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Association Between Occlusion Therapy and Optotype Visual Acuity in Children Using Data From the Infant Aphakia Treatment Study
A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Patching has been a mainstay in treating unilateral congenital cataract. However, its efficacy has not been rigorously assessed.

OBJECTIVE To examine the association between patching and visual acuity in a cohort of children treated for unilateral congenital cataract.

DESIGN, SETTING, AND PARTICIPANTS This study was a secondary analysis of a randomized clinical trial (Infant Aphakia Treatment Study) of infants born from August 1, 2004, through December 31, 2008, who were treated with 1 of 2 treatments for unilateral congenital cataract and followed up to 5 years of age. Data analysis was performed from March 1, 2013, to March 1, 2016.

INTERVENTIONS Cataract extraction and randomization to receipt of an intraocular lens vs being left aphakic for the first 5 years of life.

MAIN OUTCOMES AND MEASURES Caregivers reported patching in the previous 48 hours in quarterly semistructured telephone interviews. The mean number of hours of patching per day was calculated from surgery to the first birthday (n = 92) and between 12 and 48 months of age (n = 102). Monocular optotype acuity was assessed at 4½ years of age by a traveling examiner using the Aphakia Treatment Study HOTV protocol.

RESULTS The Infant Aphakia Treatment Study enrolled 114 children; 57 were randomized to each treatment group. At 4½ years of age, optotype visual acuity was assessed in 112 children. The current analyses exclude an additional 3 children (2 who had adverse events that limited visual potential and 1 who had Stickler syndrome), leaving 109 total children analyzed (59 female [54.1%] and 92 white [84.4%]). Caregivers reported patching their children a mean (SD) of 3.73 (1.47) hours per day in the first year of life and 3.43 (2.04) hours per day thereafter. An association between reported patching and treatment was not identified (mean difference in first year, −0.29 hours per day; 95% CI, −0.90 to 0.33 hours per day; mean difference between 12 and 48 months of age, −0.40 hours per day; 95% CI, −1.20 to 0.40 hours per day). Visual acuity was associated with reported hours of patching in the first year of life (r = −0.32; 95% CI, −0.49 to −0.13) and between 12 and 48 months of age (r = −0.36; 95% CI, −0.52 to −0.18). However, patching accounted for less than 15% of the variance in logMAR acuity at 4½ years of age.

CONCLUSIONS AND RELEVANCE These results support the association of occlusion throughout the preschool years with improved visual acuity in infants treated for unilateral congenital cataract. However, similar visual outcomes were achieved with varying amounts of patching. These conclusions should be interpreted in the context of limitations related to generalizability from incomplete data collected in a clinical trial.

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Infants born with visually significant unilateral cataracts often have poor visual outcomes. Previous reports[1-5] suggest that achieving a good outcome requires early surgical removal of the cataract, consistent optical correction, and good adherence to a regimen of occlusion of the fellow eye.

Chak and Rahi[6] report that poor adherence to occlusion is strongly associated with poor visual acuity in these children. However, others note that good outcomes are achievable with good adherence to patching in the first year of life but lower levels thereafter.[7] Adherence to occlusion therapy is likely necessary for achieving good visual acuity, but adherence and visual acuity may also predict adherence because patching is more difficult in children with poor vision.[8] The effect of adherence to occlusion therapy on visual outcome is, therefore, difficult to assess. Furthermore, although the efficacy of occlusion therapy for treating other types of amblyopia has been evaluated,[9] its efficacy in children with unilateral congenital cataract has not been rigorously examined.[10]

The Infant Aphakia Treatment Study (IATS) is a multicenter randomized clinical trial of treatment for unilateral congenital cataract. The objective is to compare visual acuity in children with a unilateral congenital cataract if an intraocular lens (IOL) is implanted at the time of cataract extraction with visual acuity in children left aphakic.[8] The IATS has documented that such eyes achieve a wide variety of visual outcomes but that visual acuity at 4½ years of age does not differ by treatment group.[11]

In the IATS, adherence to patching was assessed throughout the first 5 years of life to determine whether treatment affects adherence to patching. We previously found that, in the first year after surgery, adherence to patching was associated with sociodemographic factors but not IOL implantation[11] and that adherence to patching in the first 6 months after surgery was associated with grating acuity at 12 months of age.[12] However, visual acuity measured behaviorally is not strongly predictive of optotype acuity.[13] Furthermore, adherence to patching may become more challenging as children begin to resist patching. Therefore, the IATS provided a unique opportunity to prospectively assess the effect of adherence to occlusion therapy through 4 years of age on visual acuity among children treated for unilateral cataract. Specifically, the goals of these analyses are to determine whether implanting an IOL at the time of cataract extraction affects adherence to prescribed occlusion and to assess the association between patching and visual acuity at 4½ years of age. We hypothesized that primary IOL implantation would not be associated with adherence to occlusion therapy but that reported hours of patching would be associated with visual acuity. These questions were included as secondary outcomes in the original design of the IATS and not post hoc analyses.

