

Prevention of Myopia Onset with 0.025% Atropine in Premyopic Children

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Abstract

Purpose: To evaluate the efficacy of 0.025% atropine solution for prevention of myopic shift and myopia onset in premyopic children.

Methods: This study was designed as a retrospective cohort study. Six- to 12-year-old children with spherical equivalent refraction of $<+1$ diopter (D) (defined as premyopia), with cylindrical refraction of <-1 D, without amblyopia, and who received 0.025% atropine eye drops at bedtime every night or no treatment after follow-up for at least 12 months were enrolled. Fast myopic shift is defined as a myopic shift >-0.5 D per year.

Results: Fifty children were enrolled in the study. Twenty-four children (average age 7.6 years old) were in the 0.025% atropine group, and 26 children (average age: 8.2 years old) were in the control group. The mean spherical refraction myopic shift in the 0.025% atropine group was -0.14 ± 0.24 D/year, significantly lower than that in the control group, -0.58 ± 0.34 D/year ($P < 0.0001$). In multiple linear regression analysis, 0.025% atropine treatment was the only independent variable in preventing myopia shift. There were statistically significant differences between the 0.025% atropine group and the control group in myopia onset and fast myopic shift (21% vs. 54%, $P = 0.016$; 8% vs. 58%, $P = 0.0002$, respectively). There was no difference between the 2 groups with regard to the symptom of photophobia (16% vs. 8%, $P = 0.409$). None of the children in either group complained of near-blurred vision.

Conclusions: Regular topical administration of 0.025% atropine eye drops can prevent myopia onset and myopic shift in premyopic schoolchildren for a 1-year period.

Introduction

MYOPIA HAS BECOME A WORLDWIDE public health issue in recent years. In Taiwan and Singapore, the prevalence of myopia is 20%–30% among 6–7-year-olds.^{1,2} The myopia progression rate in Asian children is high (nearly -1 diopters [D]/year), and $\sim 24\%$ of the population become high myopes as adults.^{1,3,4} Studies have shown that myopia progresses more rapidly when children exhibit myopia at a younger age.⁵

Onset of myopia typically occurs during the early years of grade school and progresses until the eye is fully grown.^{6–8} Early onset of myopia is associated with high myopia in adult life.⁹ Myopia is a common ophthalmic condition, and high myopia can be a serious ocular problem. It may result in many ocular pathologies¹ such as retinal break, retinal detachment, choroidal neovascularization, and myopic maculopathy, which deteriorate vision and are often irreversible. High myopia, defined as refraction >-6 D, has recently become a major cause of blindness.^{10–12} After onset of myopia

in children, its progression is difficult to control, and only atropine eye drops are effective.^{13,14} However, mydriasis induced by 1% atropine and photophobia often disturb patients. Therefore, it is important to keep children in a premyopia state to prevent or postpone myopia onset.

Recent evidence suggests that increased outdoor activities and reduced long-term near-work could help prevent myopia.^{15–20} Nevertheless, there are still too few reports in the literature of medical interventions to prevent myopia onset. In this study, we investigate the effects of very low concentrations of atropine (0.025%) eye drops and hypothesize that these induce fewer photophobia side effects and could prevent myopia onset in premyopic schoolchildren.

Methods

We conducted a retrospective chart review of children who visited Chang Gung Memorial Hospital, Kaohsiung Medical Center, Taiwan, between 2001 and 2006. This study was adherent to the tenets of the Declaration of Helsinki.

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Premyopia was defined as spherical equivalent refraction (SER) $<+1$ D. Myopia was defined -1 D or greater. Children aged 6–12 years old with regular follow-ups for at least 1 year were included. Exclusion criteria included astigmatism 1 D or over; other combined ocular disease, such as amblyopia, strabismus, congenital cataract, glaucoma, corneal scar, optic neuropathy, traumatic ocular injury, uveitis, and ocular tumor; history of any ocular surgery; and any systemic diseases or conditions that may affect visual function and development, including diabetes mellitus and chromosome anomaly.

Fifty consecutive children met the above criteria and were included in the study. The treatment group included 24 premypic children who, according to their chart records, received topical 0.025% atropine eye drops at bedtime every night during the course of their follow-ups. We ask their parents to apply the eye drops for children. We checked the compliance and confirmed by asking parents and children on each of their next visits. The control group included 26 premypic children who did not receive any treatment during this period.

