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ORIGINAL ARTICLE

Myopia progression after cessation of low-dose atropine eyedrops treatment: A two-year randomized, double-masked, placebo-controlled, cross-over trial

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Abstract

Purpose: The purpose of the study was to evaluate myopia progression and axial elongation after stopping 0.01% atropine eye drops through a 2-year cross-over study.

Methods: This study was a randomized, double-masked, placebo-controlled, cross-over trial in mainland China. 220 children aged 6–12 years with spherical equivalent range of −1.00 D to −6.00 D in both eyes were enrolled in Phase 1 for 1 year. Children who had completed the first year's follow-up continued in the second phase. In Phase 2, the placebo group was crossed over to the 0.01% atropine group (referred to as the 'placebo-atropine group'), and the 0.01% atropine group was crossed over to the placebo group (referred to as the 'atropine-placebo group'). All children underwent the examination of cycloplegic refraction and axial length at a 6-month interval. Only data from right eyes were included in analysis.

Results: One hundred thirty-three subjects completed 2 years of follow-up. In the first year, the mean myopia progression in atropine-placebo group was 0.21 ± 0.08 D slower than that in placebo-atropine group. After cross-over treatment, the mean myopia progression in atropine-placebo group was 0.22 ± 0.07D faster than that in placebo-atropine group in the second year. Over 2 years, the mean myopia progression was −1.26 ± 0.66D and −1.25 ± 0.70D in the atropine-placebo and placebo-atropine groups ($p = 0.954$).

Conclusions: The difference in myopia progression between atropine-placebo group and placebo-atropine group in Phase 1 was similar to Phase 2 during the cross-over treatment. Through our cross-over trial, the results suggest that there is no rebound effect after using 0.01% atropine eye drops to prevent progression of myopia.

KEYWORDS
0.01% atropine eye drops, axial elongation, myopia progression, rebound effect

Trial Registration: http://www.chictr.org.cn identifier: ChiCTR-IOR-17013898.

1 | INTRODUCTION

The increasing prevalence of myopia has become a critical worldwide public health problem in recent decades (Baird et al., 2020; He et al., 2007; Li et al., 2013; Wu et al., 2013). In East and Southeast Asia, the prevalence of myopia has been reported to be higher (Pan et al., 2012). In China, the prevalence of myopia reaches 3.9% in grade 1 students, and 67.3% in grade 7 students (Li et al., 2013). Of note, the prevalence rate of 83.2% for myopia and 11.1% for high myopia were found in university students in central China (Wei et al., 2018). To minimize the risk of myopia-related complications such as myopic retinopathy, choroidal neovascularization and retinal detachment (Liang et al., 2008; Saw et al., 2005), several studies have been conducted in an attempt to slow or halt myopia progression.

Topical atropine, a nonselective muscarinic antagonist, has been evaluated to be the most effective on reducing the progression of childhood myopia (Chia et al., 2012; Huang et al., 2016; Li et al., 2014). However, ocular adverse effects induced by 1.0% atropine eye drops, such as blurred near vision, photophobia cycloplegia and allergy, have limited its use. In the Atropine for the Treatment of Myopia 2 (ATOM 2) study, Chia et al. (2012) reported 0.01% atropine eye drops has sustained efficacy and minimal side effects compared with 0.1% and 0.5% atropine eye drops. Therefore, 0.01% atropine eye drops is increasingly applied to clinical treatment for children with myopia. However, the ATOM 2 study was limited by the lack of a placebo control group. The low-concentration atropine for myopia progression (LAMP) study from Hong Kong, China, first provided placebo-compared data of low-concentration atropine eye drops in slowing myopia progression (Yam et al., 2019). They found that 0.05% was more effective as compared to 0.01%, and there is a slight rebound effect in the 0.05% group (Yam et al., 2019). In our first year (Phase 1) study, we found that 0.01% atropine eye drops significantly controlled the myopia progression and axial length in mainland Chinese children, compared with placebo treatment (Wei et al., 2020).