Methods

Patients and Methods

The overall design of the IATS and results of the visual acuity assessment at 4½ years of age have been previously published.[14-16] The IATS was a multicenter randomized clinical trial that com-

Key Points

Question What is the efficacy of patching to treat unilateral congenital cataract in children with deprivation amblyopia?

Findings In a secondary analysis of a randomized clinical trial of treatment for unilateral congenital cataract, an intraocular lens implanted during cataract surgery did not affect caregivers' reported adherence to prescribed patching. A greater number of reported hours of patching throughout the first 4 years of life were associated with better visual acuity.

Meaning These results support the association of occlusion throughout the preschool years with improved visual acuity in infants treated for unilateral congenital cataract.

pared the following 2 treatments for visually significant unilateral congenital cataract in children 6 months or younger born from August 1, 2004, through December 31, 2008: removal of the cataractous lens followed by contact lens (CL) correction of aphakia vs removal of the cataractous lens and IOL implantation at the time of lens extraction. Data analysis was performed from March 1, 2013, to March 1, 2016. Children were excluded if they had a corneal diameter less than 9 mm; their intraocular pressure was 25 mm Hg or greater; there was persistent fetal vasculature, causing stretching of the ciliary processes or a tractional retinal detachment; they had retinal or optic nerve disease or signs suggestive of uveitis; they were born preterm; the fellow eye had ocular disease that might reduce its visual potential; they had a medical condition known to limit the ability to obtain visual acuity at 12 months or 4 years of age; or follow-up was not feasible. Written informed consent from caregivers was obtained before participation. The study was approved by the institutional review boards of all participating institutions and was in accordance with the tenets of the Declaration of Helsinki. The current analytic data set does not have identifiers beyond date of birth.

Prescribed Patching and Visual Correction

Patching was prescribed for all children until 5 years of age. Starting the second week after cataract surgery, caregivers were instructed to have the child wear an adhesive occlusive patch over the fellow eye 1 hour daily per month of age until the child was 8 months old. Thereafter, caregivers were told to patch their child 50% of waking hours. Patches were provided to patients at no cost.

Refractive correction was prescribed for all children 100% of waking hours. Within a week after cataract surgery, aphakic patients were fitted with a silicone (Silsoft; Bausch & Lomb) or a rigid gas permeable CL with a 2.0 diopter (D) overcorrection to provide a near-point correction. A spare lens was provided to ensure that optical correction was available in the event of loss or damage. Both daily wear and extended-wear protocols were acceptable. At 2 years of age, the eye was corrected to emmetropia using a CL, and spectacles were prescribed with +3.0-D bifocal lens for near focus.

For pseudophakic infants, spectacles were prescribed by the 1-month postoperative visit if any of the following conditions existed: hyperopia greater than 1.0 D, myopia greater than

3.0 D, or astigmatism greater than 1.5 D. In children younger than 2 years, the aim was to correct the refractive error to 2.0 D of myopia; thereafter, the aim was emmetropia at distance with a near correction of +3.0 D. The phakic eye for both groups was corrected with spectacles under any of the following conditions: hyperopia greater than 5.0 D, myopia greater than 5.0 D, astigmatism greater than 1.5 D, or refractive esotropia. The aim was to correct the refractive error to the range of 0 to +3.0 D.

Assessment of Adherence

Adherence to prescribed patching was reported by caregivers in semistructured telephone interviews. The interviews were completed quarterly, starting 3 months after surgery, and covered the previous 48 hours. Caregivers were asked to report specific times when the patch was applied and either fell off or was removed. Caregivers were also asked to report use of spectacles and/or CL and hours of sleep (eFigure in Supplement 1).

