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Effects of three different doses of atropine drops on myopic progression in children during the coronavirus disease 2019 pandemic

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Abstract

This study aimed to evaluate the effects of low doses of atropine drops (0.05%, 0.025%, and 0.01% atropine sulfate) on spherical equivalent (SE) and axial length (AL) in children with myopia during the coronavirus disease 2019 pandemic. Participants were randomly classified into 4 groups: 0.05%, 0.025%, and 0.01% doses of atropine sulfate and placebo. Cycloplegic refraction diopters and AL were regularly calculated at 1, 3, 6, and 12 months after the onset of treatment. At the end of the first year, the difference in the mean SE values were −1.07±0.40 D, −0.71±0.66 D, −0.53±0.46 D, and −0.35±0.62 D in the placebo, 0.01% atropine, 0.025% atropine, and 0.05% atropine groups, respectively ($p<0.001$). During this period, the mean AL increase in the corresponding groups was 0.42±0.21, 0.37±0.24, 0.31±0.18, and 0.13±0.17 mm ($p=0.02$, $p<0.001$, $p<0.001$ in the 0.01%, 0.025%, and 0.05% atropine groups compared with the placebo group, respectively). Low-dose atropine drops may be the first choice of treatment for myopia progression owing to their ease of use and fewer side effects. All the investigated doses of atropine were statistically significantly efficient in slowing down myopia progression. However, our study revealed that 0.05% atropine best controlled both SE progression and AL elongation compared to 0.025% and 0.01% doses. We recommend initiating treatment with 0.01% atropine in children and switching to 0.025% or 0.05% atropine if adequate myopia progression control is not achieved.

Keywords: Atropine drops, childhood myopia, myopia during the pandemic, myopic progression, nearsightedness

Introduction

Recently, computers and mobile phones have become indispensable. Although the pathogenesis of accommodation disorders and myopia development remains unclear, myopia has been recognized as the most common eye disorder worldwide, particularly in East Asia. Moreover, the incidence of myopia is known to increase with age. In Hong Kong, the prevalence study by Fan et al. revealed that 454 of 3,149 children who were not myopic at baseline became myopic after 12 months [1,2].

Myopia is defined as a multifactorial disease caused by genetic and environmental factors. In particular, patients with high myopia are at a high risk of developing open-angle glaucoma, retinal detachment, myopic choroidal neovascularization, and cataracts [3]. Further, these serious conditions are known to cause permanent vision loss. Additionally, myopia affects school performance, physical activity, and social relationships among children in addition to their choice of jobs in the future [4].

Various approaches have been used to slow down the progression of myopia, including increased outdoor activity, limiting indoor activity, and applying peripheral defocus or orthokeratology contact lenses [5].

CITATION
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Atropine—a nonselective muscarinic antagonist—is commonly used for patients with myopia. In this study, we compared the efficacy and side effects of three low-dose atropine drops for slowing down myopia progression in children. Moreover, this study aimed to evaluate the efficacy of these atropine doses in slowing down myopia progression in children and to determine the most effective treatment dose that exerts no side effects (e.g., photophobia and near-vision complaints). To the best of our knowledge, this is the first placebo-controlled, low-dose atropine study conducted during the coronavirus disease 2019 (COVID-19) pandemic (from November 2019 to November 2021).

Material and Methods

This prospective single-center study included children (age, 6–13 years) with myopic refraction of ≥1.0 D in both eyes, astigmatism of <2.5 D, and documented progressive myopic progression of ≥0.75 D in the past year. Children presenting with other ocular diseases (cataract, strabismus, corneal or retinal disorder, etc.); history of using atropine, orthokeratology lens, or any other optical treatments for myopia control; and other systemic diseases were excluded from the study. This study was approved by the Ethics Committee of Istanbul Medipol University (registration number 910), and all procedures were conducted accordance with the protocols of the Declaration of Helsinki. Verbal consent and written informed consent were obtained from the participants and their parents, respectively.

