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Case Report

Deep Brain Stimulation in Sub-Thalamic Nucleus in idiopathic Parkinson's disease – our initial experience in four cases

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Abstract:

Parkinson's Disease (PD) is a chronic neurodegenerative disease . It's cardinal features are resting tremor, Rigidity, Akinesia and postural instability. Idiopathic Parkinson's disease develops mainly due to degeneration of Dopaminergic neurons of Substantia Nigra. The role of Subthalamic Nucleus (STN) in the development of Parkinsonian Tremmor and other cardinal features is not completely understood yet. However previous studies in monkeys , administration of MPTP (1-methyl-4-phenyl-1.2.3.6.-tetrahydropyridine) proved that sub thalamic nucleus has a direct role in the development of Parkinsonian tremor and other features. We used no Micro Electrode Recording (MER) system,only studied clinically that Parkinsonian tremor stopped immediately after placement of electrode and same thing happened after micro stimulation of the sensorymotor region of the sub thalamic nucleus .Then high frequency deep brain stimulation (DBS) of these same four patients were assessed six months after surgery which led to a significant reduction of Parkinsonian tremor as well as other cardinal features of PD (p< 0.001) . Both postural and resting tremor disappeared completely in three cases and significantly reduced in one case .

Key words: *Subthalamic Nucleus(STN), Deep Brain Stimulation(DBS), Ventralis Intermedius Nucleus(VIM) , Parkinson's Disease(PD), Unified Parkinson's Disease Rating Scale(UPDRS),1-methyl-4-phenyl-1.2.3.6.-tetrahydropyridine(MPTP)*

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Introduction:

Parkinson,s disease is a chronic disabling neuro degenerative disorder characterized by resting tremor , akinesia , rigidity and postural instability caused mainly by degeneration of Dopaminergic neurons of Substantia Nigra[1] . In the early stage of disease , Levodopa and/or Levodopa agonist drugs improves dramatically the motor symptoms of Parkinson's disease but after few years , this treatment is - eventually hampered by increasing the motor complications – such as "wearing-off " , "on" or "of " phenomena[2] ; even, as well as, troublesome drug induced dyskinesia[3] . Before introduction of drugs in early sixties , surgical lesioning procedures specially Pallidotomies and Thalamotomies were applied to improve these symptoms but often, it was at risk of development of irreversible and severe side effects like dysarthria or hemiparesis in unexperienced hands . Bilateral lesioning surgery dramatically increased complications and was there rarely performed[4].

Deep Brain Stimulation (DBS) in the motor thalamus- the Ventral Intermedius Nucleus (VIM) was first introduced in 1986 to treat the medically refractory tremor in PD[4] . DBS of various basal ganglia nucleus has shown to be highly effective in the treatment of several movement disorder[5] . Traditionally , in tremor the target nucleus is VIM , in hyperkinesia , the nucleus is Globus Pallidus Internus (GPi) and generally in PD features , the target nucleus is Sub Thalamic Nucleus (STN) were found to be safe and effective[6] .

Compared with lesioning , uni or bi lateral DBS is found to develop no or minimal tissue damage or complications and the main difference is that it is reversible[7]. In course of disease , the stimulation parameters can be changed as needed to maintain the corrected PD features[8]. In different randomized controlled trial DBS showed a better functional outcome with fewer side effects and therefore , DBS surgery replaces almost completely the lesion in developed countries . However . due to economic

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restriction in particular countries like Bangladesh , lesion still might be the only option[9].

