A Randomized Trial of Patching Regimens for Treatment of Moderate Amblyopia in Children

ARCHIVES EXPRESS

*The Pediatric Eye Disease Investigator Group**

Objective: To compare 2 hours vs 6 hours of daily patching as treatments for moderate amblyopia in children younger than 7 years.

Methods: In a randomized multicenter (35 sites) clinical trial, 189 children younger than 7 years with amblyopia in the range of 20/40 to 20/80 were assigned to receive either 2 hours or 6 hours of daily patching combined with at least 1 hour per day of near visual activities during patching.

Main Outcome Measure: Visual acuity in the amblyopic eye after 4 months.

Results: Visual acuity in the amblyopic eye improved a similar amount in both groups. The improvement in the visual acuity of the amblyopic eye from baseline to 4 months averaged 2.40 lines in each group ($P=.98$). The 4-month visual acuity was at least 20/32 and/or improved from baseline by 3 or more lines in 62% of patients in each group ($P>.99$).

Conclusion: When combined with prescribing 1 hour of near visual activities, 2 hours of daily patching produces an improvement in visual acuity that is of similar magnitude to the improvement produced by 6 hours of daily patching in treating moderate amblyopia in children aged 3 to 7 years.

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AMBLYOPIA IS the most common cause of monocular visual impairment in both children and young and middle-aged adults.[1,2] Occlusion therapy with patching of the sound eye has been the mainstay of amblyopia treatment. However, opinions vary on the number of hours of daily patching that should be prescribed for moderate amblyopia, ranging from as little as 1 or 2 hours to 24 hours per day.[1,3-6] No prior study has provided conclusive data on the optimal number of patching hours. To address this clinical issue, we conducted a randomized clinical trial to compare 2 hours vs 6 hours of daily patching for moderate amblyopia (20/40 to 20/80) in children younger than 7 years who were able to complete standardized optotype visual acuity testing. This study was not designed to determine the maximal extent of improvement that can be achieved with patching therapy.

METHODS

Our study, supported through a cooperative agreement with the National Eye Institute of the National Institutes of Health (Bethesda, Md), was conducted by the Pediatric Eye Disease Investigator Group at 35 clinical sites. The protocol and consent forms were approved by institutional review boards, and the parent or guardian (subsequently referred to as "parent") of each study patient gave written informed consent. Study oversight was provided by an independent data and safety monitoring committee.

PATIENT SELECTION

Eligibility testing included measurement of visual acuity in both eyes with the Amblyopia Treatment Study[7,8] visual acuity testing protocol (which uses single-surrounded HOTV optotypes), cycloplegic refraction, ocular examination, and ocular motility examination. Except for the standardization of the visual acuity testing protocol across centers, procedures were performed according to the investigator's usual routine. Visual acuity testing had to be performed within the 7 days prior to randomization, although the remainder of the examination could be completed within 2 months prior to randomization.

Eligibility criteria for the trial included age younger than 7 years, visual acuity in the amblyopic eye of 20/40 to 20/80, intereye visual acuity difference of 3 or more logMAR lines, the presence or history of an amblyogenic factor meeting study-specified criteria for strabismus and/or anisometropia, and the wearing of an optimal spectacle correction for a minimum of 4 weeks at the time of enrollment (the protocol for correction of refractive error has been previously published[9]). One pa-

**The Writing Committee served as author for the Pediatric Eye Disease Investigator Group (PEDIG). The Coordinating Center is located at the Jaeb Center for Health Research, Tampa, Fla. A list of the members of PEDIG appears on page 611. The members of PEDIG have no relevant financial interest in this article.*

Table 1. Eligibility and Exclusion Criteria

Eligibility criteria
Age<7 y
Able to measure visual acuity using the Amblyopia Treatment Study visual acuity testing protocol with the Electronic Visual Acuity Tester[8]
Visual acuity in the amblyopic eye ≤20/40 and ≥20/80
Visual acuity in the sound eye ≥20/40
Intereye acuity difference ≥3 logMAR lines
If amblyopia was previously treated, no patching treatment within 6 mo of enrollment and no other amblyopia treatment of any type (other than spectacles) within 1 mo of enrollment (any treatment more than 6 mo prior to enrollment was acceptable)
Refractive error corrected for at least 4 wk
Amblyopia associated with strabismus, refractive error/anisometropia, or both meeting the following criteria*:
Strabismic amblyopia: amblyopia (1) in the presence of either aheterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum), and (2) in the absence of refractive error meeting the criteria below for combined-mechanism amblyopia
Refractive/anisometropic: amblyopia in the presence of anisometropia ≥0.5 D of spherical equivalent or ≥1.50 D difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation, that persisted after at least 4 wk of spectacle correction.
Combined-mechanism (strabismic and anisometropic): amblyopia in the presence of (1) either a heterotropia at distance and/or near fixation or a history of strabismus surgery (or botulinum), and (2) anisometropia ≥1.00 D spherical equivalent or ≥1.50 D difference in astigmatism in any meridian that persisted after at least 4 wk of spectacle correction
Exclusion criteria
Presence of an ocular cause for reduced visual acuity
Myopia with a spherical equivalent –6 D
Prior intraocular surgery
Known skin reaction to patch or bandage adhesive

Abbreviation: D, diopters.
*Cause of amblyopia-1 was defined according to the following 3 criteria.

tient in the 6-hour patching group was enrolled with a visual acuity in the amblyopic eye of 20/100 (data included in the analyses). **Table 1** provides a complete list of the eligibility and exclusion criteria. The eligibility criteria were similar to those used in our earlier amblyopia trial comparing topical atropine sulfate 1% and patching, with the exceptions that in this study the upper limit of amblyopic visual acuity was 20/80, and myopia was not an exclusion.

