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The Effect of Amblyopia Therapy on Ocular Alignment

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Abstract

Purpose: We sought to describe the change in ocular alignment at 2 years after treatment of amblyopia in children younger than 7 years of age at enrollment. ***Methods:*** A randomized clinical trial of patching versus atropine for 6 months followed by standard clinical care for 18 months was conducted in 357 children with anisometropic, strabismic, or combined amblyopia (20/40-20/100) whose ages ranged from 3 to younger than 7 years at enrollment. Ocular alignment was evaluated at enrollment and after 2 years of follow-up. ***Results:*** At enrollment when tested at distance fixation, 161 (45%) children were orthotropic, 91 (25%) had a microtropia (1-8Δ), and 105 (29%) had a heterotropia >8Δ. Of the 161 patients with no strabismus, similar proportions of patients initially assigned to the patching and atropine groups developed new strabismus by 2 years (18% vs. 16%, $P = 0.84$). Of these cases of new strabismus, only 2 patients in the patching group and 3 patients in the atropine group developed a deviation that was greater than 8Δ. Microtropia at enrollment progressed to a deviation greater than 8Δ with similar frequency in both treatment groups (13% vs. 15%, $P = 1.00$). Of the 105 patients with strabismus greater than 8Δ at enrollment, 13% of those in the patching group and 16% of those in the atropine group improved to orthotropia without strabismus surgery. Strabismus surgery was performed in 32 patients during the 2-year study period. ***Conclusions:*** Patients who had amblyopia treatment with patching or atropine for 6 months followed by standard clinical care were found to have similar rates of deterioration and improvement of ocular alignment. When parents begin amblyopia treatment for children without strabismus, they should be warned of the possibility of development of strabismus, although it is most often a small angle deviation. Strabismus resolved after amblyopia therapy in some cases.

Current clinical guidelines based on expert opinion advise the initiation of amblyopia treatment before surgical correction of strabismus.[1] Retrospective case series provide evidence for the association of amblyopia treatment, both patching and atropine, with the development of a new

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strabismus or an increase in the magnitude of existing strabismus.[2-5] In contrast, one case series reported a decrease in the angle of strabismus after amblyopia therapy.[6] Despite the possibility of a change in the strabismic angle with amblyopia therapy, some authors have suggested that it is not necessary to defer surgical treatment once amblyopia therapy has begun. They found similar motor alignment and binocular outcomes for retrospective case series compared with similar cases in which amblyopia treatment was completed before strabismus surgery.[7,8] A third report of the results of surgery before completing amblyopia therapy found this approach satisfactory only for children with mild amblyopia.[9]

To determine the best clinical approach to the amblyopic patient with strabismus, prospective data describing the stability of strabismus from initiation through completion of amblyopia therapy would be helpful. A recent randomized clinical trial of amblyopia therapy prospectively monitored ocular alignment at every study visit as a safety measure.[10,11] After 2 years, most patients had completed active treatment of amblyopia, although a few patients remained on maintenance therapy. The purpose of this report is to describe the change of ocular alignment in children with moderate amblyopia treated with atropine, patching or both with follow-up at 2 years.

METHODS

Children 3 to younger than 7 years were enrolled in a randomized clinical trial comparing atropine with occlusion for the treatment of moderate amblyopia, 20/40 to 20/100.[10-12] The 2-year outcome examination was completed for 396 (95%) of the 419 patients enrolled in the randomized clinical trial. Thirty-nine (10%) patients did not have alignment measured at the 2-year visit, which reduced the number of patients for the current study of ocular alignment to 357 (85% of enrolled patients): 181 in the patching group and 176 in the atropine group. Thus, ocular alignment data at the 2-year outcome were available for 84% (181/215) of the patching group and 86% (176/204) of the atropine group. There were no statistically or clinically significant differences in baseline characteristics between the patients who did and did not have ocular alignment data measured at the outcome.