For effective control of myopia progression, the most obvious approach is to continue with treatment until that the progression has slowed with age to minimal levels. The mean age of myopia stabilization seems to be approximately 16 years for early childhood onset myopia (COMET Group. 2013). Since it seems difficult to use atropine throughout the whole period of childhood myopia progression, it is important to evaluate myopia progression and axial elongation after cessation of atropine in children. In the ATOM 1 study, Tong et al. (2009) reported the myopic progression after cessation of 1% atropine drops for 1 year. However, there were the only two studies that evaluated myopia progression and axial elongation after stopping 0.01% atropine eye drops (Chia et al., 2014; Yam et al., 2022). During the 1-year washout period in Singaporean children, Chia et al. (2014) reported that myopic progression was −0.87±0.52D, −0.68±0.45D and −0.28±0.33D in the 0.5%, 0.1% and 0.01% atropine groups, respectively ($p<0.001$) in the ATOM 2 study. Recently, Yam et al. (2022) showed that the myopia progression after cessation of atropine was −0.68±0.49D, −0.57±0.38D and −0.56±0.40D for the 0.05%, 0.025% and 0.01% atropine groups, respectively, in Hong Kong children. Thus, the myopia progression after stopping 0.01% atropine eye drops has not been extensively evaluated at present, especially among children in mainland China.

Therefore, in Phase 2 of our study (the second year), we aimed to evaluate the myopia progression and axial elongation after stopping 0.01% atropine eye drops through this randomized, double-masked, placebo-controlled, cross-over trial in mainland China.

2 | METHODS

2.1 | Study design

This study was a randomized, double-masked, placebo-controlled, cross-over trial which comprises two phases, in mainland China. The detailed design and methods have been described previously in Phase 1 (Wei et al., 2020). In brief, 6- to 12-year-old children with spherical equivalent (SE) refraction range of −1.00D to −6.00D in both eyes, astigmatism of less than 1.50D in both eyes, and intraocular pressure of less than 21 mmHg were enrolled in this. In Phase 1 (the first year), a total of 220 subjects were randomized to receive either 0.01% placebo or atropine eye drops at bedtime every night in both eyes for 1 year. In Phase 2 (the second year), the placebo group was crossed over to the 0.01% atropine group (referred to as the 'placebo-atropine group') and the 0.01% atropine group was crossed over to the placebo group (referred to as the 'atropine-placebo group') for 1 year. All eye drops were prepared in mono-dose preparation by Shenyang Xingqi Pharmaceutical Co, Ltd (Shenyang, PR. China). The eye drops were packaged in identical bottles. This clinical trial adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Beijing Tongren Hospital, Capital Medical University. Informed written consent was obtained from at least one parent, as well as verbal assent from each child.

2.2 | Study procedures

In Phase 2, Children underwent the same, standardized ophthalmic examinations as in Phase 1 at the 18th and 24th months. Children were offered photochromatic glasses (which darken on exposure to ultraviolet or sunlight) if their parents were worried of excessive light exposure or if they experienced glare. Children were also provided with a calendar to tick off the days when the eye drops were used and more than 80% compliance rate was considered to be included.

At each visit, spherical equivalent refraction was measured by an autorefractor (HRK7000 A; Huvitz, Gunpo, South Korea) after a cycloplegic procedure with 3 drops of 1% cyclopentolate with a 5-min interval. The measurement was performed 30 min after the installation of the third drop. A fourth drop of 1% cyclopentolate

would be given 30 min after the third drop if pupillary light reflex was still present or the pupil size was less than 6.0 mm, and the examination was repeated 15 min later. Axial length (AL) was measured on a Lenstar LS900 (Haag-Streit Koeniz, Switzerland), and the average of five readings were taken. Additionally, a detailed interviewer-administered questionnaire answered by parents was used to collect the information of their children on the age of myopia onset, number of myopic parents, time near work and outdoors activities (h/day) after school hours (Li et al., 2013, 2015). At baseline, the average age of myopia onset was 7.91 ± 1.69 years, and the time near work and outdoors activities after school hours was 3.29 ± 1.43 h/day and 1.47 ± 0.58 h/day, respectively.

