Original Article

The Preventive Role of Atropine Eye Drops on Myopia Progression: A Double-Blind Randomized Clinical Trial

Abstract

Background: In the present study, we investigated the effect of two doses of atropine eye drops versus placebo on myopia progression in children and adolescents. **Methods:** In this double-blind, randomized clinical trial, 67 patients aged 6 to 18 years with myopia of -2 to -6 D were enrolled and randomized to receive a placebo eye drop, atropine 0.1%, or 0.01% ophthalmic solution (one drop per night for 6 months). All participants were followed-up with for one year after the beginning of the study (at zero, one, three, six, and 12 months) and their spherical equivalent (SE), axial length (AL), anterior chamber depth (ACD), and far and near visual acuity (VA) and the eye drops side effects were recorded. A comparison among the groups was performed using SPSS software, version 24.0. **Results:** Spherical equivalent, AL, and ACD decreased and far VA improved in atropine groups to a greater extent than the placebo group ($P < .05$) at the 6-month follow-up. The most common side effects of atropine 0.1% eye drop included photophobia and decreased near VA. At the end of the study (six months after the cessation of atropine), a rebound effect was observed; this effect was especially severe in the 0.1% atropine group. **Conclusions:** Atropine eye drops are effective for slowing down and preventing myopia progression. However, without long-term treatment, they will have a rebound effect. A lower dose (0.01%) is suggested for reducing the side effects and rebound effects.

Keywords: *Atropine, eye drop, glass, myopia, visual acuity*

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Introduction

The commonest treatment for myopia is the use of glasses or contact lenses to correct the patient's vision; however, this method does not effect on inhibition of myopic progression.[1-4] Prevention of myopic progression is of great significance. Therefore, the treatment strategies for controlling myopia have great importance.[5-9] Pharmaceutical agents are an appropriate prevention for myopic progression in children and adolescents.[8-10]

Although some studies confirmed the effectiveness of atropine on myopia progression, the mechanism is still unknown. In the 20th century, atropine was used specifically to slow the progression of myopia and its effect was thought to be related to avoiding accommodation. But experimental studies in animals in the 1990s showed that this was not true. Multiple studies have suggested that atropine is involved in the modulation of several pathways involving cholinergic receptors or even other receptors (like GABA receptors) mainly in the retina for regulating axial length growth.[11-13] Although several studies have shown the positive effect of high-concentration atropine on myopic progression, it is not accepted as a standard treatment because of the side effects (such as photophobia, accommodation impairment, near blurred vision, and allergic reactions) and the risk of rebound myopic progression following cessation of treatment. In the last 10 years, doses of 0.01% or 0.02% atropine eye drops have been suggested as an alternative modality. However, efficacy seems to be lower with much lower concentrations but recently the LAMP study suggested 0.05% atropine eye drop, balancing efficacy versus side effects better than the others.[12,14-18] Although atropine is currently accepted as the most effective therapy for myopia progression control, researchers continue to investigate the safety and efficacy of different doses of atropine in various populations.[19-21] Accordingly, the present study aimed to investigate the effect of moderate and low-dose atropine eye drops

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on the prevention of myopia progression in children and adolescents aged 6-18 years.

Methods

The present double-blind, randomized clinical trial (RCT) was performed at the Ophthalmology Department of Amiralmomenin Hospital, Guilan University of Medical Science, from June 2018 to January 2020. Children and adolescents with myopia aged between 6 and 18 years with or without astigmatism, spherical equivalent (SE) (-2 to -6 diopters) in both eyes, without amblyopia or strabismus were considered as the study population and were enrolled in the study after their parents gave consent for their participation into the study. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1397.106) and was registered in the Iranian Registry of Clinical Trials (Code: IRCT20100414003714N3).

Exclusion criteria were the following: age more than 18 years or less than six years, presence of amblyopia, any ocular disease (cataract, retinal disease, and any strabismus), previous use of atropine, allergy to atropine, or systemic diseases (e.g., endocrine, cardiac, and respiratory diseases). Of the 93 people who entered the study, seven people left during the first phase. As a result, follow-ups were conducted with 86 people. Unfortunately, 26 people withdrew from the study for unknown reasons. Therefore, in the end, 60 people (118 eyes) were followed up with until the end of the study. In phase 1 of the study (treatment phase), 60 myopic cases aged 6-18 years with SE (-2 to -6 diopters) in each eye were randomly divided into three groups. In each group, 20 patients (40 eyes) received 0.1%, 0.01% atropine eye drops, or a placebo, which were administered once a night in both eyes (first phase) for six months. In phase 2 (washout phase), atropine was discontinued and the children were monitored for six months. The purpose of the washout phase was to evaluate the biometric changes, spherical equivalent, and possible myopic rebound.

