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Prevention of Myopia Progression with 0.05% Atropine Solution

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ABSTRACT

Aim: **The aim of this study was to evaluate the efficacy of 0.05% atropine solution for controlling myopia progression in school-aged children.**

Results: **This retrospective, case-control study enrolled myopic school-aged children who had presented at Kaohsiung Chang Gung Memorial Hospital (Kaohsiung, Taiwan) from 2001 to 2004. A group of 57 children (30 boys, 27 girls; 6–12 years of age) with regular follow-up was divided into a subgroup of 21 children (12 boys, 9 girls) who received atropine eyedrops (0.05%) every evening, and a subgroup of 36 children (18 boys, 18 girls), who remained untreated, served as controls. The changes in refractive status of 114 eyes in 57 children were collected and compared for patients treated with 0.05% atropine eyedrop and those without medical control. The initial spherical equivalent of refractive status range was between −0.5 and −5.5 D. Mean myopia progression for the group of patients treated with 0.05% atropine eyedrop (n = 21) was −0.28 ± 0.26 D/year, significantly lower than that of the control group of −0.75 ± 0.35 D/year (36 patients; $P < 0.001$). The 0.05% atropine group had a significant lower ratio of uncontrolled myopia, that progressed greater than −0.50 D in 1 year, relative to the controls (16.7% versus 77.8%; $P < 0.001$).**

Conclusions: **The results of this study demonstrate that, with regular instillation, topical 0.05% atropine is an effective agent for controlling myopia progression in a majority of school-aged children for at least a period of 1 year.**

INTRODUCTION

Axial myopia is a common ophthalmic condition. In the United States, it is estimated that 25% of the population are myopic, with pathological or high myopia affecting 0.5%–2% of the population.[1] The prevalence of myopia is higher in Asian populations than in Caucasian or African-American ones. A survey in Taiwan disclosed that the myopia rate was 12% at the age of 6 years, but increases to 84% between the ages of 16–18 years; the mean refractive status becomes myopic at the age of 9 years. The prevalence of high myopia (less than −6.0 D) increases from 0.2% at 9 years of age to 12% and 20% in boys and girls, respectively, at 18 years.[2] In Japan, pathological or high myopia affects 6%–18% of the myopic population.[3] Eyes with pathological myopia have minimum refractive errors in the range of −5.0 to −7.5 D.[4] Pathological myopia may also lead to various fundus lesions, such as choroidal neovascularization (CNV), a sight-

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threatening complication occurring in 5%–10% of individuals with high myopia.[3,5–7] Cohen et al. have reported that high myopia is the cause of 62% of CNV in patients less than 50 years of age.[8] In addition to CNV, retinal detachment with macular hole, which occurs most commonly in highly myopic eyes,[9] also causes visual impairment. Thus, prevention of myopia progression in schoolchildren is of critical importance to reduce the visual morbidities associated with high myopia in later life.

The most widely studied pharmacological agent for the inhibition of myopia progression has been atropine, a nonselective muscarinic antagonist. Several controlled, clinical trials have provided evidence that atropine can retard myopia progression in children.[10–13] Shih et al. studied 0.5%, 0.25%, and 0.1% atropine for the control of myopia in children and demonstrated significantly less myopia progression in treatment groups than in control groups. The 0.5% atropine was the most effective, but it also had the greatest dropout rate (16%) owing to intolerable photophobia, fear of long-term side-effects, allergic blepharitis, and lack of persistence with the nightly eye drops.[10]

In southern Taiwan, the subtropical climate emits strong sunlight for 9 months a year, which exacerbates the photophobia of some patients and is the major cause of the relinquishment of atropine control for myopic progression. A very low concentration of atropine (0.05%) has been used tentatively for myopia control in the school-aged children who could not tolerate even the 0.1% atropine in our hospital for a few years. In this retrospective study, we measured the rate of myopic progression over 1 year, comparing patients receiving 0.05% atropine eye drops with untreated controls. To our knowledge, this is the first investigation of 0.05% atropine treatment for the prevention of myopic progression.

