

Atropine for the Treatment of Childhood Myopia

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Purpose: To evaluate the efficacy and safety of topical atropine, a nonselective muscarinic antagonist, in slowing the progression of myopia and ocular axial elongation in Asian children.

Design: Parallel-group, placebo-controlled, randomized, double-masked study.

Participants: Four hundred children aged 6 to 12 years with refractive error of spherical equivalent -1.00 to -6.00 diopters (D) and astigmatism of -1.50 D or less.

Intervention: Participants were assigned with equal probability to receive either 1% atropine or vehicle eye drops once nightly for 2 years. Only 1 eye of each subject was chosen through randomization for treatment.

Main Outcome Measures: The main efficacy outcome measures were change in spherical equivalent refraction as measured by cycloplegic autorefraction and change in ocular axial length as measured by ultrasonography. The primary safety outcome measure was the occurrence of adverse events.

Results: Three hundred forty-six (86.5%) children completed the 2-year study. After 2 years, the mean progression of myopia and of axial elongation in the placebo-treated control eyes was -1.20 ± 0.69 D and 0.38 ± 0.38 mm, respectively. In the atropine-treated eyes, myopia progression was only -0.28 ± 0.92 D, whereas the axial length remained essentially unchanged compared with baseline (-0.02 ± 0.35 mm). The differences in myopia progression and axial elongation between the 2 groups were -0.92 D (95% confidence interval, -1.10 to -0.77 D; $P < 0.001$) and 0.40 mm (95% confidence interval, 0.35 – 0.45 mm; $P < 0.001$), respectively. No serious adverse events related to atropine were reported.

Conclusions: Topical atropine was well tolerated and effective in slowing the progression of low and moderate myopia and ocular axial elongation in Asian children. *Ophthalmology* 2006;113:2285–2291 © 2006 by the American Academy of Ophthalmology.

Myopia is the most common eye disorder in humans, affecting up to 80% of young adults in some East Asian countries such as Singapore and Taiwan,^{1,2} and between 25% and 50% of older adults in the United States and Europe.^{3–5} Studies indicate that the incidence rates of myopia in East Asia and other parts of the world are rising.^{1,6,7} In addition to the decreased visual function from optical defocus, myopia is associated with an increased lifelong risk of irreversible blinding conditions such as myopic macular degeneration, retinal detachment, and glaucoma.^{8–10} The risk of these complications rises with increasing severity of myopia. The widespread prevalence and the rising rates, the

associated visual morbidity and consequent diminution of quality of life and social disability, and the substantial costs incurred for its correction make myopia a significant public health concern.

Although the cause of myopia has not been identified and the search for effective measures to prevent its onset remain elusive, an effective treatment that can halt or slow the progression of myopia, which typically occurs during childhood, would represent a significant advance in the management of myopia.

Recent clinical trials of a variety of interventions, such as progressive addition lenses and rigid gas-permeable contact lenses, have yielded disappointing results or positive results of marginal clinical significance.^{11–13} To date, only topical atropine, a nonselective muscarinic antagonist, has been demonstrated through relatively small randomized trials to have some clinical effect on the progression of myopia.^{14–16} However, these atropine studies suffered from various methodological shortcomings such as lack of regular and detailed follow-up examinations, absence of appropriate clinical controls, and absence of masking of participants and investigators. Additionally, the safety of prolonged atropine treatment was largely ignored. In a recent evidence-based review of myopia trials, the authors concluded that there was as yet insufficient evidence to support any interven-

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tions, including atropine, to prevent the progression of myopia in children.¹⁷ Consequently, we undertook a study designed to evaluate further whether pharmacologic intervention with topical atropine can reduce the progression of myopia in children over a 2-year period and to assess the safety of the treatment.