The timing of the interviews was determined using an algorithm that distributed the preferred day of the call evenly throughout the week because patching has been reported to differ on weekdays and weekend days.[17] Caregivers were not informed in advance about when they would be contacted to complete an interview. The interviews were conducted in the caregiver's preferred language (English, Spanish, and Portuguese) by 1 of 3 trained interviewers so that the caregiver spoke with the same person on each occasion. The English-speaking interviewer performed most interviews (>95%). Interviewers were located centrally and masked to treatment assignment to minimize the possibility that the respondent would exaggerate adherence or that the interviewer's interpretation of the information would be biased by knowledge of the child's visual acuity. However, it was not possible to ensure that the interviewer remained masked to treatment group over time.

On the basis of information reported in the interview, we calculated the mean number of waking hours each day that the child was occluded for 2 specific periods: before the first birthday and between the child's first and fourth birthdays. We selected this dichotomization because the visual acuity assessment at 12 months of age may have affected subsequent patching and because it has previously been observed that patching is higher in the first year of life than thereafter.[18] We limited the analysis to children with at least 3 assessments in the first period and 5 in the second because, although reported patching is consistent over time (Cronbach α >.75), relatively large intraindividual differences were reported.

Visual Acuity Assessment

Monocular optotype acuity was assessed at 4½ years 1 month of age by a traveling examiner (E.E.H.) using the Aphakia Treatment Study HOTV test as described in previous reports.[19,20]

Statistical Analysis

Statistical analyses were conducted using SPSS statistical software, version 21 (SPSS Inc), and SAS statistical software, version 9.2 (SAS Institute Inc). t Tests were used to assess differences between the treatment groups. Pearson correlation coefficients and linear regression were used to estimate the as-

Figure 1. CONSORT Diagram for the Infant Aphakia Treatment Study
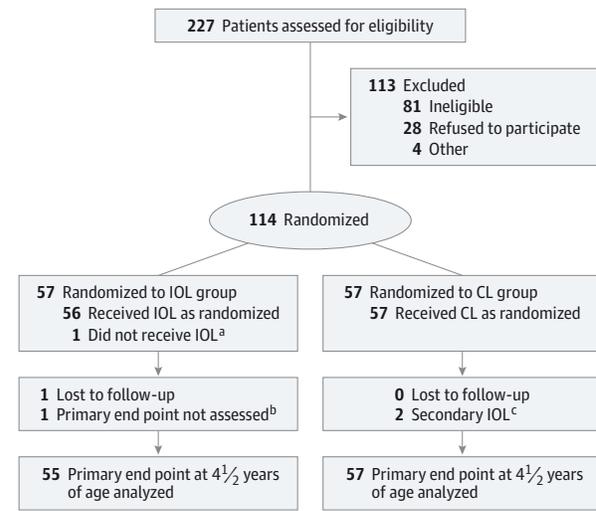
a One patient was found to have stretching of the ciliary processes intraoperatively after randomization to the intraocular lens (IOL) group. The investigator decided that an IOL could not be safely implanted, and the patient was left aphakic and treated with a cataract lens (CL).

b One patient had developmental delay and could not complete the HOTV acuity test at 4½ years of age.

c Two patients had a secondary IOL implanted at 1.3 and 3.0 years after randomization. One patient had a secondary IOL implanted at 4.7 years after randomization and after the primary end point was assessed but before the last clinical examination at 5 years of age.

sociation between patching and acuity. Statistical significance was defined at α = .05. A priori we defined the following as potential confounders because of their presumed association with vision and patching: treatment, sex, age at surgery (<49 days vs 49-269 days), socioeconomic status (private insurance vs other payment), adverse events (yes/no), and additional operations (yes/no). We included these cofounders as covariates in regression models.

Results

The IATS enrolled 114 children; 57 were randomized to each treatment group (**Figure 1**). At 4½ years of age, optotype visual acuity was assessed in 112 children. The current analyses exclude an additional 3 children: 2 who had adverse events that limited visual potential and 1 who had Stickler syndrome, which resulted in his having better visual acuity in his treated, than fellow, eye, leaving 109 total children analyzed.

