European Journal of Pediatrics (2023) 182:2597–2606
https://doi.org/10.1007/s00431-023-04921-5

RESEARCH

Prevention of myopia shift and myopia onset using 0.01% atropine in premyopic children — a prospective, randomized, double-masked, and crossover trial

Weiqun Wang[1] · Fengyan Zhang[1] · Shiao Yu[1] · Nana Ma[1] · Congcong Huang[1] · Ming Wang[3] · Li Wei[1] · Junjie Zhang[2] · Aicun Fu[1]

Received: 26 November 2022 / Revised: 1 March 2023 / Accepted: 3 March 2023 / Published online: 22 March 2023

Abstract

This study aims to evaluate the efficacy of 0.01% atropine eye drops in preventing myopia shift and myopia onset in premyopic children. A prospective, randomized, double-masked, placebo-controlled, and crossover trial was conducted over 13 months. Sixty premyopic children aged 6–12 years with cycloplegic spherical equivalent refraction (SER) > -0.75 D and $\leq +0.50$ D in both eyes were assigned in a 1:1 ratio to receive one drop of 0.01% atropine or placebo once nightly for 6 months (period 1), followed by a 1-month recovery period. Then, the 0.01% atropine group was crossed over to the placebo group, and the latter was crossed over to the 0.01% atropine group for another 6 months (period 2). The primary outcomes were changes in SER and axial length (AL), and the secondary outcomes were the proportion of myopia onset (SER ≤ -0.75D) and fast myopic shift (change in SER ≤ -0.25D) in the two periods. Generalized estimating equation (GEE) model performed a statistically significant treatment effect of 0.01% atropine compared with placebo ($p_{SER} = 0.02$, $p_{AL} < 0.001$), with a mean SER and AL difference of 0.20D (-0.15 ± 0.26D vs. -0.34 ± 0.34D) and 0.11 mm (0.17 ± 0.11 mm vs. 0.28 ± 0.14 mm) in period 1, and 0.17D (-0.18 ± 0.24D vs. -0.34 ± 0.31D) and 0.10 mm (0.15 ± 0.15 mm vs. 0.24 ± 0.11 mm) in period 2. The GEE model showed that the proportion of myopia onset ($p = 0.004$) and fast myopic shift ($p = 0.009$) was significantly lower in the 0.01% atropine group than that in the placebo group. The period effect was not statistically significant (all $p > 0.05$). A total of 0.01% atropine significantly prevented myopic shift, axial elongation, and myopia onset in premyopic schoolchildren in central Mainland China.

Conclusion: Within the limits of only two consecutive 6-month observation period, 0.01% atropine eye drops effectively prevented myopic shift, axial elongation, and myopia onset in premyopic children.

Trial registration: This trial was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR2000034760). Registered 18 July 2020.

What is Known:

- *Minimal studies on interventions for pre-myopia, despite the International Myopia Institute stating that preventing myopia is an "even more valuable target" for science and practice than reducing progression after onset.*

What is New:

- *A total of 0.01% atropine eye drops may safely and effectively reduce the proportion of myopia onset and fast myopic shift in premyopic schoolchildren.*

Keywords 0.01% atropine · Prevent · Myopia shift · Myopia onset · Efficacy

Communicated by Gregorio Milani.

Weiqun Wang and Fengyan Zhang contributed equally to this work.

✉ Aicun Fu
fuaicun2019@qq.com

Extended author information available on the last page of the article

Abbreviations

AMP	Accommodation amplitude
AL	Axial length
GEE	Generalized estimating equation
PD	Pupil diameter

Reg Regression
SER Spherical equivalent refraction

Introduction

Myopia generally occurs during the early years of elementary school and continues to progress until the eyes are fully developed [1, 2]. Earlier onset of myopia is associated with faster myopia progression and a higher final degree of myopia in adults [3, 4]. Pre-myopia [5] is a refractive state of an eye of $\leq +0.75$ D and > -0.50 D in children where a combination of baseline refraction, age, and other quantifiable risk factors provides a sufficient likelihood of the future development of myopia to merit preventative interventions. In addition, the refraction and axial length (AL) change faster in premyopic children, and their rate of change gradually slows down after myopia development [6, 7]. Therefore, effective measures should be taken to slow down the change rate of refraction and AL in premyopic children so that the refractive status remains in pre-myopia as long as possible, the age of myopia onset is postponed, and the incidence of myopia and high myopia is effectively reduced [8, 9].

Currently, there are many studies on how to control myopia progression in myopic children [10–15], and few studies have investigated how to prevent the onset of myopia in premyopic children. Although International Myopia Institute states that preventing myopia is an "even more valuable target" for science and practice than reducing progression after onset. Studies have shown that increasing outdoor time, reducing near-work time [16, 17], and administering low-dose atropine can delay myopia onset. However, only one randomized not-masked study in India (0.01% atropine) [18] and one retrospective study in Taiwan (0.025% atropine) [19] showed that low-dose atropine could prevent myopia shift in premyopic children. No data are available from randomized double-masked clinical trials. Thus, the preventing myopia onset of 0.01% atropine has not been extensively evaluated at present, especially among children in mainland China. Additionally, a crossover design has been widely used in clinical trials, including myopia-control studies [20–22]. This method, in which participants serve as their control, statistically removes between-subject variability in the background–genetic and environmental factors in case myopia control trials and therefore provides a greater statistical power (or requires a smaller sample size) than a parallel-group design [23]. Another advantage of using a crossover design was that all participants had the opportunity to use 0.01% atropine eye drops. In this prospective, randomized, double-masked, placebo-controlled, crossover trial in central Mainland China, we have found that 0.01% atropine eye drops could prevent myopia onset and AL elongation based on the parallel control data before the crossover (period 1) [24]. Inter-group comparisons before and after crossover (periods 1 and 2) and intra-group comparison when children switched between 0.01% atropine and placebo between periods were further explored in current study.

Methods

Participants

Sixty Chinese premyopic children who visited the First Affiliated Hospital of Zhengzhou University were recruited for this study between July 2020 and October 2020. This trial included participants through recruitment advertisements, and trial team members contacted participants and their parents who were interested in the trial. This study was approved by the Human Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Number: 2020-KY-286) and registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR2000034760). This study conforms to the tenets of the Declaration of Helsinki. All participants provided verbal consent and their parents or guardians provided written informed consent before the procedures.

