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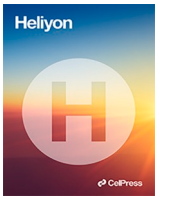

Effects of atropine 0.01% on refractive errors in children with myopia

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ABSTRACT

Background: Little is known about changes in astigmatism during atropine treatment. We aimed to explore the effects of atropine 0.01% eye drops on both spherical and cylindrical refractive errors in myopic children.

Methods: Children aged 6–14 years with myopia ≥ -6.00 D and < -0.50 D, and total astigmatism > -2.00 D in at least one eye were enrolled. Subjects were randomised either to receive atropine 0.01% once nightly with single-vision lenses or simply to wear single-vision lenses and were followed up at 3-month intervals. Cycloplegic refraction and axial length were measured. The magnitude and direction of total astigmatism (TA), corneal astigmatism (CA), and residual astigmatism (RA) were evaluated.

Results: Overall, 119 eyes (69 eyes in the atropine group and 50 eyes in the control group) were included in the final analyses after 9 months. Atropine-treated eyes showed significantly less progression of myopia than did control eyes (spherical equivalent: -0.35 ± 0.33 vs. -0.56 ± 0.49 D, $p = 0.001$; axial length: 0.20 ± 0.19 vs. 0.33 ± 0.19 mm, $p < 0.001$). Compared with control eyes (-0.04 ± 0.23 D), a significant increase in TA was observed in the atropine-treated eyes (-0.14 ± 0.29 D); this was mainly attributed to the increase in CA (-0.17 ± 0.26 D) rather than the minor decrease in RA (0.02 ± 0.32 D).

Conclusions: Atropine 0.01% was effective in preventing myopia progression, whereas 9 months of atropine treatment resulted in a clinically small, but statistically significant increase in TA in myopic Chinese children.

1. Introduction

Globally, the primary cause of visual impairment is uncorrected refractive errors, which reflect mismatches between the axial length (AL) of the eyeball and its overall optical power [1]. There are two main types of refractive errors: spherical errors, which include hyperopia and myopia, and astigmatism, which represents an optical asymmetry and could be present with hyperopia or

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myopia. The measurement of refractive error in clinical studies regarding myopia control mostly involves determination of the spherical equivalent error (SE), which is calculated as the spherical refractive error plus half the cylindrical refractive error.

The underlying pathogenesis and clinical management of myopia have attracted considerable scientific interest in recent years because of the significant rise in its prevalence and the risks of associated ocular complications. Although the mechanism is unknown, use of atropine eye drops, particularly at a lower dosage, is considered to be an effective pharmacological intervention to retard myopia progression. However, insufficient attention has been paid to the change in cylindrical refractive error, also called astigmatism, during atropine treatment. On one hand, astigmatism may disturb emmetropisation and even lead to progression of myopia by producing blurred or distorted images on the retina [2,3]. On the other hand, the total ocular astigmatism (TA) is a combination of corneal astigmatism (CA) and residual astigmatism (RA), which arises from other internal ocular components, such as the crystalline lens [4]. Atropine administration induces cycloplegia, which could then affect the biometric parameters of the crystalline lens [5,6], and may change the RA.

The aim of this randomised clinical trial was to evaluate the effect of atropine 0.01% eye drop administration on both spherical and cylindrical refractive errors in Chinese children with myopia.

2. Materials and methods

2.1. Study design and subjects

Children who visited the Eye & ENT Hospital of Fudan University and aged 6–14 years with myopia between ≥ -6.00 D and < -0.50 D, and total astigmatism > -2.00 D in at least one eye were enrolled. Excluded subjects were those with systemic and ocular diseases, those who were current or previous users of atropine or contact lenses, and those who were unable to complete all examinations. Participants were then randomly assigned to receive atropine 0.01% once nightly with regular single-vision lenses, or to wear regular single-vision lenses only. Simple random assignment was performed by one independent research assistant and the allocation was concealed until interventions were assigned. As atropine 0.01% is not commercially available in China, the eye drops dispensed to participants were prepared by the Pharmaceutical Department of Eye & ENT Hospital (0.05% atropine sulphate [1 ml] in polyethylene glycol eye drops [4 ml]).

Written informed consent was obtained from the parents or legal guardians of all participant, and either written or verbal assent was obtained from each child. The study was approved by the Ethics Committee of the Eye & ENT Hospital of Fudan University and all procedures were conducted in compliance with the tenets of the Declaration of Helsinki. The study was registered at www.chictr.org.cn under identifier ChiCTR1800017154.

2.2. Examination

All participants were planned to undergo a standardized examination at the baseline visit and follow-up visits at 3, 6, 9, and 12 months. Ocular biometric parameters, including horizontal corneal power (K1), vertical corneal power (K2), central corneal thickness (CCT), anterior chamber depth (ACD), lens thickness (LT) and AL were measured using the Zeiss IOLMaster 700 (Carl Zeiss Meditec, Inc., Dublin, CA, USA) before cycloplegia at each follow-up visit. Corneal power was calculated using a refractive index of 1.3375, which is based on the hypothesis that the ratio of the posterior corneal radius of curvature to its anterior is 0.883. The vitreous chamber depth (VCD) was calculated as follows: VCD = AL - ACD - LT.