Particularly, which nucleus causes tremor in Parkinson's Disease (PD) is still a matter of debate . Initially , it was thought that Ventralis Intermedialis Nucleus (VIM) is the only nucleus closely associated with tremor in PD[10]. The development of the 1-methyle-4-phenyl-1.2.3.6-tetrahydropyridine (MPTP) model of PD in monkey shows that there develops new physiologic resting and postural tremmors[11]. This study indicates that gross deficiency of Dopamine as induced by repeated administration of MPTP , may develop PD in monkey as PD develop in human being[11] . Also in such animal study, though it was shown that tremor in the limbs is associated with oscillatory neuronal discharges in the Globus Pallidus externus (GPe), Globus Pallidus Internus (GPi) and Sub Thalamic Nucleus (STN), lesion of the STN reduced or even abolished the tremor in MPTP monkeys[13]. Tremor arrest was indeed the earliest and most reliable sign of a therapeutically effective lesion of the STN in MPTP monkeys. Long term stimulation of STN in Parkinsonian monkey was also accompanied by supression of tremor. Despite such experimental evidence , Ventralis Intermedius (VIM) nucleus of thalamus was still the only target nucleus for many years for the control of tremor and STN was completely ignored[14,15].

There is, however , no scientific reason to ignore the STN in the mechanism of tremor and other cardinal features in PD and therefore, now it becomes the main target nucleus for deep brain stimulation in PD patients[16].

In this article , we provide the clinical evidence and therapeutic effect of DBS in STN in controlling the tremor and other cardinal features of PD[17,18,19].

Patient selection:

In selecting the appropriate patient , risk versus benefit should be assessed carefully .Parkinsonian syndrome improves by DBS only when it is Levodopa responsive idiopathic PD[20]. Except tremor , responsiveness to DBS of all other cardinal features are variable . Initially all motor symptoms respond very well to Dopaminergic medication but after few years lead to long term motor complications like disabling drug induced dyskinesia, wearing off , off or on phenomenon etc[3,21,22] . About 50% drug non-responsiveness and motor fluctuation develop after a mean of 5 years of treatment and it is high in young patients. Levodopa sensitive off symptoms; Levodopa induced dyskinesia and Tremor-these three features are well controlled by DBS[23].

Concerning STN-DBS , Dopamine responsiveness has the highest predictive value for a good and persistent motor outcome with stimulation and symptoms resistance to Dopamine are typically resistance to DBS also [24,25,4]. In Levodopa challenge test , if there is improvement of motor symptoms in at least 30% comparing to " off " state , DBS will be beneficial . "off " state assessment is performed after withdrawal of all medications for at least 12 hours. Then 1.5 times usual effective morning dose is given to assess the "on " state motor score . At least 30% motor score improvement is desirable compare to off state motor score as assessed by Unified Parkinson's Disease Rating Score (UPDRS) for a successful outcome after DBS[26,27,28]. 50% improvement of UPDRS motor score in Levodopa challenge test is shown to have best outcome. A low responsiveness to Levodopa is associated with post operative cognitive decline[25,27] . "Off" phase should cover at least 25% of awake time and should have minimum severity of 30/108 point on UPDRS motor score[28]. Peak -dose-hyperkinesias and biphasic dyskinesias as well as OFF-dystonia respond well to DBS. Severe disabling tremor is the only symptom which, upto 80 to 90%, shows excellent response to DBS even with Levodopa resistance. And that,s why , tremor is therefore a good target symptom for STN-DBS[29,30].

During the best medical ON state , if Freezing of gait, postural instability and dysarthrophonia persist , there will be no significant improvement after STN-DBS[26,27]. Atypical Parkinsonian syndrome, e.g. Multiple System Atrophy, Progressive Supra Nuclear Palsy show transient or no response to DBS[31] . Although sometimes bladder function may improve slightly after DBS, early autonomic involvementindicates atypical Parkinsonian symptoms and should be avoided for DBS[32] .

Another parameter is age for successful outcome of DBS surgery, e.g. biological age shows an inverse correlation with the improvement of motor function[26,27,33,34].

Finally, prior to implanting DBS electrodes evaluation of cognitive function and Neuropsychiatric symptoms is of crucial importance, because, in that case DBS is contraindicated.

Target points:

STN is the main target nucleus for DBS in PD . All cardinal symptoms that respond well to Levodopa , including akinesia, rigidity, tremorand postural instability can be effectively treated by STN-DBS[33,34]. The best outcome achieved by stimulation of the dorsolateral motor part of the STN but some times zona incerta shows good results[35,36].