TREATMENT PROTOCOLS

Each patient was randomly assigned with equal probability to either 2 hours or 6 hours of daily patching. Randomization was accomplished on the study's Web site using a permuted blocks design of varying block sizes, with a separate sequence of computer-generated random numbers for each clinical site.

Adhesive skin patches provided by the study (Coverlet Eye Occlusors; Beiersdorf-Jobst, Inc, Rutherford College, NC) were used unless there was a skin allergy or irritation unresponsive to local treatment with a skin emollient and a change in patch brand, in which case a spectacle-mounted occluder could be prescribed. For both treatment groups, the protocol stipulated that the assigned patching regimen was to be used for the 4-month study duration with the following exceptions: (1) if the visual acuity in the amblyopic eye improved to the same level as or 1 line worse than the acuity in the sound eye, patching could be continued at the initial number of hours or decreased at the investigator's discretion provided it was at least 7 hours per week, and (2) if the visual acuity in the amblyopic eye became better than the acuity in the sound eye or if the investigator believed that reverse amblyopia had developed, treatment could be continued, reduced, or stopped at the investigator's discretion. Prior to the 4-month masked examination, additional hours of patching or alternate therapies for amblyopia could not be prescribed even if there was no response to treatment. Parents were advised that the daily hours of patching should be continuous when possible and that periods when the child was sleeping were not to be counted as patching time.

In addition to the patching, the parent was instructed to have the child spend at least 1 hour of patching time each day doing near visual activities such as crafts, coloring, tracing, cutting out objects, connecting the dots, hidden pictures and word finds, computerized video games, reading, written homework assignments, or other activities requiring eye-hand coordination. The instruction to perform 1 hour of near visual activities was identical in the 2-hour and 6-hour patching groups.

EXAMINATION PROCEDURES

Protocol-specified follow-up visits were conducted at 5 weeks and 17 weeks (visit window, ± 1 week). Additional visits could be performed at the investigator's discretion. At baseline and each protocol-specified visit, visual acuity was measured in both eyes using the Amblyopia Treatment Study visual acuity testing protocol[7] administered by a study-certified vision tester. The test was administered using the Electronic Visual Acuity Tester developed for this study.[8]

At the 5-week visit, a parental questionnaire designed to assess the effect of amblyopia treatment on the quality of life of the child and parent (Amblyopia Treatment Index)[10,11] was completed. The questionnaire consisted of 19 items similar to those on the Likert scale, each scored from 1 to 5 with 5 representing the most difficulty. Three subscales measured the adverse effects of treatment (8 items), difficulties with compliance (6 items), and the social stigma of treatment (3 items), with internal consistency reliabilities of 0.84, 0.88, and 0.53, respectively. Items were summed to compute each subscale score and were then scaled to a common range from 1 to 5.

At the 4-month outcome examination, visual acuity testing was conducted by a study-certified vision tester who was masked to the patient's treatment group. Additional testing done at this visit included assessment of ocular alignment with a simultaneous prism and cover test (the measurement was usually performed after visual acuity testing, but the timing was not standardized, and the examiner was not always the same one who made the baseline measurement) as well as measurement of stereoacuity with the Titmus test (fly only), Randot Stereotests, and Randot Preschool Stereoacuity Test (Stereo Optical Co, Chicago, Ill).

ADHERENCE TO THE TREATMENT PROTOCOL

Adherence to the treatment protocol was assessed by having the parent maintain a calendar on which the treatment (hours of occlusion and completion of near visual activities) received each day was logged. The calendars were reviewed at the follow-up visits, and at each visit, the investigator made an assessment of the patient's adherence to the prescribed treatment (excellent, 76%-100% of prescribed treatment completed; good, 51%-75%; fair, 26%-50%; and poor, 25% or less completed). An average compliance score was computed for each patient from the adherence assessment made at each visit while a patient was receiving treatment (assigning a value of 4 for excellent, 3 for good, 2 for fair, and 1 for poor). The average scores were then used to categorize

each patient's adherence as excellent (>3.50), good (2.51-3.50), fair (1.51-2.50), or poor (≤1.50).

At the coordinating center, each follow-up examination form was reviewed to assess whether the investigator was properly prescribing the treatment protocol, and any necessary feedback was provided to the investigator.

