

Therapeutic Effects of Thalamic Electrical Stimulation in Parkinson's Disease

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Abstract

Objective: In the treatment of tremor and rigidity in patients with Parkinson's disease the nucleus ventralis intermedius of thalamus has been an exquisite target that can be localized easily on ventriculograms. This experimental study is aimed to evaluate the effects of electrical stimulation of vim nucleus on symptoms and signs of Parkinson's disease.

Methods: Eleven deep drain stimulators were stereotactically implanted in the nucleus ventralis intermedius of 10 patients who had medically intractable Parkinson's disease. Postoperative evaluations were performed using conventional Unified Parkinson's Disease Rating Scale (UPDRS). We also assessed the effects of underlying variables on the surgical outcome.

Results: Our patients were followed up for a mean period of 18 months. Considering UPDRS, all patients showed significant improvements in their tremor scores, (mean=75.75%). Thalamic stimulation decreased rigidity scores at a mean of 75.09%. The mean improvement of motor function scores was 53.02% whereas daily life activities ameliorated at a mean of 38.07%.

Conclusion: Deep brain stimulation of the nucleus ventralis intermedius has become a promising treatment option for patients with tremor dominant Parkinson's disease that do not respond to medical therapy. Cases with bilateral medically intractable symptoms can be safely treated using bilateral deep brain stimulation. In patients with previous thalamotomy, electrical stimulation can improve ipsilateral and contralateral tremor, avoiding major side effects of bilateral thalamotomy. Neurostimulation may be superior to ablative surgery, given its reversibility and modifiability of stimulation parameters, including no lesion at the stimulated site and the same and comparable outcome with minimal or reversible complications.

Keywords: Parkinson, Thalamus, Electrical, Stimulation

1. Introduction

In 1817, James Parkinson described the major clinical features of what today is recognized as a symptom complex, manifested by any combination of six cardinal features: tremor at rest, rigidity, bradykinesia, loss of postural reflexes, gait problems and the freezing phenomenon.

At least two of these features, with at least one being either tremor at rest or bradykinesia must be present for a diagnosis of definite Parkinsonism. Parkinson's disease (PD) makes up 80% of Parkinsonism. The age at onset assumes a bell shaped curve with a mean of 55 years in both sexes and a wide range in age from 20-80 (Selby G, 1968).

The core biochemical pathology in Parkinsonism is decreased dopaminergic neurotransmission in the basal ganglia. Physiologically, the decreased dopaminergic activity in the striatum leads to disinheriting of the subthalamic nucleus and the medial globus pallidus, which is the predominant efferent nucleus in the basal ganglia.

The pathology of Parkinson's disease is distinctive. Degeneration of neuromelanin containing neurons in the brain stem occurs especially in the ventral tier of pars compacta of substantia nigra and in the locus ceruleus; many of the surviving neurons contain eosinophilic cytoplasmic inclusions known as Lewy bodies, the pathological hallmark of the disease (Schoenberg B. S, 1987).

The cause of PD is unknown. Research was concentrated on genetics and exogenous toxins from cellular oxidative reactions. Several genes have been defined, usually causing young onset parkinsonism. The first (PD1) is due to the mutation in the gene for the protein alpha-synuclein located on chromosome 4q21-q22. The resulting Parkinsonism transmits in an autosomal dominant pattern. The most common occurring gene defect is PD2 on chromosome 6q25-q27 coding for a previously unknown protein named parkin (Poirier L, 1975).

Because aging is associated with loss of catecholamine containing neurons and an increase in monoamine oxidase (type A & B) activity, an endogenous toxin hypothesis has emerged (Laitinen L. V., 1996).

Despite a large number of medications available for the treatment of early and moderately advanced PD, options specifically designed for the patient with advanced disease is limited. Surgery for PD dates from 1939 to 1940 when Bucy and Klemme excised parts of the cerebral cortex to treat tremor and dystonia but this type of surgery produced hemiparesis (Fahn S., 2000; Bucy P. C., 1939).

Surgical basal ganglia lesions were introduced a few years later by Meyers who found that pallidotomy produced significant relief of tremor, rigidity and dyskinesia but with considerable mortality (Meyers R., 1940; Cooper I. S., 1954).

