Acta Med. Okayama, 2022
Vol. 76, No. 4, pp. 457–463

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Efficacy of 0.01% Atropine Eye Drops in Controlling Myopia Progression and Axial Elongation in Children: A Meta-analysis Based on Randomized Controlled Trials

Weiying Sun, and Satoshi Hasebe*

Department of Ophthalmology 2, Kawasaki Medical School, Kurashiki-City, Okayama 701-0192, Japan

To clarify the preventive effects of 0.01% atropine eye drops against myopia progression and axial elongation in children, a meta-analysis was carried out based on data obtained from PubMed and Web of Science as of August 1, 2021. Randomized controlled trials (RCTs) that enrolled myopic children who had received atropine for at least one year were included in this study, Key search terms included myopia, children, and 0.01% or low-dose atropine. Heterogeneity was quantified by I^2 statistics, and meta-analyses were performed using the fixed-effect model. Five RCTs involving 809 unique children were analyzed. One trial was excluded because of a poor Jadad score and markedly rapid myopia progression in controls. The mean effect sizes for 12 months in myopia progression and axial elongation synthesized from the remaining 4 RCTs were 0.20 (95% CI: 0.13 to 0.27) D and −0.08 (−0.11 to −0.04) mm, respectively ($p < 0.0001$). The corresponding inhibition ratios were 28% and 19%. I^2 statistics were 6% or less. Sensitivity analysis and funnel plots demonstrated the robustness of the estimation. The 0.01% atropine-induced inhibition ratio for myopia progression in Asian children was roughly half of that originally reported and did not reach the minimum requirement for clinical treatment.

Key words: myopia, 0.01% atropine, low-dose atropine, axial length, myopia progression

The Atropine for the Treatment Of childhood Myopia (ATOM) 2 study (2012) reported that administration of eye drops containing a highly diluted (0.01%) atropine, an anticholinergic neurotransmitter-blocking drug, to children demonstrated a significant preventive effect (inhibition ratio of 60%) against myopia progression, without problematic side effects or rebounding after cessation of the treatment [1]. Problems with that study were that it did not have a placebo control group and thus needed to employ historical data obtained in ATOM1 (2006) [2] to calculate the inhibition ratio, and that it found no preventive effects in terms of the axial length of the eye (AL).

Since then, however, 0.01% atropine administration has been highlighted as a novel preventive treatment. A number of replication studies with different designs have been conducted, but the reported inhibition ratios of myopic progression vary widely from 15% [3] to 80% [4]. Zhao *et al.* (2019) reported the first systematic review of 0.01% atropine treatment [5]. However, their review included only one well-documented randomized clinical trial (RCT) [6]. In addition, three of the seven trials in their meta-analysis employed data for higher concentrations of atropine (0.1-1%) instead of a placebo vehicle as the control. Consequently, they found significant preventive effects only in axial elongation and not in myopia progression. They noted high heterogeneity in the analysis, and thus the quality of the evidence obtained was low. Weak inclusion criteria led to mis-

Received December 1, 2021; accepted March 11, 2022.
*Corresponding author. Phone: +81-86-225-2111; Fax: +81-86-232-8343
E-mail: shasebe2009@yahoo.co.jp (S. Hasebe)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

leading conclusions.

In recent years, as an emergency counter against the so-called epidemic of myopia [7], 0.01% atropine eye drops have been frequently prescribed to myopic children in clinics [8,9]. Therefore, clarification of its treatment effects becomes more important when considering the application of 0.01% atropine to children and comparing its efficacy with other preventive methods. After Zhao's review, four RCTs [3,10-12] have been reported. Here, we conducted a meta-analysis including the latest RCTs.

Materials and Methods

Information source and search strategy. We searched PubMed/MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials to yield relevant studies from their inception to August 1, 2021, using Medical Subject Headings (MeSH) and free words combined with myopia, children, and low-dose or 0.01% atropine. We also screened clinicaltrials.gov and the reference lists of published reviews to identify additional relevant studies. Only studies published in English were included.

