

Intrajejunal vs oral levodopa-carbidopa therapy in Parkinson disease

A retrospective cohort study

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Abstract

Levodopa-carbidopa intestinal gel (LCIG) is a method of continuous administration of levodopa – the standard treatment in Parkinson disease (PD, a neurodegenerative disorder characterized by resting tremor, rigidity, gait impairment, and bradykinesia), thought to reduce the short-life and pulsatile problems of oral administration. We aimed to study the effects of Levodopa-Carbidopa therapy in 2 separate groups: one with intrajejunal administration of Levodopa-Carbidopa gel and the second with oral therapy.

We performed an observational retrospective Romanian cohort study on 61 patients diagnosed with PD patients, with Hoehn and Jahr 3 and 4 stages, recruited from a single regional tertiary center in Cluj-Napoca, Romania, between 2009 and 2019.

The mean adjusted UPDRS III (and similarly for UPDRS II) improved in the LCIG compared to the oral therapy group with 15.6 (95% CI 12.0–19.2, $P < .001$), and with 18.4 (95% CI 13.8–22.9, $P < .001$), stratified for the Hoehn and Jahr stages 3 and 4. There was a 41.7% (10) reduction in dyskinesia, and 29.2% reduction in wearing off/on-off at 1 year in the LCIG group compared to 0% (0) dyskinesia reduction, and 2.7% reduction in wearing off/on-off in the oral therapy group.

Continuous intrajejunal infusion of LCIG ensures a significant and clinical reduction in motor fluctuations compared to oral therapy in advanced PD, even after adjustment for important confounders.

Abbreviations: CI = confidence interval, COMT = catechol-O-methyltransferase inhibitor, IQR = interquartile range, LCIG = levodopa-carbidopa intestinal gel, MAO-B = monoamine oxidase-B, OMT = oral medical therapy, PD = Parkinson disease, PEG-J = percutaneous endoscopic transgastric jejunostomy, SD = standard deviation, STN-DBS = subthalamic nucleus deep brain stimulation, UPDRS = the unified Parkinson disease rating scale.

Keywords: LCIG, levodopa-carbidopa intestinal gel, Parkinson disease, PD

1. Introduction

Parkinson disease (PD) is a neurodegenerative disorder characterized by resting tremor, rigidity, gait impairment, bradykinesia,

sleep dysfunction, mood disorders, cognitive impairment, and dementia.^[1] The underlying pathogenesis PD is not yet fully understood. It is thought to consist of the interaction between many genetic and environmental factors. This lack of knowledge explains the inability to make a precise diagnosis in the early stages and the limitations of treatment success in the later stages.

Levodopa is the amino-acid precursor of dopamine and has the function of recharging the depleted dopamine. For more than 4 decades, levodopa was described as the most efficient treatment in PD. Because of its short plasma half-life, oral levodopa may cause pulsatile striatal receptor stimulation, which leads to dyskinesias and a wide range of complications.^[2–4] To diminish these types of complications, researchers developed levodopa-carbidopa intestinal gel (LCIG). It is delivered by using a percutaneous pump, set in place through an endoscopic intervention. This way, it leads to a constant plasma level of levodopa, therefore delivering a continuous dopaminergic stimulation.^[4]

The intrajejunal administration of LCIG is one of the most efficient and frequently recommended pharmacological combination in PD. Nevertheless, studies found a wide range of motor and non-motor complications with the treatment.^[4]

Because relevant studies engaged in the comparison between new therapeutical methods are still limited, we aimed to study the effects of levodopa-carbidopa in 2 separate groups: one with oral therapy and the second with intrajejunal administration of levodopa-carbidopa gel.

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2. Methods

2.1. Study design and setting

We performed an observational retrospective Romanian cohort study on 61 patients diagnosed with PD recruited from a single regional tertiary center in Cluj-Napoca, Romania, between 2009 and 2019.

2.2. Patients

We included PD patients with Hoehn and Jahr 3 and 4 stages, receiving oral administration of levodopa-carbidopa, or levodopa-carbidopa intrajejunal treatment. We excluded patients with an unclear diagnosis of PD, other Parkinsonian syndromes, neurodegenerative diseases, concomitant narrow-angle glaucoma, having contraindications for the placement of a nasogastric sonde or jejunal tube and oncological diseases.

