

# Effects of Atropine Treatment on Choroidal Thickness in Myopic Children

Luyao Ye,<sup>1,2</sup> Ya Shi,<sup>1,2</sup> Yao Yin,<sup>1</sup> Shanshan Li,<sup>1</sup> Jiangnan He,<sup>1</sup> Jianfeng Zhu,<sup>1</sup> and Xun Xu<sup>1,2</sup>

<sup>1</sup>Shanghai Eye Disease Prevention and Treatment Center, Shanghai Eye Hospital, Shanghai, China

<sup>2</sup>Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University, National Clinical Research Center for Eye Diseases, Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai Engineering Center for Visual Science and Photomedicine, Shanghai Engineering Center for Precise Diagnosis and Treatment of Eye Diseases, Shanghai, China

Correspondence: Jianfeng Zhu, No.380 Kangding Road, Shanghai 200040, China;

[jfzhu1974@hotmail.com](mailto:jfzhu1974@hotmail.com)

Jiangnan He, MPH, No.380 Kangding Road, Shanghai 200040, China;

[hejiangnan85@126.com](mailto:hejiangnan85@126.com)

LY and YS contributed equally as co-authors.

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**PURPOSE.** To examine the changes in choroidal thickness (ChT) after 6 months of 1% or 0.01% atropine treatment and the independent factors associated with eye elongation.

**METHODS.** A total of 207 myopic children aged 6 to 12 years were recruited and randomly assigned to groups A and B in a ratio of 1:1. Participants in group A received 1% atropine once a day for 1 week, and then once a week for 23 weeks. Participants in group B received 0.01% atropine once a day for 6 months. ChT and internal axial length (IAL) were measured at baseline, 1 week, 3 months, and 6 months.

**RESULTS.** In group A, the ChT significantly increased after a 1-week loading dose of 1% atropine ( $26 \pm 14 \mu\text{m}$ ;  $P < 0.001$ ) and the magnitude of increase stabilized throughout the following weekly treatment. The internal axial length did not significantly change at the 6-month visit ( $-0.01 \pm 0.11 \text{ mm}$ ;  $P = 0.74$ ). In contrast, a decreased ChT ( $-5 \pm 17 \mu\text{m}$ ;  $P < 0.001$ ) and pronounced eye elongation ( $0.19 \pm 0.12 \text{ mm}$ ;  $P < 0.001$ ) were observed in group B after 6 months. Multivariable regression analysis showed that less increase in ChT at the 1-week visit ( $P = 0.03$ ), younger age ( $P < 0.001$ ), and presence of peripapillary atrophy ( $P = 0.001$ ) were significantly associated with greater internal axial length increase over 6 months in group A.

**CONCLUSIONS.** One percent atropine could increase the ChT, whereas 0.01% atropine caused a decrease in ChT after 6 months of treatment. For participants receiving 1% atropine, the short-term increase in ChT was negatively associated with long-term eye elongation. Younger age and the presence of peripapillary atrophy were found to be risk factors for greater eye elongation.

**Keywords:** atropine, choroidal thickness, peripapillary atrophy, myopia control

Over the past few decades, the prevalence of myopia has substantially increased, thus becoming a public health concern.<sup>1,2</sup> High myopia can cause irreversible damage to visual acuity (VA) as myopic maculopathy develops and progresses.<sup>3,4</sup> Therefore, it is essential to find an effective and safe therapy that may prevent the progression of myopia, especially among children and adolescents. At present, 1% atropine has been demonstrated to have the strongest clinical effect on slowing myopia progression in children.<sup>5-8</sup> Yet, severe and long-lasting side effects as well as rebound after drop cessation have limited its clinical application.<sup>9,10</sup> This, in turn, has led to a surge in the popularity of using low-concentration atropine owing to fewer side effects and less rebound following atropine cessation.<sup>11-14</sup>

Decreasing the frequency of 1% atropine to once a week was associated with fewer side effects (photophobia, 0%–29%; near blurred vision, 0.6%)<sup>15-17</sup> compared with daily drug use (52.4% and 5.5%, respectively)<sup>10</sup> in the treatment of myopia or amblyopia. However, the safety of this treatment regimen (e.g., distance and near VA, pupil size, and

accommodation amplitude) has not yet been evaluated in detail.

The choroid has a role in modulating eye growth by regulating the oxygen levels of the sclera<sup>18</sup> and by secreting or transmitting retina-derived signals to sclera.<sup>19-22</sup> Previous studies have reported a negative association between the changes in choroidal thickness (ChT) and axial length (AL) in animals wearing defocus lens<sup>23,24</sup> and in longitudinal studies of myopic children.<sup>25</sup> An increase in ChT was observed among myopic children treated with orthokeratology,<sup>26,27</sup> and the short-term increase in ChT was negatively associated with long-term eye elongation.<sup>27</sup> Choroidal thickening was also observed in healthy children treated with 1% atropine for 1 week<sup>28</sup> and in myopic children administered with 0.01% atropine for less than 8 weeks.<sup>29-31</sup> However, the long-term effects of atropine on ChT in myopic children and its association with eye elongation remain unknown.

This study was conducted to explore the changes in ChT in Chinese myopic children aged 6 to 12 years treated with 1% atropine once per week or with 0.01% atropine once per day, as well as to investigate the possible association of eye

elongation with the changes in ChT and other factors during the treatment period. Additional objectives included a safety evaluation of the treatment regime.