Patients and Methods

Study Design

The Atropine in the Treatment of Myopia study was a randomized, double-masked, placebo-controlled trial designed primarily to study whether topical atropine can prevent the progression of low and moderate myopia effectively and safely in children between 6 and 12 years of age. The study and protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Singapore Eye Research Institute Review Board. Recruitment of participants was from the general public, primary schools, and ophthalmology practices through the distribution of standardized brochures and letters describing the Atropine in the Treatment of Myopia study as well as public talks. The participants were children aged between 6 and 12 years with refractive error of spherical equivalent between -1.00 and -6.00 diopters (D) who met the eligibility criteria listed in Table 1. Every child gave assent, and written informed consent was obtained from the parents or legal guardians after thorough explanation of the nature and risks of the study before enrollment. Overall study performance and child safety were reviewed by an independent data and safety monitoring committee.

Randomization

Assignments to treatment were allocated with concealment according to a computer-generated randomization list after eligibility criteria were verified. The children had an equal probability of assignment to either the atropine group or the placebo-control group. Only 1 eye of each child was chosen for treatment. The chosen eye also was selected using the randomization process. A

child was considered to be enrolled in the study once the randomization assignment and study number were issued and the child received the assigned eye drops, which were handed out on the spot promptly after randomization.

Intervention

The eyes assigned for treatment were treated with either 1% atropine sulfate or vehicle eye drops once nightly for 2 years. Both the atropine and vehicle eye drops, the latter consisting of 0.5% hydroxypropyl methylcellulose and 1:10,000 benzalkonium chloride, were specially prepared by Alcon Laboratories (Puurs, Belgium). To aid and monitor compliance with the treatment regimen, each child was given a small calendar to tick off the days when the eye drops were used. In addition, all bottles were weighed before dispensing to, and after collection from, the parent or guardian at each visit. All children, regardless of treatment allocation, were prescribed photochromatic lenses (SOLA Transitions Single Vision Lenses, Lonsdale, Australia) for the correction of their refractive errors.

Masking

To minimize observational bias, neither the study participants nor the investigators responsible for measuring the study outcomes were aware of the intervention given. Several steps were taken to preserve and monitor masking. The atropine and placebo eye drops were packaged in identical bottles so that no one was able to identify the contents. Labels on the bottle had only the study number, the eye to be treated, and the expiration date. Parents or guardians were asked to seek advice from only the coordinating investigator regarding matters pertaining to their child's treatment and not to discuss any issues related to the study with the investigators measuring the study outcomes. To mask these study investigators, both pupils of every child were dilated fully and checked by the coordinating investigator before being seen by the study investigator.

Study Procedures

Cycloplegic autorefraction was used to assess refractive errors before enrollment as well as the progression of myopia. As with all data collection procedures, autorefraction was performed only by investigators who were trained and certified on study protocols. A Canon RK5 autorefractor-autokeratometer (Canon Inc. Ltd., Tochigiken, Japan) was used throughout the study to take 5 reliable readings, both before and after cycloplegia. All 5 readings had to be 0.25 D or less apart in both the spherical and cylindrical components before they were accepted. The cycloplegic regimen consisted of 1 drop of proparacaine hydrochloride (Alcaine, Alcon-Couvreur, Puurs, Belgium) followed by 3 drops of 1% cyclopentolate hydrochloride (Cyclogyl, Alcon-Couvreur), administered approximately 5 minutes apart. Cycloplegic autorefraction measurements were taken at least 30 minutes after instillation of the third drop of cyclopentolate. Cycloplegic subjective refraction also was performed primarily for the purpose of prescribing spectacles.

After cycloplegic refraction, ocular biometry (anterior chamber depth, lens thickness, vitreous chamber depth, and overall axial length) was measured by A-scan ultrasonography with the Nidek US-800 EchoScan (Nidek Co. Ltd., Tokyo, Japan). Six measurements were obtained for each eye. The axial length measurement was based on the average of the 6 values with a standard deviation of less than 0.12 mm. Measurements were obtained independently by the masked study investigators.