2.3 | Outcomes

The SE was calculated as the spherical dioptres (D) and half of the cylinder (sphere +0.5 × cylinder). The primary outcome was myopia progression which was defined as the mean change in SE over 2 years. The secondary outcome included the change in AL over 2 years. During the treatment, subjects and parents were asked about symptoms related to blurred near vision, glare, allergy and any medical illness or side effects.

2.4 | Statistical analyses

We used SPSS version 20.0 (SPSS, Chicago, Illinois, USA) for all analyses. Only the right eyes were included in the analyses. The Change in myopia progression and axial elongation were defined as the difference between the baseline visit and follow-up visit. Continuous variables were expressed as mean ± standard deviation (SD). For continuous variables, the independent t-test was used to test the mean difference between the atropine-placebo group and placebo-atropine group. The chi-square tests were used to compare categorical variables between groups. A two-sided p-value <0.05 was considered statistically significant.

3 | RESULTS

A total of 220 subjects were enrolled in the Phase 1 study, with equal randomization to the 0.01% atropine and the placebo groups. No significant differences were found between the 0.01% atropine and the placebo groups in the baseline characteristics, included age, gender, initial SE, initial AL, age at myopia onset, parental myopia, time outdoors and near work. Of 220 participants, 61 of them did not attend the follow-up in Phase 1, and 26 of them were lost to follow-up in Phase 2, leaving 133 (60.5%) subjects included for this analysis. Figure 1 shows the randomization of the individuals and study outline for Phase 1 and Phase 2. No significant differences were found in gender, baseline spherical equivalent, baseline axial length, baseline intraocular pressure, baseline age of myopia onset, parental myopia, baseline time near work and outdoors activities, between the follow-up subjects who had completed 2 years of follow-up, and the drop-out subjects who had not completed 2 years of follow-up ($p > 0.05$, Table 1), except for age (9.90 ± 1.64 years vs. 9.24 ± 1.68 years, $p < 0.05$).

Of 133 subjects who had completed 2-year follow-up, 65 and 68 children were allocated into the atropine-placebo and placebo-atropine groups, respectively. At baseline, there was no significant difference in initial SE (−2.65 ± 1.29D vs. −2.74 ± 1.48, $p = 0.717$) and AL (24.62 ± 0.80 mm vs. 24.72 ± 0.96 mm, $p = 0.529$) between the atropine-placebo and placebo-atropine groups, respectively.

3.1 | Comparison of changes of SE and AL in the first year and the second year

The respective mean changes in SE and AL for the atropine-placebo and placebo-atropine groups at 6, 12, 18 and 24 months were showed in Figures 2 and 3.

In the first year, the mean progression of myopia for atropine-placebo group and placebo-atropine group were −0.48 ± 0.42D and −0.69 ± 0.48D, with a mean difference of 0.21 ± 0.08D ($p = 0.009$). In the second year, the mean progression of myopia for atropine-placebo group and placebo-atropine group were −0.78 ± 0.43D and −0.56 ± 0.39D, with a mean difference of 0.22 ± 0.07D ($p = 0.002$). So, the mean difference of myopia progression between atropine-placebo group and placebo-atropine group in the first year (0.21 ± 0.08D) was similar to the second year (0.22 ± 0.07D) during the cross-over treatment (Table 2).

