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**Efficacy and safety of pallidal stimulation in primary dystonia: results of the Spanish
multicentric study**

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INTRODUCTION

Dystonia is a complex clinical syndrome originated by a wide range of aetiologies. The diagnosis of dystonia is made after the evaluation of etiological, phenomenological and genetic factors (1). Medications, except in patients with dopa responsive dystonia, are of limited efficacy. Botulinum toxin injections are not applicable to patients with generalized dystonia since many muscular groups contribute to disability (2).

Clinical studies in children and adults with primary generalized dystonia (PGD) have reported beneficial effects of bilateral GPi deep brain stimulation (DBS) in both motor symptoms and disability produced by dystonia (3-5) as well as a favourable impact of DBS in the health related quality of life (HRQoL) (6). Some clinical aspects of GPi stimulation in primary dystonia still remain controversial such as the influence of disease duration or age at onset in determining the post-operative clinical outcome.

We report here the results of a multicentric study designed to assess the tolerability and clinical effects of bilateral pallidal DBS on motor impairment, functional disability, quality of life, pain, and mood in patients with medically refractory primary generalized or segmental dystonia.

PATIENTS AND METHODS

Study design and patients' eligibility

The study was a one year observational, prospective, multicenter study with a single therapeutic arm. Open-label, blind, and self-assessed evaluations were applied to investigate the efficacy and safety of bilateral GPi DBS in patients with primary dystonia.

The study was approved by the ethical committees of participating centres. Informed consent was obtained from each subject. Ten centres participated in this study.

Inclusion criteria were: 1) primary generalized or segmental dystonia; 2) age between 12 and 70 years; 3) disease duration of more than two years; and 4) functional limitation due to dystonic symptoms despite of best medical treatment. Patients with secondary dystonia and patients with focal dystonia or hemidystonia were not eligible for the study. Patients in which fixed dystonic postures had induced permanent skeletal deformities producing severe disability were also excluded. Patients with cognitive impairment (MMSE<24) or with active psychiatric symptoms were excluded. General conditions limiting life expectancy or structural brain lesions contraindicating surgery were also not eligible.

Clinical assessment

All patients entering the study were clinically evaluated at baseline, within two weeks before surgery, one month after surgery, and six months and one year after surgery. Evaluations consisted of: a) self-administered scales designed to measure quality of life, pain, caregivers' burden, and mood were used for self-assessment evaluations; b) open-label scores for motor symptoms, disability, and mood disorders were obtained by a designated neurologist in each participating centre following a Spanish version of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) (7); and c) motor BFMDRS scores were also obtained from independent blind investigators. Structured video recordings were used: films were encrypted in such a way that no reference to the visit number was included. Head and body masking was used to prevent disclosure of operative status or phase of follow-up. References to the specific hospital or the treating practitioner did not appear in any of the videos. Blind evaluators were selected among accredited experts in movement disorders. Before video evaluations, a one day meeting of video rating was performed in order to agree a common protocol for assessing dystonic symptoms in accordance

with BFMDRS guidelines. Several patients shown in videos were scored independently to obtain inter-rater agreement.

Pain related to dystonia was graded through the Faces Pain Scale, a ten-point scale (0 = no pain; 10 = worst pain) (8); HRQoL before and after surgery was analyzed by the validated Spanish version of the Short-Form General Health Survey (SF-36), a generic 36-item health survey (9, 10). We also administered the validated Spanish version of the EuroQoL5D (EQ5D) (11, 12), a self-reported generic questionnaire measuring HRQoL where health status is divided into five dimensions within three severity levels (3 worst-1 best); this includes a visual analogical scale (VAS) scored from 0 (worst) to 100 (best). Caregivers' burden was assessed using a self-administered questionnaire, a validated Spanish version of the Zarit Caregiver Burden Scale (13-15). Mood symptoms were evaluated through the Beck's Depression Inventory-II (BDI-II) (16).

Stimulation electrical parameters were adjusted according to the best judgment of local clinical investigators of the study in order to obtain the best clinical outcome while minimizing side effects. Stimulation electrical parameters were recorded at the end of the first session when the neurostimulators were switched on, at six months, and at one year follow-up.

