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CLINICAL INVESTIGATION

Efficacy and safety of 0.01% atropine for prevention of childhood myopia in a 2-year randomized placebo-controlled study

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Abstract

Purpose Atropine eye drops prevent the progression of myopia, but their use has not been tested in the Japanese schoolchildren population. Here, we evaluate the efficacy and safety of 0.01% atropine eye drops for myopia control in Japanese children.

Study design Multicenter (7 university hospitals), randomized, double-masked, placebo-controlled trial.

Methods Participants were 171 Japanese schoolchildren aged 6 to 12 years, with progressive myopia, spherical equivalence (SE) of −1.00 to −6.00 diopters (D), and astigmatism of ≤1.5 D. They were randomized to receive either 0.01% atropine (n=85) or placebo (n=86) eye drops once nightly OU for 24 months. Primary and secondary efficacy endpoints were changes in SE and axial length (AL), respectively, from baseline to month 24.

Results Data from 168 subjects were analyzed. At month 24, compliance was similar in both groups (atropine: 83.3%; placebo: 85.7%). The least squares mean change in SE and AL from baseline were, respectively, −1.26 D (95% confidence interval [CI]: −1.35, −1.17) and 0.63 mm (0.59, 0.67) for atropine and −1.48 D (−1.57, −1.39) and 0.77 mm (0.73, 0.81) for placebo. Inter-group differences were 0.22 D (95% CI: 0.09, 0.35; $P<0.001$) for SE and −0.14 mm (−0.20, −0.08; $P<0.001$) for AL. Three patients experienced mild allergic conjunctivitis side effects, with no inter-group difference in incidence (atropine: 2.4%; 2/84 patients; placebo: 1.4%; 1/84 patients).

Conclusion With good compliance, 0.01% atropine is effective and safe for preventing the progression of childhood myopia.

Keywords Myopia control · Muscarinic receptor · School children · Placebo · Eye drop

Introduction

It has recently been reported that there is an alarming increase in the number of myopia cases worldwide, and that it is quickly becoming a major global health concern, as high myopia in adults can potentially result in pathologic myopia changes that can ultimately lead to blindness [1, 2]. Moreover, in school-age children, worldwide, the increased long-period viewing of television, computer games, and smartphones indoors has led to a significant decrease in outdoor activities. Although it remains unclear, even in Japan, whether or not these environmental factors are a major cause of the proportion of elementary school students with a decimal visual acuity (VA) of less than 1.0, it has steadily been on the rise, from 19.59% in 1988, to 26.34% in 1998, 29.87% in 2008, and 34.10% today [3]. Since myopia progression is rapid during school-age years, it is very important to prevent or slow the progression in order to help maintain a child's quality of life (QOL) [4] and reduce the risk of pathologic myopia [5].

It is reported that the topical administration of atropine eye drops, a non-selective antimuscarinic agent, can suppress the progression of myopia in school-age children, as it slows or prevents axial length (AL) elongation, the primary

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cause of myopia progression in children [6, 7]. Atropine is clinically used at the concentration of 1% as a mydriatic and cycloplegic agent. However, at that concentration, the mydriatic and cycloplegic actions limit practical usage on a daily basis. Hence, several studies have been performed in an attempt to elucidate the optimal safe and well-balanced concentration of atropine eye drops for the prevention of myopia progression. In 2 previous studies performed by the Singapore National Eye Center that investigated atropine concentrations in Singapore children (the Atropine in the Treatment of Myopia (ATOM)1 and ATOM2 studies) [8, 9], the authors' findings reveal that when comparing 0.5%, 0.1%, and 0.01% atropine, the administration of 0.01% atropine resulted in fewer adverse events and a similar suppressive effect on myopic progression. Moreover, a retrospective case–control study in the United States reports that 0.01% atropine administration over a 12-month period in children aged 6 to 15 years suppressed the progression of myopia in comparison with the control group [10]. Recently, a randomized clinical trial performed in Hong Kong, China (the Low-Concentration Atropine for Myopia Progression (LAMP) Study) involving a 12-month administration of 0.01–0.05% atropine eye drops in children aged 4 to 12 years revealed a dose-dependent reduction of myopia progression and that the administration of 0.01% was effective at 12 months [11]. An extension of this trial (LAMP Phase 2 report) concluded that 0.05% was the optimal concentration in their population [12]. However, it should be noted that to date, no multicenter clinical study has been performed, and no study has been conducted to investigate the effects of atropine in Japanese children, who are considered to have ethnic and environmental differences.

We conducted a multicenter, randomized, double-masked, placebo-controlled trial involving a 2-year treatment followed by 1-year observational period to investigate the efficacy and safety of 0.01% atropine eye-drop administration and its effect on the progression of myopia in Japanese school-aged children, and report the statistical analysis results obtained after completion of a 2-year eye-drop administration.

