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Age Effect on Treatment Responses to 0.05%, 0.025%, and 0.01% Atropine

Low-Concentration Atropine for Myopia Progression Study

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Purpose: To investigate the effect of age at treatment and other factors on treatment response to atropine in the Low-Concentration Atropine for Myopia Progression (LAMP) Study.

Design: Secondary analysis from a randomized trial.

Participants: Three hundred fifty children aged 4 to 12 years who originally were assigned to receive 0.05%, 0.025%, or 0.01% atropine or placebo once daily, and who completed 2 years of the LAMP Study, were included. In the second year, the placebo group was switched to the 0.05% atropine group.

Methods: Potential predictive factors for change in spherical equivalent (SE) and axial length (AL) over 2 years were evaluated by generalized estimating equations in each treatment group. Evaluated factors included age at treatment, gender, baseline refraction, parental myopia, time outdoors, diopter hours of near work, and treatment compliance. Estimated mean values and 95% confidence intervals (CIs) of change in SE and AL over 2 years also were generated.

Main Outcome Measures: Factors associated with SE change and AL change over 2 years were the primary outcome measures. Associated factors during the first year were secondary outcome measures.

Results: In 0.05%, 0.025%, and 0.01% atropine groups, younger age was the only factor associated with SE progression (coefficient of 0.14, 0.15, and 0.20, respectively) and AL elongation (coefficient of −0.10, −0.11, and −0.12, respectively) over 2 years; the younger the age, the poorer the response. At each year of age from 4 to 12 years across the treatment groups, higher-concentration atropine showed a better treatment response, following a concentration-dependent effect (P_{trend} <0.05 for each age group). In addition, the mean SE progression in 6-year-old children receiving 0.05% atropine (−0.90 diopter [D]; 95% CI, −0.99 to −0.82) was similar to that of 8-year-old children receiving 0.025% atropine (−0.89 D; 95% CI, −0.94 to −0.83) and 10-year-old children receiving 0.01% atropine (−0.92 D; 95% CI, −0.99 to −0.85). All concentrations were well tolerated in all age groups.

Conclusions: Younger age is associated with poor treatment response to low-concentration atropine at 0.05%, 0.025%, and 0.01%. Among concentrations studied, younger children required the highest 0.05% concentration to achieve similar reduction in myopic progression as older children receiving lower concentrations. *Ophthalmology 2021;■:1−8 © 2021 by the American Academy of Ophthalmology*

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Myopia is a global public health threat that has become increasingly prevalent in recent decades, particularly in East Asia.[1−3] Approximately half of the world's population is predicted to be myopic by 2050, with as much as 10% being highly myopic,[2] which is defined as exhibiting a refractive error measuring less than −6 diopters (D). Being associated with excessive axial elongation, which in turn leads to sight-threatening complications,[4] high myopia casts both a heavy public health burden and an economic burden on society.[5]

Low-concentration atropine eye drops are an emerging therapy for myopia control in children that has demonstrated good efficacy.[6−16] The Low-Concentration Atropine for Myopia Progression (LAMP) Study revealed a concentration-dependent response for low-concentration atropine at 0.05%, 0.025%, and 0.01%, which confer respective reductions of 67%, 43%, and 27% on spherical equivalent (SE) progression compared with the placebo group over 1 year.[7] Nevertheless, treatment responses vary widely, because a proportion of children still progress quickly, despite receiving treatment.[7,17] In particular, the Atropine for the Treatment of Myopia 1 (ATOM1) Study suggested that those with a greater inherent risk of myopia progression tend to respond poorly to 1% atropine.[17]

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Notably, associated factors for poor responses to low-concentration atropine remain to be clarified. Such factors are important for serving as references for concentration adjustment; otherwise, switching to alternative or combined therapies may be necessary.

Because younger age was one of the main factors associated with faster myopic progression, we hypothesized that age at treatment influences treatment outcomes.[18,19] In this study, we aimed to assess the effect of age at treatment and other factors—including gender, baseline refraction, parental myopia, outdoor time, near work, and treatment compliance—on treatment responses to 0.05%, 0.025%, 0.01% atropine in the 2-year LAMP Study.

