

Clinical Study

Atropine 0.01% for the Control of Myopia in Chinese Children: Effect on Accommodation Functions and Pupil Size

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Background. To explore the effect of atropine 0.01% on accommodation functions and pupil size for safely and effectively controlling myopia in Chinese children. **Methods.** This was a single-center randomized clinical trial. 63 participants with myopia of at least -0.50 D and astigmatism of ≤ -2.50 D were enrolled and randomized to receive atropine 0.01% once nightly with regular single-vision lenses or to wear regular single-vision lenses, in an allocation ratio of 3 : 2. Primary outcomes included changes of accommodation functions, pupil diameter, distant and near best-corrected visual acuity (BCVA), near stereoacuity, and intraocular pressure (IOP). Secondary outcome was myopic progression at 6 months. **Results.** 61 participants completed the follow-up. Compared with the control group, the atropine-treated children showed a statistically significant increase in pupil diameter after 6 months (0.7 ± 0.7 vs. 0.1 ± 0.5 mm, $P = 0.01$). Despite the enlarged pupil, routine vision-related activities were not affected. The mean changes in accommodative functions, BCVA, near stereoacuity, and IOP, did not differ significantly between the groups. At 6 months, participants in the control group showed greater myopia progression than those in the atropine group (spherical equivalent: -0.60 ± 0.43 vs. -0.30 ± 0.42 D, $P < 0.001$; axial length: 0.35 ± 0.20 vs. 0.24 ± 0.16 mm, $P = 0.001$). **Conclusions.** Atropine 0.01% eye drops significantly increased pupil diameter less than one mm, but it did not affect accommodative functions, BCVA, near stereoacuity, and IOP. Combined with its reducing myopia progression, atropine 0.01% can be used as a safe and effective treatment for myopia in Chinese children.

1. Introduction

The total number of people with myopia is estimated to increase to 2.6 billion by 2020 and to 4.7 billion by 2050, which is almost half the global population [1]. A much higher prevalence of myopia has been noted in China compared to other countries from a combination of intrinsic (possible genetic predisposition) and extrinsic (reduced outdoor time and increased near work) factors [2,3]. In urban children, the prevalence of myopia was 5.7% in those aged 5 years, 30.1% in those aged 10 years, and 78.4% in those aged 15 years [4]. In parallel with the growing numbers with myopia, rates of high myopia have been increasing [5], and the number of people with vision loss resulting from high myopia is predicted to increase 7-fold globally from 2000 to 2050 [1].

In addition to impaired visual function, people with myopia are at a higher lifelong risk of vision-threatening ophthalmic conditions, such as myopic maculopathy, retinal detachment, and cataract. The risk of these complications increases with the severity of myopia, highlighting the importance of implementing interventions to slow the progression of myopia.

Among all the current treatments, antimuscarinic topical medication is one of the most effective interventions to slow myopia progression, whereas its use is limited by its adverse effects, such as near blur and photophobia, induced by cycloplegia and mydriasis, respectively [6]. An increasing number of studies have demonstrated the efficacy of atropine 0.01% eye drops in reducing spherical equivalent (SE) progression and axial length (AL) elongation, but its side-

effect profile has not been thoroughly validated. Previous studies showed that atropine 0.01% had a negligible effect on accommodation amplitude (AA), pupil diameter, and visual acuity, but the results were inconsistent among different studies. For instance, the Atropine for the Treatment of Myopia 2 (ATOM 2) study reported that atropine 0.01% had little effect on AA (reduced by 4.4 ± 4.9 D/year) [7]. In the Low-Concentration Atropine for Myopia Progression (LAMP) study, which was recently conducted in Hong Kong, atropine 0.01% group had a much smaller reduction in AA (-0.26 ± 3.04 D/year) [8]. Moreover, accommodation functions and pupil size are considered as important factors associated with the presence or progression of myopia. One previous study has demonstrated a significant relationship between the amount of myopia and the amplitude of accommodation [9]. Accommodative facility was considered to be an independent predictor of myopia progression as delays in attaining focus could lead to brief periods of hyperopic defocus, i.e., the plane of the best focus is behind the retina. And hyperopic defocus caused by lags of accommodation may lead to increased eye growth in animal models of myopia [10,11]. However, a reduced depth of focus due to pupil dilation after administration of atropine could decrease lag of accommodation with decreasing accommodation demand [12–14]. Important questions remain to be resolved, such as the effect of atropine 0.01% on accommodative function, pupil size, best-corrected visual acuity (BCVA) at distance and near, and near stereoacuity.

To our knowledge, few randomized controlled trials have investigated the effects of atropine 0.01% on myopia in Mainland China. The primary purpose of the present randomized clinical trial was to investigate the effect of atropine 0.01% on amplitude of accommodation, accommodative facility (AF), pupil size, distant and near BCVA, near stereoacuity, intraocular pressure (IOP), and difficulties affecting routine vision-related activities in Chinese children, with myopia progression being the secondary outcome measure.