ADVERSE REACTIONS

At each study visit, the parent was asked about skin irritation from the patching. For patients whose sound eye acuity was reduced from baseline by 2 or more lines, subsequent follow-up data (when available) were used to evaluate whether the decrease represented a real and permanent reduction.

STATISTICAL METHODS

Monte Carlo simulations were performed to estimate the sample size for a type 1 error rate of 5% based on projecting a standard deviation of 0.17 for the 4-month visual acuity scores, a mean difference between groups of 0.1 logMAR, a correlation between the baseline and outcome scores of 0.38, and a 5% rate of loss to follow-up. A minimum sample size of 160 patients was selected to have 80% power for 2 subgroup analyses based on the cause of amblyopia: (1) strabismus with a deviation of 5 or more prism diopters Δ or a history of strabismus surgery, with or without anisometropia, and (2) strabismus with a deviation less than 5Δ and no history of strabismus surgery, with or without anisometropia, or anisometropia alone. Patient recruitment continued until a prespecified ending date, and as a result of accrual being faster than originally anticipated, the final recruitment total exceeded the minimum sample size estimate. With an actual sample size of 181 patients (number completing the 4-month outcome visit), statistical power for the primary overall analysis to detect a difference of 0.1 logMAR was 99%; a treatment group difference of 0.075 logMAR could be assessed with 90% power, and a difference of 0.065 logMAR with 80% power.

The primary outcome measure was the 4-month logMAR visual acuity score in the amblyopic eye. The treatment groups were compared using an analysis-of-covariance model in which the logMAR visual acuity scores were adjusted for baseline acuity. Confounding was evaluated by including covariates of interest in the model. Patients were included in the primary analysis if they had a visual acuity measurement in the amblyopic eye within the time window of the 4-month visit or, in the absence of such a visit, if they had a visual acuity measurement that was no more than 1 month before or 3 months after this time window. Two additional analyses were conducted on the 4-month logMAR visual acuity scores: one analysis included only patients having an examination within the prespecified 4-month time window, and the other included all patients using the method of last observation carried forward to impute for missing data (ie, for patients missing the outcome examination, the visual acuity measurement recorded at the last follow-up examination was used as the outcome acuity; for patients with no follow-up, the baseline visual acuity measurement was used). Results of these 2 analyses were similar to the primary analysis (data not shown). Interaction between baseline factors (age, cause of amblyopia, and visual acuity in the amblyopic eye) and treatment group regarding the outcome visual acuity was assessed by including interaction terms in the analysis-of-covariance models. Methods used to analyze the logMAR acuity scores in the amblyopic eye at the 5-week visit paralleled the analyses conducted on the 4-month data. Patients were included in the 5-week visit analysis if they had a visual acuity measurement in the amblyopic eye within the time window of the 5-week visit or, in the absence of such a visit, if they had a visual acuity measurement no more than 8 weeks from randomization. Within treatment groups, the change in visual acuity from baseline was reported in lines. Treatment group comparisons were reported as differences in mean logMAR acuity.

A prespecified secondary outcome was defined as a 4-month visual acuity measurement that was at least 20/32 in the amblyopic eye and/or improved from baseline by 3 or more lines. For this outcome, a patient was classified as not having met these criteria if treatment other than patching (such as atropine) was used for at least 1 week or the 4-month outcome examination was missed. An exact 2-sided 95% confidence interval (CI) was computed for the difference in outcome percentages between the 2 groups.

The questionnaire subscale scores were compared between the 2 treatment groups with the Wilcoxon rank sum test. For the binocularity tests, the treatment groups were compared using the Wilcoxon rank sum test for continuous variables and the Fisher exact test for categorical variables. Reduction in visual acuity in the sound eye was assessed by comparing the proportions of patients in each treatment group whose 4-month visual acuity measurement was 2 or more lines worse than baseline with a Fisher exact test. The mean numbers of visits prior to the outcome examination in each group were compared using a *t* test.

All analyses followed the intention-to-treat principle (ie, the treatment group data were based on the randomization assignments, not on the actual treatment received or whether the treatment protocol was followed). All reported *P* values were 2-tailed. Analyses were conducted using SAS version 8.2 statistical software (SAS Institute Inc, Cary, NC).

RESULTS

Between May 2001 and May 2002, 189 patients entered the trial, with 95 assigned to the 2-hour patching group and 94 assigned to the 6-hour patching group. The number of patients enrolled per site at the 35 sites ranged from 1 to 21 (median=3). The average age of the patients was 5.2 years; 44% were girls and 85% were white. The mean visual acuity measurement in the amblyopic eye at enrollment was 0.48 logMAR (approximately 20/63), with a mean difference in acuity between eyes of 4.1 lines. The 6-hour group had a higher proportion of patients classified as having strabismic amblyopia, whereas the 2-hour group had a higher proportion with anisometropic amblyopia (*P*=.02). The baseline characteristics of the 2 groups were otherwise similar (**Table 2**).