Methods

Participants

The current study is a secondary analysis of the 2-year results from the LAMP Study,[7] a randomized, double-masked controlled trial of children 4 to 12 years of age with a refractive error of at least −1.0 D in both eyes, astigmatism of less than 2.5 D, and a documented myopic progression of at least 0.5 D in the past year. The LAMP Study participants with systemic or ocular diseases, previous experience with myopia control therapy (such as atropine, pirenzepine, orthokeratology lenses, or other optical methods), or a history of allergies to atropine (e.g., cardiac or respiratory illness) were excluded from the current study.[7] In phase 1 (the first year), participants were randomized into groups that received 0.05%, 0.025%, or 0.01% atropine or placebo eye drops once nightly in both eyes, with an allocation ratio of 1:1:1:1 stratified by age (4−6 years, 7−9 years, and 10−12 years) and gender.[7] In phase 2 (the second year), all children in the 0.05%, 0.025%, and 0.01% atropine groups continued to receive the same concentration throughout the second year, whereas the placebo group was switched to receiving 0.05% atropine from the beginning of the second year until the end of the phase (referred to as the "switch-over group" during this period).[8]

The study conformed to the tenets of the Declaration of Helsinki and was approved by the ethics committee of Hong Kong Eye Hospital, with all procedures conducted in accordance with the former. Written informed consent was obtained from parents or guardians and verbal consent was obtained from the study patients. The study is registered with the Chinese Clinical Trial Registry (identifier, ChiCTR-TRC-13004032) and the Clinical Trials Registry of the Centre for Clinical Research and Biostatistics, The Chinese University of Hong Kong (identifier, CUHK_CCT00383).

Ophthalmic Parameters and Questionnaires

The refractive status for each child before and after cycloplegia was measured using an autorefractor (Nidek ARK-510A; Nidek) on at least 2 cycles of eye drops. Five readings, all less than 0.25 D apart, were obtained and averaged. Axial length (AL) was measured using a Zeiss IOL Master unit (Carl Zeiss Meditec, Inc). Before complete cycloplegia, accommodation amplitude was calculated as the inverse of the near point of accommodation, as measured by the Royal Air Force near point rule (Harlow, Essex, United Kingdom), by moving the target inward until the N5 print became slightly blurred and then back outward until it became clear again. Both photopic and mesopic pupil sizes were measured using the OPD-Scan III (Nidek). Noncycloplegic refraction and AL were measured for the parents of participating children to obtain parental myopia data.

A validated questionnaire to collect information including time spent on outdoor activities and near works, as well as the Chinese version of the 25-item National Eye Institute Visual Function Questionnaire,[7] were administered. The former category includes time spent on sports and leisure, whereas the latter includes time spent on homework, cell phones, computers, video games, and television. A formula for calculating diopter-hours was defined consequently as: (homework hours + reading hours + cell phone hours) × 3 + (video game or home computer work hours) × 2 + (television hours) × 1. The average number of daily hours then was calculated using the formula: [(weekday daytime hours) × 5 + (weekend daytime hours) × 2] / 7.[7] Treatment compliance with trial medication was recorded according to the mean number of days per week that participant used the medication as reported by their parents. Participants were offered photochromic glasses if they experienced glare or if their parents worried about excessive light exposure. During each visit, both participants and parents were given opportunities to report any side effects experienced by the participant.

Definitions

Spherical equivalent was defined as spherical diopters plus one-half of the cylindrical diopters. Myopia, moderate myopia, and high myopia were defined as SE ≤−0.5 D, ≤−3.0 D, and ≤−6.0 D, respectively. Parental myopia was divided into 2 subgroups: (1) none or 1 parent with moderate or high myopia and (2) both parents with moderate or high myopia.

Statistical Analysis

The following factors were evaluated: (1) age at treatment, (2) gender, (3) baseline SE, (4) baseline outdoor time, (5) baseline near work time, (6) parental myopia level, and (7) treatment compliance. Factors associated with SE change and AL change over 2 years were the primary outcome measures. The associated factors during the first year were secondary outcome measures. Generalized estimating equations, with robust standard errors for longitudinal data analysis, were used to adjust the correlation between both eyes.[20] Generalized estimating equations with all factors were performed to identify significant predictors for treatment response in each of the treatment groups separately. Given the multiple comparisons, P values less than 0.01 were considered statistically significant. The interaction between treatment concentrations and age also was examined. Across the different age cohorts, estimated mean values and 95% confidence intervals (CIs) for both myopia progression and axial elongation over 2 years or 1 year were generated for each treatment group. P values for the trend of each age group were generated by using treatment groups as ordinal data (3 = 0.05% atropine, 2 = 0.025% atropine, and 1 = 0.01% atropine), and P values for trend of less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS Statistics software version 24.0 (IBM Corp) and the program R version 4.0.3 (R Foundation for Statistical Computing).

