American Academy of Ophthalmology
The Eye M.D. Association

A Randomized Trial of Levodopa as Treatment for Residual Amblyopia in Older Children

*Pediatric Eye Disease Investigator Group**
Writing Committee: Michael X. Repka, MD, MBA,[1] Raymond T. Kraker, MSPH,[2] Trevano W. Dean, MPH,[2] Roy W. Beck, MD, PhD,[2] R. Michael Siatkowski, MD,[3] Jonathan M. Holmes, BM, BCh,[4] Cynthia L. Beauchamp, MD,[5] Richard P. Golden, MD,[6] Aaron M. Miller, MD, MBA,[7] Lisa C. Verderber, MD,[8] David K. Wallace, MD, MPH[9]

Objective: To assess the efficacy and short-term safety of levodopa as adjunctive treatment to patching for amblyopia.

Design: Randomized, placebo-controlled trial.

Participants: One hundred thirty-nine children 7 to 12 years of age with residual amblyopia resulting from strabismus, anisometropia, or both combined (visual acuity [VA], 20/50−20/400) after patching.

Methods: Sixteen weeks of oral levodopa or placebo administered 3 times daily while patching the fellow eye 2 hours daily.

Main Outcome Measures: Mean change in best-corrected amblyopic-eye VA at 18 weeks.

Results: At 18 weeks, amblyopic-eye VA improved from randomization by an average of 5.2 letters in the levodopa group and by 3.8 letters in the placebo group (difference adjusted for baseline VA, +1.4 letters; 1-sided $P = 0.06$; 2-sided 95% confidence interval, −0.4 to 3.3 letters). No serious adverse effects from levodopa were reported during treatment.

Conclusions: For children 7 to 12 years of age with residual amblyopia after patching therapy, oral levodopa while continuing to patch 2 hours daily does not produce a clinically or statistically meaningful improvement in VA compared with placebo and patching. *Ophthalmology 2015;■:1−8 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Many children treated with patching for amblyopia have an incomplete response and are left with some reduction in visual acuity (VA) in the amblyopic eye.[1−3] Recognizing the incomplete effectiveness of conventional amblyopia therapy, clinicians have sought alternatives. One such ancillary treatment is oral levodopa, which is used to supplement dopamine deficiency in brains of adults with Parkinson's disease and children with dopamine-responsive dystonia. Although there is no evidence of a deficiency of dopamine in amblyopic brains, levodopa has been used by some clinicians for amblyopia treatment since 1995 on an investigational basis.[4,5] Levodopa is converted to dopamine, which seems to play an important role in retinal function and in central visual processing.[6] Improvements in VA, visual evoked potential amplitudes, or both have been reported immediately after a single dose,[7] a 1-week course,[8] or a 7-week course[4,9,10] of levodopa, but much of the improvement regressed after discontinuation of the drug. Studies investigating the use of levodopa as amblyopia treatment also have shown improvement in VA.[4,5,7,8,10−16] However, some participants experience partial regression after stopping the medication.[4,7,8,10−12,14]

A meta-analysis of 4 randomized placebo-controlled studies (110 subjects) found levodopa treatment effective with a mean improvement of 1.1 logarithm of the minimum angle of resolution lines (95% confidence interval [CI], 0.2−1.9).[17] The studies included in the meta-analysis had treatment durations ranging from 5 hours to 3 months (most subjects were treated for less than 4 weeks), included a small number of participants, and included participants 3 to 18 years of age undergoing initial treatment. Thus, as a result of these limitations, prior studies are inconclusive regarding the benefit of levodopa. Therefore, we conducted a randomized, placebo-controlled trial in children 7 to 12 years of age with residual amblyopia (VA range, 20/50−20/400) after patching treatment to assess the efficacy and short-term safety of levodopa as an adjunctive treatment to patching.

Methods

The study was supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health, Department of Health and Human Services, and was conducted according to the tenets of the Declaration of Helsinki, by the

http://dx.doi.org/10.1016/j.ophtha.2015.01.002
ISSN 0161-6420/15

Pediatric Eye Disease Investigator Group. The protocol and Health Insurance Portability and Accountability Act-compliant informed consent forms were approved by institutional review boards, and a parent or guardian (referred to subsequently as parent) of each study patient gave written informed consent. Patient assent was obtained as required by institutional review boards. Study oversight was provided by an independent data and safety monitoring committee. The study is listed on www.clinicaltrials.gov, under identifier NCT 01190813 (accessed July 18, 2014). The complete study protocol is available on the Pediatric Eye Disease Investigator Group website (www.pedig.net; accessed July 18, 2014).

Eligibility Criteria

Major eligibility criteria included age of 7 to 12 years, treatment of amblyopia with patching at least 2 hours daily for at least 12 weeks during the immediate pre-enrollment period, and no improvement of VA within 6 weeks immediately before enrollment. Eligible participants had amblyopic-eye VA of 20/50 to 20/400, fellow-eye VA of 20/25 or better, and the presence of strabismus, anisometropia, or both meeting study-specified criteria (additional eligibility criteria are listed in Table 1, available at www.aaojournal.org). Children must not have been treated previously with levodopa.