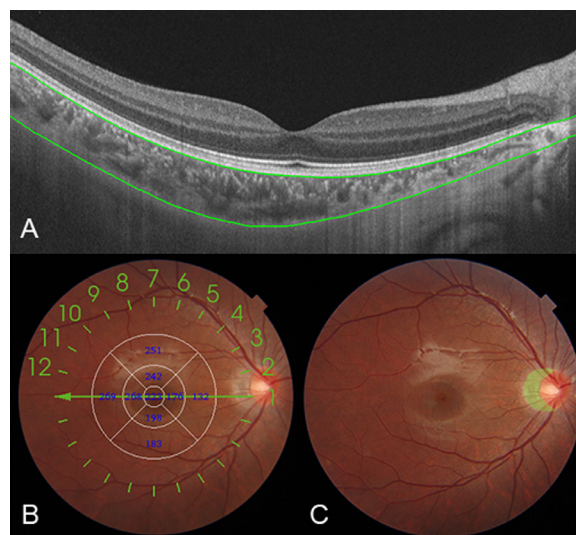
## METHODS

### Study Participants

The present study is a part of the Atropine for Children and Adolescent Myopia Progression study, which is a randomized clinical trial evaluating the efficacy and safety of atropine treatment for myopia control. The study design has been previously described.<sup>30</sup> In brief, 207 children aged 6 to 12 years with myopic refraction of at least  $-0.5$  diopter (D) and astigmatism of less than  $-2.0$  D in both eyes were enrolled in this randomized clinical trial. After excluding those with ocular diseases or severe systemic diseases, previous use of myopia interventions (such as atropine, pirenzepine, or orthokeratology lens), or allergy to atropine and cyclopentolate, children were randomly assigned to one of two groups in a ratio of 1:1: group A received 1% atropine (Dishan, Shenyang Xingqi Pharmaceutical Co., LTD., Shenyang, China), and group B received 0.01% atropine (Myopine, Shenyang Xingqi Eye Hospital Co., LTD., Shenyang, China), in both eyes. Participants in group A received 1% atropine once per day during the first week (to explore the effect of atropine cycloplegia), and then once per week for the next 23 weeks. Participants in group B received 0.01% atropine once per day over 6 months. Written informed consent forms were obtained from the participants and their parents or guardians. The study protocol was approved by the Ethics Committee of Shanghai General People's Hospital, Shanghai, China (Approval number: 201939), and registered at the Clinical Trials.gov PRS (Registration No. NCT03949101). All procedures were conducted in accordance with the tenets of the Declaration of Helsinki.

### Study Procedures

To decrease the influence of diurnal variation of choroid,<sup>32</sup> the measurement was conducted from 10:00 AM to 3:00 PM each day, and follow-ups were prearranged within 2 hours based on the time of the baseline visit. Examination procedures were performed as previously described.<sup>30</sup> Briefly, each participant underwent a series of ophthalmic examinations, including measurement of intraocular pressure using a noncontact tonometry (NT-1000; Nidek, Tokyo, Japan), pupil size using an IOL-Master 700 (Carl Zeiss Meditec AG, Jena, Germany), best-corrected distance VA in the logMAR, near VA under best-corrected distance spectacle correction at 40 cm, and near point of accommodation with best-corrected distance spectacle correction. The accommodation amplitude was calculated as the inverse of the near point of accommodation. After excluding the contradictions of cycloplegia, one drop of topical 0.5% proparacaine (Alcaine; Alcon, Fort Worth, TX) was administered in both eyes, followed by two drops of 1% cyclopentolate (Cyclogyl; Alcon) at a 5-minute interval. A third drop of cyclopentolate was given 45 minutes later if the pupillary light reflex was still present or the pupil size was less than 6.0 mm. Further drops of cyclopentolate were administered if necessary. Cycloplegia was not performed at the 1-week visit. Autorefraction was performed using an autorefractor (Topcon



**FIGURE 1.** A map showing the ChT and PPA in a healthy 9-year-old girl (right eye) obtained by swept-source optical coherence tomography. ChT, measured as the distance between the Bruch membrane (upper green line) and the choroid-sclera interface (lower green line) (A). The Early Treatment Diabetic Retinopathy Study grid was applied to the map, and the mean ChT was obtained for each sector (B). A retinal photograph centered on the optic disc in the same girl with the area of the PPA manually outlined (green shade area; C).

KR 800; Optical Corp., Guangdong, China). The AL was measured using an IOL-Master 700 (Carl Zeiss Meditec AG).

The ChT was measured using swept-source optical coherence tomography (Topcon Corp., Tokyo, Japan). The parameters were previously described.<sup>30</sup> The segmentation of each layer was automatically obtained using the built-in software, and manual segmentation was performed where the software misjudged the borderline of each layer. To determine the reproducibility of manual correction, 20 images that needed manual segmentation were randomly selected and corrected twice by a specific technician. A Bland-Altman plot showed high reproducibility of the ChT segmentation (Supplementary Fig. S1). The mean difference between two corrections was  $-0.1$   $\mu\text{m}$ , and the 95% limits of agreement ranged from  $-5$  to  $5$   $\mu\text{m}$ . The intraobserver correlation coefficient was 0.998 ( $P < 0.001$ ). The ChT was measured as the vertical distance between the Bruch membrane and the choroid-sclera interface (Fig. 1A). The Early Treatment Diabetic Retinopathy Study grid was adopted to calculate the averaged ChT in each grid sector using the built-in software. The diameters of the subfoveal, parafoveal, and perifoveal circles were 1 mm, 3 mm, and 6 mm, respectively, and they were further divided into superior, inferior, temporal, and nasal quadrants (Fig. 1B). The retinal photographs by swept-source optical coherence tomography were adopted to identify the presence of peripapillary atrophy (PPA; an inner crescent of chorioretinal atrophy with good visibility of the large choroidal vessels and the sclera; Fig. 1C) by two independent, well-trained examiners (LYY and YS). In cases of disagreement, adjudication was made by a senior ophthalmologist (JFZ).

Parents or guardians were in charge of drug administration and were required to keep medication diaries. The compliance level was classified according to the mean number of atropine use per month or week over 6 months. Participants with a medication adherence percentage of 80%

or greater (i.e., 3.2 d/mo for group A or 5.6 d/wk for group B) were considered to have good compliance<sup>33,34</sup> and were included in the analysis. Photochromatic glasses and presbyopic glasses (reading add) were provided if children experienced glare or had difficulty with near vision. Children and parents were free to report any other side effects, illness, and hospitalization during treatment. Any adverse events, regardless of whether they were related to the use of atropine, were documented.

## Outcomes

The primary outcome was the change in the average ChT over 6 months. The secondary outcomes included the changes in AL, internal AL (IAL), spherical equivalent, accommodation amplitude, pupil size, distance VA, and near VA over 6 months. IAL was defined as the distance from the anterior cornea to the anterior sclera and it was calculated by adding the subfoveal ChT as determined by swept-source optical coherence tomography to the AL measured using the IOL-Master.<sup>26</sup> The spherical equivalent was calculated as the spherical power plus one-half of the cylindrical power.