In the first year, the mean axial elongation values for atropine-placebo group and placebo-atropine group were 0.30 ± 0.20 mm and 0.37 ± 0.18 mm, with a mean difference of 0.07 ± 0.03 mm ($p = 0.033$). In the second year, the mean axial elongation values for atropine-placebo group and placebo-atropine group were 0.39 ± 0.17 mm and 0.34 ± 0.18 mm, with a mean difference of 0.05 ± 0.03 mm ($p = 0.139$). So, the mean difference of axial elongation between atropine-placebo group and placebo-atropine group in the first year (0.07 ± 0.03 mm) was similar to the second year during the cross-over period after cross-over treatment (0.05 ± 0.03 mm) (Table 2).

3.2 | Changes in SE and AL over 2 years

At the end of 2 years, the atropine-placebo group had a mean myopia progression of −1.26 ± 0.66D, compared with −1.25 ± 0.70D for placebo-atropine group (mean difference, 0.01 ± 0.12D, $p = 0.954$; Table 2). The mean axial elongation over 2 years were 0.68 ± 0.31 mm for atropine-placebo group and 0.72 ± 0.32 mm for placebo-atropine group (mean difference, 0.04 ± 0.06 mm, $p = 0.537$; Table 2).

Table 3 presents a similar distribution of change in spherical equivalent in the first year, the second year and the over 2 years. Over the 2 years, 10.77% of subjects progressed by less than 0.5D in the atropine-placebo group, compared with 13.24% in the placebo-atropine group; and 67.69% progressed by at least 1.0D in the

