

Levodopa+carbidopa in X-linked Dystonia Parkinsonism (XDP/DYT3/Lubag): A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT

Objective. X-linked dystonia parkinsonism (XDP) is an adult-onset, progressive and debilitating movement disorder described among Filipino males from Panay Island. The available oral medications have been ineffective. While chemodenervation with botulinum toxin A works and deep brain stimulation surgery is promising, these are not affordable for the vast majority of patients. Thus, we decided to look into the efficacy, safety and tolerability of levodopa+carbidopa (levodopa) versus placebo among patients with XDP.

Methods. This was a double blind, randomized, placebo-controlled clinical trial. Patients were randomized to receive levodopa or placebo for 6 months. The dose was increased gradually until 1000 mg levodopa/day is reached or until side effects appear.

Results. A total of 86 out of 94 randomized patients (91.5%) were included in the intention-to-treat cohort for the primary efficacy analysis. Nineteen patients (9 in levodopa, 10 in placebo) dropped out or were lost to follow up. There was no significant difference in the baseline and last visit Burke Fahn Marsden Dystonia Rating Scale and the part III of the Unified Parkinson's Disease Rating Scale scores between levodopa and placebo. The most common adverse events in the levodopa group were increased movements, pain and nausea/ vomiting.

Conclusion. While levodopa is safe and well-tolerated, it does not have any effect in alleviating the dystonia or parkinsonism in XDP.

Key Words: dystonia, XDP, parkinsonism, levodopa, DYT3, Lubag

INTRODUCTION

X-linked dystonia parkinsonism (DYT3, XDP, "Lubag") is an adult-onset, progressive, often debilitating movement disorder. It presents with features of dystonia and parkinsonism.¹ XDP has a prevalence of 5.74/100,000 in Panay Island and 0.31/100,000 for the Philippines.² The majority of patients present initially with focal dystonia which generalizes in 2-5 years. The dystonia co-exists or is replaced by parkinsonism usually beyond the 10th year of illness.²

Currently, there is no known cure for XDP.³ The unique phenomenology of XDP of combined parkinsonism and dystonia offers a challenge in providing pharmacologic treatment for symptomatic relief. The drugs in use for XDP are the same drugs used in generalized dystonia (anticholinergic,

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baclufen, clonazepam and other benzodiazepines, tetrabenazine and clozapine).³ The benefit of muscle afferent block and chemodeneration with botulinum toxin A have been reported.^{4,5} Deep brain stimulation (DBS) has been reported in 27 case reports and case series to be a safe and effective procedure for alleviating the disabling symptoms of XDP.⁶⁻¹⁶ DBS is being offered only in 3 medical centers in Manila (Philippine Movement Disorder Surgery Center in Cardinal Santos Medical Center, Makati Medical Center and Asian Hospital and Medical Center). However, chemodeneration and DBS are generally not available or affordable for the vast majority of patients.

Levodopa use in dystonia is both diagnostic and therapeutic, especially for dopa-responsive dystonia.¹⁷ It has been tried before in an XDP patient with report of some improvement.¹ While several articles have shown that several classes of drugs are beneficial for patients with dystonia, none of these drugs have been systematically studied specifically for XDP. Thus, we decided to evaluate the efficacy, safety and tolerability of levodopa for XDP.

METHODS

Study Design and Patient Eligibility

This was a prospective, multi-center, randomized controlled clinical trial in patients with XDP. Patients were assigned to receive either carbidopa+levodopa (levodopa) or matching placebo. The patients were recruited from 2 participating centers: Philippine Children's Medical Center in Quezon City, Philippines and Roxas City Health Office, Capiz, Philippines from June 2009 to March 2011.

Male patients with a clinical diagnosis of XDP having whatever combination or severity of dystonia and/ or parkinsonism, a family history of dystonia and/ or parkinsonism and an inheritance pattern consistent with an X-linked pattern were potentially eligible for inclusion. The authors made the clinical diagnosis of XDP by consensus. The patients may be on anticholinergics (trihexyphenidyl, biperiden) or benzodiazepines (clonazepam, diazepam) provided that the dosage was stable for at least a month prior to the enrollment and that the dosage will no longer be changed for the duration of the trial.

We excluded patients with a clinical diagnosis of secondary dystonia, systemic metabolic conditions or neurodegenerative disorders as a cause of the dystonia and parkinsonism. Patients previously treated with botulinum toxin should not have received any botulinum toxin injections for at least 12 weeks. Any patient who decided to needed to have his medications adjusted, undergo DBS or chemodeneration with botulinum toxin A were withdrawn from the study.

A sample size of 104 patients (52 patients per group) was calculated to achieve a power of 80% and detect a 10-point difference mean change in the baseline scores between the levodopa and placebo groups. The calculation was based on

the assumption that the mean change in the baseline score for the placebo group is -7 with a standard deviation of 18 using a two-sided two-sample t-test at the 0.05 level of significance.