## Statistical Analysis

According to the protocol of this clinical trial, participants in group A received 1% atropine once per week for 6 months, followed by 0.01% atropine once per day for the next 6 months. The estimated myopia progression rate for group A was assumed to be  $-0.37$  D/y, which was averaged from the myopia progression rate for daily 0.1% atropine in the Atropine for the Treatment of Myopia 2 (ATOM2) study<sup>11</sup> (which was probably close to the effect of 1% atropine of weekly use,  $-0.31 \pm 0.50$  D/y) and 75% of the myopia progression rate for daily 0.01% atropine in the Low-concentration Atropine for Myopia Progression (LAMP) study ( $-0.59 \pm 0.61$  D/y).<sup>13</sup> Participants in group B were administered with 0.01% atropine daily throughout 12 months, and the estimated myopia progression rate was

set to  $-0.59$  D/y based on the result of daily 0.01% atropine in the LAMP study.<sup>13</sup> The within-group standard deviation was assumed to be 0.6 D.<sup>13</sup> To detect a mean difference of at least 0.5 D between treatment groups,<sup>13</sup> 158 participants (79 per group) could achieve 90% power at a significance level of 0.05. By factoring in an attrition rate of 20%, this study required 198 subjects (99 per group).

The baseline characteristics were described as mean  $\pm$  standard deviation or proportion. Correlation analysis between two ocular parameters was analyzed using Pearson correlation coefficients. A  $\chi^2$  test was used to test the group differences of categorical data. The intergroup differences of continuous data were tested using the Student *t*-test or ANOVA with post hoc tests (Bonferroni). The differences in ocular parameters between the baseline and the follow-ups and the differences in ChT changes between two macular sectors were analyzed using the paired *t*-test. A generalized estimating equation model with robust standard errors for longitudinal data analysis<sup>35</sup> was used to compare the different changes in ocular parameters over time with adjustment for age and sex, accounting for repeated measurements. *P* values were adjusted for multiple comparisons with sequential Bonferroni adjustment. Multiple linear regression models were established using the IAL change over 6 months as the independent variable to assess the possible association with other ocular parameters. Statistical analysis was performed using SPSS v. 22 software (IBM, Armonk, NY, USA). A *P* value of less than 0.05 was considered statistically significant. Because the spherical equivalent ( $r = 0.89$ ;  $P < 0.001$ ), IAL ( $r = 0.97$ ;  $P < 0.001$ ), and ChT ( $r = 0.91$ ;  $P < 0.001$ ) of the right and left eyes at baseline were highly correlated, only the right eyes were involved in the analysis.

## RESULTS

### General Characteristics

A total of 240 children were assessed for eligibility. Ultimately, 207 children were recruited into the study, 104

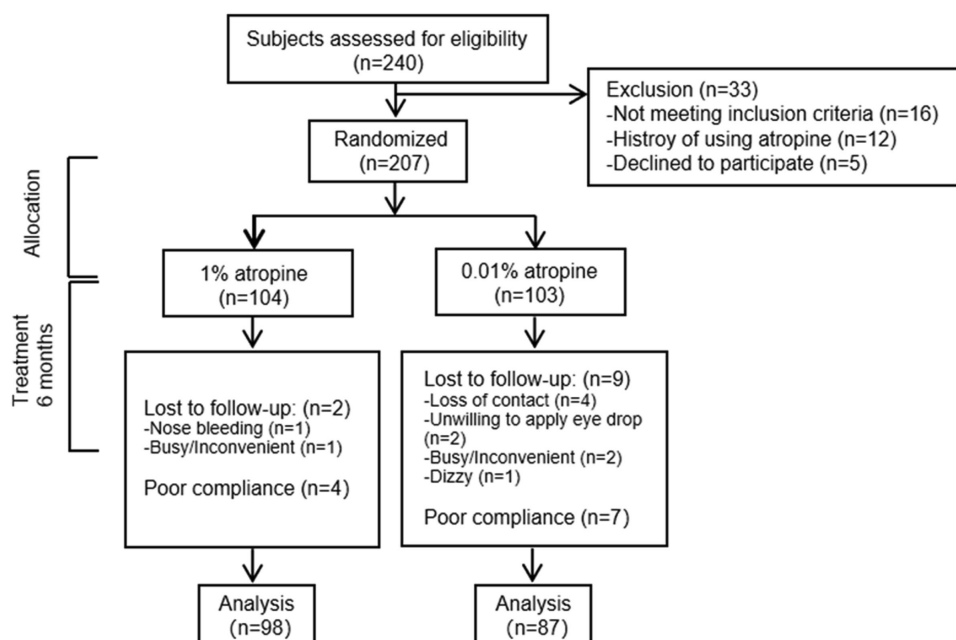


FIGURE 2. A flowchart showing participants enrolled in the Atropine for Children and Adolescent Myopia Progression study.

TABLE 1. Baseline Characteristics for All Participants and for Those Included and Excluded From the Analysis

