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ORIGINAL ARTICLE

Atropine 0.01% Eyedrops Significantly Reduce the Progression of Childhood Myopia

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Abstract

Purpose: Atropine 0.01% eyedrops have been shown to slow childhood myopic progression in primarily Asian populations. We studied its effects on an ethnically diverse population over a broad range of myopia.
Methods: A retrospective case–control study was performed on 60 children (6–15 years) with initial myopic spherical equivalents from −0.25 to −8.00 diopters (D). The primary outcome was the rate of myopic progression per year. Secondary outcomes were the proportion of subjects with slow or rapid myopic progression, atropine-related side effects, and rates of myopic progression for subgroups with low, moderate, or higher initial myopia.
Results: The average initial age (10.2 years) and refraction (−2.0 D) were identical between groups. After 1.1 ± 0.3 years follow-up, atropine subjects had significantly lower rates of myopic progression (-0.1 ± 0.6 D/year) than controls (-0.6 ± 0.4 D/year) ($P = 0.001$), including 24 of 32 (75%) with slow progression ≤ -0.25 D/year versus only 5 of 28 (18%) controls. Three atropine and 4 control subjects had rapid progression ≥ -1.00 D/year. For subjects with low initial myopia (≤ -1.00 D), 9 of 11 (82%) atropine subjects had plano or slightly hyperopic refractive changes after 1 year, while 8 of 8 (100%) controls were more myopic. Only 3 atropine subjects complained of intermittent blur or light sensitivity, not symptomatic enough to discontinue treatment.
Conclusions: Atropine 0.01% significantly reduced the rate of myopic progression over 1 year with minimal side effects. It appears most effective in children with low initial myopia and may not control rapid myopic progression in some patients. Stronger concentrations of atropine may be required to slow rapid myopic progression.

Introduction

Myopia is a major public health concern with both increasing incidence and severity.[1–5] The majority of the increase appears due to environmental factors[3]; although genetic factors such as ethnic background and parental myopia also play a role.[6–8] Myopia is not just a benign condition treated with optical correction. It is a disease associated with a higher incidence of glaucoma, retinal detachment, macular choroidal degeneration, myopic choroidal neovascularization, myopic retinoschisis, early-onset cataract, amblyopia, and strabismus.[1,3,9] Current research is focused on decreasing the severity of myopia and possibly preventing its onset entirely.[10,11]

Many treatments have been advocated to slow myopic progression: atropine eyedrops of varying concentrations,[12–14] pirenzepine 2% gel,[15] deliberate optical undercorrection,[1,16,17] increased outdoor activity and sunlight exposure,[18–20] bifocal and progressive eyeglasses,[1,3,21–23] and contact lenses (rigid gas permeable,[24] peripheral defocus,[25] and orthokeratology[26,27]). Pirenzepine and progressive eyeglasses cause a statistically significant, but clinically small reduction in the rate of myopic progression.[1,3,15] Orthokeratology causes a temporary retardation of myopia and possibly a permanent reduction in axial length, but 90% of the effect appears to wear off after 3 days.[26] There is also an increased risk of infection, with corneal staining found in up to 60% of patients.[1,26]

Atropine appears to have the strongest clinical effect on reducing the rate of myopic progression, but significant ocular side effects such as photophobia and decreased near vision and the potential for systemic side effects such as allergy, dry mouth, flushing, and constipation have limited its use.[1,12,28–30] These risks appear to be substantially mitigated by using lower concentrations of atropine.[12,28–31] Since low-concentration atropine is much better tolerated than atropine 1%, it is becoming the standard treatment in Asia, with almost 50% of myopic Taiwanese children receiving atropine eyedrops of varying concentrations.[32] Since most studies have been performed on Asian populations with high rates of myopia and myopic progression, it is unknown whether these results can be replicated in other regions with more diverse populations. We

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studied the clinical effects of atropine 0.01%, the lowest concentration shown to have an effect on myopic progression,[12] on an ethnically diverse group of children with low to moderate initial myopia.

Methods

This study was reviewed by the Institutional Review Board of Provident Health & Services and certified with exempt status. The research conformed to the principles of the Declaration of Helsinki. All data collection was compliant with the United States Health Insurance Portability and Accountability Act.