Adherence data were available from at least 3 interviews before their first birthday for 92 children, and 102 had data from at least 5 interviews between 12 and 48 months of age. Eighty-six children had at least 3 interviews in the first year and at least 5 between 12 and 48 months of age. The demographic and clinical characteristics were similar in children randomized to receive an IOL and those left aphakic[16] and similar in children included in these analyses compared with the entire sample, with the exception that children with an older age at surgery

Table 1. Characteristics of the Analyzed Sample

Characteristic	Participants, No. (%)			
	All (N = 109)	With ≥3 Adherence Assessments in First Year of Life (n = 94)	With ≥5 Adherence Assessments Between 12 and 48 mo of Age (n = 103)	With ≥3 Adherence Assessments in First Year of Life and ≥5 Adherence Assessments Between 12 and 48 mo of Age (n = 87)
Female	59 (54.1)	50 (53.2)	57 (55.3)	48 (55.2)
Private insurance	68 (62.4)	58 (61.7)	65 (63.1)	55 (63.2)
White race	92 (84.4)	80 (85.1)	88 (85.4)	75 (86.2)
Randomized to IOL	54 (54.1)	47 (50.0)	53 (51.5)	45 (51.7)
<49 d of age at surgery	47 (43.1)	48 (51.1)	45 (43.7)	44 (50.6)
Visual acuity <95% of the prediction limits at 12 mo[a]	51 (46.8)	44 (46.8)	46 (44.7)	39 (44.8)
Additional operations in first year of life	38 (34.9)	22 (23.4)	37 (35.9)	33 (37.9)
Adverse events in first year of life	23 (21.1)	22 (23.4)	22 (21.4)	20 (23.0)
No. of adherence interviews in first year				
3	NA	32 (34.0)	NA	29 (33.3)
4	NA	61 (64.9)	NA	58 (66.7)
5	NA	1 (1.1)	NA	0
No. of adherence interviews between 12 and 48 mo of age				
5	NA	NA	2 (1.9)	2 (2.3)
6	NA	NA	3 (2.9)	1 (1.1)
7	NA	NA	7 (1.9)	2 (2.3)
8	NA	NA	6 (5.8)	6 (6.9)
9	NA	NA	7 (6.8)	5 (5.7)
10	NA	NA	17 (16.5)	14 (16.1)
11	NA	NA	31 (30.1)	28 (32.2)
12	NA	NA	35 (34.0)	29 (33.3)

Abbreviations: IOL, intraocular lens; NA, not applicable.

[a] Worse than 0.42 cycles per degree.

were less likely to have at least 3 adherence assessments in the first year (**Table 1**) because of the more limited time between surgery and the child's first birthday.

Caregivers reported patching their children a mean (SD) of 3.73 (1.47) (range, 0.06-7.11) hours per day in the first year of life and 3.43 (2.04) (range, 0-9.27) hours per day between 12 and 48 months of age. No differences were identified in reported patching for children randomized to receive an IOL and those left aphakic (mean difference in first year, −0.29 hours per day; 95% CI, −0.90 to 0.33 hours per day; mean difference between 12 and 48 months of age, −0.40 hours per day; 95% CI, −1.20 to 0.40 hours per day).

Reported adherence to patching was associated with optotype visual acuity at 4½ years of age in the first and subsequent 3 years (r = −0.32; 95% CI, −0.49 to −0.13; and r = −0.36; 95% CI, −0.52 to −0.18, respectively) (**Figure 2**), and the correlation was similar for children left aphakic (first year: r = −0.36; 95% CI, −0.59 to −0.08; between 12 and 48 months of age: r = −0.29; 95% CI, −0.53 to −0.01) and for those receiving an IOL (first year: r = −0.27; 95% CI, −0.52 to 0.02; between 12 and 48 months of age: r = −0.41; 95% CI, −0.62 to −0.15). These plots visually demonstrate 2 important features: the association between increased patching and visual acuity and the variability in the association.

Findings from regression analyses support the existence of an association between adherence and visual acuity and suggest that the association is not confounded by sociodemographic factors (**Table 2**). Furthermore, adherence between 12 and 48 months of age was significantly associated with visual acuity even after adjusting for adherence in the first year of life and poor grating acuity at 12 months of age. However, together, mean hours of patching in infancy and between 12 and 48 months of age collectively accounted for a mean (SD) of less than 15.0% (14.3%) of the observed variation in visual acuity.

Children who wore a patch at least 4 hours per day throughout the first 4 years of life had the best visual acuities and those who wore a patch fewer than 2 hours per day had the worst (**Figure 3**). However, there was a wide range of visual acuity outcomes even among children who wore a patch for similar amounts, further supporting the conclusion that there is considerable interindividual variability in the association between patching and visual outcomes in these children.

