REVIEW ARTICLE

Is levodopa-carbidopa intestinal gel over- or under-utilized? A review of current evidence.

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Abstract

Levodopa-carbidopa intestinal gel (LCIG) is one of the alternative treatment options for advanced Parkinson disease (PD) patients who experience motor fluctuations and insufficient control of their symptoms despite optimized combinations of oral medications. LCIG is continuously infused through a portable pump into the proximal small intestine, and has been proven to reduce "off" time as well as increase "on" time without significantly worsening troublesome dyskinesias. In addition, growing data also suggest improvement in some non-motor symptoms and the patient's quality of life. The most common side effects of LCIG are procedural/device-related complications which can be frequent, especially within the first month of device placement, but generally mild and transient in nature. Interestingly, despite its clear efficacy and general safety and tolerability, it has not been utilized by providers to the same extent as other advanced therapies, such as deep brain stimulation surgery (DBS). In this review article, we discuss the evidence supporting LCIG's efficacy, safety, adverse effects, tolerability, cost-effectiveness as well as potential contraindications. Furthermore, we also re-evaluate LCIG's indications, utilization and potential limitations.

Keywords:

Levodopa-carbidopa intestinal gel, Parkinson disease, levodopa, motor fluctuations.

1.   Introduction

Levodopa remains as the most potent treatment for Parkinson disease (PD). However, nearly all patients eventually develop motor fluctuations or dyskinesias. The response to oral medications often fluctuate after 4-6 years of treatment in up to 75% of patients (Fernandez & Odin, 2011), and after 9 years of treatment in 90% of patients (Ahlskog & Muenter, 2001). The mechanism of motor fluctuations related to levodopa is not completely understood. It is felt to be, at least in part, the result of the short plasma half-life of levodopa and delayed gastric emptying, causing irregular absorption and unstable plasma concentration (Hardie, Lees, & Stern, 1984; Wirdefeldt, Odin, & Nyholm, 2016)

In theory, other oral treatment options, including levodopa controlled-release (CR), aim to stabilize serum dopamine level. However, they fail to reduce motor complications (Gauthier & Amyot, 1992; Sage & Mark, 1994). Adding catechol-O-methyl transferase inhibitors (such as entacapone) to provides a longer levodopa half-life, but may increase dyskinesias (Stocchi et al., 2010). Dopamine agonists

monotherapy (ropinirole, pramipexole) may help delay onset of motor complications, but they are not as effective as levodopa in controlling PD symptoms (Holloway et al., 2004; Rascol et al., 2006). Moreover, the ability of long acting dopamine agonists in reducing motor complications, in conjunction with levodopa, remains inconsistent (Olanow, Stern, & Sethi, 2009; Rascol & Perez-Lloret, 2009).

For advanced patients with motor complications, various combinations of oral medications typically no longer efficiently control their symptoms. Levodopa-carbidopa intestinal gel (LCIG), deep brain stimulation (DBS), and apomorphine subcutaneous infusion or injection are considered advanced treatment options, described to smoothen levodopa response when oral therapy fails.

The purpose of this review is to discuss the reported cumulative experience with LCIG and evaluate whether LCIG has been over or under utilized.

2.   What is LCIG?

LCIG is administered by using a portable pump which provides continuous infusion through a percutaneous endoscopic gastrostomy with a jejunal extension tube (PEG-J) into the proximal small intestine where levodopa is mainly absorbed (Fernandez & Odin, 2011). Each 100mg of LCIG cassette contains a carboxymethylcellulose aqueous gel with 20mg/ml of levodopa and 5mg/ml of carbidopa. Typically, the pump administers LCIG with a morning bolus followed by continuous infusion for 16 hours during the waking day. However, 24-hour infusion has been used to treat night time symptoms in some patients.

