Effect of Anesthesia on Microelectrode Recordings during Deep Brain Stimulation Surgery in Tourette Syndrome Patients

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Keywords

Anesthesia · Deep brain stimulation · Internal globus pallidus · Microelectrode recordings · Tourette syndrome

Abstract

Background: Deep brain stimulation (DBS) is an accepted treatment for patients with medication-resistant Tourette syndrome (TS). Sedation is commonly required during electrode implantation to attenuate anxiety, pain, and severe tics. Anesthetic agents potentially impair the quality of microelectrode recordings (MER). Little is known about the effect of these anesthetics on MER in patients with TS. We describe our experience with different sedative regimens on MER and tic severity in patients with TS. **Methods:** The clinical records of all TS patients who underwent DBS surgery between 2010 and 2018 were reviewed. Demographic data, stimulation targets, anesthetic agents, perioperative complications, and MER from each hemisphere were collected and analyzed. Single-unit activity was identified by filtering spiking activity from broadband MER data and principal component analysis with K-means clustering. Vocal and mo-

tor tics which caused artifacts in the MER data were manually selected using visual and auditory inspection. **Results:** Six patients underwent bilateral DBS electrode implantation. In all patients, the target was the anterior internal globus pallidus. Patient comfort and hemodynamic and respiratory stability were maintained with conscious sedation with one or more of the following anesthetic drugs: propofol, midazolam, remifentanyl, clonidine, and dexmedetomidine. Good quality MER and clinical testing were obtained in 9 hemispheres of 6 patients. In 3 patients, MER quality was poor on one side. **Conclusion:** Cautiously applied sedative drugs can provide patient comfort, hemodynamic and respiratory stability, and suppress severe tics, with minimal interference with MER.

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Published by S. Karger AG, Basel

Introduction

Tourette syndrome (TS) is a childhood onset neuropsychiatric disorder characterized by involuntary motor and vocal tics. An important characteristic of TS is its as-

sociation with neurobehavioral disorders such as attention deficit hyperactivity disorder and obsessive-compulsive behavior. The presence and severity of these comorbidities has a significant effect on the clinical presentation and hence on quality of life [1, 2].

The majority of patients with TS have a favorable prognosis, with all or most tics disappearing during adolescence. Still, in a small percentage of patients, symptoms get worse and require medical treatment. For this group, treatment strategies consist of cognitive behavioral therapy and/or pharmacological interventions [3]. If the response to both is inadequate, deep brain stimulation (DBS) might be an option for select cases. A recent meta-analysis reported that DBS therapy resulted in a 53% improvement in the Yale Global Tic Severity Scale [4].

The anesthetic approach during DBS procedures varies widely between centers. Traditionally, local anesthesia has been preferred to facilitate microelectrode recordings (MER) and clinical testing to optimize target localization [5, 6]. However, patients may experience anxiety, pain, or other forms of discomfort during DBS surgery. Besides these stress-related factors, TS patients may have severe motor tics, often worsened by anxiety and stress. These make surgery hazardous and increase the risk of perioperative complications (intracranial hemorrhage due to severe hypertension, tachycardia, etc.). Therefore, sedation is often desirable or even needed. There are concerns with the use of sedatives during DBS surgery because of potential effects on quality of MER. Several studies have shown that anesthetic drugs decrease neuronal firing in patients with Parkinson's disease and dystonia [7–10]. The effect on MER appears to be both drug and dose dependent but also varies depending on the underlying disease [11–16]. Therefore, data from DBS patients with Parkinson's disease and dystonia cannot be extrapolated to TS patients. To date, no studies have addressed the effect of anesthetic agents on MER quality in patients with TS. For this aim, we report our experience with different anesthetic drugs on MER quality during DBS implantation in the internal globus pallidus (GPi) in 6 patients with TS.

Materials and Methods

Subjects

We retrospectively reviewed the surgical and anesthetic records of 6 patients with TS who underwent DBS surgery in our institution between January 2010 and January 2018. The clinical outcome of these patients has been reported earlier [17–19]. For the current study, we analyzed patient data, anesthetic drug administration, as well as intraoperative respiratory and hemodynamic variables. Ad-

ditionally, we retrieved the stimulation target, the raw MER and systematically recorded numbers of motor and vocal tics.