Inclusion and exclusion criteria

The inclusion criteria were age 6–12 years, cycloplegic spherical equivalent refraction (SER) > -0.75 D and ≤ 0.50 D in both eyes, astigmatism < 1.0 D, monocular best-corrected visual acuity of 20/20 or better (Snellen chart), intraocular pressures ≤ 21 mmHg, and no other eye diseases and surgery. Exclusion criteria were previous use of atropine or pirenzepine, known past/current amblyopia or strabismus, and inability to comply with the study visit schedule.

Study design, randomization, and masked

This study included two periods (Fig. 1). All children who participated in this study were recruited and randomized to receive either one drop of 0.01% atropine or placebo eye drops in both eyes once nightly at a 1:1 ratio for the first 6 months in period 1, followed by a 1-month recovery period without using any eye drops. Simple randomization was performed independently by the statistician, placing the subject file number (1–60) in a spreadsheet of Excel (Microsoft Office 2003) and creating a column of random numbers for group allocation. Eligible children were then assigned to a 0.01% atropine or placebo group based on the random software sequence generated from Excel. Then, children in the 0.01% atropine group were crossed over to the placebo group, and those in the placebo group were crossed over to the 0.01% atropine

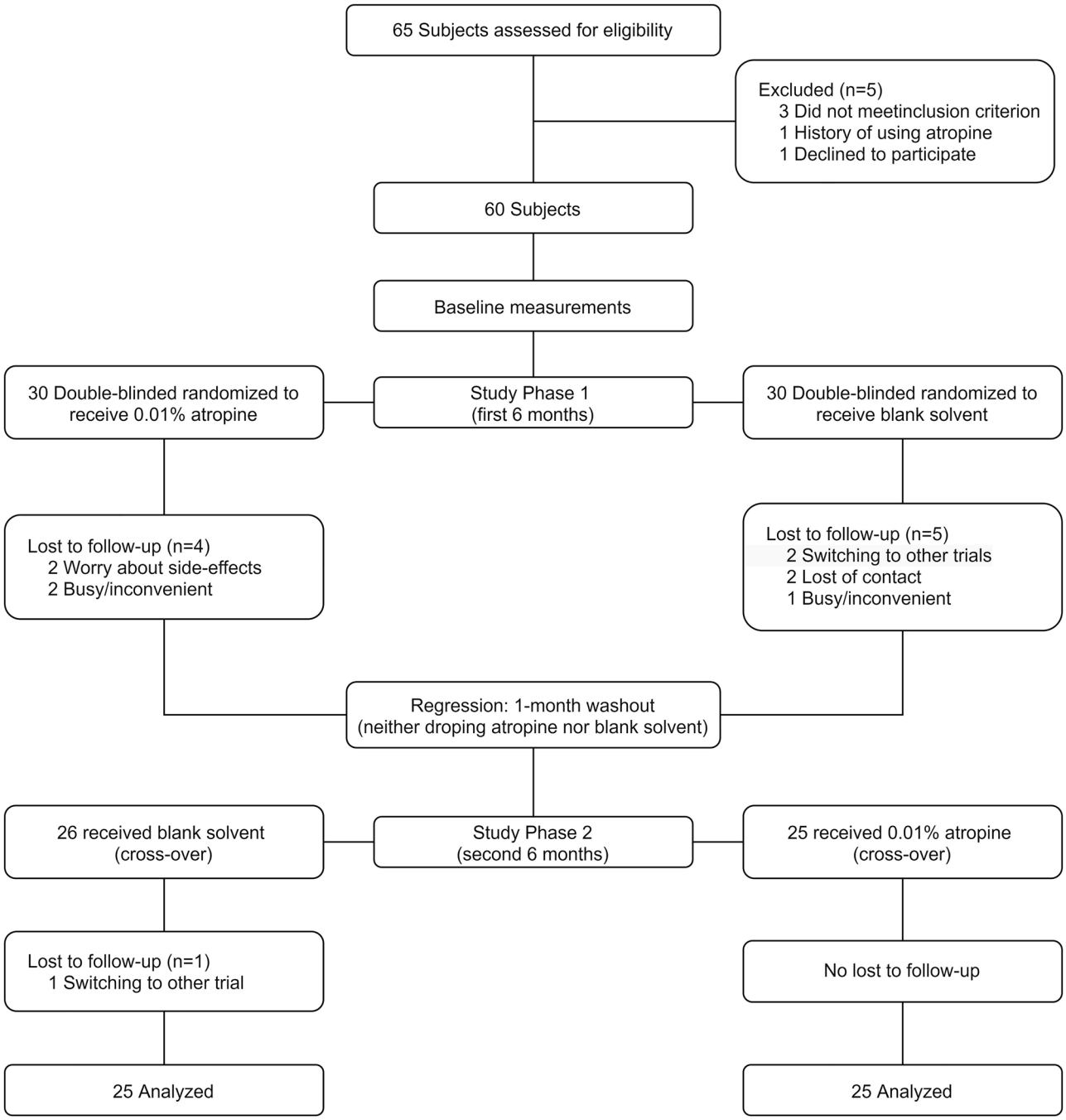

Fig. 1 Subject recruitment and randomization flowchart

group for the second 6 months in period 2. All children underwent the same standardized examination procedure at baseline and each visit. These measurements of the 1-month recovery period were noted as regression (Reg) measurements. During the follow-up, if children's uncorrected visual activity in both eyes was lower than 20/25, they were asked to wear single-vision spectacles during lessons. For this study, myopia was defined as a SER ≤ -0.75 D [25, 26].

Parents or guardians, participants, and study investigators were kept masked to the trial medications. A total of 0.01% atropine and placebo eye drops were packaged in identical bottles; thus, neither the researchers nor the participants were able to identify the contents. All the eye drops were maintained and distributed by the same doctor. In this study, study investigators, examiners, physician in charge of drug dispensing, and data analysts are different researchers.