2.3. Variables

We gathered the data from medical files and the hospital database. We set our outcome of interest the unified Parkinson disease rating scale (UPDRS) II and III reductions, and secondary the improvement in dyskinesia and wearing off/on-off in 1 year follow-up. Our exposure variable was the intrajejunal treatment compared to oral therapy. Besides these variables, we collected predictors and potential confounders, as well as variables to describe the sample better: demographic data (age, gender, place of residence), PD symptoms and evolution (disease duration, treatment duration, Hoehn and Jahr at baseline, UPDRS II and III, dyskinesia, Wearing off/on-off at baseline and 1 year follow-up), hallucinations, drug-induced psychosis, PD connex problems (mixed anxiety-depressive disorder, mild cognitive impairment, Parkinson dementia), oral treatment, additional treatments (deep brain stimulation), death, comorbidities (hypertension, atrial fibrillation, ischaemic stroke/cerebral lacunarism, type 2 diabetes, dyslipidemia, polyneuropathy), anemia related data (iron deficiency anemia, folate-deficiency anemia, B12 vitamin deficiency). UPDRS is one of the most frequently used questionnaires that follows the longitudinal course of Parkinson disease, but also the most commonly used scale in the clinical study of Parkinson disease and provides insight into the patients disease in a more objective manner.^[5,6]

All subjects in both groups were assessed with the same scales that are commonly used in the hospital practice.

To minimize selection bias, we included subjects from the same hospital and excluding similar medical entities to PD. To minimize confounding, we performed adjustments in multiple regression analyses for important potential confounder variables, and stratified analyses.

2.4. Statistical analysis

Categorical data were presented as counts and percentages. Continuous data were presented as means and standard deviations (for normally distributed data) or medians and quartiles (1 and 3, for non-normally distributed data). Comparisons between the 2 groups for categorical data were made with the Chi-Squared test or with Fisher exact test, while for continuous data were made with *t* test for independent samples

(for normally distributed data), or with Wilcoxon rank-sum test (for non-normally distributed data). To further assess the relationship between intrajejunal treatment compared to oral one, we used multivariate linear regression models, adjusted for age, Parkinson disease duration, treatment duration, Hoehn, and Yahr stage at the beginning. Since the Hoehn and Yahr stage appears to be a confounder, we also performed the same multivariate analysis, stratified by its 2 stages, 3 and 4. For all models, we checked the assumptions of residuals normality, heteroskedasticity (using the Breusch Pagan test of heteroskedasticity), linearity (using component residual plots), outliers and leverage points (Cooks D distance, studentized residuals). For multivariate models, we checked the assumptions of multicollinearity (using variance inflation factors), confounding (checking for a marked change in models coefficients when adding new variables to the model).

We removed 2 outliers/leverage points to correct for homoskedasticity – although the models were similar. Missing data was not imputed. For all statistical tests, the significance level was 0.05, and the two-tailed *P* value was calculated. All statistical analyses were performed with the R environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria), version 3.6.1.^[7]

2.5. Ethics statement

The study was performed in agreement with the Declaration of Helsinki and was approved by the “Iuliu Hatieganu” University of Medicine and Pharmacy Ethics Committee.

3. Results

A total of 61 subjects with a mean age of 70.4 years (8.5 - standard deviation, ranging from 55 to 85 years), were enrolled in the study.

The characteristics of the intrajejunal therapy group and oral therapy group are compared in Table 1. Demographically the subjects were similar except for a higher frequency of female subjects in the intrajejunal group. The intrajejunal therapy group had a statistically significant longer PD history (6 years median difference), while the duration from the initiation of treatment was not significantly different.

The baseline clinical manifestations (Hoehn and Yahr stage; UPDRS II, and III; dyskinesia; Wearing off/On-Off) of PD disease were significantly worse in the intrajejunal group compared to the oral therapy group. The observed cognitive impairment and anxiety-depressive disorder were more frequent in the intrajejunal group than the oral therapy group, but only the latter reached a statistically significant level.

