A Randomized Trial of Atropine vs Patching for Treatment of Moderate Amblyopia

Follow-up at Age 10 Years

Pediatric Eye Disease Investigator Group*

Objective: To determine the visual acuity outcome at age 10 years for children younger than 7 years when enrolled in a treatment trial for moderate amblyopia.

Methods: In a multicenter clinical trial, 419 children with amblyopia (visual acuity, 20/40-20/100) were randomized to patching or atropine eyedrops for 6 months. Two years after enrollment, a subgroup of 188 children entered long-term follow-up. Treatment after 6 months was at the discretion of the investigator; 89% of children were treated.

Main Outcome Measure: Visual acuity at age 10 years with the electronic Early Treatment Diabetic Retinopathy Study test.

Application to Clinical Practice: Patching and atropine eyedrops produce comparable improvement in visual acuity that is maintained through age 10 years.

Results: The mean amblyopic eye acuity, measured in 169 patients, at age 10 years was 0.17 logMAR (logarithm of the minimum angle of resolution) (approximately 20/32), and 46% of amblyopic eyes had an acuity of 20/25 or better. Age younger than 5 years at entry into the randomized trial was associated with a better visual acuity outcome (P < .001). Mean amblyopic and sound eye visual acuities at age 10 years were similar in the original treatment groups (P = .56 and P = .80, respectively).

Conclusions: At age 10 years, the improvement of the amblyopic eye is maintained, although residual amblyopia is common after treatment initiated at age 3 years to younger than 7 years. The outcome is similar regardless of initial treatment with atropine or patching.

Trial Registration: clinicaltrials.gov Identifier: NCT00000170

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Group Information: A complete list of the members of the Pediatric Eye Disease Investigator Group who participated in the trial appears on page 1043.

AMBLYOPIA IS A LEADING cause of monocular visual impairment. Treatment such as refractive correction, patching, and atropine eyedrops to the sound eye have been shown to improve the visual acuity of the amblyopic eye. Regression occurs in some patients after cessation of treatment for amblyopia, thereby reducing the lifetime benefit of therapy. Long-term outcome data after completion of amblyopia treatment are limited.

See also page 1071

The Pediatric Eye Disease Investigator Group (PEDIG) conducted a randomized trial that compared patching (6 hours to full-time daily in the sound eye) with atropine (1% daily in the sound eye) as treatment for moderate amblyopia (visual acuity, 20/40-20/100) in children younger than 7 years. After 6 months, approximately 3 logMAR (logarithm of the minimum angle of resolution) lines of improvement in the visual acuity of the amblyopic eyes were present in both treatment groups. After the initial 6-month treatment phase, the investigators, at their discretion, could switch, combine, or adjust the dosage of treatments. Between 6 months and 2 years, additional visual acuity improvement occurred in both original treatment groups, averaging 0.7 logMAR line. However, only 50% of amblyopic eyes had a visual acuity of 20/25 or better at the 2-year outcome. In this report, we evaluate the visual acuity of the amblyopic and sound eyes and stereacuity in the children from this trial when examined at age 10 years.

METHODS

The full study protocol has been detailed in prior publications. A brief summary of the protocol follows. Eligibility criteria for the randomized trial included age younger than 7 years, visual acuity in the amblyopic eye of

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20/40 to 20/100, visual acuity in the sound eye of 20/40 or better, interocular acuity difference of 3 or more logMAR lines, and the presence or history of an amblyogenic factor that met study-specified criteria for strabismus and/or anisometropia. Children were randomized to either patching (6 hours to full-time every day at investigator discretion) or atropine (1%, 1 drop once daily). During the first 6 months, the children maintained their randomized treatment. A protocol-specified masked outcome examination was conducted 6 months after randomization. Between 6 months and 2 years, the protocol allowed amblyopia treatment at investigator discretion but specified that patients were to be examined at least once every 6 months, with another masked outcome examination performed 2 years after randomization.

At the 2-year visit, parents of patients from a subset of participating sites (those with >5 patients enrolled and continuing with other PEDIG protocols) were invited to enter a long-term extension phase. The protocol and informed consent forms were approved by institutional review boards. Study oversight was provided by an independent data and safety monitoring committee. Written informed consent was obtained from the parent or guardian to continue follow-up with annual examinations through age 10 years and a future examination at age 15 years. All treatment prescribed during this phase was determined by the investigator. A total of 188 patients consented to participate in the extension phase. Testing at the age 10 years examination included measurement of visual acuity, cycloplegic refraction (if not measured within the prior 6 months), assessment of ocular alignment using the simultaneous prism and cover test at distance and near fixation, and an assessment of stereovision with the Randot Preschool Stereovision Test (Stereo Optical Company, Chicago, Illinois).

