Published in final edited form as:
Arch Ophthalmol. 2008 August ; 126(8): 1039–1044. doi:10.1001/archopht.126.8.1039.

A Randomized Trial of Atropine versus Patching for Treatment of Moderate Amblyopia: Follow-up at 10 Years of Age

Pediatric Eye Disease Investigator Group*

Abstract

Objectives—To determine the visual acuity outcome at 10 years of age for children less than 7 years of age when enrolled in a treatment trial for moderate amblyopia.

Methods—In a multi-center clinical trial, 419 children with amblyopia (20/40 to 20/100) were randomized to patching or atropine eye drops 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 ETDRS test.

Results—The mean amblyopic eye acuity, measured in 169 patients, at age 10 years was 0.17 logMAR (approximately 20/32) and 46% of amblyopic eyes were 20/25 or better. Age < 5 years at the time of entry into the randomized trial was associated with a better visual acuity outcome (P<0.001). Mean amblyopic and sound eye visual acuities at age 10 years were similar in the original treatment groups (P= 0.56 and 0.80, respectively).

Conclusion—At age 10 years the improvement of the amblyopic eye is maintained, although residual amblyopia is common following treatment initiated at 3 to <7 years of age. The outcome is similar regardless of initial treatment with atropine or patching.

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

Trial Registry Name—Amblyopia Treatment Study: Occlusion Versus Pharmacologic Therapy for Moderate Amblyopia

Registration Number—NCT00000170

URL—http://clinicaltrials.gov/show/NCT00000170

Introduction

Amblyopia is a leading cause of monocular visual impairment.[1, 2] Treatments including refractive correction, as well as patching and atropine eye drops to the sound eye have been shown to improve the vision of the amblyopic eye.[3–5] Regression occurs in some patients following cessation of treatment for amblyopia, thereby reducing the lifetime benefit of therapy.[6–12] Long-term outcome data after completion of amblyopia treatment are limited.

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*The writing committee listed in the acknowledgements served as author for the Pediatric Eye Disease Investigator Group (PEDIG). A list of the members of PEDIG participating in the trial also appears in the acknowledgements.
The corresponding author has obtained written permission from all persons named in the acknowledgment.

The Pediatric Eye Disease Investigator Group (PEDIG) conducted a randomized trial comparing patching (6 hours to full time daily in sound eye) with atropine (1% daily in sound eye) as treatments for moderate amblyopia (20/40 to 20/100) in children younger than 7 years of age.[3] After 6 months, about three logMAR 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 lines. However, only 50% of amblyopic eyes were 20/25 or better at the 2-year outcome.[13]

In this report we evaluate visual acuity of the amblyopic and sound eyes as well as stereoacuity in the children from this trial when examined at age 10 years.

Patients and Methods

The full study protocol has been detailed in prior publications.[3, 13] 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 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 meeting study-specified criteria for strabismus and/or anisometropia.[3]

Children were randomized to either patching (6 hours to full time every day at investigator discretion) or atropine (1%, one drop once daily). During the first 6 months, the children were kept on 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 exam occurring 2 years from randomization.

At the time of the 2-year visit, parents of patients from a subset of participating sites (those with more than 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 (IRB). 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 exams through age 10 years and a future exam at age 15 years. All treatment prescribed during this phase was determined by the investigator. One-hundred eighty-eight (188) patients consented to participate in the extension phase. Testing at the age 10 year exam included measurement of visual acuity, cycloplegic refraction (if not done within the prior six months), assessment of ocular alignment using the simultaneous prism and cover test at distance and near fixation, and an assessment of stereoacuity with the Randot Preschool Stereoacuity Test (Stereo Optical Company, 3539 N. Kenton Avenue Chicago, IL 60641).

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).[14] 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 one or more of the following: 1) ≥0.25 D increase in hyperopia, 2) ≥0.25 D increase in myopia, 3) ≥0.25D change in cylinder power, 4) ≥10 degree change in axis, or

5) an increase in hyperopia or 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.[15] 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 the time of testing was 9.0 years (range = 5.6 to 11.9 years). The amblyopic eye visual acuity was the same on both tests in 55 (39%) of the patients, 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 (58%) of the patients, 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 50 (35%) of the patients, 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 Methods

Differences in patient characteristics for those participating in the extension study versus 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-year 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 stereoacuity scores in the treatment groups.

Change in interocular acuity difference between the six-month and two-year post-randomization exams, and between the two-year post randomization exam and the age-10 exam was evaluated with paired sample t-tests. The associations between amblyopic eye visual acuity at the age 10-year outcome and baseline variables (cause of amblyopia, age at randomization, prior treatment) were evaluated in analysis-of-covariance models adjusting for baseline visual acuity, with the age 10-year visual acuity score as the dependent variable.