Based on Pineles *et al*.'s review study,[22] the sample size of the study was calculated at 31 participants in each group, considering a 95% confidence (1–a) and a power of 80%. The eligible participants were enrolled in the study by a census method. The three groups included two intervention groups, who received either 0.01% or 0.1% atropine eye drops once daily for six months, and one control group, which received placebo eye drops containing artificial tears (Tear lose) as per the same protocol. Sina Daru Company prepared the eye drops and provided them in similar containers. Atropine 0.1% and 0.01% were obtained by diluting 1 cc of atropine 1% with 9 cc and 9.9 cc of artificial tears, respectively. The placebo contained artificial tears only, manufactured by the same company.

The baseline characteristics of the participants, including their age at referral, sex, and iris color, were recorded. The same ophthalmologist examined patients one, three, and six months after starting the treatment. The physician performed a complete ocular examination for all patients and recorded the best-corrected visual acuity, cycloplegic refraction was performed using 1 drop of 0.5% cyclopentolate (Sina Darou, Co.), three times with an interval of 5 minutes, and was measured using a Tapcon MEDIZS model auto refractometer 45 minutes later. Axial length (AL) and anterior chamber depth (ACD) were measured by an ELLEX model ultrasound machine.

Six months after treatment, the intervention ceased for six months and the participants were evaluated to detect any myopic progression rebound effect. Furthermore, side effects were recorded. The primary outcome of this study was myopia progression, measured by the change in SE; the secondary outcome was the change in AL.

Statistical analysis

The collected data were input into the statistical software IBM SPSS Statistics for Windows version 24.0 (IBM Corp. 2015. Armonk, NY: IBM Corp.) used for the statistical analyses. The one-sample Kolmogorov–Smirnov test was used to determine the normal distribution of the data. The descriptive data were calculated by the mean and standard deviation (SD) and were compared among the three groups using one–way analysis of variance (ANOVA). If parametric hypotheses were not proven, the comparisons were performed using the Mann-Whitney U test. Significant differences were further analyzed for pairwise comparison between the groups, using Tukey's *post hoc* test. The trend of changes over time (the effect of time) was measured using repeated measures ANOVA based on the Greenhouse–Geisser test. For all tests, P values < .05 were considered statistically significant.

Results

Initially, 93 people entered the study, seven of whom left during the first phase. As a result, 86 people were followed up with. Unfortunately, due to the COVID-19 pandemic, another 26 people withdrew from the study. Therefore, in the end, 60 people (118 eyes) followed up until the end of the study [Figure 1].

Demographic data

The demographic information (age, sex, iris color) of the subjects is depicted in Table 1. In general, the subjects in all three groups were classified and analyzed in terms of demographic information based on age, sex, and iris color. The three groups had similar demographics (Table 1; $P > .05$).

SE changes

The mean SE values at the measured intervals (at baseline and one, three, six, and 12 months after the intervention)

