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Effect of Anesthesia on Microelectrode Recordings During Deep Brain Stimulation Surgery: A Narrative Review

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Abstract: Deep brain stimulation (DBS) is an effective surgical treatment for patients with various neurological and psychiatric disorders. Clinical improvements rely on careful patient selection and accurate electrode placement. A common method for target localization is intraoperative microelectrode recording (MER). To facilitate MER, DBS surgery is traditionally performed under local or regional anesthesia. However, sedation or general anesthesia is sometimes needed for patients who are unable to tolerate the procedure fully awake because of severe motor symptoms, psychological distress, pain, or other forms of discomfort. The effect of anesthetic drugs on MER is controversial but likely depends on the type and dose of a particular anesthetic agent, underlying disease, and surgical target. In this narrative review, we provide an overview of the current literature on the anesthetic drugs most often used for sedation and anesthesia during DBS surgery, with a focus on their effects on MERs.

Key Words: anesthesia, deep brain stimulation, Parkinson disease, movement disorders, microelectrode recordings

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In the last 2 decades, deep brain stimulation (DBS) has become established as an effective and safe treatment for several neurological and neuropsychiatric disorders.[1] It is a staged surgical procedure that involves the application of a stereotactic frame to the skull, stereotactic imaging, and placement of intracranial electrodes in deep brain structures, followed by lead internalization and pulse generator placement.[2] The degree of clinical improvement depends on appropriate patient selection and optimal electrode placement. The target is primarily defined by high-resolution imaging techniques performed preoperatively. In addition, microelectrode recordings (MERs) are used during electrode placement to accurately identify the location of the anatomic target.

MER is performed by stepwise insertion of one or more microelectrodes toward the target region. At each step, multiunit activity is assessed and classified. The variation in spontaneous firing and background activity is used to localize the specific brain target. Some neurophysiologists also assess responses to the motor or sensory stimuli to assist target localization. After identification of the brain target, test stimulation is generally performed to assess the clinical effect and side effects to define the therapeutic window.[3] In a recent study, intraoperative MER identified that the predefined target (by imaging) was suboptimal in >20% of cases, and a different trajectory was chosen for final electrode placement.[4] Nonetheless, whether MER increases the accuracy of DBS lead placement remains a matter of debate. This, however, is not within the scope of this review.

Historically, DBS is performed under local and/or regional analgesia to obtain reliable MER. During the procedure, patients may experience stress due to severe motor symptoms, pain, anxiety, or other forms of discomfort,[5] and this may result in hypertensive episodes that increase the risk of intracerebral hemorrhage.[6] To enable a comfortable and safe procedure, sedation or general anesthesia is required in some patients. There are concerns about the effects of anesthetic drugs on MER. Most commonly used anesthetic agents have direct or indirect agonistic actions on gamma-aminobutyric acid type A ($GABA_A$) receptors, and thereby potentially alter neuronal firing. In addition, other classes of anesthetic agents, such as α_2-agonists or opioids, may interfere with MER through other mechanisms. Understanding the extent to which anesthesia or sedation affects MER is crucial for correct interpretation of intraoperative neurophysiological recordings.

The aim of this narrative review is to determine whether anesthetics can be administered without adversely impacting MER during DBS surgery. We provide an overview of the current literature on the effect of anesthetics on MER quality and highlight knowledge gaps.

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METHODS

Multiple reports have been published on the effects of anesthetic drugs on electrophysiological mapping. A limitation of most is the discontinuation of anesthetic agents before the start of MER to enable optimal testing. Consequently, no firm conclusions with respect to the effects of anesthetic agents on MER can be made from such studies. We therefore only included studies in which anesthesia was continued during MER in this review.

A PubMed search was performed for articles published between 2003 and June 30, 2018. The following MeSH Terms were used: "Anesthesia," "Deep Brain Stimulation," "Microelectrode recordings," "General anesthesia," "Sedation," "Propofol," "Opioids," "Remifentanil," "Volatile anesthesia," "Sevoflurane," "Desflurane," "Isoflurane," "Dexmedetomidine." Further studies were identified by examining the reference lists of all included articles. Only studies that fulfilled the following criteria were included in the review: (1) continuous administration of intravenous or volatile anesthesia during MER registration for DBS surgery; (2) adequate documentation of anesthetic agents used during MER; (3) qualitative analysis of MER; (4) human participants older than 18 years of age and; (5) reports in English language only. Thirty-four abstracts were identified from the database search, and 23 manuscripts fulfilled the inclusion criteria.

