problem. Spurious movement or tremor can interfere with MER during DBS. Tremor is the most common cardinal symptom in PD, which is found in three-quarter of PD patients.[1] As expected, tremor-related artefacts interfering MER are commonly encountered clinically. In addition, the typical target nucleus (e.g., STN) is only a few millimetres in diameter, precise placement of DBS electrode, a crucial step to achieve desired therapeutic effect, is technically challenging, especially in a patient with severe tremor.[2] DBS electrode placement is a blind procedure; the risks of intracranial hemorrhage or injury to vital structures are correlated to the number of microelectrode trajectories.[3] We would like to use this case as a discussion point to review the current understandings on the anti-Parkinsonian effect of propofol, as well as to discuss the concerns about propofol interferences on MER.

Antitremor Effect of Propofol

Tremor pathophysiology involves complex anatomical pathways between basal ganglia, cerebellar circuits and motor cortex (►**Fig. 3**). Tremor is exhibited as there is increased cerebellothalamocortical circuit activity. For example, dopaminergic depletion of the palladium in PD or gamma-aminobutyric acid (GABA)-ergic dysfunction of the cerebellar dentate nucleus and brain stem in essential tremor (ET) cause hyperactivity of cerebellothalamocortical circuit, resulting in clinical tremor in both diseases.[4]

Table 1 Pre- and postoperative simplified Unified Parkinson's Disease Rating Scale scores in our patient

MDS-UPDRS	Preoperative score with medication-on			Postoperative score with stimulation-on, medication-off		
	Right		Left	Right		Left
Rigidity	1		4.5	1.5		0
Finger tapping	0		2	0		1
Hand movements	0		3	1		0.5
Heel tapping (toe tapping)	0		2	0		1
Tremor	3		2	0		0
Gait		0			0	
Arising from chair		0			1	
Body bradykinesia		0			0.5	
Postural stability		1			0	
Subtotal score	4		13.5	2.5		2.5
UPDRS III score		18.5			6.5	

Abbreviations: MDS, Movement Disorder Society; UPDRS, Unified Parkinson's Disease Rating Scale.

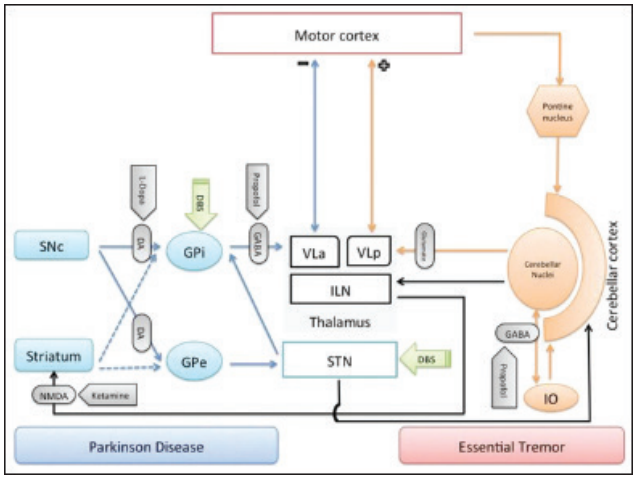

Fig. 3 Pathophysiology of tremor. The basal ganglia and cerebellum have separate pathways to the thalamus. The globus pallidus internus sends inhibitory gamma-aminobutyric acid (GABA)-ergic fibres to the ventrolateral thalamus anterior nucleus (restraining motor cortical activity), whereas the cerebellar nuclei send excitatory glutamatergic innervation to ventrolateral thalamus posterior nucleus (facilitating motor cortical activity). Subthalamic nucleus functions as a connection hub to conduct signals to the motor cortex in tremor pathophysiology. The left side of the diagram illustrates the links between basal ganglia and motor cortex (blue), which are involved in Parkinson's disease. The right side of the diagram demonstrates the links between the cerebellum and motor cortex (orange) that are responsible for essential tremor. Subthalamic nucleus anatomically connects the cerebellum to basal ganglia (black arrow) and is thought to be responsible for the shared tremor mechanisms between Parkinson's disease and essential tremor. deep brain stimulation at deep brain nucleus (subthalamic nucleus, globus pallidus), ketamine, levodopa and propofol reduces the hyperactivity of cerebellothalamocortical circuit, resulting in an antitremor effect (arrows indicating sites of action). GPi, internal part of the globus pallidus; GPe, external part of the globus pallidus; ILN, thalamic intralaminar nucleus; IO, inferior olive; RN, red nucleus; STN, subthalamic nucleus; VLa, anterior part of the ventrolateral thalamus; VLp, posterior part of the ventrolateral thalamus; ILN, thalamic intralaminar nuclei; SNc, substantia nigra pars compacta; DBS, deep brain stimulation; DBN, deep brain nucleus; PD, Parkinson's disease.