Results

The age 10-year exam was completed by 176 (94%) of the 188 patients. Their mean age was 5.2 years at enrollment (range 2.6 to 6.9 years) and 10.3 years (range 9.2 to 11.9 years) at the time of the exam; 41% were female. The mean visual acuity of the amblyopic eyes at the time of 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, gender, cause of amblyopia (anisometropia, strabismic, or 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 two-year outcome exam than patients who did not participate (mean logMAR acuity = 0.14 versus 0.19).

Treatment Prescribed

Between the 6-month exam and age 10-year exam, 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 (i.e., 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). Thirty-three percent received the alternative treatment (i.e., randomized to patching but prescribed atropine after the 6-month exam, or randomized to atropine but prescribed patching). At the time of the age 10-year exam, 88% of children had received no treatment for amblyopia within the prior year, 4% had received patching, 5% atropine or other pharmacological penalization, and 3% reported both atropine and patching.

Visual Acuity at Age 10-year Exam

At the age 10-year exam, visual acuity was measured according to protocol in 169 patients (90% of enrolled subjects). The mean amblyopic eye acuity was 0.17 logMAR (approximately 20/32) and 46% of amblyopic eyes had acuity of 20/25 or better. 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 two years (1.7 versus 1.6 lines, P=0.55), but was slightly larger at age 10 years when measured with E-ETDRS testing at age 10 years compared with two years (2.0 lines, P<0.001, Table 1).

Amblyopic eye visual acuity was similar in the two original treatment groups (difference in visual acuity between the treatment groups adjusted for baseline acuity was −0.01 logMAR, 95% confidence interval −0.06 to +0.03, Table 2). The amblyopic eye was 20/25 or better in 42% of patients originally prescribed patching and 49% of patients originally prescribed atropine (P=0.74, Table 2). 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 0.00 logMAR, 95% confidence interval −0.03 to +0.02, P=0.80.

Younger age at the time of entry into the randomized trial was associated with a better amblyopic eye visual acuity at age 10 years. Mean visual acuity at the 10 year exam was 0.14 (approximately 20/25-2) in the 68 patients <5 years old at randomization compared with 0.20 (approximately 20/32) in the 101 patients ≥5 years old (P<0.001); 57% of the patients <5 years old at randomization tested 20/25 or better compared with 38% of patients ≥5 years old (P=0.004). There was no apparent relation between cause of amblyopia (strabismus, anisometropia or combined mechanism) and the age 10-year outcome visual acuity (P=0.83).

Stereoacuity at Age 10-year Exam

The median stereoacuity at the age 10-year exam, measured with the Randot Preschool Stereoacuity Test, was 400 seconds of arc among all patients and 100 arc seconds among patients classified at baseline as having purely anisometropic amblyopia. Results were similar in the two treatment groups (P=0.87 overall and P=0.78 for patients with anisometropic amblyopia, Table 3).

Discussion

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

The outcome was slightly better in patients who were 3 to <5 years old at enrollment compared with those 5 to <7 years. This 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,[3, 13] and it is possible that the apparent age effect at the 10-year exam in our limited cohort may be due to chance. We intend to evaluate this effect again at the final age 15-year exam.

Our study design included measurement of stereoacuity 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 non-randomized study using various atropine dosages.[16] Conversely, Kushner has voiced concern about a possible negative effect of persistent cycloplegia on binocularity.[17] At the age 10-year outcome examination we found no difference in stereoacuity 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 anisometropic amblyopia.

At age 10 years a large proportion of children had residual amblyopia despite careful treatment and follow up within a clinical trial. No standardized approach to treatment for residual amblyopia was utilized by study investigators during the follow-up period. 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.[12, 18, 19] With longer follow up, higher recurrence rates of up to 58% have been reported.[9, 10, 20–22] Between the 6-month and age 10-year exams of our clinical trial, 89% of patients were treated for some period of time. However, 88% of the children received no treatment during the year prior to the age 10-year exam. As children were treated at investigator discretion including use of spectacles following the initial treatment episode, our data can not be used to estimate the chance of recurrence when all therapy is discontinued. In addition, we can not directly compare our measurements of visual acuity at the earlier study visits (6 months and 2 years post-randomization) with those at the age 10-year exam because different methods were used to measure visual acuity. Although the interocular difference was greater at the age 10-year exam using the E-ETDRS protocol than at the 2-year exam using the ATS HOTV protocol, our data directly comparing the two methods (see methods section) suggest that this was due to 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.[3] We concluded that some of this reduction was likely due to persistent cycloplegia and incorrect spectacle correction at the time the vision was measured.[3] Once the problem was recognized, the sound eye testing protocol was revised to increase the time off of atropine to 2 weeks prior to sound eye visual acuity testing. The sound eye acuity difference by treatment group was not observed at either the 2-year outcome visit[13] or the age 10-year exam.

