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Continuous subcutaneous apomorphine infusion in the early phase of advanced Parkinson's disease: A prospective study of 22 patients

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ABSTRACT

Introduction: Parkinson's disease (PD) patients usually start treatment with apomorphine infusion (APO) in later stages of advanced PD (aPD). This timing limits the evaluation of its motor efficacy and other potential clinical benefits throughout the full course of aPD.

Methods: We prospectively analyzed the effect of APO on motor and non-motor symptoms, cognitive function and quality of life (QoL) in 22 PD patients with early stage aPD, defined as: age < 71 years and diagnosis of aPD for < 3 years.

Results: At baseline, mean (±SD) age and disease duration were 59.4 ± 6.1 and 8.7 ± 3.5 years, respectively. After 6 months of APO treatment, daily *off*-time decreased from 4.98 ± 2.37 to 1.48 ± 1.47 h ($p \leq 0.001$) and UPDRS IV scores from 7.00 ± 2.58 to 5.32 ± 2.48 ($p = 0.018$). Dyskinesia did not worsen with APO despite an overall increase in levodopa equivalent daily dose. Mean NMSS scores improved with APO, from 52.50 ± 27.24 to 38.68 ± 27.17 ($p = 0.002$), with particular improvements in apathy and sleep quality. Mean PDQ-39 score was reduced with APO from 31.96 ± 11.93 to 19.27 ± 11.86 ($p \leq 0.001$). Overall, cognition did not change after APO, while slight improvements were observed in executive functioning (attention and planning). All but one patient eventually underwent subthalamic deep brain stimulation.

Conclusion: In patients with early stage initial aPD, s substantial benefit of APO was observed on motor symptoms, driven by a 70% reduction in *off*-time versus baseline, superior to that observed in previous prospective studies. APO also improved frontal dysfunction in PD patients.

1. Introduction

Advanced Parkinson's disease (PD, aPD) starts when first line therapy, oral or transdermal, fails. This timing can be challenging and, then, should be individualized. Current thinking is that the efficacy of device-aided therapies may be optimal if these treatments are applied earlier in the course of the disease [1]. Apomorphine infusion (APO) is widely used to treat motor fluctuations in aPD. Studies show that APO treatment leads to a significantly reduction of the daily *off*-time [2,3], although its effect on dyskinesia is still unclear. It has been suggested that APO is more beneficial for dyskinesia the more the levodopa daily dose is reduced [4]. Retrospective studies have not observed worsening of dyskinesia with APO treatment, however their analysis is limited [5,6]. APO has a good effect profile for some non-motor PD symptoms, often particularly resistant to other treatments, such as mood, sleep, fatigue, urinary symptoms or pain [7,8].

APO is contraindicated in cases of dementia or severe neuropsychiatric symptoms. In contrast, APO is considered suitable for use in patients without cognitive impairment or even with mild-to-moderate decline [9,10]. In these cases, the progression of cognitive impairment or the presence of hallucinations have been linked to the natural course of PD rather than to APO treatment [6]. These data are derived from retrospective studies and are therefore based on clinical observations or non specific scales, and should be interpreted with caution. To date, few studies with APO have included a standardized neuropsychological evaluation in their analyses [11–13].

Over the last decade, results from about a dozen clinical studies of APO have been published (Table 1. In most of them, patients included in

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the analysis were of older age, had poorer dopaminergic response, sometimes with relevant axial symptoms, higher non-motor symptom burden and worse quality of life than those selected for subthalamic deep brain stimulation (STN-DBS), as the *EUROINF 2* study shows [8].

We therefore undertook a study to examine the effect of APO treatment on patients in the earlier phases of aPD.