METHODS

A retrospective chart review was conducted of school-aged patients diagnosed with myopia who had visited Kaohsiung Chang Gung Memorial Hospital (Kaohsiung, Taiwan) between 2001 and 2004. Inclusion criteria were: (1) spherical equivalent of refractive status range −0.5 to −5.5 D; and (2) myopia control with a regular 0.05% atropine instillation of one drop at bedtime for more than 9 months a year, monitored by a chart record. Exclusion criteria were: (1) astigmatism greater than −2.0 D; (2) anisometropia greater than 2.0 D; (3) children with other ocular diseases, such as amblyopia, strabismus, infantile glaucoma, congenital cataract, optic nerve atrophy, corneal opacity, traumatic eye injury, uveitis, and ocular tumor; (4) history of intraocular surgery; (5) a systemic disease that may affect visual function and development, such as diabetes mellitus; or, (6) poor compliance with the change of topical medications during the course of follow-ups, based on chart record.

A retrospective chart review disclosed 21 consecutive patients (9 boys, 12 girls, ages 6–12), who fit the inclusion criteria and were subsequently regarded as the treatment group. The control group of 36 myopic patients (18 boys, 18 girls, ages 6–12) did not receive atropine or any other treatment, except for spectacles.

Initial ocular investigations at our hospital were: (1) slit-lamp examination of anterior segment and lens; and (2) biomicroscope or direct ophthalmoscope examination for fundus and optic evaluations. The spherical equivalent of refractive status was obtained first by autorefractor (KR-7000/8100; Topcon; Tokyo, Japan) after a cycloplegic procedure with initial 1% cyclopentolate, followed by two successive instillations of 1% tropicamide with a 10-min interval. Cycloplegic visual acuity with correction was then measured using a Snellen chart for confirmation. The 0.05% atropine solution was prepared by diluting 1% atropine ophthalmic solution (Colircusí Atropine 0.5% Eye Drops®; Alcon Cusí, S.A., El Masnou-Barcelona, Spain) with distilled water.

The records of refractive status obtained by the initial survey method were collected for analysis from the beginning of therapy to the last follow-up at the end of 2004. The progressions of myopia per year were calculated from (change of spherical equivalent of refractive status (diopters)/therapeutic interval (months) × 12) in the treatment group and (change of spherical equivalent of refractive status (diopters)/follow-up interval (months) × 12) in the control group. A "threshold" of −0.50 D/year was chosen as a target point for comparison between groups in accordance with the result of a recently published report of 2% pirenzepine gel on myopia control.[14] A rate of myopia progression of −0.50 D per year would result in a refractive error of −6.00 D (from 7 to

Table 1. Myopia Progression as Spherical Equivalent of Refractive Status at Baseline and After Follow-Up

	0.05% atropine	*Control*	p *value*
Initial spherical equivalent (D)	−1.58 ± 1.37	−1.41 ± 0.86	0.464
Final spherical equivalent (D)	−1.97 ± 1.41	−2.76 ± 1.23	0.002*
Duration of follow up (m)	19.9 ± 8.98	21.5 ± 10.1	0.408
Myopia progression (D/m)	−0.024 ± 0.022	−0.070 ± 0.069	<0.001*
Myopia progression (D/yr)	−0.28 ± 0.26	−0.75 ± 0.35	<0.001*

D, diopter; m, month; yr, year.
Student t-test used.
*Statistically significant ($P < 0.05$).

18 year olds) and possibly subsequent pathological retinal changes in adulthood.[4]

Statistical analysis

For continuous variables, such as age, gender, and spherical equivalent of refractive status, the Student *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 children with fast myopic progression in each group. Multivariate analysis of myopia progression in the atropine treated and the untreated groups was also carried out after adjusting for age, baseline refraction, gender, and duration of follow-up. The Statistical Package for the Social Sciences software (SPSS version 10, Chicago, IL) was used for analysis.

