

# Continuous intra jejunal infusion of levodopa-carbidopa intestinal gel by jejunal extension tube placement through percutaneous endoscopic gastrostomy for patients with advanced Parkinson's disease: a preliminary study

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**Abstract. – OBJECTIVE:** Levodopa is the gold standard in the pharmacological treatment of Parkinson's disease (PD) and its oral administration is associated with the development of disabling motor and non-motor complications in advanced disease. Levodopa is rapidly metabolized and has a short plasma half-life thus requiring frequent, repeated dosing. Impaired gastric emptying is common in PD, and likely contributes to the unpredictable motor responses observed with orally-dosed levodopa. A new therapeutic protocol for patients with advanced PD include a carbidopa/levodopa combination using continuous, modulated enteral administration achieved inserting a Jejunal Extension Tube Placement through Percutaneous Endoscopic Gastrostomy (PEG-J).

The aim of this work is to assess efficacy and safety of levodopa-carbidopa intestinal gel (LCIG) delivered continuously through an intra-jejunal percutaneous tube (PEG-J).

**PATIENTS AND METHODS:** We enrolled 11 adults with advanced PD and preserved sensitivity to L-dopa. For pre-procedural endoscopic evaluation each patient underwent a diagnostic esophagogastroduodenoscopy (EGD) 7 days before PEG-J placement to evaluate the presence of gastric anatomical or wall anomalies and the presence of oesophageal or gastric varices. Treatment with LCIG, consisting of a water-based suspension containing micronized levodopa (20 mg/mL) and carbidopa (5 mg/mL) in methylcellulose (Duodopa<sup>®</sup>), was administered by continuous jejunal infusion for 12h/day using a portable pump (CADD-Legacy) by PEG-J. Clinical evaluations were performed at baseline (T0) before LCIG initiation, and after 3 (T3) and 6 (T6) months of therapy. The efficacy and safety out-

comes were assessed by using the Unified Parkinson's Disease Rating Scale (UPDRS) parts II, III and IV.

**RESULTS:** Mean age of patients was  $71.18 \pm 5.4$  SD at LCIG initiation. Out of the 11 patients, 2 (18%) dropped-out LCIG at T3. Patients showed statistically significant ( $p < 0.05$ ) higher performances in activities of daily living and a statistically significant ( $p < 0.001$ ) lower incidence and severity of motor fluctuations, as rating by UPDRS part IV, compared to their best oral therapy. During observational period, 5 patients experienced adverse events. Success rate for PEG-J placement was 100%.

**CONCLUSIONS:** Our work shows that continuous intrajejunal infusion of LCIG ensures a reduction in motor Fluctuations compared to oral administration of levodopa-carbidopa in advanced PD. Based on our results and on the evidence emerging in the literature, this therapeutic approach should be the gold standard for therapy in these patients.

*Key Words:*

Jejunal extension tube placement, Percutaneous Endoscopic Gastrostomy (PEG-J), Parkinson disease, Levodopa-carbidopa, Intestinal gel.

## Introduction

Levodopa is the gold standard in the pharmacological treatment of Parkinson's disease (PD) and its oral administration is associated with the development of disabling motor and non-motor complications in advanced disease. Motor fluctu-