Results

Factors Associated with Treatment Outcome in the 0.05%, 0.025%, and 0.01% Atropine Groups

Of the 438 children 4 to 12 years of age initially recruited for the study, a total of 383 (87%) completed phase 1, whereas 350 (79.9%) completed follow-up by the end of phase 2 (Table S1, available at www.aaojournal.org). Throughout the 2 years, younger age was the only predictive factor associated with faster

SE progression in any of the 3 atropine groups (coefficient of 0.14, 0.15, and 0.20, respectively; Fig 1A; Table 1). For each year of younger age, mean change of SE at 2 years was 0.14 D larger (i.e., more myopic) in the 0.05% group, 0.15 D larger in the 0.025% atropine group, and 0.20 D larger in the 0.01% atropine group (Table 1). Age also was the only predictive factor for AL elongation (coefficient of −0.10, −0.11, and −0.12, respectively; Fig 1B; Table 2) among the 0.05%, 0.025%, and 0.01% atropine groups. No significant interaction effect (age × treatment group) was detected ($P = 0.53$), indicating that age and treatment have an additive effect on myopic progression (Fig 1A; Figs S1-S3, available at www.aaojournal.org).

During the first year, age also was the only factor associated with both SE progression and AL elongation among the 0.05%, 0.025%, and 0.01% atropine groups (Tables S2 and S3, available at www.aaojournal.org). In the placebo group, gender was associated with SE progression along with age, suggesting that both factors influence natural myopic progression (Fig S1; Table S2).

Age-Specific Myopia Progression in the 0.05%, 0.025%, and 0.01% Atropine Groups

Tables 3 and 4 present the estimated means for SE progression and AL elongation, respectively, across all active treatment groups over 2 years. At each year of age from 4 to 12 years, higher-concentration atropine showed a better treatment response, demonstrating a concentration-dependent effect ($P < 0.05$ for trend for each age group; Tables 3 and 4). Moreover, an age-dependent effect was observed in each treatment group: the younger the age, the poorer the treatment efficacy (Fig 1; Table 3).

The estimated mean for 2-year SE progression among 6-year-olds in the 0.05% atropine group was −0.90 D (95% CI, −0.99 to −0.82 D), which was similar to that for 8-year-olds in the 0.025% atropine group (−0.89 D; 95% CI, −0.94 to −0.83 D) and 10-year-olds in the 0.01% atropine group (−0.92 D; 95% CI, −0.99 to −0.85 D; Fig 1A; Table 3). Such figures indicate the similar treatment effect from 0.01% atropine to 0.025% atropine and from 0.025% atropine to 0.05% atropine with a 2-year age difference within the age range of 4 to 12 years (Table 3). A similar pattern was observed in the estimated means for 2-year AL elongation for all 1-year age cohorts from 4 to 12 years across all concentrations (Fig 1B; Table 4), although the age effect is smaller at approximately 1 year. Specifically, a mean 2-year AL elongation of 0.65 mm was observed for 6-year-olds in the 0.05% atropine group (95% CI, 0.61−0.69), which was similar to 0.63 mm for 7-year-olds in the 0.025% atropine group (95% CI, 0.59−0.68) and 0.65 mm for 8-year-olds in the 0.01% atropine group (95% CI, 0.63−0.68; Table 4). Including the placebo group results during phase 1, a similar pattern also was observed in SE progression (Table S4, available at www.aaojournal.org) and AL elongation (Table S5, available at www.aaojournal.org) for the first year.

Side Effects and Vision-Related Quality of Life in Various Age Groups

In terms of side effects, the mean accommodation amplitude decreased with age, whereas the mean changes in photopic pupil size were similar across all ages for each treatment group (Tables S6 and S7, available at www.aaojournal.org). The rates of both uses of photochromic glasses and photophobia were similar across all ages in all treatment groups (Tables S8 and S9, available at www.aaojournal.org). Finally, vision-related quality of life also was similar across all ages in all treatment groups (Table S10, available at www.aaojournal.org).