2. Methods

This study was a single-center randomized clinical trial conducted at the Eye & ENT Hospital of Fudan University, Shanghai, China. The study was approved by the Ethics Committee of the Eye & ENT Hospital of Fudan University. Written informed consent was obtained from the parents or legal guardians of all enrollees, and either written or verbal assent was obtained from each participant as required. The study is listed at <http://www.chictr.org.cn> under identifier ChiCTR1800017154. All procedures were conducted in accordance with the tenets of the Declaration of Helsinki.

Children who met the eligibility criteria listed in Table 1 were enrolled and randomized to receive atropine 0.01% once nightly with regular single-vision lenses or to wear regular single-vision lenses in an allocation ratio of 3:2. Because atropine 0.01% is not commercially available in China, the eye drops were prepared by the Pharmaceutical Department of Eye & ENT Hospital (0.05% atropine sulfate (1 ml) in polyethylene glycol eye drops (4 ml)) [15].

Follow-up visits were planned at 3 and 6 months after the children were assessed and randomized at the first screening visit. Examinations were conducted by study-certified examiners masked to the group allocation. At each visit, a slit lamp examination and direct ophthalmoscopy were used to evaluate the anterior and posterior segments of the eyes. Cycloplegic refraction was used to assess the refractive errors before enrollment and at 6-month visit. Cycloplegia was achieved with four drops of compound tropicamide eye drops (0.5% tropicamide and 0.5% phenylephrine eye drops; Mydrin-P, Santen Pharmaceutical, China) administered approximately 5 min apart. Cycloplegic autorefractometry was measured 30 min after the last drop using a desktop autorefractor (KR-8800, Topcon Corporation, Tokyo, Japan). Three readings, 0.25 D or less apart, in both spherical and cylindrical components were averaged. Cycloplegic retinoscopy was then performed by an experienced optometrist, and BCVA was measured using the tumbling E Early Treatment Diabetic Retinopathy Study charts (LCD backlit lamp, WH0701, Guangzhou XieyiWeishikang, Guangzhou, China) at a distance of 4 m and converted to the logarithm of the minimum angle of resolution (logMAR) scale. Before cycloplegia, AL was measured with IOL Master (version 5, Carl Zeiss Meditec, Oberkochen, Germany). Pupil size was measured with an autorefractor (ARK-510A, Nidek, Tokyo, Japan), and at least three readings (with a range of 0.5 mm) were recorded and averaged. Near BCVA, near stereoacuity, and accommodation were tested with best-corrected distance spectacle correction within 1 week of cycloplegia. At least three repetitive examinations were conducted, and the best result was recorded. Near BCVA was assessed with a reduced logMAR reading chart at 40 cm under well-lit conditions. Near stereoacuity was measured using a random-dot stereogram (RDS, Stereo Optical, Chicago, IL, USA) at 40 cm. The value was converted to log seconds of arc for analysis, and nil stereoacuity was arbitrarily assigned a value of 4 log seconds of arc. The accommodative responses were measured monocularly and binocularly. Participants were instructed to look at a cross-shaped target at the 3 D position (33 cm) and keep it as clear as possible. Accommodative demand was then increased sequentially in 0.25 D steps by adding minus lenses on top of the subjective refractive correction of the viewing eye until the linear gap in the target became “extremely blurry” and could not be cleared by the participant. At the first noticeable blur point, the participant was asked to try with maximal accommodation expended. AA was calculated as the amount of minus lens power plus the dioptric power of the test distance (3.00 D). The monocular and binocular AF were measured with a ± 2.00 D flipper at a distance of 40 cm. The participant was instructed to report as soon as a target was clear, and then the lens was flipped to the opposite power. The number of flips per minute was recorded and converted to cycles per minute, with one cycle equivalent to recognizing the target through the -2.0 D lens then the $+2.00$ D lens. IOP was measured with noncontact tonometry (NT-1000, Nidek, Tokyo, Japan).

At 3-month visit, the Chinese version of the atropine questionnaire (<http://www.pedig.net>) was administered to

TABLE 1: Eligibility criteria for the study.

Children aged 6 to 14 years
Refractive error of spherical equivalent between -0.50 D and -6.00 D ^{†‡}
Astigmatism of -2.50 D or less [†]
Best-corrected visual acuity of logMAR 0.1 or better in both eyes
No history of other ocular diseases (i.e., amblyopia, strabismus, cataract, glaucoma, and congenital retinal diseases)
In good general health with no history of significant cardiac, respiratory, or endocrine diseases
No allergy to atropine, tropicamide, and cyclopentolate
No current or previous use of atropine or pirenzepine, contact lenses, or other forms of treatment that might affect myopia progression
Willing to comply with the allocated treatment and follow-up schedule

logMAR = logarithm of the minimum angle of resolution. [†]Refraction was measured with cycloplegic retinoscopy. [‡]Refractive error of the spherical equivalent was defined as spherical refraction plus half the cylinder refraction.

parents or legal guardian to assess the impact of atropine eye drops on children and their family.