2. Patients and Methods

This prospective, non-randomised, observational study was conducted by the Movement Disorder Unit of the Hospital Clínico Universitario de Santiago de Compostela, Spain, from March 2017 to December 2020. Patients in the study met the following inclusion criteria: (1) specified criteria for treatment with STN-DBS (see Supplementary material), (2) aPD duration, defined by patient's disabling fluctuations or dyskinesia more than 25% daytime, less than three years, and (3) informed consent obtained. Exclusion criteria were (1) Mattis Dementia Rating scale score under −1.5 standard deviation, (2) Hoehn and Yahr scale score over stage 3 in the *on*-state, and (3) patients previously treated with APO (intermittent apomorphine pen injection was permitted), levodopa infusion or STN-DBS.

Patients had clinical assessments at baseline and six months after the treatment with APO. Demographical data and medication use (levodopa and levodopa equivalent daily dose -LEDD-) were recorded. Motor state was assessed as the average daily *off*-hours during the previous week and the Unified Parkinson's Disease Rating Scale (UPDRS) part II, UPDRS part III, UPDRS part IV and the dyskinesia score (section A from UPDRS part IV) in the *on*-state. Non-motor symptoms were evaluated using the Non-motor symptoms scale (NMSS), the Montgomery-Asberg depression rating scale (MADRS), the Starkstein apathy scale (SAS) and the Parkinson's disease sleep scale 2 (PDSS-2). Patients' quality of life was measured using the Parkinson's disease questionnaire 39 item (PDQ-39).

A full neuropsychological test battery was administered: global cognitive status was measured using the Mattis Dementia Rating Scale (MDRS); memory was assessed using the Rey Auditory-Verbal Learning Test (RAVLT); executive functions were evaluated by 3-piece and 4-piece Tower of Hanoi and verbal phonetic "p" and semantic "animal" fluency; working memory was measured using the digit span test of the Wechsler Adult Intelligence Scale (WAIS-digits); visual memory and visuospatial skills were evaluated using the Benton Visual Retention Test (BVRT) and the Benton Judgement of Line Orientation (BJLO).

2.1. Statistical analysis

Data are expressed as a percentage for qualitative variables and as mean and standard deviation for quantitative variables. To determine statistical differences between the treatments, we applied paired *t*-test or the Wilcoxon test, depending on the parametric or nonparametric data distribution determined by Anderson-Darling normality test and Fligner-Killeen homoscedasticity test. Given the small sample size, we calculated the Bayes Factor to parametric variables and Effect Size to nonparametric variables to determine the magnitude of the change.

For the neuropsychological battery, most of the tests used in our study have cut-off points adjusted for age and/or academic level, which helped to homogenize the variations between subjects. Standardized scores (Z) are available for the MDRS, RAVLT, WAIS III, BJLO, and Verbal Fluency tests.

3. Results

A total of 24 patients were included in the study. Two patients stopped APO treatment, one voluntarily and the other due to drug-induced psychosis (see discussion). For the remaining 22 patients (11 male, 11 women), mean age at inclusion was 59.4 ± 6.1 years and disease duration was 8.7 ± 3.5 years. At 6 months, mean daily APO dose was 73.6 ± 20.7 mg and mean daily time on APO was 15.9 ± 3.0 h (four patients had 24-hour infusion). For the patients who completed the study, adverse effects related to APO were all mild and all resolved satisfactorily. All but one patient ultimately received STN-DBS treatment.