PATIENT FOLLOW-UP

The primary outcome examination was completed by 97% of the patients in the 2-hour group and 95% in the 6-hour group (**Figure 1**). The vision tester was masked to treatment group for 94% of these examinations (96% in the 2-hour group and 93% in the 6-hour group). Prior to the outcome examination, patients in each group had a similar number of follow-up visits (mean±SD, 1.2±0.5 and 1.3±0.5 in the 2-hour and 6-hour groups, respectively; *P*=.67).

TREATMENT

Among the patients completing the outcome examination, the number of patching hours prescribed at base-

Table 2. Baseline Characteristics According to Treatment Group*

	2 h of Patching (n = 95)	6 h of Patching (n = 94)	Total (n = 189)
Sex, F	42 (44)	41 (44)	**83** (44)
Age, y			
<3	2 (2)	0	**2** (1)
3 to <4	15 (16)	8 (9)	**23** (12)
4 to <5	26 (27)	23 (24)	**49** (26)
5 to <6	29 (31)	33 (35)	**62** (33)
6 to <7	23 (24)	30 (32)	**53** (28)
Mean ± SD	5.1 ± 1.1	5.4 ± 1.0	5.2 ± 1.0
Race			
White	82 (86)	78 (83)	**160** (85)
African American	5 (5)	2 (2)	**7** (4)
Hispanic	5 (5)	7 (7)	**12** (6)
Asian American	1 (1)	1 (1)	**2** (1)
Mixed	0	4 (4)	**4** (2)
Other	2 (2)	2 (2)	**4** (2)
Prior treatment for amblyopia			
None	85 (89)	78 (83)	**163** (86)
Patching (skin)	8 (8)	11 (12)	**19** (10)
Atropine (or other cycloplegic)	1 (1)	3 (3)	**4** (2)
Patching and atropine	1 (1)	1 (1)	**2** (1)
Spectacle occluder	0	1 (1)	**1** (0.5)
Cause of amblyopia-1†			
Strabismus	29 (31)	46 (49)	**75** (40)
Anisometropia	34 (36)	29 (31)	**63** (33)
Strabismus and anisometropia	32 (34)	19 (20)	**51** (27)
Cause of amblyopia-2†			
Strabismus	39 (41)	48 (51)	**87** (46)
Anisometropia/microtropia	56 (59)	46 (49)	**102** (54)
Visual acuity in the amblyopic eye			
20/100 (ineligible)	0	1 (1)	**1** (0.5)
20/80	29 (31)	28 (30)	**57** (30)
20/63	31 (33)	31 (33)	**62** (33)
20/50	21 (22)	20 (21)	**41** (22)
20/40	14 (15)	14 (15)	
Mean ± SD, logMAR	0.48 ± 0.10	0.48 ± 0.11	**0.48** ± 0.10
Visual acuity in the sound eye			
20/40	2 (2)	3 (3)	**5** (3)
20/32	19 (20)	24 (26)	**43** (23)
20/25	30 (32)	28 (30)	**58** (31)
20/20	35 (37)	29 (31)	**64** (34)
20/16	9 (9)	10 (11)	**19** (10)
Mean ± SD, logMAR	0.07 ± 0.10	0.08 ± 0.10	0.07 ± 0.10
Intereye acuity difference, lines			
3	33 (35)	38 (40)	**71** (38)
4	34 (36)	29 (31)	**63** (33)
5	14 (15)	16 (17)	**30** (16)
6	13 (14)	10 (11)	**23** (12)
7	1 (1)	1 (1)	**2** (1)
Mean ± SD	4.1 ± 1.1	4.0 ± 1.1	4.1 ± 1.1
Refractive error in the sound eye, D‡			
≤−0.50	4 (4)	3 (3)	**7** (4)
>−0.50 to <1.00	15 (16)	9 (10)	**24** (13)
1.00 to <2.00	15 (16)	19 (20)	**34** (18)
2.00 to <3.00	12 (13)	17 (18)	**29** (15)
3.00 to <4.00	15 (16)	12 (13)	**27** (14)
≥4.00	34 (36)	34 (36)	**68** (36)
Mean ± SD	2.96 ± 2.44	3.19 ± 2.26	3.07 ± 2.35
Refractive error in the amblyopic eye, D‡			
≤−0.50	8 (8)	4 (4)	**12** (6)
>−0.50 to <1.00	4 (4)	7 (7)	**11** (6)
1.00 to >2.00	5 (5)	3 (3)	**8** (4)
2.00 to <3.00	5 (5)	9 (10)	**14** (7)
3.00 to <4.00	11 (12)	11 (12)	**22** (12)
≥4.00	62 (65)	60 (64)	**122** (65)
Mean ± SD	4.06 ± 3.20	4.18 ± 2.80	4.12 ± 3.00

Abbreviation: D, diopters.

*Data are presented as number (percentage) unless otherwise indicated.

†Patients were categorized by 2 methods for cause of amblyopia. See Table 1 for definitions for cause of amblyopia-1. For cause of amblyopia-2, strabismus category was defined as strabismus with a deviation ≥ 5△ or a history of strabismus surgery (with or without anisometropia), and anisometropia/microtropia category was defined as either (1) strabismus with a deviation < 5△ and no history of strabismus surgery (with or without anisometropia), or (2) anisometropia alone (meeting criteria for anisometropia in Table 1).