Cooper operated on a parkinsonian patient in whom he intended to perform pedunculotomy through a subtemporal approach. During dissection the anterior choroidal artery was torn and the surgery was then interrupted without cutting the cerebral peduncle. Postoperatively the patient was free from tremor and rigidity while motor and sensory functions remained intact (Cooper I. S., 1954).

Stereo tactic techniques to coagulate globus pallidus in PD were introduced in 1950 (Narabayashi H, 1978; Hallet M, 1999). Microelectrical recording allowed Narabayashi to find that lesioning of the ventral intermediate (Vim) nucleus of the thalamus was the most specific target to control tremor in PD (Narabayashi H, 1978; Denny-Brown D, 1962).

Neurosurgery reached its peak in the 1960, but declined after the introduction of levodopa. The recent resurgence of surgery was initiated by adrenal medullary transplantation. The premise of adrenal medullary transplants was that these cells, when transplanted into patients with advanced PD, would survive and function as a new source of dopamine. The disadvantages include the non-neuronal source and the rather modest survival rates of cells in laboratory studies. Fetal mesencephalic transplantation was introduced subsequently, but poses several challenges including questions of proper age of the fetus, preservation and implantation techniques, immuno-suppressions and finally ethical issues related to use of fetal material (Siegfried J., 1993).

Deep brain stimulation (DBS) of the Vim nucleus of the thalamus as an alternative to thalamotomy was introduced in Europe in 1987. The rationale for the technique was the observation made during classic thalamotomy that stimulating the target with high frequency current could stop the tremor. Thus high frequency stimulation seemed to mimic the effect of the lesion and might avoid premature side effects of an ablative lesion. By this technique, the patient would activate the stimulation whenever needed (Benabid A. L, 1996). Therefore this experimental study was aimed to evaluate the effects of electrical stimulation of the Vim nucleus of the thalamus on symptoms and signs of PD in our center from 2005 to 2008.

2. Materials & Methods

In our clinical trial, eleven deep brain stimulators were stereo tactically implanted in the ventralis intermedius (Vim) nucleus of ten patients with medically intractable PD from 2005-2008. The outcome was evaluated using Unified Parkinson's Disease Rating Scale (UPDRS).

UPDRS is a clinical rating scale to score clinical state of PD according to mental state, activity of daily life and motor function with 31 subgroups overall. In addition it scores the complications of medical treatment which includes dyskinesia freezing and fluctuation.

Our inclusion criteria for DBS were as following:

Idiopathic PD with disabling unilateral or asymmetrical tremor;

Drug induced dyskinesia;

Poor response to medical treatment;

Intolerance of optimal medical management;

Stable clinical state for the last three months;

The exclusion criteria were as following:

Parkinson plus syndromes;

Significant dementia;

Age > 75y;

Significant medical illness;

Coagulopathy or other contraindications for general surgery;

Uncooperative patients.

Patients' characteristics such as age, sex, disease duration, underlying cause, medications and their dosages, laterality of symptoms, previous functional surgery (thalamotomy) were recorded and the major clinical indices including tremor, rigidity, dyskinesia, total score of UPDRS and its subgroups including mental state, motor condition, daily life activities and side effects of medications were determined and the results were compared with preoperative values using paired t-test.

2.1 Technique of Electrical Stimulation

Under sedation, after injection of local anesthetics, stereo tactic frame was fixed on the patients head and

standard AP and lateral skull radiographs were obtained. The standard burr holes were placed 2 cm in front of the coronal suture and 3cm off the midline on the opposite of the major side of clinical manifestations. Then ventriculography with injection of water soluble contrast material (omnipaque) was performed and the target (Vim nucleus) was localized. The anatomic coordinates for the Vim nucleus lied 5-7mm in front of the anterior margin of the posterior commissure on the level of the inter-commissural line and 14-15mm off the midline of the third ventricle. The DBS system (Itrel II, Soletra) composed of a quadripolar electrode, an extension cable and an internal pulse generator (IPG). The relevant stimulation parameters which can be controlled telemetrically by use of an external console programmer after implantation of the IPG are electrode polarity, amplitude, pulse width and frequency. After implanting the electrode and examining, the IPG is inserted in the subcutaneous packet of the anterior chest wall and connected to the electrode after a period of several days to ensure the effectiveness of stimulation.

