Treatment of refractory amblyopia with levodopa associated with full-time occlusion in the dominant eye

Tratamento da ambliopia refratária com o uso de levodopa associada à oclusão total do olho dominante

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Abstract

Purpose: *To evaluate visual outcomes of levodopa treatment associated with full occlusion of the dominant eye in patients with refractory amblyopia.* ***Methods:*** *A prospective study of 19 attended patients who were subject to treatment with Levodopa and Carbidopa on doses of 0.7mg/kg/day, a ratio of 4:1 divided into three daily doses for 5 weeks, combined with full occlusion (24 hours/day) of the dominant eye. The ophthalmologic exam from previous consultations up to treatment and after 8 weeks of therapy were collected from medical record data. Patients who had completed treatment for more than 12 months were included for complete eye examination.* ***Results:*** *The mean age before treatment with levodopa was 11.0 ± 4.2 years old (varying from 7 to 23 years). The best-corrected visual acuity (Snellen chart) of the amblyopic eye before treatment was 0.24 (0.6 in logMAR) ± 0.16, after 8 weeks of treatment it was 0.47(0.3 in logMAR) ± 0.33, while during the final evaluation it was 0.46 (0.3 in logMAR) ± 0.34. There was a statistically significant improvement in vision after 8 weeks of therapy which was maintained until the final evaluation (p = 0.007).* ***Conclusion:*** *Levodopa/Carbidopa therapyat doses of 0.7 mg/kg/day at a ratio of 4:1 divided in three daily doses, associated with full occlusion of the dominant eye during 5 weeks had a significant improvement on the visual acuity of the amblyopic eye, and persisted up to 1 year after the treatment.*

Keywords: *Amblyopia; Levodopa/administration & dosage; Drug combinations*

Resumo

Objetivo: Avaliar os resultados visuais do tratamento com levodopa associada à oclusão total do olho dominante em pacientes amblíopes. **Métodos:** Estudo prospectivo de 19 pacientes atendidos e submetidos ao tratamento com levodopa e carbidopa na dose de 0,7 mg/kg/dia e proporção de 4:1, divididos em três doses diárias, durante cinco semanas, combinada a oclusão total (24 horas/dia) do olho dominante. Foram coletados dados do prontuário referentes ao exame oftalmológico da consulta anterior ao tratamento e após 8 semanas de terapia. Os pacientes com término do tratamento com mais de 12 meses foram reconvocados para exame oftalmológico completo. **Resultados:** A média de idade dos pacientes previamente ao tratamento com levodopa foi de 11,0 ± 4,2 anos (variando de 7 a 23 anos). A acuidade visual melhor corrigida (Snellen) do olho amblíope antes do tratamento foi de 0,24 (0,6 em logMAR) ± 0,16, após 8 semanas de tratamento foi de 0,47 (0,3 em logMAR) ± 0,33 e na avaliação final foi de 0,46 (0,3 em logMAR) ± 0,34. Houve melhora estatisticamente significante da visão após 8 semanas de tratamento que se manteve até a avaliação final (p = 0,007) **Conclusão:** A terapia com levodopa/carbidopa em doses de 0,7mg/kg/dia na proporção de 4:1 dividida em três doses diárias, associada à oclusão total do olho dominante durante 5 semanas, apresentou uma melhora significativa na acuidade visual do olho ambliópico e persistiu até 1 ano após o tratamento.

Descritores: Ambliopia; Levdopa/administração & dosagem; Combinação de medicamentos.

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Introduction

Amblyopia is the main cause of visual impairment in children, affecting 4% of the general population.[1,2] It consists of a unilateral or bilateral reduction of visual acuity secondary to an abnormal visual experience during early childhood which causes vision impairment and monocular blindness and is commonly associated with strabismus, anisometropia, and visual deprivation (in particular congenital cataract and ptosis).[3]

Vision development occurs in the first six years of life. However, sensory plasticity is greater in the first two years. Any obstacle to the development of vision until this age causes a rapid loss in visual acuity. However, treatment during this period also promotes rapid recovery.[4,5] Although the age at which amblyopia can be recovered is still discussed, it is considered refractory when treated in children over eight-years-old.[3]

Many children with amblyopia are treated with occlusion of the dominant eye and have an incomplete response with some decrease in visual acuity. These patients show impairment in their self-image, as well as difficulties in school, work and social relationships.[6]