Discussion

The results of this double-blind randomized control trial show a clear age-dependent effect on treatment responses to low-concentration atropine. Younger age, within the range of 4 to 12 years in our trial, was the only risk factor for poor response among the 0.05%, 0.025%, and 0.01% atropine groups. In each of the age groups, treatment response followed a concentration-dependent response: the higher the concentration, the better the response. The results suggest that among the concentrations studied (0.05%, 0.025%, and 0.01%), younger children require a higher concentration of 0.05% to achieve a similar treatment efficacy as that for older children. Given that all concentrations were tolerated well by children of all ages from 4 to 12 years, low-concentration atropine 0.05% should be administered to younger children for better myopia control. Young age at

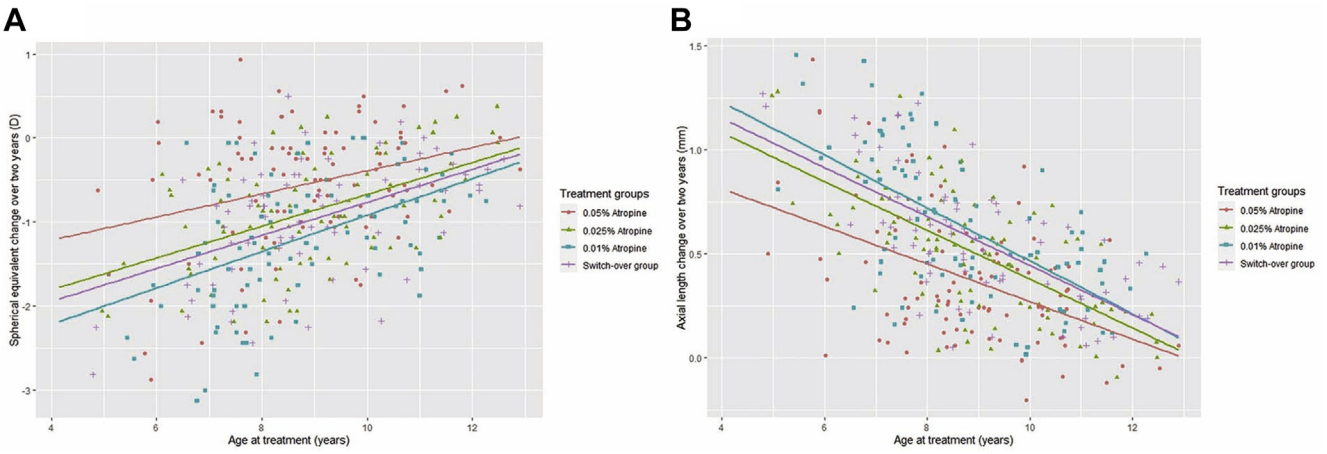

Figure 1. A, Scatterplot showing change in spherical equivalent (SE) over 2 years with age in the 0.05%, 0.025%, and 0.01% atropine groups and the switch-over group. **B**, Scatterplot showing change in axial length over 2 years with age in the 0.05%, 0.025%, and 0.01% atropine groups and the switch-over group (the placebo group during the first year, which was switched over to the 0.05% atropine group at the beginning of the second year). Scatterplot with line of best fit illustrating the relationship between age and myopia progression or axial elongation for each treatment group. D = diopter.

Table 1. Factors Regarding Change in Spherical Equivalent over 2 Years in Each Treatment Group

	0.05% Atropine (n = 93)			0.025% Atropine (n = 86)			0.01% Atropine (n = 91)		
	β (Adjusted)	Standard Error	Adjusted P Value	β (Adjusted)	Standard Error	Adjusted P Value	β (Adjusted)	Standard Error	Adjusted P Value
Age (yrs)	0.14	0.05	0.01*	0.15	0.04	<0.001*	0.20	0.05	<0.001*
Gender, no. (%)									
Female	0			0			0		
Male	−0.01	0.16	0.97	−0.02	0.14	0.91	0.23	0.15	0.14
Baseline SE (D)	0.05	0.05	0.32	0.07	0.04	0.07	0.01	0.04	0.83
Outdoor activity (hrs/day)	0.02	0.08	0.79	−0.03	0.07	0.63	−0.01	0.08	0.91
Near work (D hrs/day)	0.01	0.02	0.60	0.03	0.02	0.06	0.03	0.02	0.10
Parental myopia status, no. (%)									
None or one parent with moderate or high myopia	0			0			0		
Both parents with moderate or high myopia	−0.24	0.16	0.13	−0.10	0.14	0.47	−0.10	0.16	0.52
Treatment compliance (days/wk)	0.09	0.12	0.45	0.10	0.08	0.20	−0.03	0.09	0.72

D = diopters; SE = spherical equivalent.
Generalized estimating equations were used to adjust the correlation between eyes.
*Significant level set at $P < 0.01$.

onset is associated with high myopia development.[21] Given that children have the most years of myopic progression ahead of them to drive them into the highly myopic group, treatment of these children should be more aggressive to reduce the burden of high myopia.

