

CLINICAL IMPROVEMENT OF PARKINSONIAN SYMPTOMS MAY NOT BE UNCOUPLED BY LID RESOLUTION BY STIMULATION IN PARKINSON'S DISEASE.

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Parkinson's disease (PD) surgery field, some authors reported that the best clinical effects on akinesia and rigidity may be achieved by stimulating sites different from those producing the resolution of Levodopa Induced Dyskinesia (LID).

In 10 consecutive PD patients bilaterally implanted with quadripolar electrodes in the GPi for deep brain stimulation (DBS), we performed consecutive (six months) apomorphine tests to study the dose-response curve for dyskinesias. The clinical status was also assessed. Clinical improvement and Abnormal Involuntary Movements apomorphine - related, were assessed with different modalities. Intracranial extracellular recordings and apomorphine challenge were used to establish cells responsiveness to the drug and sensitivity of levodopa-induced dyskinesias to DBS with the selected contacts.

Before surgery and after surgery with off stimulation all the patients showed the same severe dyskinetic response to apomorphine. We observed a decrease a mean decrement of the UPDRS score of 66% and a drop from 12,5 to 1,5 of the mean score for abnormal involuntary movements (AIMs) following the administration of the larger dose of 4.5 mg of apomorphine. Monopolar stimulation by the uppermost contact produced a mean decrease of the UPDRS score of 56% and reduction of from 12,5 to 2,75 of the mean AIMs score. Stimulation with the lowermost contact produced a mean decrease of 76% but a mean AIMs score decrease from 12,5 to 4,5. NMR postoperative imaging showed that all the electrodes were located in the GPi with the lowermost contact in the ventral part of the nuclei and the uppermost contact in the border between GPi and GPe.

We suggest that bipolar stimulation of GPi is able to produce both i) amelioration of rigid-akinetic symptoms in PD and ii) reduction of levodopa-induced dyskinesias, while monopolar stimulation only produces good antiparkinsonian or antidyskinetic effects. The different results in the other groups may be explained by the hypothesis that dorsal and ventral GPi may have different functional roles. 1

to affect both dorsal and ventral GPi, may obtain all the effects seen separately with monopolar stimulation in other and i

ID and akinesia resolution by DBS

of radiofrequency lesions or the best position of quadripolar stimulating electrodes within the GPi is recently a disputed argument in Parkinson's disease (PD). Some authors reported that the best clinical effects on akinesia and rigidity are obtained with lesions different from those producing the resolution of levodopa-induced dyskinesias (LID).¹⁻³ According to these Authors, this combination make difficult to obtain both effects with a single electrode lead stimulation or a limited lesion, as often should be necessary for a good LID control is achieved, this may lead to an increase in levodopa therapy.¹⁻⁷ These considerations may strongly support the subthalamic nucleus (STN) as the ideal target in PD.⁸ STN stimulation improves so much akinesia and rigidity that levodopa therapy may be reducing the LID appearance.⁹⁻¹²

the data from four consecutive severe PD patients bilaterally implanted in the GPi with stimulating electrodes. We demonstrate that bipolar stimulation is able to produce a relevant clinical amelioration of main parkinsonian symptoms (akinesia and rigidity) to make the therapy more tolerable. At the same time the stimulation of the same site is able to counteract dyskinetic movements induced by apomorphine. Monopolar stimulation did not produce the same effects. NMR study of electrodes sites did show a positioning within the GPi of all the electrodes. We propose that bipolar stimulation and, the intra-operative procedure for the selection of the site of permanent stimulation, may influence the clinical outcome and account for the discrepancies with other groups.

3) METHODS.

Patient 1) was a male Caucasian 53 years old PD patients with 12 years disease history and 10 years of LID. Patient 2) M.F. was a male Caucasian 55 years old PD patients with 11 years disease history and 6 years of LID. 3) M.R. was a male Caucasian 48 years old PD patient with 12 years of disease history and 10 years of LID. Patient 4) B.T. was a male Caucasian 56 years old PD patient with 22 years of disease history and 4 years of LID. The clinical characteristics of the four patients are reported in Table 1.