Subjects and methods

Study design

This multicenter, randomized, double-masked, placebo-controlled, parallel-arm study was conducted at 7 university hospitals in Japan from December 2014 through September 2019. The study was conducted in accordance with the tenets set forth in the Declaration of Helsinki, and followed the "Ethical Guidelines for Clinical Research (Public Notice of the Ministry of Health, Labour and Welfare No. 415 of 2008)". The study protocol was approved by the Institutional Review Board of each institution, and written informed consent was obtained from the legal guardian of each child and from each child prior to their enrollment in the study. The entire study process meets with the Japanese laws of Clinical Research, established in 2017. The study was officially registered as a UMIN-CTR Clinical Trial (ID No.: UMIN000018041) on June 23, 2015, and subject enrollment was initiated on August 5, 2015.

Study subjects

Eligible subjects were Japanese school children aged 6 to 12 years with mild to moderate myopia (defined as cycloplegic objective spherical equivalence [SE] −1.00 to −6.00 D in both eyes) and astigmatism of ≤ 1.50 D who reportedly experienced myopia progression in the past year according to the findings of a standard school health examination. The detailed inclusion and exclusion criteria are shown in Table 1.

Randomization

After screening, eligible subjects were registered via a central registration system, and their baseline data were collected via the use of an electronic data capture system (EDC) or tele-facsimile. The data of each subject were linked to a subject identification code provided by the EDC system and anonymized. Next, the subjects were randomized to receive either 0.01% atropine eye drops or atropine-matched placebo eye drops at the ratio of 1:1. Randomized allocation was performed at each site via the permuted block method (block size: 4, ratio: 1:1), with stratification by age and sex. The allocation table was generated and maintained by a contracted professional research organization (Medical Edge Co., Ltd.). The study drugs were prepared at a good manufacturing practice (GMP) facility (Eye-Lens Pte. Ltd.). The study investigators, as well as the children and their legal guardians, were masked to the specific study drug assigned throughout the study period.

Treatment protocol

In all subjects, 1 drop of a randomly allocated drug was instilled in each eye once per night for 24 months. Since it has been reported that a hyperopic shift effect can occur in the early phase of atropine therapy, all subjects underwent an initial follow-up examination at 2 weeks after the start of treatment to obtain the second week baseline values, and were then subsequently assessed at 6, 12, 18, and 24 months after the baseline observation. At each follow-up time-point, some of the subjects were prescribed corrective glasses with a corrected distance visual acuity (VA) of at least 1.0

Table 1 Eligibility Criteria

Inclusion Criteria
1. Children aged 6 to 12 years
2. Children with reduced vision in a school health examination over the past year
3. Objective spherical equivalence between − 1.00 and − 6.00 D in both eyes, as measured under cycloplegia*
4. Anisometropia of objective spherical equivalent ≤ 1.50 D
5. Astigmatism of ≤ 1.50 D
6. Children with corrected visual acuity ≥ 1.0
7. Children with normal intraocular pressure
8. Children capable of undergoing cycloplegia
9. Children able to undergo follow-up examination in accordance with the study protocol
10. Children from whom written informed consent to participate in the study can be obtained
Exclusion Criteria
1. Abnormal binocular function
2. Amblyopia or manifest strabismus
3. Changes in objective spherical equivalent in both eyes as measured by cycloplegic and non- cycloplegic refraction are ≥ 1.00 D
4. Children with ocular diseases other than myopia
5. Children with ocular or systemic diseases that potentially have an effect on myopia or refractive power
6. Previous or current use of contact lenses, bifocals, progressive lenses, or other forms of treatment (including atropine) for myopia
7. Children with a history of cardiac or respiratory disease
8. Children with a history of pharmacotherapy for asthma over the past year
9. Children allergic to atropine, cyclopentolate, or benzalkonium chloride
10. Children who cannot use eye drops
11. Children who might possibly use contact lenses, bifocal lenses, or progressive lenses during the study period

*cycloplegic refraction were evaluated 1-h after administration of cyclopentolate 1% to both eyes at 5-min intervals two times

D = diopters

decimal VA (equivalent to 20/20 Snellen-chart visual acuity), as necessary.

All subjects and legal guardians who participated in the study received a complete and detailed instruction on how to properly administer the study drug and record the administration each day via the use of a mobile management tool. In addition, the subjects, or their legal guardians, were requested to submit (return) the remainder of the study drugs at each follow-up visit. These records were used to strictly monitor compliance with the treatment regimen. The compliance rate was defined as usage of the study drug for ≥ 75% of the days between the evaluation points.

Non-cycloplegic refractions at baseline, as well as cycloplegic refractions at 1-h after 2 topical applications of the cyclopentolate (i.e., objective SE, astigmatism, and corneal curvature radius), were assessed via examination with a properly and regularly maintained autorefractor. Following baseline measurements, a topical anesthetic was administered. Next, cyclopentolate 1% was administered to the patient's eyes at 5-min intervals, and auto-refractometry was performed 60 min after the first administration. AL was measured using a non-contact partial coherence laser interferometer (IOLMaster®; Carl Zeiss Meditec AG), and for each subject, the same device was used (i.e., no change) throughout the 24-month study period.

At baseline and at each follow-up time-point, VA, with and without correction, was measured. Measurements of distant and near VA were performed before cycloplegic refractions, and only distant VA measurements were obtained after cycloplegic refractions. The near VA was assessed at a distance of 30 cm.