Data analysis

Primary outcome measurements were improvement in the motor symptoms, disability (BFMDRS) and HRQoL scores (SF-36 and EuroQoL) in patients with primary dystonia treated with bilateral GPi stimulation. Secondary outcome variables were the safety of bilateral GPi stimulation for the treatment of primary dystonia, assessed by the incidence of permanent Adverse Events, and the effects of the intervention on patients' associated pain, mood and caregivers' burden.

Comparison of clinical, motor, functional and HRQoL measurements was carried out using repeated measures Wilcoxon tests. A two-tailed probability level of 5% ($p=0.05$) was considered significant. All statistical tests were two-tailed and were not adjusted for multiple testing. The

differences in distribution between age at onset of dystonia and duration of the disease with disability scores were analyzed by the ANOVA regression analysis.

Clinical responses were predefined as follows: a) good responders: patients showing more than 50% improvement on motor BFMDRS scores as judged by blind assessment of standardized videos at one year; b) partial responders: patients improving 25-50%; c) no responders: patients with less than 25% of improvement; d) negative changes were considered to be as worsening from the basal condition. Statistical analysis was performed using the SPSS 12.0 software package for Windows (SPSS Inc, Chicago, IL).

RESULTS

Demographic aspects

A total of 24 patients were included in the study. Twenty-two patients had PGD, and two patients had primary segmental cervical dystonia. The mean and median age of patients at enrolment was 30 ± 14 and 35 ± 0.5 years respectively. Mean disease duration was 10 ± 7 (5-26) years and mean age at onset was 20 ± 13 (13-66) years; the ratio of men and women was 1:1. There was a family history of dystonia in 6 patients (25%). Six patients in the study were DYT-1 positive (25%).

Outcome

The results refer to 22 patients since two patients were drop-outs due to adverse effects and were excluded from further analyses. None of the patients presented significant motor or functional changes during the first month after surgery. At this moment, the implanted stimulation electrodes were already in place but neurostimulation had not been yet initiated (Table 1). Clinical effects produced by bilateral GPi DBS, as assessed by the BFMDRS, are shown in Tables 1 and 2. All body segments showed statistically significant improvement in dystonia except the cranial area (eyes, voice, and swallowing). At final follow-up, eight patients presented good clinical response,

(>50% BFMDRS motor score); nine patients improved between 25-50% of the motor BFMDRS (partial responders); and five patients were considered to be non-responders (<25% improvement). Medications for dystonia were globally reduced after surgery.

We found a positive correlation between the improvement of both motor and functional BFMDRS scores and the age of patients at the moment of surgery (Rho Spearman correlation coefficient = -0.66; $p=0.001$); no correlations were found between motor and functional scores and neither age at onset of the disease (Rho Spearman correlation coefficient = 0.14; $p=0.5$) nor disease duration (Rho Spearman correlation coefficient = 0.16; $p=0.5$). Improvement of motor scores improved correlated with the presence of DYT1+ mutation but functional scores did not.

Mean MMSE scores did not change significantly all over the follow-up (basal = 28.86 ± 2.16 ; final follow-up = 28.23 ± 2.67). Beck's Depression Scale scores were 34.87 ± 12.26 before surgery, and 28.67 ± 9.58 at six months, and 27.12 ± 11.03 at twelve months follow-up ($p<0.05$).

Significant changes were seen after surgery in several areas explored through the SF-36 questionnaire, including general health, physical functioning, bodily pain, and in both physical and emotional role limitations. No significant changes were found in social function, vitality, or mental health (Figure 1). Summated physical domain scores were 36.08 ± 8.79 and 62.37 ± 8.41 ($p<0.01$) at final follow-up, while the sum of mental domain scores was 51.98 ± 14.01 preoperatively and 62 ± 13.11 (not significant) at one year visit (Figure 1).

The visual analogue scale of the EQ5D questionnaire was scored 36.25 ± 22 in basal assessment, whereas the score increased to 66.77 ± 18.6 at six months postoperatively, and to 71.57 ± 26.47 at final follow-up ($F=7.7$; $p=0.0001$). Mobility, self-care, usual activities, anxiety/depression and pain/discomfort scores also improved after surgery. Correspondingly, the faces pain scale scores improved from 3.95 ± 2.9 preoperatively to 1.83 ± 2 at six months, and 1.87 ± 1.7 at twelve months follow-up ($F=2.81$; $p=0.03$).