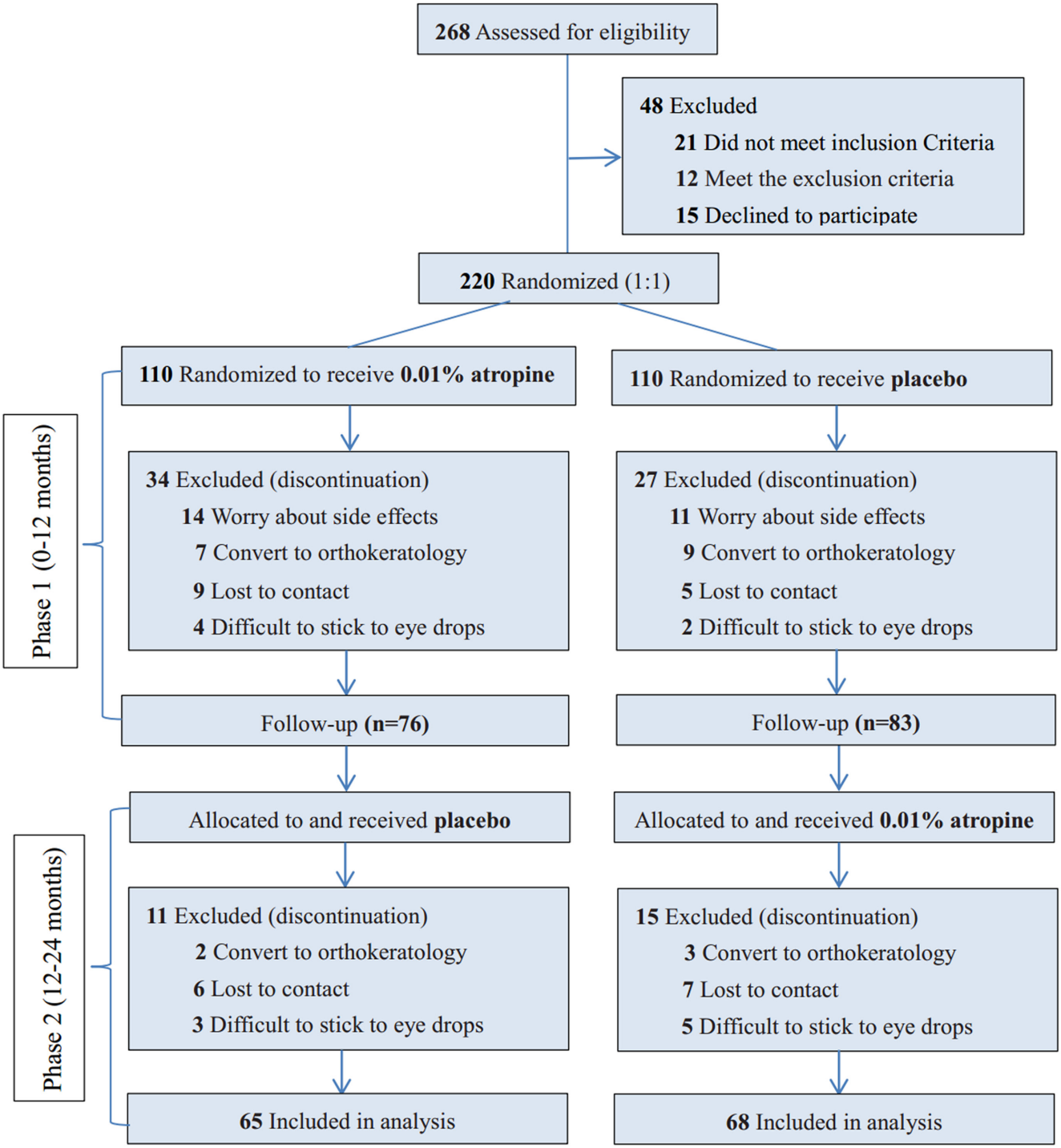

FIGURE 1 Flowchart of randomized individuals and outline for Phase 1 and Phase 2.

atropine-placebo group, compared with 67.65% in the placebo-atropine group.

3.3 | Adverse events

As reported in the first year by us previously, no serious adverse events related to atropine were found in the second year. Four children (5.9%) complained of photophobia in the switch to using 0.01% atropine group, and none of the children in the switch to using placebo group complained of photophobia. Allergic reactions were also uncommon, with 3 children occurring with allergic conjunctivitis, and one of them was in the switch to using placebo group. In the switch to using 0.01% atropine group, one child complained of near-blurred vision.

4 | DISCUSSION

In the Phase 2 of this study, we found that the mean difference of myopia progression between atropine-placebo group and placebo-atropine group in the first year was similar to the second year after cross-over treatment, and the mean myopia progression of −1.26±0.66D over 2 years in the atropine-placebo group was also similar to −1.25±0.70D for placebo-atropine group, both indicating that there was no myopic rebound after using

TABLE 1 Demographics and baseline characteristics of those completing the 2 years of follow-up versus those who have not completed 2-year follow-up in atropine-placebo and placebo-atropine groups

Variables	Completed 2 years (n = 133)	Not completed 2 years (n = 87)	p-Value
Age at baseline (years)	9.90 ± 1.64	9.24 ± 1.68	0.004
Male/female	68/65	49/38	0.450
Spherical equivalent (D)	−2.67 ± 1.41	−2.44 ± 1.36	0.237
Axial length (mm)	24.65 ± 0.89	24.50 ± 0.83	0.227
Intraocular pressure (mm Hg)	15.81 ± 2.53	15.90 ± 3.22	0.830
Age at myopia onset	8.07 ± 1.62	7.65 ± 1.77	0.086
Parental myopia, n (%)			0.106
None	9 (6.8%)	2 (2.3%)	
One	49 (36.8%)	25 (28.7%)	
Both	75 (56.5%)	60 (69.0%)	
Near work (h/d)	3.30 ± 1.36	3.26 ± 1.53	0.823
Time outdoors (h/d)	1.44 ± 0.58	1.52 ± 0.59	0.369

Abbreviation: D, dioptre.