All articles were reviewed independently by 2 investigators (M.J.B. and M.L.F.J.) and assigned a level of evidence using the Oxford Centre for Evidence-based Medicine guidelines for therapy.[7] Because of a lack of level I and II evidence, case series (level IV) and case reports (level V) were included (Table 1).

RESULTS

Propofol

Propofol is the most frequently used agent for sedation or general anesthesia during DBS surgery. It has sedative, anxiolytic, and amnestic properties, with few side effects. It provides ease of titration to a desired level of sedation, and has a rapid onset and offset of action, with minimal residual sedation.[31] A disadvantage of propofol administration during DBS surgery is its mechanism of action. Propofol potentiates the response to GABA of the GABA-receptor, and directly activates the $GABA_A$-receptor in a dose-dependent manner. Activation of $GABA_A$-receptors leads to inward movement of predominantly chloride ions, resulting in cell membrane hyperpolarization, shunting of excitatory input, and reduced excitability of neurons that potentially hinder proper assessment and classification of MER. The effect of propofol on MER depends on the amount of GABAergic innervation of the neurons studied. Subcortical nuclei vary in GABAergic cell populations. For example, the external globus pallidus (GPe), internal globus pallidus (GPi), and substantia nigra neurons are GABAergic, whereas the subthalamic nucleus (STN) consists of glutamatergic neurons. As a consequence, there might be differences in MER on the basis of the action of propofol between basal ganglia nuclei.[32–34]

Two studies have addressed the effects of propofol on pallidal neurons in patients with dystonia.[8,9] In a case study of 11 patients with segmental and generalized dystonia, 3 received propofol sedation varying from a single dose to infusion at 3 mg/kg/h.[8] Patients who received propofol showed a typical dose-related slow rate of firing and long pauses of activity in GPi and GPe neurons. In another study, the effect of propofol was determined in patients with dystonia who underwent MER under general anesthesia.[9] Six patients who received propofol (3 propofol 6 to 7.2 mg/kg/h as the sole agent, and 3 propofol 3 to 4.5 mg/kg/h with remifentanil 0.05 μg/kg/min) during MER were matched with 8 patients who received no sedation during the procedure. Spontaneous and evoked potentials were suppressed or absent and identification of border cells (transition from GPi to GPe) was more difficult during propofol administration. These studies suggest that the administration of propofol is a confounding factor for localization of the GPi and GPe with MER in dystonia, especially in higher doses (>6 mg/kg/h). However, both studies have methodological flaws, including study design and heterogeneity in disease severity, that preclude definitive conclusions.

Most experience has been gained with propofol administration during STN-DBS for patients with Parkinson disease (PD). One of the first studies evaluating the role of anesthetic drugs on outcome in STN-DBS surgery was published in 2004.[10] In this retrospective study, 15 patients with PD underwent MER under sedation with propofol (target-controlled infusion [TCI] range: 0.8 to 2.0 μg/mL) and were compared to 15 patients matched for age and PD severity who were awake during the procedure. The depth of anesthesia was targeted to a Modified Observer Assessment of Alertness/Sedation (OAA/S) score of 3 to 4. Neurophysiological monitoring was used in both groups, although there was no documentation of the effect of anesthesia on neurophysiological parameters. Patients who were awake during surgery showed better clinical improvement after DBS compared with those who were sedated. MacIver et al[11] carried out the first study systematically investigating the effects of propofol on STN neuron discharge in humans with PD. In this study, the patients were fully awake during MER registration and, after stable single-unit recordings were obtained, received either a 0.3 mg/kg bolus of propofol (7 patients) or 0.5 μg/kg remifentanil (4 patients). Propofol prolonged the refractory period of STN neurons without changing the spike amplitude, rise time, or decay time; a slight increase of the background noise was also observed. Remifentanil showed no clear changes in neuronal firing properties. Interestingly, both anesthetic agents produced substantially different effects on STN neuron short-interval discharge activity. These results suggest differential effects of anesthetic drugs on STN neuronal activity related to their different mechanisms of action.[11] This study was followed by an interesting prospective study in which 8 advanced PD patients treated with bilateral STN-DBS served as their own controls.[12] Surgery to the first operated side was performed under awake