Data collection and quality assessment. We selected the relevant clinical trials of 0.01% atropine eye drops based on the following criteria: (1) Study design: prospective studies with randomized parallel controls; (2) Participants: 4- to 15-year-old children; (3) Treatment: 0.01% atropine eye drops to both eyes once a day; (4) Outcomes: cumulative myopia progression (change in spherical equivalent refraction [SEQ]) measured by cycloplegic autorefraction and AL elongation measured by partial coherence interferometry from baseline. The following information was compiled from all studies: authors, publication year, study design, ages of participants, sample size, length of follow-up, and reported outcomes at the initial and final follow-up visits.

Data extraction. Two reviewers (SH and TF) independently extracted data using pre-established extraction tables, including the following: (1) Basic characteristics of the study, including the name of the first author, year of publication, and follow-up period; and (2) basic characteristics of the children, including age, baseline SEQ, SEQ changes, and AL changes.

Qualitative assessment. We assessed the methodological quality of each RCT for four items: random sequence generation; allocation concealment; masking of children, guardians, and clinicians; and dropout ratio. We then evaluated the quality using Jadad scores. We used those scores because double-blinding is practical for 0.01% atropine treatment, hence the potential limitations of the methodology are relatively small. Trials with Jadad scores below 4 were classified as "equivocal" [13].

Statistical analysis. The meta-analysis was performed using EZR [14] (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

The statistical heterogeneity of included studies was assessed by the Cochrane I^2 test [15]. If I^2 was 50% or less, indicating low to moderate heterogeneity, a fixed-effect model was used. If I^2 was higher than 50%, indicating a high degree of heterogeneity, a random-effects model was applied. The mean differences in SEQ and AL between the atropine and control groups with a 95% confidence interval (CI) were used to estimate treatment effectiveness. A sensitivity analysis was performed by excluding the studies one by one [16]. The percentile inhibition ratios (%) were calculated by the following equation:

$$\frac{\text{change in the control group} - \text{change in the treatment group}}{\text{change in the control group}} \times 100$$

One trial [3] reported 2-year changes, whereas the others reported only 1-year changes. As SEQ

changes and AL elongation were nearly constant throughout the follow-up period of 2 years [3], which was also demonstrated in previous trials [2,17], we considered the mean annual changes (24-month change × 0.5) as representative values.

Results

Search results. From 107 related studies retrieved in total, we included 5 RCTs in this study. The basic characteristics of the trials are shown in Table 1. There were 392 children in the atropine group and 377 children in the control group.

Risk of bias (quality) assessment. The quality of each of the five RCTs is shown in Table 2. The trials by

Fu *et al.* [10] and Zhao *et al.* [12] had Jadad scores of 3 and 1, respectively, and were classified as "equivocal" accordingly. In the former trial, randomization was conducted only when allocating the subjects between 0.01% and 0.02% atropine groups (according to a suggestion by the Institutional Review Board), but the examiners were masked to the experimental group of each subject. The relationship between the SEQ and AL changes for 12 months in the control group is shown in Fig. 1. The trial by Zhao *et al.* [12] employed a different population, whose myopia progression was significantly faster than in the other four trials (ANOVA, $p<0.001$), thus we excluded that trial from our meta-analyses. The other trials, by Yam *et al.* [6], Wei *et al.* [10], and Hieda *et al.* [3], used a placebo-controlled and double-masked method and described the method of generating random sequences in detail.

Efficacy analysis. All four trials [3,6,10,11] reported changes in SEQ. The heterogeneity I^2 was 6% ($p=0.36$), and meta-analysis was performed using a fixed-effect model accordingly [15]. As shown in a forest plot (Fig. 2), the mean difference in myopia progression between the atropine and control groups (effect size) was 0.20 D (95% CI: 0.13 to 0.27 D) and highly significant ($p<0.0001$).