2.1. Statistical Analysis. Based on a previous study [7] and our pilot study, atropine 0.01% caused a clinically significant 50% reduction in myopia progression, with a mean (SD) of 0.5 (0.6) D in the atropine group and 1.0 (0.6) D in the control group over 1 year. The sample size of 63 was required to ensure 80% power with a type I error of 0.05, assuming no more than 20% loss to follow-up in an allocation of 3 : 2. At a regular meeting in July, 2018, the Data and Safety Monitoring Committee suggested stopping the study early to avoid the faster progression of myopia in the control group. The participants in the control group with SE progression of ≥ 0.5 D at 6-month visit were recommended to receive atropine 0.01%.

All analyses included only those participants who completed 6-month follow-up. The primary outcomes include changes in the amplitude and facility of accommodation, pupil diameter, distant and near BCVA, and near stereoacuity. The secondary outcome was myopia progression from baseline to 6 months.

A change in a parameter was defined as the difference between the baseline value and the corresponding follow-up value. A χ^2 test and Fisher's exact test were used to test the group differences in categorical data. A two-sample *t*-test or the Mann-Whitney *U* test was used to test the group differences in continuous data. Both eyes of the same participant were pooled in a combined analysis using a generalized estimating equation with robust standard errors to adjust the correlation between eyes [16]. A repeated-measure analysis was performed for the longitudinal data on ophthalmic parameters between groups. A statistical significance level of 0.05 was used throughout the analysis. All statistical tests were performed with STATA 13.0 (College Station, TX, USA).

3. Results

Between July 2017 and July 2018, a total of 70 participants were assessed for their eligibility, and 63 participants were finally recruited to the study: 38 participants were allocated to the atropine group (atropine 0.01% with regular single-vision lenses) and 25 to the control group (regular single-vision lenses only) (Figure 1). The baseline characteristics

were similar in the two groups (Table 2). One participant in each group withdrew before 6-month visit.

3.1. Changes in Accommodation Functions, Pupil Diameter, and IOP. Monocular AA in the atropine group improved slightly from 9.2 ± 2.2 to 9.7 ± 2.2 D ($P = 0.13$) after 3 months and remained at 9.8 ± 2.1 D to the end of the follow-up visits ($P = 0.03$). For the control group, monocular AA increased from 9.3 ± 2.9 D at baseline to 10.0 ± 2.4 D ($P = 0.03$) at 3-month visit and decreased to 9.8 ± 2.2 D at 6-month visit ($P = 0.14$). There was no significant difference in the mean change in monocular AA between the two groups. From baseline to 6-month visit, binocular AA was slightly reduced in the atropine group (from 7.2 ± 1.9 D to 7.0 ± 1.9 D, $P = 0.86$), and slightly increased in the control group (from 7.3 ± 2.4 D to 7.4 ± 1.7 D, $P = 0.44$). Similarly, the change in binocular AA did not differ significantly between the two groups (Table 3 and Figure 2).

Monocular AF improved significantly after 6 months in both groups (from 10.6 ± 3.0 to 14.8 ± 3.6 cpm in the atropine group, from 10.5 ± 3.6 to 16.2 ± 4.0 cpm in the control group, both $P < 0.001$). The mean change in monocular AF was larger in the control group than in the atropine group at both 3-month visit ($P < 0.01$) and 6-month visit ($P = 0.03$). There was also significant increase in binocular AF in both groups over time (from 8.7 ± 3.2 to 12.8 ± 3.9 cpm in the atropine group, from 8.9 ± 3.7 to 14.0 ± 4.5 cpm in the control group, both $P < 0.001$). However, the mean change in binocular AF was significantly larger in the control group than in the atropine group only at 3-month visit ($P = 0.03$) (Table 3 and Figure 3). Given the large number of comparisons on a set of data in the present study, the difference of mean change of both monocular and binocular AF only reached a borderline significance at 6-month visit.

After treatment, a statistically significant increase in the pupil diameter was observed in the atropine group ($P < 0.001$), with an average diameter of 6.2 mm (95% CI: 6.0–6.5 mm) at baseline increasing to 7.0 mm (95% CI: 6.8–7.1 mm) at 6-month visit (Table 3). The pupil diameter remained stable in the control group over time. Compared with the control group, the atropine-treated children showed a significantly larger increase in the pupil diameter at both 3-month visit ($P < 0.01$) and 6-month visit ($P = 0.01$).