Regarding comorbidities, the cardiovascular, metabolic, were not significantly different between groups, although observed values were higher in the oral therapy group, except hypertension that was significantly different. Anemia-wise, the observed deficits were higher in the intrajejunal group, but not significantly different (except for iron deficiency anemia).

3.1. Intrajejunal therapy group-specific characteristics

Hallucinations and drug-induced psychosis were exceptional before the therapy, but a quarter of the subjects developed them after the therapy (see Table 2).

Table 1**Comparative analysis of Parkinson disease subjects receiving intrajejunal therapy and oral therapy group.**

	Intrajejunal therapy (n=24)	Oral therapy (n=37)	P value
Age (years), mean (SD)	70.12 (7.66)	70.59 (9.11)	.835
Gender (female), n (%)	11 (45.83)	8 (21.62)	.046
Place of residence (rural), n (%)	3 (12.5)	2 (5.41)	.373
Duration of PD (years), median (IQR)	15 (13.75–20.25)	9 (6–13)	<.001
Duration from initiation of therapy (years), median (IQR)	5 (3.75–7)	4 (3–6)	.461
Hoehn și Yahr stages la baseline			
3	2 (9.09)	29 (78.38)	<.001
4	20 (90.91)	8 (21.62)	
UPDRS II at baseline, median (IQR)	37 (33–39)	17 (13–24)	<.001
UPDRS II at 1 year, median (IQR)	27 (21–31.5)	24 (19–31)	.27
UDPRS II Difference at 1 year -baseline, median (IQR)	10 (6–12.5)	-7 (-8–5)	<.001
UPDRS III at baseline, median (IQR)	41.5 (38–45)	24 (18–27)	<.001
UPDRS III at 1 year, median (IQR)	30 (28.5–35.5)	30 (26–34)	.307
UDPRS III Diference at 1 year-baseline, median (IQR)	11 (8.5–13)	-7 (-10–5)	<.001
Dyskinesia at baseline, n (%)	17 (70.83)	5 (13.51)	<.001
Dyskinesia at 1 year, n (%)	8 (33.33)	6 (16.22)	.12
Dyskinesia evolution in 1 year, n (%)			
disappearing:	10 (41.67)	0 (0)	<.001
absent:	6 (25)	31 (83.78)	
persistent:	7 (29.17)	5 (13.51)	
newly occurred:	1 (4.17)	1 (2.7)	
Dyskinesia evolution at 12 months (improvement vs. same or worsening), n (%)	10 (41.67)	0 (0)	<.001
Wearing off/On-Off at baseline, n (%)	24 (100)	10 (27.03)	<.001
Wearing off/On-Off at 1 year, n (%)	17 (70.83)	14 (37.84)	.012
Wearing off/On-Off evolution in 1 year, n (%)			
disappearing:	7 (29.17)	1 (2.7)	<.001
absent:	0 (0)	22 (59.46)	
persistent:	17 (70.83)	9 (24.32)	
newly occurred:	0 (0)	5 (13.51)	
Wearing off/On-Off evolution at 12 months (improvement vs. same or worsening), n (%)	7 (29.17)	1 (2.7)	.005
Deep brain stimulation, n (%)	1 (4.17)	0 (0)	.393
Decease, n (%)	6 (25)	3 (8.11)	.136
Mixed anxiety–depressive disorder, n (%)	13 (54.17)	8 (21.62)	.009
Mild cognitive impairment, n (%)	10 (41.67)	14 (37.84)	.765
Parkinson Dementia, n (%)	4 (16.67)	4 (10.81)	.7
Drug-induced psychosis, n (%)	5 (20.83)	0 (0)	.007
Hypertension, n (%)	6 (25)	21 (56.76)	.015
Permanent atrial fibrillation, n (%)	1 (4.17)	4 (10.81)	.64
Ischaemic Stroke / cerebral lacunarism, n (%)	5 (20.83)	16 (44.44)	.06
Diabetes type II, n (%)	1 (4.17)	8 (21.62)	.076
Polyneuropathy, n (%)	16 (66.67)	22 (61.11)	.662
Dyslipidemia, n (%)	3 (12.5)	7 (18.92)	.726
Iron deficiency anemia, n (%)	5 (20.83)	1 (2.78)	.033
Folate-deficiency anemia, n (%)	5 (20.83)	6 (16.67)	.741
Vitamin B12 deficiency, n (%)	2 (8.33)	4 (11.11)	1

SD = standard deviation, IQR = interquartile range, PD = Parkinson disease, UPDRS = the unified Parkinson disease rating scale.