All trials reported changes in AL. The heterogeneity I^2 was 0% ($p=0.83$), and meta-analysis was performed using a fixed-effect model accordingly. As a forest plot

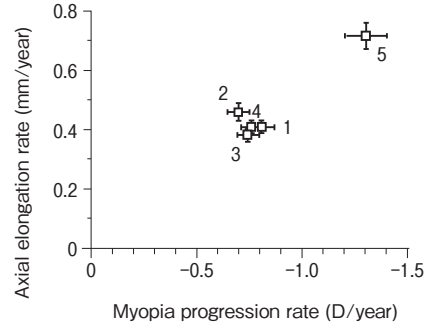

Fig. 1 Scatter plot between myopia progression rate and AL elongation rate in the control group [3,6,10–12]. Means and standard errors are shown. Numbers in the plot correspond to the study numbers given in Tables 1 and 2.

Table 1 Basic characteristics of RCTs [3,6,10–12]

No. / study / year	Area	Age range (year)	Baseline SEQ range (D)	n	Concentration (%)	Control	Follow-up (months)	Inhibition rate for myopia progression (%)	Inhibition rate for axial elongation (%)	Dropouts (%)
1/ Yam, et al. (LAMP)/ 2019	China (Hong Kong)	4–12	≦ −1.00	438	0.05 0.025 0.01	vehicle placebo	12	67 43 27	51 29 12	13
2/ Fu, et al./ 2020	China	6–14	−1.25, −6.00	336	0.02 0.01	SVL only	12	46 33	35 20	16
3/ Wei, et al/ 2020	China	6–12	−1.00, −6,00	220	0.01	vehicle placebo	12	36	22	28
4/ Hieda, et al. (ATOM-J)/ 2021.	Japan (multicenter)	6–12	−1.00, −6.00	168	0.01	vehicle placebo	24	15	18	16
5/ Zhao, et al. / 2021	China	5–14	−1.00, −6.00	40	0.01	SVL only	12	74	67	N.S.

SVL, single vision lens spectacles; N.S., not specified.

Table 2 Quality assessment of RCTs

Number / study	Randomization	Masking	Allocation concealment	Dropouts	Jaded score
1/ Yam, et al (LAMP)	adequate	adequate	adequate	adequate	5
2/ Fu, et al	inadequate	inadequate	inadequate	adequate	3
3/ Wei, et al	adequate	adequate	adequate	inadequate	5
4/ Hieda, et al (ATOM-J)	adequate	adequate	adequate	adequate	5
5/ Zhao, et al	adequate	inadequate	inadequate	N.S.	1

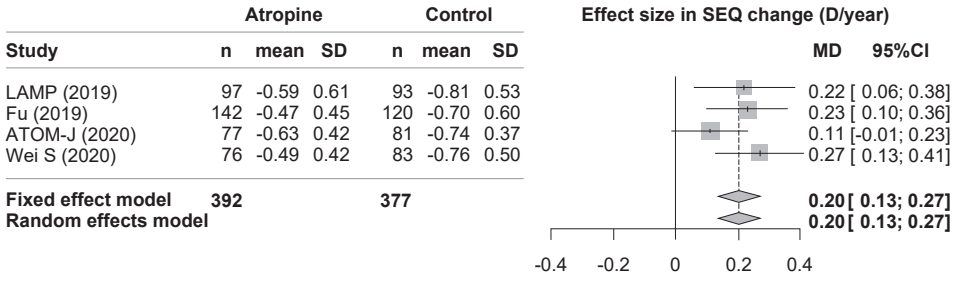

Fig. 2 Forest plot for the 12-month effect size in SEQ change (myopia progression). On this scale, positive values indicate preventive effects against myopia progression. Error bars and numbers in square brackets show the 95% confidence interval. SD, standard deviation; MD, mean difference.