Cycloplegic retinoscopy was performed by one experienced optometrist 30 min after administration of four drops of compound tropicamide eye drops (0.5% tropicamide and 0.5% phenylephrine eye drops; Mydrin-P, Santen, China), spaced 5 min apart. The distant best corrected visual acuity (BCVA) was measured using the tumbling-E Early Treatment Diabetic Retinopathy Study charts (LCD backlit lamp, WH0701, Guangzhou Weishikang, Guangzhou, China) and was recorded using the logarithm of the minimum angle of resolution scale (logMAR).

2.3. Definitions

SE was calculated by adding the spherical refractive error to half of the cylindrical refractive error. Children with astigmatism ≤ -0.50 D were classified as having clinically significant refractive astigmatism. The TA was defined as cylindrical refractive error and was recorded with a negative value, while the CA was calculated by $(1.3375–1)/r$, where r is the anterior curvature of the central radius. The cylindrical axis of CA corresponds to the meridian of the minimum corneal power. The axes of TA and CA were further classified into three groups, according to the direction of the correcting-cylinder: with-the-rule (WTR) astigmatism was defined as a direction between 0° and 30° or between 150° and 180°; against-the-rule (ATR) astigmatism was defined as a direction between 60° and 120°; and oblique (OBL) astigmatism was defined as a direction between 31° and 59° or between 121° and 149°.

Vectorial analysis converted the TA and CA from the spherocylindrical notation to J_0 and J_{45} power vectors by applying a Fourier transformation, using the following equations: $tJ_0 = (\text{-TA}/2) \times \cos(2 \times \alpha_{TA})$; $tJ_{45} = (\text{-TA}/2) \times \sin(2 \times \alpha_{TA})$; $cJ_0 = (\text{-CA}/2) \times \cos(2 \times \alpha_{CA})$; and $cJ_{45} = (\text{-CA}/2) \times \sin(2 \times \alpha_{CA})$, where α_{RA} is the cylindrical axis of TA and α_{CA} is the cylindrical axis of CA. The RA was calculated by combining rJ_0 and rJ_{45}: $RA = -2\sqrt{[(rJ_0)^2 + (rJ_{45})^2]}$ and $\alpha_{RA} = \arctan(rJ_{45}/rJ_0)/2$, while $rJ_0 = tJ_0 - cJ_0$, $rJ_{45} = tJ_{45} - cJ_{45}$, where α_{ra} is the cylindrical axis of RA and it ranges from 0° to 180° [7,8]. Positive values of J_0 represented WTR astigmatism (180° in minus cylinder notation) and negative values of J_0 represented ATR astigmatism (90° in minus cylinder notation), while positive values of J_{45} represented OBL astigmatism at axis 45° in minus cylinder notation and negative values of J_{45} represented OBL

astigmatism at axis 135° in minus cylinder notation.

2.4. Statistical analysis

The sample size was calculated based on the assumption that the mean (standard deviation) changes in SE would be 0.6 (0.6) D in the atropine 0.01% group and 1.0 (0.6) D in the control group over 1 year [9]. A sample size of 92 was required to ensure 80% power with a type I error of 0.05 to detect differences between the atropine and control groups, assuming no more than 20% loss to follow-up with an allocation of 5:4.

The mean and standard deviation are used to describe continuous variables, while the count and proportion are used to describe discrete variables. Shapiro–Wilk test was conducted to evaluate the normality of the distribution of all data sets. A two-sample *t*-test or the Mann–Whitney *U* test was used to test the differences in continuous data at baseline, while χ^2 test was used to test differences in categorical data at baseline. Final analyses included only those participants who completed the 9-month follow-up according to the intention-to-treat principle. Only eligible eyes were pooled in the final analysis using the generalized estimating equation with robust standard errors to adjust for the correlation between eyes from the same subject, with age, sex, and CCT as covariates to reduce confounding effects [10]. Pearson correlation or Spearman's rank correlation was used to assess correlation between refractive errors and other ocular parameters. Statistical significance was defined at 0.05 level (two-tailed). All statistical tests were performed with SPSS (IBM SPSS Corp., Armonk, NY, USA).

3. Results

From October 2018 to March 2019, a total of 94 subjects (167 eyes) were recruited, with 52 subjects (95 eyes) allocated to the atropine 0.01% group and 42 subjects (72 eyes) allocated to the control group (Supplement F. 1). There was no significant difference between groups in terms of demographic characteristics and ophthalmic parameters at baseline, except for CCT (Table 1).

The intended 1-year follow-up was interrupted by the global outbreak of coronavirus disease 2019 (COVID-19) and the following strict quarantine measures in early 2020. At the 9-month visit, 14 and 13 participants in the treatment group and control group, respectively, were lost to follow-up. Therefore, 119 eyes (69 eyes in the atropine group and 50 eyes in the control group) were included in the final analyses according to the intention-to-treat approach (Table 2). The eyes of subjects who failed to complete the 9-month follow-up were less myopic than those of subjects who completed at the baseline visit. Except for CCT, there were no significant differences in other demographic and ocular parameters between eyes of subjects who completed follow-up visits and those who dropped out at the baseline visit (Supplement Tab. 1).