Variables	Total			Included		Excluded		P Value <sup>†</sup>
	Group A (n = 104)	Group B (n = 103)	P Value*	Group A (n = 98)	Group B (n = 87)	Group A (n = 6)	Group B (n = 16)	
Age, y	8.98 (1.57)	8.88 (1.71)	0.67	8.94 (1.55)	8.84 (1.65)	9.50 (1.64)	9.00 (1.83)	0.50
Male gender, n (%)	49 (47.1)	49 (47.6)	0.84	49 (50.0)	44 (50.6)	0 (0.0)	10 (62.5)	0.07
Body mass index, kg/m <sup>2</sup>	17.03 (2.71)	16.75 (2.63)	0.53	17.09 (2.77)	16.87 (2.75)	16.15 (1.21)	16.12 (1.73)	0.14
Average ChT, μm	214 (45)	222 (41)	0.17	214 (45)	218 (39)	214 (49)	245 (47)	0.03
AL, mm	24.32 (0.81)	24.25 (0.72)	0.45	24.34 (0.82)	24.27 (0.74)	23.98 (0.55)	24.14 (0.61)	0.22
IAL, mm	24.54 (0.79)	24.48 (0.71)	0.55	24.57 (0.81)	24.50 (0.73)	24.20 (0.52)	24.40 (0.60)	0.27
Spherical equivalent, D	-2.11 (1.10)	-2.13 (1.10)	0.92	-2.12 (1.09)	-2.16 (1.10)	-1.85 (0.69)	-1.96 (1.07)	0.39
Presence of PPA, n (%)	65 (62.5)	73 (70.9)	0.20	62 (63.3)	67 (77.0)	3 (50.0)	6 (37.5)	0.01
Intraocular pressure, mm Hg	14.92 (2.60)	14.26 (2.25)	0.06	14.90 (2.66)	14.21 (2.23)	15.33 (1.37)	14.38 (2.45)	0.91
Distance VA, logMAR	-0.02 (0.04)	-0.03 (0.05)	0.10	-0.02 (0.04)	-0.03 (0.05)	-0.03 (0.04)	-0.01 (0.03)	0.60
Near VA, logMAR	0.01 (0.04)	0.02 (0.04)	0.13	0.01 (0.04)	0.02 (0.04)	0.01 (0.02)	0.01 (0.02)	0.36
Pupil size, mm	5.08 (1.12)	5.21 (0.85)	0.68	5.05 (1.10)	5.20 (0.82)	5.50 (0.99)	5.47 (1.13)	0.11
Accommodation amplitude, D	12.52 (3.21)	12.42 (3.36)	0.75	12.43 (3.05)	12.59 (3.49)	14.00 (4.94)	11.51 (2.41)	0.86
Parental myopia, n (%)	92 (88.5)	91 (88.3)	0.58	87 (88.8)	77 (88.5)	5 (83.3)	11 (84.5)	0.84

Data are presented as mean (standard deviation) unless otherwise indicated.

\* Comparison between the two groups enrolled in the study using the Student *t*-test for continuous data or the  $\chi^2$  test for categorical data.

† Comparison between participants included the analysis and those excluded using the Student *t*-test for continuous data or the  $\chi^2$  test for categorical data.

in group A and 103 in group B (Fig. 2). The baseline characteristics of the participants are described in Table 1. There was no significant difference between the two groups ( $P = 0.06$  to  $0.92$ ). There were 102 (98.1%) participants in group A and 94 (91.2%) in group B who completed the 6 months of treatment; 98 participants (94.2%) in group A and 87 participants (84.5%) in group B had good compliance. The baseline characteristics of the 185 children included in the analysis were similar to those of the 22 children who were excluded ( $P = 0.07$  to  $0.91$ ), except for a thinner average ChT ( $P = 0.03$ ) and a higher proportion of PPA ( $P = 0.01$ ).

### Changes in Ocular Parameters

The ocular parameters in each visit are summarized in Supplementary Table S1, and the changes in ocular parameters over time are shown in Table 2. In group A, there was an overall increase in ChT ( $26 \pm 14 \mu\text{m}$ ;  $P < 0.001$ ) after a 1-week loading dose of 1% atropine, and the magnitude of choroidal thickening remained unchanged at the 3-month visit ( $29 \pm 22 \mu\text{m}$ ;  $P = 0.47$ ) and the 6-month visit ( $27 \pm 23 \mu\text{m}$ ;  $P = 1.00$ ). The ChT in the perifoveal nasal quadrant exhibited the least increase among the horizontal sectors (all  $P < 0.05$ ), whereas the vertical changes in ChT did not significantly differ (Figs. 3A–C). There was a decrease in the AL over time ( $-0.04 \pm 0.03 \text{ mm}$ ,  $-0.06 \pm 0.09 \text{ mm}$ , and  $-0.03 \pm 0.12 \text{ mm}$  for the 1-week, 3-month, and 6-month visits, respectively; all  $P < 0.001$ ). The IAL did not significantly change at the 1-week and 6-month visits but presented a significant reduction at the 3-month visit ( $-0.04 \pm 0.08 \text{ mm}$ ;  $P < 0.001$ ). There was a significant hyperopic shift of  $0.38 \pm 0.21 \text{ D}$  during the first week ( $P < 0.001$ ), and the magnitude of change reduced to  $0.26 \pm 0.33 \text{ D}$  and  $0.28 \pm 0.37 \text{ D}$  at the end of 3 and 6 months, respectively (both  $P < 0.001$ ).

Group B presented significantly different ocular biometric changes compared with group A (all  $P < 0.001$ ). ChT was

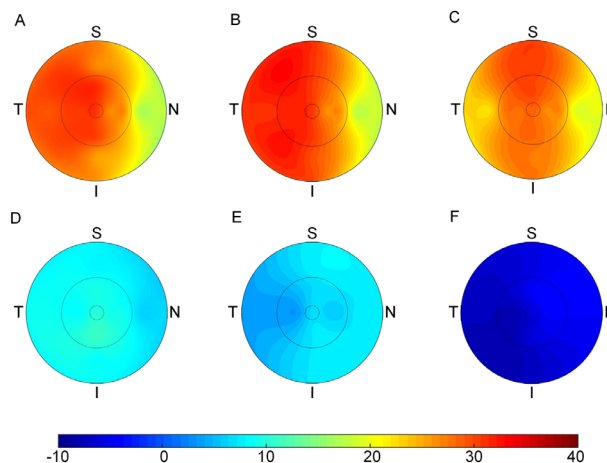


FIGURE 3. Topographic variation of the changes in ChT at the 1-week, 3-month, and 6-month visits for group A (A, B, and C, respectively) and group B (D, E, and F, respectively).

found to be slightly increased at the 1-week and 3-month visits ( $8 \pm 9 \mu\text{m}$  and  $6 \pm 12 \mu\text{m}$ , respectively; both  $P < 0.001$ ), followed by a decrease at the 6-month visit ( $-5 \pm 17 \mu\text{m}$ ;  $P < 0.001$ ). There was no significant difference in ChT change among the sectors, horizontally and vertically (Figs. 3D–F). Axial elongation and refraction progression were observed over time, with more significant changes during the second 3 months compared with the first 3 months (all  $P < 0.001$ ).