Initial ocular investigations at our hospital included slit lamp biomicroscopic examination for anterior segment, direct or indirect ophthalmoscopic examination for vitreous, retina and optic disc evaluation, and cycloplegic refraction. SER was obtained using an autorefractor (KR-7000/8100; Topcon, Tokyo, Japan) 30 min after a cycloplegic procedure initially with 1% cyclopentolate, followed by 2 successive instillations of 1% tropicamide with a 10-min interval. Cycloplegic visual acuity with correction was measured using a Landolt's C chart for confirmation. The 0.025% atropine solution was prepared by diluting a 0.25% atropine ophthalmic solution (Atropine Sulphate 0.25% Eye Drops; Wu-Fu Lab. Co., Ilan, Taiwan) with distilled water.

The SER records obtained during the initial survey were collected for analysis from the beginning of the therapy to the final follow-up. All children were not given spectacle prescription during the follow-up period. The progression of myopia per year was calculated as changes in SER (diopters)/follow-up period (months) multiplied by 12. A "threshold" of myopia shift -0.50 D/year (fast myopic shift) was chosen as a target point for comparison between groups, according to the reported result of 2% pirenzepine gel on myopia control.¹⁶

Statistical analysis

The SER of the right eye was used for further statistical analysis. For continuous variables such as age, the duration

of follow-up, and SER, the Student's *t* test was used to determine the statistical significance of the between-group differences. The chi-square test was used to compare the portion of eyes that change from premypia to myopia and the portion with more than a -0.5 D myopia shift per year change in each group. Multiple linear regression analysis of myopic shift was carried out for variables of age, sex, initial SER, and 0.025% atropine. The Statistical Package for the Social Sciences software (SPSS version 10, Chicago, IL) was used for analysis.

Results

There were 24 children in the treatment group and 26 in the control group (Table 1). The male-female ratios were 13:11 in the treatment group and 17:9 in the control group. The mean ages at the beginning of the study were 7.6 ± 1.7 years (range: 6–11) in the treatment group and 8.2 ± 2.1 years (range: 6–12) in the control group. The mean follow-up intervals were 18.4 ± 6.9 (range: 12–36) months and 16.3 ± 4.9 (range: 12–25) months in the treatment and control groups, respectively. The initial spherical equivalents were -0.31 ± 0.45 D (range: -0.875 to $+0.625$ D) in the treatment group and -0.17 ± 0.50 D (range: -0.875 to $+0.75$ D) in the control group. There were no significant differences between the 2 groups with regard to sex, age, initial SER, and follow-up period ($P = 0.419, 0.297, 0.288$, and 0.178 , respectively).

At the end of the follow-up period, the SERs were -0.49 ± 0.47 D (range: -1.75 to $+0.375$) in the treatment group and -0.96 ± 0.51 D (range: -1.75 to $+0.25$) in the control group. Figure 1 showed the initial and final cycloplegic refractions with age in each subject of the 2 groups. The mean myopic shift per year was significantly lower in the treatment group than in the control group (-0.14 ± 0.24 D, as compared to -0.58 ± 0.34 D; $P < 0.0001$, Table 1). In the multiple linear regression analysis, the 0.025% atropine was still the only variable capable of preventing myopic shift in a statistically significant way ($P < 0.0001$, Table 2). Age, sex, and initial SER were not statistically significant ($P = 0.274, 0.638$, and 0.185 , respectively).

At the final visit, 5 of 24 eyes in the treatment group (21%) had SER ≥ -1.0 D, compared with 14 of 26 eyes in the control group (54%). Comparing the proportion of eyes in the 2 groups that changed from premypia to myopia, we noted that the incidence was significantly lower in the treatment group ($P = 0.016$, Table 3). Fast myopic shift is defined as a myopic shift > -0.5 D per year. Two in 24 eyes in the treatment group (8%) and 15 in 26 eyes in the control group (58%)

TABLE 1. BASELINE DEMOGRAPHIC CHARACTERISTICS, SPHERICAL EQUIVALENT REFRACTION, AND CHANGES IN DIFFERENT GROUPS

	Control group	0.025% Atropine group	P-value
N	26	24	
Male/female	17/9	13/11	0.419
Age	8.2 ± 2.1	7.6 ± 1.7	0.297
Initial SER (D)	-0.17 ± 0.50	-0.31 ± 0.45	0.288
Final SER (D)	-0.96 ± 0.51	-0.49 ± 0.47	0.002 ^a
Follow-up (month)	16.3 ± 4.9	18.4 ± 6.9	0.178
Myopia shift (D/year)	-0.58 ± 0.34	-0.14 ± 0.24	<0.0001 ^a

^aRepresents statistically significant ($P < 0.05$).