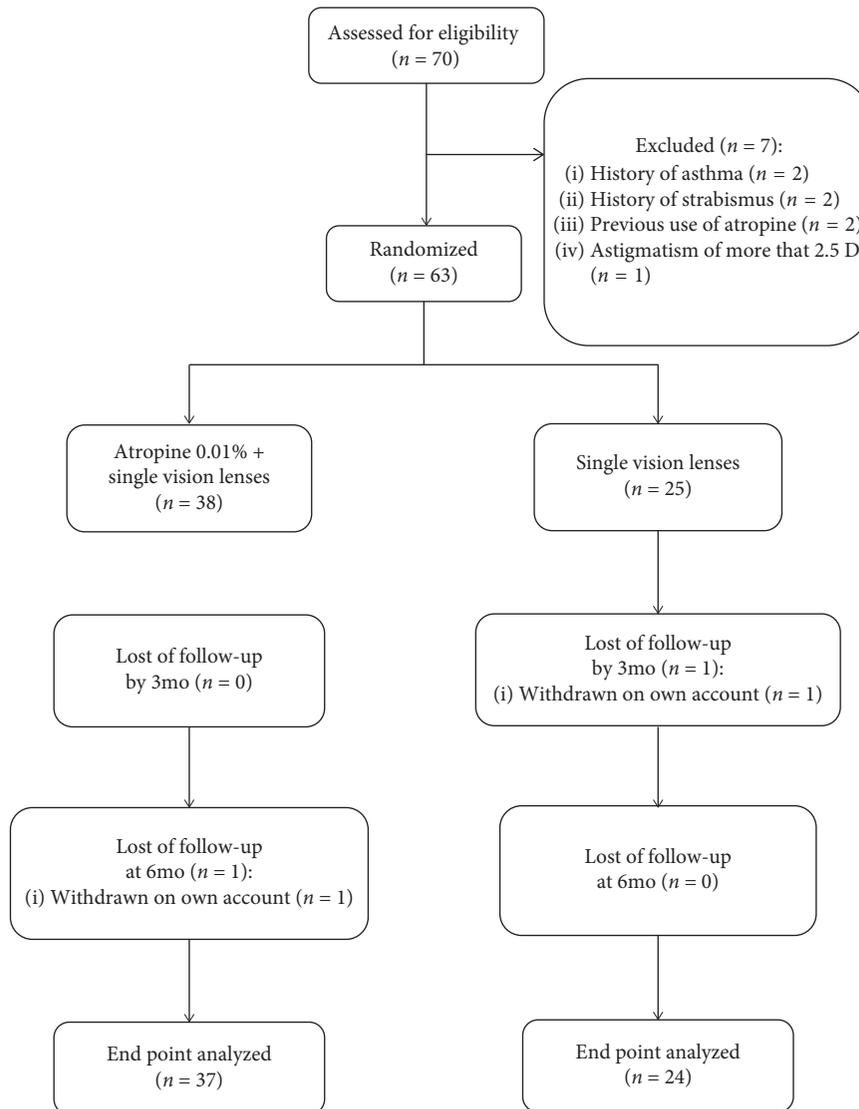


FIGURE 1: Consolidated Standards of Reporting Trials (CONSORT) flow diagram. D = diopter.

The IOP of the atropine group was not affected by atropine use over time (from 16.4 ± 2.8 to 16.2 ± 2.6 mmHg, $P = 0.44$). The mean changes in IOP were similar in the two groups (between-group 3 months: $P = 0.37$; 6 months: $P = 0.52$) (Table 3).

3.2. Changes in Distant and Near BCVA, Near Stereoacuity, and Vision-Related Activities. Near BCVA, distant BCVA, and near stereoacuity in the two groups remained stable during follow-up ($P > 0.05$) (Table 3). And the mean changes in near BCVA, distant BCVA, and near stereoacuity were similar between the two groups at both follow-up visits. Near-work problems were not reported frequently, with only two children (5.3%) complaining of difficulty in writing, coloring, or drawing. No difficulties in participating in outdoors activities, such as running, jumping, or riding, or allergic reaction were reported. However, 11 parents (28.9%) expressed concerns about the side effects related to atropine eye drops.

3.3. Changes in SE and AL. At 6 months, statistically significant progression of myopia was observed in both groups (both $P < 0.001$). The participants in the control group showed greater progression than those in the atropine group (Table 3). Of the participants in the atropine group, 59.4% progressed by < 0.5 D, compared with 31.9% in the control group, whereas 6.3% in the atropine group progressed by ≥ 1.0 D, compared with 21.3% in the control group ($P < 0.002$) (Figure 4).

A statistically significant increase in AL was detected in both groups from baseline to 6-month visit (both $P < 0.001$), and the changes in AL in the control group were larger than those in the atropine group (Table 3).

4. Discussion

Atropine has been considered as the treatment most likely to slow myopia progression [17]. However, its adverse effects make the long-term use of atropine 1% impractical, despite its confirmed efficacy [18]. The concentration of atropine has

TABLE 2: Baseline characteristics of the children in the two study groups.