Treatment

The patients were given a starting dose of 125 mg levodopa/ day in 2 divided doses (¼ tablet of 25/250 mg tablet) and subsequently uptitrated until the maximum dose (1000 mg levodopa/ day) was reached or until treatment side effects appear. The uptitration schedule was increased by ¼ tablet for the next 2 weeks, then by ½ tablet for the next 4 weeks, then by 1 tablet thereafter. Patients randomized to placebo had a similar uptitration schedule. Upon completion of the study or withdrawal from the study, all patients were advised to downtitrate their medications under the supervision of the study team. The patients were then followed up in the clinics.

Randomization and Masking

Each treatment assignment was computer generated and sealed in sequentially numbered envelopes. The envelope with the lowest number was opened upon enrollment after confirming the eligibility of the patient and obtaining the informed consent. The treatment allocation assignment was concealed from the members of the study team and the patient.

Assessments and Outcome

Patients were examined at baseline and at 2, 4, 6, 8, 12, 16, 20, and 24 weeks after randomization. At each examination, patients were scored using the part III of the Unified Parkinson's Disease Rating Scale (UPDRS part III) and the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS).^{18,19} At each follow up, the patients were assessed for adverse events.

The primary measure of efficacy was the change in the total UPDRS part III and BFMDRS scores from baseline to the week 24 visit.

Statistical Analysis

Data on continuous scales were summarized as means along with standard deviation. Categorical type of data was presented as frequency distributions. Independent t-test was used to compare the two treatment groups at 5% level of significance, two-tailed. The difference in the mean change from baseline and last visit between the two groups was also estimated at 95% confidence level. The primary statistical analyses were performed according to intention-to-treat.

Patients who were unable to complete the study (including dropouts, lost to follow up) but took at least one dose of the study drug, with one post-baseline evaluation were included in the analysis. In these patients, the last available observation was carried forward. The nature, frequency and severity of adverse events were described. Stata 12 was used for the analysis.

Ethical considerations

Written informed consent was obtained from all patients or their legal representatives. The study was approved by the Ethics Review Board of the Philippine Children’s Medical Center.

RESULTS

A total of 104 patients were screened and 94 patients were randomized (n=49 in the levodopa group, n=45 in the placebo group). Five patients (n=3 in the levodopa group, n=2 in the placebo group) withdrew immediately following the first visit (before the first efficacy assessment) and were not included in the efficacy analysis. An additional 3 patients (n=3 in the placebo group) were not included in the analysis due to incomplete data (missing baseline UPDRS part III or BFMDRS scores and other clinical data). The other 86 patients (91.5%) formed the intention-to-treat cohort for the primary efficacy analysis (see Figure 1). There was no significant difference in baseline characteristics among treatment groups (see Table 1).

Analysis of Efficacy Measures

The 24-week total mean (± SD) BFMDRS scores (last observation carried forward) was 27.42 (24.95) for the levodopa group and 30.40 (21.99) for the placebo group. The mean (SD) change in total BFMDRS score from baseline was 3.88 (23.07) for the levodopa group and -0.125 (17.70) for the placebo group (see Table 2). This was not statistically significant.

The 24-week mean (± SD) UPDRS part III scores (last observation carried forward) was 21.54 (17.72) for the levodopa group and 29.40 (22.04) for the placebo group. The mean (SD) change/ reduction in total UPDRS part III score from baseline was higher for the levodopa group [9.25 (18.35)] than the placebo group [5.62 (17.04)]. However, this did not reach statistical significance (Table 2). The mean (SD) dose of levodopa taken by patients was 811.20 (254.44) mg.

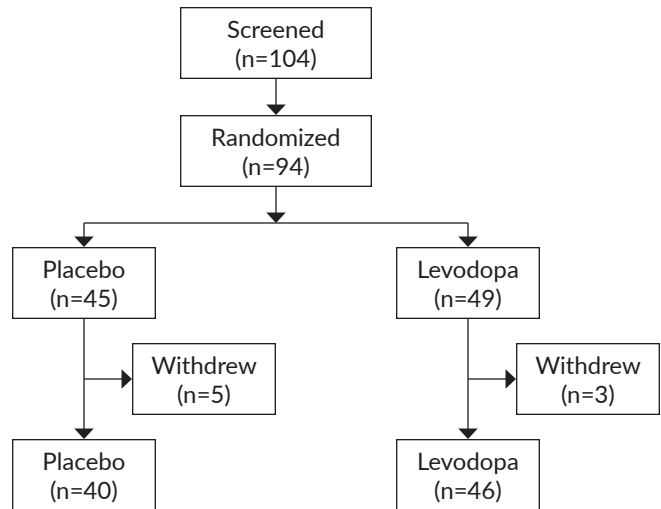


Figure 1. Patient disposition through screening and randomization.

Twenty-six patients (53%) reached the highest dose (1000 mg) while 2 patients were on the lowest dose (125 mg).

Analysis of Safety and Tolerability

During the course of the study, a total of 19/94 patient (20.2%) dropped out. Fourteen patients (14.9%) were lost to follow up (n=6 for levodopa, n=8 for placebo) despite efforts to locate them. The other 5 patients (n=3 for levodopa, n=2 for placebo) withdrew from the study.