**VISUAL ACUITY TESTING**

Visual acuity was measured by a study-certified vision tester with an electronic modification of the testing protocol developed for the Early Treatment Diabetic Retinopathy Study (E-ETDRS). Acuity testing was repeated if the visual acuity score was worse than 20/20 (<83 letters) and there was a difference between the cycloplegic refraction and the correction used for testing that met 1 or more of the following: (1) a 0.25-diopter (D) or greater increase in hyperopia, (2) a 0.25-D or greater increase in myopia, (3) a 0.25-D or greater change in cylinder power, (4) a 10° or greater change in axis, or (5) an increase in hyperopia or a decrease in myopia that would lead the investigator to change the patient’s refractive correction.

During the initial phase of the study (through 2 years of follow-up), visual acuity was measured with the single-surrounded HOTV Amblyopia Treatment Study protocol. To explore the difference in the visual acuity measured with the HOTV and E-ETDRS methods, at the first post–2-year visit, visual acuity was measured by both methods on the same day in 142 patients. The mean age at testing was 9.0 years (age range, 5.6-11.9 years). The amblyopic eye visual acuity was the same on both tests in 55 patients (30%), 1 line better with HOTV in 46 (32%), 2 or more lines better with HOTV in 29 (20%), 1 line better with E-ETDRS in 10 (7%), and 2 or more lines better with E-ETDRS in 2 (1%). The sound eye visual acuity was the same in 82 patients (58%), 1 line better with HOTV in 40 (28%), 2 or more lines better with HOTV in 5 (4%), 1 line better with E-ETDRS in 13 (9%), and 2 or more lines better with E-ETDRS in 2 (1%). The interocular difference was the same in 30 patients (33%), 1 line smaller with HOTV in 45 (32%), 2 or more lines smaller with HOTV in 21 (15%), 1 line smaller with E-ETDRS in 21 (15%), and 2 or more lines smaller with E-ETDRS in 5 (4%).

**STATISTICAL ANALYSES**

Differences in patient characteristics for those participating in the extension study vs those not participating were evaluated to discover potential bias. Amblyopic eye and sound eye visual acuity was compared between randomized treatment groups as a continuous variable in analysis of covariance models adjusted for baseline acuity. A logistic regression model was used to compare the proportions of eyes in each treatment group with amblyopic eye visual acuity of 20/25 or better. Seven patients who completed the age 10 years outcome examination but had visual acuity tested with a method other than the E-ETDRS protocol were not included in the primary visual acuity analysis. An analysis that included the visual acuity data from the 7 patients produced results similar to the primary analysis (data not shown). The exact Wilcoxon rank sum test was used to compare stereovision scores in the treatment groups.

Change in interocular acuity difference between the 6-month and 2-year postrandomization examinations and between the 2-year postrandomization examination and the age 10 years examination was evaluated with paired-sample t tests. The associations between amblyopic eye visual acuity at the age 10 years outcome and baseline variables (cause of amblyopia, age at randomization, and prior treatment) were evaluated in analysis of covariance models that adjusted for baseline visual acuity, with the age 10 years visual acuity score as the dependent variable.

**RESULTS**

The age 10 years examination was completed by 176 of the 188 patients (94%). Their mean age was 5.2 years (age range, 2.6-6.9 years) at enrollment and 10.3 years (age range, 9.2-11.9 years) at the age 10 years examination; 41% were female. The mean visual acuity of the amblyopic eyes at entry into the randomized trial was 0.53 logMAR (approximately 20/63), with a mean interocular difference in acuity of 4.5 lines. The cohort was comparable to randomized patients who did not participate in the extension study in terms of age, race, sex, cause of amblyopia (anisometropia, strabismus, or a combined mechanism), baseline visual acuity in the amblyopic and sound eyes, baseline interocular acuity difference, baseline mean spherical equivalent refractive error, prior treatment before randomization, and randomized treatment group. However, patients who participated in the extension study had better amblyopic eye visual acuity at the 2-year outcome examination than patients who did not participate in the extension study (mean logMAR acuity, 0.14 vs 0.19).