Table 1. Eligibility Criteria for the Atropine in the Treatment of Myopia Study

Children aged 6 to 12 years
Refractive error of spherical equivalent between -1.00 D to -6.00 D in each eye as measured by cycloplegic autorefraction
Anisometropia of spherical equivalent less than or equal to 1.50 D as measured by cycloplegic autorefraction
Astigmatism of -1.50 D or less as measured by cycloplegic autorefraction
Distance vision correctable to logMAR 0.2 or better in both eyes
Normal intraocular pressure of <21 mmHg
Normal ocular health other than myopia
In good general health with no history of cardiac or significant respiratory diseases
No allergy to atropine, cyclopentolate, proparacaine, and benzalkonium chloride
No previous or current use of contact lenses, bifocals, progressive addition lenses, or other forms of treatment (including atropine) for myopia
Normal binocular function and stereopsis
No amblyopia or manifest strabismus, including intermittent tropia
Willing and able to tolerate monocular cycloplegia and mydriasis

D = diopters; logMAR = logarithm of the minimum angle of resolution.

Sample Size and Power

Postulating that the eyes in the placebo-control group would progress by a mean of -1.00 D per year,¹⁵ and anticipating a projected effect difference of 20% (with standard deviation of 0.5 D) between the atropine versus the placebo-control group and allowing a 15% attrition rate, 400 children would be sufficient for a power of 90% with a 2-sided test of 5%.¹⁸

Outcome Measures

Efficacy. The primary outcome was progression of myopia, defined as the change in spherical equivalent refractive error (SER) relative to baseline. The baseline assessment took place 2 weeks after commencement of treatment, that is, the pretreatment visit. This was necessary because atropine induces an additional cycloplegic effect that could lower further the SER. As such, a run-in period allowed for stabilization of the cycloplegic effect, thus making comparison of SER between the baseline and subsequent visits more meaningful. The SER was calculated for each of the 5 cycloplegic autorefraction measurements per eye, and the mean of the 5 SER measures then was computed. Progression of myopia was analyzed by expressing refractive error as 3 components: M (spherical equivalent), J0 (dioptric power of a Jackson cross cylinder at axis 0), and J45 (dioptric power of a Jackson cross cylinder at axis 45), as determined by Fourier decomposition.¹⁹ The secondary outcome was change in axial length during follow-up relative to baseline measured by A-scan ultrasonography.

Safety. The primary safety outcome monitored was the occurrence of adverse events. The relationship of the event to the study medication was assessed by the investigators as none, unlikely, possible, probable, or definite. Other safety variables monitored included best-corrected visual acuity using the Early Treatment Diabetic Retinopathy Study chart, intraocular pressure (using non-contact tonometry), slit-lamp biomicroscopy, and fundus examination. In addition, multifocal electroretinography was used to assess the retinal function in a subset of children in each of the 2 groups. This has been previously described.²⁰

Statistical Analyses

All statistical analyses were based on the intention-to-treat principle and performed using SPSS software version 11.5 (SPSS Inc., Chicago, IL). The clinical baseline measurements and demographic characteristics between the 2 treatment groups were evaluated by 2-sample *t* tests or Mann-Whitney *U* tests for continuous variables, depending on satisfaction of the normality and homo-

geneity assumptions, and the association with categorical variables was assessed using a chi-square or Fisher exact test. The analysis for efficacy outcomes was based on evaluation of the magnitude of change in SER and axial length between follow-up and baseline using a paired *t* test or Wilcoxon signed rank test. A multiple regression model was used to evaluate the association between changes in SER and axial length, adjusting for relevant covariates. There were no interim analyses of efficacy.

Results

Between April 1999 and September 2000, 400 children were enrolled in the study, with equal randomization to the atropine group and to the placebo-control group. In each group of 200 children, 100 right eyes and 100 left eyes were assigned for treatment. At the initial pretreatment visit, there were no significant differences between the groups in mean age, gender, and racial distribution (Table 2). Likewise, there were no significant differences between the groups in terms of refractive and biometric characteristics. Mean myopia in the atropine-treated eyes was -3.36 ± 1.38 D, and in the placebo-treated eyes it was -3.58 ± 1.17 D. The mean myopia in the fellow untreated eyes of those children in the atropine group and placebo group was -3.40 ± 1.35 D and -3.55 ± 1.21 D, respectively. The atropine-treated eyes and placebo-treated eyes had identical mean axial lengths of 24.80 mm. This was comparable with the mean axial lengths of 24.81 mm and 24.76 mm in fellow untreated eyes in the atropine and placebo group, respectively.