Patient demographics and clinical scores at baseline and 6 months after initiation of APO treatment are shown in Table 2. APO improved almost all the motor and non-motor symptoms of PD compared with baseline values. APO treatment led to a significant decrease in mean daily hours of *off*-time (4.98 ± 2.37 to 1.48 ± 1.47, $p \leq 0.001$), UPDRS II scores in the *on*-state (8.27 ± 3.77 to 6.50 ± 3.64, $p = 0.047$) and UPDRS IV scores (7.00 ± 2.58 to 5.32 ± 2.48, $p = 0.018$). Dyskinesia scores did not worsen after APO initiation, despite an overall increase in LEDD (1446 ± 464 to 1676 ± 521 mg, $p = 0.011$). A subanalysis showed that dyskinesia trend even to worsen if APO treatment do not led to a significant reduction in levodopa intake (Fig. 1). Total levodopa daily dose was significantly reduced with APO treatment (1145 ± 436 to 856 ± 424 mg, $p \leq 0.001$). At baseline, levodopa accounted for 79.2% of the LEDD in contrast to the 51.1% following treatment with APO. Mean NMSS score was decreased significantly with APO (52.50 ± 27.24 to 38.68 ± 27.17, $p = 0.002$), and individual domains of sleep and fatigue, mood and miscellaneous all showed significant improvement ($p = 0.014$, $p = 0.006$ and $p = 0.006$, respectively). Urinary symptoms got better, close to statistical significance ($p = 0.054$). Apathy significantly improved with APO (7.00 ± 7.16 to 3.14 ± 2.85, $p = 0.008$), while depression did not. Sleep quality significantly improved with APO compared to baseline (22.75 ± 8.33 to 16.90 ± 8.63, $p = 0.001$). No cases of worsening impulsivity were observed in this series of patients. Mean PDQ-39 scores were reduced significantly with APO (31.96 ± 11.93 to 19.27 ± 11.86, $p \leq 0.001$). Individual domains for mobility ($p \leq 0.001$), daily life activities ($p \leq 0.001$), stigma ($p = 0.020$) and bodily discomfort ($p = 0.002$) reached the most significant improvements.

Table 1

	N	Age (years)	PD duration (years)	*Off*-time (hours)	*LEDD* (mg)	*UPDRS III* (*on*-state)	*UPDRS IV*	*NMSS*	*PDQ-8 / PDQ-39*[a]
Martínez-Martín et al, 2011	17	59.5	12.1	-	1077	36.9	10.0	105.9	55.7
Drapier et al, 2012	23	62.3	13.9	-	1372	18.3	-	-	-
Martínez-Martín et al, 2015	43	62.3	14.0	-	-	30.8	10.0	82.4	49.9
Drapier et al, 2016	142	66.7	11.6	-	1154	18.4	8.5	-	41.2
Auffret et al, 2017	12	65.9	13.8	2.8	1227	17.7	8.1	-	-
Sesar et al, 2017	93	67.3	11.9	5.4	1098*	22.2	-	-	-
Borgemeester et al, 2017	45	70.9	10.8	3.9	1269	-	-	-	-
Houvenaghel et al, 2018	22	57.5	11.1	-	1088	11.1	7.0	-	38.8
Katzenschlager et al, 2018	53	63.9	11.8	6.7	1486	30.6	-	-	32.7
Sesar et al, 2019(group 1)	18	63.0	12.9	5.4	1232*	14.1	-	-	-
Dafsari et al, 2019(APO group)	38	61.6	13.5	-	1198	29.5	9.0	76.4	43.5
Present study	**22**	**59.4**	**8.7**	**5.0**	**1446**	**12.6**	**7.0**	**52.5**	**32.0**

*Only levodopa.

[a] PDQ-8 and PDQ39 are both expressed as a percentage.

Table 2
Baseline characteristics of PD patients included in most recent apomorphine infusion studies.

