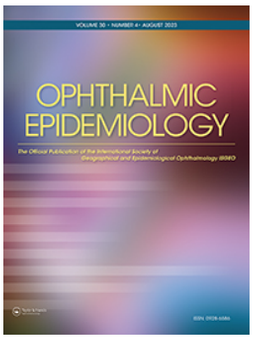

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# Effect of Low-Concentration Atropine Eye Drops in Controlling the Progression of Myopia in Children: A One- and Two-Year Follow-Up Study

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**ABSTRACT**

**Purpose:** Atropine eye drops have been shown to slow the progression of myopia, but there has been limited research on the effectiveness of 0.05% atropine in treating myopia. This study aimed to investigate the safety and efficacy of 0.05% atropine eye drops in controlling myopia in children.

**Methods:** The study included 424 participants aged 6 to 12 years between January 1, 2015, and January 1, 2021. Of these, 213 were randomly assigned to the 0.05% atropine group and 211 to the placebo group. The cycloplegic spherical equivalent (SE), axial length (AL), corneal curvature (K), and anterior chamber depth (ACD) were measured using IOLMaster. The lens power and corneal astigmatism were also determined. The changes in ocular biometric parameters were compared between the two groups, and the contributions of ocular characteristics to SE progression were calculated and compared.

**Results:** Over a 12-month period, the changes in spherical equivalent were −0.03 ± 0.28 and −0.32 ± 0.14 in the atropine and placebo groups, respectively ($P = .01$). The changes in axial length were 0.06 ± 0.11 and 0.17 ± 0.12, respectively ($P = .01$). At 18 and 24 months, there were significant differences in axial length and spherical equivalent between the atropine and placebo groups. Multiple regression models accounting for changes in AL, K, and lens magnification explained 87.23% and 98.32% of SE changes in the atropine and placebo groups, respectively. At 1 year ($p = .01$) and 2 years ($p = .03$), there were significant differences in photophobia between the atropine and placebo groups.

**Conclusions:** This two-year follow-up study demonstrates that 0.05% atropine eye drops are safe and effective in preventing the development of myopia in school-aged children.

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Atropine; 0.05% concentration; myopia

## Introduction

Myopia, also known as nearsightedness, is a common condition that typically begins in childhood. It occurs when the eye is overloaded, causing images of distant objects to focus in front of the retina, resulting in blurred distance vision.[1] The global prevalence of myopia affects nearly 2 billion people, which accounts for 28.3% of the world's population. Among them, 277 million people suffer from severe myopia, which is 4.0% of the world's population.[2] In many countries, the prevalence of myopia in adults ranges from 10–30%, while in young adults in East and South-East Asia, it can be as high as 80–90%.[3] It is important to note that corneal and lens myopia, which is different from normal axial myopia in etiology, has different risk factors and requires different preventive and clinical treatment methods.[4]

Myopia is strongly associated with education and near-work activities, outdoor activities, genetic factors, eye growth, and gene-environment interactions.[5] Due to the role of multiple factors in myopia and the potential dangers it poses, there have been significant advances in treatments for myopia,[6] Animal and human studies have practical implications for the treatment of myopia, suggesting that reducing regulatory hysteresis, reducing central and peripheral defocus, and blocking myopic signaling in the eye can slow the progression of myopia.

Given the limited information on the signaling pathways for myopia development, current treatments for controlling myopia progression include optical corrections such as bifocal spectacle lenses, progressive additive spectacle lenses, undercorrection, orthokeratology lenses (OK), multifocal contact lenses, and increased exposure to outdoor activities.[7] However, all of these methods have shown poor results in preventing myopia progression.[4,8–10] Furthermore, each treatment has its own drawbacks. For example, bifocal spectacle lenses are thick and heavy, causing visual distortion and discomfort during intense

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physical and outdoor activities. Progressive additive spectacle lenses have a long adaptation period, high cost, and are not suitable for intense physical and outdoor activities. Under-correction is not conducive to long-term vision protection and may lead to further increases in myopia. Orthokeratology lenses (OK lenses) require daily wear and are not suitable for patients with high myopia, which may cause eye discomfort. Multifocal contact lenses have a long adaptation period, high cost, and may cause eye discomfort. Increased exposure to outdoor activities requires more time and effort and is not suitable for harsh weather conditions.[1,11,12] Therefore, choosing an optical, accessible, inexpensive, and well-tolerated treatment which can make observers immediately aware of the benefits of improved vision and can be help for very young children.

Atropine, a non-specific anti-muscarinic antagonist, is considered a potential pharmacological intervention for myopia control.[13] It is the most extensively studied drug for this indication, with numerous retrospective cohort studies and randomized controlled trials. A meta-analysis of four randomized controlled trials showed that daily use of high-dose atropine eye drops (0.5–1.0%) and low-dose atropine eye drops (0.1% and 0.01%) had a significant effect in slowing down the progression of myopia in children (0.53 D per year).[14] Animal studies in juvenile marmosets have shown that topical atropine at 1% and 0.1% increases lens thickness and affects the anterior segment of the lens.[15] However, recent studies have focused on short-term follow-up and have failed to address the lack of progress in follow-up studies over 2 years.