Participants were classified into four groups: 0.05%, 0.025%, and 0.01% doses of atropine sulfate and placebo. Bottles containing atropine sulfate combined with sterile distilled water were prepared at the Medipol University Laboratory and were regularly changed (every 15 days). For the placebo group, the bottles were filled with artificial tear drops of 0.5% sodium carboxymethylcellulose (Refresh Tears, Allergan, Irvine, California, USA). Participants instilled the drops into both eyes at bedtime, and the right eyes of all participants were examined in the present study for spherical equivalent (SE) and axial length (AL) values. For all participants, the following were assessed at each visit: distant best-corrected visual acuity (BCVA), biomicroscopic examination, SE measurement with KR800 (Topcon, Japan) auto refractometer, and topographical AL with Aladdin HW 3.0 Optical Biometer and Corneal Topographer (Topcon, Japan) device. AL examinations were performed five times, and standard deviations of <0.05 mm were recorded and averaged. Further, the participants were examined at 1, 3, 6, and 12 months after the first examination. In addition, the children and their parents were asked about side effects associated with the drops and whether they instilled the drops regularly every night. They reported that when they forgot to instill the drops before bedtime, the drops were instilled immediately when they remembered during the day. In contrast, participants who forgot to instill the drops more than once in 1 week were excluded from the study. Best-corrected visual acuities were measured using the Topcon CV5000 (Topcon, Japan) phoropter device in the decimal system. Moreover, cycloplegic autorefraction was measured after administering two separate eye drops: cyclopentolate 1% (Sikloplejin, Bilim İlaç İstanbul, Turkey) and tropicamid 1% (Tropamid, Bilim İlaç İstanbul, Turkey). These drops were administered at 2-min intervals and repeated thrice with a time gap of ≥40 min from the first administration. Both eyes of all participants were examined three times using the KR800 Auto Refractometer, and the average of the results obtained were calculated. SE was calculated as spherical power plus half of the cylindrical power in diopters.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, ver. 18.0, Chicago, IL) program. We examined the right eye of all participants, and those who presented with missing examination values were excluded from the study. Baseline SE and AL values were compared using independent sample t-tests, and analysis of variance was used to evaluate >2 pairs. Progressive SE and AL elongation values were calculated using the SPSS program, and each dose group was compared with the placebo group using the t-test.

Results

Overall, 128 children with ≥0.75 D progressive myopia for the past year were included in the present study. All participants were followed up at the Medipol University Ophthalmology clinic before starting this prospective study. Of 128 children, 91 attended the examinations and completed a 12-month follow-up (from November 2019 to November 2021). The distant best-corrected visual activity of all children was 1.0 decimal/0.0 logMAR in both eyes.

The placebo group, 0.01% atropine group, 0.025% atropine group, and 0.05% atropine group comprised 20 (10 girls, 10 boys), 21 (12 girls, 9 boys), 24 (12 girls, 12 boys), and 26 (11 girls, 15 boys) children, respectively, and there were no statistical differences among the groups in terms of sex (p=0.79) [Table 1].

The mean age of the participants was 9.95 (7–13) years in the placebo group, 9.80 (9–13) years in the 0.01% atropine group, 9.62 (7–13) years in the 0.025% atropine group, and 9.73 (7–13) years in the 0.05% atropine group, and there were no statistical differences among the groups in terms of their mean age (p=0.96) [Table 1].

Table 1. Initial characteristics of the groups

	Placebo (n=20)	0.01% Atropine (n=21)	0.025% Atropine (n=24)	0.05% Atropine (n=26)	P value
Age	9.95±2.25	9.80±2.22	9.62±2.18	9.73±2.06	0.96
Sex (female/male)	10/10	12/9	12/12	11/15	0.79
Axial Length	24.65±0.94	24.92±0.87	24.76±0.91	24.60±0.94	0.39
Spherical Equivalent	−3.38±1.13	−3.94±0.60	−3.82±1.32	−3.29±1.62	0.22
History of Myopic Progression	−0.92±0.40	−0.88±0.39	−0.96±0.43	−0.91±0.46	0.38