	Baseline	APO	*p-value*	*Effect size*
Age (years)	59.41 ± 6.12	–		
PD evolution (years)	8.73 ± 3.52	–		
APO dose (mg/hour)	–	4.81 ± 1.17		
APO (hours by day)	–	15.87 ± 3.03		
off time (hours)	4.98 ± 2.37	1.48 ± 1.47	≤0.001	large
UPDRS II *on*	8.27 ± 3.77	6.50 ± 3.64	0.047	small
UPDRS III *on*	12.64 ± 5.53	11.77 ± 6.68	0.492	ns
UPDRS IV	7.00 ± 2.58	5.32 ± 2.48	0.018	large
Dyskinesia score	2.77 ± 2.20	3.09 ± 2.24	0.432	ns
LEDD (mg)	1446 ± 464	1676 ± 521	0.011	moderate
Levodopa (mg)	1145 ± 436	856 ± 424	≤0.001	large
NMSS	52.50 ± 27.24	38.68 ± 27.17	0.002	large
Cardiovascular	1.00 ± 1.75	0.27 ± 0.88	0.092	ns
Sleep/fatigue	10.41 ± 5.69	7.23 ± 5.28	0.014	moderate
Mood	13.18 ± 11.04	9.32 ± 13.66	0.006	large
Perceptual/ Hallucinations	0.18 ± 0.85	0.27 ± 1.28	1	ns
Gastrointestinal	4.50 ± 5.54	4.59 ± 5.43	0.925	ns
Urinary	6.36 ± 5.13	4.91 ± 4.77	0.054	ns
Sexual	5.82 ± 6.44	4.23 ± 5.42	0.092	ns
Miscellaneous	10.23 ± 6.84	7.05 ± 8.29	0.006	large
MADRS	13.00 ± 10.73	11.73 ± 9.17	0.253	ns
SAS	7.00 ± 7.16	3.14 ± 2.85	0.008	large
QUIP-RS	2.00 ± 5.15	2.41 ± 6.45	1	ns
PDSS-2	22.75 ± 8.33	16.90 ± 8.63	0.001	large
PDQ-39	31.96 ± 11.93	19.27 ± 11.86	≤0.001	large
Mobility	45.45 ± 25.10	21.93 ± 23.97	≤0.001	large
Daily life activities	39.76 ± 21.00	20.27 ± 15.92	≤0.001	large
Emotional wellbeing	37.48 ± 19.46	28.98 ± 19.27	0.059	ns
Stigma	25.01 ± 33.30	16.77 ± 24.35	0.02	large
Social support	4.92 ± 11.68	5.68 ± 20.48	1	ns
Cognition	11.86 ± 9.96	13.94 ± 15.06	0.754	ns
Communication	19.31 ± 20.14	16.29 ± 17.90	0.164	ns
Bodily discomfort	37.12 ± 25.55	19.32 ± 20.48	0.002	large

Results from neuropsychological evaluation are shown in Table 3 (see Supplementary material for the absolute scores for each test). Evaluation at 6 months showed slight improvements in some frontal tasks. Time used to resolve the 3-piece and 4-piece Tower of Hanoi was significantly lower with APO (94.95 ± 71.08 to 73.14 ± 43.86 s, p = 0.029 and 240.70 ± 110.32 to 167.05 ± 74.73 s, p = 0.014, respectively), as well as attention subscale of MDRS (-0.05 ± 0.73 to 0.26 ± 0.52, p = 0.047). Phonetic fluency, another sensitive test for frontal dysfunction commonly used in PD, improved with APO treatment compared to baseline, to near statistical significance when evaluating direct scores (p = 0.065). Overall cognition did not change with APO treatment.

4. Discussion

Treatment with APO resulted in a substantial improvement in motor fluctuations in this population of patients in the early stages of aPD. Mean daily *off*-time was reduced by almost 70% (-3.50 h) compared to baseline. This improvement is much greater than the reductions of 33%