TABLE 1. Summary of the Findings of Studies Investigating the Impact of Anesthetic Agents on Microelectrode Electrode Recordings

References	Study Design	LoE	Patients	Disease	Target	Anesthetic Agent	Dose	Anesthesia	Effect of Anesthesia on MER
Hutchison[8]	Retrospective	IV	3	Dystonia	GPi/GPe	Propofol	Range from the single bolus of 70 mg to 3 mg/kg/h	Sedation	Dose-dependent suppression of firing rates and increase in burstiness of GPi neurons
Venkatraghavan[9]	Retrospective	IIIb	6	Dystonia	GPi/GPe	Propofol (3 patients)	6-7.2 mg/kg/h	General	Spontaneous and evoked potential are absent or decreased under propofol > 6 mg/kg/h
						Propofol+remifentanil (3 patients)	3-4.5 mg/kg/h/0.05 μg/kg/min		
Maltête[10]	Retrospective	IIIb	15	PD	STN	Propofol	TCI target 0.8-2.0 μg/mL	Sedation	STN neuronal activity could be obtained, no documentation of MER quality
Maciver[11]	Prospective	IIIb	11	PD	STN	Propofol (7 patients)	0.3 mg/kg (bolus)	Sedation	Both propofol and remifentanil produce minor alterations in STN discharge activity
						Remifentanil (4 patients)	0.05 μg/kg (bolus)		
Kim[12]	Prospective	IIIb	8	PD	STN	Propofol+fentanyl	1.5 mg/kg/h/0.15 μg/kg/h	Sedation	No significant differences in mean firing rate between sedation and awake condition. Bursting patterns more frequently observed under sedation
Lee[13]	Retrospective	IV	16	PD	STN	Propofol+fentanyl	1.5 mg/kg/h/0.15 μg/kg/h	Sedation	MER signals slightly attenuated but STN could be well delineated
Lefaucheur[14]	Retrospective	IIIb	34	PD	STN	Propofol	TCI target 1.5-2.3 μg/mL	General	STN neuronal activity could be obtained, no documentation of MER quality, but no differences, in clinical outcome between awake and sedation group
Duque et al[15]	Retrospective	V	1	PD	STN	Propofol+remifentanil	NA	General	Spontaneous firing patterns of STN and SNr neurons were similar to spontaneous neuronal discharges compared with patients who were operated under awaken conditions
Hertel[16]	Retrospective	IV	9	PD	STN	Propofol	NA	General	STN bursting pattern could be identified, widening of the background baseline noise could not be identified
Moll[17]	Retrospective	IV	11	PD	STN	Propofol+remifentanil	3-9 mg/kg/h/0.05-0.3 μg/kg/min	General	Excessive burst discharges under propofol anesthesia
Raz[18]	Prospective	IIIb	16	PD	STN	Propofol	3 mg/kg/h	General	Spiking activity and background noise significantly decreased
Martinez-Simon[19]	Prospective	IV	9/11	PD	STN/GPi	Propofol	TCI target 0.5-2.5 μg/mL	Sedation	Propofol has a dose-dependent effect on the beta power amplitude
						Dexmedetomidine	0.2 μg/kg/h	Sedation	
Sanghera[20]	Retrospective	IIIb	11/6	PD/dystonia	GPi/GPe	Desflurane	End-tidal concentration 1.5%-4.6%	General	Significant differences in the rates and patterns of discharge of the GPe and GPi neurons in dystonia in PD patients
Lin[21]	Retrospective	IV	10	PD	STN	Desflurane	0.5-1.0 MAC	General	Typical firing pattern of STN and SNr neurons were observed
Lin[22]	Retrospective	IIIb	10	PD	STN	Desflurane	0.6-0.7 MAC	General	Decreased firing frequencies in STN neurons, decrease in power for background activities, the low-frequency oscillation was enhanced
Yamada[23]	Retrospective	IIIb	15	PD	STN	Sevoflurane	End-tidal concentration 1.0%-2.5%	General	No interference with identification of the dorsal and ventral margins of the STN
Alam[24]	Prospective	IIIb	9/6	Dystonia/ Tourette syndrome	GPi	Sevoflurane +remifentanil	End-tidal concentration 1.5%-2.5%/0.1-0.2 μg/kg/min	General	Suppression of mean firing rate and burst activity in the GPi in dystonia patients. Higher firing rate and mean peak frequency in patients with dystonia compared to patients with Tourette syndrome