Variation in the associations between risk factors and treatment responses has been observed in other studies. In the ATOM1 study, among 182 myopic children who had received 1% atropine for 1 year, 22 children (12.1%) with poor treatment responses were found to be younger, to have 2 myopic parents, and to have higher baseline myopia.[17] However, in another study of lower atropine concentrations from Taiwan conducted with 97 children in treatment groups that were administered 0.05% to 0.1% atropine and 20 children in the control group, higher baseline SE was associated with poor response, although age was not.[22] A recent study of 133 children receiving 0.01% atropine suggested that lower baseline myopia and maternal myopia were factors associated with poor response.[23] Regarding the current study, the randomized, controlled design enabled the direct comparison of risk factors associated with treatment responses across all treatment groups; our results thus ascertained that age is the main factor associated with treatment responses to low concentration atropine. Our results affirmed previous observations made in the ATOM1 study suggesting that younger patients tend to respond poorly to treatment because of greater inherent risk of myopia progression.[17] In addition, the first-year results of our trial suggested that younger age and female gender are risk factors for natural

Table 2. Factors Regarding Axial Length Elongation (in Millimeters) over 2 Years in Each Treatment Group

	0.05% Atropine (n = 93)			0.025% Atropine (n = 86)			0.01% Atropine (n = 91)		
	β (Adjusted)	Standard Error	Adjusted P Value	β (Adjusted)	Standard Error	Adjusted P Value	β (Adjusted)	Standard Error	Adjusted P Value
Age (yrs)	−0.10	0.02	<0.001*	−0.11	0.02	<0.001*	−0.12	0.02	<0.001*
Gender, no. (%)									
Female	0			0			0		
Male	−0.01	0.06	0.93	0.00	0.06	0.99	−0.02	0.07	0.72
Baseline SE (D)	−0.02	0.02	0.30	−0.03	0.02	0.05	−0.01	0.02	0.51
Outdoor activity (hrs/day)	−0.01	0.03	0.72	0.02	0.03	0.51	0.01	0.04	0.79
Near work (D hrs/day)	−0.004	0.01	0.61	−0.008	0.01	0.29	−0.009	0.01	0.31
Parental myopia status, no. (%)									
None or one parent with moderate or high myopia	0			0			0		
Both parents with moderate or high myopia	0.07	0.06	0.24	0.04	0.06	0.44	0.05	0.07	0.48
Treatment compliance (days/wk)	−0.04	0.05	0.43	−0.04	0.03	0.23	0.00	0.04	0.99

D = diopter; SE = spherical equivalent.
Generalized estimating equations were used to adjust the correlation between eyes.
*Significant level set at $P < 0.01$.

Table 3. Estimated Mean of Myopia Progression over 2 Years in Different Ages of Active Treatment Groups

Age (yrs)	0.05% Atropine		0.025% Atropine		0.01% Atropine		P Value for Trend*
	No. of Patients	*Estimated Mean (95% Confidence Interval)*	*No. of Patients*	*Estimated Mean (95% Confidence Interval)*	*No. of Patients*	*Estimated Mean (95% Confidence Interval)*	
4	1	−1.20 (NA)	1	−1.60 (NA)	NA	NA	0.03†
5	4	−1.12 (−1.19 to −1.04)	2	−1.44 (−1.53 to −1.36)	4	−1.75 (−1.98 to −1.52)	
6	6	−0.90 (−0.99 to −0.82)	7	−1.23 (−1.34 to −1.12)	7	−1.54 (−1.72 to −1.36)	<0.001
7	17	−0.79 (−0.87 to −0.71)	17	−1.04 (−1.15 to −0.94)	20	−1.40 (−1.46 to −1.34)	<0.001
8	24	−0.57 (−0.63 to −0.51)	21	−0.89 (−0.94 to −0.83)	22	−1.24 (−1.31 to −1.18)	<0.001
9	18	−0.45 (−0.52 to −0.39)	15	−0.81 (−0.87 to −0.75)	12	−1.05 (−1.17 to −0.93)	<0.001
10	16	−0.27 (−0.35 to −0.21)	12	−0.61 (−0.68 to −0.54)	13	−0.92 (−0.99 to −0.85)	<0.001
11	5	−0.07 (−0.17 to 0.02)	8	−0.40 (−0.49 to −0.32)	12	−0.80 (−0.91 to −0.69)	0.01‡
12	2	0.07 (−0.24 to 0.39)	3	−0.24 (−0.38 to −0.10)	1	−0.55 (NA)	