ations are a common problem in the long-term management of PD, resulting in disability and impaired quality of life<sup>1</sup>. The mechanisms behind levodopa-associated motor complications are not fully understood, but are hypothesized to be related to the inability of conventional levodopa regimens to provide physiologic, continuous dopaminergic stimulation<sup>2</sup>. Levodopa is rapidly metabolized and has a short plasma half-life of approximately 90 min (when administered with carbidopa), thus requiring frequent, repeated dosing and producing fluctuations in drug plasma levels. It is absorbed mainly in the proximal small intestine, and gastric emptying plays an important role in determining the absorption of conventional oral levodopa formulations. Impaired gastric emptying is common in PD, and likely contributes to the unpredictable motor responses observed with orally-dosed levodopa<sup>3</sup>. Treatment of patients with advanced PD remains difficult. Therapeutic options include high frequency deep brain stimulation of the sub-thalamic nucleus or globus pallidus internus, and continuous subcutaneous infusion of apomorphine or continuous intestinal infusion of levodopa/carbidopa<sup>4</sup>. A new therapeutic protocol for patients with advanced PD include a carbidopa/levodopa combination using continuous, modulated enteral administration via a portable pump. Levodopa/ carbidopa intestinal gel (LCIG) is a caboxymethyl cellulose aqueous gel administered via a portable infusion pump (CADD-Legacy Duodopa, Smiths Medical, St Paul, MN, USA) attached to a cassette to which a small trans-abdominal tube is attached. Immediate absorption of the drug in the intestinal mucosa is achieved by a jejunal extension tube placement through a permanent percutaneous endoscopic gastrostomy tube (PEG-J). The typical approach involves a percutaneous endoscopic gastrostomy, pull method, with the placement of a jejunal extension tube (PEG-J), which requires a combination of procedures designed to ensure that no organ is interposed between the abdominal wall and the gastric surface. Lack of trans-illumination in maximal endoscopic light settings is a major contraindication for PEG-J. The PEG is an endoscopic procedure that allows the insertion of a probe in the stomach passing through the abdominal wall front. It has initially been used for enteral feeding of all those patients who could not feed on naturally, because of severe neurological injury post traumatic or post ischemic. In recent years it has been identified a

new indication PEG at that time is in fact used in PD to allow in continuous administration of a drug in duodenum. For this purpose within the PEG must be positioned a smaller catheter whose end comes in jejunum. Experimental studies suggest that motor complications are due to non-physiological, intermittent administration of the drug, and can be reduced with continuous delivery. Levodopa-carbidopa intestinal gel (LCIG) delivered continuously via PEG-J has been reported, mainly in small open-label studies, to significantly alleviate motor complications in PD<sup>5-9</sup>.

Aim of the present study is to assess efficacy and safety of levodopa-carbidopa intestinal gel delivered continuously through PEG-J.

## Patients and Methods

All participants provided written informed consent with a protocol approved by the local Ethics Committee. We enrolled 11 adults (mean age  $71.18 \pm 5.4$  SD at LCIG initiation) with advanced PD and preserved sensitivity to L-dopa ( $\geq 40\%$ ) but fluctuations in motor performance (with off time  $\geq 3$  hours per day) and/or dyskinesia altering significantly the activities of daily life in spite of an optimized oral treatment. Exclusion criteria were: contraindication to Duodopa<sup>®</sup> (hypersensitivity to levodopa and carbidopa, or any of the excipients; angle-closure glaucoma; kidney and liver failures; severe heart failure; severe cardiac arrhythmia; acute stroke; pheochromocytoma; hyperthyroidism; Cushing syndrome; association with non-selective MAOIs and selective MAOIs-A); dementia; severe psychosis; concomitant treatment by continuous infusion of apomorphine or deep brain stimulation, severe coagulopathy (International Normalized Ratio (INR) more than 1.3 and a platelet count lower than  $50 \times 10^9/L$ ), portal hypertension, gastric anatomical anomalies. For pre-procedural endoscopic evaluation each patient underwent a diagnostic EGD 7 days before PEG-J placement to evaluate the presence of gastric anatomical or wall anomalies and the presence of oesophageal or gastric varices. Treatment with LCIG, consisting of a water-based suspension containing micronized levodopa (20 mg/mL) and carbidopa (5 mg/mL) in methylcellulose (Duodopa<sup>®</sup>), was administered by continuous jejunal infusion for 12h/day using a portable pump (CADD-Legacy) by PEG-J. Clinical evaluations were performed at baseline (T0) before LCIG initiation, and after