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The mean SE was −3.38 (±1.13) D in the placebo group, −3.94 (±0.60) D in the 0.01% atropine group, −3.82 (±1.32) D in the 0.025% atropine group, and −3.29 (±1.62) D in the 0.05% atropine group, and there were no statistical differences among the groups in terms of the mean SE (p=0.22). The mean AL of the corresponding groups was 24.65 (±0.94), 24.92 (±0.87), 24.76 (±0.91), and 24.60 (±0.94) mm, and there was no statistical difference among the groups (p=0.39) [Table 1].

The mean historical myopic progression was −0.92±0.40 D, −0.88±0.39 D, −0.96±0.43 D, and −0.91±0.46 D in the placebo group, 0.01% atropine group, 0.025% atropine group, and 0.05% atropine group, respectively, and there was no statistical difference among the groups (p=0.38) [Table 1].

The most important side effects of atropine treatment were near-vision problems and photophobia. None of these significant side effects required drug discontinuation among the 91 patients who completed the 12-month follow-up. Initially, 20 (77%) of the 26 participants in the 0.05% atropine group, 15 (62%) of the 24 participants in the 0.025% atropine group, and none of the participants in the 0.01% atropine group had mild near-vision problems. Moreover, none of the participants discontinued medications during this study, although adverse effects were particularly noted in both 0.05% and 0.025% atropine groups. Another adverse effect of atropine drops was photophobia, which was observed in 15 (57%) of the 26 participants in the 0.05% atropine group, 10 (42%) of the 24 participants in the 0.025% atropine group, and none of the participants in the 0.01% atropine group. Notably, compared to near-vision complaints, photophobia was less common in all groups. Moreover, the incidences of near-vision complaints and photophobia declined with time, and none of the participants reported any side effects that affected their activities of daily living at the end of the second month of treatment.

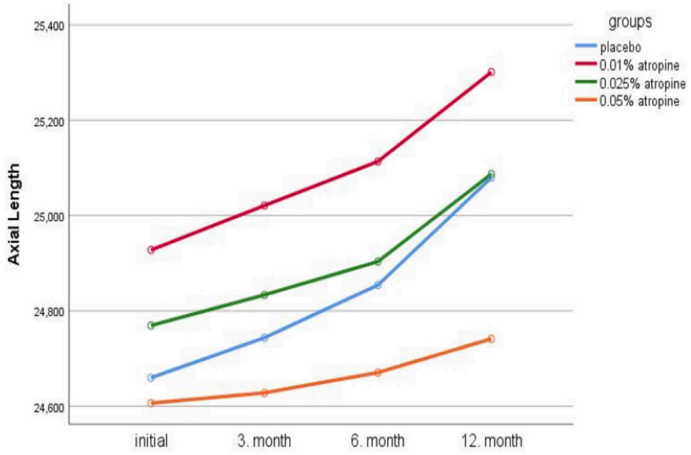

Figure 1. Axial lenght change of the groups during the 12 months period. Axial lenght change of the placebo group was compared with that of the atropine groups, and there was statistically significant difference (p=0.027, p<0.001, p<0.001 in the 0.01%, 0.025%. and 0.05% atropine groups compared with the placebo, respectively

The mean AL change at the end of 12 months was 0.42±0.21, 0.37±0.24, 0.31±0.18, 0.13±0.17 mm in the placebo group, 0.01% atropine group, 0.025% atropine group, and 0.05% atropine group, respectively. Figure 1 shows the AL changes in these groups over the 12 months. Further, AL changes in the placebo group were compared with those in the atropine groups, and the results revealed a statistically significant difference (p=0.02, p<0.001, p<0.001 in the 0.01%, 0.025%, and 0.05% atropine groups compared with placebo, respectively) [Table 2].