Discussion

Our analyses suggest that implantation of an IOL at the time of cataract extraction does not affect adherence to prescribed

Figure 2. Scatterplots Showing the Association Between Optotype Visual Acuity at 4½ Years of Age and Reported Mean Hours of Daily Patching in the First Year of Life and Between 24 and 48 Months of Life
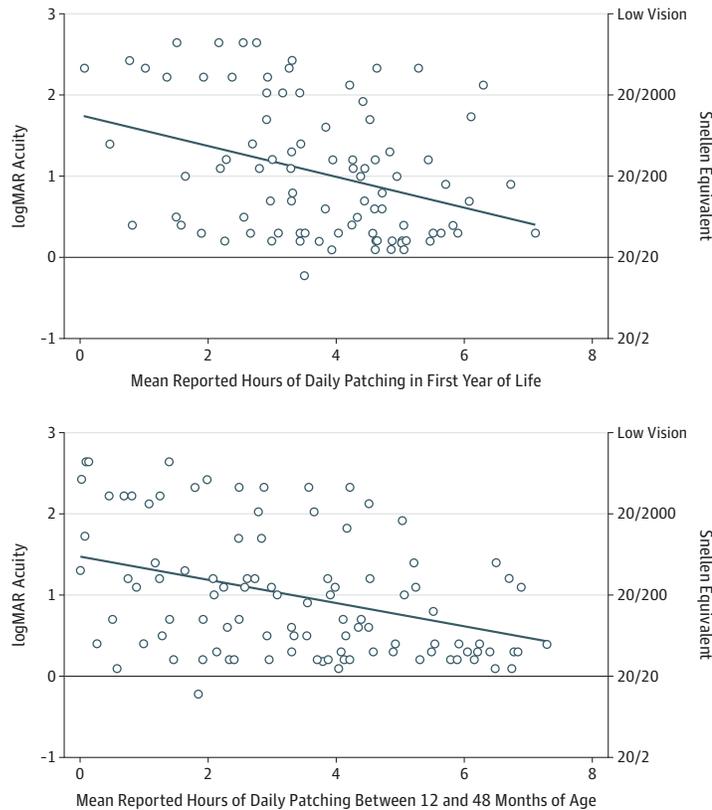

Table 2. Linear Regression of the Association Between the Mean Number of Hours of Patching per Day on Optotype Visual Acuity at 4½ Years of Life in the Infant Aphakia Treatment Study

| | Reported Mean Hours of Patching per Day | | | |
| | First Year of Life | | Between 12 and 48 Months of Age | |
Model	β (95% CI)[a]	P Value	β (95% CI)	P Value
Unadjusted	−0.077 (−0.125 to −0.03)	.002	−0.059 (−0.093 to −0.026)	.001
Adjusting for race, sex, age at surgery, insurance type, any adverse events in first year, any additional operations in first year[b]	−0.075 (−0.12 to −0.030)	.002	−0.055 (−0.089 to −0.022)	.002
Adjusting for above plus adherence in first year of life	NA	NA	−0.051 (−0.084 to −0.018)	.003
Adjusting for above plus visual acuity at 12 mo[c]	NA	NA	−0.040 (−0.075 to −0.005)	.02

Abbreviation: NA, not applicable.

[a] The β value represents the expected change in transformed visual acuity associated with a 1-hour increase in reported mean hours of daily patching.

[b] White vs other, male vs female, less than 48 days vs 49 to 269 days, and private insurance vs other pay.

[c] Better than 4.2 cycles per degree vs worse than 4.2 cycles per degree.

occlusion therapy and that the earlier observation of a lack of difference in visual acuity between aphakic and pseudophakic children[16] is unlikely attributable to an effect of treatment on adherence to patching. Furthermore, our data support a hypothesized association between patching and visual acuity in infants treated for unilateral congenital cataract. These findings are consistent with most previous assessments[7,21,22] of the importance of occlusion therapy to vision rehabilitation in these children. Furthermore, patching in the first year of life and thereafter contributed to visual acuity.

However, we also found substantial variability in the association between patching and visual acuity. The number of hours wearing a patch in the first year of life and in the subsequent 3 years accounted for approximately 10% of the observed variance in optotype acuity at 4½ years of age, and together this accounted for less than 15%. Thus, there is considerable variation in visual outcome given a specific amount of patching. This finding is similar to the findings of the study by Stewart et al[23] in older children with other types of amblyopia in whom adherence to occlusion therapy was monitored using occlusion-dose monitors. Although they found a monotonic association between total dose of occlusion and visual outcomes, there was substantial variability.