3.2. Description of the oral therapy group specifics

The oral therapy group received in majority levodopa with carbidopa, about half of them received monoamine oxidase-B inhibitors and dopaminergic agonist, followed by amantadine, and the least frequent anticholinergic agents or catechol-O-methyltransferase inhibitors (see Table 3).

3.3. Comparative disease evolution under treatment

The evolution of PD clinical manifestations was statistically significant and clinically clearly better in the intrajejunal therapy group compared to the oral therapy regarding UPDRS II and III improvement, dyskinesia, and wearing off/On-Off at 1 year (see Table 1). Moreover, the oral therapy group had a diminishing of

all the previously stated clinical manifestations at a year follow-up compared to the baseline evaluation. The difference in dyskinesia improvement in favor of intrajejunal therapy was of 47.47%, and statistically significant. While the difference in wearing off/On-Off improvement in favor intrajejunal therapy was of 26.47%, and statistically significant.

In order to check if the UPDRS II and III improvement, in 1 year, in the intrajejunal group, compared to oral therapy, was not due to other variables, we performed an adjustment in a multiple linear regression adjusting for age, Parkinson disease duration, treatment duration, Hoehn and Yahr stage at the beginning (see Table 4 and Table 5). In all the models the intrajejunal treatment had the most important effect in improving UPDRS II and III compared to all the other variables. Its effect was both important

Table 2
Characteristics of the intrajejunal therapy group.

Characteristic	Number (%) (n = 24)
Administration of Levodopa-Carbidopa on the nasogastric tube(test phase) but without administration of intrajejunal Levodopa-Carbidopa	4/24 (16.67)
Hallucinations	
Hallucinations before PEG-J	1/24 (4.17)
Number of years of hallucinations before PEG-J	0: 23/24 (95.83); 3: 1/24 (4.17)
Hallucinations after PEG-J	6/24 (25)
Hallucinations after PEG-J number of months, median (IQR)	0 (0–0.75)
Drug-induced psychosis	
Drug-induced psychosis before PEG-J	0/24 (0)
Drug-induced psychosis after PEG-J	6/24 (25)

IQR = interquartile range, PEG-J = percutaneous endoscopic transgastric jejunostomy.

and statistically significant. The determination coefficient for the univariate and for the multivariate models containing the intrajejunal treatment was important (above 0.74). All multivariate models were statistically significant. The relation between intrajejunal treatment and UPDRS II and III remained similar even after adjustment, and even on stratified analyses regarding the Hoehn and Yahr stage.

4. Discussions

Using the data collected during a decade in a tertiary clinical center, this analysis compared the clinical outcomes, side effects and complications between 2 separate groups of PD patients treated with LCIG and oral therapy. We found that UPDRS II and III scores statistically and clinically improved in the LCIG group compared to the oral therapy group, and the results stayed stable even after adjusting for age, disease duration, treatment duration, and stratified for Hoehn and Yahr stage at the beginning of the therapy. Dyskinesia, and wearing Off/On-Off diminished

Table 3
Drugs used for the patients under oral therapy.

Characteristic	Number (%) (n = 37)
Levodopa-Carbidopa	36 (100.00)
MAO-B Inhibitors	20 (55.56)
Dopaminergic Agonists	15 (41.67)
Anticholinergic Agents	2 (5.56)
Amantadine	7 (19.44)
COMT inhibitor (Entacapone)	4/35 (11.43)

MAO-B = monoamine oxidase-B, COMT = catechol-O-methyltransferase inhibitor.

statistically and clinically in the LCIG group compared to the oral therapy group.

A study performed by Nyholm et al on 24 patients with advanced PD, compared daytime intraduodenal levodopa-carbidopa gel infusion as monotherapy with oral conventional combination therapies.^[8] The median total UPDRS score at the end of each treatment arm was 53 with Conventional and 35 with Infusion (*P* < .05) and infusion provided lower median scores in all parts of the UPDRS, a result similar to ours.