	Atropine group Mean (SD), <i>n</i> = 38	Control group Mean (SD), <i>n</i> = 25	<i>P</i> value
Age (yr)	8.7 (1.6)	8.7 (1.8)	0.89
Female, <i>n</i> (%)	19 (50.0)	11 (44.0)	0.64
Spherical equivalent (D)	-1.94 (1.17)	-1.78 (1.15)	0.39
Axial length (mm)	24.21 (0.90)	24.33 (0.64)	0.12
Near BCVA (logMAR)	0.00 (0.00)	0.00 (0.00)	—
Distant BCVA (logMAR)	0.01 (0.02)	0.00 (0.01)	0.70
Age at wearing spectacle (yr)	8.2 (1.7)	7.6 (1.7)	0.23
Paternal myopia status, <i>n</i> (%)			
No myopia	8 (21.1)	2 (8.0)	
SE < 6.0 D	23 (60.5)	16 (64.0)	0.32
SE ≥ 6.0 D	7 (18.4)	7 (28.0)	
Maternal myopia status, <i>n</i> (%)			
No myopia	7 (18.4)	6 (24.0)	0.74
SE < 6.0 D	22 (57.9)	12 (48.0)	
SE ≥ 6.0 D	9 (23.7)	7 (28.0)	
Accommodation amplitude (D)			
Monocular	9.3 (2.2)	9.3 (2.8)	0.73
Binocular	7.4 (2.2)	7.3 (2.3)	0.63
Accommodation facility (cpm)			
Monocular	10.6 (2.9)	10.9 (4.0)	0.87
Binocular	8.7 (3.2)	9.2 (4.0)	0.54
Pupil diameter (mm)	6.3 (1.0)	6.3 (1.1)	0.54
Near stereoacuity (log (seconds of arc))	1.4 (0.2)	1.4 (0.1)	0.17
Intraocular pressure (mmHg)	16.5 (2.8)	15.4 (3.1)	0.05

D = diopter; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; cpm = cycles per minute.

been modified to limit its side effects while trying to maintain its benefits [19, 20].

The effects of atropine 0.01% on AA were slightly inconsistent among different studies. In the last phase of the ATOM 2 study, all children with myopia progression of ≥0.50 D in the washout year were restarted on atropine 0.01% for further 24 months [21]. The loss of AA of 2.54 D during the retreatment was smaller than the change noted in eyes treated with atropine 0.01% during the first phase (-4.6 D) although it was also considered clinically insignificant and recovered to level similar to those in untreated children at 2-month visit after stopping atropine 0.01%. In the LAMP study, the atropine 0.01% group had minimal accommodation loss similar to the placebo group (-0.26 ± 3.04 vs. -0.32 ± 2.91 D/year, *P* = 0.89). Direct comparison of our study with the other two studies should be made with caution because AA was calculated as the inverse of the near point of accommodation in the ATOM 2 study and the LAMP study. Compared with the minus lens method used in our study, the push-up method used in those studies is more likely to be affected by the eye's depth of focus, reaction time, and instrumentation errors [22]. In our study, three children in the treatment group complained of blurred near vision in the first 1-2 weeks. It was speculated that AA may be reduced at an early stage and then recovered within 3 months. The early evaluation of AA would help us understand the effect of atropine 0.01% on AA more precisely.

Few previous studies have provided measurement of AF, which should also be affected by accommodative paresis. AF was tested to evaluate the ability of the eye to alter its

accommodation rapidly and accurately. Allen and O'Leary reported that AF was the main independent predictor of myopia progression, and lower facility rates were associated with increased myopia progression [9]. In contrast, AF improved significantly over time in our study, and the control group showed even greater improvement than the atropine 0.01% group at 3-month visit. However, the AF measurement is subjective, depending on the speed of the response. Therefore, there is no guarantee that different participants use the same criteria of clarity or the same response speed to initiate the alternation of the lens. AF could also be improved by repeating the same test procedure at every follow-up visit. This suggests that using simple clinical measurement of subjective AF as an indicator of accommodation status may be misleading [23].

A relatively small dilation of the pupil was observed during the treatment. The varying degrees of pupil dilation observed in different studies could be attributed to different methods under different lighting conditions during measurement, which makes direct comparisons difficult. However, routine vision-related activities were not affected by atropine 0.01% in this study, despite the enlarged pupil.

Near stereoacuity was not reduced in the atropine group, which means that the binocular cooperation between the eyes and the visual acuity of each eye were preserved well in this study. There was no significant atropine-induced increase in IOP. A retrospective cross-sectional study also found that neither the treatment duration nor the cumulative dose of atropine was statistically significantly associated with IOP [24].

TABLE 3: Ophthalmological parameters at follow-up visits†.