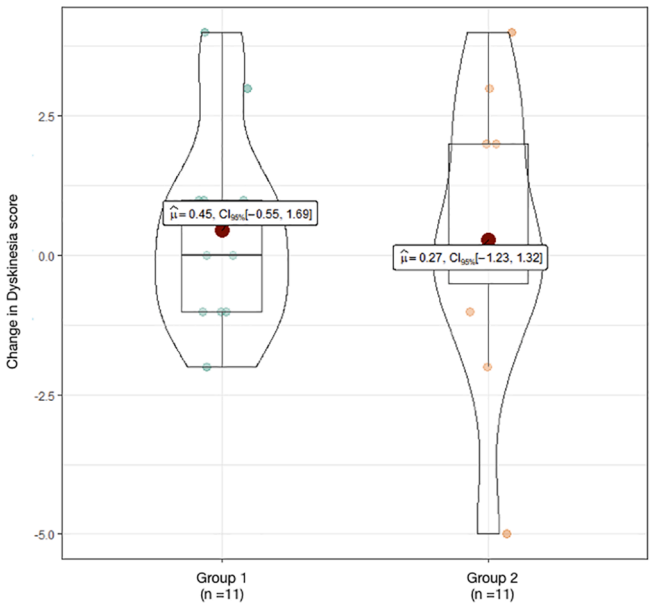

Fig. 1. Dyskinesia change based on levodopa reduction. Group 1 included patients that did not reach a 25% reduction in levodopa intake after initiation of APO, while Group 2 included patients with >25% reduction. The Y-axis represents the dyskinesia score change between both evaluations (negative values show a reduction in dyskinesia score). After verifying the normality of the dyskinesia score change variable using the Anderson-Darling test (Group 1: A = 0.4188, *p*-value = 0.268; Group 2: A = 0.3549, *p*-value = 0.392), and homoscedasticity using the Fligner-Killeen test (Chi (DF): 0.356, *p*-value = 0.55), a *t*-test was performed (*p*-value = 0.847).

Table 3
Patient demographics and clinical scores before (baseline) and 6 months after initiation of apomorphine infusion (APO).

	Baseline	**APO**	***p-value***	***Effect size***
MDRS	−0.32 ± 0.65	−0.20 ± 0.80	0.562	ns
Attention	−0.05 ± 0.73	0.26 ± 0.52	0.047	moderate
Perseveration	−0.30 ± 0.78	−0.32 ± 0.76	0.631	ns
Construction	−0.27 ± 0.61	−0.39 ± 0.79	0.758	ns
Conceptualization	−0.18 ± 0.55	−0.14 ± 0.46	0.967	ns
Memory	0.12 ± 0.81	−0.20 ± 1.05	0.174	ns
3p Hanoi Tower (seconds)	94.95 ± 71.08	73.13 ± 43.86	0.029	moderate
4p Hanoi Tower (seconds)	240.70 ± 110.32	167.05 ± 74.73	0.014	large
RAVLT Immediate recall	−0.30 ± 1.37	−0.50 ± 1.25	0.347	ns
RAVLT delayed recall	−1.09 ± 1.26	−0.94 ± 1.20	0.599	ns
WAIS-III	0.35 ± 0.68	0.42 ± 0.79	0.654	ns
BJLO	0.29 ± 0.96	0.09 ± 1.15	0.304	ns
Verbal fluency				
Phonetic fluency	−0.33 ± 0.82	−0.17 ± 0.63	0.143	ns
Semantic fluency	−0.62 ± 0.83	−0.53 ± 0.66	0.559	ns

[11] and 53% [14], reported in previous prospective studies of APO. Nevertheless, our result is similar to the reduction of 74% found in our retrospective analysis of data from patients treated with APO before STN-DBS [15], and the figures of 79% and 78% reported in the largest retrospective series to date [2,6]. UPDRS IV scores were also reduced

after APO, as observed in other studies [8,13,16]. However, this cannot be attributed to an improvement in dyskinesia, as dyskinesia score was unchanged compared to baseline. Dyskinesia did not worsen with APO treatment despite the substantial increase in LEDD increase. This is probably due to the decrease in the pulsatile dopaminergic stimulus. However, in animal models of PD, a compensatory D1 receptor functional hypersensitivity of the direct pathway in the context of chronic levodopa intake, was demonstrated as a key factor in the development of a *prodyskinetic* state [17,18]. Apomorphine, contrary to other dopamine agonists, had a high affinity for this receptor [19]. Historically, it has been suggested that APO has greater benefit in terms of dyskinesia the more the levodopa dose is reduced [4,20]. Levodopa reduction in this study was similar to others [3,6,13,15].