No changes were found in any item of the Zarit scale before and after surgery (basal score was 45.29 ± 13.3 , at six months 48.28 ± 12.9 , and 46.25 ± 10.8 at twelve months).

Adverse effects and complications of therapy

No mortality was observed during the study. Six of the 24 patients presented adverse events (25%). Four of these (16.6%) were considered serious adverse events.

In one patient a mild left hemiparesia was observed during the operation. Brain MRI performed immediately after electrode implantation revealed bleeding in the right lenticular nucleus and internal capsule (1.5 X 2 X 2cm). The motor problem resolved completely three months after surgery. One patient presented with acute reoccurrence of dystonic symptoms two months after GPi because of fracture of the cable, which was explanted and replaced. One patient presented several days after surgery with retroauricular pain in the region of the cables connecting the electrodes with the Kinetra that resolved with symptomatic treatment. Two patients presented transitory dysphagia and dysarthria after surgery. All the above explained complications occurred within the first three months after surgery.

Two patients were drop-outs before the first per protocol follow-up visit: one patient presented an infection in the scalp and the other because of a skin allergic reaction in the area of the Kinetra. Both problems resolved after explantation of the system.

DISCUSSION

Bilateral GPi DBS significantly improved dystonic symptoms as revealed by both open and blind assessments. Improvement of disability, pain, and mood was also observed. Seventeen of the 22 patients who completed the study achieved good or partial response to pallidal DBS. As previously reported by others (4), this therapy improved dystonia in all body segments except in the cranial region. Five patients were considered not responders. The degree of improvement observed in our patients is similar to that seen in the French and German multicentric studies (4-5).

We found a positive association between motor improvement with DBS and patients' age at the moment of surgery but not with disease duration or age at onset of dystonic symptoms. The presence of DYT-1 mutation was associated with better motor scores after surgery but not with the improvement of functional scores. Mood showed a mild but significant improvement after surgery, probably reflecting upgrading of motor function. This effect has been also observed in previous studies (20, 21). We found a mean 40% improvement in the physical aspects of the HRQoL, including motor functioning and pain. In contrast, we did not observe significant changes in social function and mental health. Previous studies on HRQoL in PGD had also shown pallidal stimulation to improve more the physical than the mental component of the SF-36 six months after surgery (4-6, 22). Despite the global improvement seen in a majority of patients caregivers' burden did not change after surgery when evaluated through a widely used scale tested in a Spanish population of Parkinson's disease patients (19). In this version, the proposed cut-off to determine caregiver's overload is 47 points (mild 47-55, intense >55, sensitivity 84.6%, specificity 85.3% the first and 89.7% and 94.2% respectively for the second). Since caregivers were subject to a mild overload, the Zarit scale could be not sensitive enough to detect minor changes in caregivers' burden after surgery.

In summary, in the present study GPi DBS proved significantly improved motor symptoms, pain, quality of life and mood. Younger age at the moment of surgery correlates positively with motor and functional outcome.

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Table 1. A: Open-label (A) and blind scores of the BFMDRS before and after surgery in each body segment (¶) for $p < 0.05$ in comparison between baseline and one year follow-up; (*) for $p < 0.05$ in comparison between baseline and one year follow-up. Values are reported as means \pm SD. Values are reported as means \pm SD.

A)