The clinical course of the four patients was very similar. After initial benefit from therapy (3-7 years), "on-off" fluctuations and marked LID were observed. After observation, the best therapeutic effects did not avoid one to two hours of severe dyskinesias after each administration, preventing patient's walking ability, followed by an "off" period. The true "on" period between dyskinetic phases was often reduced to a few minutes. Hoehn & Yahr stage in "off" was 5 and during "on" phase was between 2 and 3. They were all tested with mental deterioration and dementia or systemic disease. After 15 days of therapy withdrawal, in the four preoperative days, we administered to the patients different doses of subcutaneous apomorphine (1.5, 3.0, and 4.5 mg in different days) to study the complete dose-response curve for abnormal involuntary movements (AIMs) assessed by a modified Abnormal Involuntary Movements Scale.¹⁴ Repeated domperidone 30-40 mg doses were associated with the test dose. We selected a dose for the intraoperative test producing a clear clinical improvement although not so large to induce dyskinesias. The test dose was administered two times in order to verify the reproducibility of the response. Electrodes implantation in each patient was performed under general anesthesia in two operating sessions separated by one month. The surgical technique was similar to that reported by Limousine et al.¹³ The craniotomy allowed five simultaneous trajectories, with four trajectories each at 2 mm apart from the central one, arranged in "x" shape.

electrodes, 1.0-1.5 M Ω) inserted into each trajectory, allowed to record single and multi-unit activity as well to stimulate (10-100 Hz, 80-200 μ s pulse width, 0-150 Volts) with an external stimulator (Grass model 8800 coupled to a stimulus isolation unit). Intraoperative high frequency stimulation was used to assess the electrode producing the best clinical results (20-30% reduction) on three sessions a subcutaneous apomorphine injection of the selected test dose was performed. Simultaneous extracellular recording of identified GPi neurones showed a clear cut apomorphine-induced firing decrease.¹⁵ The selected trajectory for the permanent electrode showed more evident anti-parkinsonian effects among those in which apomorphine-sensitive cells have been recorded. The clinical effects were always tested. The permanent quadripolar electrodes were positioned according to trajectories laying between 60 and 80 degrees and between 65 and 75 degrees in the coronal plane. After one month from the last surgical section, two permanent Medtronic ICS electrodes were positioned, connected to the upper contact (positive) of each electrode referred to the lower one (negative) with a stimulation pulse width, voltage 2.9-5.3 V. Only bilateral stimuli were assessed and adjusted in each side to obtain the best clinical effects. The symptoms in the post-surgery period were much more evident than during the intraoperative test because the lower electrode resistance was high. Thus pharmacological therapy was administered only during the night when stimulation was off (10 p.m.-08 a.m. = off time). To perform the dose-response curve without stimulation, the stimulators were not switched on in the morning in the testing day and in the evening before according to CAPIT procedure.¹⁶ Results of stimulation were assessed in different days at the same day with the stimulators either in bipolar or monopolar mode. The effects of stimulation, either bipolar or monopolar (uppermost or lowermost versus cage positive) on AIMs were assessed by means of new dose-response curves to apomorphine performed with and without stimulation session. The apomorphine-induced U.P.D.R.S. amelioration was also compared in the five following conditions: i) before surgery; ii) after surgery bipolar stimulation on; iii) after surgery bipolar upper stimulation on; iv) after surgery bipolar lower stimulation on; v) after surgery monopolar upper stimulation on. The aim was to assess whether the antiparkinsonian effect of the drug was reduced by stimulation. This analysis was performed by means of non parametric Wilcoxon test.

After bilateral bipolar stimulation, akinesia and rigidity were reduced of a range between 63.45% and 71.43% in comparison to the pre-surgery results. The results reported in Table 2 show that bilateral bipolar stimulation of GPi produced a mean clinical improvement of 66.32% in U.P.D.R.S. score and of 56.52% in comparison to the post-surgery off stimulation score. Moreover AIMs induced by the larger dose of apomorphine were almost completely blocked by bipolar GPi stimulation. The range of AIMs produced by 4.5 mg of apomorphine in the four patients before surgery with off stimulation was from 12,5 to 11,5, while decreased to a range between 0 and 5 (mean 1,5) with bipolar stimulation. Bipolar monopolar stimulation with the upper leads counteracts apomorphine dyskinetic effects in a satisfactory manner (see Table 2). The range of AIMs induced by 4.5 mg of apomorphine was 2,75 (range 1 and 5), although less efficient than bipolar stimulation, but produced a clinical amelioration (see Table 2) significantly ($p < 0.05$ Wilcoxon test) lower than that observed with bipolar stimulation (56.40% versus 66.32%). Bipolar stimulation with the lower contacts produced an AIMs counteraction significantly ($p < 0.05$) less efficient (mean 4,5 range:2-7) than bipolar and upper monopolar stimulation (see Table 3). The clinical improvement of U.P.D.R.S. score was on the contrary the mean range 64.88-84.83, $p < 0.05$). See Table 2.