Treatment

Participants were assigned randomly (using a permutated block design stratified by site and by baseline VA) in a 2:1 ratio to 3 times daily use of oral levodopa 0.76 mg/kg with carbidopa 0.17 mg/kg (subsequently referred to as levodopa) or oral placebo. Carbidopa is added to levodopa to reduce peripheral side effects. All participants had 2 hours of daily patching prescribed and took oral medication for 16 weeks, with a 4-day taper of the oral medication before the primary outcome examination 2 weeks later (at 18 weeks). A central pharmacy compounded the study medication based on body weight. Levodopa and placebo were placed in identical gelatin capsules.

Follow-up

Before the 18-week primary outcome visit, office visits occurred at 4, 10, and 16 weeks ($\pm$1 week) after randomization and phone calls to the parent at 2, 7, and 13 weeks ($\pm$1 week) to review treatment and dosing. After the primary outcome visit, follow-up continued through 26 weeks, with participants and investigators remaining masked to treatment group. If the amblyopic-eye VA had improved by 5 letters or more between baseline and the 16-week visit, patching was continued and the randomized oral study medication was resumed until the 26-week visit. If improvement was less than 5 letters, confirmed by a retest, study medication and patching were stopped and additional treatment was at investigator discretion.

Testing Procedures and Data Collection

Visual acuity was measured in each eye (right eye first) by a study-certified VA tester using the Electronic Early Treatment of Diabetic Retinopathy Study VA protocol.[18] Ocular alignment was measured with the simultaneous prism and cover test. Stereoacuity was measured with the Randot Preschool Stereotest (Stereo Optical Co, Inc, Chicago, IL).

At each visit, the occurrence of adverse events was solicited and a symptom survey (17 items with a 5-level Likert scale from which an average score was calculated) was completed by the participant and by the parent. Neurologic examinations were not performed. Treatment compliance was assessed by review of a calendar log maintained by the participant and parent documenting the amount of patching and consumption of study medication each day and by counting the remaining capsules.

Statistical Analysis

The primary outcome measure was change in amblyopic-eye VA from baseline to 18 weeks. The sample size was chosen to provide sufficient power for 2 secondary outcomes: the proportion with improvement of 10 letters or more from baseline to 18 weeks and the proportion with 20/25 or better amblyopic-eye VA at 18 weeks. A sample size of 129 participants provided 80% power with 1-sided type I error rate of 5% to reject the hypothesis of no difference between groups if the proportion improved was 30% in the levodopa group compared with 10% in the placebo group. With 129 participants, assuming a 1-sided type I error rate of 4.85%, there was 96% power to detect a difference in mean VA between treatment groups at 18 weeks adjusted for baseline and for 1 interim analysis for futility if the true difference was 5 letters with standard deviation of 7 letters and 82% power if the true difference was 3.75 letters. The planned sample size was increased to 138 to account for an expected 5% loss to follow-up. The α level was set to 0.0485 for the primary analysis to adjust for α spending of 0.015 for 1 interim analysis for efficacy conducted when outcome data were available for 50% of participants.

The primary analysis was a treatment group comparison of mean VA letter scores obtained at the 18-week primary outcome examination adjusted for baseline acuity in an analysis of covariance model. A 1-sided *P* value was computed from this model to test the primary hypothesis, and the 2-sided 95% CI was computed to obtain the magnitude of the treatment effect that is consistent with the data.

The primary analysis followed the intent-to-treat principle. For participants who did not have a visit in the $\pm$1 week window for the primary outcome visit, data from a visit between 14 and 27 weeks after randomization were used, if available. Multiple imputation by the Monte Carlo Markov chain method[19] was used for missing 18-week VA outcomes based on treatment group, baseline VA, and VA scores from completed follow-up visits. Alternative analyses including data only from participants who completed the 18-week examination with no imputation and adjustment for baseline covariates that were imbalanced between treatment groups (cause of amblyopia and anisometropia) yielded results similar to the primary analysis (data not shown). The primary efficacy analyses were repeated for other time points (4, 10, 16, and 26 weeks).

The treatment effect in subgroups according to baseline factors of gender, race, age, and amblyopic-eye VA at randomization was assessed by including interaction terms in the analysis of covariance models. Fisher exact tests were used to evaluate if there were treatment group differences with respect to preplanned secondary outcomes (the proportion with $\geq$10 letters improvement from baseline to 18 weeks and the proportion with $\geq$20/25 amblyopic-eye VA at 18 weeks). The 1-sided *P* values and 2-sided 95% exact CIs were computed to test the secondary hypotheses and to obtain the range of differences in proportions that were consistent with the data. It was not possible to adjust for baseline VA in these secondary analyses because of the small number of subjects meeting secondary outcome criteria.

The Fisher exact test was used to evaluate whether there was a treatment group difference in the proportion of subjects reporting at least 1 adverse event. Additional treatment group comparisons included (1) change in fellow-eye VA from randomization to the 18-week visit using an analysis of covariance model, adjusting for the fellow-eye VA at randomization, (2) stereoacuity at the 18-week visit using the Wilcoxon rank-sum test, and (3) symptom