Both treatment groups followed a structured treatment protocol with atropine or patching as determined by their randomization until the 6-month outcome examination.[10,12] The patching group initially was prescribed from 6 hours to full-time daily patching at investigator discretion, while the atropine group was initially prescribed one drop of atropine sulfate 1% daily. After the first 6 months, treatment was prescribed at investigator discretion.[11]

The majority of patients in both groups were prescribed amblyopia therapy for at least some time between 6 months and 2 years after enrollment (91% in the patching group and 84% in the atropine group). The treatment regimens prescribed beyond 6 months until the 2-year outcome were patching for 83% of children treated with patching during the initial 6 months and atropine for 76% of children treated with atropine during the initial 6 months. Similar proportions of patients were prescribed the other treatment for some period between 6 months and 2 years (29% in the patching group and 26% in the atropine group). Between 6 months and 2 years both patching and atropine were prescribed, although not generally concurrently, for 20% in the patching group and 18% in the atropine group (these patients are included with the percentages of patients both continued on treatment and switched to the other treatment). At the time of the 2-year outcome examination, about one-third of patients were still being treated for amblyopia (34% in the patching group and 35% in the atropine group). These data differ slightly from those published in the 2-year outcome report because this report excludes 39 children who did not have alignment measured at outcome.[11]

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Refractive correction was at investigator discretion except that the investigators were to fully correct anisometropia of 0.50D or more and they were required to place patients with esotropia in full cycloplegic refraction-determined hypermetropic spectacles. The spectacles were worn for at least 4 weeks before enrollment. Investigators were free to adjust spectacle power at their discretion prior to the 2-year outcome visit. A cycloplegic refraction was required by the protocol within 6 months of the 2-year outcome examination.

Alignment was measured at baseline and outcome by a study-certified investigator with the simultaneous prism and cover test at distance and near while wearing the prescribed correction as determined by the investigator. Alignment data were reported by the investigator according to protocol in three alignment categories: 0, 1-8Δ, or >8Δ, rather than by actual measured deviation. Since alignment was not the primary outcome measure for the randomized clinical trial, no attempt was made to mask the investigator to the patient's assigned treatment group. If the patient was using atropine, the protocol specified that alignment was to be determined with the patient off atropine for at least two weeks.

Eight patients were still prescribed atropine at the time of the 2 year visit and 12 had the drop stopped between 4 and 13 days prior to the visit. Nine patients were randomized initially to patching and 11 to atropine. Eleven had deviations in the same alignment category at baseline and 2 years. Five worsened one category, whereas 4 improved one category. These patients are included in all analyses. The study protocol did not restrict the investigators from recommending strabismus surgery.

Distributions of baseline and 2-year outcome characteristics were compared between patients with and without 2-year follow-up ocular alignment data and between the atropine and patching groups using Fisher's exact test for categorical characteristics and the Wilcoxon rank sum test for continuous characteristics. To investigate the possible association between visual acuity improvement and change in the size of a strabismus, we selected the subgroup of children with a large angle deviation at baseline. We compared the change in visual acuity among those with no deviation, microstrabismus, and large angle deviation at the 2-year outcome visit using analysis of variance (ANOVA). We investigated a possible association between a change in the size of the strabismus and a change in the amount of hypermetropic correction in the prescribed spectacles during follow-up. To do this we calculated the difference in the amount the plus spectacle correction was reduced from the cycloplegic refractions at baseline and at outcome for the patients who changed alignment category. The mean change in hypermetropic correction then was tested for difference from zero using the paired t-test. All reported *P* values are 2-tailed. Analyses were conducted using SAS version 8.2 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows the proportions of patients in each of the outcome categories for the entire cohort and the 2 randomized treatment groups stratified by baseline distance deviation. For children with orthotropia at distance fixation at baseline, 5 (3%) developed a new deviation greater than 8 Δ at the 2 year follow-up (2 in the patching group, 3 in the atropine group). The deviation was esotropia in 3 and exotropia in 2. One of these patients in the atropine group underwent strabismus surgery. The detection of a new microtropia in children who initially had no deviation occurred in 23 (14%) patients (16% in the patching group and 13% in the atropine group). Twenty (87%) of these new microtropias were esotropias.

There were 91 children with a microtropia (1-8Δ) measured at distance fixation at baseline. Eighty-five (93%) of these microtropias were esotropias. The microtropias improved to no measured deviation in 33 of 91 (36%) and deteriorated to a heterotropia >8Δ in 13 of 91 (14%) of cases. One child in each treatment group underwent strabismus surgery for an esotropia

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which deteriorated to an angle >8Δ. There was no apparent difference between treatment groups based on the initial treatment assignment.