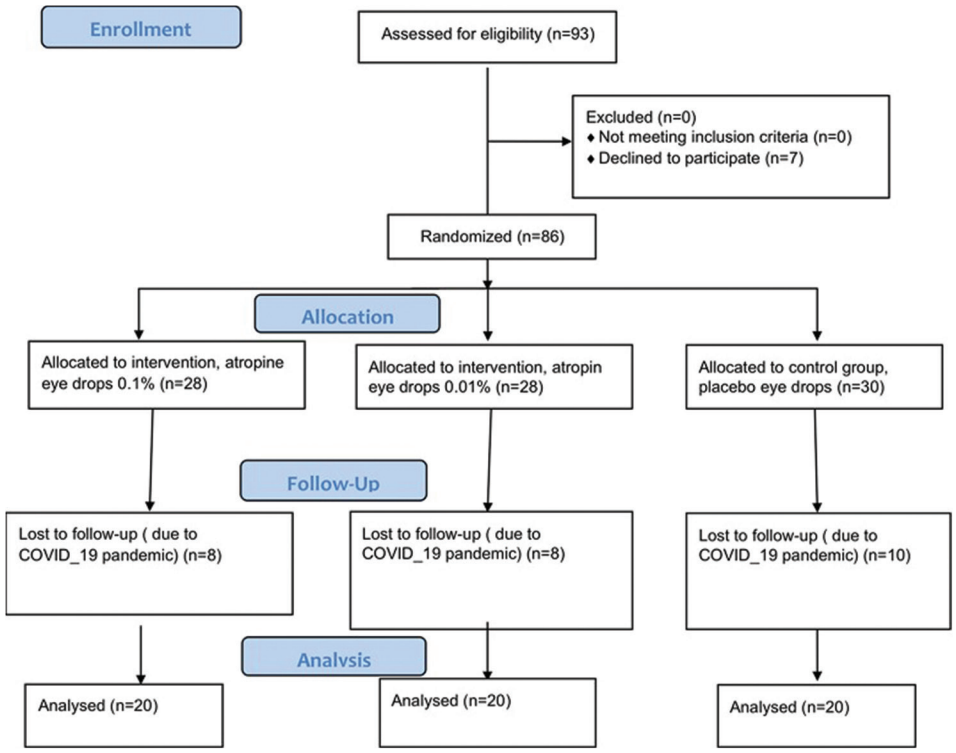

Figure 1: The flow diagram for patient enrollment into the study

Table 1: The baseline characteristics of the three groups

Variable	Categories	Total	Placebo	0.1% Atropine	0.01% Atropine	*P*
Age (years), mean±SD		11.12±3.59	12.00±3.57	11.44±3.59	9.75±3.37	0.108*
Age categories, *n*. (%)	< 10 years	30 (44.8)	8 (36.4)	11 (44.0)	11 (55.0)	0.417†
	10-15 years	21 (31.3)	8 (36.4)	6 (24.0)	7 (35.0)	
	> 15 years	16 (32.9)	6 (27.3)	8 (23.0)	2 (10.0)	
Sex, *n*.(%)	Girl	32 (47.8)	9 (40.9)	14 (56.0)	9 (45.0)	0.561†
	Boy	35 (52.2)	13 (59.1)	11 (44.0)	11 (55.0)	
Iris color, *n*.(%)	Brown	40 (59.7)	13 (59.1)	16 (64.0)	11 (55.0)	0.827†
	Light	27 (40.3)	9 (40.9)	9 (36.0)	9 (45.0)	

*The results of One-Way ANOVA, †The result of Chi-square test

are shown in Table 2. As indicated, a significant difference among the study groups was observed only at six months (P = .013). The effects of the time group were all significant (P < .001). In the placebo group, the mean SE was different at the end of the study than at the baseline (P < .001), indicating increased myopia by time, but not at other intervals vs. baseline (P > .05). In the 0.1% atropine group, the mean SE was different three and six months after the intervention compared to the baseline (both P < .001), indicating decreased myopia, but not at 1 and 12 months (P = .116 and.999, respectively). Similarly, in the 0.01% atropine group, the mean SE was different three and six months after the intervention compared to the baseline (both P < .001) but not at one and 12 months (both P = .999). Comparing the mean SE differences between intervals among the groups showed that all three groups had significant differences at all interval comparisons (P < .05; Table 2). The trend of changes in SE values in each group shows a steeper decrease in the 0.1% atropine group than in the 0.01% atropine group [Figure 2a].

A comparison of the mean SE difference at six months vs. the baseline based on participants' age categories (<10, 10-15, and >15 years) showed no differences among the participants in the placebo group (P = .270) or in the 0.1% atropine group (P = .057), although there was a significant difference in the 0.01% group (P = .021). The mean ± SD of SE difference was 0.32 ± 0.23 for participants aged <10 years, 0.18 ± 0.13 for those aged 10-15 years, and 0.06 ± 0.07 for those aged >15 years; *post hoc* tests showed a significant difference between the age ranges of >15 and <10 years (P = .048) but not between other groups (P = .091 for < 10 years vs. 10-15 years; P = .551 for 10-15 years vs. >15 years).