### Changes in Ocular Parameters With Baseline Characteristics

The relationship between the changes in ocular parameters over 6 months and baseline characteristics are presented in Table 3 and Figures 4 and 5. In group A, participants

TABLE 2. Changes in Ocular Biometry Over 6 Months in Different Treatment Groups

Variables	Group A (n = 98)		Group B (n = 87)		P Value <sup>‡</sup>
	Mean (SD)	Range	Mean (SD)	Range	
Average ChT, $\mu\text{m}$					
Baseline to 1 week	26 (14) <sup>*</sup>	−15 to 82	8 (9) <sup>*</sup>	−13 to 31	<0.001
Baseline to 3 months	29 (22) <sup>*</sup>	−19 to 106	6 (12) <sup>*</sup>	−22 to 38	<0.001
Baseline to 6 months	27 (23) <sup>*</sup>	−12 to 93	−5 (17) <sup>*</sup>	−68 to 58	<0.001
P value <sup>‡</sup>	0.47, >0.99, >0.99		>0.99, <0.001, <0.001		
AL, mm					
Baseline to 1 week	−0.04 (0.03) <sup>*</sup>	−0.12 to 0.01	−0.01 (0.02) <sup>*</sup>	−0.08 to 0.04	<0.001
Baseline to 3 months	−0.06 (0.09) <sup>*</sup>	−0.30 to 0.19	0.08 (0.07) <sup>*</sup>	−0.09 to 0.20	<0.001
Baseline to 6 months	−0.03 (0.12) <sup>*</sup>	−0.37 to 0.30	0.19 (0.12) <sup>*</sup>	−0.10 to 0.49	<0.001
P value <sup>‡</sup>	0.03, <0.001, 0.71		<0.001, <0.001, <0.001		
IAL, mm					
Baseline to 1 week	−0.01 (0.02)	−0.07 to 0.04	0.00 (0.02)	−0.05 to 0.05	0.001
Baseline to 3 months	−0.04 (0.08) <sup>*</sup>	−0.24 to 0.24	0.08 (0.07) <sup>*</sup>	−0.11 to 0.21	<0.001
Baseline to 6 months	−0.01 (0.11)	−0.26 to 0.34	0.19 (0.12) <sup>*</sup>	−0.10 to 0.48	<0.001
P value <sup>‡</sup>	<0.001, <0.001, 0.74		<0.001, <0.001, <0.001		
Spherical equivalent, D					
Baseline to 1 week	0.38 (0.21) <sup>*</sup>	−0.13 to 0.88	−0.09 (0.20) <sup>*</sup>	−0.50 to 0.50	<0.001
Baseline to 3 months	0.26 (0.33) <sup>*</sup>	−0.50 to 1.13	−0.08 (0.25) <sup>*</sup>	−0.63 to 0.88	<0.001
Baseline to 6 months	0.28 (0.37) <sup>*</sup>	−0.50 to 1.25	−0.27 (0.34) <sup>*</sup>	−1.00 to 0.63	<0.001
P value <sup>‡</sup>	<0.001, 0.66, 0.03		>0.99, <0.001, <0.001		
Distance VA, logMAR					
Baseline to 1 week	0.00 (0.05)	−0.18 to 0.18	0.00 (0.05)	−0.10 to 0.10	0.94
Baseline to 3 months	−0.00 (0.05)	−0.10 to 0.10	0.00 (0.05)	−0.10 to 0.10	0.83
Baseline to 6 months	−0.01 (0.05)	−0.12 to 0.12	−0.01 (0.07)	−0.18 to 0.18	0.52
P value <sup>‡</sup>	0.28, 0.11, 0.27		0.13, 0.46, 0.32		
Near VA, logMAR					
Baseline to 1 week	0.68 (0.23) <sup>*</sup>	0.00 to 1.00	0.01 (0.08)	−0.16 to 0.40	<0.001
Baseline to 3 months	0.04 (0.13) <sup>*</sup>	−0.18 to 0.70	−0.01 (0.04)	−0.18 to 0.11	<0.001
Baseline to 6 months	0.02 (0.12)	−0.15 to 1.00	−0.02 (0.05)	−0.22 to 0.10	0.11
P value <sup>‡</sup>	<0.001, 0.002, <0.001		0.09, 0.23, 0.11		
Pupil size, mm					
Baseline to 1 week	2.48 (1.20) <sup>*</sup>	0.12 to 4.90	0.83 (0.95) <sup>*</sup>	−1.60 to 3.90	<0.001
Baseline to 3 months	1.87 (1.75) <sup>*</sup>	−0.04 to 4.40	0.85 (0.70) <sup>*</sup>	−1.30 to 3.80	<0.001
Baseline to 6 months	1.59 (1.24) <sup>*</sup>	−0.10 to 4.00	0.20 (1.20)	−1.40 to 2.80	<0.001
P value <sup>‡</sup>	<0.001, <0.001, <0.001		0.22, <0.001, <0.001		
Accommodation amplitude, D					
Baseline to 1 week	−11.55 (3.73) <sup>*</sup>	−19.50 to −4.75	−2.88 (3.42) <sup>*</sup>	−12.10 to 5.00	<0.001
Baseline to 3 months	−4.25 (2.98) <sup>*</sup>	−15.50 to 3.50	−1.81 (2.97) <sup>*</sup>	−11.00 to 4.00	<0.001
Baseline to 6 months	−3.01 (3.85) <sup>*</sup>	−14.40 to 4.30	−1.11 (3.71) <sup>*</sup>	−13.00 to 4.20	0.02
P value <sup>‡</sup>	<0.001, <0.001, <0.001		<0.001, <0.001, <0.001		

The data are the changes from baseline visits for each group.

<sup>\*</sup>  $P < 0.05$  for comparisons between the baseline and the follow-ups using the paired  $t$ -test.

<sup>‡</sup> Comparisons between the two groups using the Student  $t$ -test.

<sup>‡</sup> A generalized estimating equation model with robust standard errors was used to compare the different changes in the ocular parameters over time with adjustment for age and sex, accounting for repeated measurements. Multiple comparisons with sequential Bonferroni adjustment were performed between baseline to 1 week and baseline to 3 months, baseline to 3 months and baseline to 6 months, and baseline to 1 week and baseline to 6 months, respectively.

with higher myopic refraction at baseline, longer AL at baseline, or the presence of PPA exhibited less increase in ChT in all nine macular sectors than those with lower myopic refraction, shorter AL, or normal fundus, respectively (all  $P < 0.05$ ). Significantly greater eye elongation was observed in participants with higher myopic refraction or the presence of PPA (all  $P < 0.05$ ). There was an increasing trend of eye elongation in participants with a longer baseline AL, although the differences among AL categories were statistically insignificant. In group B, however, these changes in ocular parameters did not significantly differ across groups ( $P = 0.11$  to  $0.47$ ).