	Baseline	Post-op	p	6 Months	p	12 Months	p
Motor Score							
Eyes	0.29 \pm 0.71	0.41 \pm 0.8	.317	0.39 \pm 0.9	.236	0.17 \pm 0.7	.236
Mouth	1.86 \pm 2.92	2.25 \pm 3.1	.705	0.84 \pm 1.5	.051	0.58 \pm 1.0	.054
Speech/swallowing	4.54 \pm 5.14	4.77 \pm 5.6	.763	3.10 \pm 3.1	.180	2.70 \pm 2.5	.285
Neck	4.40 \pm 3.35	4.25 \pm 3.3	.109	2.11 \pm 2.4	.008	2.00 \pm 2.0	.007
Right arm	7.13 \pm 5.07	6.83 \pm 4.9	.129	2.00 \pm 2.0	.001	1.82 \pm 2.2	.001
Left arm	6.13 \pm 4.68	5.72 \pm 4.2	.271	1.84 \pm 2.1	.001	1.88 \pm 1.8	.005
Trunk	8.54 \pm 4.58	7.33 \pm 3.9	.066	3.00 \pm 3.6	.001	3.05 \pm 3.3	.001
Right leg	4.68 \pm 4.24	5.50 \pm 3.8	.317	2.21 \pm 2.3	.005	2.64 \pm 2.9	.032
Left leg	4.68 \pm 3.82	4.94 \pm 2.9	.564	2.05 \pm 2.0	.002	2.17 \pm 2.2	.011
Total	42.2\pm22	42.02\pm21	.097	17.56\pm12	.001	17.05\pm12	.001
Disability score							
Speech	1.59 \pm 1.33	1.50 \pm 1.3	.817	1.47 \pm 1	.763	1.58 \pm 1	.589
Writing	1.81 \pm 1.18	1.72 \pm 1	.461	1.15 \pm 0.8	.05	1.35 \pm 0.9	.061
Eating	1.72 \pm 1.45	1.5 \pm 1.4	.102	0.68 \pm 0.7	.006	0.76 \pm 0.9	.007
Swallowing	1 \pm 1.15	0.88 \pm 1	.480	0.47 \pm 0.6	.058	0.58 \pm 0.7	.190
Hygiene	1.68 \pm 1.17	1.77 \pm 1	.931	0.94 \pm 0.8	.003	0.88 \pm 0.6	.002

Dressing	1.54±1.14	1.5±0.9	.890	0.68 ± 0.6	.002	0.58 ± 0.6	.001
Gait	3.04±1.17	2.83±0.9	.102	1.68 ± 0.8	.001	1.88 ± 0.9	.001
Total	12.40±7.19	11.72±6	.330	6.63±4.1	.001	7.64±3.9	.001

B)

	Baseline	6 Months	12 Months
Eyes	0.33±0.2	0.31±0.8	0.23±0.7
Mouth	1.87±2.54	0.95±1.2	0.76±0.6
Speech/ swallowing	4.89±2.23	4.15±2.9	3.78±2.5
Neck	5.13±2.45	3.56±2.8 (¶)	2.9±2 (*)
Right arm	8.12±3.57	6.98±1.9 (¶)	4.79±2.2 (*)
Left arm	7.45±3.38	4.01±1.7 (¶)	3.8±1.8 (*)
Trunk	9.15±2.26	3.89±2.8 (¶)	3.61±3.3 (*)
Right leg	4.72±2.67	3.97±1.9	2.97±2.9 (*)
Left leg	4.78±2.12	3.18±1.5 (¶)	3.14±2.2 (*)
Total	46.4±21.4	31.0±17.5 (¶)	26.1 ±16.3 (*)

Table 2. Effect size and magnitude of change observed for different measures.

	Mean	Magnitude of change	Effect size*
BFMDRS Motor score (blind)			
Baseline	46.4		
6 Months	31.0	-33.19%	-0.57
12 Months	26.1	-50.22%	-0.86
BFMDRS Motor score (open)			
Baseline	42.2		
6 Months	17.56	-58.38%	-1.12
12 Months	17.05	-59.59%	-1.14
BFMDRS Disability score (open)			
Baseline	12.40		
6 Months	6.63	-46.53%	-0.80
12 Months	7.64	-38.39%	-0.66
SF-36			
Physical health summary			
Baseline	34.19		
6 Months	45.03	31.70%	0.88
12 Months	44.53	30.24%	0.84
Mental health summary			
Baseline	42.51		
6 Months	48.33	13.70%	0.41
12 Months	49.92	17.43%	0.52
EQ-5D			
EQ-5D Index			
Baseline	0.4103		
6 Months	0.6731	64.05%	1.31
12 Months	0.6315	53.91%	1.10
VAS			
Baseline	40.45		
6 Months	69.12	70.88%	1.34
12 Months	65.00	60.70%	1.14

For the effect size, values higher than 0.20, 0.50, and 0.80 represent small, moderate and great changes, respectively (40, 41).