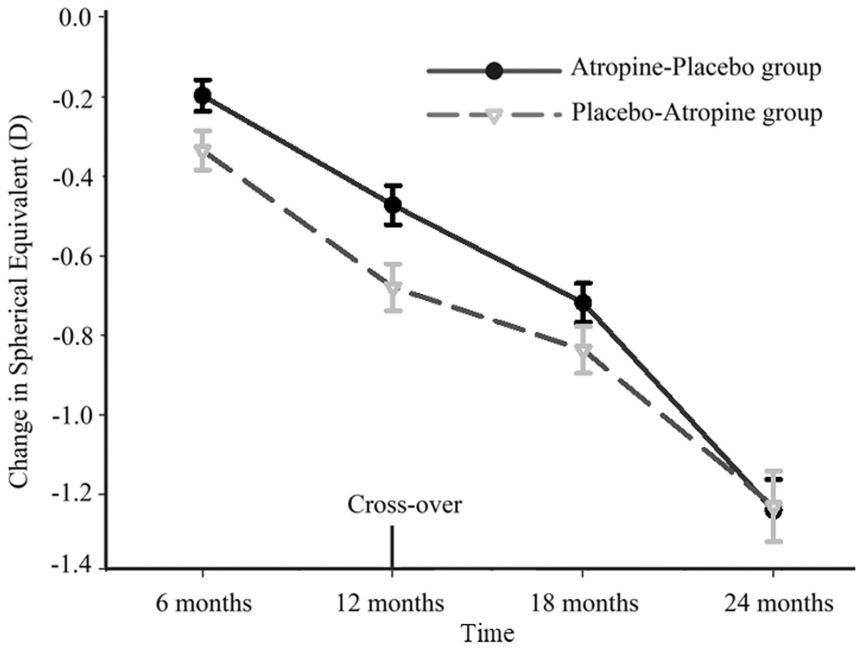

FIGURE 2 Mean change for spherical equivalent in the atropine-placebo and placebo-atropine groups over 2 years. Error bars represent one standard error.

atropine 0.01% eye drops to prevent progression of myopia. During a two-year period, if children choose to use 0.01% atropine only for 1 year, there is no difference between using atropine in the first year or the second year. To our knowledge, this study is the first randomized, double-masked, placebo-controlled, cross-over trial to explore the myopia progression after cessation of atropine in mainland China.

Our study showed that the 0.01% atropine eye drops significantly slowed the progression of myopia as compared to controls after cross-over treatment in the second year, with a mean difference of −0.22D/year. In 2018, the low-concentration atropine for myopia progression (LAMP) study in children aged 4–12 years in China provided the first placebo-compared results of 0.01% atropine eye drops in slowing myopia progression, showing that the mean myopia progression after 1 year was −0.59 ± 0.61D in the 0.01% atropine group compared with −0.81 ± 0.53D in the placebo group (Yam et al., 2019). Another study in children aged 6–14 years from China, Fu et al. (2020) reported the myopia progression over 1 year was −0.47 ± 0.45D and −0.70 ± 0.60D in the group of atropine 0.01% and the placebo group respectively. Age at baseline was a significant factor associated with myopic progression (Parssinen et al., 2021), so we enrolled children aged 6–12 years old, similar to the above two studies. For those Chinese children enrolled in the above two studies, the mean differences of myopia progression between 0.01% atropine and placebo groups in the LAMP study (−0.22D/year) and the study by Fu et al. (−0.23D/year) were almost the same with our results (−0.22D/year). Clark and Clark (2015) evaluated 60 children aged 6–15 years in a retrospective study in the United States, reporting the 0.01% atropine eye drops