LCIG was initially developed in Sweden in the 1990s. It has been approved and used in several countries in Europe since 2004 for advanced PD treatment (Wirdefeldt et al., 2016). More global utilization of the drug started less than a decade ago. From 2009 to 2017, approximately 13,000 patients globally have used LCIG. Within the U.S., around 900 patients have been commercially placed with LCIG since its FDA approval in 2015 (AbbVie, personal communication, September 9, 2017). In comparison, with in the same time period, about 13,000 PD patients have undergone DBS implantation in the U.S. (Medtronic, personal communication, September 16, 2017). Subcutaneous apomorphine infusion has yet to be approved in the U.S.

3.   Pharmacokinetics and pharmacodynamics

LCIG has been shown to provide a stable levodopa plasma level. Therefore, likely a more sustained dopamine level in the striatum. Nyholm et al were the first group that described stable pharmacokinetics with LCIG infusion through PEG-J tube. Plasma levodopa, carbidopa, and levodopa metabolite levels were measured in serial blood samples of 18 patients during infusion and washout, showing consistent plasma level of levodopa over 16 hours (Nyholm et al., 2013). Moreover, the stable rise in dopamine level in the striatum was shown in an in vivo study using serial [11C] raclopride Positron-emission tomography scan (Politis et al., 2017).
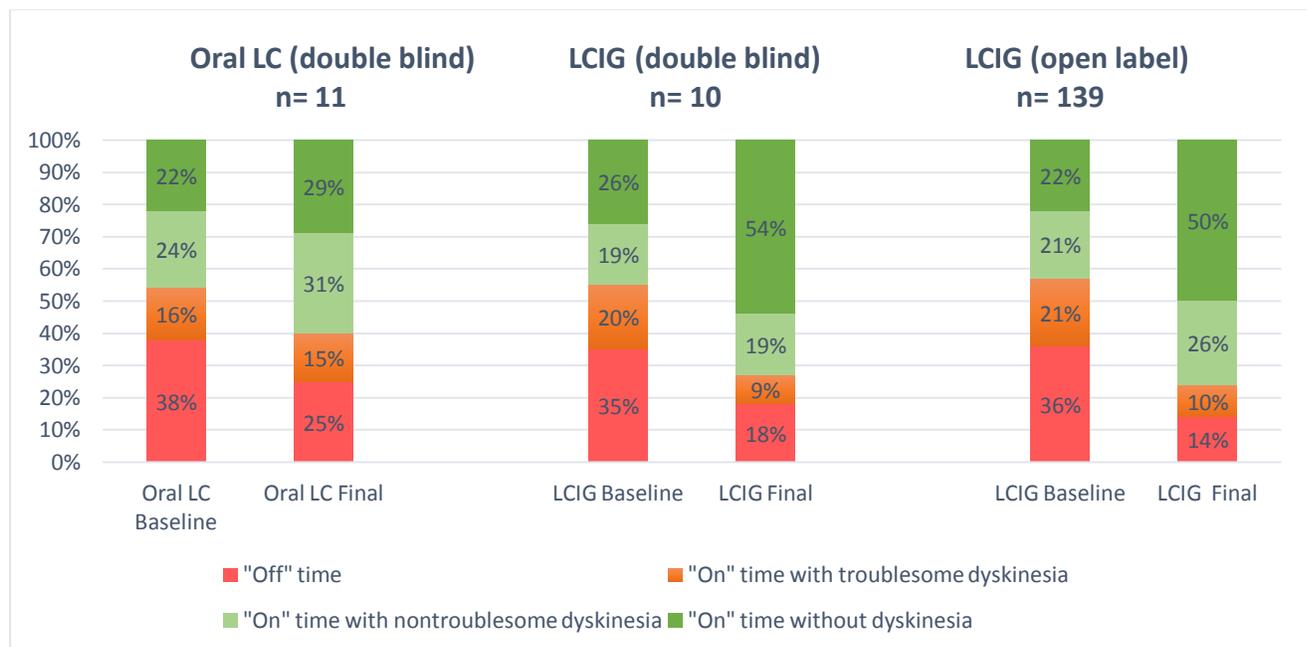
4.   Efficacy on motor symptoms

Many open-label studies and observational studies have consistently described LCIG's efficacy in reducing motor fluctuations and improving motor performance using the Unified Parkinson Disease Rating Scale (UPDRS) in advanced PD patients (Antonini, Yegin, Preda, Bergmann, & Poewe, 2015; Bohlega et al., 2015; Caceres-Redondo et al., 2014; Fasano, Ricciardi, Lena, Bentivoglio, & Modugno,

2012; Reddy et al., 2012). Its efficacy on improving motor fluctuation was noted in up to 90% of advanced PD patients who received LCIG as a last line therapy (Devos, 2009).

