Journal of the Neurological Sciences 377 (2017) 6–11

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Liquid levodopa-carbidopa in advanced Parkinson's disease with motor complications

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ARTICLE INFO

Article history:
Received 12 February 2016
Received in revised form 3 March 2017
Accepted 22 March 2017
Available online 23 March 2017

Keywords:
Parkinson's disease
Motor complications
Liquid
Levodopa
Dyskinesia

ABSTRACT

While levodopa, carbidopa, ascorbic acid solution (LCAS) therapy has been used in patients with advanced Parkinson's disease (PD) for many years, long-term follow-up data is scarce. The present study aimed to determine the long-term retention rate for LCAS therapy, and to identify the causes of LCAS therapy withdrawal. Our study included a series of 38 patients with PD (14 men and 24 women) who underwent LCAS treatment between 2011 and 2013 to alleviate motor complications that were not satisfactorily controlled by optimized conventional anti-parkinsonian treatment at the Seoul National University Hospital. All patients were admitted to educate them about and initiate LCAS treatment for 2–5 days, and were then followed up as outpatients. The mean follow-up duration was 12.8 months, and three main reasons for LCAS treatment discontinuation were worsening of wearing-off symptoms (8 patients), persistent dyskinesia (4 patients), and poor drug adherence (4 patients). Fourteen patients (36.8%) maintained the LCAS treatment after 12 months, and were categorized as the treatment-retention group. The mean percentage of *on* time without dyskinesia significantly increased from 33.6 ± 17.6% to 57.0 ± 27.7% after LCAS initiation ($p = 0.016$) in the treatment-retention group. Twelve patients (31.6%) were still receiving LCAS treatment after 30 months. LCAS treatment can be a non-device assisted therapeutic option for patients who have no access to advanced therapies such as deep brain stimulation and infusional treatments.

1. Introduction

As Parkinson's disease (PD) progresses, various motor and non-motor manifestations complicate its long-term management [1–4]. Motor complications, including wearing-off, dopaminergic-induced dyskinesia, and off-dystonia, are seen in more than half of patients after 5 years of pharmacologic treatment [1,4], and negatively impact the health-related quality of life (QoL) of patients in the late stage of PD [5,6].

In the past decade, deep brain stimulation (DBS) [7], continuous subcutaneous apomorphine infusion (CSAI) [8], and duodenal levodopa infusion (DLI) [9] have been introduced for the treatment of the severe motor complications of PD. All three device-assisted treatments have been reported to be effective in recent clinical studies on selected patient populations [7–11]. However, not all patients with PD are eligible for or have access to such device-assisted options. This can be for a range of reasons, including contra-indications for invasive treatments, as well as medical co-morbidities, cognitive and neuropsychiatric status, or pharmaceutical regulatory issues [10–15]. For instance, the CASI treatment is not yet approved for the treatment of PD in Korea. Moreover, all of these therapeutic interventions require expensive and sophisticated hardware, which are not immune to device failures, infections, and other device-related adverse events that may result in treatment discontinuation [12,15–17].

Levodopa, carbidopa, ascorbic acid solution (LCAS) therapy for motor complications is not a new therapeutic option [3,18–23]. Clinical case series [19] and randomized cross-over studies were conducted using this therapy in the 1990s [20–22]. Prior works have suggested that LCAS treatment can provide a shorter time to peak plasma levodopa

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http://dx.doi.org/10.1016/j.jns.2017.03.039
0022-510X/

levels following dose administration compared to the standard tablet form [19–22,24]. In a randomized controlled study by Pappert et al., LCAS treatment effectively improved motor complications in 23 patients with advanced PD over a 4-week period [20]. An extension study of that cohort over 9 years was published as an abstract [22]. Although previous studies have demonstrated that LCAS treatment can reduce motor complication, long-term follow-up data is scarce, and no clinical information is available on causes of withdrawal, adverse events, and changes in non-motor symptoms after prolonged LCAS treatment [19–22].

To address this issue, we report our long-term findings of LCAS therapy with special reference to patient populations that might be more likely to benefit from this therapy, and what can be expected in terms of tolerability and adverse events during the treatment.

2. Materials and methods

2.1. Study patients and treatments

The present study included patients with idiopathic PD who underwent LCAS therapy between 2011 and 2013 for motor complications that had not been satisfactorily controlled with optimized conventional anti-parkinsonian treatment at the Seoul National University Hospital. We excluded patients who did not meet the United Kingdom Brain Bank diagnostic criteria, or patients who did not have available medical records.