Outcome measures

The primary efficacy endpoint was myopia progression, defined as the change in objective SE from baseline to after 24-months continuous administration of the study drug. The secondary efficacy endpoints were the changes in AL from baseline to after 24 months of atropine therapy, as well as the changes in objective SE and AL from baseline to each follow-up time-point. Safety endpoints were incidence of treatment-emergent adverse events (TEAEs) and study drug-related TEAEs, abnormal findings on the ocular surface, cornea, retina and accessory visual structures, accommodative function, intraocular pressure (IOP) measured by non-contact tonometers, and pupil diameter throughout the 24-month treatment period.

Pupil diameter was measured by automatic image analysis based on the vertical and horizontal lengths of the pupil. Images for analysis were obtained using an infrared camera, with photos taken at a fixed distance from the eye. However, accommodation amplitude was not measured at all the institutions and therefore was not included in the current analysis.

Sample size

Based on previously reported study results in Singapore (atropine) [4] and Japan (placebo) [13], the protocol of this present study was structured with the assumption that the progression of myopia over the 2-year study period would be −0.55 D in the 0.01% atropine group and −1.10 D in the placebo group, and that the standard deviation would be 1.0 D. Based on that assumption, and for a power of 90% and 5% significance level, the sample size was calculated to be 90 subjects per group, with an estimated dropout rate of 20%.

Statistical analysis

All data were analyzed based on the intention-to-treatment principle. The primary analysis was performed in the full analysis set (FAS), and robustness of the results was explored through sensitivity analysis in the per-protocol set (PPS). The repeated-measure endpoints were analyzed with linear mixed models that included intervention, dummy variables for time, intervention-by-time interactions as covariates, and the subjects as a random effect. The covariance structure was a completely general (i.e., unstructured) covariance matrix. The results were reported as the least squares means with 95% confidence interval (CI) at each time-point. Subgroup analysis according to 9 enrollment factors (i.e., age, sex, uncorrected distant and near VA, SE, AL, photopic and mesopic pupil diameter, and cycloplegic subjective astigmatism) was conducted with the linear mixed models and interaction tests. Values obtained from both eyes were included in the model. Subjects were classified into 2 subgroups using a median as the threshold. Fisher's exact test was used to compare the group difference in the occurrence of adverse events. A P-value of < 0.05 was considered statistically significant, and all P-values were two-sided without multiplicity adjustment. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.).

Results

Between August 2015 and September 2016, a total of 171 subjects were enrolled in the study. Of those, 85 were allocated into the atropine group and 86 into the placebo group (Fig. 1). Since 1 subject in the atropine group and 2 in the placebo group withdrew from the study prior to administration of the study drug, the FAS ultimately consisted of 84 subjects in each group. During the study period, 10 additional subjects were excluded due to their inability to continue the follow-up examinations. Thus, the resultant PPS included 77 subjects of the atropine group and 81 subjects of the placebo group.

Our findings revealed that the baseline characteristics of both groups were similar (Table 2). Less than half in each group were men (38/84 atropine vs 36/84, placebo), the mean age in both groups was approximately 8.99 years, and the mean uncorrected distance VA was about 0.2 OU in each group. Overall, there were no differences found between the right and left eyes in both groups. The overall baseline means were − 2.95 D for SE and 24.5 mm for AL. In all subjects, no initial hyperopic shift was observed at the 2-week monitor visit (Online Resource 1). However, from that point forward, myopia progression occurred in all subjects over the 2-year study period. At month 24 from the second week baseline, the mean SE in the placebo group was found to have decreased by −1.48 D (95% CI −1.57, −1.39), while the mean AL increased by 0.77 mm (95% CI 0.73, 0.81). During that same 24-month period, those changes were reduced in the group that underwent atropine therapy; i.e., SE decreased by −1.26 D (95% CI −1.35, −1.17) and AL increased by 0.63 mm (95% CI 0.59, 0.67)(Table 3, Fig. 2). In addition, a sensitivity analysis for the primary endpoint using the PPS population provided similar results to the primary analysis (Online Resource 2).

In both groups, there was no significant change in IOP over the 24-month period in comparison with the IOP values recorded at the time of enrollment. However, in the atropine group, the photopic pupil diameter was significantly increased at the 2-week (baseline) and 12-month observation periods. In both groups, no changes in the mesopic pupil diameters were observed (Fig. 3). At 24-months after baseline, 70 subjects (83.3%) in the 0.01% atropine group and 72 subjects (85.7%) in the placebo group were found to have been compliant with the study protocol.

In subgroup analysis for the changes in SE, treatment-by-subgroup interactions were observed for uncorrected near VA and the mesopic pupil diameter. Subjects with an uncorrected near VA of < 1.0 and with a mesopic pupil diameter of < 7.1 mm experienced a greater change in SE than was observed in the counterpart subgroups. It should be noted that no difference from the placebo group was observed in the subjects with a mesopic pupil diameter of ≥ 7.1 mm. In addition, no interactions were observed in relation to age, sex, photopic pupil diameter, with atropine treatment (Fig. 4).

Interactions were observed for enrolled AL values and mesopic pupil diameter to assess changes in AL. Subjects with enrolled AL ≥ 24.4 mm and mesopic pupil diameter < 7.1 mm experienced a greater change in AL than observed in the counterpart subgroups (Fig. 5).