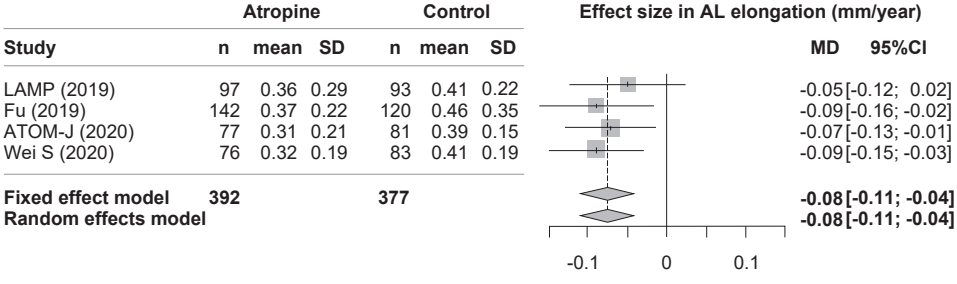

Fig. 3 Forest plot for the 12-month effect size in AL elongation. On this scale, negative values indicate preventive effects against axial elongation.

(Fig. 3) shows, the effect size was −0.08 mm (95% CI: −0.11 to −0.04 mm) and also highly significant ($p < 0.0001$).

The effect sizes above correspond to inhibition ratios of 28% and 19%, respectively, when using number-weighted mean changes in the control groups of the four trials [3,6,9,10] (−0.71 D and 0.40 mm for SEQ change and AL elongation, respectively) as the denominator.

Sensitivity analysis and publication bias. We performed a sensitivity analysis [15,16] for myopia progression and axial elongation. When the trial by Fu *et al.* [10], which had a low Jadad score, was included in the analysis, the mean effect size in SEQ change was 0.19 (95% CI: 0.11 to 0.27) D and that in AL elongation was −0.07 (−0.11 to −0.04) mm. Next, when we excluded ATOM-J, the only RCT conducted on Japanese children, the mean effect size in SEQ change was 0.20 (0.10 to 0.26) D and that in AL elongation was −0.08 (−0.12 to −0.05) mm. The mean effect sizes above were similar to those when all four trials were included, demonstrating the robustness of the overall outcome estimate. In addition, the mean effect sizes calculated with fixed-effect and random-effects models were equal in both myopia progression and axial elongation, revealing that the difference in the estimates among the trials included in the meta-analysis was small.

Funnel plots for myopia progression and axial elongation for 12 months are shown in Fig. 4. The plots were scattered symmetrically around the vertical axis of the mean difference, with no clear publication bias [16]. However, the number of trials included was insufficient to confirm this by statistical testing.

Discussion

Our meta-analysis based on RCTs confirmed that 0.01% atropine administration is effective at slowing myopia progression and axial elongation in Asian children with low to moderate myopia. The overall 12-month effect sizes we estimated for SEQ and AL myopia were 0.20 D and −0.08 mm, respectively. These effect sizes correspond to inhibition ratios of 28% and 19%, respectively. At present, a limited number of

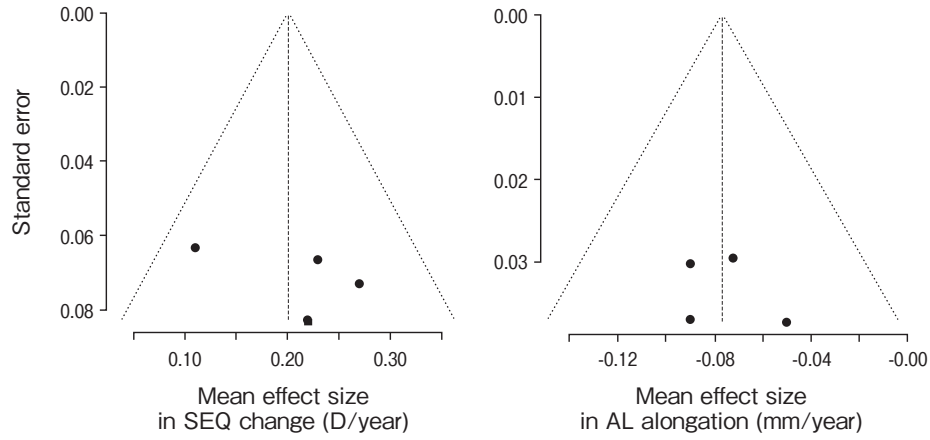

Fig. 4 Funnel plots for the 12-month effect size in SEQ change (left) and AL elongation (right). The vertical lines at the center mark the mean effect sizes of all trials, the sides of the funnel mark the 95% confidence interval, and the dots correspond to individual intervention outcomes.