**TREATMENT PRESCRIBED**

Between the 6-month examination and the age 10 years examination, 89% of the children were prescribed some form of amblyopia treatment other than spectacles for at least part of the time. For 66% of the children who were treated, no treatment other than the treatment assigned through randomization was prescribed (ie, patching was the only treatment prescribed for those randomized to the patching group and atropine was the only treatment prescribed for those randomized to the atropine group). Of the patients, 33% received the alternative treatment (ie, randomized to patching but prescribed atropine after the 6-month examination or randomized to atropine but prescribed...
At the age 10 years examination, visual acuity was measured with the E-ETDRS protocol (Table 2). The mean sound eye acuity was −0.03 logMAR in each group (approximately 20/20), and the mean interocular acuity difference was 0.2 logMAR (2.0 lines), with 64% of children having an interocular acuity difference of more than 1 line. The mean interocular acuity difference measured withamblyopic eye visual acuity was similar in 6 months and at 2 years (1.7 vs 1.6 lines; $P = .55$) but was slightly larger at age 10 years when measured with the E-ETDRS at age 10 years compared with at 2 years (2.0 lines, $P < .001$) (Table 1).

Amblyopic eye visual acuity was similar in the 2 original treatment groups (difference in visual acuity between the treatment groups adjusted for baseline acuity was −0.13 logMAR; 95% confidence interval, −0.20 to −0.06) (Table 2). The mean sound eye acuity was −0.03 logMAR in each group (approximately 20/20), and the difference between the treatment groups adjusted for baseline acuity was 0 logMAR (95% confidence interval, −0.03 to 0.02; $P = .80$).

Younger age at entry into the randomized trial was associated with a better amblyopic eye visual acuity at age 10 years. The mean visual acuity at the age 10 years examination was 0.14 (approximately 20/25−2) in the 68 patients younger than 5 years at randomization compared with 0.20 (approximately 20/32) in the 101 patients 5 years or older at randomization ($P < .001$); 57% of the patients younger than 5 years at randomization tested 20/25 or better compared with 38% of patients 5 years or older at randomization ($P = .004$). No apparent relation was found between cause of amblyopia (strabismus, anisometropia, or a combined mechanism) and the age 10 years outcome visual acuity ($P = .83$).

**VISUAL ACUITY AT THE AGE 10 YEARS EXAMINATION**

At the age 10 years examination, visual acuity was measured according to protocol in 169 patients (90% of those enrolled). The mean amblyopic eye acuity was 0.17 logMAR (approximately 20/32), and 46% of amblyopic eyes had an acuity of 20/25 or better. The mean sound eye acuity was −0.03 logMAR (approximately 20/20), and the mean interocular acuity difference was 0.2 logMAR (2.0 lines), with 64% of children having an interocular acuity difference of more than 1 line. The mean interocular acuity difference measured with HOTV was similar at 6 months and at 2 years (1.7 vs 1.6 lines; $P = .55$) but was slightly larger at age 10 years when measured with the E-ETDRS at age 10 years compared with at 2 years (2.0 lines, $P < .001$) (Table 1).

**STEREOACUITY AT THE AGE 10 YEARS EXAMINATION**

The median stereoeacuity at the age 10 years examination, measured with the Randot Preschool Stereoeacuity Test, was 400 arc seconds among all patients and 100 arc seconds among patients classified at baseline as having...
purely anisometropic amblyopia. Results were similar in the 2 treatment groups ($P = .87$ overall and $P = .78$ for patients with anisometric amblyopia) (Table 3).

### Table 3. Stereoacuity Testing at the Age 10 Years Examination

<table>
<thead>
<tr>
<th>Randot Preschool Stereotest Arc Seconds</th>
<th>Overall (n = 152)</th>
<th>Patching Group (n = 76)</th>
<th>Atropine Group (n = 76)</th>
<th>Overall (n = 63)</th>
<th>Patching Group (n = 37)</th>
<th>Atropine Group (n = 26)</th>
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<td>≥800</td>
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<td>58</td>
<td>61</td>
<td>84</td>
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<td>79</td>
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<td>43</td>
<td>41</td>
<td>63</td>
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<td>13</td>
<td>9</td>
<td>19</td>
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<td>19</td>
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</tbody>
</table>

a The $P$ values from the Wilcoxon rank sum test for difference in distribution between treatment groups were .87 for all patients and .78 for patients with anisometric amblyopia.

b Includes only patients who met the criteria for anisometric amblyopia at enrollment.

c Treatment group assigned to at randomization.