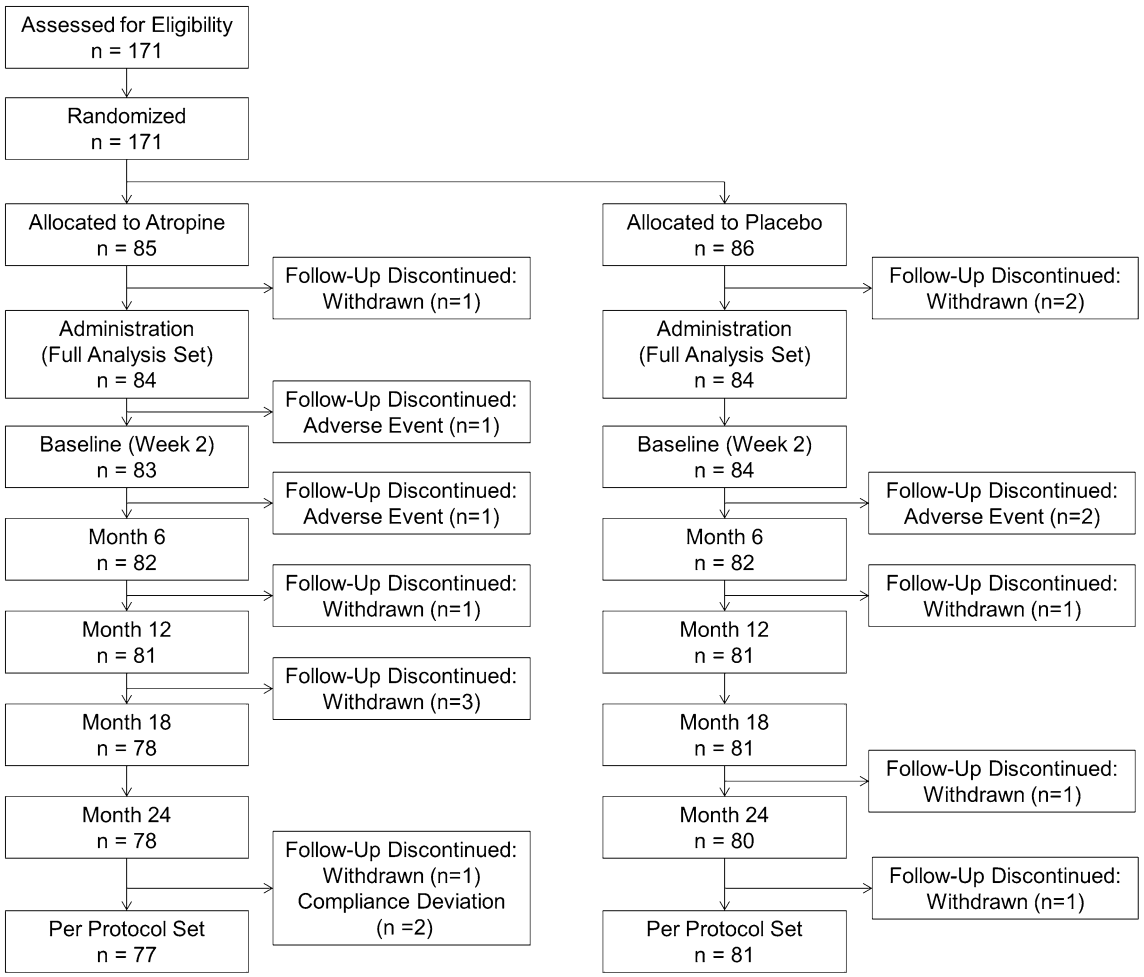

Fig. 1 Flowchart of the subjects throughout the 24-month study period

Table 2 Baseline Characteristics of the 168 Children in the Study

n	Atropine		Placebo	
	84		84	
Sex (male/female)	38/46		36/48	
Age (years)	8.99 ± 1.44		8.98 ± 1.50	
	Right eye	Left eye	Right eye	Left eye
Uncorrected distance VA	0.20 ± 0.15	0.19 ± 0.13	0.20 ± 0.14	0.20 ± 0.13
Uncorrected near VA	0.92 ± 0.33	0.94 ± 0.33	0.95 ± 0.26	0.96 ± 0.26
Uncorrected distance VA (logMAR)	0.79 ± 0.29	0.81 ± 0.28	0.80 ± 0.28	0.79 ± 0.27
Uncorrected near VA (logMAR)	0.08 ± 0.23	0.07 ± 0.23	0.05 ± 0.18	0.04 ± 0.18
Spherical equivalent (D)	− 2.92 ± 1.43	− 2.90 ± 1.38	− 2.96 ± 1.24	− 2.97 ± 1.22
Degree of astigmatism (D)	− 0.48 ± 0.33	− 0.53 ± 0.34	− 0.48 ± 0.28	− 0.47 ± 0.32
Axial length (mm)	24.41 ± 0.86	24.40 ± 0.87	24.50 ± 0.69	24.48 ± 0.70
Intraocular pressure (mmHg)	15.30 ± 2.53	15.63 ± 2.66	15.96 ± 2.39	16.00 ± 2.51
Photopic pupil diameter (mm)	4.89 ± 1.29	4.68 ± 1.34	4.67 ± 1.02	4.72 ± 1.06
Mesopic pupil diameter (mm)	7.35 ± 1.23	7.33 ± 1.05	7.13 ± 0.69	7.26 ± 0.92