‡Spherical equivalent.

line was the same throughout follow-up for 86 of the patients in the 2-hour group and 67 of the patients in the 6-hour group. In 6 patients in the 2-hour group and 18 patients in the 6-hour group, patching time was decreased from the number of hours prescribed at baseline (as permitted in the protocol) because the visual acuity in the amblyopic eye became within 1 line of, the same as, or better than the visual acuity in the sound eye. In the 6-hour group, 1 patient was prescribed a spectacle-mounted occluder as a substitute for patching because of skin irritation, 2 patients were increased to full-time patching (deviation from the protocol), 1 patient whose visual acuity in the amblyopic eye had not improved 3 lines was decreased to 2 hours per day (deviation from protocol), and 1 patient was switched from patching to atropine at the request of the parent. In the 2-hour group, no patients were prescribed a higher number of patching hours or an alternate treatment.

Patient adherence with the prescribed treatment was judged by the investigator to be excellent in 58%, good in 25%, fair in 14%, and poor in 3% of patients in the 2-hour group and excellent in 37%, good in 37%, fair in 15%, and poor in 11% of patients in the 6-hour group.

EFFECT OF TREATMENT ON VISUAL ACUITY IN THE AMBLYOPIC EYE

Substantial improvement in visual acuity from baseline to 4 months occurred in both the 2-hour group and 6-hour group (**Table 3** and **Figure 2**), and the course of visual acuity improvement appeared similar in the 2 treatment groups (**Figure 3**). At the 5-week visit, visual acuity had improved from baseline by an average of 1.84 lines in the 2-hour group and 1.92 lines in the 6-hour group (mean difference in logMAR acuity between groups, –0.007; 95% CI, –0.050 to 0.036). At 4 months, 79% of patients in the 2-hour group and 76% of patients in the 6-hour group had improved by 2 or more lines from baseline. Improvement from baseline to 4 months averaged 2.40 lines in each group (mean difference in logMAR acuity between groups, 0.001; 95% CI, –0.040 to 0.042), and a visual acuity measurement of 20/32 or better and/or 3 or more lines of improvement from baseline were achieved by 62% of patients in both the 2-hour and 6-hour groups. The results were not altered either by adjusting for the imbalance between groups in the distribution of amblyopia causes or by using the best amblyopic eye acuity attained at any visit instead of the 4-month visual acuity measurements (mean difference in logMAR acuity between groups, –0.007; 95% CI, –0.046 to 0.032). There was no statistical evidence for an interaction between treatment group and either patient age ($P=.76$), cause of amblyopia ($P=.85$), or baseline visual acuity of the amblyopic eye ($P=.96$) (**Table 4**).

ADVERSE EFFECTS OF TREATMENT

There was no significant difference between groups in the percentage of patients whose visual acuity in the sound eye was decreased from baseline at the outcome examination. At the 4-month examination, visual acuity in the sound eye was decreased from baseline by 1 line in 13 patients (14%) in the 2-hour group and 13 patients (15%) in the 6-hour group and by 2 or more lines in 6 (7%) and 8 patients (9%) in the 2 groups, respectively ($P=.59$). No patients were considered by the investigator to have developed reverse amblyopia.

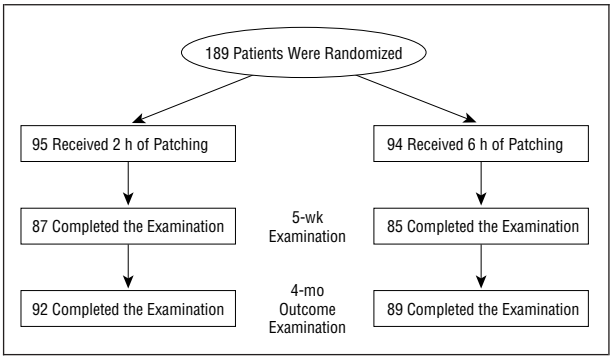


Figure 1. Flowchart showing study completion for each treatment group. In the 2-hour patching group, 67 patients completed the outcome examination within the time window (16-18 weeks), 2 were early (12 to <16 weeks), and 23 were late (>18 to 31 weeks). Among the 3 patients with incomplete follow-up, 1 completed the 5-week visit but then dropped out, and 2 were enrolled but had no further follow-up. In the 6-hour patching group, 69 patients completed the outcome examination within the time window, 3 were early, and 17 were late. Among the 5 patients with incomplete follow-up, 3 completed the 5-week visit but then dropped out, and 2 were enrolled but had no further follow-up.

Assessment of ocular alignment at the outcome examination found that among patients with no ocular deviation at baseline, 1 patient in each group was noted to have an intermittent exotropia at the 4-month examination (12Δ in the 2-hour group and 18Δ in the 6-hour group), and 2 patients in the 2-hour group and 1 patient in the 6-hour group were noted to have a small-angle strabismus (1Δ to 8Δ) at distance fixation. Four patients in the 2-hour group and 1 patient in the 6-hour group had a preexisting esotropia that increased by more than 10Δ.