Table 2: The comparison of spherical equivalent, anterior chamber depth, and axial length among the study groups in the measured intervals

	Variable	Placebo	0.1% Atropine	0.01% Atropine	*P*
Spherical equivalent	Baseline	-1.92±0.93	-1.86±0.70	-2.12±0.99	0.409*
	After 6 months	-2.15±0.89	-1.49±0.68	-1.88±0.99	0.013*
	After 12 months	-2.15±0.89	-1.89±0.67	-2.13±0.97	0.347*
	Month 6 vs. baseline	-0.15±0.36	0.38±0.32	0.24±0.21	<0.001†
	Month 12 vs. baseline	-0.23±0.30	-0.03±0.20	-0.01±0.16	<0.001†
Anterior chamber depth	Baseline	3.63±0.25	3.58±0.29	3.57±0.29	0.577*
	After 6 months	3.69±0.29	3.54±0.28	3.52±0.28	0.016*
	After 12 months	3.70±0.21	3.60±0.27	3.60±0.27	0.096*
	Month 6 vs. baseline	0.06±0.12	-0.04±0.08	-0.05±0.10	<0.001†
	Month 12 vs. baseline	0.08±0.10	0.01±0.11	0.03±0.12	0.047†
Axial length	Baseline	24.00±0.54	23.95±0.56	23.88±0.70	0.702*
	After 6 months	24.08±0.54	23.87±0.56	23.80±0.63	0.078*
	After 12 months	24.10±0.53	24.03±0.53	23.92±0.65	0.373*
	Month 6 vs. baseline	0.09±0.15	-0.08±0.11	-0.09±0.11	<0.001†
	Month 12 vs. baseline	0.10±0.14	0.08±0.07	0.04±0.09	0.020†

*The results of One-Way ANOVA, †The result of repeated measures ANOVA

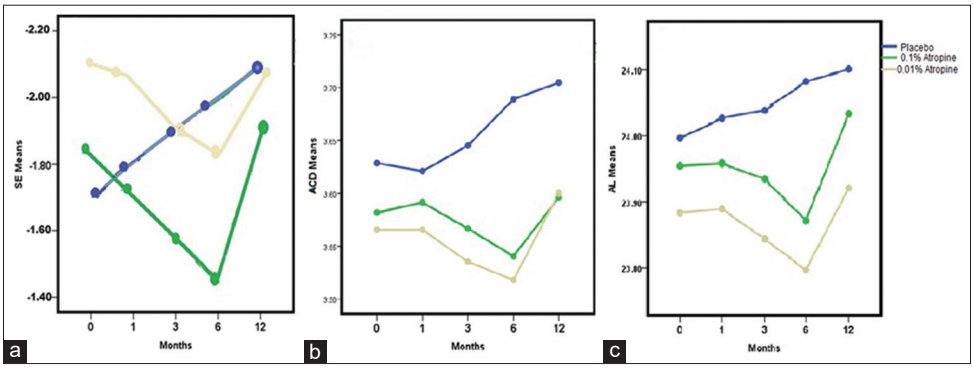

Figure 2: The trend of changes in spherical equivalent (a), anterior chamber length (b), and axial length (c) among the three study groups in the measured intervals

Anterior chamber depth and axial length

The mean ACD values of the three study groups at the measured intervals are shown in Table 2, which indicates a significant difference only at six months (P = .016). The effects of time, group, and time-group were all significant (P < .001). In the placebo group, the mean ACD was different at six and 12 months vs. baseline (P < .001 and P = .024, respectively), indicating increased values over time but not at the intervals of one or three months (P > .05). In the 0.1% atropine group, the mean ACD was different at six months after the intervention vs. baseline (P = .032), indicating that the value increases over time but not at other intervals (P > .05). In the 0.01% atropine group, no differences in mean ACD were found between the measured intervals and the baseline (P > .05).

The trend of changes in ACD values in each group is depicted in Figure 2b. The figure shows a decreasing trend in ACD in both intervention groups, followed by an increasing trend after the cessation of the intervention. In the placebo group, a constantly increasing trend was observed.

The mean AL values at the measured intervals indicated no difference among the three study groups (P > .05; Table 2). The effects of time, group, and time-group were all significant (P < .001). In the placebo group, the mean AL was different three, six, and 12 months after the intervention compared to the baseline (P = .038, P = .011, and P < .001, respectively), indicating a mild increase over time. In the 0.1% atropine group, the mean AL decreased for six months and then increased 12 months after the intervention when compared to the baseline (both P < .001). In the 0.01% atropine group, the mean AL was different at six months than at the baseline (both P < .001) but not at other intervals (P > .05).