VA = visual acuity; D = diopters

Data are expressed as mean ± standard deviation (SD) or the number of subjects

logMAR = logarithm of the Minimum Angle of Resolution

Table 3 Primary Analysis of Spherical Equivalent and Axial Length using Mixed Models

	Atropine	Placebo	Change from baseline	
	LS mean (95% CI)	LS mean (95% CI)	Difference (95% CI)	*P*-value
Spherical equivalent (D)				
Baseline (2-week)	−2.91 (−3.20, −2.62)	−2.98 (−3.27, −2.69)		
6-month	−3.27 (−3.56, −2.98)	−3.42 (−3.70, −3.13)		
Change from baseline	−0.36 (−0.45, −0.27)	−0.43 (−0.52, −0.34)	0.07 (−0.05, 0.20)	0.261
12-month	−3.60 (−3.89, −3.31)	−3.76 (−4.05, −3.47)		
Change from baseline	−0.69 (−0.78, −0.60)	−0.77 (−0.87, −0.68)	0.08 (−0.05, 0.21)	0.215
18-month	−3.97 (−4.26, −3.68)	−4.12 (−4.41, −3.83)		
Change from baseline	−1.06 (−1.15, −0.97)	−1.14 (−1.23, −1.05)	0.08 (−0.05, 0.21)	0.228
24-month	−4.17 (−4.46, −3.88)	−4.46 (−4.75, −4.18)		
Change from baseline	−1.26 (−1.35, −1.17)	−1.48 (−1.57, −1.39)	0.22 (0.09, 0.35)	<0.001
Axial length (mm)				
Baseline (2-week)	24.43 (24.27, 24.60)	24.51 (24.34, 24.68)		
6-month	24.61 (24.44, 24.77)	24.73 (24.56, 24.90)		
Change from baseline	0.17 (0.13, 0.22)	0.22 (0.17, 0.26)	−0.05 (−0.11, 0.02)	0.143
12-month	24.78 (24.62, 24.95)	24.90 (24.73, 25.07)		
Change from baseline	0.35 (0.30, 0.39)	0.39 (0.34, 0.43)	−0.04 (−0.10, 0.02)	0.200
18-month	24.94 (24.77, 25.10)	25.11 (24.94, 25.27)		
Change from baseline	0.50 (0.46, 0.55)	0.60 (0.55, 0.64)	−0.10 (−0.16, −0.03)	0.003
24-month	25.06 (24.90, 25.23)	25.28 (25.11, 25.45)		
Change from baseline	0.63 (0.59, 0.67)	0.77 (0.73, 0.81)	−0.14 (−0.20, −0.08)	<0.001

LS = least squares; CI = confidence interval

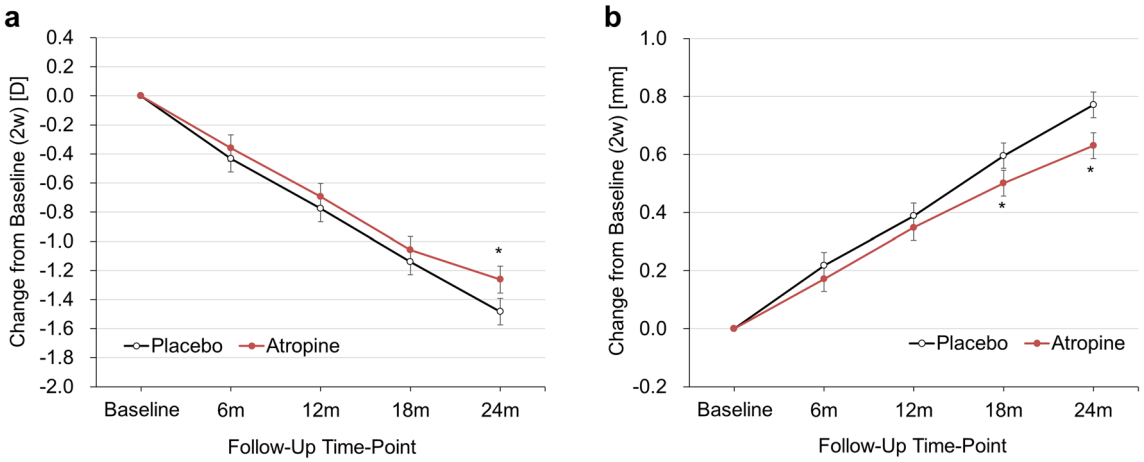

Fig. 2 Mean changes in spherical equivalent (a) and axial length (b) from week 2 (baseline) to month 24. Least squares mean and 95% confidence interval (CI). *$P < 0.05$ (vs. Placebo). w = week; m = month; D = diopter

Adverse events

During the 24-month study period, 2 subjects had non-serious adverse events; in the atropine group 1 subject with suspected hemiplegic alteration migraine due to light sensitivity, and in the placebo group 1 subject with optic-disc hemorrhage. Another 2 subjects also experienced side effects; in the atropine group 1 subject with photophobia, and in the placebo group 1 subject with near-vision impairment. Two subjects in each group were discontinued due to adverse events. The causative adverse events in the atropine group were symptoms of photophobia and suspected hemiplegic alteration migraine, all of which were thought by the investigator to be related to the study treatment. Between both groups, no significant differences in the changes of corrected distance VA before