The question remains regarding the effectiveness and safety of 0.05% atropine eye drops in controlling myopia in children. Excessive axial elongation can result in mechanical elongation and thinning of the retina, choroid, and sclera, leading to degenerative effects and complications of myopia, such as myopic choroidal neovascularization. Therefore, I argue that atropine can effectively control the progression of myopia in children. The study was conducted in the form of a survey, with data being gathered through follow-up studies over a period of 2 years.

## Materials and methods

This study is a single-center, randomized, blinded, and controlled study conducted from January 1, 2015, to January 1, 2021. It was approved by the ethics committee of Tianjin Medical University Eye Hospital and the institutional review board (IRB) (Clinical Trial Registry NO: LYUS023452). These studies also comply with the Declaration of Helsinki, according to the CONSORT guidelines. All patients were informed and signed an informed consent form.

## Study subjects

The eligible participants for this study were Chinese schoolchildren aged 6 to 12 years old who had mild to moderate myopia, defined as objective spherical equivalence (SE) and binocular astigmatism between −1.00 to −6.00 D, and astigmatism ≤ 1.50 D. The study aimed to report on the progression of myopia based on the results of regular school health checks from the previous year.

The inclusion criteria for the study were children with reduced vision in a recent school health examination, children with corrected visual acuity less than 1.0, children with normal intraocular pressure, children who could undergo follow-up examinations following the study protocol, children from whom written informed consent to participate in the study could be obtained, and children capable of undergoing cycloplegia.

On the other hand, children with abnormal binocular function, amblyopia, or manifest strabismus, changes in objective spherical equivalent in both eyes as measured by cycloplegic and non-cycloplegic refraction of less than 1.00 D, children with ocular diseases other than myopia, and children with ocular or systemic diseases that may affect myopia or refractive power were excluded from the study. Additionally, children who were allergic to atropine, cyclopentolate, or benzalkonium chloride, and those who may wear contact lenses, bifocal lenses, or progressive lenses throughout the trial period were not included.

## Randomization

Authorized personnel will register through a central registration system after verification and collect their reference data using an electronic data collection system (EDC) or telex. The data of each subject will be anonymized and paired with a subject identification code transmitted by the EDC system. Subsequently, patients will be given either 0.05% atropine eye drops or sodium citrate for atropine eye drops. A permutation block approach, stratified by age and sex, will be used to randomly allocate each location (block size: 4, ratio: 1:1). A contracted professional research body, Medical Edge Ltd, will prepare and maintain the mapping table. The experimental medication will be created in a GMP-certified manufacturing facility, Eye Lens Pte. Ltd. The identification of research-specific medications will be blinded to researchers, children, and their caretakers.

## Treatment protocol

All participants will receive medication in both eyes once a night for 24 months. As hyperopic transitions were

recorded early in atropine treatment, all patients will have a first follow-up visit 2 weeks after treatment, medication will begin at 2 weeks, and subsequent assessments will be conducted 6 weeks later. The treatment will last for 12 months, followed by 18 months of baseline follow-up and 24 months of follow-up.

All study participants and their legal guardians were provided with comprehensive and detailed instructions on the proper administration of study medication and the recording of daily doses using a mobile delivery device. Additionally, subjects or their legal guardians were required to surrender the remaining medication for testing at each visit. These records were used to closely monitor adherence to treatment regimens. The adherence rate was defined as the number of days with ≥ 75% study drug intake between assessment time points.

Initial non-mydriatic and mydriatic refraction, including objective SE, astigmatism, and corneal radius of curvature, were performed using appropriate machine examinations. Throughout the 24-month study period, a partially coherent non-contact laser interferometer (IOL Master®; Carl Zeiss Meditec AG) was used on each patient. Visual acuity was measured with and without correction at baseline and at each time point. Distance and near vision were measured before mydriatic refraction, and only distance vision was measured after mydriatic refraction.

## Outcome measures

All ocular biological tests in this study were conducted following a complete cycloplegic cycle, which consisted of at least two eyes drop cycles. Five readings were taken and averaged, with each reading being less than 0.25 D. The spherical equivalent refractive index was calculated by adding half of the spherical power to the cylindrical power. Biometric parameters of the eye were measured using ZEISS IOLMaster (Carl Zeiss Meditec, Inc., Dublin, CA). The average value of K was obtained by averaging K1 and K2. Corneal astigmatism was calculated as the absolute difference between K1 and K2 values.[16] All measurements were taken for both eyes during the first visit every six months for two years.[17] The sample size for each group was 90, with a calculated dropout rate of 20% at 90% and 5% significance levels.

## Statistical analysis

Changes in ocular biometric parameters were calculated by subtracting the initial visit values from the planned follow-up visit values. The differences between the final data groups were analyzed using chi-square test and Fisher's exact test for categorical data, and variance analysis for continuous data. The differences between biometric parameters and baseline at each time point were calculated for both eyes. Missing data values were imputed based on the breakdown of other variables in the dataset. P-values were generated from generalized estimating equations with specified standard errors to adjust for correlations and compare multiple eyes. Two input methods and a stepwise linear regression selection method were used to establish the relationship between changes in spherical equivalent (dependent variable) and changes in age, sex, and axial length. K represents the power of the lens. The R2 adjusted value was used to represent the proportion of variance in the dependent variable predicted by the independent variables in the regression model. An unrelated regression was used to test whether the coefficients of the linear regression models were the same for the different treatment groups. Statistical analysis was performed using SPSS statistical software version 24 (IBM Corp., Armonk, NY) and Stata software version 14.0 (Stata Corp., College Station, TX). Due to multiple statistical comparisons, *P* values less than 0.01 were considered statistically significant.