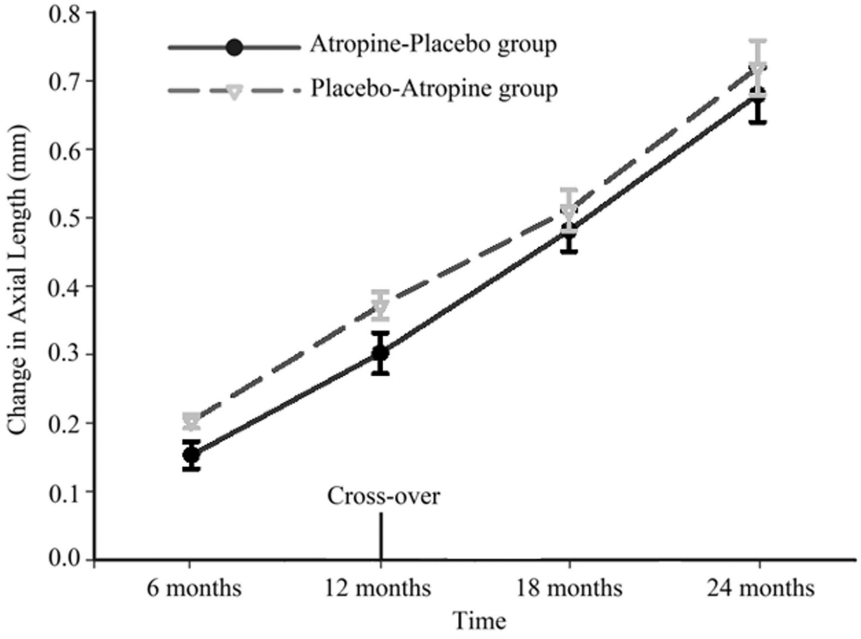

FIGURE 3 Mean change for axial length in the atropine-placebo and placebo-atropine groups over 2 years. Error bars represent one standard error.

TABLE 2 Mean change in spherical equivalent and axial length at follow-up visits

Change	Atropine-placebo group	Placebo-atropine group	Difference	95% CI	*p*-value
Spherical equivalent, D					
First year					
Baseline to 6 months	−0.20 ± 0.33	−0.34 ± 0.37	0.14 ± 0.06	0.02–0.26	**0.027**
Baseline to 12 months	−0.48 ± 0.42	−0.69 ± 0.48	0.21 ± 0.08	0.05–0.37	**0.009**
Second year					
12 months to 18 months	−0.25 ± 0.26	−0.16 ± 0.26	0.09 ± 0.05	0.00–0.18	0.059
12 months to 24 months	−0.78 ± 0.43	−0.56 ± 0.39	0.22 ± 0.07	0.08–0.36	**0.002**
Two years					
Baseline to 24 months	−1.26 ± 0.66	−1.25 ± 0.70	0.01 ± 0.12	−0.24-0.23	0.954
Axial length, mm					
First year					
Baseline to 6 months	0.15 ± 0.12	0.20 ± 0.10	0.05 ± 0.02	0.01–0.09	**0.013**
Baseline to 12 months	0.30 ± 0.20	0.37 ± 0.18	0.07 ± 0.03	0.00–0.14	**0.033**
Second year					
12 months to 18 months	0.18 ± 0.09	0.14 ± 0.10	0.04 ± 0.02	0.01–0.08	**0.024**
12 months to 24 months	0.39 ± 0.17	0.34 ± 0.18	0.05 ± 0.03	0.02–0.11	0.139
Two years					
Baseline to 24 months	0.68 ± 0.31	0.72 ± 0.32	0.04 ± 0.06	−0.08-0.15	0.537

Note: Bold values indicate statistical significance ($P<0.05$).

significantly reduced myopia progression (−0.10 ± 0.60D/year) as compared to controls (−0.60 ± 0.4D/year). Therefore, 0.01% atropine eye drops have inconsistent effects on different races and should be taken seriously. The fact that those of populations of European origin are more sensitive to cycloplegic agents due to less pigmented eyes, on average, may lead to a lower progression rate.