A total of 27 patients (29.3%) (n=16 for levodopa; n=11 for placebo) reported adverse events at least once during the course of the study. The most commonly reported adverse experiences in the levodopa group were any pain (n=7), increased involuntary movements and nausea/ vomiting (n=6 each) and imbalance (n=4). In the placebo group, the most commonly reported adverse experiences were increased involuntary movements (n=7), any pain (n=5) and dysphagia and imbalance (n=2 each) (Table 3).

Table 1. Patient characteristics at baseline

	Levodopa (SD) (n=49)	Placebo (SD) (n=45)	p value
Age, in years	46.6 (9.3)	49.9 (9.5)	NS
Duration of illness, in years	6.13 (7.06)	6.20 (5.12)	NS
BFMDRS score	31.89 (24.46)	28.96 (25.70)	NS
UPDRS part III score	30.96 (20.96)	33.78 (25.76)	NS

Table 2. Mean change in baseline scores of levodopa and placebo

	Mean	Std. Dev.	Difference (95% Confidence Interval)	Two-tailed p-value
BFMDRS Score				
Levodopa	3.88	23.07	4.00 (-4.91, 12.92)	0.3744
Placebo	-0.125	17.70		
UPDRS part III Score				
Levodopa	9.25	18.25	3.63 (-4.13, 11.40)	0.3525
Placebo	5.62	17.04		

Table 3. Nature and frequency of adverse events according to treatment group*

	Levodopa (n= 16)	Placebo (n=11)
Dizziness	3	0
Nausea/ vomiting	6	1
Increased involuntary movements	6	7
Any pain (chest, nape, head, abdominal, generalized)	7	5
Imbalance	4	2
Anorexia	1	1
Insomnia	1	0
Tinea corporis	1	0
Dysphagia	1	2
Paresthesias	1	0

*total is more than the n

While 16 patients from the levodopa group reported side effects/ adverse events, only 3 patients dropped out due to these side effects. In the other cases, the dose was reduced and these patients were able to complete the study. In the placebo group, 6 patients dropped out due to the adverse events. There was 1 death in the levodopa group and this was deemed not related to the study drug.

DISCUSSION

This double-blind, randomized clinical trial was the first drug trial involving levodopa in patients with XDP and showed that levodopa does not alleviate the dystonic or parkinsonian symptoms of XDP. While there was a greater reduction in the UPDRS part III scores (9.25 vs. 5.62) in the levodopa group, this was not statistically significant.

The non-responsiveness to levodopa may mean that the pathology in XDP is not amenable to dopamine replacement.²⁰ In the dystonic phase, with depletion of striosomes leading to increased striatal dopamine action, treatment with levodopa could even have worsened the dystonia; while in the parkinsonian phase with depletion of the matrix leading to decreased matrix-based projections, levodopa replacement could conceivably have no effect.

While the gene nor the protein has not been discovered yet, several lines of evidence point to involvement of dopamine metabolism: there is evidence of TAF1 dysfunction in peripheral models of XDP.²¹ Also, one of the disease specific changes (DSC3) has been found to affect genes in vesicular transport and dopamine metabolism.²² Finally, genomic sequencing analysis has revealed decreased expression of the dopamine receptor D2 gene.²³ Perhaps the mechanism of dopamine involvement in XDP may be too complex for symptoms to respond to levodopa replacement alone, and a combination of therapeutic strategies aside from dopamine replacement, such as anticholinergics and benzodiazepines should be considered.

This trial has several limitations. At the time we were conducting this study, genetic testing was not yet available

in the Philippines. Thus, the diagnosis of XDP was purely clinical, as assessed and agreed upon by the authors. Another factor was that this trial was done in a mostly rural setting, and logistical factors such as transport of patients and communication certainly played a significant role. Another limitation might be that the target sample of 104 patients was not reached. However, we enrolled 94 patients and this already represented 30% of the XDP cases in the registry. At the time this study was being undertaken, there were only 312 survivors as recorded in the registry.² Despite these limitations, this was the first drug trial involving XDP patients. This study shows that it is feasible to conduct drug trials in this population and in the local setting.

In summary, levodopa alone does not have any effect in alleviating the dystonia or parkinsonism in XDP. Levodopa was well tolerated during the trial and adverse events were not more common in patients receiving levodopa than in those receiving placebo.

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

Dr. Jamora serves on the advisory board of Lundbeck Phils. and Torrent Phils. He has received honoraria/ CME grants from the Philippine offices of Allergan, Innogen, Lundbeck, Medichem, Natrapharm, Sandoz, Sun and Torrent. He has on-going research grants from the Collaborative Center for X-linked Dystonia Parkinsonism (CCXDP), St. Luke's Medical Center Quezon City and the Philippine Neurological Association. Drs. Teleg, Cordero, Villareal-Jordan, Lee and Pasco have nothing to disclose.

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