	Atropine group Mean (SD), <i>n</i> = 37	Control group Mean (SD), <i>n</i> = 24	<i>P</i> value
Spherical equivalent (D)			
Mean change over 6 mos	-0.30 (0.42)	-0.60 (0.43)	< 0.001*
Axial length (mm)			
Mean change over 3 mos	0.12 (0.12)	0.19 (0.14)	0.004*
Mean change over 6 mos	0.24 (0.16)	0.35 (0.20)	0.001*
Accommodation amplitude (D)			
Monocular			
Mean change over 3 mos	0.5 (2.7)	0.7 (2.1)	0.75
Mean change over 6 mos	0.6 (2.2)	0.5 (2.3)	0.80
Binocular			
Mean change over 3 mos	0.1 (2.1)	0.3 (1.8)	0.62
Mean change over 6 mos	-0.2 (1.9)	0.1 (2.3)	0.57
Accommodation facility (cpm)			
Monocular			
Mean change over 3 mos	2.0 (3.3)	3.7 (3.0)	<0.01*
Mean change over 6 mos	4.2 (4.0)	5.7 (3.6)	0.03*
Binocular			
Mean change over 3 mos	1.7 (3.6)	3.5 (3.1)	0.03*
Mean change over 6 mos	4.0 (4.0)	5.0 (3.5)	0.29
Pupil diameter (mm)			
Mean change over 3 mos	0.8 (0.7)	-0.1 (0.5)	<0.01*
Mean change over 6 mos	0.7 (0.7)	0.1 (0.5)	0.01*
Near BCVA (logMAR)			
Mean change over 3 mos	0.00 (0.00)	0 (0.00)	-
Mean change over 6 mos	0.00 (0.00)	0 (0.00)	-
Distant BCVA (logMAR)			
Mean change over 3 mos	-0.01 (0.02)	-0.00 (0.01)	0.62
Mean change over 6 mos	-0.00 (0.02)	-0.00 (0.02)	0.57
Near stereoacuity (log (seconds of arc))			
Mean change over 3 mos	0.0 (0.2)	0.0 (0.1)	0.22
Mean change over 6 mos	0.0 (0.2)	0.0 (0.1)	0.82
Intraocular pressure (mmHg)			
Mean change over 3 mos	0.6 (2.5)	0.2 (2.0)	0.37
Mean change over 6 mos	-0.3 (2.8)	0.1 (2.6)	0.52

D = diopter; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; cpm = cycles per minute. †Repeated-measure analyses were performed for the ophthalmic parameters, with treatment group, time, and the interaction between time and group included in the model. *Significant at 0.05.

The ATOM 2 study confirmed the efficacy of atropine 0.01% with a significantly lower myopia progression rate of -0.49 ± 0.63 D/2 years than that in the placebo group in the ATOM 1 study (-1.20 ± 0.69 D/2 years) [7]. The LAMP study showed that the change in SE in the atropine 0.01% group was -0.59 ± 0.61 D over 1 year [8]. In the present study, atropine 0.01% effectively reduced myopia progression of -0.30 ± 0.42 D/6 months (a reduction of 50% compared with the control group). The efficacy of atropine 0.01% in our study appears to be less than that in the ATOM 2 study but similar to that in the LAMP study. It was noted in the ATOM 2 study that participants in the atropine 0.01% group progressed by -0.43 D after the first year, but the myopia progression rate then slowed significantly in the second year, with only 0.06 D progression. A long follow-up period is required to identify the possible cumulative efficacy of atropine 0.01%.

The control of axial elongation has been considered crucial in preventing myopia progression, with a strong correlation between AL and refractive status. In our study,

the increase in AL was 0.24 ± 0.16 mm after administration of atropine 0.01% for 6 months, which was a reduction of 31% compared with the control group. The progression of AL in the LAMP study was 0.36 ± 0.29 mm/year (a reduction of 12%). A 1 mm increase in AL was equivalent to myopia progression of -1.25 D in our study compared with -1.64 D/mm in the LAMP study. Each component of the visual system interacts closely with other components during the myopic process [25]. For instance, lens thinning appears to compensate for the increase in AL during normal eye growth. In myopic individuals, the thickness and power of the lens decrease further to compensate for the extra increase in AL [26]. Whether these lens changes explain, even partly, the efficacy of atropine 0.01% in retarding SE progression and whether this is an active or a passive process will be assessed in our future research.

Our study confirmed the efficacy and safety of atropine 0.01% eye drops. However, some children showed suboptimal or no response to atropine 0.01%. Alternative treatment options, such as the twice-daily application of atropine

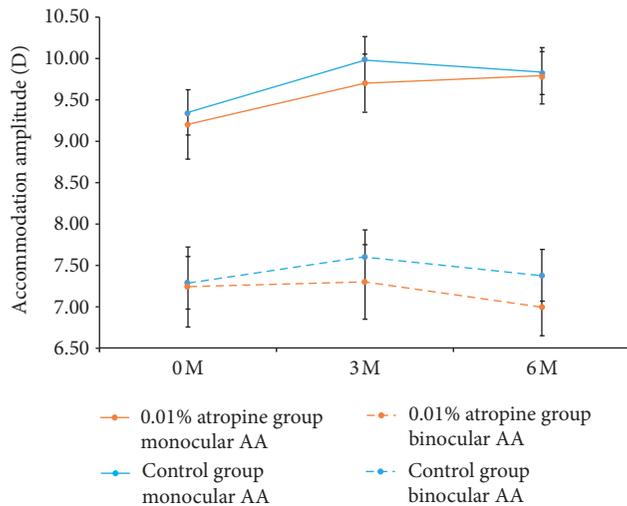


FIGURE 2: Mean and SE of AA in the atropine and control groups at baseline and follow-up visits. There was no significant difference in monocular and binocular AA between the two groups at two follow-up visits. SE = standard error; AA = accommodation amplitude; D = diopter.

