

Long-term Ventralis Intermedius Thalamic Stimulation for Parkinsonian Tremor

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Long-term thalamic stimulation in the ventralis intermedius nucleus (Vim) has been recently introduced to treat parkinsonian or essential tremor refractory to drugs (1–8). Stereotactic neurosurgery is used to place electrical leads in the nuclei of the basal ganglia. This procedure has gained worldwide recognition during the last decade because of its reversibility and low morbidity, particularly after bilateral placement. In Italy, Broggi et al. (9) first carried out a Vim thalamic stimulation in a patient with posttraumatic tremor. However, only since 1995 has chronic Vim thalamic stimulation obtained widespread acceptance in Italy (10).

PATIENTS AND METHODS

Between March 1995 and February 1997, 27 patients (8 women, 19 men) received thalamic stimulation in Italy. They all suffered from idiopathic Parkinson's disease (average disease duration, 6.4 years; range, 1 to 14 years). In each patient, tremor responding poorly to drug therapy was the major symptom. Six patients had implantation bilaterally; the remaining 21 had implantation unilaterally (19 in the left Vim; 14 in the right). The average age at time of implantation was 60.6 years (range, 33 to 75 years). The patients underwent preimplantation evaluations consisting of brain magnetic res-

onance imaging (MRI), short- and long-term drug challenge, neuropsychologic evaluation, and videotaped Unified Parkinson's Disease Rating Scale (UPDRS). The following inclusion criteria were adopted: (a) the diagnosis of idiopathic Parkinson's disease (IPD) was made based on the U.K. Parkinson's Disease Brain Bank criteria (11); (b) UPDRS-III₂₀ score was equal to or higher than 2; and (c) no severe akinesia, rigidity, or motor fluctuations (otherwise, patients were considered for subthalamic nucleus (STN) or globus pallidus interna (GPI) implantation) were observed.

Three Italian centers using different neurosurgical procedures were involved. In 12 patients, the stereotactic procedure was performed (under local anesthesia) by means of a modified Talairach frame; then, after a precoronal approach, ventriculography was employed to obtain precise delineation of the midline of the third ventricle and of the anterior (AC) and posterior (PC) commissures. The Vim coordinates were determined using lateral radiographic views according to a proportional geometric scheme based on the AC-PC line (12). The same procedure, but using a modified Leksell frame, was employed for six patients. In the remaining nine patients, a CRW Radionics frame and stereotactic TC with stereoplan assistance was used.

In all cases, a Medtronic (Medtronic, Inc., Minneapolis, MN) quadripolar lead (model 3387) was placed in the target, and its location was considered satisfactory when tremor suppression was obtained with a stimulation intensity lower than 2 to 3 V (pulse width, 60 microseconds; frequency, 130 Hz). Stimulation testing was performed using a Medtronic screening device (model 3635). Microelectrode cell recordings were not performed.

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Approximately 1 week after implantation, brain imaging [computed tomography (CT) or MRI scan] was used to confirm placement. The effects of the stimulation on tremor were tested using any available combination, determined by occurrence of clinical improvement and of side effects. The implanted lead was later connected with a cable to an implantable pulse generator (IPG; Medtronic, model 7424) under general anesthesia at a subsequent surgical session.

RESULTS

Programmed evaluations were established at 1, 3, 6, and 12 months after implantation. The average follow-up time until March 1997 was 0.9 years (range, 0.1 to 2) years. In 2 of the 27 patients, this procedure was not completed: In one patient, the electrode was not connected to the IPG because of the occurrence of a small cerebral hematoma following surgery; in another, the electrode was withdrawn following infection. In three patients, a "microthalamotomy-like effect" was reported. This consisted of transient tremor suppression induced by the electrode implantation, with reappearance of tremor after 2 to 6 days.

As shown in Table 87-1, there was significant tremor improvement after long-term Vim stimulation. This improvement was greater in the upper limbs than in the lower and remained stable during the follow-up period.

Tremor was completely or almost completely suppressed (reappearance of a slight or moderate tremor on occasion, e.g., under stress) in 21 patients (77.7%), was slightly reduced in 4 (14.8%), and unchanged in 2 (7.4%). A slight reduction of rigidity was reported in three patients, and moderate relief of bradykinesia was observed in three. Antiparkinsonian drugs were decreased in seven patients (25.9%). In all cases, even when tremor control was not completely suppressed, patients reported definite improvement in their quality of life.

Of a total of 33 thalamic implantations, the following complications occurred: one intracranial hemorrhage with subsequent total recovery; one skin ero-

sion, one electrode breakage, two local infections (leading to a new implantation in one case), two lead replacements (attributable to a dislocation in one case and to lead breakage in the other), and three catheter disconnections.

The following side effects were reported:

1. Paresthesias of slight or moderate intensity were reported by 17 patients (62.9%) when switching the IPG on, disappearing after a few seconds in all cases.
2. Dysarthria was observed in five patients with a left-side implant, in two with a right-side implant, and in four with bilateral implants. When stimulation was stopped, speech impairment recovered.
3. Paradoxical increase of tremor was noticed in seven patients (22.2%) when stimulation was turned off. This was considered to be a "rebound effect" or natural worsening of the patient's tremor.
4. Moderate weakness was reported by three patients with a bilateral implant and by one with a unilateral implant (14.8%).
5. Subjective dysequilibrium was reported by one patient (3.7%).
6. Headache and nausea were referred by one patient (3.7%); these clinical features were unrelated to IPG activation.