Regarding binocularity testing, there was no difference between groups in responses recorded at the outcome examination for the Randot Stereotests ($P=.89$ for contour test, $P=.28$ for random dot shapes test, and $P=.87$ for suppression test) or the Randot Preschool Stereoacuity Test ($P=.47$).

For the patients who completed the 5-week visit, the Amblyopia Treatment Index was completed by 79 (91%) of 87 parents in the 2-hour group and 74 (87%) of 85 parents in the 6-hour group. In both treatment groups, the questionnaire results indicated that the treatment was well tolerated. The questionnaire scores were similar between the 2-hour and 6-hour groups on the adverse effects subscale (median = 2.13 for both; $P=.70$) and treatment compliance subscale (median = 2.33 for both; $P=.52$), but on the social stigma subscale (which included questions related to the patch making the child feel different from other children and to other children staring at the child when the patch is on), the median score was worse in the 6-hour group compared with the 2-hour group (3.00 vs 2.67; $P=.01$).

COMMENT

We evaluated the comparative effectiveness of prescribing 2 hours and 6 hours of daily patching in the treat-

Table 3. Visual Acuity in the Amblyopic Eye at the 4-Month Outcome Examination by Treatment

	2 h of Patching (n = 92)		6 h of Patching (n = 89)
Lines of improvement from baseline to the outcome examination			
<–1	0		1 (1)
–1 to +1	19 (21)		20 (22)
+2	32 (35)		23 (26)
≥+3	41 (45)		45 (51)
Mean ± SD	2.40 (1.34)		2.40 (1.63)
Difference between treatment groups in mean logMAR acuity at outcome examination		0.001	
95% CI for difference		(–0.040 to 0.042)	
Visual acuity of 20/32 or better and/or ≥3-line improvement from baseline‡	59 (62)		58 (62)
95% CI for difference		0 (–14 to 14)	

Abbreviation: CI, confidence interval.
*Data are presented as number (percentage) unless otherwise indicated.
†Adjusted for baseline visual acuity in analysis-of-covariance model.
‡For purposes of analysis, patients not completing the 4-month visit (3 in the 2-hour group and 5 in the 6-hour group) and 1 patient in the 6-hour group treated with atropine were considered to have not met these criteria. For this measurement, n = 95 in the 2-hour group and n = 94 in the 6-hour group.

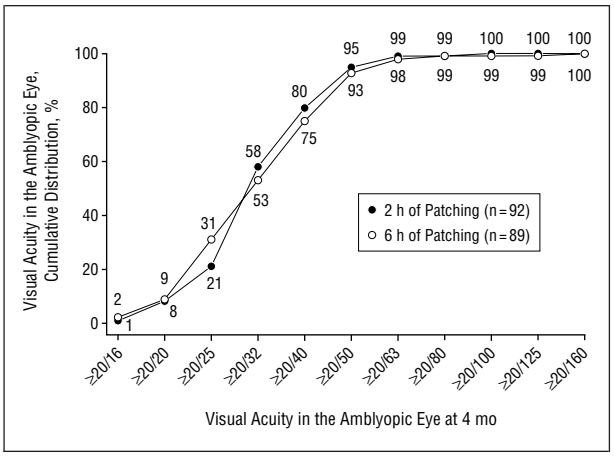
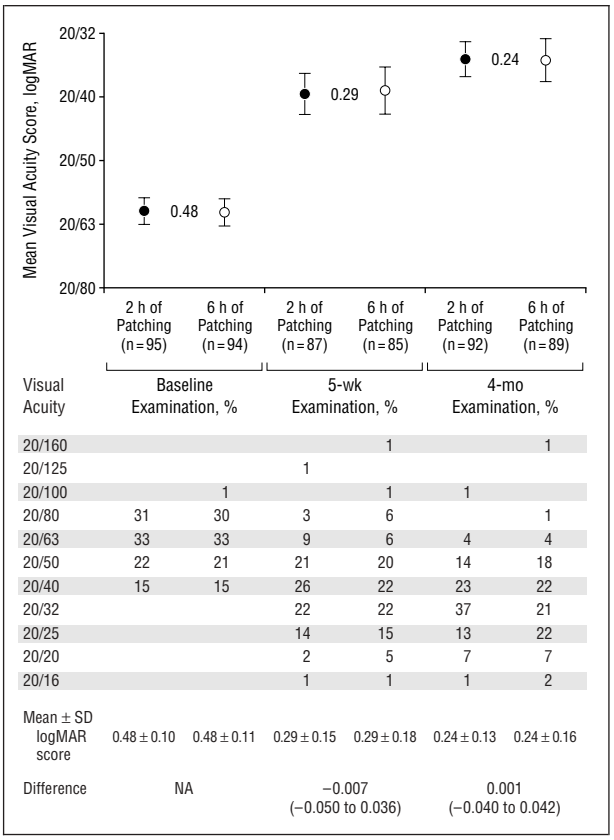


Figure 2. Cumulative distribution of visual acuity scores in the amblyopic eye at the 4-month outcome examination according to treatment group.