A retrospective chart review identified patients who were prescribed nightly atropine 0.01% eyedrops and patients not on eyedrops who were prescribed eyeglasses to correct myopia. All eyedrops were compounded by the same compounding pharmacy (Leiter's Compounding Pharmacy, San Jose, CA). Cases were selected using the following inclusion criteria: ages 6–15 when starting therapy, initial myopic spherical equivalent ≥ -0.25 and ≤ -8.00 diopters (D), and astigmatism ≤ -2.0 D. Exclusion criteria included the following: <0.8 years of follow-up, medical conditions that predisposed to higher myopia [Marfan syndrome, Stickler syndrome, retinopathy of prematurity (ROP), etc.], abnormal ocular refractive anatomy (keratoconus, lenticonus, spherophakia, etc.), and any history of intraocular surgery. Although anisometropia was not an exclusion criterion, all cases and controls had <1 D difference in myopic spherical equivalence between the eyes. Cases were matched to controls with initial myopia within ±0.50 D and age within ±6 months. Power analysis showed an 80% probability of detecting a 25% reduction in the rate of myopic progression with 60 total subjects. An investigator masked to the final refractive outcome performed the matching of cases and controls.

Since cycloplegic refraction was not routinely performed at all study visits, the main outcome variable was the rate of change per year of the spherical equivalent noncycloplegic manifest refraction of the right eye performed by 1 of 3 physicians. Secondary outcomes included any reported side effects from the atropine, the proportion of subjects with rapid (≥ -1.0 D/year)[14] or slow (≤ -0.25 D/year) myopic progression, and the rates of progression for subgroups of non-Asian subjects and subjects with low (≤ -1 D), moderate (< -1 to ≤ -2 D), or higher (> -2 D) initial myopia. Since ethnicity was not typically recorded in the medical record, surnames and US census data were used to determine the ethnic distribution of subjects. Statistical comparisons were made using a paired *t*-test for the overall rate of myopic progression and unpaired *t*-tests for the subgroup analyses of the rates of myopic progression for non-Asian subjects and subjects with different levels of initial myopia.

Results

Forty-nine children were identified who were prescribed atropine 0.01% eyedrops. Two subjects were excluded with a history of ROP, 3 subjects were too young or too old, and 12 subjects lacked sufficient follow-up, leaving 32 subjects as cases. Matched controls, based on age and initial myopic spherical equivalent, were found for only 28 of the cases. Two unmatched cases were 8-year olds with myopic spherical equivalents of −6.00 and −7.88 D and 2 were 14-year olds with myopic spherical equivalents of −0.63 and −0.50 D.

Table 1. Summary Data for the Rate of Myopic Progression per Year

	Atropine group	*Control group*	P-*values*
Gender, F/M	13/15	15/13	
Ethnicity: Asian (%)	8 (29)	3 (11)	
Caucasian (%)	15 (54)	12 (43)	
Hispanic (%)	3 (11)	13 (46)	
African American (%)	2 (7)	—	
Initial age (years)	10.2 ± 2.2	10.2 ± 2.2	0.96
Follow-up (years)	1.1 ± 0.3	1.1 ± 0.3	0.26
Initial Rx (D)	−2.0 ± 1.6	−2.0 ± 1.5	0.54
Change in Rx (D)	−0.1 ± 0.5	−0.7 ± 0.4	**0.0002**
Rate (D/year)	−0.1 ± 0.6	−0.6 ± 0.4	**0.001**

The atropine and control groups were identical at the onset of treatment, but after 1 year showed highly significant differences using paired *t*-tests in both the change in refraction and the rate of myopic progression per year (bold values).

F, female; M, male; Rx, spherical equivalent manifest refraction; D, diopters.