Harries[25]	Retrospective	IV	26	PD	STN	Isoflurane	NA	General	Good-quality MER of the STN, burst frequency ranged between 25 and 50 Hz, widening of the background noise
Castrioto[26]	Retrospective	IIIb	20	Dystonia	GPi/GPe	Isoflurane	End-tidal concentration 0.3%-0.5%	General	Reduction of firing rates in GPi and GPe under isoflurane anesthesia
Rozet[27]	Retrospective	IIIb	13	PD	STN	Dexmedetomidine	0.3-0.6 μg/kg/h	Sedation	MER unimpaired in every case
Morace[28]	Retrospective	IV	11	PD	STN	Dexmedetomidine	0.3-0.6 μg/kg/h	Sedation	Recognizable STN activity in all cases
Elias[29]	Retrospective	IV	7	PD	STN	Dexmedetomidine	0.1-0.4 μg/kg/h	Sedation	MER unimpaired with dose < 0.5 μg/kg/h
Krishna[30]	Prospective	IIIb	10	PD	STN	Dexmedetomidine	0.1-1.0 μg/kg/h	Sedation	In high dose increase in firing rate and decrease in burstiness, without modulation of beta oscillatory activity

Level of evidence (third column).[7] No level I and II evidence was identified. IIIa, systematic review with homogeneity of case-control studies; IIIb, individual case-control studies; IV, case series (and poor-quality cohort and case-control studies); V, expert opinion.

GPe indicates external globus pallidus; GPi, internal globus pallidus; LoE, level of evidence; MAC, minimal alveolar concentration; MER, microelectrode recordings; NA, not applicable; PD, Parkinson disease; SNr, substantia nigra; STN, subthalamic nucleus; TCI, target-controlled infusion.

conditions while the second side was operated with sedation using propofol (1.5 mg/kg/h) and fentanyl (0.15 μg/kg/h). There was no significant difference in the mean firing rate between both the 2 sides, although a bursting pattern was more frequently observed during sedation. The authors reported that the STN could be identified in both awake and sedated states. Two years later, the same group retrospectively analyzed 16 advanced PD patients who underwent bilateral STN-DBS surgery and received continuous sedation for both sides.[13] MER signals were slightly attenuated, but the STN borders could be identified.

The first documentation of neurophysiological mapping during STN-DBS under general anesthesia with propofol was published in 2008.[14] In this retrospective study, clinical outcome was assessed in 34 PD patients under general anesthesia with propofol (TCI range: 1.5 to 2.3 μg/mL), guided by a bispectral index (BIS) target of 60, and remifentanil infusion 0.05 μg/kg/min, and compared with 20 PD patients who received no anesthesia. There were no clinically relevant differences between groups, suggesting that DBS electrode implantation performed under general anesthesia might not decrease the efficacy of the procedure. However, the group sizes were small in this study; thus, this conclusion should be interpreted with caution. Although perioperative neurophysiological mapping was used in this study, the effects of anesthesia on MER were not discussed.[14] A case report of a PD patient who underwent STN-DBS under BIS-guided anesthesia with propofol and remifentanil supports these findings.[15] At a BIS of 60 to 65, the firing patterns of STN and substantia nigra neurons were similar to spontaneous neuronal discharges in patients with PD operated under awake conditions. In this report, details of the dose of administered anesthetic agents were not provided. In a retrospective case series, 9 patients with advanced PD (mean Hoehn and Yahr status of 4.2) underwent STN-DBS under general anesthesia because excessive fear or severe back pain prevented an awake procedure.[16] Patients received general anesthesia with propofol, and the dose was lowered to 15 to 25 mL/h during MER registration; unfortunately, propofol concentrations were not reported. In all patients, the STN could be identified; typical bursting cells were present with frequencies between 25 and 50 Hz. However, a significant widening of background noise on entering the STN was not present. In addition, clinical improvement was comparable with patients who underwent DBS surgery awake.[16] Similar findings were reported in a case series of 11 PD patients under general anesthesia with propofol (3 to 9 mg/kg/h) and remifentanil (0.05 to 0.3 μg/kg/min).[17] The STN was clearly delineated, although characteristic increases in background noise were not observed. Another study in 16 patients with PD focused on propofol dose and MER.[18] All patients in this study were awake at the beginning of the procedure, and propofol infusion (3 mg/kg/h) was started after STN entry until patients were lightly sedated (measured with either entropy or BIS). Spiking activity and background activity decreased significantly after the