Visual Acuity	Baseline Examination, %		5-wk Examination, %		4-mo Examination, %	
20/160				1		1
20/125			1			
20/100		1		1	1	
20/80	31	30	3	6		1
20/63	33	33	9	6	4	4
20/50	22	21	21	20	14	18
20/40	15	15	26	22	23	22
20/32			22	22	37	21
20/25			14	15	13	22
20/20			2	5	7	7
20/16			1	1	1	2
Mean ± SD logMAR score	0.48 ± 0.10	0.48 ± 0.11	0.29 ± 0.15	0.29 ± 0.18	0.24 ± 0.13	0.24 ± 0.16
Difference	NA		–0.007 (–0.050 to 0.036)		0.001 (–0.040 to 0.042)	

Figure 3. Visual acuity measurements in the amblyopic eye in each group at baseline, 5 weeks, and 4 months. The point estimates and 95% confidence intervals are shown. The difference between treatment groups in mean logMAR acuity and the 95% confidence intervals were adjusted for baseline visual acuity.

ment of moderate amblyopia (20/40 to 20/80) in 189 children younger than 7 years. The study, which was conducted at both university- and community-based practices, was designed to approximate usual clinical practice, with the exceptions being (1) the use of randomization to determine the treatment prescribed, and (2) the use of a standardized protocol to measure visual acuity. We found that amblyopia improved with both patching regimens and that there was no demonstrable advantage to the greater number of patching hours, either in the rapidity of improvement or in the magnitude of improvement after 4 months of treatment.

We found no indication that 6 hours of prescribed patching compared with 2 hours was associated with a higher rate of adverse effects on the visual acuity in the sound eye, ocular alignment, or binocularity. However, in clinical practice, concerns for the potential adverse effects of patching have typically been related to full-time patching in patients younger than those included in our study. Although the parent questionnaire completed after the first 5 weeks of treatment indicated that both patching regimens were well tolerated, the parents of patients in the 6-hour group reported more concern with the social stigma of wearing the patch than the parents of those in the 2-hour group.

We did not believe that we could practically include an untreated control group in this trial. Thus, our conclusion that both patching regimens improved visual acuity is based on overwhelming clinical experience indicating that

Table 4. Visual Acuity in the Amblyopic Eye at 4 Months According to Baseline Patient Characteristics*

Baseline Characteristic	No. of Patients (2 h, 6 h)	Mean Lines of Improvement From Baseline		*P* Value for Interaction†
		2 h of Patching	6 h of Patching	
Sample size	(92,89)	2.40	2.40	
Sex				
M	(50,49)	2.48	2.45	.96
F	(42,40)	2.31	2.35	
Race				
White	(80,74)	2.30	2.31	.87
Other	(12,15)	3.08	2.87	
Age, y				
<5	(41,30)	2.29	2.30	.76
≥5	(51,59)	2.49	2.46	
Cause of amblyopia-1‡				
Strabismus	(29,43)	2.38	2.40	.85
Anisometropia	(34,28)	2.53	2.46	
Anisometropia and strabismus	(29,18)	2.28	2.33	
Cause of amblyopia-2‡				
Strabismus	(37,44)	2.35	2.39	.73
Anisometropia/microtropia	(55,45)	2.44	2.42	
Refractive error in the sound eye, D§				
<+3.00	(33,31)	2.70	2.74	.78
≥+3.00	(59,58)	2.24	2.22	

Abbreviation: D, diopters.

*Eight patients without a 4-month examination are not included (3 in the 2-hour patching group and 5 in the 6-hour patching group).

†The *P* values are for the interaction between the characteristic and treatment from a model that included baseline amblyopic eye acuity, treatment group, and the characteristic in analysis-of-covariance models with the 4-month amblyopic eye acuity as the dependent variable.

‡Patients were categorized by 2 methods for cause of amblyopia. See Table 1 for definitions for cause of amblyopia-1. For cause of amblyopia-2, strabismus category was defined as strabismus with a deviation ≥ 5△ or a history of strabismus surgery (with or without anisometropia), and anisometropia/microtropia category was defined as either (1) strabismus with a deviation < 5△ and no history of strabismus surgery (with or without anisometropia), or (2) anisometropia alone (meeting criteria for anisometropia in Table 1).

§Spherical equivalent.

substantial improvement of amblyopia rarely occurs without treatment and the fact that the amount of observed improvement (an average of 2.4 lines at 4 months) substantially exceeded any potential learning or age effect.[7,8,12] The magnitude of the learning or age effect on the visual acuity of the amblyopic eyes was likely similar to the observed improvement from baseline to the 4-month visual acuity outcome in the sound eyes of patients (mean change, 0.14 lines). A slight overestimate of the amount of improvement attributable to 4 months of patching could also have occurred from including some patients with anisometropia who had been wearing their optimal spectacle correction for only 4 weeks at the time of enrollment. Such patients might have experienced some improvement during the study due to the spectacles alone. Although the inclusion of these cases would not have affected the relative treatment group comparison and thus would have no bearing on our conclusions, it could have produced a slight overestimate of the absolute amount of improvement experienced by such patients in both treatment groups.