3. Results

In this clinical trial, eleven deep brain stimulators were implanted in the Vim nucleus of 10 patients with clinically intractable PD.

Five of the electrodes (45.5%) were implanted in males and the other 6 (54.5%) were implanted in females. The electrodes were placed on the side contralateral to the side with maximal involvement.

The mean age of the patients was 47.7 y. Six patient had positive family history of PD.

Mean duration of the disease was about 10 years, the minimum of the period was 6 and the maximum was 15 years. Nine patients had bilateral tremor and only one patient had pure unilateral tremor (left side).

The drugs and doses used for medical treatment before and after electrical stimulation are summarized in table 1.

The major clinical indices including tremor, rigidity, bradykinesia and dyskinesia were scored using UPDRS and the scale subgroups including mental status before and after treatment are summarized in table 2.

The mean of the follow-up period was 18.4 months. After electrical stimulation one patient showed superficial scalp wound infection which was controlled by oral antibiotics and one patient needed IPG replacement after 4 years of implantation. None of the patients had motor, verbal or visual complications. All of our cases complained of transient paresthesia but permanent paresthesia occurred in 5 (45.5%) of the patients.

4. Discussion

Chronic deep brain stimulation (DBS) has been used for decades in the treatment of intractable pain. As early as the 1970s, its place in the therapeutic management of movement disorders was investigated. Not until Benabid and Siegfried demonstrated the efficacy of thalamic DBS in large series of patients however DBS became widely accepted as a therapeutic option for the treatment of movement disorders.

In particular chronic stimulation of the Vim nucleus of the thalamus is considered a valid and safe method of alleviating tremor (Krauss J. K, 2001). Since August 1997, unilateral thalamic DBS has been approved in the USA for refractory essential and Parkinsonian tremor (Meyers R, 1940).

Our study showed significant improvement in the tremor scale (tremor at rest + action tremor), $p=0.007$. The mean value of improvement in the tremor scale was 75.75%.

Krauss et al, studying 45 PD patients in 2001, showed that after electrical stimulation of thalamus, 51% of patients showed excellent (>90%) recovery in tremor, 36% showed good results (70-90%) and 11% showed mild improvement (Caparros-Lefebvre D., 1993).

In our patients 36% had an excellent improvement, 9.1% had good and 54.5% showed fair results. All our patients had improvements greater than mild level. Patients whose symptoms lasted more than 10 years showed greater recovery than those with duration less than 10 years ($p=0.044$).

Baseline tremor severity and general medical condition had no effect on the responsiveness of tremor to electrical stimulation ($p=0.56$).

Most of the previous studies have confirmed the efficacy of DBS on tremor but mentioned negligible effect on rigidity at the same time (Benabid AL, 1996). But our patients showed improvement in rigidity uniformly. The average amount of improvement of the severity of rigidity relative to the baseline was 75.09% in our patients, which is considered a significant decrease relative to presymptomatic state ($p=0.0003$) and is much more pronounced considering other studies (Siegfried Taub E, 1998).

It might be explained by the fact that our method of electrode placement targeting VIM is more anterior relative to VIM or propagation of the current to more ventral portions stimulating VOA concurrently, causing a

considerable improvement in rigidity.

As shown in table 2, our patients showed no statistically significant decline in bradykinesia, dyskinesia, mental status or side effects attributable to their medication.

General clinical state was mild (UPDRS=0-40) in 1 patient, severe (UPDRS>80) in 1 patient, and moderate (UPDRS=40-80) in the remainder (81.8%). After DBS, the general clinical state was mild in 63.6%, and moderate in 36.4%. None of our patients were in severe clinical state after the procedure. The average recovery in general clinical state was 38.07% relative to baseline state in our patients (table2). General clinical state of our patients shows a significant improvement after the electrical stimulation as shown in table2, ($p=0.0005$). The daily life activities in our patients recovered considerably (26.23%) relative to the preoperative state ($p=0.05$) (table2).