Figure 3. Box Plot Showing the Association Between Reported Hours of Patching in the First Year of Life and Between 12 and 48 Months of Life and Optotype Visual Acuity at 4½ Years of Age in the Infant Aphakia Treatment Study
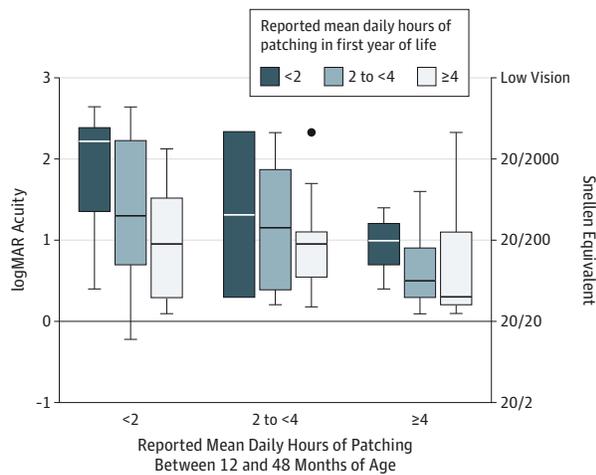
The boxes represent the interquartile range (ie, 25th percentile to 75th percentile) of visual acuity associated with each combination of patching in the first year of life and patching between 12 and 48 months of age, with the whiskers representing the full range of vision excluding any outliers, indicated by the circle. The center line indicates the median visual acuity.

There are a number of study limitations. First, although assessing the association between adherence to patching and visual acuity was included in the initial study design, it was not powered for the current question. In addition, the number of children in certain subgroups was relatively small. For example, only 3 children wore a patch fewer than 2 hours per day in the first year of life and a mean of at least 4 hours per day in the subsequent 3 years. Thus, there may have been inadequate power to identify small differences in adherence between treatment groups or in the effect of adherence on grating visual acuity.

In addition, although the IATS is a randomized clinical trial, there may be residual confounding by factors that are associated with visual acuity and adherence. We attempted to account for this by controlling for sociodemographic factors, age at surgery, adverse outcomes, and surgery. However, it is possible that there are other confounders of which we are unaware.

The use of clinical trial data also limits the generalizability of these results. The participating surgeons were highly skilled, and the participants provided with patches, CLs, and spectacles. The quarterly adherence telephone calls may also modify the amount of patching that was achieved. Thus, the observed association between patching and visual outcomes in other settings may be different from what we observed.

Preliminary analyses also suggest that caregivers who completed fewer adherence interviews reported somewhat less patching than caregivers who completed more interviews. However, this difference is not statistically significant, and given that adherence data are available on more than 80% of IATS participants, we do not believe that these differences explain our findings.

Finally, we believe that the association between adherence and visual acuity is bidirectional. Children with the best vision may less resistant to prescribed patching and therefore may wear patches more than children with poorer vision. For example, half (52.1%) of the children with grating acuity of better than 4.2 cycles per degree at 12 months of age wore a patch approximately the same amount (±1 hour per day) before and after their first birthdays; only 14 (29.2%) wore a patch much less (≤1 hour per day) after their first birthday than they had earlier. In contrast, only one-third (n = 13) of the children with poor vision at 12 months of age wore a patch the same amount (±1 hour per day) as their first birthday, whereas 17 (43.6%) of these children wore a patch substantially less than before (≤1 hour per day). The fact that patching is easier in children with better vision would have the effect of overestimating the association between patching and visual acuity. Even so, we believe that the facts that visual acuity is associated with patching before 12 months of age and that visual acuity is associated with adherence to patching between 12 and 48 months of age in models that account for visual acuity at 12 months of age and patching before that point support our conclusion that patching throughout the preschool years contributes to visual outcome.

Conclusions

These data suggest that adherence to occlusion therapy throughout the first 4 years of life contributes to better visual acuity in children treated for unilateral congenital cataract, although there is considerable individual variation. These data might be used to support caregivers' continuing efforts to prescribe patching and can provide them with encouragement about the efficacy of patching, even if they have previously been unable to fully adhere to the prescribed patching regimen.

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