There were 105 children with a heterotropia greater than 8Δ at baseline, 91 with esotropia. Strabismus surgery was performed on 29 of 105 (28%) children prior to the 2-year outcome examination. Surgery was performed in a similar percentage of patients in the patching group compared with the atropine group (31% vs. 24%, respectively, $P = 0.39$). Of the unoperated patients, 49 of 76 (64%) experienced an improvement of their alignment after amblyopia therapy alone. Fifteen of the 76 children (20%) had their strabismus resolve completely (7 in the patching group and 8 in the atropine group). Twelve of 65 (18%) esotropias and 3 of 11 (27%) exotropias resolved without surgery, $P = 0.45$).

We performed an analysis to explore whether there was a relationship between the chance of strabismus improvement and the improvement in visual acuity. For patients with a large angle deviation at baseline who did not have strabismus surgery, the mean change in visual acuity was 4.7 logMAR lines (±2.1) for patients whose strabismus resolved, 3.5 (±1.6) for patients who improved to a microdeviation (1-8Δ), and 3.5 (±1.9) for patients whose strabismus did not improve to 8Δ or less (ANOVA F-test $P = 0.073$).

To test the hypothesis that changes in the spectacle correction may have influenced the change in alignment including resolution of a heterotropia, we calculated the difference in the reduction of hypermetropic correction in the prescribed glasses used at baseline and outcome. For the patients whose strabismus improved without surgery, there was no change (mean = 0.06 diopters, $P = 0.82$, paired t-test for difference from 0) in the amount of plus lens undercorrection. For those patients with orthotropia at baseline and whose alignment deteriorated to a microtropia or a heterotropia >8Δ, the average amount of underplus in the prescribed spectacles was reduced by a mean of 0.39 diopters at the outcome examination ($P = 0.03$, paired t-test for difference from 0).

A similar pattern of change in ocular alignment was observed with near deviations. Twenty-eight (19%) of 150 patients with no deviation at baseline developed a new near deviation (12 in the atropine group and 16 in the patching group). Thirty (23%) of 130 patients with a heterotropia >8Δ at near underwent surgery (17 (26%) in the patching group and 13 (20%) in the atropine group). Of the remaining 100 patients, 18 (18%) showed resolution of strabismus (9 (18%) in each group). For patients with a large-angle deviation at near at baseline who did not have strabismus surgery, the mean change in visual acuity was 3.9 logMAR lines (SD ± 2.7) for patients whose strabismus resolved, 3.7 (±1.5) for patients who improved to a microtropia, and 3.2 (±2.0) for patients whose strabismus did not improve to less than 8Δ (ANOVA $P = 0.38$).

DISCUSSION

Previous authors have suggested that patching might disrupt fusion, leading to a sensory deviation, and that atropine by altering accommodative vergence, also might lead to strabismus.[2-5] In our 2-year prospective study we found that amblyopia treatment is associated infrequently with the development of significant strabismus. Although 14% of children measured with orthotropia at baseline developed a microstrabismus in this clinical trial, only 5 (3%) were measured with a heterotropia of more than 8 Δ. We found similarly low rates for both atropine and patching initial treatment groups.

In this trial, the decision to perform surgery was not part of the protocol but was made by the investigator. When strabismus surgery was performed, it was almost exclusively performed on children with deviations >8Δ at enrollment, and not on patients who developed strabismus during their time on treatment.

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Some patients with strabismus at baseline were measured to have an improvement (heterotropia >8Δ to microtropia or orthotropia; microtropia to orthotropia) in alignment without strabismus surgery. More than one-third of patients with a microtropia at baseline had no deviation measured after amblyopia therapy. Even more surprising was the chance of a patient with a heterotropia greater than 8Δ improving without strabismus surgery. Nearly one-half of patients reduced their angle to 8Δ or less, and 14% improved to orthotropia. This improvement was seen irrespective of treatment group assignment or presence of esotropia or exotropia at baseline. Our data show a trend to greater alignment improvement in those patients with more improvement in visual acuity. It seems likely that the treatment-related increase in acuity was associated with an improvement in fusion that led to an improved control of the strabismus.