Oral levodopa is used to complement the dopamine deficiency in the brains of adults with Parkinson's disease and children with Dopamine-Responsive Dystonia. Although there is no evidence of a dopamine deficiency in the brain of patients with amblyopia, levodopa has been used by some physicians for the treatment of amblyopia since 1995 on an investigational basis.[7,8]

Studies in deprived amblyopic animals have suggested that neurotransmitters are involved in visual plasticity and may partially restore visual acuity in adult cats. Changes in evoked potentials and electroretinogram have been observed in patients with Parkinson's, indicating the participation of dopamine in the physiology of vision.[9] In a previous clinical trial, there was a significant improvement in visual acuity in patients who were considered as having refractory amblyopia with levodopa/benserazide combined with partial occlusion of the dominant eye, followed by a total occlusion period.[10] Improvements in visual acuity and evoked visual potentials were also reported in other studies with levodopa, but much of the improvement was regressed from drug discontinuation.[11]

Thus, this study aims to evaluate the visual results of levodopa therapy associated with total occlusion of the dominant eye in refractory amblyopic patients in an attempt to elucidate questions about their benefit after 8 weeks and after 1 year of treatment.

Methods

Study Design

A prospective study was conducted at Altino Ventura Foundation, Recife-PE, Brazil. The hospital ethics committee approved this study, which followed the tenets of the Declaration of Helsinki. Patients screened with refractory amblyopia were invited to participate (Table 1).

An initial clinical evaluation was performed with anamnesis and complete ophthalmologic examination after informed consent was obtained and a detailed explanation of the present study was provided.

The initial sample consisted of 28 patients: 6 were excluded because they did not perform the treatment correctly and 3 were lost in the follow-up (Figure 1). Nineteen patients were included with treatment indication with Levodopa and Carbidopa combined with the total occlusion (24h/day) of the dominant eye and with a follow-up time of at least 1 year after the medication was used. Patients who did not have the recommended occlusion or who stopped taking the drug for more than one day were excluded from the analysis.

Table 1
Inclusion and exclusion criteria for entry into study

Inclusion	Exclusion
Between7and 30 yearsold	Amblyopia still reversible with traditional occlusion
	Active ocular disease, infection or allergies
	Systemic condition or taking medications that may affect a study outcome variable

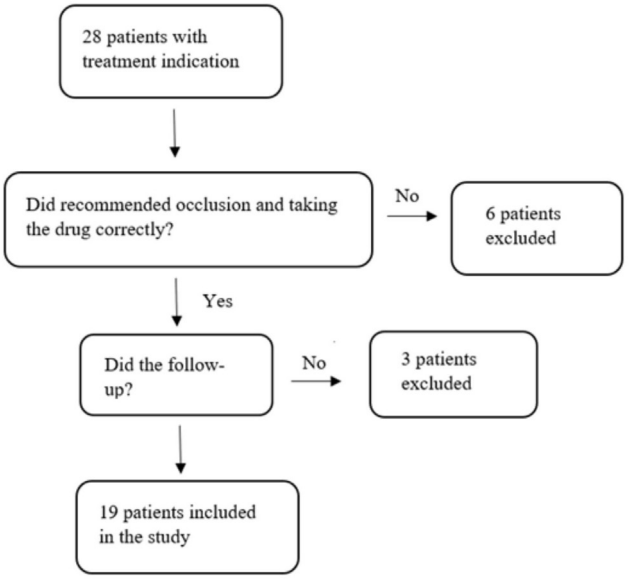

Figure 1: Flow diagram of study selection process.

Data collection

Forms with epidemiological information and ophthalmological exams previous to treatment (visit 1) and within 8 weeks of therapy (visit 2) were completed. The current visual acuity of patients was verified on visit 3. Neurological examination was not performed during the visits. On visit 3, patients were questioned about side effects and adverse reactions during therapy.

Vision was measured through the Snellen chart at 3 meters, with the best optical correction for ametropias throughout the study. The best-corrected visual acuity (BCVA) was considered to correspond to the line where the patient could read more than half of the optotypes. The concept of anisometropia used was a difference of refraction between the eyes above 2 diopters (D).[12] Improvement in treatment was considered when a gainin 2 lines of vision was achieved on the Snellen chart.