Anesthetic Management

All patients underwent a multidisciplinary preoperative assessment to be eligible for DBS surgery. For surgery, standard monitoring was applied including a three-lead electrocardiogram, pulse oximetry, inspiratory and expiratory O₂ and CO₂ analysis, and blood pressure monitoring. DBS surgery was performed under local anesthesia with conscious sedation. The skin puncture sites of the stereotactic frame pins and the surgical incision sites were infiltrated with a 50:50 mixture of lidocaine 1% and levobupivacaine 0.5% with epinephrine (1:100,000). A variety of anesthetic drugs were used at the discretion of the responsible anesthesiologist (Table 1). The anesthesiologists goal was to obtain adequate tic reduction and pain control without affecting the airway reflexes and respiratory or cardiovascular function (Modified Observer's Assessment of Alertness/Sedation score between 0 to –1). Sedation was given as continuous intravenous infusion. After DBS electrode implantation, patients received general anesthesia with either volatile or intravenous anesthetics for tunneling of the extension cables and placement of the pulse generator. Postoperatively, patients were transferred to the postanesthesia care unit for at least 24 h for hemodynamic and neuro-monitoring.

Surgical Procedure

A Leksell stereotactic frame (Elekta, Stockholm, Sweden) was placed. Then, the patient underwent a CT scan with the frame in situ. The CT image was co-registered with a previously performed MRI scan. The following stereotactic coordinates of the anterior part of the GPi were used: 12 mm lateral, 6–9 mm anterior, and 0–3 mm superior to the midcommissural point. Following target identification, a burr hole was drilled in line with the planned trajectory, and multiple-electrode extracellular single-unit MER were performed. After visual and auditory confirmation, macrostimulation and neurological testing were carried out to assess stimulation-induced side effects. Finally, a quadripolar electrode was placed (model 3387 or 3389; Medtronic, Minneapolis, MN, USA) at the optimal level and trajectory with the second deepest contact (contact1) at the level of the pallidal target that gave no side effects or only at highest stimulus intensity. In case MER recordings were poor, electrode placement was based on test stimulation only (for further surgical details, see Smeets et al. [17]). Within 24 h, a postoperative CT scan was made to evaluate the position of the electrodes and to detect nonsymptomatic hemorrhages.

Microelectrode Recordings

Up to 5 microelectrodes were used to record neuronal activity along the trajectory for mapping purposes. Recording took place from 10 mm above target to ≤5.5 mm beneath target in 0.5- or 1.0-mm steps. When the GPi was targeted, the electrode passed through the striatum, external globus pallidus, and finally GPi (Fig. 1). The electrode signal was sampled at 20 or 25 kHz and bandpass filtered online (160–5,000 Hz) (MicroMacroElectrode, ISIS MER; Inomed Medizintechnik GmbH, Emmendingen, Germany) and saved for offline analysis.

Data Processing and Analysis

All analyses were conducted using custom-written MATLAB code (V2012B; MathWorks). To separate spikes representing single

units from spikes representing other neurons or noise, spike waveforms were sorted using principal component analysis and K means clustering. Clusters representing single units were manually selected using visual and auditory inspection and were confirmed as such by inspecting their autocorrelation. Vocal and motor tics that led to recording artifacts were counted by visual and auditory inspection. Tics that were recorded by multiple electrodes were counted once.

The discovery rate of single units and the rate of tics were analyzed for each patient per hemisphere. The discovery rate of single units per site was calculated by taking the total number of single units identified in the hemisphere divided by the total number of recording sites in order to balance the differences between hemisphere and patients. Tic rate was calculated as the number of tics normalized by the total length of recording. The discovery rate was used to classify the hemisphere into poor or good recordings. Hemispheres with a discovery rate higher than 0.1 were considered good, whereas hemispheres with a discovery rate lower than 0.1 were considered poor.