Eyedrops

Details of the methods of preparation of 0.01% atropine have been published elsewhere and are briefly described here [14, 27]. The 0.01% atropine eye drops (3 mL sealed bottle, pH = 5.4–5.6, storage at 15–25 °C, discarded eye drops after the bottle was opened for 1 month) were prepared by dissolving atropine sulfate powder (Shaoxing Minsheng Medical Co., Ltd., Zhejiang, China) with normal saline under sterile conditions and added preservative (0.3 mg/mL ethylparaben). This preservative fully meets the requirements of Chinese Pharmacopoeia and will not affect the experimental results. The shelf life of 0.01% atropine was over 6 months, and its properties were stable (The D30 concentration against D0 of 0.01% atropine measured by high-performance liquid chromatography was 98.2% after opening the bottle for 1 month). A blank solvent without atropine was used as a placebo.

Each child was dispensed three bottles of eye drops after the first examination and each subsequent follow-up. Children had to bring back the three bottles given on the previous visit at each reexamination. Treatment adherence was assessed based on the remaining amount of eye drops. One drop of eye drops is approximately 0.04 ml. Each child used more than 2.4 ml each month, and the remaining eye drops were less than 0.6 ml per bottle. If the remaining eye drops in any bottle exceeded 10% of the total amount in each bottle (0.3 ml, then plus 0.6 ml, approximately 1 ml), then their treatment adherence was not good.

Study procedures

The details of the examination method for the cycloplegic autorefraction, AL, accommodation amplitude (AMP), pupil diameter (PD), and discomfort symptoms have been published elsewhere and are available in the Supplementary files [14, 28] (supplementary file 1). SER was calculated as the sphere plus half of the cylindrical power. A validated questionnaire was used to collect information, including the time spent on outdoor activities and near work at enrollment [29].

Data analysis

The sample size was calculated based on the results of previous studies [16, 19]. We assume that 0.01% atropine reduces the myopia shift by at least − 0.22 D with a standard deviation of 0.34D, assuming a power of 90% with a two-sided test of 5%. Considering a dropout rate of 15%, 60 participants were adequate.

Only data from participants who completed the 13-month visit were used for the statistical analysis and were analyzed on an intention-to-treat, and only right-eye data were included in the statistical analysis. Continuous baseline variables were tested using the Shapiro–Wilk test and expressed as mean ± standard deviation (normal distribution) and evaluated using a paired *t*-test. Categorical variables were expressed as percentages (%) and evaluated using the chi-square test. The generalized estimating equation (GEE) model after adjusting for covariates was used to determine the changes in SER, AL, AMP, and PD. $p < 0.05$ was considered statistically significant. All statistical analyses were performed with the software package R, version 4.2.2 (R Foundation for Statistical Computing, Beijing, China). The geepack package (version 1.3.9) was used for the GEE model.

Results

Of the 60 Han Chinese children enrolled in the study, 51 and 50 successfully completed the first 6-month and full 13-month visits, respectively (Fig. 1). At baseline, no differences were found in all the baseline parameters between the 0.01% atropine and placebo groups (All $p > 0.05$; Table 1). Ten children (five in each group) dropped out, including nine in period 1 (four in the 0.01% atropine group and five in the placebo group) and one (in the placebo group) in period 2. There were no statistically significant differences in the baseline parameters between the children who dropped out and completed the full 13 months visit (All $p > 0.05$, supplementary file 2). Three children (one and two in 0.01% atropine and placebo group, respectively) had poor treatment adherence in period 1, and they were included in the ten drop-out children.

SER and AL changes before and after crossover (Table 2, Figs. 2, 3, 4, and 5)

GEE model after adjusting for age and baseline SER showed a statistically significant difference in the change in SER and AL of the 0.01% atropine group compared with that of the placebo group ($F_{SER} = 5.30$, $p = 0.02$; $F_{AL} = 18.27$, $p < 0.001$), with a mean SER and AL difference of 0.20 D and 0.11 mm in period 1, and 0.17D and 0.10 mm in period 2, the period effect was not statistically significant (all $p > 0.05$), indicating that the order of the periods of 0.01% atropine use did not affect its efficacy. The power of the test calculated by SER was approximately 0.93. There was no statistically significant difference in the change in SER (− 0.05 ± 0.05D vs. − 0.05 ± 0.07D) and AL (0.02 ± 0.05 mm vs.0.02 ± 0.06 mm) from 6 months to Reg in either group and between the two groups (all $p > 0.05$).

Proportion of myopia onset and fast myopic shift before and after crossover (Table 3)

The GEE model after adjusting for age and baseline SER showed that the proportion of myopia onset ($F = 8.50$, $p = 0.004$) and

Table 1 Baseline characteristics of all the participants, mean ± SD or *n* (%)

Variables	0.01% atropine first *n* = 30	Placebo first *n* = 30
Male, *n* (%)	14 (47%)	15 (50%)
Age (year)	8.6 ± 1.72	8.5 ± 1.74
Body mass index (kg/m2)	16.5 ± 2.71	17.5 ± 2.33
Intraocular pressure (mmHg)	16.6 ± 2.46	17.4 ± 3.41
Accommodative amplitude (D)	15.17 ± 3.24	15.09 ± 3.08
Pupil diameter (mm)	6.10 ± 0.57	5.98 ± 0.78
Spherical equivalent refraction (D)	− 0.19 ± 0.28	− 0.21 ± 0.32
≤ + 0.50 and > 0	12 (40%)	13 (43%)
≤ 0 and > − 0.50	14 (47%)	14 (47%)
≤ − 0.50 and > − 0.75	4 (13%)	3 (10%)
Axial length (mm)	23.59 ± 0.77	23.61 ± 0.75
Corneal curvature (D)	42.83 ± 1.22	42.71 ± 1.18
Corneal astigmatism (D)	1.13 ± 0.53	1.01 ± 0.41
Anterior chamber depth (mm)	3.61 ± 0.16	3.56 ± 0.23
Outdoor activity (hours per day)※	2.41 ± 1.36	2.37 ± 1.39
Near work (dioptic hours per day) #	14.0 ± 1.92	14.1 ± 2.01
Parental myopia		
− − (neither parent myopic)	8 (27%)	7 (23%)
+ − (one parent myopic)	10 (33%)	9 (30%)
+ + (both parents myopic)	12 (40%)	14 (47%)