Three hundred forty-six (86.5%) children completed the 2-year study. Of the 44 who did not, 10 were from the placebo-control group and 34 from the atropine group. The mean pretreatment refractive and biometric characteristics of the children who were lost to follow-up were similar to that of the entire treatment group to which they belonged. At 1 year, the mean progression of myopia in the placebo-treated eyes was -0.76 ± 0.44 D. In the atropine-treated eyes, however, there was a reduction of myopia by 0.03 ± 0.50 D ($P < 0.001$; Fig 1). Concomitantly, the mean axial elongation in the placebo-treated eyes was 0.20 ± 0.30 mm, but in the atropine-treated eyes there was a slight reduction in axial length by -0.14 ± 0.28 mm ($P < 0.001$; Fig 2).

At 2 years, the mean progression of myopia and axial elongation in the placebo-treated eyes was -1.20 ± 0.69 D and 0.38 ± 0.38 mm, respectively. In the atropine-treated eyes, myopia progression was only -0.28 ± 0.92 D, whereas the axial length remained essentially unchanged compared with baseline (-0.02 ± 0.35 mm). The differences in myopia progression and axial elongation

Table 2. Pretreatment Characteristics of the Atropine in the Treatment of Myopia Study Patients

Characteristic	Placebo Group (n = 200)		Atropine Group (n = 200)	
	Treated Eye (n = 200)	Untreated Eye (n = 200)	Treated Eye (n = 200)	Untreated Eye (n = 200)
Mean age (yrs)		9.2		9.2
Male (%)		52.5		57.5
Chinese race (%)		93.0		95.0
Indian race (%)		5.0		3.0
Right eye	100	100	100	100
Left eye	100	100	100	100
Refractive error (D)	-3.58 ± 1.17	-3.55 ± 1.21	-3.36 ± 1.38	-3.40 ± 1.35
Axial length (mm)	24.80 ± 0.84	24.76 ± 0.86	24.80 ± 0.83	24.81 ± 0.84

D = diopters.

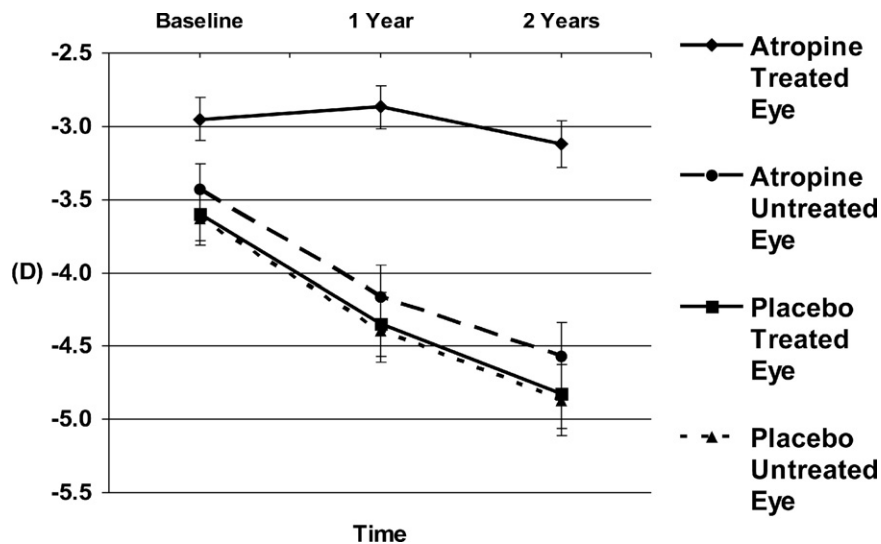


Figure 1. Graph showing mean spherical equivalent change from baseline. D = diopters.

between the 2 groups were -0.92 D (95% confidence interval, -1.10 to -0.77 D; $P < 0.001$) and 0.40 mm (95% confidence interval, 0.35 – 0.45 mm; $P < 0.001$), respectively. The changes in refractive error and axial length in the nontreated eyes of children in both the atropine group and placebo-control group paralleled that of the placebo-treated eyes (Figs 1, 2).