Abbreviations: D, diopter; SER, spherical equivalent refraction.

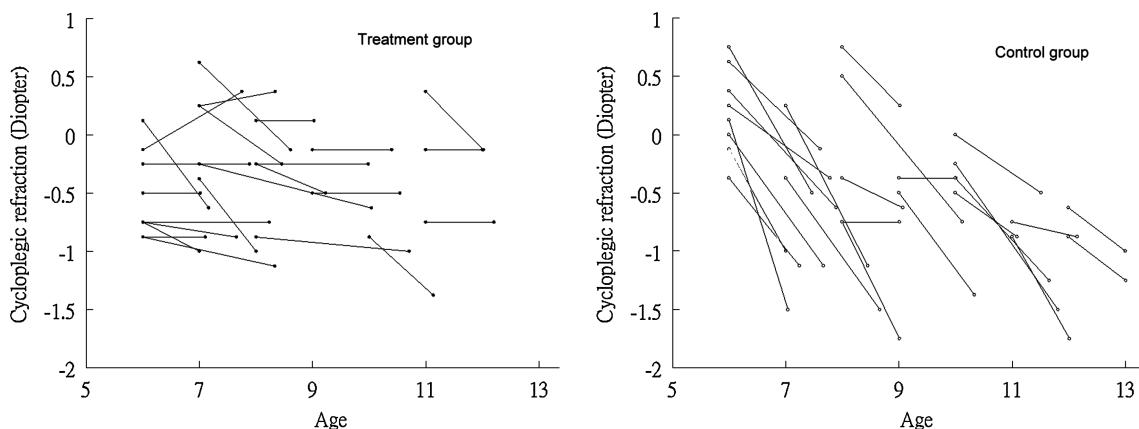


FIG. 1. The initial and final cycloplegic refractions with age in each subject of 2 groups.

exhibited fast myopic shift. The 0.025% atropine group had significantly fewer children with fast myopic shift than did the control group ($P = 0.0002$, Table 3).

Four children in the treatment group (16%) complained of photophobia, compared with 2 children in the control group (8%). There was no significant difference between these 2 groups ($P = 0.409$). None of the children in either group complained of near-blurred vision. No systemic side effects were reported in the treatment group.

Discussion

The premyopia status alerts us to the possibility of myopia onset in the coming year.²¹ This study showed that over half of premyopic children in the control group (54%) became myopic. Intervention to delay the onset of myopia in premyopic children may prevent myopia progression in later life and reduce the incidence of high myopia in adults. This study showed that 0.025% atropine could successfully delay the onset of myopia and prevent myopia shift in premyopic schoolchildren. To our knowledge, this is the first report of 0.025% atropine effectively preventing myopia.

Low hyperopic refractive error is an important risk factor for future myopia.^{21,22} After myopia onset, myopia progression is difficult to control in children. A previous study showed a nearly -1 D per year progression in myopic schoolchildren in Asia.^{3,4} According to a SCORM study, younger children experience more myopia progression over a 3-year period.²³ The results of a 7-year COMET study indicates that myopia at a younger age is a significant risk

factor for high myopia.⁵ Therefore, it is important to maintain hyperopic or premyopic status in schoolchildren.

The definition of myopia varies, ranging from SE of -0.25 D to -1.0 D in recent studies.¹⁴ Williams et al. first defined the term *premyopia* as a refractive error between plano and $+0.5$ D.²⁴ Since the myopia progression rate can be as high as -1 D/year in Asian children,^{3,4} in this study we defined premyopia as SER of $<+1$ D. Within this range, the initial SER status did not have statistical significance in the myopic shift; only 0.025% atropine intervention had significance. In the control group, over half of children with SER in this range became myopic and exhibited fast myopic shift. This suggested that initial SER between $+1$ D could be a sign for further myopic shift and onset.