Non-motor symptoms, assesses using the NMSS, improved with APO. Sleep and fatigue, mood and miscellaneous were the items that showed the most improvement. The convenience of APO to treat non-motor symptoms of aPD has been demonstrated in a previous study [7], however, its results have not been replicated [8,21]. In our study, the non-motor symptom burden at baseline was low as the patients were in a relatively early phase of the aPD. In fact, cardiovascular or cognitive symptoms were scarcely represented in NMSS scores. Depression and apathy were evaluated in this study using specific scales. APO improved apathy in this study, but not depression similar to the results found in another study using specific scales (Lille Apathy Scale and MADRS) [12]. Sleep quality, assessed by the PDSS-2, was improved with APO. In this study, only four patients used APO during the night. Therefore, it seems that this improvement in sleep quality is not due to the improvement in night-time *off*-state, a key observation in patients receiving overnight APO [22,23]. We did not identify any worsening or onset of impulse control disorder. APO was discontinued in one patient who developed a psychotic episode with hospitalization. Although APO was stopped and the patient put on neuroleptic treatment, symptoms remained the same.

Overall cognition did not show changes after APO in our study. Although mean scores for short verbal memory, visual memory and visuospatial skills were lower compared to baseline, they did not reach statistical significance. By contrast, we found a slight improvement in executive functions. Patients with APO were faster completing the Tower of Hanoi, even 4-piece Tower of Hanoi, more complex and less conditioned to learning effect than the 3-piece Tower of Hanoi. Attention, assessed using MDRS, also improved. Phonetic fluency improved with APO compared to baseline, close to statistical significance. Mean scores for working memory were higher compared to baseline, as were scores for delayed memory and semantic fluency. Both of these functions depends on frontal functioning for the retrieval of information, but they failed to reach statistical significance (Fig. 2). These data are similar to those from studies that apply a rigorous cognitive evaluation before and after APO treatment [11–13], although these focus on frontal tasks examination. Interestingly, they even link the improvement in executive functioning to a normalization of brain metabolism [12].

Dopamine regulates locomotion through the nigrostriatal pathway, but it also regulates reward and cognition through the mesolimbic and mesocortical pathways [24]. The nigrostriatal pathway, with its central role in PD, also acts on reward and cognition [25,26]. D1 and D2 receptors of the nucleus accumbens modulate the reward induced by natural stimuli through the mesolimbic pathway. The nigrostriatal pathway participates in this modulation in a dual manner. While D1 receptors promote reward through the direct pathway, D2 receptors facilitate aversion through the indirect pathway. D1-like receptors (D1 and D5), as well as D2 receptors, are expressed in the prefrontal cortex, which takes part in executive functions through the mesocortical pathway. D1 and D2 receptors of the nigrostriatal pathway also contribute to its modulation.

The profile of cognitive impairment in PD is usually frontal or frontosubcortical, with predominantly executive and visuospatial dysfunction, and relatively preserved memory. Mood disorders are common in PD. Depression and apathy usually coexist. However apathy may be isolated in PD [27]. Apathy has been related to the emotional distress that characterizes depression, but also to reward system dysfunction, executive dysfunction, and auto-activation deficit [28]. Then, apathy has prominent dopaminergic connections and reflects a hypodopaminergic state in the mesocortical and mesolimbic pathways, and probably, nigrostriatal pathway.

Both apathy and executive functioning improved with APO in this study. Apomorphine is a potent dopamine agonist with activity on all subclasses of dopamine receptors. Its particular activity on D1 receptors of the direct pathway could enhance its effect on reward and cognition. The same happens with D5 receptors, located in prefrontal cortex. Our

