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Deep brain stimulation: Subthalamic nucleus electrophysiological activity in awake and anesthetized patients

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HIGHLIGHTS

- This paper analyses the subthalamic nucleus neuronal activity in parkinsonian patients undergone DBS surgery.
- In our patients general anesthesia did not alter any neuronal activity when compared to local anesthesia, keeping the feasibility of microelectrode recording, an important feature to identify the subthalamic nucleus area.
- Ketamine can be proposed as an alternative anesthetic drug during DBS surgery for those patients who do not accept an awake technique.

ABSTRACT

Objective: The purpose of this study was to evaluate changes in subthalamic nucleus (STN) neuronal activity in Parkinson's disease (PD) patients during deep brain stimulation (DBS) surgery under general anesthesia, and to compare these data with those recorded in the same subjects during previous surgery under local anesthesia.
Methods: Five patients with advanced PD, who had previously undergone bilateral STN-DBS under local anesthesia, underwent re-implantation under general anesthesia (with an anesthetic protocol based on the intravenous infusion of remifentanyl and ketamine) owing to surgical device complications. The microelectrode recording (MER) data obtained were analyzed by an off-line spike-sorting software. Neurophysiological data (number of spikes detected, mean firing rate, pause index and burst index) obtained under local and general anesthesia were then evaluated and compared by means of statistical analysis.
Results: We found no statistically significant difference between the first and second surgical procedures in any of the neurophysiological parameters analyzed.
Conclusions: Bilateral STN-DBS for advanced PD with MER guidance is possible and reliable under a ketamine-based anesthetic protocol.
Significance: General anesthesia can be proposed for those patients who do not accept an "awake surgery" for clinical reasons, such as excessive fear, poor cooperation or severe "off"-medication effects.

1. Introduction

Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is one of the most effective treatments for advanced idiopathic Parkinson's disease (PD) (Limousin et al., 1998; Limousin and Martinez-Torres, 2008; Benabid et al., 2009). The postoperative

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clinical outcome depends on the quality of the inclusion clinical criteria and of lead targeting, which is based on neuroimaging techniques and intraoperative electrophysiology (microelectrode recordings – MER – and macro- or micro-stimulation) (Hutchison et al., 1998; Rodriguez-Oroz et al., 2001; Welter et al., 2002).

Surgery is usually performed while the patient is awake, off drug therapy and under local anesthesia, as this condition enables to obtain reliable MER and allows the evaluation of the intraoperative stimulation-induced improvement in parkinsonian signs and dyskinesias, as well as possible adverse effects caused by the diffusion of current to adjacent structures such as the internal capsule or medial lemniscus (Houeto et al., 2003). However, general anesthesia may be needed for specific groups of PD patients who are afraid to undergo surgery while awake or suffer from chronic pain syndromes, severe "off-medication" movements and severe dystonia.

In such cases, general anesthesia may improve patient acceptance of DBS, thereby increasing the number of patients who can be treated. Nevertheless, it can interfere with MER by lowering or eliminating spontaneous neuronal firing (Ruskin et al., 1999; Hutchison and Lozano, 2000) and hinder the evaluation of the clinical benefits of intraoperative stimulation by suppressing motor signs such as tremors and rigidity (Anderson et al., 1994; Bohmdorfer et al., 2003). Moreover, the patient cannot report subjective adverse effects, such as paresthesia or abnormal motor activity due to stimulation of adjacent structures.

To what extent different anesthetic drugs may influence MER is not yet completely known, as they exert inhomogeneous effects on different regions of the brain. Few reports are available in the literature and no prospective, randomized, blind studies comparing the clinical outcome of surgery performed under general anesthesia with that of an awake technique have been performed (Velly et al., 2007).