## Results

From January 1, 2015, to January 1, 2021, a total of 424 subjects were enrolled in the study, with 213 subjects allocated to the atropine group and 211 subjects to the placebo group. During the two-year follow-up, one patient was lost to follow-up in the atropine group and two patients in the control group. Therefore, the atropine group consisted of 212 subjects, and the placebo group consisted of 209 subjects (Figure 1).

Our results indicated that the baseline characteristics of the two groups of patients were similar (Table 1). Approximately half of the patients were male (112/100 in the atropine group and 100/109 in the placebo group), and the mean age was 7.99 ± 0.98 years in the atropine group and 8.28 ± 1.02 years in the placebo group. The mean uncorrected distance VA was 0.77 ± 0.23 in the atropine group and 0.82 ± 0.20 in the placebo group. No differences were found between the left and right eyes of the two groups. The overall baseline means were −2.99 ± 1.23 D for SE and 23.82 ± 0.88 mm for AL in the atropine group and −2.11 ± 1.01 D for SE and 24.52 ± 2.13 mm for AL in the placebo group. No statistical differences were observed in the other baseline results (Table 1).

## Follow-up on ocular biometric changes after 2 years

Table 2 summarizes the changes in ocular biometric parameters, including AL, spherical equivalents, average

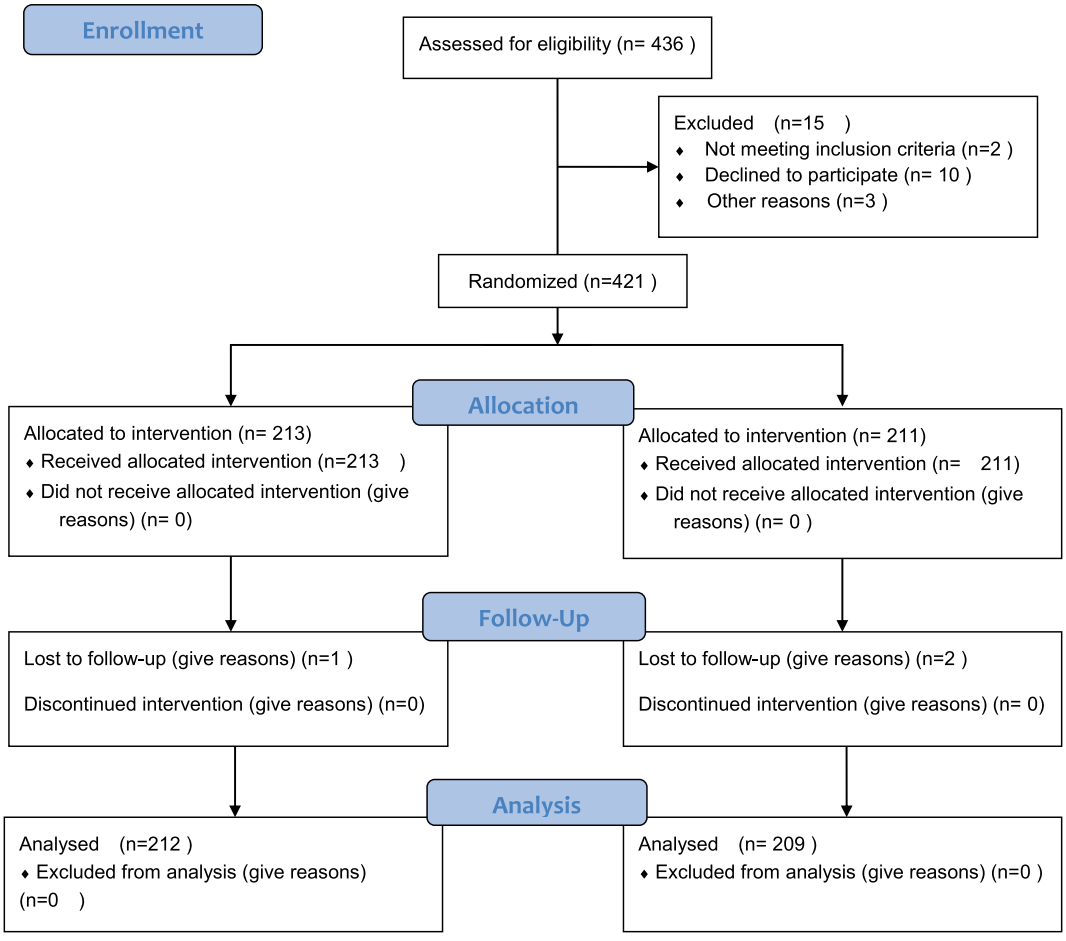


**Figure 1.** Flow chart.

**Table 1.** Baseline demographics and ocular parameters of study participants.

| | Atropine | | Placebo | | |
|---|---|---|---|---|---|
| | Right eye | Left eye | Right eye | Left eye | P value |
| n | 212 | | 209 | | 0.87 |
| sex(male/female) | 112/100 | | 100/109 | | 0.66 |
| age(years) | 7.99 ± 0.98 | | 8.28 ± 1.02 | | 0.83 |
| uncorrected distance VA | 0.21 ± 0,11 | 0.18 ± 0.09 | 0.22 ± 0.10 | 0.20 ± 0.13 | 0.12 |
| uncorrected near VA | 0.93 ± 0.22 | 0.92 ± 0.23 | 0.95 ± 0.13 | 0.97 ± 0.23 | 0.23 |