NA = not available (mean or standard deviation is not available because of the insufficient sample sizes).
Estimated mean was generated in generalized estimating equations by adjusted age, gender, baseline refraction, outdoor time, near work activities, parental myopia, treatment compliance, and treatment groups.
*Significant level set at $P < 0.05$. *P* values for trend of each age group were generated by using treatment groups as ordinal data (3 = 0.05% atropine, 2 = 0.025% atropine, and 1 = 0.01% atropine).
†Ages 4 and 5 were combined to generate the *P* value for trend because of insufficient sample sizes.
‡Ages 11 and 12 were combined to generate the *P* value for trend because of insufficient sample sizes.

myopia progression, with 0.17 D per 1 year younger and 0.18 D larger (i.e., more myopic) in female patients, respectively; however, no effect of gender was found in the atropine groups. This may be attributed to the smaller risk effect of gender in myopia progression compared with that of age.

An important finding of this study is the age-dependent effect in each treatment group, along with a concentration-dependent response in each age group. Although both age and concentration level of atropine are significant factors for SE progression and AL elongation, no evidence was found of interaction between them, for example, their combined effects working additively. In the analysis of estimated means for 2-year SE progression and AL elongation, we found that younger children required a higher concentration to achieve a similar efficacy as that for older children treated using lower concentrations. For example, the myopia progression of 10-year-olds in the 0.01% group was similar to that of the 8-year-olds in the 0.025% group and of the 6-year-olds in the 0.05% group over 2 years. These findings support the notion that younger children require higher-concentration atropine to yield greater treatment effects.

Our study also observed that younger children generally have a greater accommodation amplitude ($P = 0.02$),[24] and therefore have similar, if not better, tolerance against accommodation loss because of low-concentration atropine treatment (Table S6). In particular, children 4 years of age in

Table 4. Estimated Mean of Axial Length Elongation over 2 Years in Different Ages of Active Treatment Groups

Age (yrs)	0.05% Atropine		0.025% Atropine		0.01% Atropine		P Value for Trend*
	No. of Patients	*Estimated Mean (95% Confidence Interval)*	*No. of Patients*	*Estimated Mean (95% Confidence Interval)*	*No. of Patients*	*Estimated Mean (95% Confidence Interval)*	
4	1	0.79 (NA)	1	0.95 (NA)	NA	NA	0.03†
5	4	0.72 (0.69–0.76)	2	0.87 (0.80–0.95)	4	0.98 (0.90–1.07)	
6	6	0.65 (0.61–0.69)	7	0.75 (0.71–0.79)	7	0.86 (0.79–0.93)	0.002
7	17	0.53 (0.50–0.56)	17	0.63 (0.59–0.68)	20	0.76 (0.74–0.79)	<0.001
8	24	0.41 (0.39–0.43)	21	0.53 (0.51–0.55)	22	0.65 (0.63–0.68)	<0.001
9	18	0.32 (0.29–0.35)	15	0.47 (0.44–0.50)	12	0.54 (0.48–0.61)	<0.001
10	16	0.21 (0.17–0.24)	12	0.34 (0.31–0.37)	13	0.48 (0.45–0.51)	<0.001
11	5	0.09 (0.08–0.10)	8	0.22 (0.18–0.25)	12	0.36 (0.31–0.40)	0.048‡
12	2	−0.01 (−0.15 to 0.13)	3	0.13 (0.07–0.19)	1	0.22 (NA)	