3.1. Longitudinal changes in refractive errors and axial parameters

After 9 months, children in the treatment group exhibited significantly less myopic progression in SE than did those in the control group (-0.35 ± 0.33 D vs. -0.56 ± 0.49 D, $p = 0.001$). Among atropine-treated eyes, 58.0% had progressed by < 0.5 D as compared with only 38.0% among control eyes, and 1.5% of eyes in the atropine group had progressed by ≥ 1.0 D, as compared with 22.0% in the control group ($p < 0.001$) (Fig. 1).

The extent of axial elongation was significantly smaller in the atropine-treated group than in the control group (0.20 ± 0.19 vs. 0.33 ± 0.19 mm, $p < 0.001$). The difference in VCD changes between the two groups was also statistically significant, while mean changes in other axial measurements, including ACD, CCT, and LT, were similar between the two groups at the three follow-up visits.

Although the myopic shift in spherical refraction was markedly smaller in the atropine group, a significant increase in TA was observed at the same time (within-group comparison: $p < 0.05$) (Fig. 2). In atropine-treated eyes, the change in TA over 9 months ranged from −1.25 D to 0.50 D, as compared with −0.50 D to 0.50 D in control eyes. The difference in the mean change in TA between

Table 1
Baseline characteristics of the enrolled 167 eyes.

	Atropine Group N = 95	Control Group N = 72	P value
Age (yr)	8.91 (1.74)	8.28 (1.87)	0.160
Female (%)	48 (50.5%)	47 (65.3%)	0.057
SE (D)	−2.18 (1.19)	−2.05 (1.48)	0.117
SR (D)	−1.93 (1.14)	−1.80 (1.28)	0.425
TA (D)	−0.49 (0.46)	−0.49 (0.57)	0.168
CA (D)	−1.15 (0.56)	−1.13 (0.53)	0.262
AL (mm)	24.57 (0.95)	24.42 (0.81)	0.688
CCT (μm)	556.75 (35.80)	538.67 (27.57)	<0.001*
ACD (mm)	3.76 (0.19)	3.72 (0.19)	0.195
LT (mm)	3.39 (0.14)	3.36 (0.14)	0.138
VCD (mm)	17.43 (0.86)	17.34 (0.79)	0.714
BCVA (logMAR)	0.00 (0.02)	0.00 (0.02)	0.451

SE: spherical equivalent, SR: spherical refraction, TA: total astigmatism, CA: corneal astigmatism, AL: axial length, CCT: central corneal thickness, ACD: anterior chamber depth, LT: lens thickness, VCD: vitreous chamber depth, BCVA: best corrected visual acuity.
*Between-group difference at $P < 0.05$.

Table 2
Mean changes in ocular parameters from baseline to 9 months.

	Atropine Group N = 69	Control Group N = 50	P value
SE (D)			
mean change over 3 mos	−0.10 (0.26)†	−0.25 (0.21)†	0.020*
mean change over 6 mos	−0.26 (0.37)†	−0.33 (0.45)†	0.267
mean change over 9 mos	−0.35 (0.33)†	−0.56 (0.49)†	0.001*
SR (D)			
mean change over 3 mos	−0.08 (0.21)	−0.27 (0.21)†	0.004*
mean change over 6 mos	−0.18 (0.37)†	−0.31 (0.48)†	0.065
mean change over 9 mos	−0.28 (0.37)†	−0.54 (0.47)†	<0.001*
TA (D)			
mean change over 3 mos	−0.05 (0.22)	0.04 (0.17)	0.071
mean change over 6 mos	−0.15 (0.27)†	−0.06 (0.25)	0.026*
mean change over 9 mos	−0.14 (0.29)†	−0.04 (0.23)	0.013*
CA (D)			
mean change over 3 mos	−0.07 (0.28)	−0.03 (0.22)	0.447
mean change over 6 mos	−0.08 (0.25)†	−0.08 (0.27)†	0.932
mean change over 9 mos	−0.17 (0.26)†	−0.13 (0.29)†	0.424
RA (D)			
mean change over 3 mos	−0.02 (0.30)	−0.05 (0.24)	0.575
mean change over 6 mos	0.08 (0.28)†	0.00 (0.34)	0.165
mean change over 9 mos	0.02 (0.32)	−0.05 (0.30)	0.185
AL (mm)			
mean change over 3 mos	0.06 (0.10)†	0.12 (0.08)†	0.007*
mean change over 6 mos	0.13 (0.14)†	0.23 (0.13)†	<0.001*
mean change over 9 mos	0.20 (0.19)†	0.33 (0.19)†	<0.001*
CCT (μm)			
mean change over 3 mos	−0.30 (4.63)	0.17 (6.15)	0.632
mean change over 6 mos	−0.05 (5.19)	0.55 (7.62)	0.556
mean change over 9 mos	−0.88 (6.01)	−0.34 (6.24)	0.606
ACD (mm)			
mean change over 3 mos	0.02 (0.04)†	0.00 (0.04)	0.103
mean change over 6 mos	0.02 (0.04)†	0.03 (0.06)†	0.744
mean change over 9 mos	0.03 (0.04)†	0.03 (0.06)†	0.503
LT (mm)			
mean change over 3 mos	0.00 (0.03)	0.01 (0.05)	0.159
mean change over 6 mos	0.00 (0.04)	−0.01 (0.04)	0.388
mean change over 9 mos	−0.01 (0.04)	−0.01 (0.05)	0.834
VCD (mm)			
mean change over 3 mos	−0.03 (0.20)†	0.01 (0.14)†	0.005*
mean change over 6 mos	−0.02 (0.17)†	0.03 (0.12)†	<0.001*
mean change over 9 mos	0.00 (0.13)†	0.04 (0.14)†	<0.001*
BCVA (logMAR)			
mean change over 3 mos	0.00 (0.02)	0.00 (0.02)	0.692
mean change over 6 mos	0.00 (0.02)	0.00 (0.02)	0.692
mean change over 9 mos	0.00 (0.02)	0.00 (0.02)	0.309