Some patients with no strabismus on enrollment had a microtropia documented at the 2-year examination. This change occurred in 14% of patients with similar frequency in both atropine and patching groups. It is possible that some of these children might have had a microstrabismus at enrollment that was obscured by the reduced visual acuity or cooperation of the young child.

There are several limitations to our data. We measured the deviations with the simultaneous prism and cover test, but did not collect the exact size of the ocular deviations. Therefore, we are unable to report whether there were changes in alignment within the group of patients with deviations greater than 8 Δ between baseline and outcome. In addition, it is possible the improvement in alignment associated with amblyopia therapy was experienced primarily by children with moderate size deviations, rather than by children with larger deviations. It is also likely that patients with larger strabismus angles would undergo strabismus surgery. Therefore, the patients who completed the study without strabismus surgery might have had smaller angles of strabismus at baseline and been more likely to resolve or improve to a microstrabismus.

A second limitation is associated with spectacle correction. Although the investigators were instructed to prescribe full cycloplegic refraction determined hyper-metropic correction for their esotropic patients at baseline, they were free to adjust spectacle power at their discretion at subsequent visits. A change in power of the spectacles could be responsible for changes in ocular alignment. In an exploratory analysis we found no evidence of a spectacle adjustment in which plus power was increased for the esotropic patients with improved alignment or decreased for the esotropic patients with worsened alignment in an effort to maintain control of the alignment with the spectacles.

Third, because nearly every strabismic patient (90%) enrolled in this study had esotropia, the impact of amblyopia therapy on children with exotropia is unknown. Also, changes of alignment from orthotropia to microstrabismus or the reverse could be the result of variability of the measurement. Such changes in classification (eg, orthotropia to microtropia, or microtropia to heterotropia) should be viewed cautiously. Larger changes with a shift of at least 8Δ from orthotropia to heterotropia greater than 8Δ or the reverse would be less prone to measurement variability.

Finally, these data on alignment change do not show a causal relationship between amblyopia therapy and motor alignment, nor do they demonstrate whether the better time for strabismus surgery is during amblyopia treatment or once treatment is concluded. A study with an untreated control group would be needed to answer the former question and a clinical trial needed to answer the latter question. These motor alignment outcomes could represent the natural history in the setting of current amblyopia treatment. This study also lacks a baseline measure of binocular vision; hence, we are unable to correlate a change in alignment to a change in binocular vision with amblyopia treatment.

In conclusion, children who undergo amblyopia treatment with patching or atropine have similar low rates of deterioration and improvement of their ocular alignment. Whether this

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change in alignment is caused by prescribed amblyopia therapy is not known. However, parents of children with no strabismus or microstrabismus should be forewarned that there is a chance of a new or worse strabismus developing during treatment, but parents of children with strabismus may also be informed that there is also a chance of improvement.

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TABLE 1

Alignment at 2 years grouped by baseline alignment

	Total (N = 357)	Patching (n = 181)	Atropine (N = 176)
Baseline alignment = No deviation	N = 161	N = 82	N = 79
2-year alignment			
No deviation	133 (83%)	67 (82%)	66 (84%)
1−8 Δ	23 (14%)	13 (16%)	10 (13%)
>8 Δ	4 (2%)	2 (2%)	2 (3%)
Surgery prior to 2-year examination	1 (1%)	0	1 (1%)
Baseline alignment = 1−8 Δ	N = 91	N = 45	N = 46
2-year alignment			
0	33 (36%)	17 (38%)	16 (35%)
1−8 Δ	45 (49%)	22 (49%)	23 (50%)
>8 Δ	11 (12%)	5 (11%)	6 (13%)
Surgery prior to 2-year examination	2 (2%)	1 (2%)	1 (2%)
Baseline alignment = >8 Δ	N = 105	N = 54	N = 51
2-year Alignment			
0	15 (14%)	7 (13%)	8 (16%)
1−8 Δ	34 (32%)	18 (33%)	16 (31%)
>8 Δ	27 (26%)	12 (22%)	15 (29%)
Surgery prior to 2-year examination	29 (28%)	17 (31%)	12 (24%)