start of propofol infusion. Within 17 minutes after cessation of propofol, STN activity returned to presedation baseline.[18] More recently, a prospective study in 9 PD patients quantified the effect of propofol on basal ganglia neuronal activity with local field potentials (LFPs).[19] LFPs represent the aggregate activity of small populations of neurons through their extracellular potentials. LFP activity was measured during different estimated peak effect-site propofol concentrations (0.5 to 2.5 μg/mL) and compared with a control group; the beta power of LFPs decreased by 12.7% with every increase of 0.5 μg/mL of propofol.

Interpretation of studies investigating the effects of propofol on MER in the STN in PD patients is challenging. Study populations are small, and there is large heterogeneity in dose strategies, with conflicting results. However, the available literature suggests that propofol has a dose-dependent effect on MER, and impacts MER even at low doses (Table 2). The lack of high-quality studies underlines the need for prospective trials to elucidate the optimal propofol dose that balances sufficient patient comfort with minimal impact on MER such that accurate target identification is not affected.

Volatile Anesthetic Agents

The mechanism of action of volatile anesthetic drugs is complex. Most produce generalized slowing but increased the amplitude of electroencephalographic activity.[7] At a molecular level, the presynaptic release of neurotransmitters is influenced and postsynaptic response altered by anesthetic drugs. It is believed that volatile anesthetic agents inhibit excitatory presynaptic channel activity mediated by neuronal nicotinic, serotonergic, and glutaminergic receptors, whereas postsynaptic channel activity is enhanced through $GABA_A$ and glycine receptors.[35] There are few reports in the literature on the use of volatile anesthetic agents during MER in DBS surgery. One of the first, published in 2003, recorded neuronal discharge rates in 15 dystonia patients (11 with desflurane anesthesia and 4 awake) and compared them to a cohort of PD patients undergoing pallidotomy (6 with desflurane anesthesia and 72 awake).[20] Recordings were obtained from putamen, GPi, and GPe neurons. Putamen neurons in both dystonia and PD patients discharged slowly and had irregular discharge patterns, and the effects of anesthesia on neuronal activity were minimal in both groups. Discharge rates of GPe and GPi neurons were also minimally affected in dystonia patients, and there were no significant differences between awake and anesthetized patients. In contrast, there was a significant decrease in discharge rates and a significant increase in the irregularity of discharge in anesthetized compared with awake PD patients. Although criticisms can be made about the methodology of this study, the findings suggest that desflurane anesthesia has a more profound effect on GPi and GPe neuronal activity in PD compared with dystonia patients.[20] Subsequently, a retrospective study of 10 PD patients who underwent STN-DBS surgery with desflurane anesthesia (0.5 to 1.0 minimum alveolar concentration) found that typical firing patterns were observed in both STN and substantia nigra neurons.[21] More recently, desflurane 0.6 to 0.7 minimum alveolar concentration was used for general anesthesia during DBS implantation in 10 patients with PD, and clinical outcomes compared with those of 9 patients who underwent the procedure awake.[22] Desflurane resulted in a decrease in background and spike signal power, and lower firing frequencies, but had no significant effect on single-cell activity in STN neurons. Clinical outcomes on the basis of the Unified Parkinson's Disease Rating Scale were comparable in desflurane and awake groups at 6 months.