### Factors Associated With the Eye Elongation Over 6 Months

A negative association was observed between the changes in IAL and ChT over 6 months in both groups ( $r = -0.48$  and  $r = -0.27$  for groups A and B, respectively; both  $P < 0.01$ ). In group A, the IAL change at the 6-month visit was negatively associated with the change in ChT at the 1-week visit ( $r = -0.27$ ,  $P = 0.01$ ; Fig. 6A) and the baseline age ( $r = -0.26$ ,  $P = 0.01$ ; Fig. 6B). Multivariable regression analysis was established to identify independent factors associated with IAL changes over 6 months in each group. Because the

TABLE 3. Changes in Ocular Parameters Stratified by Baseline Characteristics

	Group A (n = 98)				Group B (n = 87)			
	N	Average ChT, μm	AL, mm	IAL, mm	N	Average ChT, μm	AL, mm	IAL, mm
Baseline refraction								
-0.5 to <-1 D	12	45 (33)	-0.09 (0.15)	-0.03 (0.13)	10	-6 (32)	0.18 (0.20)	0.17 (0.17)
-1 to <-2 D	37	29 (21)	-0.06 (0.08)	-0.01 (0.07)	31	-9 (13)	0.21 (0.12)	0.21 (0.12)
-2 to <-3 D	31	25 (18)	-0.03 (0.14)	0.00 (0.12)	27	-7 (15)	0.20 (0.11)	0.19 (0.12)
≤ -3 D	18	13 (14)	0.05 (0.14)	0.06 (0.13)	19	3 (15)	0.14 (0.07)	0.15 (0.07)
P value		0.001	0.02	0.04		0.13	0.32	0.47
Baseline AL								
≤24 mm	31	35 (25)	-0.06 (0.10)	-0.01 (0.09)	32	-9 (18)	0.22 (0.11)	0.22 (0.10)
24< to 25 mm	45	25 (23)	-0.03 (0.13)	0.00 (0.11)	41	-3 (18)	0.16 (0.14)	0.16 (0.14)
>25 mm	22	19 (14)	-0.00 (0.14)	0.03 (0.13)	14	0 (12)	0.19 (0.07)	0.18 (0.06)
P value		0.04	0.31	0.41		0.16	0.11	0.13
Presence of PPA								
Without	36	42 (25)	-0.09 (0.12)	-0.04 (0.11)	20	-9 (19)	0.22 (0.13)	0.21 (0.15)
With	62	18 (15)	0.00 (0.12)	0.03 (0.11)	67	-4 (17)	0.18 (0.12)	0.18 (0.11)
P value		<0.001	<0.001	0.001		0.25	0.33	0.25

The data are the changes from baseline visits for each group, presented as mean (standard deviation).

P value for comparisons among refraction and AL groups using ANOVA, or between participants with and without PPA using the Student t-test.

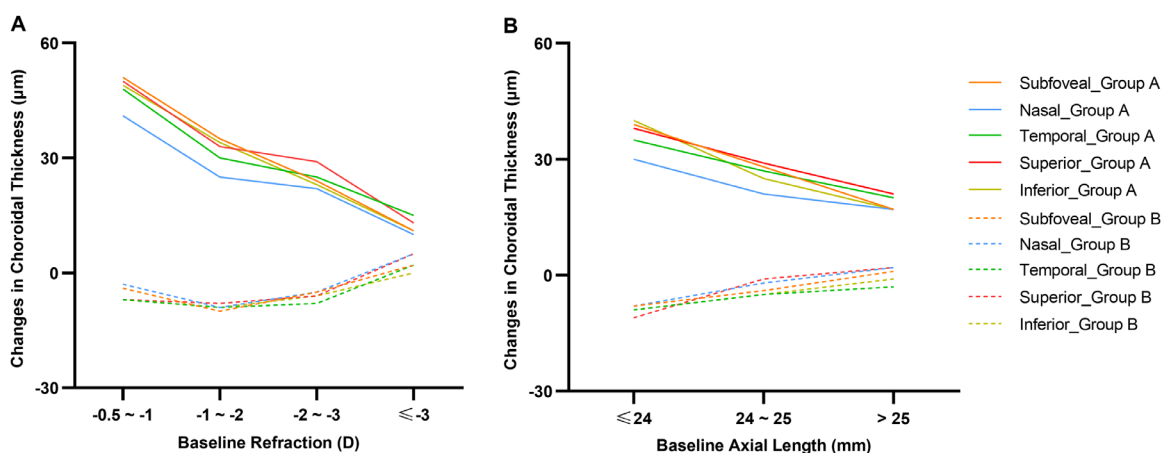


FIGURE 4. The changes in ChT over 6 months under the fovea and at four quadrants stratified by baseline refraction (A) and AL (B) for two treatment groups.

presence of PPA was significantly associated with the baseline refraction and the baseline AL (both  $P < 0.001$ ), only the presence of PPA was added into the model. The results showed that the IAL change over 6 months was negatively associated with age ( $P < 0.001$ ) and the change in ChT at the 1-week visit ( $P = 0.03$ ), and positively correlated with the presence of PPA ( $P = 0.001$ ) adjusting for age and sex in group A (Table 4). In group B, the IAL change at the 6-month visit was negatively correlated with age ( $r = -0.50$ ,  $P < 0.001$ ), but was not associated with the change in ChT at the 1-week visit ( $P = 0.81$ ).

### Adverse Events and Changes in Associated Ocular Parameters

In group A, the changes in accommodation amplitude and pupil size at the 6-month visit were  $-3.01 \pm 3.85$  D ( $P < 0.001$ ) and  $1.59 \pm 1.24$  mm ( $P < 0.001$ ), which were lower

than the changes at the 1-week and 3-month visits (both  $P < 0.001$ ). Fewer changes in accommodation amplitude and pupil size were observed in group B compared with group A (all  $P < 0.05$ ). The distance VA and near VA did not significantly change over 6 months in both groups.