The trend of changes in AL values in each group indicates a decreasing trend for six months in intervention groups, followed by an increase until the end of the study [Figure 2c]. In the placebo group, a constantly increasing trend was observed.

Visual acuity

The mean best-corrected far and near visual acuity of the groups at each interval are shown in Table 3. Considering Far visual acuity (FVA), a significant difference among the study groups was observed only at six months (P = .009). The effects of time, group, and time-group were all significant (P < .001), except for the effect of time on the placebo group. In the 0.1% atropine group, the mean FVA decreased three and six months after the intervention when compared with baseline (both P < .001) but it was not different at 1 or 12 months (P = .265 and P = .242, respectively). In the 0.01% atropine group, the mean FVA was different three and six months after the intervention compared to the baseline (P = .003 and P < .001) but not at one or 12 months (P = .858 and. 999, respectively).

Considering best-corrected near visual acuity, a significant difference was observed among the three groups' mean values recorded one, three, six, and 12 months after the intervention (P < .05; Table 3). The effects of time, group, and time-group were all significant (P < .001), except for the effect of time on the placebo group. In the 0.1% atropine group, the mean Near visual acuity (NVA) increased at one, three, six, and 12 months when compared to the baseline (P = .023, P < .001, P < .001, and P = .017, respectively).

Side effects

No side effects were observed in the placebo group. Meanwhile, four patients in the 0.1% atropine group (16%) had a headache (no patients in the 0.01% group experienced headaches; P = .032); 11 patients in the 0.1% atropine group (44%) and four patients in the 0.01% atropine group (20%) had photophobia (P = .001); 11 patients in the 0.1% atropine group (44%) had blurred vision (no patients in the 0.01% group had blurred vision; P < .001); and one patient in each of the intervention groups developed a skin allergy (P = .751).

Discussion

In the present double-blind placebo-controlled RCT, the results showed that myopia progression, calculated by SE, significantly decreased in the groups treated with atropine 0.1% and 0.01% when compared with the placebo group for the first six months after treatment. These results suggest that atropine is an effective therapy option for preventive myopia progression in children and adolescents. We suspect that the clinical effect of atropine on myopia progression is attributed to the reduced AL, as suggested by the results, which resulted in improved FVA and NVA. However, at the end of the study (six months after the cessation of the eye drops), a rebound effect was observed in most of the studied parameters, including AL and SE. These findings suggest that the clinical effect requires continuous treatment.

However, many studies have evaluated the efficacy of atropine in the control of myopia progression but there is no agreement on the ideal dose and treatment time. Some researchers have suggested diluting the concentration of atropine and continuing with daily applications to reduce adverse effects and increase treatment compliance, while other groups have suggested maintaining a concentration of 1% weekly or even once a month.[15-18] Furthermore, variations in study methods, myopia severity, the age range of children included, measured parameters, selection

Table 3: The comparison of spherical equivalent, anterior chamber length, and axial length among the study groups in the measured intervals

	Variable	Placebo	0.1% Atropine	0.01% Atropine	*P*
Far visual acuity	Baseline	0.063±0.046	0.057±0.036	0.070±0.051	0.454*
	After 1 month	0.062±0.047	0.050±0.040	0.068±0.049	0.226*
	After 3 months	0.061±0.044	0.042±0.031	0.57±0.47	0.107*
	After 6 months	0.061±0.045	0.033±0.028	0.048±0.044	0.009*
	After 12 months	0.063±0.045	0.064±0.039	0.067±0.042	0.880*
	Month 1 vs. baseline	0.00±0.01	-0.01±0.02	0.00±0.01	0.065†
	Month 3 vs. baseline	0.00±0.01	-0.02±0.02	-0.01±0.02	0.003†
	Month 6 vs. baseline	0.00±0.01	-0.02±0.02	-0.02±0.02	<0.001†
	Month 12 vs. baseline	0.00±0.01	0.01±0.02	0.00±0.02	0.039†
Near visual acuity	Baseline	0.003±0.011	0.005±0.014	0.001±0.007	0.340*
	After 1 month	0.003±0.011	0.017±0.027	0.004±0.013	0.001*
	After 3 months	0.002±0.09	0.022±0.029	0.007±0.015	0.001*
	After 6 months	0.003±0.009	0.030±0.025	0.008±0.014	0.001*
	After 12 months	0.002±0.009	0.010±0.016	0.012±0.00	0.017*
	Month 1 vs. baseline	0.00±0.00	0.01±0.02	0.00±0.01	0.001†
	Month 3 vs. baseline	0.00±0.01	0.02±0.02	0.01±0.01	<0.001†
	Month 6 vs. baseline	0.00±0.01	0.02±0.02	0.01±0.00	<0.001†
	Month 12 vs. baseline	0.00±0.01	0.01±0.01	0.00±0.01	0.017†