※: Outdoor activity = outdoor exercise + outdoor leisure activity. #: Nearwork = 3* (homework + reading + playing on cell phone) + 2* (using computer + playing video game) + 1* (watching TV)

Table 2 Changes in SER and AL in the two groups at each period (mean ± SD) #

	Study period	0.01% atropine first	Placebo first
SER (D)	1		
	0–3 months	− 0.08 ± 0.19	− 0.18 ± 0.20
	0–6 months	− 0.15 ± 0.26	− 0.34 ± 0.34
	Reg	− 0.05 ± 0.05	− 0.05 ± 0.07
	2		
	Reg–10 months	− 0.20 ± 0.20	− 0.09 ± 0.20
	Reg–13 months	0.34 ± 0.31	− 0.18 ± 0.24
AL (mm)	1		
	0–3 months	0.08 ± 0.09	0.15 ± 0.11
	0–6 months	0.17 ± 0.11	0.28 ± 0.14
	Reg	0.02 ± 0.05	0.02 ± 0.06
	2		
	Reg–10 months	0.12 ± 0.08	0.09 ± 0.06
	Reg–13 months	0.24 ± 0.11	0.15 ± 0.15

SER spherical equivalent refraction, *AL* axial length

#Generalized estimating equation model after adjusting for age and baseline SER showed a statistically significant difference in the change in SER and AL of the 0.01% atropine group compared with that of the placebo group ($F_{SER} = 5.30$, $p = 0.02$; $F_{AL} = 18.27$, $p < 0.001$), and the period effect was not statistically significant (all $p > 0.05$)

fast myopic shift ($F = 6.81$, $p = 0.009$) were significantly lower in the 0.01% atropine group than that in the placebo group, with the proportion of myopia onset of 12% vs. 36% and 13% vs. 41% in periods 1 and 2, respectively, and the corresponding results of the fast myopic shift of 40% vs. 76% and 40% vs. 72%. The period effect was not statistically significant (all $p > 0.05$).

AMP, PD, and adverse events (Table 4)

The GEE model after adjusting for age showed a significant decrease in AMP ($F = 3.04$, $p = 0.04$) and an increase in PD ($F = 4.93$, $p = 0.03$) with 0.01% atropine compared with placebo. The period effect was all not statistically significant (all $p > 0.05$). In the 0.01% atropine group, the PD increased by 0.53 mm and AMP decreased by 1.19 D after 6 months (remained stable from 3 to 6 months), and they recovered to baseline levels after the Reg. The results of post-crossover in period 2 are the same as in period 1. AMP and PD remained stable over time in the two periods in the placebo group.

Photophobia, wearing of single-vision spectacles, and other adverse events

In the 0.01% atropine and placebo groups, five (20%) and two (8.0%) children in period 1 ($p = 0.42$) and four (16%,) and two (8.0%) children in period 2 ($p = 0.66$) were photophobic in bright sunlight. Photophobia was resolved by wearing sun hats or sunglasses during outdoor activities and disappeared in all children except one in the 0.01% atropine group in period 2 (disappeared after discontinuing 0.01% atropine for 4 days). No near-vision blur or other uncomfortable symptoms were observed in either group. Sixteen children wore single-vision spectacles during lessons, including nine children in period 1 (two and seven in the 0.01% atropine and placebo group, respectively) and three and four children in the corresponding two groups in period 2. In the 0.01% atropine group, two participants had a mild headache, and 1 subject had influenza. In the placebo group, there was 1 case each of gastroenteritis and influenza.

Discussion

Using a prospective, randomized, double-masked, placebo-controlled, and crossover trial design, this clinical study demonstrated that once-nightly administration of 0.01% atropine eye drops could prevent myopic shift and axial elongation and reduce the proportion of myopia onset and fast myopic shift in premyopic Chinese schoolchildren compared with placebo treatment over two consecutive 6-month visits.

So far, only two studies have observed low dose-atropine to prevent myopia onset [18, 19]. Jethaniet al. [18] reported that 0.01% atropine can reduce the myopic shift and axial

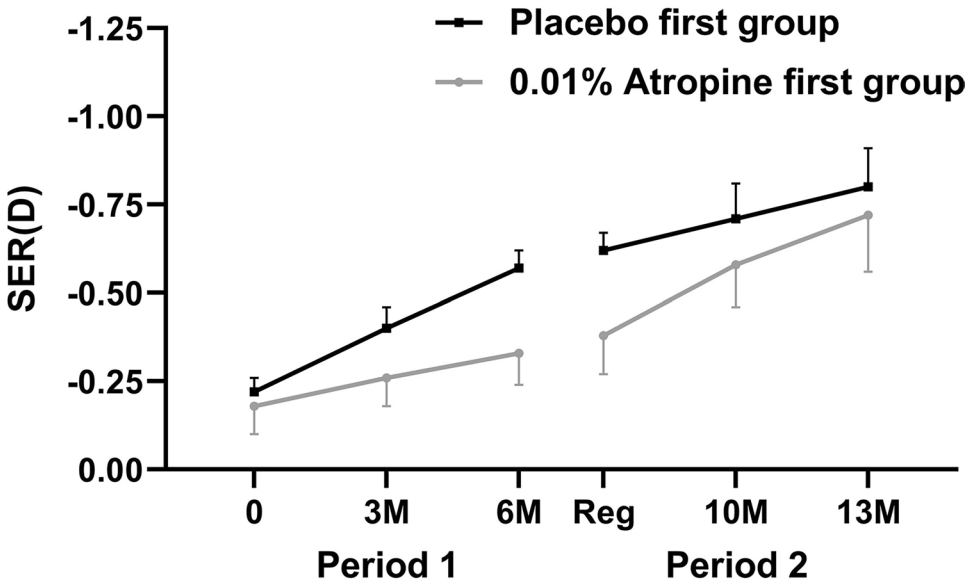

Fig. 2 SER in 0.01% atropine and placebo groups during study periods 1 and 2. Reg indicates after the 1-month recovery period without using eye drops. Error bars represent standard error. SER, spherical equivalent refraction; M, month