One retrospective study investigated the effect of sevoflurane on the neuronal activity of the STN in PD patients.[23] Fifteen patients who received 1.0% to 2.5% sevoflurane and fentanyl were compared with 10 whose procedures were performed under local anesthesia. Characteristic neuronal activity of the STN was recorded in all patients under general anesthesia, and postoperative clinical improvements were

TABLE 2. Summary of the Evidence of the Effect of Anesthetic Agents on Microelectrode Recordings During Deep Brain Stimulation Surgery

Parkinson Disease	Target	Dose	Firing Rate	Burst Discharge	Background Activity	Target Identification	Level of Evidence
Propofol	STN	≤1.5 mg/kg/h	≈	≈	≈	+	C
Dexmedetomidine	STN	≤0.6 μg/kg/h	≈	≈	≈	+	B
Volatile anesthetics							
Desflurane	STN	≤0.6 MAC	≈	?	≈	+	C
Sevoflurane	STN	1.0%-2.5%$	?	?	?	+	C
Dystonia							
Propofol	GPi	3-6 mg/kg/h	↓	↑	?	+/−	C
Volatile anesthetics							
Desflurane	GPi/GPe	1.5%-4.5%$	↓	?	↓	?	C
Sevoflurane	GPi	1.5%-2.5%$	↓	↓	?	?	C
Isoflurane	GPi/GPe	0.3%-0.5%$	↓	↓	?	?	C

Recommendations are classified according to the criteria of the Oxford Centre for Evidence-based Medicine (far right column).[7]

A, consistent level 1 studies; B, consistent level 2 or 3 studies or extrapolations from level 1 studies; C, level 4 studies or extrapolations from level 2 or 3 studies; D, level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

↓ indicates decrease; ↑, increase; +/- , probably; +, possible; $ end-tidal concentration; ?, no available literature; ≈, no clear effect; GPe, external globus pallidus; GPi, internal globus pallidus; MAC, minimum alveolar concentration; MER, microelectrode recordings; STN, subthalamic nucleus.

comparable between the groups. In contrast, sevoflurane resulted in significant differences in neuronal discharges in a study of patients with dystonia and Tourette syndrome (TS) who underwent DBS-GPi under general anesthesia.[24] Nine patients with primary dystonia and 6 with TS received 1.5% to 2.5% sevoflurane and remifentanil 0.1 to 0.2 μg/kg/min; 6 patients with primary dystonia operated under local anesthesia served as controls. Sevoflurane anesthesia suppressed the mean firing rate and burst activity in the GPi in dystonia patients. Of interest were the subtle differences between dystonia and TS patients. Patients with dystonia had a higher firing rate and higher mean peak frequency in bursts compared with those with TS, whereas the average total numbers of bursts and patterns were similar. These findings suggest that the influence of sevoflurane anesthesia on firing characteristics might differ between disease states.

Two retrospective studies investigating the impact of isoflurane anesthesia have been published.[25,26] The first was carried out in 26 PD patients undergoing STN-DBS with isoflurane and nitrous oxide/oxygen anesthesia, although the minimum alveolar concentration of isoflurane during MER was not reported.[25] Nevertheless, the authors noted excellent MER of the STN with good long-term clinical outcomes. In contrast, a more recent study of 20 dystonia patients operated with isoflurane (0.9% to 1.3% end-tidal concentration) and nitrous oxide/oxygen (70%:30%) anesthesia found that both GPi and GPe firing rates were depressed despite a reduction in isoflurane concentration (to 0.3% to 0.5% end-tidal concentration) 10 minutes before starting MER (so that single-unit activity could be observed). The potential impact of nitrous oxide on MER was not discussed.[26]

In summary, the evidence on the effects of volatile anesthetics on MER consists of 8 clinical trials with small sample sizes in which different volatile anesthetic agents and different surgical targets were investigated. Because of this heterogeneity in disease states, targets, and anesthetic agents, it is difficult to draw definitive conclusions on the effects of volatile anesthesia on MER. However, as with propofol, low concentrations of sevoflurane, desflurane, and isoflurane all appear to alter neuronal activity. Moreover, there is evidence that anesthetic effects on target neuronal activity differ between disease states. Therefore, it is premature to conclude that volatile anesthetics can be used safely. We therefore recommend avoiding volatile anesthetics during DBS procedures in which MER is used because there are alternatives that, according to the current literature, can be used more safely.