A recent systematic review described 3 well-designed randomized controlled trials that support the efficacy of LCIG (Wirdefeldt et al., 2016). The first is a crossover trial involving 12 advanced PD patients comparing LCIG through nasoduodenal infusion versus a combination of oral sustained-release and immediate-release levodopa. Motor examinations were recorded and analyzed. The study showed a significant increase in the "on" state, a decrease in "off" state, along with decreased dyskinesias in the LCIG group (Nyholm et al., 2003). Another randomized study named the DIREQT study (Duodopa Infusion: Randomized Efficacy and Quality of life Trial) also compared LCIG nasoduodenal infusion

monotherapy against optimized oral medications in 24 advanced PD patients. Motor function was assessed through video scoring by blinded investigators, as well as patients' self-assessed diaries. The median UPDRS score improved from 53 to 35, along with a significant decrease in "off" time, and an increase in functional "on" time without increasing dyskinesias in the infusion (Nyholm et al., 2005). The third randomized trial was a 12-week double-blinded, double-dummy multicenter trial in Germany, New Zealand, and the USA, which showed a reduction of "off" time by an average of 4.04 hours in the LCIG group as compared to 2.14 hours in oral immediate-release levodopa-carbidopa group. In addition, there was an increase in mean "on" time without bothersome dyskinesias by 4.11 hours in the LCIG group compared to 2.24 hours in the oral levodopa-carbidopa group (Olanow et al., 2014). (See Figure 1).

Figure 1. Proportion of time spent in each motor stage in the double blind and open label LCIG trials*.

*This graph is adapted from data of a post hoc analysis study (Antonini et al., 2016). Patient data was from a double-blind (Olanow et al., 2014) and open label study (Fernandez et al., 2015) adjusted for a 16-hour waking day PD diary data.

Finally, the largest international, 54-week, open-label study also reported a significant decrease in "off" time by 4.4 hours, an increase in "on" time without troublesome dyskinesia by 4.8 hours, and a decrease in "on" time with troublesome dyskinesia by 0.4 hour (Fernandez et al., 2015). (See Figure 1).

5. Efficacy on non-motor symptoms

To date, there are no randomized controlled trials that have primarily evaluated the non-motor effects of LCIG. There are, however, small, short- and long-term, open-label studies that report significant improvement in non-motor symptoms using the Non-Motor Symptoms Scale (NMSS), ranging from 17-65% (Bohlega et al., 2015; Caceres-Redondo et al., 2014; Honig et al., 2009; Reddy et al., 2012). A recent larger open-label study specifically evaluating the long-term non-motor benefit of LCIG in 39 advanced PD patients over 60 weeks showed significant improvement in NMSS from baseline in several domains namely, sleep/fatigue, attention/memory, gastrointestinal tract, urinary and sexual function (Standaert et al.).

Reduction in anxiety was reported in 2 of 13 patients with motor fluctuations who switched from oral medication to LCIG in another prospective 12-month study. Eight patients reported less sleep disturbance as a result of improvement in nocturnal akinesias (Eggert et al., 2008). Finally, a case report also described cognitive improvement with LCIG (Sanchez-Castaneda et al., 2010).

6. Efficacy on quality of life

There are several studies evaluating quality of life in PD patients. Two randomized controlled trials both showed that LCIG improved quality of life. One is a double-blind, double-dummy trial in 26 centers which demonstrated significant improvement of quality of life using the Parkinson Disease Questionnaire (PDQ-39) and Clinical Global Impression Scale-Improvement subscale (CGIS-I) in the LCIG group as compared to the oral levodopa group (Olanow et al., 2014). The DIREQT study showed improvement in the PDQ-39 and the 15 Dimensional Quality of Life Instrument (15D). Sixty-seven percent of patients chose to continue LCIG infusion treatment (Nyholm et al., 2005).