At the end of the 2-year treatment period, almost two thirds (65.7%) of atropine-treated eyes had progressed less than -0.50 D, whereas 13.9% had progressed more than -1.00 D. In contrast, 16.1% and 63.9% of placebo-treated eyes had progressed less than -0.50 D and more than -1.00 D, respectively. Figure 3 summarizes the frequency of distribution of the various rates of progression of myopia after 1 and 2 years.

No serious adverse events related to atropine were reported. Reasons for withdrawal were: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%), and others (0.5%). There was no deterioration in best-corrected visual acuity. Similarly, intraocular pressure changes were within 5.5 mmHg, with no absolute read-

ings of more than 21 mmHg. No lenticular, optic disc, or macular changes were reported.

Discussion

Key Findings

The results of our study indicate that a once-nightly dose of 1% atropine eye drops achieved a reduction in progression of low and moderate childhood myopia compared with placebo treatment that is both statistically and clinically significant. Over a 2-year period, atropine treatment achieved approximately a 77% reduction in mean progression of myopia compared with placebo treatment. This finding is strongly corroborated by the concomitant findings in ocular biometry, where there was essentially no change in mean axial length in the atropine-treated eyes compared with a

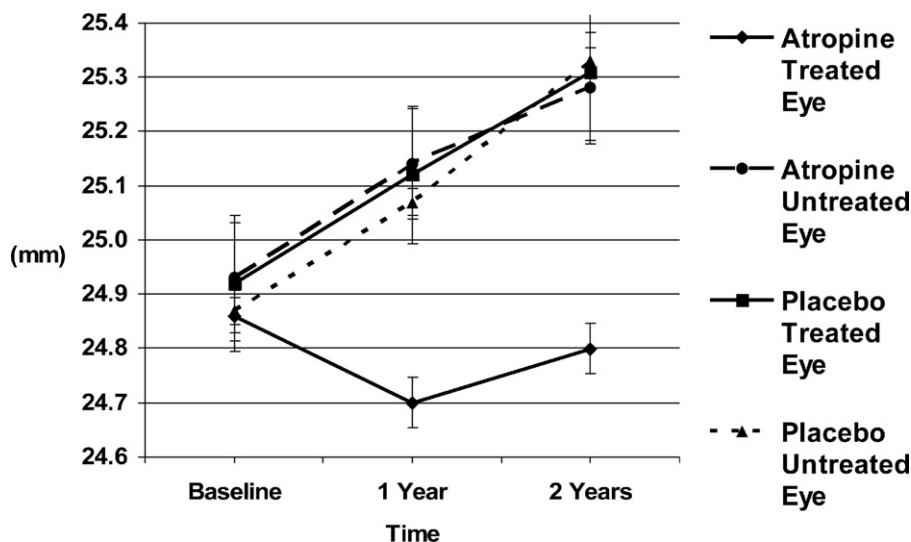


Figure 2. Graph showing mean axial length change from baseline.