elongation in premyopic schoolchildren. The randomized not-masked study was performed with participants at an average age of 7.7 years and SER less than + 1.00 D. They found that the changes in SER in the 0.01% and control groups were − 0.31D and − 0.76D, respectively, and the corresponding changes in AL were 0.12 mm and 0.21 mm over 1 year. In comparison with Jethani's study (follow-up time was converted to 1 year in the current study), there were similar changes in SER in the 0.01% atropine and control groups between the two studies. However, there were less changes in AL in Jethani's study than in the current study both in 0.01% atropine (0.12 mm vs. 0.34 mm) and control groups (0.21 mm vs.0.56 mm). The more changes in AL in the current study may be related to the different machines in which AL was measured in both studies. Studies [30, 31] demonstrated that the AL measured with A-can (Jethani's study) was shorter than that measured with IOLmaster (current study). Another study by Fang et al. [19] reported that 0.025% atropine can delay the onset of myopia and myopic shift in premyopic schoolchildren after 1 year. Their participants were children aged 6–12 years with an average SER of − 0.31D. They found significant differences in myopia onset (defined as < − 1.0D) between the 0.025% atropine and placebo groups (21% vs. 54%). Additionally, they found that the mean myopic shift per year in the 0.025% atropine group was significantly lower than that in the placebo group (− 0.14D vs. − 0.58 D). In comparison with Fang's studies, in the placebo groups, there was no difference in the myopic shift between the two studies. However, in the atropine group, more myopic shift was found in the current study (− 0.14D vs. − 0.28D). The difference in the myopic shift in the low-dose atropine group may be related to the differences in the participant's age, baseline SER, and atropine concentration used between the two studies. Studies have demonstrated the higher the dose of a low dose of atropine, the better the control of myopia progression [10–14]. This dose-dependent response to atropine may also occur in pre-myopic schoolchildren after using low-dose atropine.

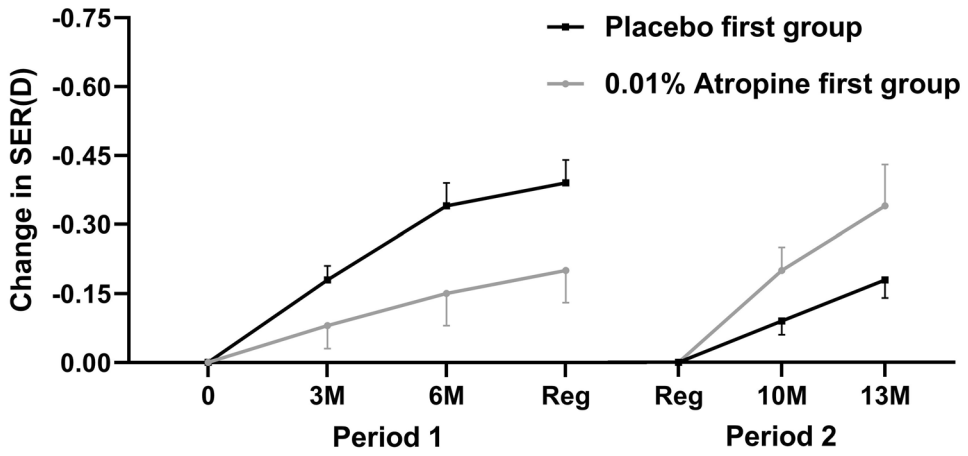

Fig. 3 Changes in SER from baseline in period 1 (Reg in period 2) in 0.01% atropine and placebo groups during study periods 1 and 2. Reg indicates after the 1-month recovery period without using eye drops. Error bars represent standard error. SER, spherical equivalent refraction; M, month

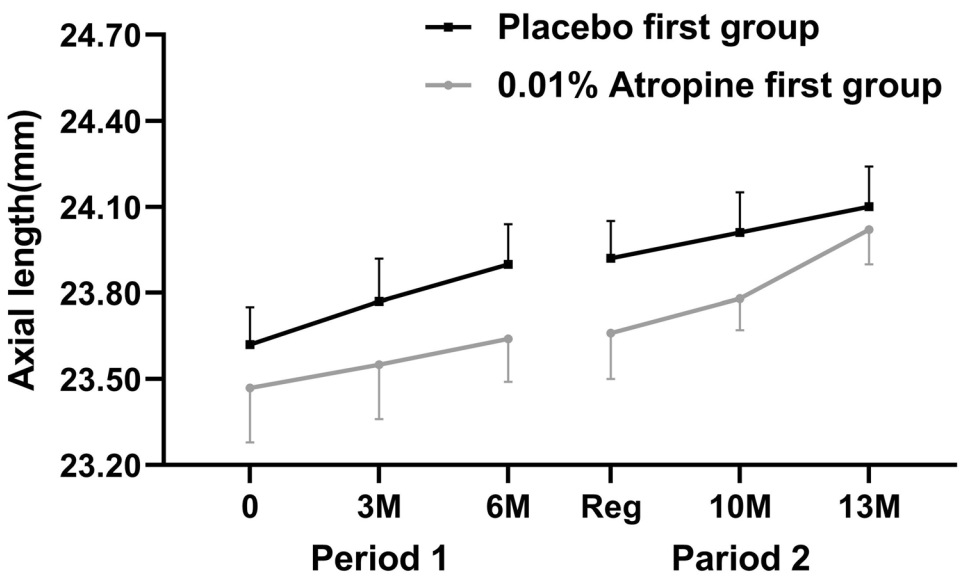

Fig. 4 Axial length in 0.01% atropine and placebo groups during study periods 1 and 2. Reg indicates after the 1-month recovery period without using eye drops. Error bars represent standard error. M, month

Additionally, there were significant differences in the changes in AL between 0.01% atropine and placebo groups (0.17 mm vs. 0.28 mm) and 0.01% atropine synchronously controlled axial elongation in premyopic children.