Several other open-label studies also showed significant improvement of quality of life with LCIG. A large, multicenter, observational study in 18 countries in Europe involving 375 advanced PD patients who were treated with LCIG showed significant improvement in the short form 8-item Parkinson Disease Questionnaire (PDQ-8) and EuroQuol-5 Dimensions Scale (EQ-5D) score (Antonini et al., 2015). In a prospective, open-label study of 28 patients with LCIG treatment, an improvement in the patients' quality of life was noted, using the PDQ-8, but not with the caregivers (Sensi et al., 2014). Finally, another recent prospective study showed improvement in quality of life in both patients and caregivers (Ehlers et al., 2015).

7. Safety, adverse effect and tolerability

Adverse effects may be categorized into 2 main groups, namely, adverse effect from levodopa itself, and the adverse effect related to the procedure or device/infusion system. In general, LCIG has similar side effects as oral levodopa such as nausea, sleep disturbance, weight loss, hallucination, dyskinesia, mood disturbance (Wirdefeldt et al., 2016). A long-term safety study with follow-up of more than 10 years has not reported unexpected side effects and there is no evidence of tolerance to LCIG (DANMODIS/SWEMODIS, 2008).

The integrated safety data of LCIG from 4 prospective studies, namely (Olanow et al., 2014), (Fernandez et al., 2015), (Slevin et al., 2015), and NCT00360568 showed that while 76% (300/395) of the patients had procedure-, or device-related adverse events, most were transient with the majority opting to continue treatment with LCIG. Seventeen percent (68/395) were considered serious adverse events. The most common adverse event was a complication of device insertion, accounting for 41% (160/395). Abdominal pain was experienced by 36% (142/395). "Procedural pain" accounted for 27% (107/395). Other adverse events included wound infection in 26% (104/395), incision site erythema in 22% (87/395), excessive granulation tissue in 22% (86/395), procedural site reaction in 16% (65/395), post procedural discharge in 13% (51/395), pneumoperitoneum in 6% (24/395), peritonitis in 2.8% (11/395), device dislocation in 2.3% (9/395), device occlusion in 1% (4/395) and small intestine obstruction in 1% (4/395) (Lang et al., 2016).

Another commonly mentioned but controversial side effect of LCIG is polyneuropathy.

A prospective study reported polyneuropathy in 47.8% (11/ 23) of patients treated with LCIG for up to 36 months (Merola, Romagnolo, et al., 2016). However, it was reported only in 2.8% (9/324) of patients in a largest prospective, open-label, 54-week study (Fernandez et al., 2015). The etiology of polyneuropathy associated with long term levodopa exposure is unclear. It was felt to be associated with vitamin B12 deficiency, neurotoxicity associated with high homocysteinemia, and high dose of levodopa (Merola, Romagnolo, et al., 2016). Supplementation of vitamin B12 and reduction of LCIG dose helped to improve neuropathy symptoms in some patients (Toth, Brown, Furtado, Suchowersky, & Zochodne, 2008).

As noted earlier, most adverse events were mild to moderate and transient. Overall, adverse events resulted in discontinuation of LCIG treatment in 17% of patient (72/412), with only 2.4% were due to device insertion complication (Lang et al., 2016). Moreover, despite the seemingly high frequency of side effects, patient's satisfaction with LCIG has been found to be quite satisfactory in a multicenter study in Belgium. This study showed high scores of patient global appreciation (mean score 7.6, maximum score 10), family appreciation of the LCIG on daily life (mean score 7.4, maximum score 10) and patient rated user-friendliness of the LCIG system (mean score 6.9, maximum score 10) (Pickut, van der Linden, Dethy, Van De Maele, & de Beyl, 2014).