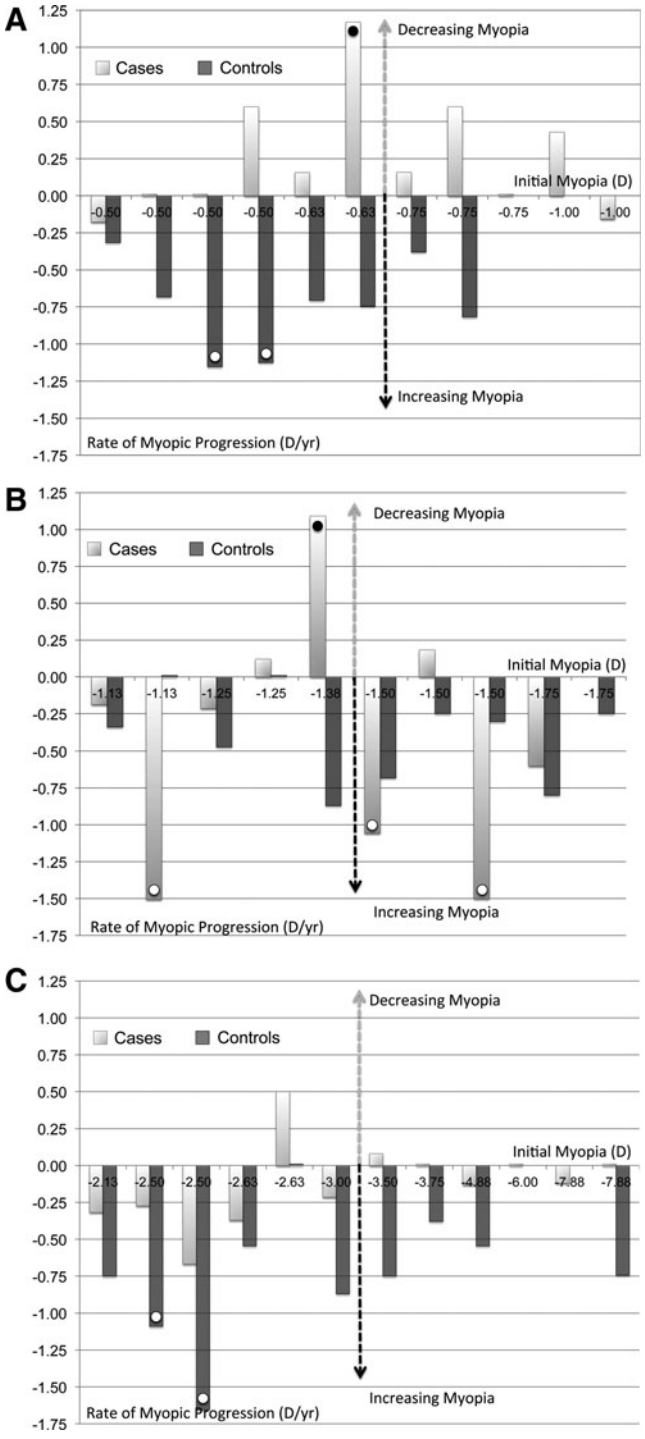
The demographic information is summarized in Table 1. The average initial age, initial myopic spherical equivalent, and follow-up periods were identical between groups. For the primary outcome, the rate of myopic progression was −0.1 D/year for cases (95% confidence interval −0.3 to +0.1) compared with −0.6 D/year for controls (95% confidence interval −0.8 to −0.4), $P = 0.001$. Comparing only non-Asian cases with non-Asian controls, the rate of myopic progression was −0.2 D/year for cases compared with −0.6 D/year for controls ($P = 0.003$), nearly identical to the results for all subjects. Resting pupil dilation and range of accommodation were not typically recorded before or after initiation of therapy. Two cases complained of intermittent light sensitivity to bright sunlight and 1 case with a history of migraine

Table 2. Subgroup Analysis for the Rate of Myopic Progression per Year

	Atropine group	*Control group*	P-*values*
Low (≤ -1.0 D) initial myopia			
Initial age (years)	10.8 ± 2.3	9.5 ± 2.4	0.26
Initial Rx (D)	−0.7 ± 0.2	−0.8 ± 0.3	0.51
Follow-up (years)	1.0 ± 0.3	1.2 ± 0.4	0.20
Rate (D/year)	+0.3 ± 0.4	−0.7 ± 0.3	**0.00003**
Moderate (> -1.0 to ≤ -2.0 D) initial myopia			
Initial age (years)	9.9 ± 2.7	10.3 ± 2.0	0.74
Initial Rx (D)	−1.5 ± 0.3	−1.4 ± 0.2	0.25
Follow-up (years)	1.0 ± 0.2	1.1 ± 0.1	0.76
Rate (D/year)	−0.3 ± 1.1	−0.5 ± 0.6	0.59
Higher (> -2.0 D) initial myopia			
Initial age (years)	10.2 ± 2.3	10.8 ± 2.4	0.60
Initial Rx (D)	−4.1 ± 2.1	−3.5 ± 1.7	0.52
Follow-up (years)	1.0 ± 0.1	0.9 ± 0.1	0.43
Rate (D/year)	−0.2 ± 0.3	−0.8 ± 0.4	**0.0005**