The role of GABA in the pathophysiology of tremor is well described in neurology literature, especially in ET. It is interesting to know that GABA agonists, such as primidone, topiramate, gabapentin, and ethanol, are used to treat ET.[5] In contrast to ET, the role of GABA are less well studied in PD and atypical parkinsonian syndromes.[6,7] A previous neuro-radiology study has demonstrated the decrease in [^{11}C]-flumazenil uptake in striatum on positron emission tomography scan, suggesting of GABA depletion, was inversely correlated with the motor symptoms in vascular Parkinsonian patients.[8] Hall *et al.* performed an interesting study in unilaterally symptomatic PD patient using magnetoencephalography (MEG) to characterise neuronal network activity of the primary motor cortex. Following administration of benzodiazepine (0.05 mg/kg of Zolpidem), tremor and other parkinsonism symptoms on the contralateral side were significantly reduced, and less movement-related beta desynchronisation was demonstrated on the MEG.[9] The author concluded that the anti-Parkinsonian tremor effect is acting through GABA activation. In echoing with our case, a previous report described a similar observation that propofol abolished tremor for 8 h in two parkinsonian patients after thalamotomy. In that case, the authors postulated that propofol might act through the GABA receptor in extra-thalamic tremor pathway.[10] With the available evidence, it suggests GABA activation in a certain part of tremor pathway might play a key role in the anti-Parkinsonian tremor effect on PD patients.

Although the precise underlying mechanism of anti-Parkinsonian tremor effect of propofol is not well investigated, it is not uncommon to observe loss of resting tremor in unparalysed PD patients during anesthetic induction in non-DBS procedures, which might thought to be related to cortical suppression. One of the interesting observation in our case is the dose of propofol when anti-Parkinsonian tremor effected, is quite low, which has no interference with DBN activities on

MER. It implied the effective dose for anti-Parkinsonian tremor is much lower than the effective dose for sedation, indicating the differential sensitivity of DBN (subcortical neurons) and cortical neurons towards anesthetic agents. It is also reasonable to question whether other anesthetic agents (GABA agonists) possess the same effect. A previous case report described ketamine abolished tremor and dyskinesia in a PD patient, which postulated to be through N-methyl-D-aspartate receptor activation.[11] Further study is required to evaluate the underlying mechanism, dose-response relationship and whether other anesthetics exert similar effects in the tremor pathway. On the other hand, propofol can also cause myoclonus; however, the dose-response relationship between myoclonus and the anti-tremor effect is yet to be determined.

Concerns of Propofol during Microelectrode Recording

The common methods of DBN localisation include neuronavigation, MER and macrostimulation techniques.

High fidelity magnetic resonance imaging enables generation of highly accurate coordinates to grossly locate the DBN, and placement of DBS electrode is further finely adjusted according to the MER and microstimulation.

MER is typically started at 10 to 15 mm above the targeted nucleus. The electrode is advanced by a microdrive and look for occurrence and disappearance of STN-specific bursting pattern of electrophysiological activity to determine the border of STN. The length of the STN, the presence of movement-responsive neurons, and distance from the STN border to adjacent structures are used as MER criteria to determine the best trajectory for permanent electrode implantation. Since the electrophysiological activities of DBN are very small (50-200 μV) and sensitive to anesthetic agents, anesthetic suppression of MER during placement of electrodes becomes one of the major concerns affecting the accuracy of mapping during DBS.[2]

Macrostimulation, referring to an *in vivo* test stimulation of deep brain electrode, physical examination is used to check for side effects due to overstimulation of surrounding nucleus and to assess the clinical effect of DBS. A fully awake patient is required to participate neurological examination during macrostimulation. A previous study has showed adjustment of electrode placement after macrostimulation were required in 17%-87% of STN-DBS patients with average target adjustments of 1 to 4 mm.[2] Thus, a highly controlled anesthetics is desirable to achieve the best procedural benefit.