The generalized estimating equation model was used to assess the difference between two groups over time, with age, sex, and CCT as covariates. SE: spherical equivalent, SR: spherical refraction, TA: totalastigmatism, CA: corneal astigmatism, RA: residual astigmatism, AL: axial length, CCT: central corneal thickness, ACD: anterior chamber depth, LT: lens thickness, VCD: vitreous chamber depth, BCVA: best corrected visual acuity.
*Between-group difference at $P < 0.05$.
†Within-group difference at $P < 0.05$.

the two groups was significant at the 9-month visit (between-group comparison: $p = 0.01$). The prevalence of TA in the atropine group increased from 52.17% at baseline to 68.12% at the 9-month visit ($p = 0.06$), while the prevalence of TA in the control group plateaued at 56%–64% ($p = 0.84$).

The distribution of the TA axis during the follow-up period is illustrated in Fig. 2. Among eyes with TA, 34 (94.44%) had WTR astigmatism and two (5.56%) had ATR in the atropine group at baseline. Additionally, at the 9-month visit, all 47 eyes with TA had WTR astigmatism. In the control group, 27 eyes (90.00%) had WTR astigmatism and three eyes (10.00%) had ATR at the start of the study, while 29 eyes (93.55%) had WTR astigmatism and two eyes (6.45%) had ATR after 9 months.

In terms of CA, both groups showed a significant increase over time (atropine group: range −0.70 D–0.62 D, control group: range −0.74 D–0.92 D), whereas the difference in its mean change was not significantly different between groups (−0.17 D vs. −0.13 D, $p = 0.42$). In the atropine group, the prevalence of CA increased from 89.86% at baseline to 98.55% at the 9-month visit ($p = 0.02$), whereas it remained at 92%–98% in the control group ($p = 0.56$). The distribution of CA axes in two groups remained virtually unchanged during follow-up (Fig. 2).

At the 9-month visit, the ranges of change in RA were −0.55 D–1.31 D in the atropine-treated eyes and −0.57 D–0.96 D in the control eyes. There was no significant difference in the mean changes in RA between the two groups at multiple visits. Moreover, the prevalence of RA in the two groups did not change markedly at the follow-up visits. ATR was predominant in eyes with RA, whereas

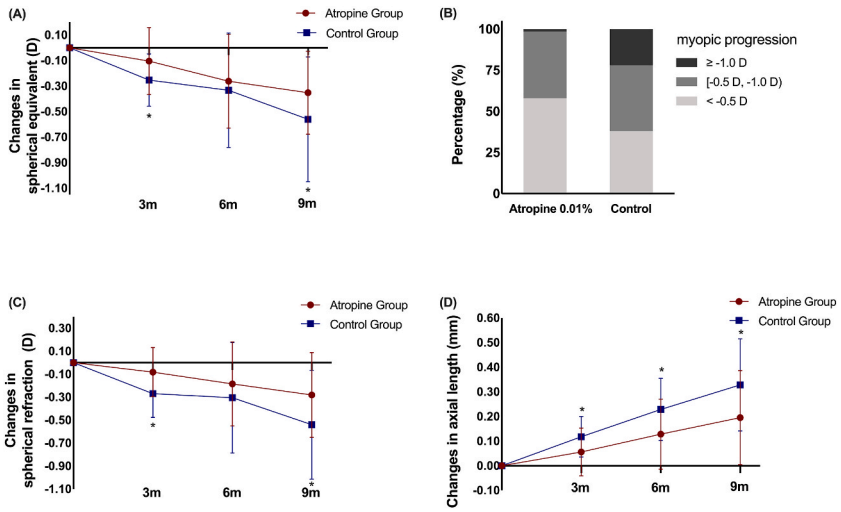

Fig. 1. Changes in spherical equivalent, spherical refraction and axial length in the atropine group and the control group during follow-up, and the distribution of myopic progression in the atropine group and the control group at the 9-month visit.