3 (T3) and 6 (T6) months of therapy. The efficacy and safety outcomes were assessed by Unified Parkinson's Disease Rating Scale (UPDRS) parts II (exploring activities of daily living), III (assessing motor performance), IV (evaluating complications of therapy, encompassed dyskinesia time and severity, off-period time, early morning dystonia), and Hoehn and Yahr stage (H&Y, rating disease severity). The levodopa equivalent daily dose (LEDD) was calculated both for dopamine agonists + L-dopa (total LEDD) undertaken during daytime at T0 and for dopamine agonist + L-dopa/carbidopa gel administered during daytime after LCIG initiation. We used a Boston Scientific PEG-J for an endoscopic placement procedure, effectuated in accord to International Guidelines<sup>10</sup>. The patient is placed in a supine position and a diagnostic esophagogastroduodenoscopy is performed. The gastrostomy site is carefully selected and marked by adequate endoscopic air insufflation to bring the gastric wall in apposition with the abdominal wall, and obtaining optimal trans-abdominal light illumination and external finger or digital indentation. The optimal site is usually in the left upper quadrant about 2-4 cm below the costal margin or occasionally in the epigastric area. After administration of local anesthesia (10 mL 1% xylocaine) using a 25-gauge needle and advance the needle vertically into the stomach under endoscopic guidance, is performed a skin incision. A large-bore (13.5-gauge) needle with covers heath (cannula) is advanced following the prior needle path into the stomach, guided by endoscopy. Then, the needle is removed and the PEG wire is brought through the cannula into the stomach and grasped by the endoscopic snare. The endoscope with secured wire is withdrawn through the mouth. The oral end of the wire is usually looped. The wire tip is first passed through the open loop at the tip of the feeding tube. The wire loop is then opened and the internal bumper of the PEG tube is passed through. The wire and the PEG tube are firmly knotted. The external surface of the internal bumper and external tubing are lubricated. Then the wire is pulled slowly and firmly from the abdominal side, bringing the introducer tube and the PEG from mouth through the stomach and the abdominal wall to outside, leaving the internal bumper inside the stomach against the gastric mucosa. An external bumper or bolster is applied over the PEG tubing next to the skin. Optional post-procedure endoscopy can be performed at the discretion of the endoscopist

to document the internal bumper's location and to rule out accidental esophageal injury during PEG pull-through. To convert PEG tube to PEG jejunal tube (PEG-J) a jejunal extension tube (9 or 12 French) is inserted through a large diameter PEG tube. The inserted jejunal extension tube can be grasped endoscopically and dragged into the small bowel. Endoclips can be applied to anchor the jejunal tube in the small bowel minimizing the risk of proximal migration<sup>11</sup>.

Each procedure was performed with conscious sedation with midazolam and propofol intravenously administered. A post-procedure large spectrum intravenous antibiotic therapy was administered. Technical success of the PEG-J placement procedure was evaluated at day 1 by a contrasted abdominal x-ray. To estimate safety of LCIG infusion, all adverse events (AEs, mild, moderate or severe) were registered during PEG-J tube infusion.

### **Statistical Analysis**

For the analysis of differences among groups regarding clinical variables we used non-parametric tests (Kruskal-Wallis H test to compare three samples, and the Mann-Whitney U test to compare two samples) to avoid biases due to the small sample size. A *p* value less than 0.05 was considered statistically significant. Analyses were performed with SPSS version 13 (SPSS Inc., Chicago, IL, USA)

### **Results**

Demographic features, LEDD characteristics and clinical results at T0, T3 and T6 visits were summarized in Table I. Out of the 11 patients, 2 (18%) dropped-out LCIG at T3: one patient withdrawal due to AEs (confusion and hallucinations) and the other one due to lack of compliance to the treatment. As expected, LCIG infusion did not modified motor performance and L-dopa sensitivity in "on" state, as assessed by UPDRS part III. Therefore, during intra-jejunal infusion therapy patients showed statistically significant (*p* < 0.05) higher performances in activities of daily living and a statistically significant (*p* < 0.001) lower incidence and severity of motor fluctuations, as rating by UPDRS part IV, compared to their best oral therapy. During observational period, 4 patients (33%) experienced mild AEs; one patient (9%) experimented moderate AEs, as showed in Table II. Success rate for PEG-J place-