At present, only two studies have evaluated myopia progression and axial elongation after stopping cessation of 0.01% atropine eye drops. In the ATOM 2 study, Chia et al. (2014) reported myopic progression in children aged 6 to 12 years was −0.87 ± 0.52D, −0.68 ± 0.45D and −0.28 ± 0.33D in the 0.5%, 0.1% and 0.01% atropine groups, respectively, during the 1-year washout period. Recently, in the low-concentration atropine for myopia progression (LAMP) Study, Yam et al. (2022) found that the myopia progression after cessation of atropine was −0.68 ± 0.49D, −0.57 ± 0.38D and −0.56 ± 0.40D for the 0.05%, 0.025% and 0.01% atropine groups, respectively, in Hong Kong children aged 4–12 years. A rebound effect is more likely that once the drug treatment has ceased,

TABLE 3 Distribution of change in spherical equivalent in the first year, the second year and over 2 years

Variable	Change in spherical equivalent		
	0 to +0.49D, *n* (%)	+0.5 D to +0.99D, *n* (%)	≥+1.0 D, *n* (%)
First year			
APG	36 (55.38)	21 (32.31)	8 (12.31)
PAG	26 (38.24)	25 (36.76)	17 (25.00)
Second year			
APG	14 (21.54)	30 (46.15)	21 (32.31)
PAG	32 (47.06)	25 (36.76)	11 (16.18)
Two years			
APG	7 (10.77)	14 (21.55)	44 (67.69)
PAG	9 (13.24)	13 (19.12)	46 (67.65)

Abbreviations: APG, atropine-placebo group; PAG, placebo-atropine group.

the normal rate of progression will return. In our study, although the mean progression of myopia (−0.78±0.43D) between 12 and 24 months after cessation of 0.01% atropine was even higher as compared to that recorded in the ATOM 2 study (−0.28±0.33D) and the LAMP study (−0.56±0.40D), it seems that no rebound effect was found after using 0.01% atropine eye drops to prevent progression of myopia. First, the mean difference of myopia progression between atropine-placebo group and placebo-atropine group in the first year was similar to the second year during the cross-over treatment. Second, the ratio of mean myopia progression to axial elongation for atropine-placebo group after cessation of 0.01% atropine (2.0D/mm) in the second year was similar to the first year in placebo-atropine group when treated with placebo (1.9D/mm). The differences in research periods explain the variation in myopia progression between our results and the ATOM2 and LAMP studies. It should be noted that both the results in the ATOM 2 study in Singapore represent data collected a decade earlier than the present study. In addition, the differences in age, age of myopia onset, time near work and outdoors activities in the samples may also explain the variation in myopia progression in the above studies.

We also found that there were no significant differences between the atropine-placebo group and placebo-atropine group at the end of 2 years in terms of myopia progression (−1.26±0.66D vs. −1.25±0.70D). These results further imply that there was no rebound effect after using 0.01% atropine eye drops to prevent progression of myopia, otherwise the progression of myopia in atropine-placebo group would increase even more due to the rebound effect in the second year, resulting in more myopia progression at the end of 2 years. Although the 2-year progression of myopia was similar in two groups, it does not exclude the possibility of rebound effect. The natural progression of myopia generally becomes faster at first and then gradually decreases. Thus the potential effect of 0.01% atropine eye drops can be greater in younger children.

The strength of present study included its randomized, double-masked, and placebo-controlled cross-over trial design to evaluate the myopia progression and axial elongation after stopping 0.01% atropine eye drops. However, the present study has some limitations. First, this study only explored the efficacy and rebound phenomenon of low-concentration atropine eye drops at level of 0.01%. Thus, further studies should be carried out to compare the rebound effect of various low concentration of atropine, such as 0.01%–0.05%, in mainland China. Second, the study only conducted follow-up for 1 year after the cessation of 0.01% atropine eye drops. In addition, the relatively high loss to follow-up is also a limitation of this study. However, there is no significant differences in initial SE and AL for those who had completed 2 years of follow-up between two groups.

5 | CONCLUSIONS

The mean myopia progression of −1.26±0.66D over 2 years in the atropine-placebo group was also similar to −1.25±0.70D for placebo-atropine group. Through our cross-over trial, the results suggest that there is no rebound effect after using 0.01% atropine eye drops to prevent progression of myopia. In the future, further studies can be conducted in more detail with various low concentration of atropine and more years of follow-up to investigate the rebound effect.

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