In the current study, for premyopic children after using 0.01% atropine in the first 6 months, the control rates of SER progression and AL elongation were approximately 59% and 39%, respectively. Our results are similar to the 1-year results of Jessini et al. (59% and 43%) [18]. In four 1-year prospective randomized controlled studies on Asian children with myopia using 0.01% atropine, the control rates of SER progression were 21%, 33%, 36%, and 43%, respectively, and the control rates of AL elongation were 0%, 15%, 20%, and 22%, respectively [11, 14, 32, 33]. By controlling SER progression and AL elongation, the effect of 0.01% atropine was found to be better in premyopic children than in those with myopia. The different efficacies of 0.01% atropine on premyopic or myopic children may be related to the different change rates of SER and AL over time in the two different refractive statuses. Mutti et al. [6] and Xiang et al. [7] found that AL elongation and SER progression accelerated before the onset of myopia, and their rate of change gradually decreased after the onset of myopia. However, why premyopic children with rapid AL elongation and SER progression have better effects after treatment with 0.01% atropine remains unknown. Therefore, refractive development files for schoolchildren must be established as soon as possible. Once their refractive status reaches the premyopic stage, 0.01% atropine eye drops might be an alternative method to reduce the myopic shift.

The amount of change in PD, AMP, and their change trend over time and the most common ocular symptom of photophobia were consistent with our previous study in myopic children administering 0.01% atropine [14]. Photophobia is presumably associated with reduced pupillary responsiveness and increased PD [34]. However, photophobia disappeared in most children with prolonged medication

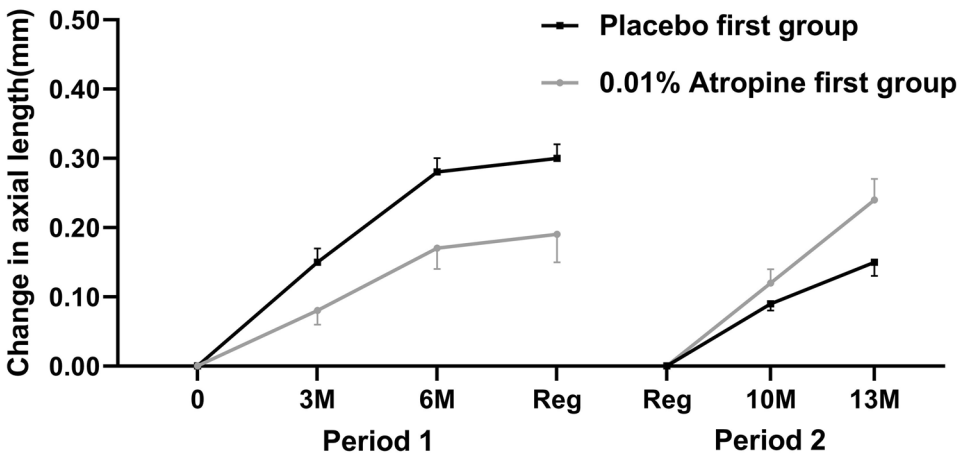

Fig. 5 Changes in axial length from baseline in period 1 (Reg in period 2) in 0.01% atropine and placebo groups during study periods 1 and 2. Reg indicates after the 1-month recovery period without using eye drops. Error bars represent standard error. M, month

Table 3 Proportion of myopia onset and fast myopic shift in the two groups at each period, *n* (%) #

	Study period	0.01% atropine first	Placebo first
Proportion of myopia onset	1 (0–6 months)	3/25 (12)	9/25 (36)
	2 (Reg–13 months)	9/22 (41)	2/16 (13)
Proportion of fast myopic shift	1 (0–6 months)	10/25 (40)	19/25 (76)
	2 (Reg–13 months)	18/25 (72)	10/25 (40)

SER spherical equivalent refraction, myopia onset (defined as SER ≤ −0.75D), Fast myopic shift (defined as the change in SER ≤ -0.25 D) in each period

#Generalized estimating equation model after adjusting for age and baseline SER showed that the proportion of myopia onset ($F = 8.50$, $p = 0.004$) and fast myopic shift ($F = 6.81$, $p = 0.009$) was significantly lower in the 0.01% atropine group than that in the placebo group, and the period effect was not statistically significant (all $p > 0.05$)

time, which may be related to drug tolerance and compensation, however, not pupil miosis over time [14].

The strengths of this study include its randomized, double-masked, placebo-controlled, and cross-over trial design. However, the current study has several limitations. First, the SER of participants was ≤ 0.50 D and > −0.75 D, which varied slightly from the proposed definition of pre-myopia by the International Myopia Institute (IMI) (defined pre-myopia as SER ≤ +0.75 D and > −0.50 D) [5]. It was difficult for us to recruit participants who met enrollment criteria (such as SER ≤ +0.75 D and > −0.50 D) and were willing to participate in the current trial in the short term. Additionally, the definition of myopia (some studies defined as SER ≤ −0.75 D [25, 26]) and pre-myopia (define SER < +1.0 D and > −1.0 D in studies about low-dose atropine for preventing myopia onset [18, 19]) varied slightly among different studies. However, the results of the article did not change if we removed the seven participants with SER ≤ −0.50 D and > −0.75 D (not reported herein). Second, it was apparent that SER progression and AL elongation occurred in both groups during period 1, especially in the placebo group, so the starting SER and AL were not the same in the two groups at the start of period 2. Although the interpretation of period 1 data is unaffected by these considerations, the data from period 2 must be interpreted with caution. Nevertheless, the results of the analysis of variance, in which efficacy was similar for periods 1 and 2, suggest that period 2 data support period 1 findings. Third, we could not avoid the potential for the unmasking of some participants due to atropine-induced photophobia and dilated pupil as well as other studies about low-dose atropine eyedrops. Additionally, the observation period was only 6 months, and some myopia control studies found large treatment effects of low-dose atropine over the first year that do not continue to accrue [35, 36]. Thus, further long-term studies in premyopic participants with SER ranges consistent with the IMI definition should be conducted in the future.