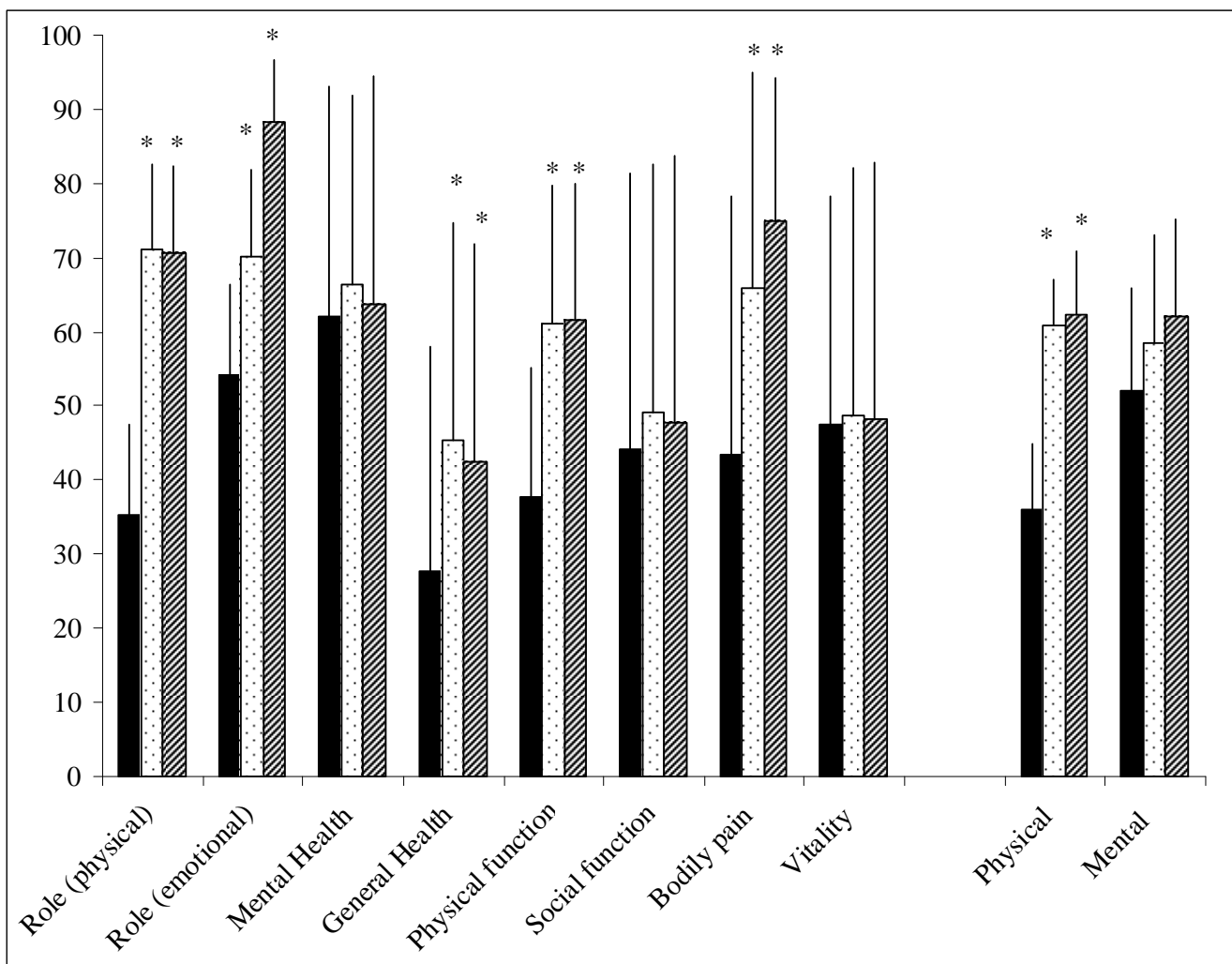


Figure 1. Mean SF-36 survey scores and standard deviations obtained preoperatively (black bars), at six months follow-up (dotted bars) and at 12 months follow-up (bars with lines). The dimension sub-scores for the eight categories are shown and the sums of the physical and mental dimensions are also represented. Scores are from 0 (worse) to 100 (best). Significant for $p < 0.05$ is shown as *.