We retrospectively identified a series of 38 patients admitted to our movement disorder center due to disabling motor complications who received LCAS therapy. All patients were admitted to the hospital to initiate LCAS treatment for 2–5 days, and were then followed up as outpatients. During the hospital stay, they were educated about the methods of making, storing, and adjusting the LCAS dose [2,18]. The patients were switched overnight from the original anti-parkinsonian medications to LCAS, according to their levodopa-equivalent daily dose (LEDD) that was calculated based on the patients' previous dopaminergic regimen [25]. In detail, two powdered 1 g tablets of ascorbic acid and 4–8 tablets of levodopa-carbidopa (250 mg/25 mg) translated from the LEDD of each patient's original dopaminergic medications were added to tap water to make a total volume of 1 L daily [2,3]. The initial hourly dose of LCAS was calculated from the number of wake-hours during which LCAS was applied [19,20]. Ascorbic acid was added to the liquid form of levodopa-carbidopa in order to avoid oxidation and to maintain acidity [23]. The prepared solution was stored at 4 °C in a conventional refrigerator. Each interval dose was usually taken regularly on an hourly basis but varied from 1 h and 1.5 to 2 h according to the patient's clinical needs and preferences. Patients were educated to titrate the volume of LCAS depending on the clinical condition. They were recommended that LCAS be taken in upright position, and allowed to take LCAS up to 2–3 times upon awakening in the morning [2,3].

All participants in the present study were followed up on an outpatient basis after a stable LCAS regimen was determined and they were comfortable with titrating the dose. We attempted to use LCAS as monotherapy, but other anti-parkinsonian medications such as dopamine agonists, catechol-*O*-methyltransferase (COMT) inhibitors, monoamine oxidase-B (MAO-B) inhibitors, or amantadine were added at the discretion of the treating neurologist. At admission, pre-LCAS motor assessment, including the Unified Parkinson's Disease Rating Scale (UPDRS) part III and part IV, were performed in *on* without dyskinesia ("good *on*") after the first or second daily treatment dose of their original tablet dopaminergic medications. At the first outpatient visit after LCAS initiation, post-LCAS motor assessment was administered after the patient had reached the *on* condition without dyskinesia within about 20 to 60 min after receiving LCAS treatment. Patients' non-motor features were assessed using the Non-motor Symptoms Scale (NMSS). At every outpatient visit, the administration and the preparation of LCAS made by patients and/or caregiver was monitored under clinician supervision. Patients were interviewed for adverse events and completed an assessment of motor complications including the durations of dyskinesia and the *off* period. The diagnoses of wearing-off, peak-dose dyskinesia, and diphasic dyskinesia were determined based on the clinical interviews conducted by movement disorders specialists [1,4]. Medical records were reviewed to collect demographic and clinical information. This study was approved by the institutional review board (IRB) at the Seoul National University Hospital (IRB approval number: H-1506-041-769), and informed consent requirement was waived for this retrospective study.

2.2. Statistical analysis

Treatment-retention was defined as maintaining LCAS treatment for 12 months or more. Patients who stopped LCAS treatment within 1 year were categorized into the treatment-discontinuation group. Predictors of treatment-retention were assessed with univariate analyses, using the chi-square test or Fisher's exact test for categorical data and the Mann-Whitney *U* test for continuous variables between the groups. To investigate independent predictors of LCAS treatment-retention, the variables with p values < 0.10 in the univariate analysis were introduced into a multivariate logistic regression. The p value criteria in the forward stepwise regression (likelihood-ratio based) for the entrance and removal of the variables were set at 0.05 and 0.10, respectively. Hosmer-Lemeshow tests were conducted to test the goodness-of-fit for the multivariate regression model. In the treatment-retention group, we used the McNemar test or the Wilcoxon signed-rank test to statistically analyze the differences between the baseline and follow-up clinical data. p values < 0.05 were considered to indicate statistical significance with no adjustments for performing multiple comparisons due to the explorative nature of the study. Kaplan-Meier survival plots were used to estimate the time until withdrawal of LCAS treatment. All statistical analyses were performed using IBM SPSS statistics version 19.0 (IBM Corporation, Somers, NY).

3. Results

The average age of the 38 patients (14 males and 24 females) identified was 60.0 ± 8.5 years, and PD symptom duration was 11.9 ±

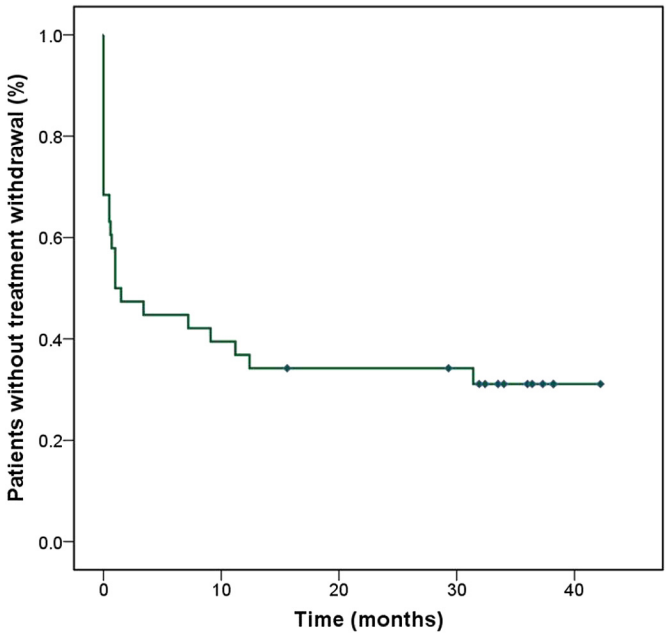

Fig. 1. Kaplan-Meier survival plot for the retention and discontinuation rate of levodopa, carbidopa, ascorbic acid solution (LCAS) treatment.