RESULTS

There were 21 patients (42 eyes) in the treatment group and 36 patients (72 eyes) in the control group. All were residents of southern Taiwan. The male-female ratios were 12:9 and 18:18 in the treatment and control groups, respectively. The mean ages at the beginning of the study for the treatment and control groups were 8.38 ± 1.47 years (range, 6–12) and 8.11 ± 1.12 years (range, 6–12), respectively. No statistical differences were observed when comparing gender ($P = 0.461$) and age ($P = 0.266$) between the two groups. The mean therapeutic interval of the treatment group and the follow-up interval of the control group were 19.95 ± 9.04 and 21.47 ± 10.02 months, respectively. Eight (8) patients in the treatment group had a therapeutic interval of 2 or more years.

Baseline spherical equivalent of refractive status ranged from −0.5 to −5.5 D (mean, −1.58 ± 1.37) and −0.5 to −4.25 D (mean, −1.41 ± 0.86) for the treatment and control groups, respectively. The between-group difference was not statistically significant ($P = 0.464$). After an interval of follow-up, the myopia had progressed to −1.97 ± 1.41 D and −2.76 ± 1.23 D for the treatment and control groups, respectively. Mean myopia progression per year (Table 1) in the former group was significantly lower than the latter (−0.28 ± 0.26 D versus −0.75 ± 0.35 D; $P < 0.001$). The result of multivariate linear regression showed that two factors, the use of atropine and age, were associated with the degree of myopia progression. The rate of myopia progression was inversely proportional to the age. After adjusting

Table 2. 0.05% Atropine Treatment and Predictors of Myopic Progression Using Multiple Linear Regression

	Myopic progression rate (D/yr)		
	Unadjusted	*Adjusted*	P
Atropine*	0.45	0.55 (0.33~0.57)	<0.0001
Age (y)	0.10	0.30 (0.05~0.15)	<0.0001
Gender	0.05	0.06 (−0.07~0.16)	0.4020
Right or left eye	−0.002	−0.003 (−0.12~0.11)	0.9680
Initial refraction	0.002	0.01 (−0.06~0.06)	0.9320
Follow-up (m)	0.001	0.03 (0.00~0.01)	0.6840

Values in parentheses are 95% confidence interval. *Yes = 1, no = 0.

the variables of age, baseline refraction, gender, laterality, and duration of follow-up, the myopia progression in the atropine treatment group was still significantly lower than that of the untreated group (Table 2). Children with a spherical equivalent of refractive status greater than −1.5 D were recorded to use spectacles in the majority of cases in both groups. Only one case in the treatment group used bifocal spectacles.

The myopia was judged to be relatively stationary when its progression was less than −0.5 D over 1 year, or as a poor control when it was equal to or greater than −0.5 D. Thirty-five (35) eyes (83.33%) in 18 of the children in the treatment group had a relatively stationary myopia, compared to only 16 eyes (22.20%) in 10 cases of the control group. By comparing the proportions of stationary myopia between the two groups using the χ^2 test ($\chi^2 = 40.07$, $P < 0.001$; Table 3), one can see a significant difference.

DISCUSSION

The results of this study demonstrate that, with regular instillation, 0.05% atropine is an effective control agent for myopia progression in school-aged children. To our knowledge, such a low concentration of atropine has not previously been considered for control of myopia progression. One (1) percent atropine was not recommended as first-line medication for control of myopia progression in the report of Yen et al., owing to the resultant photophobia, which stopped children from attending gymnastic classes and limited their time outdoors.[12] The efficacy of atropine with a lower concentration has been evaluated in the later study of Shih et al., who showed significant effects on control of myopia progression at concentrations of 0.5%, 0.25%, and 0.1%. The highest concentration (0.5%) was the most effective, with 61% of the students not suffering myopia progression for the course of 2 years. By contrast, only 42% of those receiving the 0.1% atropine experienced no myopic progression. However, such a high concentration had adverse side-effects, such as discouraging many of the children attending our hospital from using atropine, even in the form of the 0.1% solution, as a regimen for myopia control. Additionally, many doctors do not favor the use of atropine for fear of possible UV-related long-term retinal damage[15] owing to the prolonged cycloplegic effects. Nevertheless, a recent investigation of retinal function in children who used atropine eye drops daily over 2 years for myopia control failed to show any significant effects on a multifocal electroretinogram (mfERG).[16]

Table 3. Ratios for Fast and Slow Myopia Progression in 0.05% Atropine Treatment and Control Group

Myopia progression (Diopter per year)	*<0.50 D*	*≥0.50 D*	*Total eyes*
0.05% atropine	35 (83.3%)	7 (16.7%)	42 (100.0%)
Control	16 (22.2%)	56 (77.8%)	72 (100.0%)

$\chi^2 = 40.07$; $P < 0.001$.