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

our findings. The age 10-year 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, following treatment for amblyopia initiated at 3 to <7 years of age. The outcome is similar regardless of whether initial treatment was with atropine or patching. We plan to perform a final exam of all of the children in the long-term follow-up phase at age 15 years.

Acknowledgements

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Supported by National Eye Institute of National Institutes of Health, Department of Health and Human Services (EY011751).

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The Pediatric Eye Disease Investigator Group

Clinical Sites that Participated in the Extension Study

Sites are listed in order by number of patients in the extension study. The number of patients is noted in parenthesis preceded by the site location and the site name. Personnel are listed as (I) for Investigator, (C) for Coordinator, and (V) for Visual Acuity Tester.

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*Center received support utilized for this project from an unrestricted grant from Research to Prevent Blindness Inc., New York, New York.

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Table 1

Interocular Acuity Difference from Randomization to the Age 10-Year Visit

	At Randomization N=169	HOTV Testing at 6 Month Outcome N=169	HOTV Testing at 2 Year Outcome N=169	E-ETDRS Testing at Age 10 Years N=169
Distribution of Interocular Acuity (lines acuity amblyopic eye minus sound eye)*	n (%)	n (%)	n (%)	n (%)
≥ +3	169 (100%)	47 (28%)	45 (27%)	55 (33%)
+2		45 (27%)	27 (16%)	40 (24%)
+1		38 (22%)	53 (31%)	51 (30%)
0		27 (16%)	31 (18%)	20 (12%)
−1		6 (4%)	11 (7%)	1 (1%)
−2		4 (2%)	2 (1%)	2 (1%)
≤ −3		2 (1%)	0	0
Mean logMAR lines (SD)	4.5 (1.4)	1.7 (1.7)	1.6 (1.7)	2.0 (1.6)

* At 6 months and at 2 years post-randomization, visual acuity was measured with the ATS-HOTV visual acuity testing protocol. At the age 10-year exam, visual acuity was measured with the E-ETDRS protocol. Seven patients measured with techniques other than E-ETDRS at the age 10-year exam are excluded from this table. When ATS-HOTV was used, interocular acuity was calculated as the difference between the amblyopic eye and sound eye logMAR line acuities, where at age 10-years when E-ETDRS was used, the interocular acuity was calculated as the difference between the amblyopic eye and sound eye letter scores, rounded to the nearest logMAR line.

Table 2

Visual Acuity of Amblyopic Eyes at the Age 10-year Visit

	Overall N=169*	Patching Group† N=85	Atropine Group † N=84
Cumulative Distribution of Visual Acuity Scores at Age 10 years (Snellen Equivalent)		**Cumulative %**	
20/50 or better	94%	95%	93%
20/40 or better	87%	85%	89%
20/32 or better	74%	69%	79%
20/25 or better	46%	42%	49%
20/20 or better	22%	16%	29%
20/16	4%	1%	6%
		Mean logMAR (SD)	
	0.17 (0.15)	0.19 (0.14)	0.16 (0.16)
Difference between Randomized Treatment Groups in Mean logMAR Acuity at Age 10-year‡ Exam	-	−0.01	
95% Confidence Interval for Difference	-	(−0.06 to +0.03)	

*Seven patients were tested with other methods of acuity testing not in table (five with HOTV testing 20/20, 20/25 (2), 20/32, and 20/40 and two with Snellen testing 20/20 and 20/25).

†Treatment group at time of randomization.

‡Adjusted for baseline visual acuity in analysis-of-covariance model. A positive difference indicates that the mean patching group scores were better than the mean atropine group scores.

Table 3

Stereoacuity Testing at the Age 10-year Visit

	All Patients				Patients with Anisometropic Amblyopia *			
	Overall	**Patching Group†**	**Atropine Group†**	**P-value‡**	**Overall**	**Patching Group†**	**Atropine Group†**	**P-value‡**
	Cumulative %				**Cumulative %**			
Randot Preschool (arc sec)	**N=152**	**N=76**	**N=76**	0.87	**N=63**	**N=37**	**N=26**	0.78
800 or better	59%	58%	61%		84%	84%	85%	
400 or better	53%	57%	50%		79%	84%	73%	
200 or better	42%	43%	41%		63%	65%	62%	
100 or better	33%	34%	32%		54%	51%	58%	
60 or better	18%	17%	18%		30%	24%	38%	
40	11%	13%	9%		19%	19%	19%	

* Includes only patients meeting criteria for anisometropic amblyopia at enrollment.

† Treatment group assigned to at the time of randomization.

‡ P-value from Wilcoxon Rank Sum Test for difference in distribution between treatment groups.