Table 2. Axial length and spherical equivalent change of the groups with p values

	Placebo	0.01% Atropine	0.025% Atropine	0.05% Atropine
12month axial length change (mm)	0.42±0.21	0.37±0.24	0.31±0.18	0.13±0.17
12month spherical equivalent change (D)	−1.07±0.40	−0.71±0.66	−0.53±0.46	−0.35±0.62
P value AL, placebo vs atropine		0.02	<0.001	<0.001
P value SE, placebo vs atropine		<0.001	<0.001	<0.001

The mean SE change at the end of 12 months was 1.07±0.40 D, 0.71±0.66 D, 0.53±0.46 D, and 0.35±0.62 D in the placebo group, 0.01% atropine group, 0.025% atropine group, and 0.05% atropine group, respectively. Figure 2 shows the SE changes in the groups over a 12-month period. The differences between SE change in the placebo group and all atropine groups were statistically significant (p<0.001) [Table 2].

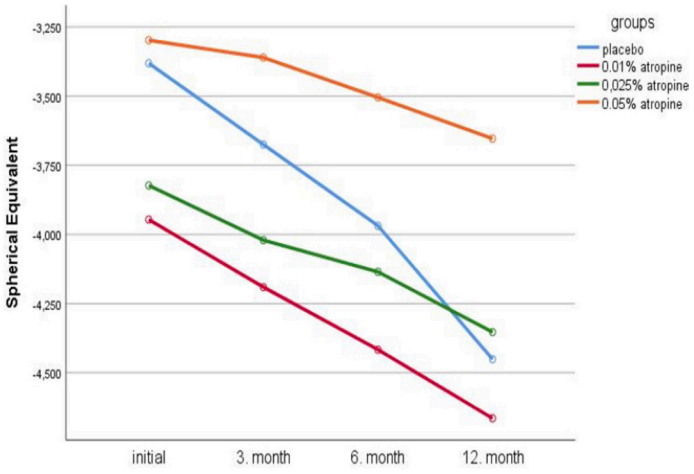

Figure 2. Spherical equivalent change of the groups during the 12 months period. Statistically significant differences in spherical equivalent change of the placebo group compared with the atropine groups and all dosages of the atropine groups were found (p<0.001)

Discussion

The ATOM 1 study by Chua et al. revealed an increased SE of −1.20±0.69 D and an increased AL of 0.38±0.38 mm in eyes instilled with the placebo at the end of the second year of treatment. In the eyes other than those in which 1% atropine was instilled, the increase in SE was −0.28±0.92 D, whereas the change in AL was −0.02±0.35 mm, which remained almost

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constant [6]. Our study revealed an increased SE of −0.35±0.62 D at the end of 1 year and an increased AL of 0.13±0.17 mm despite using one-twentieth of this dose (0.05% atropine). In the present study, the placebo group exhibited an increased SE of −1.07±0.40 D and an increased AL of 0.42±0.21 mm. Moreover, compared with the ATOM1 study, a one-year increase in AL and progression of SE was higher in the placebo group, whereas the efficacy of the 0.05% dose was lower in our study. However, this may be attributed to lifestyle changes caused by the COVID-19 pandemic, which led to an acceleration of myopia progression; therefore, the treatment effectiveness appeared low. The progression of SE within 1 year in the placebo group of our study was similar to the progressions in the placebo groups of ATOM 1 in 2 year study, indicating the prominent effect of the pandemic on myopia progression.

The ATOM 2 study by Chia et al. compared 0.5%, 0.1%, and 0.01% atropine doses and revealed that the SE myopia progression at 2 years was −0.30±0.60 D, −0.38±0.60 D, and −0.49±0.63 D, respectively [7]. Our study revealed the progression of −0.71±0.66 D at the end of 1 year of treatment with the common dose of 0.01% atropine. This low effectiveness may be attributed to the pandemic conditions. We believe that the impact of the pandemic would have been more clearly comparable if the ATOM2 trial had been placebo-controlled.