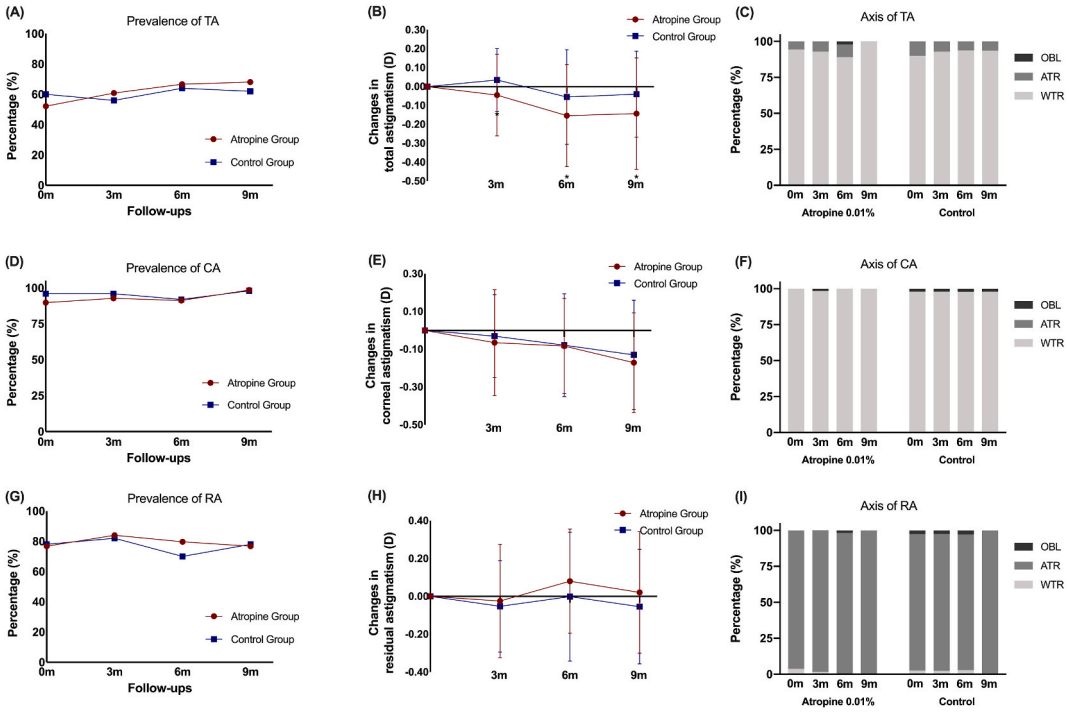

Fig. 2. The prevalence of total astigmatism (TA), corneal astigmatism (CA) and residual astigmatism (RA), and the changes in the magnitude and direction of TA, CA and RA in the atropine group and the control group during follow-up.

two atropine-treated eyes (3.77%) had WTR, one control eye (2.56%) had WTR, and one control eye (2.56%) had OBL astigmatism at the baseline visit. At the 9-month visit, all eyes with RA showed ATR astigmatism.

By further converting the three types of astigmatism from the spherocylindrical notation to J_0 and J_{45} power vectors, we found that both tJ_0 and cJ_0 increased over 9 months in the two groups, and there was a significant difference in the increase in tJ_0 between the atropine group and the control group (tJ_0: 0.09 ± 0.15 vs. 0.03 ± 0.11 D, $p = 0.02$) (Fig. 3). Other vectors, including tJ_{45}, cJ_{45}, rJ_0 and rJ_{45}, remained stable during thd follow-up visits (Table 3).