**Table I.** Demographic and clinical features of patients before (T0) and after (T3, T6) LCIG initiation.

Parameter	T0 (n = 11)	T3 (n = 11)	T6 (n = 9)	p-value
Age at PD onset (years)	57.9 ± 12.6	–	–	–
Age at LCIG initiation (years)	71.2 ± 5.4	–	–	–
Disease Duration (years)	15.4 ± 7.3	–	–	–
H and Y stage	3 ± 0.5	–	–	–
UPDRS III (off)	42.4 ± 5.2	–	–	–
UPDRS III (on)	26.1 ± 5.53	26.3 ± 5.6	28.2 ± 5.8	0.40
UPDRS II (on)	21.5 ± 8.52	14.4 ± 9.1	12.7 ± 7.4	0.02
UPDRS IV (on)	10.3 ± 3.6	4.4 ± 3.5	2.7 ± 1.9	< 0.001
LEDD (mg daily)	1057.4 ± 450.4	872.3 ± 359.8	898.2 ± 368.7	0.40

LCIG: levodopa-carbidopa intestinal gel; UPDRS: Unified Parkinson's Disease Rating Scale; LEDD: levodopa equivalent daily dose; T0: baseline; T3, T6: after 3 and 6 months of LCIG therapy.

ment was 100%. Technical difficulties verified in one patient due to duodenal bulb anatomical anomaly causing a prolongation in duration time of the endoscopic procedure. In one patient post-procedure x-ray revealed a PEG-J tube kinking which was endoscopically corrected on day 2. In one patient, tube dislodgement on day 7 caused for repeating procedure.

## Discussion

All patients suffering from PD, during the course of the disease, must irremediably resorting to levodopa, the most powerful dopaminergic medication available, to obtain a degree of control of symptoms<sup>12,13</sup>. One of the main problems in the long-term management of these patients is considerable variability, both in terms of clinical response that side effects levodopa related. Unfortunately, most of the subjects that respond to levodopa gradually develop motor complications during long-term therapy, not present at the beginning. These motor complications are essentially represented by motor fluctuations (motor fluctuations on/off, akinesia upon waking and freezing) and involuntary movements (dyskinesias and dystonias)<sup>2,14,15</sup>. The pathogenesis of these disorders is not fully understood but it is certainly due to the

dopaminergic transmission. According to studies conducted in animal models, would be the pharmacokinetic changes, employees from the different modes of taking the drug, to determine phenomena of tolerance and sensitization (reverse tolerance) in the basal ganglia<sup>16,17</sup>. In summary, the route of administration of the drug, through fluctuations in plasma levels of levodopa in the case of oral administration, would be responsible for the variability of the clinical efficacy and adverse reactions<sup>18</sup>. In fact, the conventional levodopa regimens would not guarantee a physiological continuous dopaminergic stimulation. The impaired gastric emptying is frequently found in patients with PD and is probably one of the key factors which affects the reliability of oral administration of levodopa (in addition to its short half-life) given that drug absorption takes place mainly in the small intestine proximal<sup>3</sup>.

To overcome these problems but mainly to maintain constant plasma concentration of levodopa, the continuous dopaminergic stimulation is the best approach<sup>19</sup>. Therapeutic options available for advanced PD are high frequency deep brain stimulation of the subthalamic nucleus or globus pallidus internus, continuous subcutaneous infusion of apomorphine, and the continuous infusion duodenal levodopa/carbidopa. In our study we evaluated the efficacy and safety of LCIG delivered continuously via PEG-J with the UPDRS. Our results shows that LCIG compared to oral therapy allows to minimize motor fluctuations and improve quality of life and self-government of PD patients, after 3 and 6 months of treatment. Moreover, PEG-J, as described in the literature, was confirmed as a safe and effective procedure. In fact, our data show a success rate of 100% and easily solvable technical complications in only one case.

**Table II.** Adverse event reported during LCIG infusion.

Adverse event	Number of patients (%)
Granuloma	4 (36%)
PEJ kinking/dislocation	2 (18%)
Hallucinations	1 (9%)
Orthostatic hypotension	1 (9%)
Confusion	2 (18%)

## Conclusions

Our work shows that continuous intrajejunal infusion of levodopa-carbidopa intestinal gel ensures a reduction in motor fluctuations compared to oral administration of levodopa-carbidopa in advanced PD. This is further evidence of the role that the pharmacokinetics of levodopa plays in the development of motor disorders associated with its administration. Based on these findings and on the evidence emerging in the literature, we believe that this therapeutic approach should be the rule in these patients.

## Conflict of Interest

The Authors declare that there are no conflicts of interest.

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