A study on 11 patients with advanced PD analyzed the efficacy and safety of LCIG delivered continuously through an intrajejunal percutaneous tube (PEG-J).^[9] LCIG contained a water-based suspension with micronized levodopa (20 mg/ml) and carbidopa (5 mg/ml) in methylcellulose (Duodopa) and was administered by continuous jejunal infusion for 12 hour/day using a portable pump (CADD-Legacy) by PEG-J.^[9] The efficacy and safety outcomes were assessed by using the UPDRS parts II, III, and IV and were performed at baseline (T0) before LCIG initiation, and after 3 (T3) and 6 (T6) months of therapy.^[9] The result was that patients showed statistically significant (*P* < .05) higher performances in activities of daily living, statistically significant (*P* < .001) lower incidence and severity of motor fluctuations, as rating by UPDRS part IV, compared to their best oral therapy and the success rate for PEG-J placement was 100%.^[9] Previous research found that continuous intrajejunal infusion of LCIG provide a significant clinical improvement and improves UPDRS,^[10–13] a result similar to ours. However, device and procedural complications, while generally of mild severity,

Table 4
The unified Parkinson disease rating scale II improvement (UPDRS II at therapy initiation minus UPDRS II at 12 months follow-up) assessment by univariate analyses, then in relation with therapy in multivariate regression, adjusted for age, Parkinson disease duration, treatment duration, Hoehn and Yahr stage at the beginning, and in stratified multivariate analysis by Hoehn and Yahr stage.

	Unstratified analyses						Stratified by Hoehn & Yahr = 3			Stratified by Hoehn & Yahr = 4			
	B	(95% CI)	P value	R2	B adjusted*	(95% CI)	P value	B adjusted**	(95% CI)	P value	B adjusted**	(95% CI)	P value
Age (years)	-0.17	(-0.42–0.08)	.183	0.03	-0.12	(-0.24–0)	.042	0.003	(-0.08–0.09)	.941	-0.33	(-0.58–0.08)	.011
Parkinson's disease duration (years)	0.52	(0.2–0.84)	.002	0.16	-0.02	(-0.22–0.18)	.845	-0.08	(-0.25–0.09)	.342	0.06	(-0.30–0.41)	.741
Treatment duration (years)	0.24	(-0.71–1.19)	.614	0.005	-0.21	(-0.72–0.3)	.422	-0.09	(-0.58–0.41)	.724	-0.21	(-1.04–0.62)	.605
Hoehn and Yahr stage at the beginning	9.29	(5.7–12.88)	<.001	0.32	0.33	(-2.46–3.11)	.815	-	-	-	-	-	-
Therapy (intrajejunal vs. oral)	15.17	(13.17–17.18)	<.001	0.80	15.19	(12.37–18.01)	<.001	15.4	(12.46–18.34)	<.001	14.72	(10.25–19.19)	<.001
Adjusted R2					0.81			0.8			0.74		

* model containing all the variables in the table.

** model containing all the variables in the model, excepting the stratifying variable (Hoehn and Yahr stage); R² – coefficient of determination.

CI = confidence interval.

Table 5
The unified Parkinson disease rating scale III improvement (UPDRS III at therapy initiation minus UPDRS III at 12 months follow-up) assessment by univariate analyses, then in relation with therapy in multivariate regression, adjusted for age, Parkinson disease duration, treatment duration, Hoehn and Yahr stage at the beginning, and in stratified multivariate analysis by Hoehn and Yahr stage.