Dexmedetomidine

The rationale for the use of dexmedetomidine in DBS surgery relates to its mechanism of action. Dexmedetomidine is a specific and selective α_2-adrenoceptor agonist that has sedative, anxiolytics, and antinociceptive effects through activation of central presynaptic and postsynaptic α_2-adrenergic receptors in the locus ceruleus. It has no established effect on GABA-receptors, making it suitable as a sedative during neurophysiological mapping.[36–38] However, there is consistent evidence from animal studies that the STN receives direct noradrenergic innervation.[39,40] In 6-hydroxydopamine-lesioned rodents, local infusion of both α_1-agonists and α_2-agonists affects the firing activity of STN neurons.[41,42] Recently, translational research in PD patients showed involvement of the noradrenergic system in the regulation of the subthalamo-cortical loop.[43] Theoretically, therefore, medication that modulates the noradrenergic system should affect MER during STN-DBS.

Rozet et al[27] were the first to report on the effects of dexmedetomidine on MER. In this retrospective analysis of STN-DBS, MER were recorded during continuous dexmedetomidine infusions in 13 PD patients and compared with those from a control group of 9 patients undergoing the same procedures without sedation. The severity of PD in both groups was comparable. Dexmedetomidine infusion rates were adjusted to an OAA/S score of 4, and the dose range during MER registration was 0.3 to 0.6 μg/kg/h. In all patients, MER was unimpaired by dexmedetomidine infusion. A recent study of 11 PD patients found similar results of typical activity of the STN during dexmedetomidine infusion 0.3 to 0.6 μg/kg/h.[28] These results are in agreement with another retrospective analysis of 7 PD patients who received continuous dexmedetomidine infusion with sedation depth targeted with BIS monitoring.[29] With a dexmedetomidine dose of 0.1 to 0.4 μg/kg/h and BIS > 80, good-quality MER was obtained and was comparable to recordings from patients who were fully awake. However, during higher infusion rates (> 0.5 μg/kg/h) with BIS <80, there was suppression of subthalamic neuronal discharge. In another retrospective report in patients with advanced PD, firing properties of dorsal and ventral STN neurons were examined during continuous dexmedetomidine administration.[30] Seven patients received dexmedetomidine 0.1 to 1.0 μg/kg/h (27 STN cells), and data were compared with those from 11 patients without sedation (29 STN cells). Dexmedetomidine at high doses was associated with an increase in firing rate, but a significant decrease in burstiness. Although a dose-dependent effect was not demonstrated in this study, the authors recommend that high-dose dexmedetomidine should not be used. In addition, the effects of dexmedetomidine on MER were not associated with an altered spike oscillation in the beta frequency band or LFP beta power.[30] These findings are in line with more recently published work in which there were no significant differences in the relative beta power of LPFs between dexmedetomidine 0.2 μg/kg/h in 10 PD patients and control recordings.[19]

On the basis of the limited current literature, most evidence indicates that low-dose dexmedetomidine has only minimal effect on MER. Because of its favorable mechanism of action, it is our opinion that low-dose dexmedetomidine (< 0.6 μg/kg/h) is a safe agent during DBS surgery.

DISCUSSION

DBS surgery is a well-established therapy for symptom control in patients with medically intractable neurological and psychiatric disorders. The optimal effects of DBS rely to a significant extent on accurate identification of surgical targets and accurate positioning of implanted electrodes. Despite rapid advances in modern neuroimaging techniques, recent reports have shown additional

benefits of MER during DBS surgery. MER plays an important role in target localization and confirmation in most centers, and physiological localization of target areas will remain a key part of DBS surgery in the coming decades. As a consequence, the debate on the effect of anesthetic drugs on MER will continue.

The general consensus remains that the use of anesthetic agents should be minimized during MER, although this position is not fully supported by adequate scientific research. The available literature is sparse and consists largely of small uncontrolled retrospective case series, with substantial heterogeneity in patient cohorts, targets, and choice of anesthetic drugs. There is an urgent need for well-designed, controlled trials designed to identify the dose-dependent effects of anesthetics on MER during DBS surgery. The first prospective trials have been registered, and their results, which will provide more guidance for the anesthesiologist to optimize anesthetic management during DBS surgery, are eagerly awaited. On the basis of current evidence, we recommend avoiding anesthetic drugs during MER whenever possible. If sedation is required, low-dose dexmedetomidine should be considered.

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