It was necessary to gradually increase the amplitude of the stimulation during the first 2 to 3 months after implantation. The average amplitude at the time of implant was 2.5 V (range, 1 to 6 V); the average amplitude at time of last visit was 2.8 V (range, 0.8 to 4.1 V).

Stimulation was performed using only one electrode ("monopolar": electrode negative with case positive) in ten cases, using two electrodes (one negative and the other positive) in the remainder.

DISCUSSION

This report describes a multicenter study on the outcome of Vim thalamic stimulation in Parkinson's

TABLE 87-2

Study	I
Ref. 6	
Ref. 5	
Ref. 2	
Present report	
Vim, ventro-interm	

disease. The multicenter study showed the ability of the observed results to closely the normal variability in a country. The three patients underwent different stereotactic procedures keeping with earlier reports of high-frequency stimulations for essential tremor.

In a North American multicenter study, results were obtained in 100 patients, 45 of whom were treated with 45 patients, 20 with tremor, the others being with dystonia. Three months after surgery, the mean clinical tremor score was 3.5 when the IPG was turned on, compared with 4.5 when it was off. Included three resolving in one patient, seizures. The stimulation included paresthesias and dysequilibrium (4%) and tremor occurring when stimulation was not mentioned in the report. Tremor could be related

TABLE 87-1. Average UPDRS-III₂₀ score in 25 patients, comparing the time of implantation and the last visit

UPDRS-III ₂₀	Preimplantation	Last visit	Variation
Upper limb	3.50	0.93	-73.42%
Lower limb	2.21	0.84	-61.99%

UPDRS-III₂₀, Unified Parkinson's Disease Rating Scale.

TABLE 87-3

Study	N
Ref. 2	80

Ref. 13 20

Present report 20

IPD, idiopathic Parkinson's disease

TABLE 87-2. *Synopsis of results in published series of Vim stimulation of parkinsonian tremor*

Study	Implantations	Satisfactory tremor suppression	Technique for target localization
Ref. 6	19	63%	Stimulation only
Ref. 5	10	70%	Stimulation only
Ref. 2	111	85%	Neuronal recording and stimulation
Present report	31	68%	Stimulation only

Vim, ventro-intermediate thalamic nucleus.

disease. The multicenter design allows greater variability of the observed data, thus resembling more closely the normal variations among different centers in a country. The three participating centers used different stereotactic procedures, as is customary among different neurosurgical clinics. The present data are in keeping with earlier reports on the efficacy of Vim high-frequency stimulation in parkinsonian and essential tremor.

In a North American multicenter trial, satisfactory results were obtained in four centers (13). The study dealt with 45 patients, 20 of whom had parkinsonian tremor, the others being affected by essential tremor. Three months after surgery, with stimulation off, the mean clinical tremor score was 2.89, falling to 1.36 when the IPG was turned on. Complications included three resolving intracranial hemorrhages and in one patient, seizures. Side effects related to stimulation included paresthesias (56%), paresis (8%), and dysequilibrium (4%). A paradoxical increase of tremor occurring when stimulation is turned off (2,5) was not mentioned in this study (14). Rebound tremor could be related to a tolerance phenomenon,

requiring gradual increase of stimulation amplitude to suppress tremor during the follow-up period. Tolerance could be due to a decreased biologic response (habituation) of the neuroanatomic system involved in tremor generation.

Results and side effects of published series of Vim implants are summarized in Tables 87-2 and 87-3. Clinical efficacy depends on a precise target location, as Vim is close to the internal capsule and to other thalamic nuclei. The use of microelectrode recordings and the monocentric design of the study are likely explanations for better results reported by the group in Grenoble (2).

The recent development of new targets for the treatment of parkinsonian signs and symptoms raises the question as to whether targets other than the Vim are specific for parkinsonian tremor. Preliminary data indicate that subthalamic implants are effective on parkinsonian tremor (15) but do not indicate whether they can be used to treat tremor in all parkinsonian patients. Further studies are required, to elucidate the exact indications for Vim surgery in parkinsonian patients.

TABLE 87-3. *Side effects and complications in different series*

Study	No. of patients	Side effects (transient)	Complications
Ref. 2	80 IPD	Dysarthria (22.5%) Paresthesias (9%)	Microhematoma (6.25%) Skin lesions (necrosis, granuloma, seroma) (6.25%) Lead replacement (3.75%)
Ref. 13	20 IPD, +25 ET	Disequilibrium (7.5%) Contralateral dystonia (5%) Paresthesias (56%) Paresis (8%) Dysarthria (6%) Disequilibrium (4%)	Hemorrhage (15%) Seizure (5%)
Present report	27 IPD	Paresthesias (62.8%) Dysarthria (40.7%) Weakness (14.8%) Headache (3.7%) Dysequilibrium (3.7%)	Catheter disconnection (11.1%) Skin problems (necrosis, infection) (11.1%) Lead replacement (7.4%) Electrode breakage (3.7%) Hemorrhage (3.7%)

IPD, idiopathic Parkinson's disease; ET, essential tremor.

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Since the first clinical trial in Parkinson's disease decade ago, more than 2 received implants of 1 cephalic tissue into the st of this approach to patient years of grafting studies (3,4). These studies have onic mesencephalic grafted striatum, restore reverse some of the motor in parkinsonian rodents. From the clinical perspective, the most transplantation is the dopamine transmission that have lost their normality in the striatum. any other therapeutic approach.

Although several approaches have been made which transplantation can be PD, this approach must be an important procedure. The chapter are to analyze clinical trials and to briefly improve the functional condition.

CONCLUSIONS

1. Grafted embryonic striatum inhibit short- and long-term PD. This conclusion is the result of increased striatum using