In group A, 80.6% and 66.3% of participants reported photophobia and near blurred vision with a mean duration

TABLE 4. Multiple Regression Analysis of Associated Factors With the Changes in IAL in Group A (n = 98)

Variables	B (95% CI)	P Value
Age, y	-0.025 (-0.039 to -0.012)	<0.001
Sex	-0.002 (-0.042 to 0.038)	0.903
One-week change in ChT, 10 μm	-0.016 (-0.031 to -0.002)	0.030
PPA, baseline	0.078 (0.035 to 0.122)	0.001

$R^2 = 0.259$ .

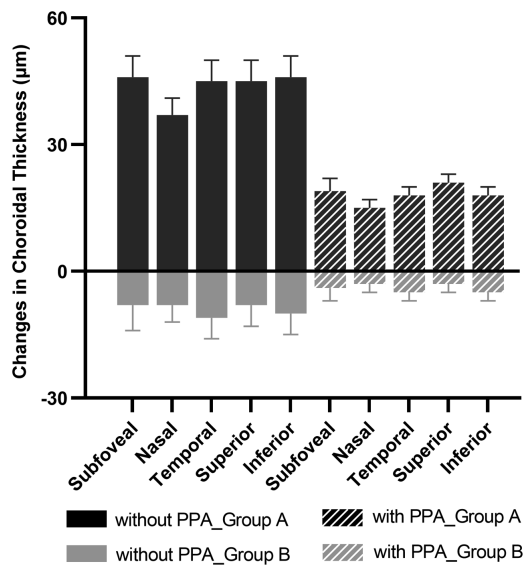


FIGURE 5. The changes in ChT over 6 months under the fovea and at four quadrants sectors stratified by the presence of PPA for two treatment groups.

of 3.4 days and 4.3 days, respectively. Also, 30.6% and 10.2% of participants needed photochromic glasses and presbyopic glasses, respectively. In group B, 6.9% and 1.1% of participants reported photophobia and near blurred vision, respectively, with no need for photochromic glasses or presbyopic glasses. Among all participants enrolled in the study, allergic conjunctivitis was reported in two participants from group B; dizziness occurred in two participants from group B; rubella was reported in one participant from group B; and nose bleeding occurred in two participants from group A and one participant from group B.

## DISCUSSION

In this study, we explored the changes in ChT over 6 months and the independent factors associated with eye elongation. Our results revealed that there was a significant increase in the ChT after a 1-week loading dose of 1% atropine, and the magnitude of increase stabilized throughout the following weekly treatments. The IAL did not significantly change over 6 months. Conversely, 0.01% atropine (administered daily) led to a decrease in the ChT and pronounced eye elongation after 6 months. Moreover, among participants receiving 1% atropine, the short-term increase in ChT was negatively associated with long-term eye elongation. Younger age and the presence of PPA were risk factors for greater eye elongation. Also, weekly use of 1% atropine was evaluated to render endurable side effects.

### The Changes in ChT

Our results revealed a significantly thickened ChT after a 1-week loading dose of 1% atropine, which was consistent with findings from Zhang et al ( $15 \pm 16 \mu\text{m}$ ).<sup>28</sup> The magnitude of choroidal thickening was maintained throughout the following weekly treatments. Notably, the impact of weekly use of 1% atropine on ChT cannot be concluded from the present study owing to the influence of the loading dose during the first week. The underlying mechanisms

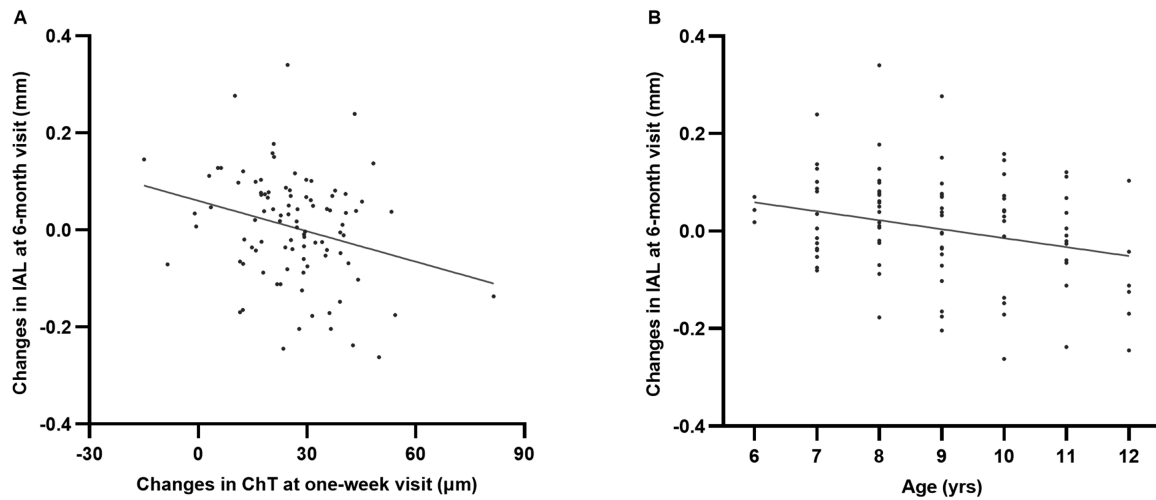
of this choroidal thickening after atropine treatment remain unclear. Based on the previous animal studies,<sup>36,37</sup> nitric oxide may participate in the choroidal thickening induced by atropine,<sup>38</sup> possibly by influencing the blood flow and the stromal components of the choroid via relaxation of the choroidal vascular and nonvascular smooth muscles. Moreover, dopamine could also be responsible for the choroidal thickening induced by atropine. Intravitreal injection of atropine in chicks' eyes can increase dopamine release from the retina,<sup>39</sup> and D2 agonist has been found to increase the ChT in chicks wearing negative lenses.<sup>40</sup> Previous studies have found a thinning of the ChT during accommodation,<sup>41</sup> probably via the biomechanical force between ciliary muscle and choroid.<sup>42</sup> Thus, the biomechanical effect on the ChT may go into the opposite direction when the ciliary muscle was relaxed by atropine. Further research is needed to demonstrate the underlying mechanisms for choroidal thickening.