#### COMMENT

Most of the improvement with patching or atropine treatment appears to be maintained until age 10 years. However, approximately half of children with moderate amblyopia (visual acuity, 20/40-20/100) initially treated at age 3 years to younger than 7 years have mild residual amblyopia at age 10 years (visual acuity, <20/25). Outcomes were similar in the original treatment groups of atropine and patching.

The outcome was slightly better in patients who were aged 3 years to younger than 5 years at enrollment compared with those aged 5 years to younger than 7 years. This outcome could be because younger age at initiation of treatment might be advantageous if plasticity decreases with age or a shorter duration of amblyogenic insult might reduce the severity of the effect on the visual sensory system. We had not observed an age relationship at younger ages in the full randomized cohort, and it is possible that the apparent age effect at the age 10 years examination in our limited cohort may be because of chance. We intend to evaluate this effect again at the final age 15 years examination.

Our study design included measurement of stereovision to determine whether the amblyopia treatments had different effects on the development of binocularity. Simons et al. suggested a beneficial effect for atropine in a nonrandomized study using various atropine dosages. Conversely, Kushner has voiced concern about a possible negative effect of persistent cycloplegia on binocularity. At the age 10 years outcome examination, we found no difference in stereovision outcome between children originally treated with patching and those originally treated with atropine, whether analyzed overall or when the analysis was restricted to the children with pure anisometric amblyopia.

At age 10 years, many children had residual amblyopia despite careful treatment and follow-up within a clinical trial. No standardized approach to treatment for residual amblyopia was used by study investigators during the follow-up. In a future trial, we intend to investigate the management of residual amblyopia to determine whether increased intensity of treatment, including combined therapies, would further reduce the visual acuity deficit in the amblyopic eye.

Recurrence of amblyopia has been commonly reported after reduction or cessation of amblyopia treatment. During the first year after treatment reduction, rates of recurrence of 24% to 27% have been reported. With longer follow-up, higher recurrence rates of up to 58% have been reported. Between the 6-month and age 10 years examinations of our clinical trial, 89% of patients were treated for some period. However, 88% of the children received no treatment during the year before the age 10 years examination. Because children were treated at investigator discretion, including use of spectacles after the initial treatment episode, our data cannot be used to estimate the chance of recurrence when all therapy is discontinued. In addition, we cannot directly compare our measurements of visual acuity at the earlier study visits (6 months and 2 years after randomization) with those at the age 10 years examination because different methods were used to measure visual acuity. Although the interocular difference was greater at the age 10 years examination using the E-ETDRS protocol than at the 2-year examination using the HOTV Amblyopia Treatment Study protocol, our data directly comparing the 2 methods (see the “Visual Acuity Testing” subsection of the “Methods” section) suggest that this difference was because of the different testing methods and not a true worsening of visual acuity.

In our previous report, after 6 months of treatment, more patients in the atropine-treated group than in the patching group had a transient reduction in visual acuity of the sound eye. We concluded that some of this reduction was likely due to persistent cycloplegia and incorrect spectacle correction when the visual acuity was measured. Once the problem was recognized, the sound eye testing protocol was revised to increase the time not taking atropine to 2 weeks before sound eye visual acuity...
Clinical Sites

Clinical sites that participated in the extension study are listed in order by number of patients in the extension study (the number of patients is noted in parentheses after the site location). Personnel are listed as (I) for investigator, (C) for coordinator, and (V) for visual acuity tester. An asterisk indicates the center received support used for this project from an unrestricted grant from Research to Prevent Blindness Inc, New York, New York.

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Our results are subject to potential selection bias in that patients who participated had better amblyopic eye visual acuity at the 2-year outcome examination than patients who did not participate (approximately 3 letters on average better). As a result, our observed amblyopic eye acuity at the age of 10 years may be slightly overestimated. We could not identify other sources of bias to

Clinical testing. The sound eye acuity difference by treatment group was not observed at either the 2-year outcome visit or the age 10 years examination.
explain our findings. The age 10 years visit completion rate was high (94%). In addition, visual acuity testing was performed with a standardized protocol to ensure consistency across sites.

In summary, at age 10 years, the visual acuity improvement achieved in amblyopic eyes is maintained, although residual amblyopia is common, after treatment for amblyopia initiated at age 3 years to younger than 7 years. The outcome is similar regardless of whether initial treatment was with atropine or patching. We plan to perform a final examination of all of the children in the long-term follow-up phase at age 15 years.

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REFERENCES