| uncorrected distance VA(LogMAR) | 0.77 ± 0.23 | 0.81 ± 0.19 | 0.82 ± 0.20 | 0.80 ± 0.23 | 0.83 |
| uncorrected near VA(LogMAR) | 0.08 ± 0.11 | 0.09 ± 0.12 | 0.05 ± 0.11 | 0.06 ± 0.13 | 0.18 |
| Spherical equivalent (D) | &-2.99 ± 1.23 | &-2.89 ± 1.23 | &-2.11 ± 1.01 | &-2.73 ± 1.53 | 0.27 |
| Degree of astigmatism (D) | &-0.45 ± 0.21 | &-0.55 ± 0.22 | &-0.45 ± 0.21 | &-0.46 ± 0.12 | 0.12 |
| Axial length (mm) | 23.82 ± 0.88 | 24.92 ± 1.23 | 24.52 ± 2.13 | 24.99 ± 1.98 | 0.34 |
| Intraocular pressure (mmHg) | 15.20 ± 2.83 | 15.82 ± 1.92 | 15.66 ± 0.98 | 15.23 ± 0.92 | 0.65 |
| Photopic pupil diameter (mm) | 4.99 ± 0.89 | 4.88 ± 1.83 | 4.73 ± 1.67 | 4.82 ± 1.03 | 0.83 |
| Mesopic pupil diameter (mm) | 7.92 ± 1.02 | 7.67 ± 1.02 | 7.02 ± 0.23 | 7.39 ± 0.98 | 0.25 |
| **Corneal curvature(D)** | | | | | |
| Average | 43.23 ± 1.09 | 42.01 ± 2.02 | 43.11 ± 2.83 | 41.33 ± 2.17 | 0.87 |
| Flattest | 41.93 ± 2.98 | 43.88 ± 2.17 | 42.38 ± 3.11 | 47.32 ± 2.65 | 0.55 |
| Steepest | 45.83 ± 1.73 | 45.23 ± 2.08 | 41.03 ± 1.78 | 39.32 ± 0.99 | 0.83 |
| anterior chamber depth(mm) | 3.92 ± 0.67 | 3.23 ± 0.56 | 3.72 ± 0.34 | 3.42 ± 0.32 | 0.23 |
| central corneal thickness(μm) | 550.23 ± 25.38 | 573.92 ± 13.23 | 573.46 ± 23.98 | 523.38 ± 32.18 | 0.88 |
| Corneal astigmatism (D) | 1.76 ± 0.76 | 1.26 ± 0.56 | 1.53 ± 0.34 | 1.63 ± 0.23 | 0.13 |
| Lens power (D) | 22.93 ± 1.98 | 22.76 ± 1.32 | 21.88 ± 1.30 | 23.98 ± 2.18 | 0.73 |

K, lens power, anterior chamber depth, flattest K, steepest K, and corneal astigmatism in the 0.05% atropine and placebo groups at 12, 18, and 24 months. Over 12 months, the change in spherical equivalent was −0.03 ± 0.28 and −0.32 ± 0.14 in the atropine and placebo groups, respectively ($P = .01$). The change in axial length was 0.06 ± 0.11 and 0.17 ± 0.12 in the atropine and placebo groups, respectively ($P = .01$). Moreover, at 18 and