Each atropine and control subgroup was statistically equivalent at the outset of treatment, but only the low and higher initial myopia subgroups showed highly significant differences at follow-up in the rate of myopic progression per year (bold values) using unpaired *t*-tests. The moderate initial myopia subgroups did not show any significant differences with treatment.

headaches complained of intermittent blurred vision. No case was symptomatic enough to discontinue the atropine eyedrops. The 4 cases without age-matched controls had an average rate of myopic regression, not progression, of +0.4 D/year, so inclusion of these cases with proper controls would likely have enhanced the difference between cases and controls. Those 4 cases were included in subsequent unpaired statistical analyses. Overall, 24 of 32 (75%) cases had slow myopic progression ≤ -0.25 D/year versus only 5 of 28 (18%) controls. Three of 32 (9%) cases had rapid myopic progression ≥ -1.00 D/year versus 4 of 28 (14%) controls.



The subgroup analyses for initial myopia are summarized in Table 2. Both lower ($\leq$1.00 D) and higher (> -2.00 D) myopia cases had significantly less myopic progression than controls, but the moderate (> -1.00 to ≤ -2.00 D) myopia subgroup did not show a significant difference with treatment. All 3 cases with rapid myopic progression began treatment with moderate myopia (Fig. 1B).

Although gender was not factored into matching cases and controls, *post hoc* analysis revealed that both groups had a similar distribution of genders (Table 1). Finally, 5 matched cases and 5 controls were older than 12 at the outset of the study, with identical average ages (13.6 years) and initial myopic spherical equivalents (−2.9 D). The older cases had a rate of myopic change of +0.1 D/year (decreasing myopia) compared with −0.5 D/year for older controls (increasing myopia), both within the 95% confidence intervals of the results for the main outcome variable.

Discussion

These results support the effectiveness of nightly atropine 0.01% eyedrops in significantly reducing the progression of childhood myopia in children from diverse ethnic backgrounds. Chia et al. in the ATOM2 study reported an average rate of myopic progression of −0.49 D for the atropine 0.01% treatment group over a 2-year period, resulting in an annual rate of −0.25 D/year, within the 95% confidence of this study.[12] Their slightly faster rate of myopia might be attributed to including only Asian subjects 12 years and younger with higher levels of initial myopia (at least −2 D at enrollment). Some studies report a higher rate of myopic progression in controls than was measured in our control group. Shih et al. noted an annual myopic increase of −1.06 D/year in a study limited only to Asians.[14] Even with a lower rate of myopic progression in our control group, we still found a highly significant reduction in myopic progression with treatment. This reduction in myopia appears permanent, persisting up to 4 years in the cases with prolonged administration of nightly atropine.

The strongest clinical improvement was found in the low initial myopia subgroup. Most prior studies of atropine eyedrops excluded this level of myopia,[12–14] but our results are almost identical to those found by Fang et al. using 0.025% atropine in premyopic children.[11] The study found that a slightly stronger

FIG. 1. Graphs of the rate of myopic progression from initial myopia. **(A)** Low initial myopia (≤ -1.0 D): Every case in this subgroup had slow myopic progression $\leq$ −0.25 D/year and 9 of 11 (82%) had plano or hyperopic refractive changes after 1 year, including 1 case with $> +1.0$ D hyperopic change (marked with *black dot*). Every control had increasing myopia, including 2 controls with rapid myopic progression > -1.0 D/year (marked with *white dots*). **(B)** Moderate initial myopia (> -1.0 and ≤ -2.0 D): 3 cases in this subgroup had rapid myopic progression > -1.0 D/year (marked with *white dots*) and 1 case had $> +1.0$ D hyperopic change (marked with *black dot*). There were no significant differences in myopic progression between cases and controls within this subgroup. **(C)** Higher initial myopia (> -2.0 D): This subgroup was most directly comparable to the ATOM2 study,[12] which required at least −2.0 D of myopia at study entry. Every case had a slower rate of myopic progression than his or her control and none had rapid myopic progression ≥ -1.0 D/year compared with 2 controls (marked with *white dots*). D, Diopter.

concentration of atropine reduced the rate of progression to −0.14 D/year in the treatment group compared with −0.58 D/year in the control group.[11] Most of our low myopic cases became partially or completely spectacle free compared to worsening myopia in every control subject (Fig. 1A).