The apomorphine-induced U.P.D.R.S. amelioration following the three doses of apomorphine in the five conditions (before surgery, after surgery bipolar on in bipolar, monopolar upper and monopolar lower stimulation) are reported in Table 4. It is evident that the “on stim

tion of the percentage apomorphine-induced amelioration of the U.P.D.R.S. score. This reduction is in accordance with the stimulation itself.

After surgery before Itrel II positioning, showed that the electrodes were positioned in the GPi in all the hemispheres, the lower part of the nucleus and the uppermost contact in the border between the GPi and GPe according to the trajectories report

strate in four consecutive PD patients that permanent bipolar stimulation of the GPi may dramatically ameliorate parkinsonian (71.43%) and abolish antiparkinsonian therapy-induced dyskinesias as well. These findings seem to be in contrast with the data of Krack and coll.³ data are somewhat more comparable to our findings because their intra-operative procedure employs both multiple electrodes in different trajectories and test stimulation from the same electrodes to assess clinical effects on rigidity and LID. A main not comparable aspect is that no mention is given by the Authors about the angles of the trajectories in the coronal and sagittal planes. In an apparently similar procedure, they showed that the best antiparkinsonian effects with unilateral stimulation, were obtained with the upper contacts of the permanent electrodes, while the best anti-LID effects were obtained by means of the lower contacts. Moreover stimulation of the GPi for LID effects, also produced a reduced antiparkinsonian efficacy of levodopa therapy that the authors parallel to the post-operative results reported by other authors after GPi lesions.⁴ Similar results have been reported by Bejjani et al.²

Our results may appear to be different, almost the opposite because the lower lead produced the larger antiparkinsonian effect while the upper produced the larger LID effects. Thus, the differences between the two procedures must be highlighted. The main difference is that our permanent stimulation was used in unilateral mode either with bipolar or monopolar mode. The bilateral stimulation probably produces a potentiation of the effects of stimulation used by Krack and coll in their studies. Our intra-operative data on the effect of unilateral test stimulation show a much larger reduction (71.43%) than those observed with bilateral permanent stimulation (66-76%). Moreover the bipolar stimulation between the upper and lower contacts in each electrode may produce a coupling of the effects observed separately by the previous works and by ourselves in the unilateral stimulation. It can be hypothesised that bilateral bipolar stimulation might have produced similar results also in the series of findings reported by Krack and coll.

This difference must be explained: why the upper contact stimulation is producing a larger antiparkinsonian effect in Krack series, while we observed a larger LID effect utilising the lower contact. This difference may be the result of a different positioning of the electrodes in the pallidal groups.

The management of the pallidal complex (GPe and GPi) is very complicated. The coronal and sagittal angles for electrode positioning were what we consider the optimal positioning of the electrode: the lower contact in the postero-ventral GPi and the upper contact in the GPe at the border between the GPe and the GPi. We do not know the trajectory followed by Krack and coll., but the lower contact was positioned at the same ventro-posterior site of the GPi since the Authors aimed their trajectory to the optic tract. However a different orientation, without or with small coronal inclination, or with smaller sagittal inclination, both may produce a different positioning of the electrode. If the postero-ventral part of the GPi, then the upper may result more peripheral and less inside the core of the pallidal complex. If the upper part of the GPi, then the lower may be out of the postero-ventral part. This may account for the different clinical results.

coll procedure⁹ does not include an intraoperative test with apomorphine thus avoiding the possibility to test the effect of the selected area. GPi cells have been reported to be inhibited by dopaminergic agonists or dopamine precursor both in MPTP monkey and patients.^{15, 18} From the functional point of view, it could be relevant to ensure that GPi cells of the selected area are those that respond to dopaminergic treatment.

Reduced reduction of levodopa effect was reported by Krack and coll³, and presumed by Krack and coll.¹ in patients series reported by the mentioned authors do not agree.²⁰ Similar reduced efficacy of levodopa therapy following GPi stimulation has been reported by Verhagen and coll.⁴ after pallidotomy. We observed a “reduced” percentage efficacy of apomorphine during stimulation in the improved status of the patients when the stimulus was on both in bipolar and in monopolar mode. This can be considered a stimulation which improves the clinical status so that apomorphine may only produce a smaller improvement.