To rule out factors that might contribute to data quality, data were divided into groups according to different characteristics of the population (first and second operated side, age, patients with propofol and without propofol) and applied on ANOVA (repeated measures two-factor ANOVA with patient ID as random factor or one-factor ANOVA with $p < 0.05$ in both cases) to compare tic measures. For neuronal measures (coefficient of variation and spikes per seconds), we used a repeated measurement two-factor ANOVA with depth as random factor with $p < 0.05$.

Results

Patient Demographics, Anesthesia Management, and Electrophysiology

We obtained electrophysiological data and anesthesia records for analysis from 6 patients. The recordings were separated per hemisphere enabling an analysis of the MER per hemisphere, giving a total of 12 different datasets. Demographic data, comorbidities, anesthetic agents used, target and neurophysiological data, vital parameters, and perioperative complications are reported in Table 1. All patients were satisfied with the amount of sedation (Modified Observer's Assessment of Alertness/Sedation score between 0 and -1).

Tic Severity and Quality of Recordings

In total, we obtained 213 single units and registered 213 vocal tics as well as 212 motor tics. The mean tic rate was 2.9 tics/min (3.4 standard deviation) for vocal tics and 3.2/min (4.7 standard deviation) for motor tics. There was no relation between the number of tics and the number of single units found. Some patients with a high number of single units also had a high number of tics. Also, we could not find any relation between the number of single units and the severity of the tics.

Table 1. Demographic data, anesthesia, perioperative hemodynamic and respiratory measurements, as well as target and electrophysiological data from the 6 patients

Patient	Sex	Age, years	Comorbidities	Anesthesia	SBP, mm Hg	Oxygen saturation	Target	Electrodes, n	Hemisphere	MER quality	Total tics	Single units	Average	Preoperative YGTSS	Postoperative YGTSS	Perioperative complications
1	M	54	Atrial fibrillation, hypertension, depression, obesity	Remifentanyl: $0.01-0.02 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ Clonidine: $0.2-0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ Midazolam: $1 \text{ mg}\cdot\text{h}^{-1}$	100-140	94-98%	GPI	5	Left	**	13	17	0.23	46	9	None
									Right	*	4	3	0.04			
2	F	40	Obsessive-compulsive disorder, generalized anxiety disorder, Asperger syndrome	Remifentanyl: $0.08 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	115-120	93-97%	GPI	3	Right	*	11	3	0.07	42	9	None
									Left	**	23	24	0.48			
3	M	55	-	Remifentanyl: $0.01 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ Propofol: $0.75 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$	115-150	94-98%	GPI	5	Right	**	18	37	0.30	40	NA	None
									Left	**	16	19	0.15			
4	M	35	Obesity	Remifentanyl: $0.02-0.03 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ Propofol: $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$	120-150	97-98%	GPI	3	Right	**	99	13	0.13	40	16	None
									Left	**	149	26	0.26			
5	M	18	-	Remifentanyl: $0.12 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	100-150	94-98%	GPI	1	Right	*	184	0	0.00	39	24	None
									Left	**	129	4	0.13			
6	M	19	Depression	Dexmedetomidine: $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$	100-120	99-100%	GPI	3	Right	**	0	19	0.26	32	10	None
									Left	**	4	21	0.28			

GPI, internal globus pallidus; MER, microelectrode recordings; NA, not applicable; SBP, range of systolic blood pressure during deep brain stimulation; YGTSS, Yale Global Tic Severity Scale; * poor quality; ** good quality.

Fig. 1. Case illustration of the DBS electrode position and MER trajectories in the right hemisphere of patient 6. A three-dimensional representation of the striatum (yellow), external globus pallidus (GPe) (green), and GPi (blue) in patient 6 is provided using fusing postoperative CT with the preoperative MR and CT images. The central, medial, and posterior MER trajectories are visualized. The small red and green squares are identified intraoperatively by the neurophysiologist as GPe or GPi activity, respectively. The final position of the DBS electrode (central trajectory) is visualized on the top. The boxes show examples of 2 s of MER activity recorded in the central trajectory. The figure is generated using Suretune software (Medtronic).