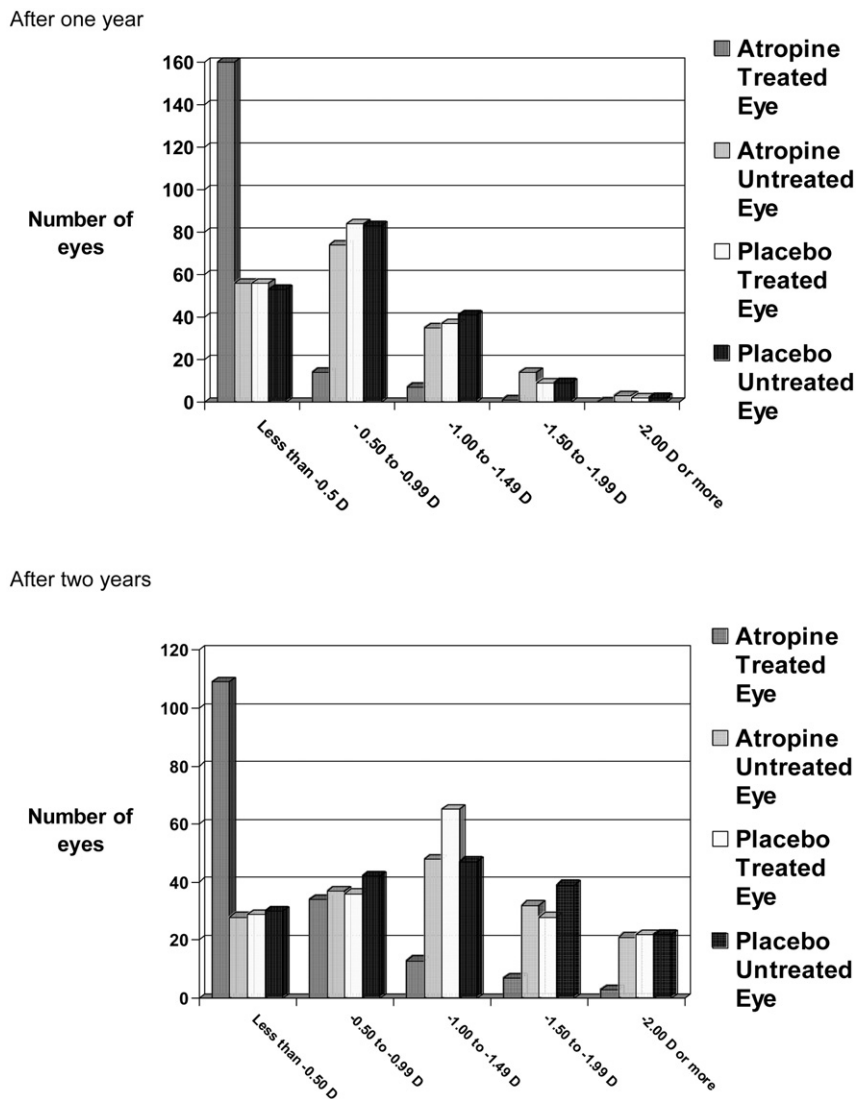


Figure 3. Graphs showing distribution of progression of myopia after 1 and 2 years. D = diopters.

mean increase of approximately 0.38 mm in the placebo-treated eyes and the untreated fellow eyes in both atropine and placebo groups. Our study also showed that atropine treatment was well tolerated generally and that no serious adverse effects were observed. This is supported by our electrophysiological assessment of a subset of study patients in which multifocal electroretinography results indicated that long-term atropine use had little effect on retinal function, with the retina-on response affected more than the retina-off response.²⁰

Possible Mechanisms

Much like the cause of myopia, the mechanism of action of atropine in retarding progression of myopia and axial elongation is not understood clearly. Initially, its use was based on the putative role of excessive accommodation in causing myopia.²¹ However, atropine also is effective in preventing myopia in animal models, where myopic eye growth can

develop even after abolition of accommodation has been achieved by destruction of the Edinger-Westphal nucleus or after optic nerve section.²² These results suggest alternative mechanisms and sites of action for atropine at, for example, either the retina or the sclera.

Comparison with Other Studies

The first report of atropine treatment for myopia was by Wells in the nineteenth century.²³ Since then, a number of other studies also have evaluated the efficacy of atropine in preventing the progression of childhood myopia. However, a recent literature search to identify articles for inclusion in an evidence-based review revealed the scarcity of well-designed randomized controlled trials of atropine treatment.¹⁷ A range of concentrations (0.1%–1%) of atropine eye drops was evaluated in 3 separate, relatively small trials involving schoolchildren in Taiwan, and the rate of progression of myopia in the atropine group was significantly lower

compared with that of the control group. In one of these studies, the mean progression of myopia in eyes treated with 1% atropine was -0.22 D, versus -0.91 D in the eyes treated with normal saline.¹⁴ Almost similar results were obtained in 2 subsequent studies of 0.5% atropine, where the progression rate of myopia in eyes treated with atropine was -0.28 D per year and -0.93 D per year in eyes not receiving treatment.^{15,16} The magnitude of efficacy (0.79 D) seen in the first 12 months of the present study is just slightly larger than that in previously published studies.