A slight increase in ChT was observed in participants receiving 0.01% atropine for 3 months, which was consistent with other studies ( $5\text{--}6 \mu\text{m}$ ).<sup>29,31</sup> Yet, an opposite change in ChT was observed at the 6-month visit ( $-5 \pm 17 \mu\text{m}$ ). It could be that the effect of 0.01% atropine on choroid attenuated after the first 3 months of use and ChT decreased as AL elongates<sup>25</sup> during the second 3 months. In contrast, participants may experience more significant myopia progression and axial elongation during the second 3 months (autumn and winter) compared with the first 3 months (summer and autumn),<sup>43</sup> probably owing to the more time spent on near work and less time spent outdoors. Accordingly, increased choroidal thinning with greater ocular growth<sup>25</sup> could be observed during the second 3 months, which may outweigh the slight choroidal thickening originally caused by 0.01% atropine. A longer observation period of at least 1 year is required to indicate the underlying mechanisms.

### The Changes in IAL and Its Association With ChT Changes

Because the changes in ChT can influence AL, the IAL was adopted in the present study, revealing the true nature of the ocular growth.<sup>26</sup> No significant change in IAL was observed in group A after 6 months of treatment; conversely, participants receiving 0.01% atropine presented pronounced eye elongation. Increasing evidence has revealed the role of the choroid in modulating eye growth.<sup>18–22</sup> In this study, the changes in ChT at the 6-month visit were negatively associated with the IAL changes over 6 months in both groups. Similar results were found in myopic children treated with orthokeratology.<sup>26,27</sup> These findings suggest that the choroidal thickening may participate in ocular growth retardation, probably by influencing the synthesis activity of molecular signals and the transmission ability of choroid,<sup>19–22</sup> or by increasing the ChT and choroidal blood flow<sup>44–46</sup> and mitigating scleral hypoxia.<sup>18</sup>

We found that the ChT change at the 1-week visit was negatively associated with the IAL change over 6 months in group A, which suggests that the short-term increase in ChT after a loading dose of 1% atropine may predict long-term eye elongation with weekly treatment. However, daily use of 1% atropine for 1 week caused severe side effects; thus, a shorter duration of the loading dose, which can indicate long-term eye elongation, should be further explored by future studies.



**FIGURE 6.** (A) Scatter plots showing the changes in IAL over 6 months of treatment and the changes in ChT at the 1-week visit in group A ( $y = -0.002x + 0.06$ ;  $P = 0.01$ ). (B) Scatter plots showing the changes in IAL over 6 months of treatment and baseline age in group A ( $y = -0.02x + 0.17$ ;  $P = 0.01$ ).

### Factors Associated With the Eye Elongation in Group A

Previous studies have indicated that younger age<sup>14,47</sup> and higher myopic refraction at baseline<sup>47,48</sup> were risk factors for myopia progression in myopic children treated with atropine. As seen in group A, the ocular growth over 6 months was negatively correlated with the baseline age and myopic refraction. Furthermore, the presence of PPA resulted as another independent factor for eye elongation in participants receiving 1% atropine. The relatively small difference in IAL change between patients with and without PPA could be attributed to the limited course of observation. PPA is an early optic deformation associated with axial elongation-induced optic disc rotation found in myopes.<sup>49</sup> The development and enlargement of PPA are risk factors for pathologic myopia.<sup>50,51</sup> The true nature of the more pronounced eye elongation in patients with the presence of PPA remains unclear. We speculate that the optic deformation and scleral stretching may influence the function of the retina, retinal pigment epithelium, and choroid, eventually resulting in less choroidal thickening and more eye growth. The insignificant association between IAL change and the baseline AL indicated that the AL, a two-dimensional parameter, could not comprehensively reflect the ocular deformation.

### The Safety of Atropine Treatment

Ocular parameters related to side effects were fully evaluated in the current study. The changes in accommodation amplitude and pupil size with weekly use of 1% atropine over 6 months were comparable with those of the 0.1% atropine group in the ATOM2 study (administrated daily,  $-2.77 \pm 1.03$  D and  $2.42 \pm 0.91$  mm over a year, respectively)<sup>11</sup> and of the 0.05% atropine group in the LAMP study (administrated daily,  $-2.38 \pm 2.70$  D and  $1.06 \pm 1.07$  mm over 4 months, respectively).<sup>13</sup> Higher incidences of photophobia and near blurred vision were reported in the current study when compared with the previous studies with weekly or monthly use of 1% atropine (photophobia, 0%–62.1%;

near blurred vision, 0.6%–19.7%).<sup>15–17,52</sup> However, these side effects were enduring considering the short duration and the low need for photochromic or presbyopic glasses. Much lower incidences of photophobia and near blurred vision were found in participants treated with 0.01% atropine daily, which were similar to those in the LAMP study (2.1% and 1.8%, respectively).<sup>13</sup>

### Limitations

The present study has some limitations. First, the present study did not include a placebo control group. The findings from the ATOM study<sup>5,11</sup> and the LAMP study<sup>13</sup> clearly showed the efficacy of atropine treatment compared with a placebo, rendering a placebo arm unethical. Second, a 6-month follow-up period may not be enough for providing sufficient information on the efficacy of an atropine treatment regime and the suitable course, as well as the rebound after cessation. Third, although all parents or guardians were required to keep medication diaries, it was not possible to evaluate the accuracy with which this was done and thus may influence the results. Fourth, the pupil size was measured under normal circumstances (estimated to 150 lux); thus, the baseline pupil size was larger than the reported one in previous studies with 300 lux.<sup>11,13</sup> Fifth, time for outdoor activities and time spent on near work, which have been identified as risk factors for high myopia,<sup>53</sup> were not taken into consideration in the present study.

### CONCLUSIONS

Our data suggested that 1% atropine could increase ChT, whereas 0.01% atropine caused a decrease in ChT after 6 months of treatment. For participants receiving 1% atropine, the short-term increase in the ChT may predict long-term eye elongation. Myopic children with the presence of PPA should be closely monitored because they have a relatively poor response to 1% atropine and are at a high risk of developing high myopia and pathologic myopia.



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