Moreover, atropine treatment was interrupted for 1 year at the end of 2 years, and the development of rebound myopia was lesser in the low-dose group (0.01% atropine) than in the other higher dose groups in the ATOM2 Phase 2 study by Chia et al. Moreover, myopia progression was −1.15±0.81 D at the end of 3 years in the group using 0.5% atropine, whereas it was −0.72±0.72 D in the group using 0.01% atropine. Chia et al. also reported that 0.01% atropine drops demonstrated a better cure and a lower side-effect rate and rebound effect after they were instilled into the eyes [8,9]. The highest dose of atropine used in our study was 0.05%, which one-tenth of the 0.5% atropine dose at which excessive rebound was observed. Therefore, it is important to evaluate the effectiveness of the doses used in our study.

In 2019, the LAMP study by Yam et al. compared 0.05%, 0.025%, 0.01% doses of atropine with placebo. After 1 year, the mean SE change was −0.27±0.61 D, −0.46±0.45 D, −0.59±0.61 D, and −0.81±0.53 D in the 0.05% atropine, 0.025% atropine, 0.01% atropine, and placebo groups, respectively ($p<0.001$) [10]. These progression rates were −0.35±0.62 D, −0.53±0.46 D, −0.71±0.66 D, and −1.07±0.40 D in our study at the same doses, respectively. This finding is proportional to the increase in myopia progression owing to the changes in lifestyle during the COVID-19 pandemic.

However, the treatment options for myopia are limited. Moreover, the effect of myopia undercorrection in the treatment of myopia progression remains controversial [11,12]. In particular, orthokeratology lenses may be effective, but their use may cause ocular discomfort or allergic eye reactions [13,14]. In contrast, atropine therapy for preventing myopia progression is both easy to use and has few side effects. Moreover, its effectiveness has been proven in several studies, including the present one.

Initially, 20 (77%) of the 26 participants, 15 (62%) of the 24 participants, and none of the participants in the 0.05%, 0.025%, and 0.01% atropine groups had mild near-vision problems, respectively. Moreover, photophobia was observed in 15 (57%) of the 26 participants, 10 (42%) of the 24 participants, and none of the participants in the 0.05%, 0.025%, and 0.01% atropine groups, respectively. No side effects affecting daily life were observed in any of the participants at the end of the second month.

The current study revealed no statistically significant difference in terms of AL and SE values among all groups at the beginning of treatment ($p=0.39$ and $p=0.22$, respectively).

A statistically significant difference was found in slowing down of myopia progression in the 0.05%, 0.025%, and 0.01% atropine groups. SE change after 12 months was −0.35±0.62 D, −0.53±0.46 D, and −0.71±0.66 D in the 0.05%, 0.025%, and 0.01% atropine groups, respectively. However, it was −1.07±0.40 D in the placebo group ($p<0.001$), and atropine effects appeared to be dose dependent.

AL change during the 12-month study was 0.42±0.21, 0.37±0.24, 0.31±0.18, and 0.13±0.17 mm in the placebo, 0.01% atropine group, 0.025% atropine group, and 0.05% atropine group, respectively, and a significant difference was found among all groups ($p=0.02$, $p<0.001$, and $p<0.001$ in the 0.01%, 0.025%, and 0.05% atropine groups, respectively, compared with the placebo group).

Conclusion

In conclusion, side effects caused by all doses were observed only at the beginning of treatment; however, no side effects were affecting the activities of daily living of the children at the end of the second month of the treatment. The efficacy of the doses used in this study was found to be the maximum in the 0.05% atropine group, although the efficacy of treatment was statistically significant for all doses during the pandemic period. In the 1-year period before the start of treatment, there was approximately one diopter of SE progression per year in all atropine groups. With atropine treatment, the significant effect of slowing down SE progression was observed in all these groups. We recommend starting the treatment with 0.01% atropine in children and switching to 0.025% or 0.05% atropine if adequate myopia progression control is not achieved.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
This study was approved by the Ethics Committee of Istanbul Medipol University with registration number 910, all procedures were conducted following the tenets of the Declaration of Helsinki.

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