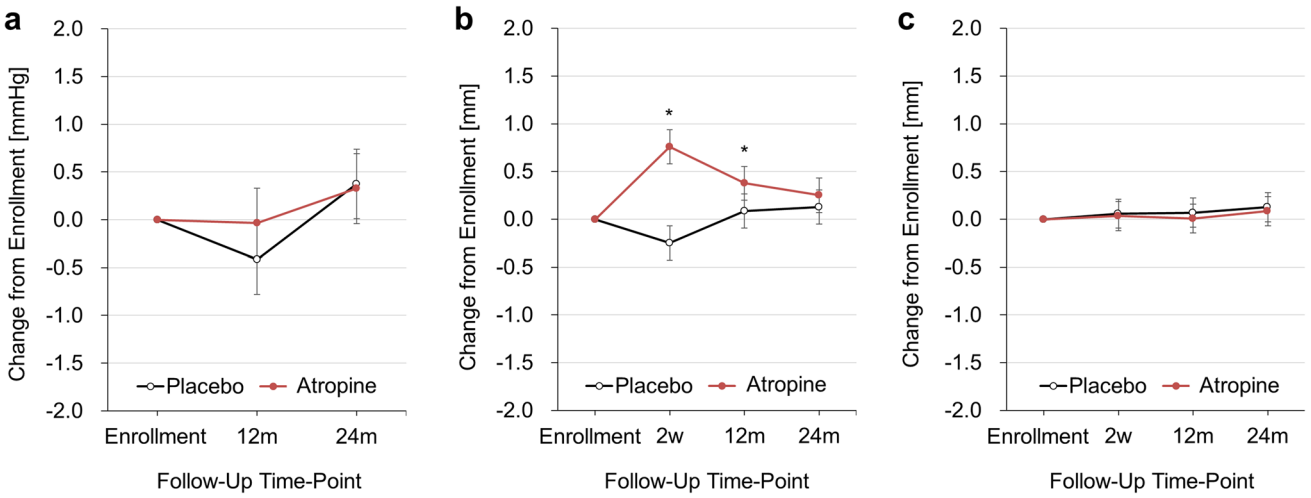

Fig. 3 Mean change in intraocular pressure (a), photopic pupil diameter (b), and mesopic pupil diameter (c) at randomization, 2 weeks, 12 months, and 24 months in the 168 children. Least squares mean and 95% CI. *$P < 0.05$ (vs. Placebo)

Subgroup	n			Difference of Change from Baseline (Spherical Equivalent [D])				Interaction
	All Subjects	Atropine	Placebo	Mean LS(95%CI)	Mean LS	95%CI	*P*-value	*P*-value
Age (years)								
<9	69	33	36		0.12	-0.10, 0.33	0.29	0.32
≥9	99	51	48		0.26	0.11, 0.42	<0.001	
Sex								
male	74	38	36		0.14	-0.07, 0.35	0.19	0.33
female	94	46	48		0.28	0.11, 0.45	<0.001	
Uncorrected distance visual acuity								
<0.2	90	45	45		0.23	0.05, 0.41	0.01	0.55
≥0.2	78	39	39		0.21	0.02, 0.40	0.03	
Uncorrected near visual acuity								
<1.0	36	20	16		0.45	0.15, 0.75	0.003	0.04
≥1.0	100	45	55		0.19	0.03, 0.35	0.02	
Spherical equivalent (D)								
≤-2.7	82	40	42		0.27	0.08, 0.46	0.005	0.17
>-2.7	86	44	42		0.22	0.05, 0.40	0.01	
Degree of astigmatism (D)								
≤-0.42	88	46	42		0.24	0.05, 0.43	0.01	0.54
>-0.42	80	38	42		0.19	0.02, 0.37	0.03	
Axial length (mm)								
<24.4	85	47	38		0.25	0.06, 0.43	0.009	0.89
≥24.4	80	36	44		0.24	0.05, 0.43	0.01	
Photopic pupil diameter (mm)								
<4.6	81	40	41		0.32	0.14, 0.50	<0.001	0.10
≥4.6	86	43	43		0.13	-0.06, 0.31	0.19	
Mesopic pupil diameter (mm)								
<7.1	83	39	44		0.48	0.29, 0.67	<0.001	<0.001
≥7.1	84	44	40		-0.02	-0.20, 0.16	0.83	
				-0.5 0.0 0.5 1.0				

Fig. 4 Forest plot of the difference in spherical equivalent at 24 months in the pre-specified subgroups. D = diopter; LS = least squares; CI = confidence interval

and after instillation was observed. The decrease in corrected near VA before and after instillation was greater in the atropine group (Online Resource 3), yet there were no cases of dropout in that group due to near-distance visual impairment.