Atropine, a nonselective muscarinic antagonist, is the most widely studied pharmacological agent for the prevention of myopia progression in children. Several controlled clinical trials have provided evidence that various concentrations of atropine can retard or slow myopia progression in children.^{3,25-28} Shih et al. used 0.5%, 0.25%, and 0.1% atropine for the control of myopia in children and demonstrated significantly less myopia progression in the high-concentration atropine group (0.5%) than in the control group. The higher concentrations of atropine, including 1% or 0.5%, were more effective than the lower concentrations, but were accompanied by a greater dropout rate (16%) due to intolerable photophobia, blurred near vision, and fear of long-term ocular or systemic side-effects.³ In southern Taiwan, the tropical climate results in strong sunlight for 9 months out of the year, exacerbating the photophobia of some patients who

TABLE 2. 0.025% ATROpine TREATMENT AND PREDICTORS OF MYOPIC SHIFT USING MULTIPLE LINEAR REGRESSION

	Myopic shift (D/year)		P-value
	Unadjusted	Adjusted	
Age	0.03	0.18 (-0.015, 0.82)	0.166
Sex	0.03	0.05 (-0.14, 0.21)	0.670
Initial refraction	-0.12	-0.16 (-0.32, 0.06)	0.187
0.025% Atropine ^a	0.41	0.57 (0.23, 0.58)	<0.0001
Follow-up (month)	0.01	0.15 (-0.06, 0.03)	0.232

Value in parentheses are 95% confidence interval.

^aYes = 1, no = 0.

Abbreviation: D, diopter.

TABLE 3. THE RATE OF MYOPIA ONSET AND FAST MYOPIC SHIFT DURING FOLLOW-UP PERIOD

	<i>Control group</i>	<i>0.025% Atropine group</i>	<i>P-value</i>
Onset of myopia (%)	14/26 (54%)	5/24 (21%)	0.016 ^a
Fast myopic shift (-0.5 D/year or greater)	15/26 (58%)	2/24 (8%)	0.0002 ^a

Onset of myopia is defined as SER -1.0 D or greater.

^aRepresent chi-square test, $P < 0.05$.

Abbreviations: D, diopter; SER, spherical equivalent refraction.

received atropine treatment. Photophobia due to the mydriasis effect of atropine is the primary reason to discontinue its use in controlling myopia. We previously reported the effectiveness of topical low concentration, 0.05% atropine in controlling myopia progression in myopic schoolchildren.²⁶ In this study, the very low concentration of 0.025% atropine could effectively maintain premyopic status in children and prevent myopia onset. A lower rate of photophobia was noted in the treatment group, and no children complained of near-blurred vision.

To date, atropine eye drops are the only treatment demonstrated to have a consistent effect on the retardation of myopia progression.^{13,14} However, the actual mechanisms responsible for this effect are still unclear. Accumulating evidence now suggests that the development of myopia is a multifactorial process in humans and that excessive near work or prolonged reading could be the main cause of myopia.²⁹⁻³⁴ Initially, atropine was used based on the putative role of excessive accommodation in causing myopia.³⁵ However, it is still unclear whether excessive or sustained accommodation plays a role to produce tension in the ciliary muscle on choroidal tension and scleral stretch.³⁶ On the other hand, previous studies in chicks showed that atropine reduces myopia progression via a nonaccommodation mechanism.³⁷ Even though it is still unclear whether atropine inhibits accommodation and myopia progression by inference, low concentration of atropine in this study showed the possible effect on prevention of myopia onset and maintenance of premyopia status. Further studies for clarifying the mechanism are warranted.

Recent reports have shown that participating in outdoor activities is a protective factor against myopia.^{15,17,19} However, it is sometimes difficult to change the behaviors of the children themselves, especially in crowded Asian cities. Key changes might include parents placing less academic stress on children, parents accompanying children outdoors, and governments changing educational policies to include more outdoor classes. It can be difficult for parents who work full time to accompany children as they spend more time outdoors in urban environments. Therefore, medical intervention such as very low concentration of atropine (0.025%) might provide an alternative for preventing myopia onset in the premyopic children. The 0.025% atropine might be used in children at higher risk of becoming myopic, for example, those with low hyperopia or premyopic status, and those who participate in fewer outdoor activities and more near work.

There was 1 patient in the treatment group with a 0.5 D hyperopic shift in the end of study. The mild hyperopic shift after atropine treatment was also noted in previous studies.^{38,39} It might be due to stronger cycloplegic response and persistent inhibition of myopic shift by long-term atropine use. In the treatment group, 6 children had myopic shift over than -0.3 D/year. In the nontreatment group, 3 patients

did not have myopia shift >-0.12 D/year. There was no significant difference in factors of age, sex, and initial SER within each group. The small sample size might limit the further investigations in this study. The limitations of this study were its retrospective nature and small sample size. Further large-scale, prospective, randomized study is necessary.

In conclusion, a very low concentration of atropine (0.025%) effectively prevented myopia onset and myopic shift in premyopic schoolchildren. In addition, it seldom induced the symptoms of photophobia and near-blurred vision.

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Author Disclosure Statement

There is no proprietary interest for each author.

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