The amount of improvement that occurred during the 4 months of the trial should not be considered as the maximum amount of improvement that can occur with patching. In our study design, the 4-month follow-up period did not represent the period during which we expected the maximum treatment benefit to be achieved for all patients. Rather, it represented the maximum length of time we believed that the fixed treatment regimen (2 hours or 6 hours daily) could be maintained before either an increase in the prescribed number of patching hours or a switch to an alternate treatment for amblyopia might be necessary. In our previously reported trial comparing atropine and patching for moderate amblyopia,[13] the amount of improvement seen after 4 months in the patients prescribed 6 hours of daily patching who had a visual acuity measurement in the amblyopic eye at enrollment of 20/40 to 20/80 was similar to that found in this study (change from baseline: 2.48 vs 2.40 lines; 62% of patients in each study with a visual acuity measurement in the amblyopic eye of 20/32 or better and/or 3 or more lines of improvement from baseline). In the earlier study, among the patients in the patching group whose visual acuity was worse than 20/20 at 4 months, 46% improved by at least 1 additional line at 6 months. Therefore, it is likely that neither group in this study achieved the maximum possible improvement by 4 months, although we have no reason to believe that the 6-hour group would show greater additional improvement than the 2-hour group from subsequent therapy.

Our results must be viewed in the context that in addition to patching the sound eye, the parents of the patients in both groups were given a common instruction in clinical practice: to have the child perform near visual activities for at least 1 hour that the patch was worn each day. We do not know whether performing near visual tasks during a portion of the occlusion time contributed to the improvement in visual acuity of the amblyopic eye or whether the observed improvement in acuity resulted from occlusion alone. We

are not aware of any published studies that have prospectively evaluated whether performing near visual activities while the sound eye is occluded is beneficial in the treatment of amblyopia, although benefits have been reported in retrospective studies and case series.[6,14-16] We are planning a randomized trial to address this issue.

We could identify no sources of bias or confounding to explain our findings. The follow-up visit rate was high in both groups, and missing data from patients who dropped out of the study did not influence the interpretation of results. Baseline visual acuity in the amblyopic eye was similar between the 2 groups. There was a slight imbalance between groups in the distribution of causes of amblyopia; however, adjusting for this factor in analysis indicated that it did not confound the results. Although the patients, parents, and investigators were by the nature of this study unmasked to the treatment group assignments, masking to the primary visual acuity outcome measurement was achieved in 94% of cases. Visual acuity testing was performed with a standardized protocol using an instrument developed specifically for this study to ensure consistency of testing across our many sites.[8] The sample size for the trial was selected to have sufficient power to evaluate the treatment effect in subgroups based on cause of amblyopia. As a result, for the overall primary analysis, the statistical power was 90% to detect a treatment group difference of 0.075 logMAR (about 4 letters) and 80% to detect a difference of 0.065 logMAR (about 3 letters). It is unlikely that a true benefit of meaningful improvement for 6 hours of patching compared with 2 hours of patching exists but was not detected in this study.

In translating our results into clinical practice, the findings must be viewed in the context of the clinical profile of the cohort enrolled in the study. The eligibility criteria for enrollment were broad, with the intention to include most children with moderate strabismic and/or anisometropic amblyopia (specifically excluding deprivation amblyopia) younger than 7 years who were developmentally able to perform an HOTV optotype visual acuity testing protocol, effectively setting a lower age limit of about 3 years. To avoid including prior treatment failures in the study, enrollment was restricted to children who either had not been previously treated for amblyopia or had not received patching treatment within 6 months of enrollment and had not received other amblyopia treatment of any type (other than spectacles) within 1 month of enrollment. A 3-line difference in visual acuity between eyes was required (1) to assure that a true reduction in visual acuity was present, and (2) to have a sufficient depth of amblyopia to be able to assess improvement with treatment. In designing the trial to mirror a real-world situation, we limited compliance aids to those commonly used in clinical practice: an instruction sheet about treatment and a calendar on which to record at home the treatment received each day. Nevertheless, we recognize that patients participating in a clinical trial may differ from those in usual practice, and our patients' level of compliance may have been better than what may be typically achieved.

Although the benefit of a minimal amount of daily occlusion has been reported in retrospective studies and case series,[4,16-18] we are not aware of any prior prospective trial that has compared 2 or fewer hours of daily occlusion with a greater intensity of occlusion. We recognize that our results relate to the prescription of a specific number of patching hours rather than to the actual number of hours of occlusion performed. Although we asked the parents to maintain a compliance calendar and the investigators made an assessment of compliance at each visit, these data are insufficient for an analysis based on the actual number of patching hours performed. Such a study awaits the availability of a simple and acceptable occlusion dose monitor.[18-20]

In summary, when combined with prescribing 1 hour of near visual activities, 2 hours of daily patching appears to be as effective as 6 hours in treating moderate amblyopia in children aged 3 to 7 years. The shorter duration of patching may ease the implementation of patching therapy and monitoring of compliance for some parents.

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