One of our population was the relatively young age at disease onset and at operation time. This may be a condition explaining the results in our group. However this does not seem to be a main difference with other groups patients because Krack and coll²¹ recently reported that stimulated GPi young-onset PD patients of a mean age of 51 years at surgery time, with a mean disease history of 16 years. After their U.P.D.R.S. section III score improved from 53.6 to 32.5 which is only the 39.4% of improvement.

Our data demonstrate that bilateral bipolar stimulation of the GPi may simultaneously produce antiparkinsonian and anti-dyskinetic effects. In the possibility to have pro-dyskinetic effect of STN stimulation, our data should suggest a caution in selecting in all the patients for STN DBS in Parkinson's disease. A adequate trial comparing the STN stimulation effects with those of GPi in the same patients is necessary. We imply that a selected population will be implanted bilaterally in both sites STN and GPi and that afterwards the clinical effects can be compared.

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Table 2

Tot. UPDRS incr % Bipolar			Patients	Tot. UPDRS incr % Mono UP		
Pre-Post off	Pre-Post on	Post off-on		Pre-Post off	Pre-Post on	Post off-on
13,6	71,43	67,12	AP	13,1	53,57	46,58
13,1	63,45	57,94	FM	13,1	65,52	60,32
21,37	64,78	45,63	MR	21,37	52,2	26,21
15,7	65,62	55,4	BT	15,7	54,3	43,7
15,94	66,32	56,52	Mean	15,82	56,40	44,20

Tot. UPDRS incr % Mono Low		
Pre-Post off	Pre-Post on	Post off-on
13,1	64,88	59,59
13,1	84,83	82,54
21,37	79,87	68,93
15,7	75,84	69,01
15,82	76,36	70,02

Table 4

Tot. UPDRS incr % PRE			Patients	Tot. UPDRS incr % POST-OFF		
Apo 1.5mg	Apo 3 mg	Apo 4,5 mg		Apo 1.5mg	Apo 3 mg	Apo 4,5 mg
22	28,5	23	AP	51	64	23
9	41	50	FM	8	41	50
0,5	93	83	MR	27	60	58
11	35,3	50	BT	27,2	54	42,5
10,6	39,7	51,5	Mean	28,3	54,75	43,4
POST-ON Bipolar			Patients	POST-ON Mono Up		
Apo 1.5mg	Apo 3 mg	Apo 4,5 mg		Apo 1.5mg	Apo 3 mg	Apo 4,5 mg
0,5	0,5	0,5	AP	21	20	22
41	80	22	FM	38	0,8	0,9
25	35	39	MR	17	42	63
22,3	37,8	19,7	BT	24	19,6	27,6
22,2	38,3	20,3	Mean	25,0	20,6	28,4
POST-ON Mono Low						
Apo 1.5mg	Apo 3 mg	Apo 4,5 mg				
0,8	15	20				
4	9	0,9				
43	52	43				
15	24,8	20				
15,7	25,2	20,97				

Table 1

CHARACTERISTICS OF PARKINSON'S DISEASE GROUP

Age surg	PD diagn	LD onset	LTTS	W/O	Dysk	LD before
53	41	42	43	Y	Y	1500
52	41	42	46	Y	Y	1200
56	34	43	47	N	Y	880
48	35	40	45	N	Y	1000

Table 3

AIMs PRE				AIMs POST OFF		
Apo 1.5mg	Apo 3 mg	Apo 4,5 mg	Patients	Apo 1.5mg	Apo 3 mg	Apo 4,5 mg
4	6	10	AP	4	6	7
2	12	20	FM	0	5	18
0	5	10	MR	4	5	11
0	6	10	BT	2	5	10
1,5	7,25	12,5	Mean	2,0	5,25	11,5
AIMs POST-ON Bipolar				AIMs POST-ON Mono Up		
Apo 1.5mg	Apo 3 mg	Apo 4,5 mg	Patients	Apo 1.5mg	Apo 3 mg	Apo 4,5 mg
0	0	0	AP	1	2	1
0	2	0	FM	1	1	3
7	4	5	MR	0	7	5
2	1	1	BT	1	1	2
2,25	1,75	1,5	Mean	0,75	2,75	2,75
AIMs POST-ON Mono Low						
Apo 1.5mg	Apo 3 mg	Apo 4,5 mg				
0	0	2				
2	8	6				
0	5	7				
1	3	3				
0,75	4,0	4,5				