Table 4 Accommodation amplitude and pupil diameter by a study group at each stage of the trial (mean ± SD) #

	Study phase	0.01% atropine first	Placebo first
Accommodation amplitude (D)	1		
	Baseline	15.06 ± 3.25	15.02 ± 3.00
	3 months	13.67 ± 2.04	15.49 ± 2.95
	6 months	13.87 ± 1.75	15.41 ± 2.88
	Reg	14.92 ± 3.01	15.18 ± 2.91
	2		
	10 months	14.90 ± 2.36	13.22 ± 3.13
	13 months	14.74 ± 1.85	13.41 ± 2.95
Pupil diameter (mm)	1		
	Baseline	5.97 ± 0.65	5.94 ± 0.82
	3 months	6.62 ± 0.63	6.06 ± 0.67
	6 months	6.50 ± 0.79	5.86 ± 0.60
	Reg	5.99 ± 0.71	5.84 ± 0.87
	2		
	10 months	6.03 ± 0.68	6.54 ± 0.45
	13 months	5.95 ± 0.62	6.58 ± 0.61

#Generalized estimating equation model after adjusting for age showed a statistically significant difference in the change in accommodation amplitude and pupil diameter of the 0.01% atropine group compared with that of the placebo group ($F_{\text{accommodation amplitude}} = 3.04$, $p = 0.04$; $F_{\text{pupil diameter}} = 4.93$, $p = 0.03$), and the period effect was not statistically significant (all $p > 0.05$)

In conclusion, our preliminary findings showed that 0.01% atropine eye drops effectively prevented myopic shift, axial elongation, and myopia onset in premyopic children. This study provides useful guidance and experience for the clinical use of low-dose atropine to prevent myopic shift and myopia onset in premyopic schoolchildren in central Mainland China.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-023-04921-5.

Acknowledgements We thank all the teenagers and their parents who participated in this study.

Authors' contributions Study concept and design: Aicun Fu, Weiqun Wang, Fengyan Zhang, Junjie Zhang. Acquisition, analysis or interpretation of data: Aicun Fu, Shiao Yu, Nana Ma, Congcong Huang, Ming Wang, Li Wei. Revised paper for important intellectual content and final approval of the version submitted for publication: Aicun Fu, Shiao Yu, Weiqun Wang, Fengyan Zhang. Study supervision: Aicun Fu. All authors read and approved the final manuscript.

Funding This work was supported by the Key Scientific Research Project of Universities of Henan Education Department (Grant number 22A320024).

Data Availability The datasets generated during and/or analysed during the current study are not publicly available due to [REASON(S) WHY DATA ARE NOT PUBLIC].

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Human Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Number: 2020-KY-286).

Consent to participate Written informed consent was obtained from all individual participants and their parents.

Competing interests The authors declare no competing interests.

References

1. Fredrick DR (2002) Myopia. Br Med J 324:1195–1199. https://doi.org/10.1136/bmj.324.7347.1195
2. Parssinen O, Kauppinen M, Viljanen A (2014) The progression of myopia from its onset at age 8–12 to adulthood and the influence of heredity and external factors on myopic progression. A 23-year follow-up study. Acta Ophthalmol 92:730–739. https://doi.org/10.1111/aos.12387
3. Hu Y, Ding XH, Guo XX, Chen YX, Zhang J, He MG (2020) Association of age at myopia onset with risk of high myopia in adulthood in a 12-year follow-up of a Chinese Cohort. JAMA Ophthalmol 138:1129–1134. https://doi.org/10.1001/jamaophthalmol.2020.3451
4. Parssinen O, Kauppinen M (2019) Risk factors for high myopia: a 22-year follow-up study from childhood to adulthood. Acta Ophthalmol 97:510–518. https://doi.org/10.1111/aos.13964
5. Flitcroft DI, He MG, Jonas JB, Jong M, Naidoo K, Ohno-Matsui K, Rahi J, Resnikoff S, Vitale S, Yannuzzi L (2019) IMI - Defining and classifying myopia: a proposed set of standards for clinical and epidemiologic studies. Invest Ophthalmol Vis Sci 60:M20–M30. https://doi.org/10.1167/iovs.18-25957
6. Mutti DO, Hayes JR, Mitchell GL et al (2007) Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Invest Ophthalmol Vis Sci 48:2510–2519. https://doi.org/10.1167/iovs.06-0562
7. Xiang F, He MG, Morgan IG (2012) Annual changes in refractive errors and ocular components before and after the onset of myopia in Chinese children. Ophthalmology 119:1478–1484. https://doi.org/10.1016/j.ophtha.2012.01.017
8. Wu PC, Chuang MN, Choi J, Chen H, Wu G, Ohno-Matsui K, Jonas JB, Cheung CMG (2019) Update in myopia and treatment strategy of atropine use in myopia control. Eye 33:3–13. https://doi.org/10.1038/s41433-018-0139-7
9. Modjtahedi BS, Abbott RL, Fong DS, Lum F, Tan D, Task Force M (2021) Reducing the global burden of myopia by delaying the onset of myopia and reducing myopic progression in children the academy's task force on myopia. Ophthalmology 128:816–826. https://doi.org/10.1016/j.ophtha.2020.10.040
10. Li FF, Yam JC (2019) Low-concentration atropine eye drops for myopia progression. Asia-Pac J Ophthalmol 8:360–365. https://doi.org/10.1097/apo.0000000000000256
11. Yam JC, Jiang YN, Tang SM et al (2019) 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 126:113–124. https://doi.org/10.1016/j.ophtha.2018.05.029
12. Yam JC, Li FF, Zhang XJ et al (2020) Two-year clinical trial of the low-concentration atropine for myopia progression (LAMP) study phase 2 report. Ophthalmology 127:910–919. https://doi.org/10.1016/j.ophtha.2019.12.011
13. Yam JC, Zhang XJ, Zhang YZ et al (2022) Three-year clinical trial of low-concentration atropine for myopia progression (LAMP) study: continued versus washout phase 3 report. Ophthalmology 129:308–321. https://doi.org/10.1016/j.ophtha.2021.10.002
14. Fu AC, Stapleton F, Wei L, Wang WQ, Zhao BX, Watt K, Ji N, Lyu Y (2020) Effect of low-dose atropine on myopia progression, pupil diameter and accommodative amplitude: low-dose atropine and myopia progression. Br J Ophthalmol 104:1535–1541. https://doi.org/10.1136/bjophthalmol-2019-315440
15. Del Valle IG, Alvarez-Lorenzo C (2021) Atropine in topical formulations for the management of anterior and posterior segment ocular diseases. Expert Opin Drug Deliv 18:1245–1259. https://doi.org/10.1080/17425247.2021.1909568
16. He MG, Xiang F, Zeng YF, Mai JC, Chen QY, Zhang J, Smith WN, Rose K, Morgan IG (2015) Effect of time spent outdoors at school on the development of myopia among children in China a randomized clinical trial. JAMA-J Am Med Assoc 314:1142–1148. https://doi.org/10.1001/jama.2015.10803
17. Huang HM, Chang DST, Wu PC (2015) The association between near work activities and myopia in children-a systematic review and meta-analysis. PLoS ONE 10:15. https://doi.org/10.1371/journal.pone.0140419
18. Jethani J (2022) Efficacy of low-concentration atropine (0.01%) eye drops for prevention of axial myopic progression in premyopes. Indian J Ophthalmol 70:238–240. https://doi.org/10.4103/ijo.IJO_1462_21
19. Fang PC, Chung MY, Yu HJ, Wu PC (2010) Prevention of myopia onset with 0.025% atropine in premyopic children. J Ocular Pharmacol Ther 26:341–345. https://doi.org/10.1089/jop.2009.0135
20. Hasebe S, Ohtsuki H, Nonaka T, Nakatsuka C, Miyata M, Hamasaki I, Kimura S (2008) Effect of progressive addition lenses on myopia progression in Japanese children: a prospective, randomized, double-masked, crossover trial. Invest Ophthalmol Vis Sci 49:2781–2789. https://doi.org/10.1167/iovs.07-0385
21. Swarbrick HA, Alharbi A, Watt K, Lum E, Kang P (2015) Myopia control during orthokeratology lens wear in children using a novel study design. Ophthalmology 122:620–630. https://doi.org/10.1016/j.ophtha.2014.09.028
22. Anstice NS, Phillips JR (2011) Effect of dual-focus soft contact lens wear on axial myopia progression in children. Ophthalmology 118:1152–1161. https://doi.org/10.1016/j.ophtha.2010.10.035
23. Wellek S, Blettner M (2012) On the proper use of the crossover design in clinical trials part 18 of a series on evaluation of scientific publications. Dtsch Arztebl Int 109:276–281. https://doi.org/10.3238/arztebl.2012.0276
24. Yu SA, Lv Y, Wang WQ, Cui C, Wei L, Huang CC, Ma NN, Zhao BX, Zhang JJ, Fu AC (2022) Effects of 0.01% atropine eye drops on the prevention of myopia onset among schoolchildren: a randomized, double-blind, controlled trial. Chinese J Exp Ophthalmol 40:533–540. https://doi.org/10.3760/cma.j.cn115989-20210821-00470
25. Rahi JS, Cumberland PM, Peckham CS (2011) Myopia over the lifecourse: prevalence and early life influences in the 1958 British Birth Cohort. Ophthalmology 118:797–804. https://doi.org/10.1016/j.ophtha.2010.09.025
26. Williams KM, Bertelsen G, Cumberland P et al (2015) Increasing prevalence of myopia in Europe and the impact of education. Ophthalmology 122:1489–1497. https://doi.org/10.1016/j.ophtha.2015.03.018
27. Wang M, Cui C, Sui Y, Yu SA, Ma JX, Fu AC (2022) Effect of 0.02% and 0.01% atropine on astigmatism: a two-year clinical trial. BMC Ophthalmol 22:9. https://doi.org/10.1186/s12886-022-02385-z