Discussion

Although previous studies report that myopia progression in school-age children is suppressed by atropine eye drops

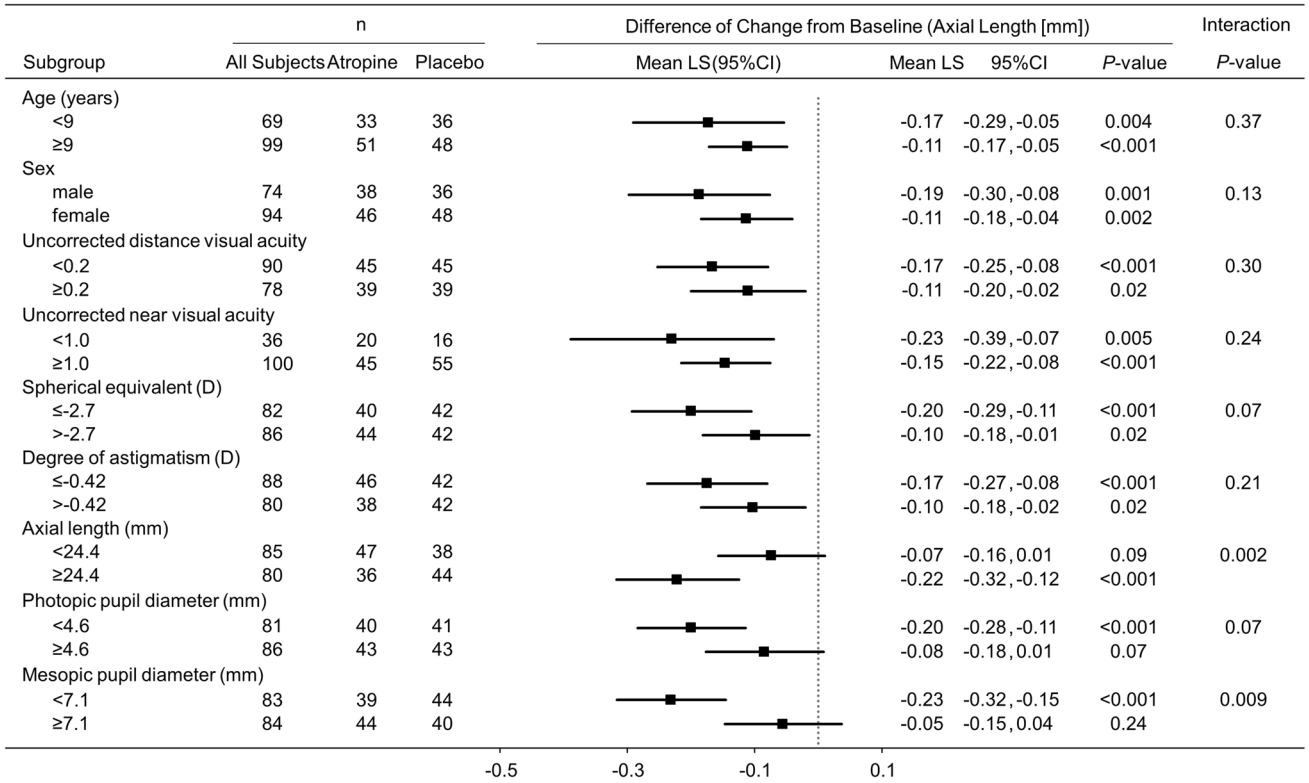

Fig. 5 Forest plot of the difference in axial length at 24 months in the pre-specified subgroups. LS = least squares; CI = confidence interval; D = diopter

(i.e., 0.01% to 1.0%) via nonselective antimuscarinic activity [6, 7, 11], further evidence is still required, including the effects of its long-term use. In this multicenter, randomized clinical trial involving 168 school-age children, our findings clearly revealed that, based on the data of the SE and AL changes, a 2-year treatment with 0.01% atropine eye drops reduces myopia progression, yet the reduction was moderate. The atropine eye-drop treatment was well tolerated with very few side effects, and the compliance rate was > 80%, similar to that of the placebo.

In this study, atropine was tested only at the concentration of 0.01%, since the findings in the ATOM1 [8] and ATOM2 [9] studies indicate no significant differences in the reduction of myopia progression between atropine concentrations of 0.01% and 0.5%, at which point atropine seemed to inhibit the SE increase. However, the effect on AL elongation in those studies was unclear. Another reason why atropine was tested only at the concentration of 0.01% is because a rebound phenomenon reportedly occurs at doses of 0.1% or greater [14]. In this study, 0.01% atropine eye drops slowed down the progression of myopia at the end of 2 years (i.e., a reduction of 0.22 D for SE and −0.14 mm for AL compared with the placebo eye drops). Although the findings in this multicenter clinical trial verify that 0.01% atropine eye drops are effective for childhood myopia progression in relation to Japanese lifestyles and habits, they also illustrate that it takes as long as 2 years to receive the beneficial effects of atropine.