The anesthetic effects on MER are complex. Several factors can modify the effect of anesthetics, including the site of target nuclei (STN, globus pallidus internus [GPi], ventromedial thalamic nucleus), the disease state (PD, ET and dystonia), the severity of the disease (variable degree of neuronal depletion). Following the report that propofol infusions at 50 μg/kg/min significantly decreased STN neuronal activity (-23.2%),[12]

Table 2 Review of patient outcomes following deep brain stimulation using microelectrode recording technique under general anesthesia

Study	Study design	Sample size	Anesthetic agents	UDPRS-III score reduction	LEDD reduction	Conclusion
Kim et al[19]	Comparison study	8	Propofol + remifentanil (one side) LA (the contralateral side)	67%	N/A	No significant difference in the mean firing rate between the left and the right side MERs
Fluchere et al[14]	CS	213	Sevoflurane	61% (1 y) 37% (5 y)	46% (1 y) 49% (5 years)	STN stimulation performed under controlled GA is efficient and has similar short- and long-term motor effects to local anesthesia
Harries et al[15]	CS	82	Isoflurance + N_2O (26 patients) Propofol + remifentanil (56 patients)	22.89 (1 y)	58.1% (1 y)	Satisfactory MER of the STN were able to obtain under GA
Lin et al[16]	CS	10	Desflurance (0.5-1 MAC)	5.42% (6 mo)	N/A	Typical neuronal firing patterns of the STN and substantia pars nigra reticulata were able to observe in all patients
Hertel et al[17]	CS	9	Propofol (0.1-0.2 mg/kg/min) Remifentanil	24%	N/A	All patients had satisfactory MER and STN
Maltête et al[18]	Case-control study	30 (15:15)	Propofol (TCI: 0.8-2 ng/mL)	N/A	N/A	Both GA and LA group has was markedly improved the parkinsonian motor disability score The GA group has higher residual parkinsonian motor score than LA group

Abbreviations: CS, case-series; N/A, not available; GA, general anesthesia; LA, local anesthesia; LEDD, levodopa equivalent dose; UDPRS, Unified Parkinson's Disease Rating Scale; TCI, target controlled infusion; MERs, microelectrode recordings; STN, subthalamic nucleus; MAC, minimum alveolar concentration.

many neurosurgical teams decided to avoid propofol altogether during DBS. There was also similar report about anesthetic suppression (propofol) on MER during GPi-DBS in dystonia patients, where the anesthetic suppression was more pronounced in dystonia patients than PD patients.[13]

In contrast to these reports, there are several case series reporting successful MER and motor outcomes in PD patients undergoing STN-DBS with general anesthesia (propofol or volatile anesthetics) (►**Table 2**).[14-18] Interestingly, all these studies found MER were not affected by controlled general anesthesia and were able to detect bursting STN pattern in all study cases. Although one of the typical features of STN (widening of background noise baseline) were lost during general anesthesia, the overall motor outcomes and symptoms improvement were comparable between general anesthesia and historical controlled data under local anesthesia.[14-18] While anesthetic suppression is a genuine phenomenon; but under controlled general anesthesia condition, presumably a higher dose of anesthetics were used, MER and patient outcomes were no clinical differences based on non-randomized data. The avoidance of propofol or other anesthetic agents on MER in all DBS patients appears to be over-concerned, especially in some patients who might benefit from adequate sedation during this prolonged procedure.

Conclusion

We present an interesting DBS case where low dose propofol infusion suppressed Parkinsonian tremor, facilitated MER and the successful placement of DBS electrodes. Further studies are needed to investigate the dose-response relationship of propofol and if other drugs can facilitate MER during DBS.

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Conflict of interest

None.

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