No significant effect was found in cases with initial myopia > -1.0 to ≤ -2.0 D, primarily because that subgroup contained the only 3 cases with rapid myopic progression (Fig. 1B). It is unclear why the atropine effect was less pronounced in this subgroup. It may be a statistical anomaly because outliers might skew the results in a small sample, as shown by the very large standard deviation (±1.1 D) in the rate of myopic progression in this subgroup compared to the other subgroups (maximum standard deviation of ± 0.6 D for all other subgroups, Table 2). The lack of a statistically significant response in this group, plus the subset of cases with rapid myopic progression despite treatment, highlights the existence of patients who may not respond to dilute atropine eyedrops. While our rate of rapid myopic progression (9%) was much lower than the 37%–50% rate found in prior studies of Asian children treated with stronger concentrations of atropine,[12,14] a substantial percentage of myopic children may prove resistant to the effects of atropine regardless of ethnic background.

Our study also included older subjects than prior atropine studies. Most prior studies used an upper boundary of 12–13 years, but myopic progression has been demonstrated beyond early adolescence, stabilizing by 16 years or older.[29,33] Although we only analyzed a small number of older subjects, we found that older controls continued to have progressive myopia while older cases experienced a significant regression of myopia.

This study has some important limitations, including its retrospective nature and relatively small sample size. Since atropine to treat myopia is off the Food and Drug Administration label and the 0.01% concentration is not readily available, treatment initially was only offered to children with a clinically perceived higher probability of rapid myopic progression (highly myopic parents, younger age at onset of myopia, and/or demonstrated rapid myopic progression). Later, because of early favorable clinical responses to therapy plus the lack of significant side effects, atropine was offered to a broader range of myopic children. The early selection bias, however, should have skewed the results toward more myopic progression in the cases, but the opposite result was found.

Another important limitation is the use of manifest refractions at all study points. Many subjects had cycloplegic refractions at some point in their care, but most did not undergo cycloplegic refractions at all study points, so only manifest refractions were used throughout the study. These refractions were performed at all visits by 1 of 3 experienced physicians using standard techniques to control overminusing, such as red–green balancing and nonmydriatic retinoscopy, but any overminusing might exaggerate myopic progression, especially if atropine 0.01% produced clinically apparent cycloplegic effects. Atropine 0.01% has been shown to have no initial hyperopic shift and minimal effect on accommodation,[12] however, and the same refraction techniques were used to examine both groups, so potential measurement errors should be balanced and not affect the overall results.

Atropine appears to exert its antimyopic effect through a nonaccommodative mechanism, bypassing the lens and ciliary body to act on receptors within the retina, retinal pigment epithelium, or sclera. Antimuscarinic medications have been shown to inhibit cell proliferation in human scleral fibroblasts.[34] The identification of a potential site of action for atropine, the M4 subtype of muscarinic receptor,[35] may allow a more targeted therapy with fewer side effects, although it will be difficult to demonstrate fewer side effects than has been documented with atropine 0.01%.

Future studies on atropine might focus on optimizing the concentration of atropine to control myopia without inducing side effects and titrating the dose based on individual short-term and long-term responses to therapy. Lower concentrations may eventually prove most effective because stronger concentrations may saturate or upregulate muscarinic receptors, mitigating their therapeutic efficacy. In addition, lower concentrations have been shown to have a minimal rebound of increased myopia after cessation of therapy, providing a better final refractive outcome.[28] Finally, enhanced screening methods and prediction models to detect early myopia or even premyopia may allow intervention in time to potentially cure myopia.[36]

In conclusion, atropine 0.01% significantly reduced the rate of myopic progression over 1 year with minimal side effects. It was most effective in children with low initial myopia and did not control rapid myopic progression in some patients. The optimum dosage to control myopia is yet to be determined and may need to be titrated based on the individual response to therapy, with some myopic children possibly resisting the effects of atropine altogether.

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Author Disclosure Statement

No competing financial interests exist.

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