RCTs are available for meta-analysis. However, all of the RCTs we included in the analysis were reported within the last 3 years and, compared with the previous reviews [5,17-21], were well-designed trials of 0.01% atropine treatment. The sensitivity analysis [16] and funnel plots demonstrated that both the overall effect sizes in SEQ and AL are robust, with no clear publication bias. We thus consider these effect sizes to be the best estimates at present and to serve as a useful reference when considering the application of this treatment in clinics.

It should be noted that the low-concentration atropine for myopia progression (LAMP) study suggested that younger age is associated with poor treatment response to 0.01% atropine [22], although the ATOM-J study found no significant difference in the effect sizes between younger and older age groups (cutoff level: 9 years old) [3]. The age range at baseline (shown in Table 1) and mean myopia-progression and axial-elongation rates in the control group (shown in Fig. 1) were all similar among the RCTs incorporated in our meta-analysis. These similarities in study population likely contributed to the consistency of the estimates across the trials, which was also demonstrated by the low overall heterogeneity (I^2: 6% or less).

From a clinical point of view, the U.S. Food and Drug Administration (FDA) and the International Myopia Institute (IMI) consider inhibition ratios of 30% [23] and 40% [24] in myopia progression, respectively, to be the minimum requirement for clinical preventive treatment of myopia progression. The inhibition ratio found in our meta-analysis (28%) did not reach this requirement. According to large-scale epidemiological studies, the risks of myopic macular degeneration and retinal detachment, which were recognized only as complications of high-grade myopia, increase in parallel with the degree of myopia also in mild to moderate myopia [25]. Bullimore *et al.* predicted that, regardless of the degree of myopia, the risk of myopic macular degeneration will be reduced by 40% if myopia progression can be reduced by 1 D [26]. To receive this level of benefit from this treatment, the preventive effects must continue for at least 5 years. Therefore, we may consider using it at higher concentrations, as suggested by the LAMP study [6,27] and the trial by Fu *et al.* [10], or in combination with an optical-based preventive treatment.

Another novel technology to slow myopia progression is defocus-incorporated soft contact lenses (MiSight®, CooperVision), which is the first and currently only FDA-approved treatment. The design of the concentric rings bifocal lens produces a myopic defocus of 2.5 D at all distances, which aims to employ the emmetropization mechanism to prevent excessive axial elongation. Four well-designed RCTs were conducted in Hong Kong, Spain, Europe, and the United States [28-31]. The 12-month effect sizes for myopia progression and axial elongation in those studies ranged from 0.10 to 0.24 D and from −0.11 to −0.06 mm, respectively. The effect size that we estimated from the 0.01%

atropine trials (0.20 D and −0.08 mm) was within these ranges. However, it may not be reasonable to directly compare the effect sizes between the two treatments because the myopia progression in the control group of the MiSight® trials (0.36-0.41 D/year) was almost half of that of the 0.01% atropine trials. The RCTs incorporated in our meta-analysis involved only Asians, and racial and regional differences in myopia progression may make the comparison difficult, although percentile inhibition ratios may help. Nine ongoing RCTs of low-dose atropine eye drops in different countries are now registered in the ClinicalTrials.gov database. It is possible that we will come to a different conclusion on effect sizes once their results are reported, especially those regarding Caucasian children.

In conclusion, this meta-analysis based on the latest RCTs confirmed that 0.01% atropine treatment significantly inhibits myopia progression and axial elongation. However, the inhibition ratio for myopia progression when this treatment is provided solely to Asian children with low to moderate myopia was roughly half of that originally reported in the ATOM studies [1, 2] and does not reach the minimum requirement for clinical treatment indicated by the FDA [23] or IMI [24].

Acknowledgments. We thank Osamu Hieda for providing the SD values of autorefraction and axial length measurements at the 24-month visit in their RCT [3]. English proofreading was performed by Medical English Service.

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