In contrast, the LAMP Study recently performed in Hong Kong, China, shows a clear difference in SE and AL between atropine eye-drop concentrations of 0.01%, 0.025% and 0.05% during the 1-year study period [11]. In that study, 0.01% atropine reportedly reduced SE progression (−0.59 D for 0.01% atropine versus −0.81 D for the placebo), although no improvement in AL (0.36 mm for 0.01% atropine versus 0.41 mm for the placebo) was observed at the end of the 1-year study period. However, as already noted, results may take as long as 2 years; as such, if the placebo group was kept over 2 years in the LAMP Study, 0.01% atropine may show effects on AL. Recently, results of an extension of the LAMP Study (Phase 2 report) were published, in which the treatment of the placebo group was switched to 0.05% atropine at the end of the first year [12]. However, the lack of placebo group in the second year limits direct comparison. Overall, the period of the treatments differed among studies, as well as did ethnical varieties and the subjects' age; e.g., the LAMP Study enrolled children ranging in age from 4 to 12 years, and the mean age in the LAMP Study (8.4 years) was younger than that in the ATOM studies (9.5 years) and this present study (9.0 years). Moreover, it should be noted that the LAMP Study had greater baseline SE (− 3.85 D)

and AL (24.8 mm) in the placebo group compared with the placebo group in this present study (−2.96 D and 24.5 mm). The yearly myopia progression of the SE of the placebo group in the ATOM studies, the LAMP Study, and this present study were −0.60, −0.81, and −0.74 D, respectively. Moreover, the sample size in this study was smaller than in the LAMP Study. It should also be noted that the effect of atropine may be influenced by the environment, including country, culture, and lifestyle. The difference in epidemiology and risk factors between ethnicity and cultures are known, as well as the effect of the environment on myopia progression [2, 5]; hence, the effects of atropine may also be impacted by these and should be considered when comparing studies. However, although the results in this present study cannot be directly compared with the findings in other studies, the efficacy of 0.01% atropine in Japanese children appears to be similar to that observed in other countries in which the problem of childhood myopia exists.

It is possible that some factors are associated with a subject's specific response to 0.01% atropine. We addressed this issue via a subgroup analysis based on enrollment data. The strong interactions on treatment-by-subgroup were observed for uncorrected near VA and mesopic pupil diameter in SE, as well as the enrolled AL and mesopic pupil diameters in AL. These findings suggest that there may be a special target population of children with myopia for atropine treatment. A further clinical study focusing on subgroups is needed to re-confirm these findings.

It is reported that accommodative and/or non-accommodative response via muscarinic and/or nicotinic acetylcholine receptors are involved in the progression of myopia [15–17]. Moreover, the relationship between pupil dilatation and the reduction in myopia progression has reportedly not been clarified [18]. Muscarinic receptors are reportedly all expressed in the retina, sclera, choroid, and ciliary body [19]. Reportedly, the relatively selective M_1 muscarinic antagonist pirenzepine is thought to be useful for suppressing the progression of myopia, as it has no effect on the pupil [20], and although it has reportedly been used in clinical trials, it appears to have not been effective on the suppression of axial elongation [21]. Interestingly, in the LAMP Study, a concentration-dependent increase in photopic and mesopic pupil sizes was reportedly observed over the 1-year study period [11]. In contrast, the findings in this study showed an increased photopic pupil size in the early phase and no change in the mesopic pupil size in the 0.01% atropine group. Thus, further study is needed to elucidate whether or not pupil dilation is one of adverse effects, or is even necessary, for the inhibition of myopia progression.

It should be noted that in this study, near-distance visual impairment did not occur in the 0.01% atropine group, the adverse events had little influence on accommodation in daily use. The incidence of adverse effects in the 0.01% atropine group was low (2.4%), and similar to that in the placebo group (1.2%). Moreover, all adverse effects were suspected to be mild allergic conjunctivitis. Combined with the findings in the previous studies [22, 23], we believe that 0.01% atropine is safe to use.

It should be noted that this study did have some limitations. First, although 0.01% atropine eye-drop administration was found to be effective at 24 months of use, the effects of longer-term use have yet to be elucidated. In addition, although the preliminary findings in the study by Tan and colleagues [14] showed that 0.01% atropine appears to have little effect on the rebound of myopia progression, further study is needed to elucidate the long-term effect after the 2-year administration is discontinued. Therefore, the time course after discontinuing the treatment will be confirmed in our subjects as well. Second, our study was performed without a concentration range of atropine. Both the LAMP and ATOM2 studies showed a concentration-dependent response, with 0.05% showing better efficacy in the LAMP Study [9, 12]. Additionally, it appears that this therapy possibly requires a continuous administration of the eye drops during the child's growth period. Thus, further study is needed to discover whether or not 0.01% atropine is the optimal concentration. Third, our study did not measure accommodation amplitude or accommodative function in all institutions. Fourth, environmental factors have the potential to affect myopia progression; however, detailed lifestyle data was not collected in this study, limiting its comparison between groups, and this should be considered when interpreting the results. Nonetheless, owing to the study's randomized multicenter design, significant bias in environmental factors between the groups is unlikely. Finally, bias may have occurred due to the fact that 10 of the 168 subjects were unable to complete the 2-year follow-up period. However, the follow-up rates were not significantly different between the groups, and sensitivity analysis showed a robustness of the results from primary analysis.

In conclusion, the findings in this present study show that 0.01% atropine eye drops can safely and effectively attenuate the progression of myopia in Japanese school-age children, however, long-term administration is necessary for a beneficial outcome. Further study is needed to determine the optimal atropine concentration, and if 0.01% is adequate for populations with a small pupil size.

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