Our clinical experience shows that the instillation of 0.05% atropine at bedtime was relatively more tolerable than other regimens, such as cyclopentolate and atropine at concentrations of 0.1% or above, despite the inevitable mydriatic effect. The combined results of the chart records and telephone interviews revealed that 7 children had photophobia in the morning, 1 of whom had persisted to the afternoon. Also, 2 children had hampered near vision when reading and none had an irritating or allergic reaction to the 0.05% atropine solution. Nonetheless, complications associated with eyedrops may not be fully revealed on a chart or during a telephone interview.

In the study of Shih et al., 1% tropicamide was used for the control group, which resulted in a myopic progression of −1.06 ± 0.61 D per year.[10] Yen et al., recorded comparable myopic progression of −0.914 D in 1 year when using saline instillation as the control treatment.[12] In our study, children unwilling to use atropine or any other cycloplegic agent for prevention of myopia were enrolled in the control group. The result of multivariate linear regression of all cases showed that age, in addition to the use of atropine, was inversely proportional to the degree of myopia progression. Most of our patients (51 of 57; 89%) were 6–9 years old at the beginning of follow-up, with a mean progression of myopia ranging from −0.50 to −0.77 D per year. On the contrary, the remaining 6 children (ages 10–12) had a mean myopia progression of less than −0.40 D per year. A study of a large case number of children of 10 years of age or above is required to clarify the relationship between age and rate of myopia progression. Our −0.75 D progression in the control group was close to the data in a report from Sin-

gapore with the 3-year cumulative means ranging from −1.71 to −2.40 D in 7- to 9-year-old school children,[17] but still less than the progression observed in the two aforementioned studies performed in Taiwan 5 and 15 years ago.[10,12] It appears reasonable to suggest, however, that some newly emerging risk factors for myopia progression, such as Internet and computer use, may have only a minor influence on children 6–12 years of age. More importantly, parents should devote more attention to, and be more aggressive with, the control of myopia progression in their children than 10–20 years ago, using their personally unpleasant and inconvenient experiences of myopia.

Our study had a number of shortcomings. Firstly, the mean follow-up period of less than 20 months was relatively short compared to the earlier investigation,[10] so the long-term efficacy of 0.05% atropine for myopia control could not be determined. It was also noted that a few patients failed to respond to the treatment after application for longer than 1 year. Secondly, this retrospective study was based on a chart review. Patients may cease treatment in less than 6 months because of a subjective perception of worsening visual acuity or rapid progression of myopia. Those individuals who made themselves available for the regular instillation of atropine and subsequent follow-ups at our hospital may have simply been responders to the treatment instead of a true representation of the general population. On the other hand, patients who attended our medical center may have already visited several local clinics without good myopia control and could be particularly susceptible to the environmental and genetic factors of myopia progression. Therefore, further study with a prospective design is required to better estimate the efficacy of 0.05% atropine. Thirdly, no commercial 0.05% atropine solution was available, so the eye drops were prepared by diluting 1% atropine solution with distilled water. This may also have reduced the preservative concentration, thereby decreasing the chance of allergic reaction. Also, fluctuations in the concentration of atropine among bottles cannot be accurately estimated.

CONCLUSIONS

Despite the inability to avoid side-effects, such as photophobia, even at very low concentrations of atropine, our study shows that 0.05% atropine is still a good choice for preventing myopia progression in a certain portion (two thirds of our cases) of schoolchildren. We suggest that the 0.05% atropine regimen is a good starting point as medical treatment for the control of myopia progression. Encouraging children who receive this treatment to wear hats and schedule outdoor gymnastic classes in the afternoon instead of the early morning may alleviate concerns of undesirable side-effects. Further prospective and randomized studies are required to confirm the efficacy of low-dosage atropine treatment.

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