**Table 2.** Changes in refractive error and ocular biometrics in atropine and placebo group.

| | | atropine($n = 212$) | placebo($n = 209$) | overall P value | P Value (in Pair Comparisons |
|---|---|---|---|---|---|
| Baseline and 12 months | △Spherical equivalent (D) | &-0.03 ± 0.28 | &-0.32 ± 0.14 | 0.01 | 0.01 |
| | △Axial length (mm) | 0.06 ± 0.11 | 0.17 ± 0.12 | 0.02 | 0.01 |
| | △Average K(D) | &-0.03 ± 0.12 | 0.03 ± 0.17 | 0.35 | 0.63 |
| | △Lens power (D) | &-0.18 ± 0.34 | &-0.20 ± 0.22 | 0.89 | 0.23 |
| | △anterior chamber depth(mm) | 0.02 ± 0.05 | 0.02 ± 0.02 | 0.98 | 0.31 |
| | △Flattest K(D) | &-0.05 ± 0.13 | &-0.04 ± 0.13 | 0.67 | 0.69 |
| | △Steepest K(D) | 0.02 ± 0.21 | 0.05 ± 0.24 | 0.76 | 0.23 |
| | △Corneal astigmatism (D) | 0.13 ± 0.23 | 0.10 ± 0.21 | 0.56 | 0.44 |
| Baseline and 18 months | △Spherical equivalent (D) | &-0.16 ± 0.42 | &-0.63 ± 0.28 | 0.02 | 0.01 |
| | △Axial length (mm) | 0.13 ± 0.11 | 0.33 ± 0.13 | 0.02 | 0.01 |
| | △Average K(D) | &-0.02 ± 0.11 | &0.03 ± 0.13 | 0.32 | 0.14 |
| | △Lens power (D) | &-0.27 ± 0.23 | &-0.37 ± 0.31 | 0.34 | 0.25 |
| | △anterior chamber depth(mm) | 0.05 ± 0.02 | 0.04 ± 0.04 | 0.78 | 0.52 |
| | △Flattest K(D) | &-0.11 ± 0.14 | &-0.07 ± 0.13 | 0.13 | 0.11 |
| | △Steepest K(D) | 0.08 ± 0.22 | 0.08 ± 0.21 | 0.25 | 0.32 |
| | △Corneal astigmatism (D) | 0.17 ± 0.21 | 0.12 ± 0.23 | 0.25 | 0.34 |
| Baseline and 24 months | △Spherical equivalent (D) | &-0.31 ± 0.52 | &-0.92 ± 0.42 | 0.02 | 0.01 |
| | △Axial length (mm) | 0.23 ± 0.21 | 0.42 ± 0.12 | 0.01 | 0.01 |
| | △Average K(D) | &-0.05 ± 0.11 | 0.02 ± 0.10 | 0.75 | 0.35 |
| | △Lens power (D) | &-0.37 ± 0.28 | &-0.45 ± 0.30 | 0.42 | 0.23 |
| | △anterior chamber depth(mm) | 0.06 ± 0.04 | 0.05 ± 0.05 | 0.23 | 0.42 |
| | △Flattest K(D) | &-0.13 ± 0.12 | &-0.09 ± 0.22 | 0.32 | 0.78 |
| | △Steepest K(D) | 0.08 ± 0.21 | 0.09 ± 0.19 | 0.66 | 0.98 |
| | △Corneal astigmatism (D) | 0.18 ± 0.27 | 0.18 ± 0.26 | 0.87 | 0.32 |

24 months, there were significant differences in the changes of axial length and spherical equivalent between the atropine and placebo groups. There were also statistically significant differences in the cumulative changes in AL and SE over 12, 18, and 21 months. The average K, lens power, anterior chamber depth, flattest K, steepest K, and corneal astigmatism remained stable in each group after 12, 18, and 24 months.

## Corneal parameters and lens power follow up 2 years

Table 3 summarizes the effect of changes in ocular biometrics on SE progression at each concentration, including changes in K, AL, and lens magnification (adjusted for age and sex). At all atropine concentrations, myopia progression was primarily due to prolongation of the AL, accounting for more than 70% of myopic progression, followed by the lens and corneal strength. After adjustment for K and slow changes, the multiple regression model explained 87.23% and 98.32% of the change in SE in the atropine and placebo groups, respectively, which was 0.05% (Table 4, Model 3). In the placebo group, linear regression showed an A1 coefficient of −2.11, corneal astigmatism of −0.23, and lens strength of −1.83 (Table 4, Model 4).

## Adverse events

At a 24-month follow-up, 63 patients were found to require photochromatic glasses needed intervention in the atropine intervention group and 83 patients

**Table 3.** Corneal parameters and lens power at each time point.

| | atropine($n = 212$) | placebo($n = 209$) | overall P value | time |
|---|---|---|---|---|
| **average K(D)** | | | | |
| 6 mos | 43.22 ± 1.25 | 43.21 ± 2.15 | 0.25 | <0.001 |
| 12 mos | 43.22 ± 0.69 | 43.21 ± 1.24 | 0.85 | |
| 18 mos | 43.26 ± 2.61 | 43.36 ± 1.62 | 0.62 | |
| 24 mos | 43.25 ± 2.14 | 43.62 ± 1.88 | 0.54 | |
| **Flattest K(D)** | | | | |
| 6 mos | 43.25 ± 1.36 | 43.62 ± 1.02 | 0.62 | <0.001 |
| 12 mos | 42.23 ± 1.69 | 42.62 ± 2.61 | 0.35 | |
| 18 mos | 42.62 ± 2.14 | 42.61 ± 2.15 | 0.28 | |
| 24 mos | 43.69 ± 2.68 | 43.45 ± 1.68 | 0.16 | |
| **Steepest K(D)** | | | | |
| 6 mos | 44.56 ± 2.69 | 43.69 ± 1.86 | 0.61 | <0.001 |
| 12 mos | 44.62 ± 1.85 | 44.32 ± 2.62 | 0.28 | |
| 18 mos | 44.56 ± 2.56 | 44.61 ± 1.97 | 0.21 | |
| 24 mos | 44.11 ± 1.85 | 44.32 ± 2.95 | 0.22 | |

(*Continued*)