When sedation or general anesthesia is required during microelectrode insertion, propofol is the most frequently used anesthetic drug. However, when propofol is used, differences in the pattern of neuronal activity among individual target sites and within the same target site have been reported in different diseases, such as dystonia or PD (Hutchison et al., 2003; Maltete et al., 2004). Moreover, owing to the sensitivity of subcortical areas of the brain to GABA receptor-mediated medications, propofol can make MER impossible (Ruskin et al., 1999; Hutchison and Lozano, 2000) and may cause dyskinetic effects (Krauss et al., 1996; Deogaonkar et al., 2006) or suppress tremor (Bohmdorfer et al., 2003), thus causing misunderstanding of intraoperative testing and hindering surgery.

Another interesting problem related to propofol is its occasional tendency to cause sneezing (Tao et al., 2008). Although sneezing may seem harmless and readily resolves when propofol is stopped, it leads to patient discomfort, interferes with physiological mapping, and causes sudden increase in arterial pressure that could result in intracranial hemorrhage (Fabregas et al., 2002). Sneezing is described during "conscious sedation" with propofol and dexmedetomidine without endotracheal intubation (Fabregas et al., 2002; Tao et al., 2008).

There is also evidence that the pharmacokinetic behavior of propofol in patients with Parkinson's disease may differ from that seen in the population in which the target-controlled infusion models were developed (Fabregas et al., 2002); these features may invalidate those anesthetic regimens (i.e. conscious sedation) in which propofol is lowered as far as possible before MER is started.

Dexmedetomidine at low-dose infusion rates (0.3–0.6 g/kg/h) may be a better choice; in addition to its hemodynamic stability and analgesic properties, its non-GABA-mediated mechanism of action does not interfere with MER (Rozet et al., 2006; Elias et al., 2008). Consequently, there are a number of reports on the successful use of this drug during functional surgery, both alone (Bekker et al., 2001; Mack et al., 2004; Rozet, 2008) and in combination with intermittent propofol.

Ketamine is frequently described as a "unique drug" because it exerts hypnotic, analgesic and amnesic effects. It acts basically as an antagonist of the glutamate receptors NMDA and produces an anesthetic state which has been called "dissociative anesthesia", characterized by analgesia and changes in vigilance and perception; the patient rapidly goes into a trance-like state, with wide-open eyes and nystagmus. The patient is unconscious, amnesic and deeply analgesic. This state is a result of reduced activation in the thalamic-cortical structures and increased activity in the limbic system and hippocampus (Sinner and Graf, 2008). In animal models, but not yet in humans, it has been shown that ketamine does not alter either the number of active basal ganglia neurons or their spontaneous firing rate (Kelland et al., 1991).

The objective of this study was to investigate the effect of a ketamine-based anesthetic protocol on spontaneous STN neuronal activity in a population of PD patients who underwent bilateral STN-DBS surgery under general anesthesia, and to compare the neurophysiological results with those obtained in the same patients who had previously undergone the same surgical procedure under local anesthesia.

2. Patients and methods

2.1. Patients

A total of 5 patients (3 women and 2 men) affected by advanced idiopathic Parkinson's disease, diagnosed according to Brain Bank Criteria, underwent bilateral STN-DBS: their clinical features are summarized in Table 1.

With regard to their motor deficit, they fulfilled the criteria of the Core Assessment Program for Surgical Interventional Therapies in PD (Defer et al., 1999). The patients were assessed by means of current clinical rating scales: the Unified Parkinson's Disease Rating scale (UPDRS), modified Schwab and England score, and the Hoehn and Yahr scale.

Table 1
Clinical features of the parkinsonian patients who underwent bilateral STN-DBS.

Patients	Sex	Clinical pattern	Age	Time between the 1st and 2nd surgery (days)	Baseline UPDRS-III at 1st surgery off-medication	Baseline UPDRS-III at 2nd surgery off-medication
P.L.	F	Tremor-dominant	54	187	60	60
Z.M.R.	F	Akinetic-rigid	51	267	79	79
B.M.	M	All cardinal motor signs (akinesia, rigidity, rest tremor)	69	347	66	67
S.A.	M	Akinetic-rigid	59	221	46	46
B.M.	F	Akinetic-rigid	56	316	30	31