Levodopa induced dyskinesia improved by implanting DBS electrode at Globus Pallidus Internus (GPi) nucleus[37,38]. The effect on OFF-symptoms might be

less pronounced. However, the excellent reduction of dyskinesias allows a further increase of Dopaminergic medications[39,40,33].

In PD patients, only tremor can be immediately and effectively controlled by implanting DBS electrode in Ventralis Intermedius Nucleus (VIM) of Thalamus but there is no effect on akinesia and rigidity . Therefore , VIM-DBS is performed in PD patients only in older age group people with unilateral tremor dominant PD[5].

The Pedunculopontine Nucleus (PPN) has recently came to the target point of interest of DBS implantation in early as well as late PD[41].

Patients and Methods

Deep Brain Stimulation

4 patients with PD, all of who had tremor and other cardinal features of PD e.g. rigidity , akinesia and postural instability and their motor complications were uncontrollable by the available therapeutic approaches were surgically treated by implanting electrodes in STN for long term stimulation.Pre operativecharacteristics of the patients are summarized in table 1. The Unified Parkinson Disease Rating Scale (UPDRS) was used for global pre and post operative evaluation. For post-operative evaluation we assessed after six months.Pre-operative "ON" and "OFF" state UPDRS were scored to select the ideal patient for Deep Brain Stimulation (DBS) surgery. The "OFF " was defined as motor assessment after 12 hours without antiparkinsonian drugs and "ON" is defined as motor evaluation after injestion of one and half times the usual optimum morning dose of Levodopa e.g on the basis of " Levodopa challenge test ". Minimum 30% improvement in UPDRS scoring at ON state comparing with the OFF state were selected for DBS surgery.

Procedure and targeting the STN

Firstly , we do very high resolution MRI in different sequences specially T1 and T2 at 1mm interval . Then we used the navigation soft ware " Neuroinspire "to calculate the coordinates X, Y , & Z for targeting the dorso-lateral STN nucleus . Then after fixing the Leksell frame to patient's head we do a CT scan . This CT scan and previously done MRI we fuse digitally in the same Neuroinspire soft ware and finally we re-establish those X,Y & Z coordinates in relation to the same patient's head . Finally after fixing the frame to the OT table and under local anaesthesia we insert two electrodes in two (Right & Left) Subthalamic Nucleus (STN) in each patient . Immediate after insertion temporarily the tremor goes away due to mechanical injury to the nucleus by the electrodes. Then we check the impedance of those electrodes and finally check the correct position of the electrodes by doing an another CT scan And lastly we connect these electrodes to the battery placed underneath the skin of left chest wall under general anaesthesia.

It is to be noted that the subthalamic nucleus (STN) is an almond shaped nucleus. For targeting the STN, the average coordinates are 2-3mm behind the midcommissural point (AC-PC line) , that is called Y axis . 12-14 mm either right or left lateral to AC-PC is X axis and 4to 6mm below the AC-PC is Z axis .

Clinical result

We treated four patients with bilateral STN stimulation and assessed after six months. Stimulation parameters were – Amplitude range from 1.5V to 4 V ; Pulsewidth range from 90 to 120ms and Frequency from 120 to 180 Hz. Assessment at six month was carried out.

There was marked reduction of tremor both at rest and during action in all patients (Table2) . Same efficacy reported by Crack et al., in terms of tremor reduction by DBS monitored for 3-6 months.

Table-I

Patients selected for STN-DBS (n=4)

General criteria for selection

Patient No.	Sex	Age (yrs)	PD (yrs)	LDopa (yrs)	LDopa Dose(mg)	Tremor Score (OF)	Tremor Score(ON)	UPDRS OF	UPDRS ON
1	F	62	12	11	1100	22	10	4743.51%	3027.77%
2	M	65	10	9	1400	23	12	5651.85%	3532.40%
3	F	58	9	9	1000	20	10	4541.66%	3128.70%
4	M	42	12	11	825	18	8	4339.81%	3027.77%

STN, sub thalamic nucleus; PD, Parkinson,s Disease ; UPDRS, Unified Parkinson,s Disease Rating Scale ; DBS , Deep Brain Stimulation

Tremor Score Maximum=33

Table-II

Tremor reduction by DBS in the STN assessed by tremor score

Patient no.	Tremor score (R + P)*	
	Preoperative	Postoperative after six months
1	22	0
2	23	1
3	20	0
4	18	0

DBS, deep brain stimulation; STN, sub thalamic nucleus; R+P, resting + postura
Tremor score was maximum 33.