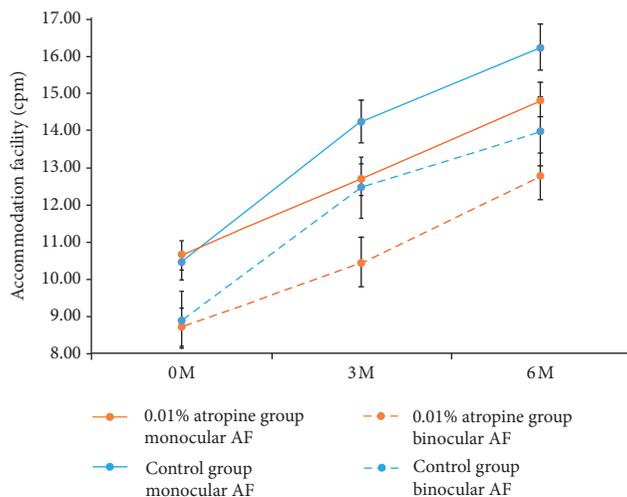


FIGURE 3: Mean and SE of AF in the atropine and control groups at baseline and follow-up visits. There was significant difference in both monocular and binocular AF between the two groups at 3-month visit. SE = standard error; AF = accommodation facility; cpm = cycles per minute.

0.01% or a once-weekly application of high-concentration atropine (0.5% or 1.0%) could be considered for these children. More randomized clinical trials should be conducted to determine which child would most benefit from topical atropine treatment (in terms of age, myopic status, and other risk factors), when atropine treatment should be started and stopped, and the length of treatment (long-term effectiveness and safety). Moreover, identifying the specific site of action of atropine may allow more targeted therapy with fewer adverse effects in the future.

The strength of our study is that it provides a much more detailed side-effect profile of atropine 0.01%. Nevertheless,

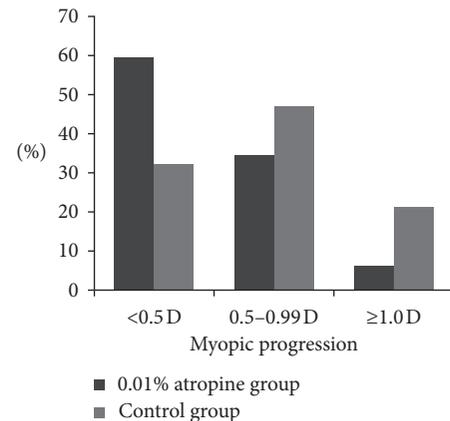


FIGURE 4: Distribution of myopic progression in the atropine and control groups at 6-month follow-up. In the atropine group, 59.4%, 34.3%, and 6.3% participants progressed by <0.5 D, 0.5–0.99 D, and ≥1.0 D, respectively. In comparison, 31.9%, 46.8%, and 21.3% participants in the control group progressed by <0.5 D, 0.5–0.99 D, and ≥1.0 D, respectively. D = diopter.

several limitations of the study must be acknowledged. First, it was a single-center study with a relatively small sample size, thereby reducing the power of the statistical tests. Second, the intended 1-year follow-up was reduced because of the greater progression of myopia in the control group. Therefore, the long-term efficacy and safety of atropine 0.01% were not assessed well. Third, the indicators of accommodation were subjective, which may have biased the results.

5. Conclusion

The eye drops containing atropine 0.01% used in this study significantly increased pupil diameter less than one mm, while routine vision-related activities were not affected despite the enlarged pupil. Besides, the accommodative functions, BCVA, near stereoacuity, and IOP were not affected by administration of atropine 0.01%. Combined with its reducing myopia progression, atropine 0.01% can be used as a safe and effective treatment for myopia in Chinese children.

Data Availability

The datasets used to support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References