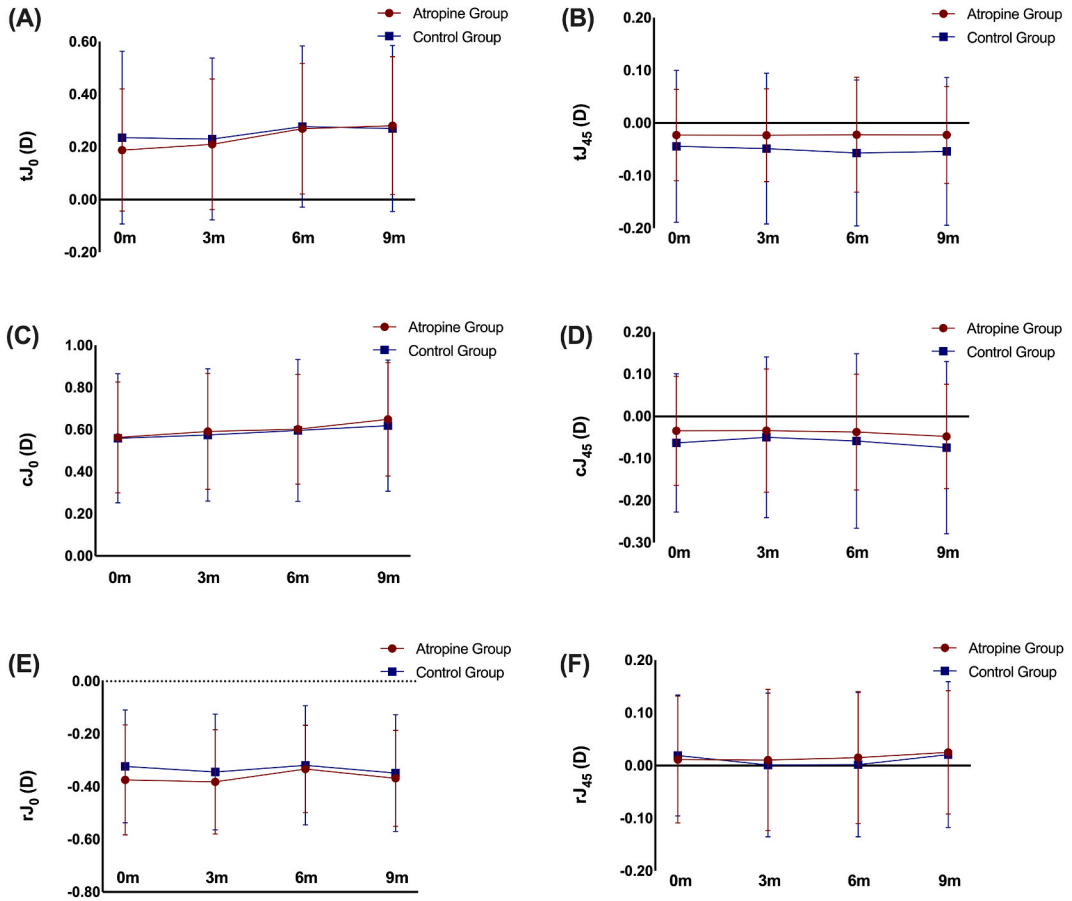

Fig. 3. Changes in J_0 and J_{45} vectors of total astigmatism (TA), corneal astigmatism (CA) and residual astigmatism (RA) in the atropine group and the control group during follow-up.

3.2. Relationship between refractive errors and AL

At the baseline visit, the initial SE of the total study population correlated significantly with the initial TA ($r = 0.517$, $p < 0.001$), initial CA ($r = 0.252$, $p = 0.006$) and initial RA ($r = -0.236$, $p = 0.010$). In the control group, there was a significant negative correlation between the progression of SE and the initial TA ($r = -0.481$, $p < 0.001$) and initial CA ($r = -0.420$, $p = 0.002$). There was also a significant positive correlation between the elongation of AL and the initial TA ($r = 0.579$, $p < 0.001$) and initial CA ($r = 0.507$, $p < 0.001$). On the other hand, in the atropine group, progression of SE was only significantly negatively correlated with initial RA ($r = -0.243$, $p = 0.044$) (Table 4).

For measurements of J_0 vectors, tJ_0 of the total study population correlated positively with cJ_0 ($r = 0.652$, $p < 0.001$) and rJ_0 ($r = 0.325$, $p < 0.001$). tJ_{45} of the total study population was positively correlated with cJ_{45} ($r = 0.507$, $p < 0.001$) and rJ_{45} ($r = 0.196$, $p = 0.03$). Moreover, cJ_0 was negatively correlated with rJ_0 ($r = -0.399$, $p < 0.001$), as was cJ_{45} and rJ_{45} ($r = -0.679$, $p < 0.001$), suggesting that there is a compensatory relationship between CA and RA.

During follow-up visits, the mean change in tJ_0 correlated positively with rJ_0 in both groups (atropine group: $r = 0.574$, $p < 0.001$; control group: $r = 0.546$, $p < 0.001$), instead of cJ_0. The mean change in tJ_{45} correlated positively with rJ_{45} (atropine group: $r = 0.457$, $p < 0.001$; control group: $r = 0.667$, $p < 0.001$) (Fig. 4). Furthermore, the mean change in cJ_0 was significantly negatively correlated with the mean change in rJ_0 in atropine-treated eyes ($r = -0.618$, $p < 0.001$), as well as in the control eyes ($r = -0.736$, $p < 0.001$). Similarly, the mean changes in cJ_{45} and rJ_{45} were negatively correlated in both atropine-treated eyes ($r = -0.715$, $p < 0.001$) and control eyes ($r = -0.720$, $p < 0.001$).

4. Discussion

In the current study, although the follow-up was terminated early, at the 9-month visit, atropine-treated eyes still showed significantly less myopic progression in both refraction (37.5% reduction) and axial elongation (39.3% reduction). Nevertheless, a statistically significant increase in cylindrical refractive error was concurrently observed in atropine-treated eyes.

Wei et al. reported a mean myopia progression of -0.49 ± 0.42 D and a mean axial elongation of 0.32 ± 0.19 mm over 1 year in the

Table 3
Means changes in polar vectors J_0 and J_{45} of three types of astigmatism from baseline to 9 months.

	Atropine Group N = 69	Control Group N = 50	P value
tJ_0 (D)			
mean change over 3 mos	0.02 (0.11)	−0.01 (0.08)	0.117
mean change over 6 mos	0.08 (0.13)†	0.04 (0.14)†	0.116
mean change over 9 mos	0.09 (0.15)†	0.03 (0.11)†	0.016*
tJ_{45} (D)			
mean change over 3 mos	0.00 (0.05)	0.00 (0.04)	0.648
mean change over 6 mos	0.00 (0.08)	−0.01 (0.06)	0.285
mean change over 9 mos	0.00 (0.09)	−0.01 (0.07)	0.502
cJ_0 (D)			
mean change over 3 mos	0.03 (0.14)	0.02 (0.11)	0.567
mean change over 6 mos	0.04 (0.13)†	0.04 (0.13)†	0.931
mean change over 9 mos	0.09 (0.13)†	0.06 (0.15)†	0.332
cJ_{45} (D)			
mean change over 3 mos	0.00 (0.09)	0.01 (0.10)	0.952
mean change over 6 mos	0.00 (0.10)	0.00 (0.11)	0.808
mean change over 9 mos	−0.01(0.10)	−0.01 (0.11)	0.254
rJ_0 (D)			
mean change over 3 mos	−0.01 (0.18)	−0.02 (0.12)	0.605
mean change over 6 mos	0.04 (0.15)†	0.00 (0.17)	0.220
mean change over 9 mos	0.01 (0.18)	−0.03 (0.16)	0.307
rJ_{45} (D)			
mean change over 3 mos	0.00 (0.11)	−0.02 (0.11)	0.399
mean change over 6 mos	0.00 (0.13)	−0.02 (0.12)	0.355
mean change over 9 mos	0.01 (0.12)	0.00 (0.12)	0.597