	Unstratified analyses				Stratified by Hoehn & Yahr=3				Stratified by Hoehn & Yahr=4				
	B	(95% CI)	P value	R2	B adjusted*	(95% CI)	P value	B adjusted**	(95% CI)	P value	B adjusted**	(95% CI)	P value
Age (years)	-0.22	(-0.51-0.07)	.138	0.04	-0.2	(-0.31-0.08)	.001	-0.14	(-0.24-0.03)	.010	-0.33	(-0.58-0.07)	.014
Parkinson's disease duration (years)	0.68	(0.35-1.02)	<.001	0.23	0.12	(-0.07-0.3)	.209	0.07	(-0.14-0.27)	.500	0.14	(-0.19-0.46)	.385
Treatment duration (years)	0.12	(-0.98-1.23)	.824	0.001	-0.26	(-0.74-0.22)	.285	-0.06	(-0.66-0.54)	.827	-0.28	(-1.06-0.49)	.461
Hoehn and Yahr stage at the beginning	10.79	(6.57-15.02)	<.001	0.32	-0.54	(-3.33-2.25)	-.54	-	-	-	-	-	-
Therapy (intrajejunal vs oral)	18.14	(15.99-20.29)	<.001	0.84	17.76	(14.92-20.6)	17.76	15.6	(12.01-19.18)	<.001	18.35	(13.84-22.87)	<.001
Adjusted R ²					0.86			0.78			0.81		

* model containing all the variables in the table.

** model containing all the variables in the model, excepting the stratifying variable (Hoehn and Yahr stage); R² – coefficient of determination.

CI = confidence interval.

were present and were explained by the severity and progression of the disease.^[10-13]

A long-term retrospective study analyzing advanced therapies in PD including oral medical therapy (OMT), LCIG and subthalamic nucleus deep brain stimulation (STN-DBS), found that OFF time improved to the same extent in STN-DBS and LCIG (-62% vs -54.5%; *P*=.830) and worsened with OMT (+78.6%; *P*<.001). Our study similarly found improvement in Wearing off/On-Off in LCIG compared to OMT. STN-DBS and LCIG yielded greater improvement on dyskinesia compared to OMT (dyskinesia duration: -66.1% vs -9.0% vs +24.2% [*P*=.001]^[14] similar to our study were dyskinesia at 1 year improved in the LCIG group compared to OMT group. The vast majority of studies have reported positive outcomes in motor complications with reduced duration of OFF time, increased ON time and plasma drug levels were maintained relatively stable in patients with LCIG therapy.^[15-22]

4.1. Study limitations

The study has several limitations. Even though the sample size was not that large, the results are highly statistically significant, and the adjusted coefficients and confidence intervals for the main results are distant from the value of 0, thus suggesting a strong force of association. As with any observational study designs, residual confounding cannot be excluded even if we adjusted for several variables in the multivariate analysis. More extensive studies with more confounder adjusted models are warranted. Nevertheless, the large determination coefficient and the large adjusted coefficients suggest that this association is more likely to withstand adjustment for other confounders. Unknown confounders may diminish the association between intrajejunal treatment and disease progression.

The fact that the clinical status of PD patients was poorer in the intrajejunal group compared to the control group is normal since intrajejunal therapy is initiated in more advanced stages. Moreover, we tried to have subjects in both groups as homogenous as possible, thus limiting them to having only stage 3 and 4 for the Hoehn and Yahr stage. However, even with

this initial difference, the improvement in outcomes in the intrajejunal group is important.

Since the cohort of PD patients has characteristics similar to patients from regional tertiary centers, the results are generalizable to this type of population. The reduced set of exclusion criteria helps to this generalizability.

Having taken into account the statistically significant and clinically important relation between intrajejunal treatment and clinical manifestations of PD, after adjustment for important confounders, for a cohort of similar subjects with advanced stage of PD, and also the similar findings of other studies, we have good arguments sustaining this relationship.

5. Conclusions

Continuous intrajejunal infusion of LCIG ensures a statistically significant and clinical important reduction of UPDRS II and III, compared to oral therapy in advanced PD patients, and the results stayed stable even after adjusting for age, disease duration, treatment duration, and stratified for Hoehn and Yahr stage at the beginning of the therapy. The same differences were found also for dyskinesia and wearing Off/On-Off that were diminished in the LCIG group.

Author contributions

Luminita Celia Popa carried out the study, analyzed the data, and wrote the paper; Daniel Corneliu Leucuta made substantial contributions to the analysis of the data, interpretation, and revised the drafts; Nicoleta Tohanean analyzed the data; Stefan-Lucian Popa made contributions to the conception of the manuscript; L. Perju-Dumbrava analyzed the data, supervised the work and critically revised the manuscript. All authors read and approved the final manuscript.

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