Table-III

Clinical improvement by STN-DBS assessed by UPDRS motor score

UPDRS before surgery OFF state	UPDRS before surgery ON state	UPDRS after DBS (six months after surgery)	UPDRS improved by DBS surgery(%)	Average Improvement
47(43.51%)	30 (27.77 %)	18 (16.66 %)	61.70 %	63.33 %
56 (51.85 %)	35 (32.40 %)	20 (18.51 %)	64.30 %	(p<0.001)
45 (41.66 %)	31 (28.70 %)	17 (15.74 %)	62.21 %	
43 (39.81 %)	30 (27.77 %)	15 (13.88 %)	65.13 %	

STN, subthalamic nucleus ; DBS, deep brain stimulation ; UPDRE, unified Parkinson,s disease rating scale
UPDRS motor score maximum 108

Not only the tremor but also the other cardinal features like rigidity, bradykinesia were also improved . And along with the limb movements , body posture , gait , walk, standing from chair , facial expression , speech, swallow , memory were all improved by DBS. All these were assessed by UPDRS score and shown in table 3. The UPDRS score decreased in " OFF " period average by 63.33% (p<0.001) along with the Levodopa dose reduced significantly.

There was no significant post-operative complications only mild depression developed in one patient.

Discussion:

In general , the tremor related neuronal activity , microstimulation intraoperatively and after that long term high frequency stimulation prove that STN is the important structure in the mechanism of tremor in PD though whether the STN plays the primary role or mediate the other basal ganglionic structure to do the such , it is still not clear.

VIM is the well stablished structure in development of PD and MPTP monkey[17,20]. Positron Emmission Tomography (PET) shows that there is increase blood flow in cerebellar vermis, sensory motor area , premotor cortical area in PD tremor which is similar to any type of " Tremor Like " repetitive movement in normal people. These areas show decreased blood flow after DBS in VIM[44] . Though Cerebellum and VIM are not connected directly to basal ganglia structures and hardly considered as tremor producing structures in Parkinson,s disease.

Dopamine depletion results in reduced inhibition of the Gaba-amino—butyric – acid (GABA) which causes excessive inhibition of the Globus Pallidus Externa (GPe) which causes functionally hypoactivity. Normally there is a reciprocal balance berween GPe inhibitory activity and the excitatory effect of STN. Excessive GPe inhibition leads to increased firing rate in STN. The oscillatory low frequency firing cluster cells inGPe due to reduced inhibition results in excessive STN activity which could only be abolished by inactivating the cortex[14] .

All these above observations indicates that STN have the property of discharge in brust in Dopamine deficiency . Furthermore , the STN not only exerts the excitatory effect on both Globus Pallidum (GP)

components but also control synchronizinglarge number of GP neurons. We therefore suggest that tremor in PD is well controlled by DBS in STN[9] . Though, still there is no exclusive available data regarding the origin of oscillation in basal ganglia , but hopefully , in future , there will be available data to change the view that VIM in thalamus may not be the cause of tremor and STN is the only structure for DBS to control the tremor in PD[11,19,39] .

Grenoble's group shows that , though the initial effect of DBS in STN or VIM to control tremor in PD is same , in case of VIM DBS , after 5-10 years, there develops severe dyskinesias and "OFF" episodes . On the contrary, STN stimulation improves all cardinal features of PD without complications in long term follow-up. All these suggest that , STN might be the effective target considered for the treatment of all cardinal features if PD with mainly the severe PD[16,18,19].

Conclution:

Till today , excellent result can only be achieved through STN-DBS to control the all cardinal features of PD including severe tremor .Except only in few cases of severe unilateral tremor with extreme age , the VIM nucleus of thalamus or in cases of severe dyskinesias, Globus Pallidus Internus (GPi) might be the target nucleus .

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