Treatment

Treatment consisted of Levodopa/Carbidopa at a dose of 0.7 mg/kg/day and a ratio of 4:1 divided into three daily doses

after meals for 5 weeks, combined with the total occlusion (24h/day) of the dominant eye. Patients maintained complete occlusion until there were no more gains on the Snellen chart between two visits within a one-month interval, and were instructed to initiate partial occlusion of 6h/day until one year of treatment.

Statistical Analysis

Numerical variables were expressed by their means and standard deviations (SD) and the categorical variables were expressed by their absolute and relative frequencies. The Friedman test and Student's T-test were used for evaluating the mean differences between visits, while the Chi-squared test was used for evaluating the differences in frequency.

Results

In evaluating the demographic profile of the analyzed patients, it was observed that the age ranged from 7 to 23 years, with an average of 11 ± 4.2 years, and they were predominantly female (63%). Among the clinical characteristics found, the most prevalent cause of amblyopia was the combination of strabismus and anisometropia (42%), with isolated strabismus (26%) being the second major cause. Hyperopia (63%) was the main source of ametropias. Foveal visuscopy (89%) was greater than extrafovealvisuscopy (10%), and the follow-up time was 1 year (Table 2).

Table 2
Clinical and demographic characteristics of patients with amblyopia treated with levodopa (n=19)

Age (mean ± standard deviation) in years-old	**11.0 ± 4.2**
7 to 12	14 (73,7)
13 to 17	3 (15,8)
>17	2 (10,5)
Gender	
Male	7 (36)
Female	12 (63)
Cause of amblyopia	
Strabismus	5 (26)
Ametropia	2 (10)
Anisometropia	3 (15)
Strabismus + anisometropia	8 (42)
Ametropia	
Myopia	5 (26)
Hyperopia	12 (63)
Astigmatism > 3 D	3 (15)
Visuscopy (amblyopic eye)	
Foveal	17 (89)
Extrafoveal	2 (10)
Follow-up (mean ± standard deviation) in years	**2.5 ± 1.6**
1 to 3	13 (68)
> 3	6 (15)

Results expressed by mean and n(%).

There was an increase in visual acuity greater than two lines of sight in 13 patients (68%) after 8 weeks of levodopa (L-dopa) treatment and remained after 1 year of therapy in 10 of the 19 patients (52%).The mean BCVA at the beginning of the treatment was 0.24 (0.6 in logMAR) ± 0.24 (ranging from 0.10 to 0.50) on a decimal scale. It improved to 0.47 (0.3 inlogMAR) ± 0.33 (ranging from 0.10 to 1.00) after 8 weeks of therapy, remaining at 0.46 (0.3 inlogMAR) ± 0.34 (ranging from 0.13 to 1.00) in the last evaluation, with a statistically significant difference between these measures ($p = 0.007$). The BCVA found at visit 1 was lower than that observed at visits 2 and 3 ($p < 0.05$). There was no statistical difference between BCVA on visits 2 and 3 ($p = 0.615$). None of the patients reported side effects or adverse reactions during the 5 weeks of treatment with Levodopa/Carbidopa.

Table 3 presents the lines of improvement after treatment. For comparison of results, patients were divided into three groups: group 1 (7 to 12 years), group 2 (13 to 17 years) and group 3 (older than 17 years).

Table 3
Lines of improvement after treatment

AGE	Group 1 Lines of improvement	AGE	Group 2 Lines of improvement	AGE	Group 3 Lines of improvement
7	2	13	4	19	4
7	5	13	5	23	3
7	0	16	3		
8	0				
8	0				
9	0				
9	3				
9	2				
10	5				
10	6				
10	2				
10	3				
10	2				
11	7				

When comparing the initial progress with the final improvement, it was found that 10 of the 13 patients who achieved progress in their initial BCVA (at 8 weeks) maintained a statistically significant improvement after a period of more than one year of treatment ($p = 0.003$) (Table 4).