NA = not available (mean or standard deviation) is not available because of insufficient sample sizes.
Estimated mean was generated in generalized estimating equations by adjusted age, gender, baseline refraction, outdoor time, near work activities, parental myopia, treatment compliance, and treatment groups.
*Significant level set at $P < 0.05$. *P* values for trend of each age group were generated by using treatment groups as ordinal data (3 = 0.05% atropine, 2 = 0.025% atropine, and 1 = 0.01% atropine).
†Ages 4 and 5 were combined to generate the *P* value for trend because of insufficient sample sizes.
‡Ages 11 and 12 were combined to generate the *P* value for trend because of insufficient sample sizes.

the 0.05% atropine group exhibited the greatest increase of 1.28 mm in photopic pupil size (Table S7). Nevertheless, because this increase in photopic pupil size is still within the cutoff of 3 mm, 0.05% atropine remains tolerable for children 4 to 12 years of age.[25,26] This trend in tolerance also is supported by similar rates for photophobia and use of photochromic glasses, in addition to similar scores on the Chinese version of the 25-item National Eye Institute Visual Function Questionnaire for all ages represented in our study.

Our results have important implications for the management strategies of low-concentration atropine therapy for myopia control. A stepwise increase in atropine concentration, starting from 0.01%, currently is recommended if treatment response is suboptimal.[27] Yet this study found that a higher concentration (i.e., 0.05%) should be administered as a starting dose for younger children, given that they have a greater risk of myopia progression. When 0.05% atropine is used as such, the age difference at which a similar efficacy can be achieved using other concentrations amounts to 2 years compared with 0.025% atropine, 4 years compared with 0.01% atropine, and 6 years compared with placebo within the age range of 4 to 12 years. Moreover, our data also highlighted that no other factors are associated with treatment response, regardless of the child's baseline refraction errors or parental myopia status. This is of clinical importance, because it implies that when considering the atropine concentration for myopia control in children, only the age of the child, not baseline SE or parental myopia, should be considered.

Rather than determine the natural risk factors for myopia progression among children in the general population, this study was designed to investigate factors associated with atropine treatment responses among children receiving treatment. The randomized trial design of our study uniquely enabled the evaluation of risk factors for individual treatment groups, and the comparison among groups allowed us to observe the effects of various atropine concentrations on the risk factors associated with treatment response. Our study included an extended age range, to as young as age 4 years, compared with previous studies of atropine for myopia,[10,28] allowing evaluation of treatment effect on young children whose progression rates are faster. Nevertheless, one limitation of this study is that factors such as reading time and outdoor time were obtained through validated questionnaires, which are prone to recall bias; measurements using wearable sensors could be more precise. In addition, treatment compliance is a postbaseline factor that could have been affected by the atropine concentration group and could have impacted change in SE directly. Nevertheless, treatment compliance was similar among all treatment groups in our study. Furthermore, prestudy myopia progression, which also could be predictive, was not included in our evaluation. Another limitation is the switch of the placebo group over to 0.05% atropine treatment during the second year, therefore eliminating the opportunity to continue comparisons with a placebo group. Nevertheless, the 2-year results remain valuable because they ascertained that age is the only risk factor associated with treatment response in the 0.05%, 0.025%, and 0.01% atropine groups, as well as that the age-dependent effect remains throughout the 2 years.

Conclusions

Younger age is associated with poor treatment outcomes for low-concentration atropine at levels of 0.05%, 0.025%, and 0.01% for myopia control. Other factors including baseline SE and parental myopia status contribute no effects. Among atropine concentrations studied, younger children required the highest 0.05% concentration to achieve similar reduction in myopic progression as older children receiving lower concentrations. Finally, all the concentrations used in our trial were tolerated well by children of all ages from 4 to 12 years.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at Hong Kong Eye Hospital approved the study. All research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from parents or guardians and verbal consent was obtained from the study patients. The study is registered with the Chinese Clinical Trial Registry (identifier; ChiCTR-TRC-13004032) and the Clinical Trials Registry of the Centre for Clinical Research and Biostatistics (CCRB), The Chinese University of Hong Kong (identifier: CUHK_CCT00383).

No animal subjects were included in this study.

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Data collection: Li, X.Zhang, Tang, Yam

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Abbreviations and Acronyms:
AL = axial length; **ATOM1** = Atropine for the Treatment of Myopia 1; **CI** = confidence interval; **D** = diopter; **LAMP** = Low-Concentration Atropine for Myopia Progression; **SE** = spherical equivalent.

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