Previous assessment of safety of atropine treatment was restricted to the recording of known side effects of atropine, but the reported rates of complications or adverse events were highly variable. For example, in the study by Yen et al,¹⁴ every participant receiving 1% atropine had photophobia, whereas another study also using 1% atropine reported an incidence of photophobia of only 18%.²⁴ In our study, glare and photophobia were greatly minimized with the use of photochromatic lenses.

Strengths and Limitations

In addition to the merits of a randomized, double-masked, placebo-controlled trial design, a strength of our study is the presence of several controls: the untreated fellow eye of children in the atropine group, the placebo-treated eyes, and the untreated eyes of children in the control group. Further strengths include the use of cycloplegic autorefraction to assess primary efficacy outcomes. More significantly, we also assessed a secondary outcome by performing ocular biometry in all participants. The other strengths of the study are a larger sample size and higher retention rate compared with previous studies.

A weakness of any randomized study with atropine eye drops, including our study, is the potential for unmasking of the participants attributable to the atropine-induced mydriasis and cycloplegia. In the atropine group, children who covered their untreated eye noted the blurring of near vision in the atropine-treated eye, whereas astute parents might have noted the anisocoria, although the dark brown irises of our study population make the cursory identification of anisocoria somewhat more difficult. Investigators responsible for assessing both efficacy outcomes, however, always remained masked because they performed the refraction and biometry only after the child had received the bilateral cyclopentolate regimen, which, like atropine, induces mydriasis and cycloplegia.

The treatment regimen adopted in the study has 2 clinical side effects, however, that may be ameliorated in a clinical context. First, long-term unioocular treatment of myopia is impractical and unsatisfactory because the myopia in the untreated fellow eye may continue to progress, thus resulting in anisometropia and aniseikonia. Moreover, the risk of myopic complications in the untreated eye remains undiminished. In the clinical situation, bilateral treatment will obviate this problem. However, the primary reason for adopting a unioocular treatment design in this study was because bilateral atropine treatment would result in bilateral blurred near vision with functional consequences such as difficulty with near work activity, that is, reading, writing,

and so forth. To overcome this problem, participants would have to use either bifocal or progressive addition lenses. This would mean introducing a potential treatment confounder into the study because progressive addition lenses were, at that time, being evaluated as an intervention for slowing myopia progression.^{11,12}

Second, treatment with an atropine concentration of 1% produces some unwanted side effects, such as glare and photophobia because of pupillary dilatation and blurring of near vision resulting from induced cycloplegia. In view of the limitations and problems associated with unioocular 1% atropine treatment, further dose-determining studies are needed to identify an optimal atropine regimen for bilateral treatment.

The duration of atropine treatment in this study was only 2 years, and therefore we could not assess whether atropine will continue to have an effect on progression of myopia beyond 2 years of treatment. This information on the durability of atropine is important because the period of myopia progression and ocular axial growth commonly seen in Asian children extends beyond 2 years. Additionally, this paper has not addressed the refractive changes after cessation of atropine treatment. It is not known if the slower rate of myopia progression and axial elongation will be maintained or if there will be a rebound phenomenon that would negate the positive treatment effects.

To this end, we have embarked on a new randomized clinical trial to assess the efficacy, safety, and functional impact of 3 different atropine concentrations for the bilateral treatment of childhood myopia. This study will be longer than the present study and also will evaluate the changes in progression of myopia after cessation of atropine treatment.

In summary, the Atropine in the Treatment of Myopia study provides strong evidence that the progression of low and moderate childhood myopia can be slowed pharmacologically. Further research is required to elucidate the mechanism of action, to evaluate the safety and efficacy of bilateral atropine treatment beyond 2 years, and to identify characteristics of children who will derive maximum benefit from treatment.

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