8.   Cost-effectiveness

There has been no study primarily evaluating the cost-effectiveness of LCIG in the US that we are aware of. However, there were studies in other countries that suggested that LCIG is cost-effective. A United Kingdom study evaluating the cost-effectiveness of LCIG, based on quality adjusted life years gain (QALY) within 5 years of 12 advanced PD patients, showed a lower incremental cost per QALY in LCIG (£36,024) compared with the standard care (£39,644) (Lowin et al., 2011). While a large open-label, prospective, observational study evaluating healthcare cost of LCIG in 77 patients through 3 years of follow-up in Sweden and Norway showed an increase in the monthly costs per patient during the initiation of LCIG, and an increased cost in relation to the severity of symptoms and impairment of quality of life, the overall costs were stable across LCIG-naïve, LCIG treatment less than 2 years, and LCIG treatment of 2 years or more (mean monthly

cost £8226 ± 5952) (Palhagen et al., 2016). Finally, another recent Irish study, using the Markov model on a hypothetical cohort of 100 PD patients, suggested that LCIG is cost-effective when compared with standard oral therapy and apomorphine injection (Lowin et al., 2017).

9.   Potential contraindications

There are no absolute exclusionary criteria for LCIG. Some clinicians impose a limit on the patient's age. Indeed, a prospective study suggested a better outcome in patients who had less psychiatric and behavioral symptoms and at a younger age of LCIG utilization (Sensi et al., 2014). The Scandinavian Movement Disorders Consensus guideline regarding LCIG treatment for PD recommended to avoid LCIG in patients with contraindication for abdominal surgery, complicated medical conditions such as serious hepatic, renal, cardiac diseases, endocrine conditions that may cause sympathetic over-activity, neurologic diseases (such as recent or acute stroke), and lastly, glaucoma. Similar to DBS, another contraindication is significant dementia. However, clinicians with expertise in both LCIG and DBS use tend to have a higher threshold for cognitive impairment for LCIG than DBS, meaning a patient with mild/early dementia that is typically deemed as contraindicated for DBS may still be a reasonable candidate for LCIG. The concomitant use of non-selective monoamine oxidase (MAO) inhibitors is another contraindication. MAO-A inhibitors should be discontinued at least 2 weeks prior to starting LCIG treatment (DANMODIS/SWEMODIS, 2008).

Finally, in rare cases, having DBS in place may not be an absolute contraindication for LCIG. In fact, a recent study has shown that LCIG can also be an additional therapy in patients with refractory symptoms despite having DBS (Regidor, Benita, Del Alamo de Pedro, Ley, & Martinez Castrillo, 2017).

10.   LCIG in comparison with apomorphine and DBS

There is no randomized controlled trial directly comparing LCIG with apomorphine and DBS. A systematic review assessing the relative effectiveness of levodopa infusion, apomorphine infusion, and DBS showed benefit in all three treatment options and suggested that treatment selection for patients should be based on clinical judgment as well as patient preference (Clarke, Worth, Grosset, & Stewart, 2009). An open-label, non-randomized, observational study comparing subcutaneous apomorphine infusion and LCIG showed improvement in motor complications and quality of life in both groups. However, the LCIG group had markedly better improvement in non-motor symptoms. There was an improvement in NMSS scores in 75% of patients in the LCIG group and 40% of patients in the apomorphine group. In particular, sleep, fatigue, gastrointestinal, urinary, and sexual domains were better in the LCIG group. On the other hand, mood and apathy were better in the apomorphine group (Martinez-Martin et al., 2015).

Lastly, there was a 5-year retrospective review data evaluating activities of daily living (ADL), and motor complication of total 60 PD patients with similar baseline and cognitive status who were treated with subthalamic nucleus deep brain stimulation (STN-DBS), LCIG or oral medication treatment (OMT). This study showed better improvement in "off" time, dyskinesia duration and dyskinesia severity in both STN-DBS and LCIG group, compared with OMT. The STN-DBS group was statistically superior to the LCIG group in terms of improvement of dyskinesia duration. Dyskinesia severity was relatively

better in the STN-DBS than LCIG. Both STN-DBS group and LCIG group were similar in having less deterioration in ADL, compared to OMT. Long term complications in the STN-DBS group were similar to the OMT group, and were less than in the LCIG group (Merola, Espay, et al., 2016).