The effect of electrical stimulation on patient's disability is dependent to the main cause of patient's disability. If the patient is crippled mostly due to bradykinesia we cannot hope that VIM stimulation recovers the patients' performance significantly as thalamic DBS is almost ineffective on bradykinesia (Pollak P, 1998).

The importance of daily life activities in our patients was more pronounced when patients were older than 40 years ($p=0.05$).

As the baseline daily activity, tremor or rigidity measured by UPDRS had no effect on the recovery of daily life activities, we can assume that age>40y has an independent effect on patient's daily activities.

In our study the patients showed a decrease in their daily consumption of medication, it did not reach a statistically significant level (table1). As 90.9% of our cases had bilateral symptomatology, this might cause our patients to continue their medication.

Siegfried and Tauch in their large study on 300 cases of thalamotomy and electrical stimulation of thalamus, described dysarthria, dysphonia and dysphagia in more than 1/4th of their patients after destructive procedures, but the frequency of these complications were much less in the patients treated by DBS (Habrler C, 2007; Vitek J.L., 2008).

The results of deep brain stimulation of the VIM in other recent studies are summarized in table 3.

5. Conclusions

In summary, side effects of DBS are much less than destructive procedures and are considered more acceptable to patients. In addition the side effects can be alleviated with changing stimulation parameters. Today stereo tactic procedures have developed a vast field of alternatives for neurological surgeons especially for movement disorders. Although the application of DBS has been debated much in the literature, our study is the first one in Iran studying the application of these systems in a systematic way. We hope that our results which are comparable to the results obtained by other investigators encourage other Iranian neurosurgical centers to utilize this safe and effective method for Iranian parkinsonian population.

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Table 1. Drug consumption dose before and after DBS in our patients

Drug	Pre DBS		Post DBS	
	Consumption dose (mg/d)	Patients	Consumption dose (mg/d)	Patients
Levodopa	970.44	11(100%)	461.36	9(8.81%)
Artan	6.18	9(8.81%)	1.45	5(45.5%)
Amantadin	145.45	7(63.6%)	81.82	5(45.4%)
Bromocriptin	2.95	5(45.5%)	2.95	4(36.4%)
Selegeline	2.00	2(18.2%)	0.90	1(9.1%)

Table 2. UPDRS subgroups before and after DBS in our patients

variable	mean before DBS	Mean after DBS	Mean recovery%	P
tremor	11.36	3.81	75.75	0.0007
rigidity	6.36	2.27	75.04	0.0003
bradykinesia	1.72	1.72	0.00	0.9999
dyskinesia	3.81	2.54	31.17	0.4697
mental state	4.81	4.55	14.16	0.8507
Daily activities	18.00	13.18	26.23	0.0535
motor function	37.36	18.00	53.02	0.0003
drug effects	5.40	4.00	37.07	0.4895
general state	59.18	35.63	38.07	0.0005

Table 3. Long-term (greater than 12 months) efficacy studies of DBS for Parkinson's Disease (PD)

Author	No. of Cases	Results
Albanese et al. [1999]	27	Tremor remained stable during follow-up period; rebound tremor in 22%; stimulation parameters stabilized after first 3 months
Benabid et al. [1996]	91	Stable stimulation efficacy in 96% of operative sides; rebound tremor in 42%; stable stimulation parameters after first few months
Blond et al. [1992]	10	Long-term tremor control maintained; rebound tremor in 57% (not separated by diagnosis); voltage increased over time
Hariz et al. [1999]	22	Those with 'good' effect decreased from 90 to 70% from week 1 to last follow-up; rebound tremor in 32%; stimulation parameters stabilized after 6 months
Krauss et al. [2001]	45	Marked or excellent tremor control in 87% (only results of last follow-up reported)
Kumar et al. [1999]	11	Long-term tremor control maintained; stimulation parameters stabilized after 3 months; rebound tremor in 27%
Lyons et al. [2001]	12	Stable tremor control, however, UPDRS motor score not significantly different than baseline at long-term follow-up; no change in stimulation parameters,
Tasker, [1998]	16	Long-term control of tremor and other PD symptom.