Select Stim: Selective stimulation of the subthalamic nucleus in Parkinson*s disease
"A feasability study"

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON33676

Source
ToetsingOnline

Brief title
Select Stim

Condition

- Movement disorders (incl parkinsonism)
- Nervous system, skull and spine therapeutic procedures

Synonym
Parkinson disease, Parkinsonism

Research involving
Human

Sponsors and support

Primary sponsor: Neurochirurgie
Source(s) of monetary or material Support: NWO;Smartmix

Intervention

Keyword: deep brain stimulation (DBS), Parkinson, subthalamic nucleus (STN)

Outcome measures

Primary outcome

There are two main endpoints to measure the feasibility. First, the patients burden and outcome. We will interview the patient and ask him to fill in a standardized questionnaire. Only if the burden is acceptable, we will start with the main study (average marks for each testing must be above 5 to continue with a RCT). Thereby the motor symptoms must be significantly less pronounced with stimulation than pre-operatively.

Secondly, the technical feasibility depends on the possibility to register the potentials, evoked by motor cortex stimulation in the STN (so-called evoked potentials). These potentials have to be clearly identifiable in order to recognize the motor part of the STN. This is necessary as in the final study we want to compare the results of selective stimulation of the motor part of the STN with results of the classical procedure.

Secondary outcome

Cognition, and in particular impulsivity, and affect, will be assessed by neuropsychological testing and a self-report questionnaire, the Positive and Negative Affect Scale (Watson et al 1988). Neuropsychological testing covers the main cognitive domains but the study parameters are related to the

performance on tasks in the relevant domain of executive functioning, including word fluency, the Stroop (Lezak, 2004), a finger precuing task (Adam et al, 2002) and the Iowa Gambling Task (Bechera et al., 1994). (These are not endpoints of the feasibility trial.)

Advantage of fMRI above TMS or double contrast MRI in the planning of the OR.

Study description

Background summary

Parkinson disease (PD) is a common neurodegenerative disorder, characterized by motor symptoms. Patients are initially treated successfully with drugs (e.g. levodopa), unfortunately use is limited due to severe side effects. In the advanced stages of PD neurosurgical treatment is the next therapeutic option.
As a result of dopamine depletion in PD the subthalamic nucleus (STN) displays a characteristic burst activity. This burst activity results in dysregulation of the electrical activity of the cortico-basal ganglia-thalamo-cortical circuitry and is expressed by Parkinsonian symptoms. That is why the STN is a main target for deep brain stimulation (DBS) in PD. Long-term follow-up (since 1993) shows long lasting beneficial effects on the motor function of PD patients.
Despite the beneficial motor effects there are important negative side-effects of STN DBS. These include both cognitive and affective changes during stimulation, 40% has one of these side effects. 10% experience difficulties during their daily functioning due to altered cognition or personality changes. Presently, the underlying mechanism of these stimulation induced behavioral changes is not fully understood and therefore adequate treatment is lacking.
The STN can be divided in three functionally and anatomically segregated parts: a motor part, a cognitive part and a limbic part. Our hypothesis is that changes in cognition and behavior during STN DBS are related to stimulation of the non-motor parts of the STN.
Currently, good candidates are excluded from STN DBS because of the high risk of behavioral disorders.

Study objective

The primary objective is to avoid cognitive and affective side effects and

maintain the beneficial motor effects by selective stimulation of the STN motor part. With the Select Stim project we want to improve the classical operation procedure, in such way that the behavioral side effects will be less present and the motor symptoms of the disease will be treated. In a later stage, we want to compare the classical treatment in comparison to this new method. The outcome we are interested in are the Parkinson symptoms, but also the side effects of the stimulation on cognitive functioning, mood and behavior. The main objective of this feasibility study is to measure the patients burden and to test the technical feasibility.

The feasibility study will answer the following: is targeting of the subthalamic nucleus, using stimulation of the motor cortex and registration in the subthalamic nucleus technically achievable? The primary goal is to determine the technical feasibility and the patient tolerance. If the method is technical achievable and well tolerated by the patients, we want to give answer to the main question with a randomized trial.

Study design

The first stage consists of a feasibility study. Three patients will be enrolled and evaluated. Blinding and randomization is not necessary. Depending on the results of this minor feasibility study, we will proceed with the second stage, which is the randomized controlled trial.

Intervention

The intervention is an expansion of the classical STN DBS procedure. The targeting using the multichannel registration system by stimulation of the motor cortex and registration of the subthalamic nucleus will be added to the procedure. For this procedure, it is necessary to place a subdural strip under the skull.

Study burden and risks

The burden for the patients rests within lengthened operation time and the pre-operative preparation. The preparation for this study will contain a functional MRI. The patient needs to lie in the scanner for a prolonged time (max. 30 min.). And an TMS will be performed to localise the hand area on the motor cortex, which will take about 60 minutes. This test is not painful. The operation will be lengthened with one hour per side.

Adverse events related to the implantation of the subdural strip electrodes for the motor cortex stimulation are described in epilepsy research where these strips are also used. The most important complications involve bleeding, infection, transient neurological deficit, intracranial hypertension, seizures. A large retrospective study (185 patients with epilepsy who had an implantation

of a subdural strip) shows that strip electrode implantation is rarely associated with complications, e.g. epidural hematoma 1.6%, subdural hematoma 1.1%, brain edema 1.1%, postoperative infection 1.1%, transient aphasia 1.1%, occurrence of non-habitual seizures 2.7%. Most of these published complications are in context of prolonged (e.g. several days) monitoring in epilepsy treatment. We expect the risk of seizures to be lower in Parkinson disease patients. Moreover, in this study the subdural strips are only used for just an hour for recording and stimulation of the motor cortex. So, the risk of the various complications mentioned above will probably be even lower.
The strips will be implanted through the same burr hole through which the five depth electrodes are implanted like in the classical procedure. Only if this appears to be impossible during the procedure, a second burr hole will be made. The risk of this (bleeding and infection) is very low (less than 0.25%).

In the first two patients seizures occurred. The first patient had a seizure after the surgery, which was countered by the administration of diphantoin. The second patient had only clonic movements of the hand, which also disappeared after administration of anti-epileptic drugs. Both patients recovered well.
They are now seizure free and have no additional neurological deficits. To prevent seizures in the next patient we will load him with diphantoin. The risk of seizures is very small with the administration of diphantoin.
The most important side effects of diphantoin are nausea, vomiting, obstipation and anorexia, also dizziness ataxia, nystagmus, speech disturbances, tremor, apathy, visual disturbances, nervosity, hallucinations and neuropathy. The adverse effects are mainly reported after long term treatment.
After intravenous administration hypotension can occur and cardiotoxic reactions, collaps and/ or central depression; incidentally dyskinesias. The injection site can hurt, show inflammation and necrosis of the skin. The diphantoin will be loaded in a safe time spam (90min) through a safe intravenous line by the anesthetist in the srugery room.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with the clinical findings consistent with idiopathic Parkinson Disease (PD) and who suffer from severe response fluctuations and/or dyskinesias, despite optimal drug treatment, who are candidates for DBS.

Exclusion criteria

Those PD patients suffering from severe psychiatric co-morbidities and cognitive decline, e.g. dementia and psychosis, are excluded from this study. The mini mental state exam (MMSE) score is not allowed to be <24. Other exclusion criteria are the same as for the classical STN DBS operation: significant cerebral atrophy, causative factors of PD, multiple white matter lesions or focal brain anomalies and a Hoehn and Yahr stage of 5 at the best moment of the day.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2008
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	09-06-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-12-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-07-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL21387.068.08