The generalized estimating equation model was used to assess the difference between two groups over time, with age, sex, and CCT as covariates. tJ_0 and tJ_{45}: J_0 and J_{45} vectors of total astigmatism, cJ_0 and cJ_{45}: J_0 and J_{45} vectors of corneal astigmatism, rJ_0 and rJ_{45}: J_0 and J_{45} vectors of residual astigmatism.
*Between-group difference at $P < 0.05$.
†Within-group difference at $P < 0.05$.

Table 4
The relationship between refractive errors at baseline and changes of spherical equivalent refraction and axial length.[a]

	Whole	Atropine Group		Control Group	
	SE at baseline	change of SE	change of AL	change of SE	change of AL
TA at baseline	0.517	−0.071	0.092	−0.481	0.579
	<0.001*	0.565	0.452	<0.001*	<0.001*
CA at baseline	0.252	−0.187	0.183	−0.420	0.507
	0.006*	0.123	0.132	0.002*	<0.001*
RA at baseline	−0.236	−0.243	0.142	0.137	−0.044
	0.010*	0.044*	0.246	0.343	0.760

SE: spherical equivalent, TA: total astigmatism, CA: corneal astigmatism, RA: residual astigmatism, AL: axial length.
*Significant difference at $P < 0.05$.
[a] The upper row value of each cell represents correlation coefficient (r) and the lower row value represents statistical difference (P value).

atropine 0.01% group, as compared with −0.76 ± 0.50 D and 0.41 ± 0.19 mm in the placebo group [11]. Fu and colleagues found changes of −0.47 ± 0.45 D and 0.37 ± 0.22 mm in SE and AL, respectively, in the atropine 0.01% group, and −0.70 ± 0.60 D and 0.46 ± 0.35 mm in the control group, respectively, after 12 months [12]. The mean changes in myopic progression of atropine-treated eyes and control eyes in our study (0.21 D and 0.13 mm) were comparable with those in the aforementioned studies. In contrast, the efficacy of atropine 0.01% was somewhat attenuated in the LAMP study, presumably because of the younger age of their study population, which has been associated with a poor treatment response [13].

Interestingly, atropine-treated eyes in this study showed a statistically significant increase in TA during the follow-up visit. Similarly, the Atropine in the Treatment of Myopia (ATOM) study investigated the effects of long-term monocular use of atropine 1% daily on astigmatism in Singaporean children and observed a clinically small, but statistically significant, increase in total ocular cylindrical power in atropine-treated eyes (0.30 ± 0.19 D) and in placebo-treated eyes (0.33 ± 0.18 D) over 2 years [14]. Wang et al. reported a mean increase of −0.34 D of TA over 12 months in the atropine 0.01% group, whereas the change was not significantly different from that in the control group (−0.25 D) [15]. The mean increase of 0.12–0.16 D per year of TA noted in the ATOM study was similar to that noted in atropine-treated eyes in our study.

The prevalence rate of total TA reported in children varied widely among different studies because of differences in measurement methods [16], the age or ethnicity of the study population [17,18], and the definition of astigmatism [19]. In the present study, half of the eyes were defined as astigmatic at baseline, reflecting a greater prevalence than in other studies [20,21]. However, this study was a

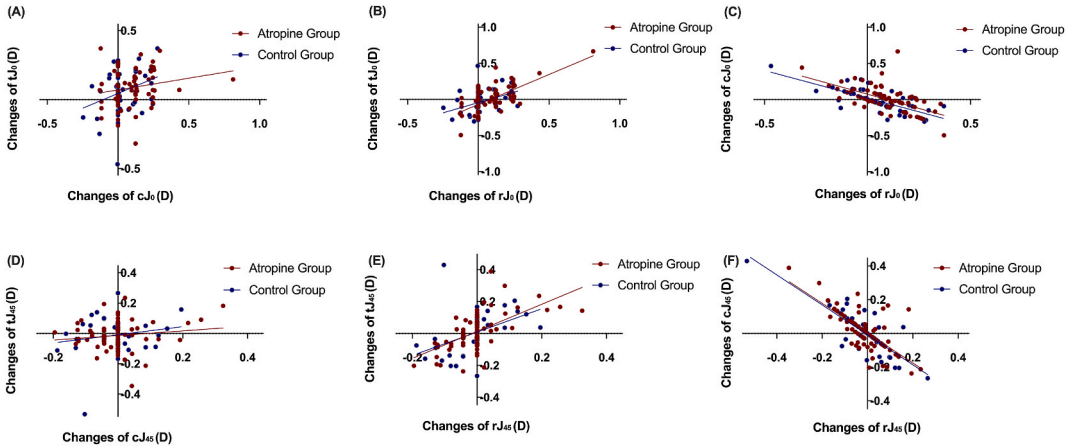

Fig. 4. Scatter plots and regression lines depicting the relationships between changes of J_0 and J_{45} vectors of total astigmatism (TA), corneal astigmatism (CA) and residual astigmatism (RA) in the atropine group and the control group from baseline to 9-month visit.