Table 4
Initial improvement x Final improvement in patients treated with levodopa

		Final improvement		
		No	**Yes**	**p-value***
Initial improvement	No	6	0	0,003
	Yes	3	10	

*Fisher's exact test

Discussion

Levodopa is a precursor of dopamine and its traditional use is in Parkinson's disease. Because dopamine does not cross the blood-brain barrier, the treatment that attempts to increase its concentrations in the central nervous system uses levodopa, which transports through the barrier and is transformed into dopamine. Since levodopa can also be converted to dopamine at the peripheral level, causing undesirable effects, carbidopa

is simultaneously administered to inhibit this transformation. Dopamine is a neurotransmitter present in the amacrine and interplexiform cells of the retina and central nervous system. Through action on D1 and D2 receptors in the retina, it influences the receptive field properties of the retinal neuron at the communicating junctions between the horizontal cells and in the adaptive light movements between the cones and rods.[6]

In this study, we demonstrated that visual acuity was statistically significantlyimproved after Levodopa/Carbidopa therapy with an enhancement maintained for more than 1 year after treatment. The long-term effect of this treatment has been questioned in published studies.[6,11]

Patients were subdivided into three groups, considering age, since brain plasticity is still relevant in patients under 17-years-old,(13) which may generate a bias when compared with older patients. Recent studies indicate the possibility that brain plasticity may remain relevant for a longer period than previously thought, which makes this division more important.[14,15]In our study, there was a range of sightlines regardless of age.

Recent publications, such as the multicenter randomized clinical trial of the pediatric ocular disease investigations group of 2015, concluded that amblyopic patients did not benefit from Levodopa/Carbidopa-based treatment.[11] However, there are some divergent points in the treatment form used in this study and in the present study. The dose that is administered to patients at the Altino Ventura Foundation is adjusted for weight and the dominant eye occlusion is 24 hours per day. Other well-conducted publications showed a positive association of amblyopia improvement with the medication in test when combined with total occlusion of the dominant eye, with this being a great differential in the studies with negative associations because they only used the occluder for 2 hours per day in the dominant eye for 12 weeks [8, 16, 17] and the Levodopa dosage was three times lower than in the PEDIG study.[11, 18]

Although this had a small follow-up study, the cause of the difference in the results of this study compared with other important clinical trials was probably the longer occlusion period during treatment and some differences in the screening of eligible patients for medication. Foveal visuscopy in the amblyopic eye was an important criterion in the selection of these patients. We believe that foveal visuscopy is important in Levodopa therapy success, instead of extrafoveal visuscopy. Patients were not excluded from treatment due to age restriction, as other studies were conducted with patients older than 8 yearsold. However, patients were excluded from Levodopa therapy in this study if they had still reversible amblyopia with traditional occlusion. No adverse effects were observed during our treatments, which is the same as reported in previous studies.[10,11]

Amblyopia is a relatively common pathology and has an important consequence on the reduction in quality of life, causing an impact on family life, social interaction, difficulty in performing daily tasks and behavioral changes.[19] These impacts can be reduced with this possible treatment. Unlike other studies, this study was not limited to the age of the patients because refractory amblyopia (the disease in question in this study) is diagnosed after 7 years.

Limitations of our study include the absence of a control group and the limited sample number. In addition, an assessment of the effectiveness of the effect of occlusion and levodopa alone may also be considered a limitation.

Despite this, the results point to a favorable response to the treatment of refractory amblyopia with the use of Levodopa with total occlusion.Some reports on the relationship between amblyopia and Levodopa as treatment in the last 5 years can be observed in Table 5.

Table 5
Summary of studies showing age x dose x occlusion time

Study	Age, y	Dose L-dopa/ carbidopa mg/kg 3 times daily	Occlusion time	Conclusion
Sofi IA (2016)[12]	5 to 20	2.0 + 0.2	Full time	Improvement
PEDIG (2015)[11]	7 to 12	0.76 + 0.17	2 hours/daily	Didnot improve
Orge FH (2015)[20]	46	2.0 + 0.5	Full time	Improvement
Dadeya (2009)[17]	3 to 12	1.5 + 3.0	Full time	Improvement
Bhartiya (2002)[16]	6 to 18	0.62 + 0.15	Full time	Improvement

Conclusion

This study confirms the positive results of this treatment, showing that the visual acuity of the amblyopic eye after the use of Levodopa/Carbidopa for five weeks associated with total occlusion of the dominant eye obtained a significant improvement and that it remained after 1 year of treatment.

A larger case series and longer follow-up are necessary to thoroughly evaluate this combined treatment. The possibilities for improvement with this therapy are still open, which demands a deeper understanding of the theme.

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