**Table 3.** (Continued).

| | atropine($n$ = 212) | placebo($n$ = 209) | overall P value | time |
|---|---|---|---|---|
| **Corneal astigmatism(D)** | | | | |
| 6 mos | 1.51 ± 0.25 | 1.34 ± 0.19 | 0.62 | <0.001 |
| 12 mos | 1.52 ± 0.68 | 1.30 ± 0.36 | 0.36 | |
| 18 mos | 1.56 ± 0.14 | 1.32 ± 0.24 | 0.45 | |
| 24 mos | 1.54 ± 0.32 | 1.42 ± 0.31 | 0.36 | |
| **anterior chamber depth(mm)** | | | | |
| 6 mos | 3.72 ± 0.25 | 3.71 ± 0.31 | 0.25 | <0.001 |
| 12 mos | 3.77 ± 0.36 | 3.76 ± 0.14 | 0.45 | |
| 18 mos | 3.71 ± 0.18 | 3.75 ± 0.25 | 0.41 | |
| 24 mos | 3.45 ± 0.52 | 3.45 ± 0.42 | 0.42 | |
| **Bennett-Rabbetts lens power(D)** | | | | |
| 6 mos | 22.61 ± 2.36 | 22.76 ± 1.95 | 0.69 | <0.001 |
| 12 mos | 22.45 ± 1.63 | 22.68 ± 2.69 | 0.58 | |
| 18 mos | 22.68 ± 1.54 | 22.69 ± 1.52 | 0.25 | |
| 24 mos | 22.69 ± 1.95 | 22.64 ± 1.86 | 0.61 | |

**Table 4.** Linear regression for change in spherical equivalent and ocular biometric.

| | | 0.05% atropine | | | Placebo | | |
|---|---|---|---|---|---|---|---|
| variables | | β coeffcient | standard error | p value | β coeffcient | standard error | p value |
| Model 1 | △Axial length (mm) | &-2.21 | 0.12 | <0.02 | &-2.93 | 0.18 | <0.001 |
| | Adjusted R2%) | 89.23 | | | 67.32 | | |
| Model 2 | △Axial length (mm) | &-2.93 | 0.08 | <0.001 | &-2.88 | 0.12 | <0.001 |
| | △Lens power (D) | &-0.78 | 0.09 | <0.001 | &-0.33 | 0.33 | <0.001 |
| | Adjusted R2%) | 92.12 | | | 67.99 | | |
| Model 3 | △Axial length (mm) | &-2.11 | 0.03 | <0.001 | &-2.13 | 0.32 | <0.001 |
| | △Corneal astigmatism (D) | &-0.67 | 0.09 | <0.001 | &-0.77 | 0.33 | <0.001 |
| | △Lens power (D) | &-1.32 | 0.23 | <0.001 | &-1.99 | 0.23 | <0.001 |
| | Adjusted R2%) | 87.23 | | | 98.32 | | |
| Model 4 | △Axial length (mm) | &-2.11 | 0.03 | <0.001 | &-2.99 | 0.32 | <0.001 |
| | △Corneal astigmatism (D) | &-0.23 | 0.01 | <0.001 | &-0.32 | 0.22 | <0.001 |
| | △Lens power (D) | &-1.83 | 0.03 | <0.001 | &-1.23 | 0.03 | <0.001 |
| | Gender (M1,F2) | &-0.03 | 0.05 | 0.32 | &-0.31 | 0.02 | 0.032 |
| | Age | &-0.08 | 0.03 | 0.13 | 0.09 | 0.01 | 0.34 |
| | Adjusted R2%) | 89.23 | | | 99.32 | | |

in the placebo group. 2 subjects accept progressive glasses needed in the atropine group, and 3 subjects in the placebo group. For allergic conjunctivitis, there are 6 subjects in the atropine group and 6 subjects in the placebo group. In addition, 7 subjects were located in hospitalization in the atropine group and 5 subjects in the placebo group. Thus, there is no significant difference among photochromatic glasses needed, progressive glasses needed, allergic conjunctivitis, and hospitalization between the two groups. However, the atropine group and placebo group have been shown significant differences for photophobia at 1 year ($p$ = .01) and 2 years ($p$ = .03) (Table 5).

## Discussion

Although progress in the treatment of myopia with atropine has been reported in previous studies, more clinical studies need to be included, including studies of its long-term effectiveness, side effects.[18] In our study, we co-enrolled and analyzed a total of 421 children in school and our results found that 0.05% of atropine treatment over two years controlled the progression of myopia. At the same time, the adverse events of atropine treatment were similar concerning the control group.

This may suggest a potential biological difference of the drops between both studies, and therefore different

**Table 5.** Side effects and adverse events.

| | atropine($n$ = 212) | placebo($n$ = 209) | overall P value |
|---|---|---|---|
| Photochromatic glasses needed | 63(29.71) | 83(39.71) | 0.25 |
| Progressive glasses needed | 2(0.94) | 3(1.42%) | 0.09 |
| Photophobia at 1 y | 67(31.60) | 22(10.52) | 0.01 |
| Photophobia at 2 y | 16(7.54) | 8(3.82) | 0.03 |
| Allergic conjunctivitis | 6(2.83) | 6(2.87) | 0.85 |
| Hospitalization | 7(3.30) | 5(2.39) | 0.61 |

efficacies.[19–21] First, previous studies have analyzed differences in the effect of different concentrations of atropine in the control of myopia, but there is no clear conclusion. ATOM studies have found that treatment with different concentrations of atropine including 0.01%, 0.5% has no significant effect on the progression of myopia.[22,23] In the above study, it was found that 0.01% of atropine eye drops can significantly delay the progression of myopia within 2 years but the study is also affected by factors such as Japanese lifestyle and habits. In a study in China, the results of three different atropine concentrations (0.01%, 0.025%, and 0.05%) drops were analyzed to control myopia within 1 year, and Atropine eye drops 0.05%, 0.025%, and 0.01% reduced myopia progression according to a concentration-dependent response, with 0.05% atropine being more effective in controlling SE progression and AL prolongation.[16] Besides, our study first had a relatively long follow-up time, and further used the method of randomized controlled study to confirm the effect of atropine treatment for myopia at different concentrations. This provides important evidence for further elucidating the role of atropine in the treatment of myopia.