single hospital-based study that focused on children with low to moderate myopia, which could partly explain the high prevalence of total astigmatism, since both clinical association and genetic susceptibility has been shown for the development of myopia and astigmatism in some prior studies [22,23].

In addition to the magnitude of astigmatism, the relationship between the axes of astigmatism and myopia development was also investigated in multiple clinical studies and animal experiments [24–28]. Nevertheless, there is no consensus on the role of astigmatism in myopia onset and progression to date, and the association should be interpreted with caution because of the potential bias related to incorporating half of the astigmatic value into the SE value. In accordance with previous findings in children with an East Asian background [8,17,18], the direction of TA in this study was predominantly WTR, whereas the change in axis was minor, probably due to the relatively short follow-up period.

It is accepted that total TA can be divided into at least two components—CA, which can be independently measured, and RA, which is defined as the vectorial difference between TA and CA on doubled-angle polar coordinates. To evaluate the influence of atropine eye drops on the distribution and relationship between these components of astigmatism further in this study, CA was calculated using a refractive index of 1.3375, which represented the total refractive power arising from both the anterior and posterior surfaces of the cornea. Thus, RA was considered to be caused by asymmetric curvatures or a tilting position of the crystalline lens. Similar to TA, the prevalence of CA and RA $\leq$ 0.50 D was rather high in the present study. The CA was predominantly WTR, while RA was predominantly ATR.

In the ATOM study, there was a mean increase in CA of 0.10–0.13 D per year in atropine-treated eyes (0.27 $\pm$ 0.13 D/2 years) and placebo-treated eyes (0.22 $\pm$ 0.14 D/2 years), which was comparable to that in our study [14]. Similarly, CA increased -0.28 ± 0.35 D and -0.26 ± 0.26 D in the atropine 0.01% group and control group respectively after a 2-year follow-up in another study [15]. The effects of atropine on RA were not investigated in the two aforementioned studies. In the present study, we found that atropine-treated eyes showed a mean decrease of 0.08 D in RA at the 6-month visit, followed by a small increase of 0.06 D at the 9-month visit, while the direction of RA remained stable over time. In line with the ATOM study, the small but significant increase in tJ_0 in atropine-treated eyes was mostly attributed to the change in cJ_0, rather than that in rJ_0 [14].

Relationships among different refractive errors were also evaluated in our study. At the beginning of the follow-up, both TA and CA correlated positively with SE, while the mean RA correlated negatively with SE. Interestingly, during the 9 months of treatment, the progression of SE was significantly correlated with the initial TA and CA in control eyes but was significantly correlated with only the initial RA in atropine-treated eyes. The negative correlations between initial J_0 and J_{45} vectors of CA and RA, along with the negative correlations between the respective changes in J_0 and J_{45} vectors during follow-up visits, indicated a compensatory relationship between CA and RA.

Overall, the average increase in TA in atropine-treated eyes was clinically insignificant in the present study, although a change in TA of up to -1.25 D occurred in certain individuals within the 9-month period. Moreover, the clinically small but statistically significant increase in TA in atropine-treated eyes was mainly attributed to the increase in CA rather than to the minor decrease in RA. However, the compensatory relationship between CA and RA persisted throughout the trial. Differences in changes in astigmatism and the relationship with myopic progression between atropine-treated eyes and control eyes might have resulted from changed contractile responses of the ciliary body during atropine treatment. Moreover, atropine could have potential effects on the cornea, conjunctiva, lens, or sclera [29–31] due to the presence of multiple muscarinic acetylcholine receptors in all these tissues.

This study has several limitations. Firstly, this was a single-centre study, and the sample size was relatively small. Secondly, the intended 1-year follow-up was compromised by the COVID-19 pandemic, which limited the ability to draw more definitive conclusions. Thirdly, according to the ATOM study, the difference in rJ_0 and cJ_0 between atropine-treated and atropine-untreated eyes or placebo-treated eyes disappeared by 1 year after discontinuation of atropine intervention [14]. Thus, a long-term follow-up study is required to determine whether the increase in astigmatism during atropine treatment is transient or permanent after drug withdrawal.

In conclusion, the administration of atropine 0.01% eye drops is effective in preventing the progression of spherical refraction and elongation of AL and has potential effects on increasing TA in Chinese school-age children with myopia over a 9-month treatment period.

Author contribution statement

Xingxue Zhu: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Yuliang Wang: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yujia Liu: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Chaoying Ye: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xingtao Zhou: Conceived and designed the experiments; Wrote the paper.

Xiaomei Qu: Conceived and designed the experiments; Wrote the paper.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e18743.

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