In terms of cost-effectiveness, there is an ongoing randomized controlled study in the Netherlands, named the INVEST study (Infusion versus Stimulation in Parkinson disease). This study aims to evaluate the cost-effectiveness between LCIG versus DBS as a primary outcome. The study is also planned to evaluate motor symptoms, non-motor symptoms, quality of life as secondary outcomes (Van Poppelen et al., 2016).

11. LCIG utilization and potential limitations

Interestingly, LCIG may not be considered by many as an equal alternate treatment in the advanced PD population, with great disparity in the US and in other countries in the utilization of LCIG versus DBS. It may even be viewed by some as the ultimate last resort, when DBS or apomorphine subcutaneous infusion or injection are contraindicated or have failed. Based on available data, this may not be well-deserved or justified.

There are many reasons that may have dampened LCIG's utilization. First of all, it requires a multidisciplinary team of providers including a surgeon or gastrointestinal specialist, movement disorders clinician, and perhaps a specialized nurse who could advise, educate, troubleshoot, train, and coordinate care for the patient and caregivers. Therefore, not many facilities have the capacity to offer this multidisciplinary approach required for this treatment. Secondly, since it has only been recently

approved in most countries. Many local providers may not have reached the sufficient comfort level to offer this treatment in the long-term. Training courses or educational conferences or workshops for providers would be helpful in addressing any concerns that prevent optimal utilization of LCIG. Thirdly, despite the fact that adverse events are mild to moderate and data consistently showed very good satisfaction from patients and caregivers, some providers and patients may have concerns about its maintenance burden and high frequency of adverse events. Finally, other reasons include: the earlier introduction of DBS with its consistently impressive (and often times life-changing) efficacy unlike any appreciated with oral therapy; the significant cost of LCIG; and, the initial need for prolonged hospitalization amongst the first set of countries that offered it.

Taking into consideration all the available data, despite the reported high frequency of adverse events of LCIG, it should not be considered as a "last resort" in severe PD compared to other advanced therapies, nor should it be viewed as inferior to them. On balance, while a high frequency of adverse events may have been reported with LCIG treatment, few of these lead to treatment discontinuation, most are mild and transient, and its reported improvements in "off" states, "on" states without troublesome dyskinesias, activities of daily living, and quality of life are comparable to that of DBS. In addition, it is likely to alleviate several non-motor symptoms. Therefore, when a clinician becomes comfortable with its use, and has developed a good two-way communication and partnership with a gastrointestinal proceduralist (similar to that required between a neurologist and neurosurgeon when offering DBS), this advanced treatment option should be generally viewed as an equal alternative to DBS and other available advanced treatments.

Decisions should be made on a case by case basis that considers the patient's main indications, relative contraindications, and preference. A significant subset of the advanced PD population are likely to experience significant improvement with *any* advanced treatment option. Nonetheless, there are specific scenarios where one treatment may be prioritized over the other. Data support that DBS, for example, be prioritized in PD patients with medication-refractory tremor, abdominal co-morbidities, and perhaps significant troublesome dyskinesias. On the other hand, LCIG can be offered in a broader spectrum of PD patients, including older patients, and those with some (bot not severe) cognitive impairment, behavioral and physical co-morbidities, especially those that have crossed a team's threshold for neurosurgical intervention. However, vigilance is required in the early and prompt recognition of gastrointestinal and procedural complications, and proper care and maintenance needs to be strongly emphasized to the patient and caregiver.

12.   Conclusion

LCIG has been consistently proven to be an effective treatment for improving motor fluctuations in PD. It has been reported to also improve non-motor symptoms, activities of daily living, and quality of life in PD patients. Current evidence shows that it is generally safe and well-tolerated in most patients. The reported adverse events of LCIG, although frequent, are oftentimes mild to moderate in severity and transient. LCIG, therefore, should not be considered as a "last resort" in severe PD compared to other advanced therapies. Currently, its utilization appears to be undeservedly limited. Decisions on choosing LCIG, as with any other alternate treatment for advanced PD, should be made on a case by case basis considering the patient's main indications, relative contraindications, and preference.

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