Recently, extended results from the LAMP study (phase 2 report) were published, wherein the placebo treatment was replaced with 0.05% atropine at the end of the first year. The study demonstrated that 0.05% atropine was twice as effective as 0.01% atropine over two years, and it remained the optimal concentration among the tested atropine concentrations to slow the progression of myopia.[24] However, it should be noted that the observation time of this study was only one year, which means that the observation period was relatively short. Additionally, the sample size of this study was smaller than that of the LAMP study. Furthermore, it is important to consider that the effects of atropine can be influenced by various environmental factors, such as country, culture, and lifestyle. Epidemiological differences, risk factors between ethnicities and cultures, and environmental influences on the progression of myopia are well-known.[25] Therefore, further studies are needed to investigate the efficacy of 0.05% atropine for controlling myopia.

In our current study, we have discovered that the use of 0.05% atropine over a two-year period effectively controlled the progression of myopia. Furthermore, the adverse effects of atropine treatment were similar to those of the control group, which is consistent with previous research. Yam et al. found that atropine eye drops with concentrations of 0.05%, 0.025%, and 0.01% slowed the progression of myopia, with 0.05% being the most effective in controlling spherical equivalent (SE) progression and axial length (AL) prolongation for one year.[16] Topically, atropine 0.05% is an effective drug in controlling myopia progression for at least one year in most school-aged children.[26] Li et al. studied the effect of age and other factors on the response to atropine treatment and found that younger children required up to 0.05% atropine to achieve the same reduction in myopia progression.[27] A meta-analysis systematically evaluated the safety and efficacy of atropine in controlling myopia progression and suggested that 0.05% atropine may be the optimal dose for monitoring myopia progression.[28] However, Lutz Joachimsen et al. found that adverse events of topical atropine in Caucasian children with progressive myopia were higher at 0.05% than in Asian children at 0.01%, which may affect absorption and compliance. Nevertheless, our two-year follow-up study findings demonstrate that eye drops containing 0.05% atropine are safe and effective in preventing the development of myopia in school-aged children. Additionally, most of the previous LAMP and ATOM studies had a short follow-up period of one year, whereas our study had a follow-up period of two years, providing a new basis for studying the effect of low concentrations of atropine in the treatment of myopia.

The strength of this study lies in its double-blind, placebo-controlled randomization design of a relatively large sample of study participants followed up for 2 years. What's more, in performing repeated biometry measurements, the possible bias would be minimized by using generalized estimating equations, including data from both eyes to assess changes over time. Measurements were carried out with the IOLMaster after complete cycloplegia, which avoided the effect of accommodation.[29] Our study allowed direct comparisons between different atropine concentrations with placebo to ascertain the atropine effects on ocular biometric parameters.

Notably, this study has some limitations. First, although 0.05% atropine eye drops are effective after 24 months of use, the long-term effect is unclear. Second, there was no atropine concentration range in our study. Both the LAMP and ATOM2 studies showed concentration-dependent responses, with the 0.05% LAMP study showing better efficacy.[23] Also, this treatment may require long-term use of eye drops as the child grows. Whether the 0.05% atropine concentration is the optimal concentration needs further investigation. Third, this survey does not measure the breadth or function of all institutional housing. Fourth, environmental factors may influence myopia progression; however, this study did not collect detailed lifestyle data, which limits consideration of between-group comparisons when interpreting the results.

## Conclusion

The findings of this study indicate that the use of eye drops containing 0.05% atropine is both safe and effective in reducing the progression of myopia in school-aged children. Positive outcomes were observed after a long-term treatment of 2 years. However, further research is required to determine the optimal concentration of atropine and its suitability for younger students.

## Consent for publication

We all agree to publication.

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## Author contribution

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## Data availability statement

The data used to support the findings of this study are included in the article.