*The results of One-Way ANOVA, †The result of repeated measures ANOVA test

of the control group, duration of administration, and follow-up after the cessation of treatment among studies[22] make it difficult to draw comparisons and definite conclusions. Similar to the present study, Pérez-Flores *et al*. included children with myopia between -2D and -6D, astigmatism <1.50D, and documented history of annual progression of myopia ≥-0.5D; the results of administrating 0.01% atropine for 12 months showed slower myopia progression than in the previous year.[23] Although this study confirms the efficacy of 0.01% atropine, consistent with the results of the present study, the study was limited because of the lack of a control group. A comparison between a 0.01% atropine group and a placebo group in another recent study also confirmed the safety and efficacy of this dose of atropine eye drop on myopia progression in children,[24] which is in line with the results of the present study. One of the most impressive studies about the effect of atropine on myopia progression was performed by Chia *et al*.; the researchers compared the effects of atropine 0.5%, 0.1%, and 0.01%, administered for 24 months among 400 children aged 6-12 years. The results indicated that fewer side effects were associated with 0.01% atropine, while the efficacy was similar across different concentrations.[17] Clark performed a retrospective study on 60 children (6-15 years) with SE of -0.25 to -8.00 D and reported lower myopia progression after about a year of administrating 0.01% atropine when compared to a control group, with minimal side effects,[25] which confirms the results of the present study, although they did not include a 0.1% atropine group in their study. Furthermore, the initial SE considered for the inclusion of patients into this study involved both mild cases and high myopic children and showed a better outcome in patients with an initially lower SE, while we aimed to evaluate the outcomes on children with moderate myopia by considering an initial SE within -2 to -6D. Another concern is the rapid myopia progression in some children, which results in failed responses to treatment in some cases.[25]

A report from the American Academy of Ophthalmology, which reviewed 17 studies, indicated less myopic progression with atropine compared with a control group, with a rebound effect after cessation. This report indicated less effectiveness of lower doses (0.01% vs. 0.5% and 0.1%) during one to two years of treatment, while the low dose of atropine (0.01%) had the advantage of a weaker rebound and fewer side effects.[22] Considering the side effects, we also observed higher rates of headache, photophobia, and blurred vision in the 0.1% atropine group compared with the 0.01% atropine group, which is consistent with the results of this report. We did not observe any loss of accommodation, pupil dilation, or near visual loss in any of the two doses in the present study, which were reported by Chia *et al*.[26] Pérez-Flores *et al*. also showed that 0.01% atropine eye drops had mild and infrequent side effects,[23] which is consistent with the results of the present study, confirming the safety of 0.01% atropine.

In the present study, we evaluated changes in AL and ACD associated with the two doses of atropine. The results, although statistically significant, were minimal and not clinically significant. Furthermore, at the end of the study, the 0.1% atropine group showed rebound effects for all parameters, including AL, ACD, FVA, and NVA.

One of the limitations of the present study was the small number of patients in each group, which was caused by the coincidence of the study with the COVID-19 pandemic, which resulted in the disagreement of parents to allow their children to attend follow-up visits. Furthermore, the process of myopia progression is not the same in all children and several factors, such as the severity of myopia, progression rate, and accommodative lags, can influence it; such factors were not considered in the present study, which could have confounded the results.

Conclusions

The comparison of moderate-dose and low-dose atropine eye drops in the present study showed that low-dose atropine (0.01%) is as effective as moderate-dose atropine (0.1%) for controlling myopia progression. Considering the risk of side effects, which are more commonly observed in high-dose atropine, it is suggested to use 0.01% atropine.

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Declaration of patient consent [User 4]

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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