- [1] B. A. Holden, T. R. Fricke, D. A. Wilson et al., "Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050," *Ophthalmology*, vol. 123, no. 5, pp. 1036–1042, 2016.
- [2] C.-W. Pan, D. Ramamurthy, and S.-M. Saw, "Worldwide prevalence and risk factors for myopia," *Ophthalmic and Physiological Optics*, vol. 32, no. 1, pp. 3–16, 2012.
- [3] J. Zhao, X. Pan, R. Sui, S. R. Munoz, R. D. Sperduto, and L. B. Ellwein, "Refractive error study in children: results from shunyi district, China," *American Journal of Ophthalmology*, vol. 129, no. 4, pp. 427–435, 2000.
- [4] M. He, J. Zeng, Y. Liu, J. Xu, G. P. Pokharel, and L. B. Ellwein, "Refractive error and visual impairment in urban children in southern China," *Investigative Ophthalmology & Visual Science*, vol. 45, no. 3, pp. 793–799, 2004.
- [5] L. L. Lin, Y. F. Shih, C. K. Hsiao, and C. J. Chen, "Prevalence of myopia in Taiwanese schoolchildren: 1983 to 2000," *Annals of the Academy of Medicine, Singapore*, vol. 33, no. 1, pp. 27–33, 2004.
- [6] J. J. Walline, K. Lindsley, S. S. Vedula, S. A. Cotter, D. O. Mutti, and J. D. Twelker, "Interventions to slow progression of myopia in children," *Cochrane Database of Systematic Reviews*, no. 1, Article ID CD004916, 2011.
- [7] A. Chia, W. H. Chua, Y. B. Cheung et al., "Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (atropine for the treatment of myopia 2)," *Ophthalmology*, vol. 119, no. 2, pp. 347–354, 2012.
- [8] J. C. Yam, Y. Jiang, S. M. Tang et al., "Low-concentration atropine for myopia progression (lamp) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control," *Ophthalmology*, vol. 126, no. 1, pp. 113–124, 2019.
- [9] P. M. Allen and D. J. O'Leary, "Accommodation functions: co-dependency and relationship to refractive error," *Vision Research*, vol. 46, no. 4, pp. 491–505, 2006.
- [10] E. L. Smith and L. F. Hung, "The role of optical defocus in regulating refractive development in infant monkeys," *Vision Research*, vol. 39, no. 8, pp. 1415–1435, 1999.
- [11] E. L. Smith, "Spectacle lenses and emmetropization: the role of optical defocus in regulating ocular development," *Optometry and Vision Science*, vol. 75, no. 6, pp. 388–398, 1998.
- [12] W. N. Charman, "The eye in focus: accommodation and presbyopia," *Clinical and Experimental Optometry*, vol. 91, no. 3, pp. 207–225, 2008.
- [13] W. N. Charman and H. Radhakrishnan, "Accommodation, pupil diameter and myopia," *Ophthalmic and Physiological Optics*, vol. 29, no. 1, pp. 72–79, 2009.
- [14] N. López-Gil, J. Martín, T. Liu, A. Bradley, D. Díaz-Muñoz, and L. N. Thibos, "Retinal image quality during accommodation," *Ophthalmic and Physiological Optics*, vol. 33, no. 4, pp. 497–507, 2013.
- [15] Z. Chen, S. Huang, J. Zhou, X. Qu, X. Zhou, and F. Xue, "Adjunctive effect of orthokeratology and low dose atropine on axial elongation in fast-progressing myopic children—a preliminary retrospective study," *Contact Lens and Anterior Eye*, vol. 42, no. 4, pp. 439–442, 2019.
- [16] R. L. Williams, "A note on robust variance estimation for cluster-correlated data," *Biometrics*, vol. 56, no. 2, pp. 645–646, 2000.
- [17] J. Huang, D. Wen, Q. Wang et al., "Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis," *Ophthalmology*, vol. 123, no. 4, pp. 697–708, 2016.
- [18] M. Y. Yen, J. H. Liu, S. C. Kao, and C. H. Shiao, "Comparison of the effect of atropine and cyclopentolate on myopia," *Annals of Ophthalmology*, vol. 21, no. 5, pp. 180–187, 1989.
- [19] A. C. Chou, Y. F. Shih, T. C. Ho, and L. L. Lin, "The effectiveness of 0.5% atropine in controlling high myopia in children," *Journal of Ocular Pharmacology and Therapeutics*, vol. 13, no. 1, pp. 61–67, 1997.
- [20] Y.-F. Shih, C.-H. Chen, A.-C. Chou, T.-C. Ho, L. L.-K. Lin, and P.-T. Hung, "Effects of different concentrations of atropine on controlling myopia in myopic children," *Journal of Ocular Pharmacology and Therapeutics*, vol. 15, no. 1, pp. 85–90, 1999.
- [21] A. Chia, Q. S. Lu, and D. Tan, "Five-year clinical trial on atropine for the treatment of myopia 2: myopia control with atropine 0.01% eyedrops," *Ophthalmology*, vol. 123, no. 2, pp. 391–399, 2016.
- [22] H. B. David, J. E. Bruce, and M. A. Peter, "Clinical measurement of amplitude of accommodation: a review," *Optometry in Practice*, vol. 15, pp. 75–86, 2014.
- [23] P. M. Allen, W. N. Charman, and H. Radhakrishnan, "Changes in dynamics of accommodation after accommodative facility training in myopes and emmetropes," *Vision Research*, vol. 50, no. 10, pp. 947–955, 2010.
- [24] T. E. Wu, C. C. Yang, and H. S. Chen, "Does atropine use increase intraocular pressure in myopic children?," *Optometry and Vision Science*, vol. 89, no. 2, pp. E161–E167, 2012.
- [25] W. Meng, J. Butterworth, F. Malecaze, and P. Calvas, "Axial length of myopia: a review of current research," *Ophthalmologica*, vol. 225, no. 3, pp. 127–134, 2011.
- [26] Y.-F. Shih, T.-H. Chiang, and L. L.-K. Lin, "Lens thickness changes among schoolchildren in Taiwan," *Investigative Ophthalmology & Visual Science*, vol. 50, no. 6, pp. 2637–2644, 2009.