## References

1. Baird PN, Saw SM, Lanca C, et al. Myopia. *Nat Rev Dis Primers*. 2020;6(1):99. doi: 10.1038/s41572-020-00231-4
2. Holden BA, Fricke TR, Wilson DA, et al. Global prevalence of myopia and high Myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123(5):1036–1042. doi: 10.1016/j.ophtha.2016.01.006
3. Resnikoff S, Jonas JB, Friedman D, et al. Myopia - a 21st century public health issue. *Invest Ophthalmol Vis Sci*. 2019;60(3):Mi–Mii. doi: 10.1167/iovs.18-25983
4. Bullimore MA, Ritchey ER, Shah S, Leveziel N, Bourne RRA, Flitcroft DI. The risks and benefits of myopia control. *Ophthalmology*. 2021;128(11):1561–1579. doi: 10.1016/j.ophtha.2021.04.032
5. Zhu QR, Liu LQ. Relationship between myopia and light exposure. *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2021;52(6):901–906. doi: 10.12182/20211160205
6. Shinojima A, Negishi K, Tsubota K, Kurihara T. Multiple factors causing myopia and the possible treatments: A mini review. *Front Public Health*. 2022;10:897600. doi: 10.3389/fpubh.2022.897600
7. Modjtahedi BS, Abbott RL, Fong DS, Lum F, Tan D. 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*. 2021;128(6):816–826. doi: 10.1016/j.ophtha.2020.10.040
8. Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res*. 2021;83:100923. doi: 10.1016/j.preteyeres.2020.100923
9. Cooper J, Tkatchenko AV. A Review of current concepts of the etiology and treatment of Myopia. *Eye Contact Lens*. 2018;44(4):231–247. doi: 10.1097/icl.0000000000000499
10. Wu PC, Chuang MN, Choi J, et al. Update in myopia and treatment strategy of atropine use in myopia control. *Eye (Lond)*. 2019;33(1):3–13. doi: 10.1038/s41433-018-0139-7
11. Morgan IG, French AN, Ashby RS, et al. The epidemics of myopia: Aetiology and prevention. *Prog Retin Eye Res*. 2018;62:134–149. doi: 10.1016/j.preteyeres.2017.09.004
12. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. *Lancet*. 2012;379(9827):1739–1748. doi: 10.1016/s0140-6736(12)60272-4
13. Ganesan P, Wildsoet CF. Pharmaceutical intervention for myopia control. *Expert Rev Ophthalmol*. 2010;5(6):759–787. doi: 10.1586/eop.10.67
14. Huang J, Wen D, Wang Q, et al. Efficacy comparison of 16 interventions for Myopia control in children: A network meta-analysis. *Ophthalmology*. 2016;123(4):697–708. doi: 10.1016/j.ophtha.2015.11.010
15. Whatham AR, Lunn D, Judge SJ. Effects of monocular atropinization on refractive error and eye growth in infant new World Monkeys. *Invest Ophthalmol Vis Sci*. 2019;60(7):2623–2630. doi: 10.1167/iovs.18-24490
16. Yam JC, Jiang Y, Tang SM, et al. Low-concentration atropine for myopia progression (LAMP) Study: A randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in Myopia Control. *Ophthalmology*. 2019;126(1):113–124. doi: 10.1016/j.ophtha.2018.05.029
17. Rabbetts RB. *Bennett And Rabbett's Clinical Visual Optics*. Bennett and Rabbett's clinical visual optics; 2007.
18. Medina A. The cause of myopia development and progression: Theory, evidence, and treatment. *Surv Ophthalmol*. 2022;67(2):488–509. doi: 10.1016/j.survophthal.2021.06.005

19. Jonas JB, Wang YX, Dong L, Guo Y, Panda-Jonas S. Advances in myopia research anatomical findings in highly myopic eyes. *Eye Vis (Lond)*. 2020;7(1):45. doi: 10.1186/s40662-020-00210-6
20. Lejoyeux R, Benillouche J, Ong J, et al. Choriocapillaris: Fundamentals and advancements. *Prog Retin Eye Res*. 2022;87:100997. doi: 10.1016/j.preteyeres.2021.100997
21. Yu Q, Zhou JB. Scleral remodeling in myopia development. *Int J Ophthalmol*. 2022;15(3):510–514. doi: 10.18240/ijo.2022.03.21
22. Chua WH, Balakrishnan V, Chan YH, et al. Atropine for the treatment of childhood myopia. *Ophthalmology*. 2006;113(12):2285–2291. doi: 10.1016/j.ophtha.2006.05.062
23. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). *Ophthalmology*. 2012;119(2):347–354. doi: 10.1016/j.ophtha.2011.07.031
24. Yam JC, Li FF, Zhang X, et al. Two-year clinical trial of the low-concentration atropine for myopia progression (LAMP) Study: phase 2 report. *Ophthalmology*. 2020;127(7):910–919. doi: 10.1016/j.ophtha.2019.12.011
25. Rudnicka AR, Kapetanakis VV, Wathern AK, et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. *Br J Ophthalmol*. 2016;100(7):882–890. doi: 10.1136/bjophthalmol-2015-307724
26. Lee JJ, Fang PC, Yang IH, et al. Prevention of myopia progression with 0.05% atropine solution. *J Ocul Pharmacol Ther*. 2006;22(1):41–46. doi: 10.1089/jop.2006.22.41
27. Li FF, Zhang Y, Zhang X, et al. Age effect on treatment responses to 0.05%, 0.025%, and 0.01% atropine: Low-concentration atropine for Myopia progression study. *Ophthalmology*. 2021;128(8):1180–1187. doi: 10.1016/j.ophtha.2020.12.036
28. Mei H, Zhao L, Li W, et al. Inhibition of ferroptosis protects house ear institute-organ of Corti 1 cells and cochlear hair cells from cisplatin-induced ototoxicity. *J Cell Mol Med*. 2020;24(20):12065–12081. doi: 10.1111/jcmm.15839
29. Li FF, Kam KW, Zhang Y, et al. Differential effects on ocular biometrics by 0.05%, 0.025%, and 0.01% atropine: low-Concentration Atropine for Myopia Progression Study. *Ophthalmology*. 2020;127(12):1603–1611. doi: 10.1016/j.ophtha.2020.06.004