For vocal tics, there were significant differences between patients, but not within individual patients between the first or second hemisphere to be operated (patient ID factor: $F(5, 5) = 6.78$, $p = 0.006$; order factor: $F(1, 5) = 1.66$, $p = 0.255$; repeated-measures 2 factor ANOVA with patient ID as random factor). For motor tics, there were no significant differences between patients or sides (patient ID factor: $F(5, 5) = 0.9$, $p = 0.547$; order factor: $F(1, 5) = 0.82$, $p = 0.406$). Therefore, we combined data from the two hemispheres for further analysis of between-patient differences. To test for age differences, we performed a median split of patients. We observed no differences in the rate of vocal or motor tics between age groups (one-factor ANOVA, vocal tics $F(1, 5) = 1.17$, $p = 0.330$; motor tics $F(1, 5) = 0.38$, $p = 0.563$) or between patients with or without propofol (vocal tics, $F(2, 4) = 0.71$, $p = 0.544$, motor tics, $F(2, 4) = 0.76$, $p = 0.525$).

Discussion

In this retrospective study, we analyzed and quantified the effect of anesthetic agents on GPi neuronal activity, tic severity, and vital parameters during DBS surgery in 6 TS patients. The type of anesthetics varied case by case. Overall, in each patient, no sedative drug-related side effects occurred, and adequate patient comfort was

achieved. However, the number of tics and the quality of the MER was highly variable between and within patients (i.e., between hemispheres).

A variety of factors may contribute to poor quality recordings, such as patient-related factors (motor and/or vocal tic severity) or technical problems (design of the electrophysiology setup and data processing) [20]. Another important factor that might contribute to the quality of MER is the use of sedative drugs.

The rationale for sedation in DBS surgery is diverse. During a procedure, patients may experience pain, anxiety, or other forms of discomfort. These factors may lead to intraoperative hypertensive episodes which increase the risk of intracerebral hemorrhage [21]. DBS for TS patients has some specific considerations which warrant consideration of the use of sedation and/or analgesia [11, 22]. First, patients may have severe motor tics, which could become worse in stressful situations. With the patients' head fixed by the stereotactic frame, this may lead to potentially dangerous situations. In addition, the presence of tics may ensure difficulties in neurophysiological mapping as shown in Figure 2. Second, the presence of mental health comorbidities such as attention-deficit hyperactivity disorder and anxiety disorders should be taken into consideration. These comorbidities can become more manifest during the DBS procedure.

While analgesia and sedation are typically desirable, nearly all sedative agents affect the quality of MER. The

Fig. 2. An example of MER is shown. The y-axis represents the depths in millimeters, and the x-axis represents the recording time in seconds. The left figure demonstrates an example of poor-quality recordings with multiple tics and no single units (patient 5). The right figure demonstrates an example of good-quality recordings with few tics and multiple single units (patient 6).

degree of interference depends on the type and dosage of the agents but also on factors, such as disease severity and target nuclei [23, 24]. The depressant influence of sedative agents on neuronal activity can partly be explained by the large amount of gamma-aminobutyric acid (GABA) input to the target nuclei. GABA is an important inhibitory neurotransmitter in the basal ganglia and thalamus. It has been shown that enhancement of GABAergic input, in both human and animal studies, alters the level and pattern of firing activity of pallidal neurons in normal and pathological conditions [24–27]. Anesthetic agents, such as the benzodiazepines and propofol, potentiate the inhibitory actions of GABA and therefore have a major effect on single-cell activity. However, a recent study in dystonia patients has shown that effects of propofol are also dose dependent. In high doses, GPi neuronal firing rates and patterns were more suppressed than with low dose [13].

In our study, 2 patients received a moderate dose of propofol ($<4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) with remifentanyl. In both patients, good quality recordings could be obtained with adequate tic reduction. These findings are in line with results found during GPi DBS in dystonia patients; however, there are no comparable data available in TS patients [13].