28. Cui C, Li XJ, Lyu Y, Wei L, Zhao BX, Yu SA, Rong JB, Bai YH, Fu AC (2021) Safety and efficacy of 0.02% and 0.01% atropine on controlling myopia progression: a 2-year clinical trial. Sci Rep 11:8. https://doi.org/10.1038/s41598-021-01708-2
29. Fu AC, Stapleton F, Li W, Wang WQ, Zhao BX, Watt K, Yu SA, Cui C, Lyu Y (2021) Risk factors for rapid axial length elongation with low concentration atropine for myopia control. Sci Rep 11:7. https://doi.org/10.1038/s41598-021-88719-1
30. Goyal R, North RV, Morgan JE (2003) Comparison of laser interferometry and ultrasound A-scan in the measurement of axial length. Acta Ophthalmol Scand 81:331–335. https://doi.org/10.1034/j.1600-0420.2003.00092.x
31. Rose LT, Moshegov CN (2003) Comparison of the Zeiss IOLMaster and applanation A-scan ultrasound: biometry for intraocular lens calculation. Clin Exp Ophthalmol 31:121–124. https://doi.org/10.1046/j.1442-9071.2003.00617.x
32. Wei SF, Li SM, An WZ, Du JL, Liang XT, Sun YY, Zhang DX, Tian JX, Wang NL (2020) Safety and efficacy of low-dose atropine eyedrops for the treatment of myopia progression in Chinese children a randomized clinical trial. JAMA Ophthalmol 138:1178–1184. https://doi.org/10.1001/jamaophthalmol.2020.3820
33. Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D (2012) 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 119:347–354. https://doi.org/10.1016/j.ophtha.2011.07.031
34. Loughman J, Flitcroft DI (2016) The acceptability and visual impact of 0.01% atropine in a Caucasian population. Br J Ophthalmol 100:1525–1529. https://doi.org/10.1136/bjophthalmol-2015-307861
35. Kinoshita N, Konno Y, Hamada N, Kanda Y, Shimmura-Tomita M, Kaburaki T, Kakehashi A (2020) Efficacy of combined orthokeratology and 0.01% atropine solution for slowing axial elongation in children with myopia: a 2-year randomised trial. Sci Rep 10:11. https://doi.org/10.1038/s41598-020-69710-8
36. Tan Q, Ng ALK, Choy BNK, Cheng GPM, Woo VCP, Cho P (2020) One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomised clinical trial. Ophthalmic Physiol Opt 40:557–566. https://doi.org/10.1111/opo.12722

Authors and Affiliations

Weiqun Wang[1] · Fengyan Zhang[1] · Shiao Yu[1] · Nana Ma[1] · Congcong Huang[1] · Ming Wang[3] · Li Wei[1] · Junjie Zhang[2] · Aicun Fu[1]

[1] The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450000, China

[2] Henan Eye Institute, Henan Provincial People's Hospital, Zhengzhou 450000, China

[3] Beijing Aier Intech Eye Hospital, Beijing 100021, China