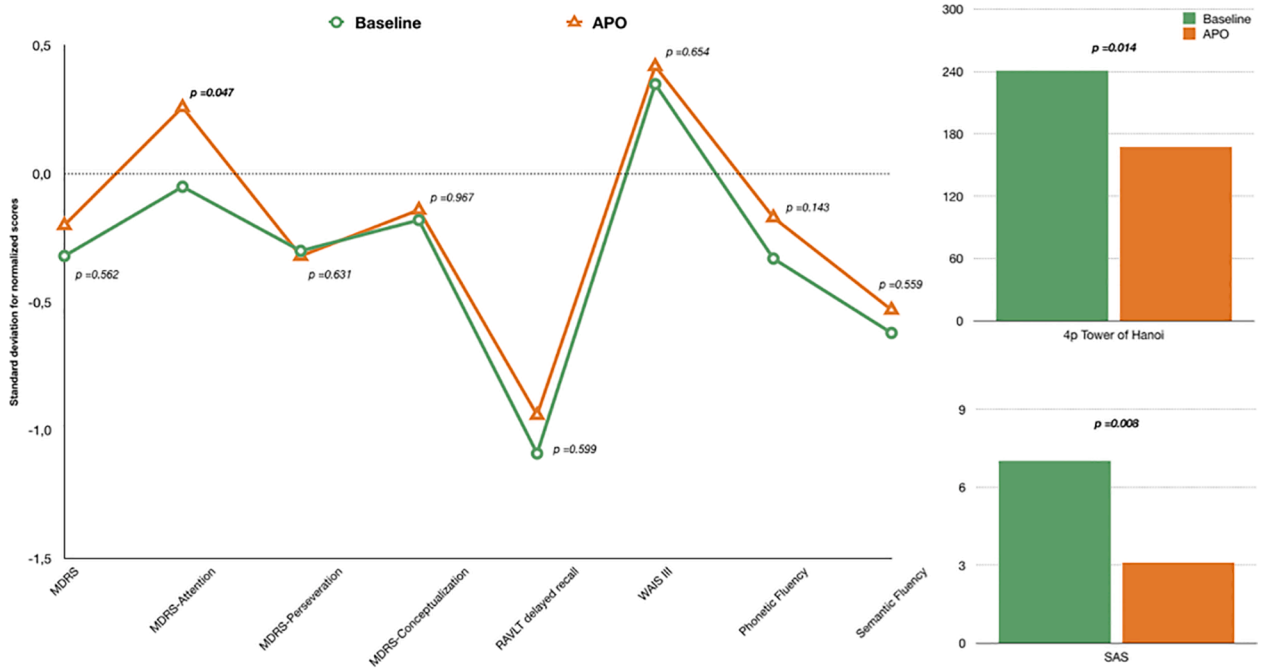

Fig. 2. Comparison between baseline and APO mean scores for frontal tasks and apathy (frontal dysfunction).

findings support the efficacy of APO improving PD frontal dysfunction.

Patients enrolled in this study were in an early phase of aPD. Compared to APO-treated patients in other series, they had a shorter PD duration, predominantly levodopa-responsive motor fluctuations and a reduced non-motor symptom burden. In comparison, APO patients in other series are in more advanced disease with worse dopaminergic response and more severe non-motor symptoms. In fact, baseline characteristics of these patients are quite similar to the frequently-cited *EARLYSTIM* study which evaluated the early use of STN-DBS [29]. In our study, PD patients had less advanced disease than than would usually be considered for infusion treatment, and the effect of APO on motor fluctuations was more substantial than previously reported.

Our study has some limitations. The sample size was relatively small, however it is similar to other APO prospective studies. The majority of our patients were on APO while waiting for DBS. We have not analyzed a group of more advanced patients treated with APO to compare.

Advanced PD is a challenging condition for which, despite its name, several effective treatment options are available, either surgery or infusion therapies. When conventional therapies begin to fail and are no longer able to control motor symptoms of PD, a shift to device-aided therapies is mandatory. The earlier we start such treatment, the better the patient's quality of life will be. As we have shown in this study, APO is very effective in early phases of aPD, which makes it a good treatment option to adequately control disease symptoms in this stage.

Ethics approval

The study has been approved by the Research Ethics Committee of Santiago (Project identification code 2018/339). Informed consent was obtained from each patient or from their relatives, after a full explanation of the procedures.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2021.100129.

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