In 2 patients, remifentanyl, a pure μ -opioid receptor agonist, was used as a sole sedative agent. The quality of the recordings in these patients varied between the first operated hemisphere and the second. There was no difference in the surgical procedure or anesthesia management that could explain this difference. Therefore, this might be due to physiological aspects of the patient, like tiredness or lower levels of stress, which normally leads to a reduction of the tics. In DBS surgery, remifentanyl is often combined with propofol or dexmedetomidine, as part

of a conscious sedation strategy. Little is known about the effect of remifentanyl on neurophysiological mapping. We are not aware of any studies in which solely remifentanyl was used during DBS surgery in TS patients. In one study, the effect of remifentanyl on MER of the STN showed that there was little effect on neuronal discharges [28]. However, there are also data suggesting that opioids may indirectly modulate GABAergic activity [29].

One patient received a combination of continuous intravenous midazolam, remifentanyl, and clonidine. On one hemisphere, good quality MER could be obtained but, on the other, no good neurophysiological mapping was possible. The general consensus is to avoid the use of benzodiazepines in DBS surgery because they act as direct GABA agonists. Benzodiazepines bind to benzodiazepine-binding sites on GABA_A receptors and allosterically modulate the response of the channel upon GABA binding. As a consequence, the amplitude or decay time of the GABA-mediated inhibitory postsynaptic potential is increased leading to a higher inhibitory tone of GABAergic synapses and a reduction of firing [5, 30–32]. However, the consensus is based on theoretical considerations as clinical studies are lacking.

The effect of benzodiazepines on the GABA receptor are dose dependent which likely explains the good quality of the MER in this patient. As part of a balanced sedation technique, clonidine was also used. Clonidine, an α_2 -agonist, has sedative and analgesic properties. Of interest are the effects of clonidine on the nucleus accumbens. It has been shown that clonidine causes a dose-dependent increase of GABA output [33]. In addition, animal studies have also shown a direct GABAergic projection from the nucleus accumbens to the globus pallidus [34]. Therefore, clonidine may decrease neuronal activity in the globus pallidus; however, we did not observe such effects as neuronal firing remained intact. In this patient, we did not find an explanation for the difference in MER between both hemispheres. The anesthetic agents used should be ruled out as a cause of inadequate registration because no medication adjustment was made during registration of the two sides.

In 1 patient, continuous dexmedetomidine was administered during DBS surgery without reducing the dose during neurological mapping. With dexmedetomidine, the patient was comfortable with adequate tic reduction and good MER quality. Like clonidine, dexmedetomidine is a selective α_2 agonist with sedative, anxiolytic, and analgesic properties without respiratory depression. Dexmedetomidine primarily affects receptors in the locus coeruleus and has minimal effects on

cortical areas [35]. A number of case series in patients with Parkinson's disease has demonstrated the safe use of low-dose dexmedetomidine ($<0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) during STN DBS surgery with minimal effects on MER [8, 14, 16, 36]. At high doses, however, a decrease in bursts has been reported [37]. No clinical studies have been reported on the use of dexmedetomidine and its effects on MER in TS patients so far.

Conclusion

It is a challenging task for the anesthesiologist to strike a balance between adequate tic suppression and preventing or limiting suppression of neuronal activity to enable electrophysiological target identification. This case series suggests that the use of low-dose sedation in TS patients is feasible without impairment of neurophysiological mapping. A patient-specific approach reduces discomfort for the patient and reduces perioperative complications, thereby enabling proper DBS lead placement by the neurosurgeon.

Statement of Ethics

The study was approved by the hospital's institutional review board committee (METC Maastricht University Medical Center, The Netherlands, date of approval December 4, 2018, protocol number 184214).

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

The study received department funds only.

Author Contributions

M.J.B.: Conception and design, drafting the manuscript. A.M.A.S.: Data analysis, drafting the manuscript. A.Y.J.M.S.: Design, critical revision of the manuscript. R.B.: Data analysis, critical revision of the manuscript. L.A.: Design, critical revision of the manuscript. A.R.A.: Design, critical revision of the manuscript. W.F.B.: Conception and design, critical revision of the manuscript. M.J.R.: Data analysis, designed figures, revision of the manuscript. M.L.F.J.: Conception and design, supervised development of the manuscript, drafting the manuscript. All authors gave a final approval of the manuscript before submission.

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