

# An intervention trial on efficacy of atropine and multi-focal glasses in controlling myopic progression

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## ABSTRACT.

**Purpose:** This randomized clinical trial assessed the treatment effects of atropine and/or multi-focal lenses in decreasing the progression rate of myopia in children.

**Methods:** Two hundred and twenty-seven schoolchildren with myopia, aged from 6 to 13 years, who were stratified based on gender, age and the initial amount of myopia were randomly assigned to three treatment groups: 0.5% atropine with multi-focal glasses, multi-focal glasses, and single vision spectacles. Each subject was followed for at least eighteen months. These results report on the 188 patients available for the follow-up.

**Results:** The mean progression of myopia in atropine with multi-focal glasses group (0.41 D) was significantly less than the multi-focal (1.19 D) and single vision group (1.40 D) ( $p < 0.0001$ ). But no significant difference was noted between the last two groups ( $p = 0.44$ ). The progression of myopia was significantly correlated with the increases of axial length ( $r = 0.65$ ,  $p = 0.0001$ ), but not with the changes of corneal power ( $r = -0.09$ ), anterior chamber depth ( $r = -0.023$ ), lens thickness ( $r = -0.08$ ), or intra-ocular pressure ( $r = -0.008$ ).

**Conclusion:** The 0.5% atropine with multi-focal lenses can slow down the progression rate of myopia. However, multi-focal lenses alone showed no difference in effect compared to control.

**Key words:** atropine – multi-focal lens – myopia – randomized trial.

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Myopia is a significant public health problem in Taiwan (Lin et al. 1999). Juvenile-onset myopia usually shows progression after the onset of myopia. Jensen reviewed data from 49 nine- to twelve-year-old Danish children who did not receive medication in a two-year study (Jensen 1991). The mean progression rate was 1.14 D in 2 years. The longitudinal study in Taiwan showed the progression rate to be even faster. Several efforts have been made to halt the progression of myopia with optical correction as well as with topical cycloplegia; however, no specific methods have been successful.

Optical methods of correction and inhibition of myopia progression include wearing contact lenses or regular, bifocal, or multi-focal spectacles. It has been suggested that wearing bifocal lenses may result in a slower progression rate of myopia (Oakley & Young 1975; Goss & Grosvenor 1990; Parssinen & Lyyra 1993). However, most of these studies were not randomized or found no significant evidence to support that bifocal lenses provide more effective intervention than the traditional single lens. Perhaps, bifocals do not control accommodation at all working distances nor do they necessarily allow clear vision at all work-

ing distances. The presence of a blurred retinal image has been suggested as a possible cause of myopia. The use of progressive lenses is also based on this rationale.

Besides, atropine has also been proposed as a treatment to prevent myopic progression (Brodstein et al. 1984; Bedrossian 1971; Chou et al. 1997; Shih et al. 1999). Many of the studies were retrospective reviews of patient charts and suffered from significant design flaws. Authors compared dissimilar patient populations, did not control for observer bias, had poor follow-up, and did not have sufficient power to identify small treatment effects. The goal of this study is to determine if therapeutic interventions can slow the progression of juvenile-onset myopia. We will use two intervention strategies to answer this question. First, we will compare the rate of myopia progression in children prescribed with progressive lenses versus a control group prescribed single vision distance lenses. Second, we will study a group of children prescribed atropine and progressive lenses and compare them with the control group. This study will employ a double-blind randomized design to minimize the effect of potential biases.

## Methods

The three treatments we used in this clinical trial are regular single vision lenses, multi-focal lenses, and 0.5% atropine with multi-focal lenses. For participants fitted with multi-focal progressive lenses, HOYALUX3 plastic lens were used. For single regular lenses, polycarbonate plastic lenses were used. Subjects were in-

structed to wear the glasses all the time, and those fitted with multi-focal were instructed to use the near add part for reading (lowering the eyes rather than lowering the head). The eyedrops were instilled once per day at bedtime. The study design was initially intended to be a two by two factorial experiment. However, using atropine with regular single vision lenses would induce poor compliance in wearing glasses because it would be hard for children to read, thus this treatment was not considered. The recruitment period ended at the twelfth month and the trial was completed at the eighteenth month.

The school children aged from 6 to 13 years old, who were interested in participating in the trial had to meet the inclusion/exclusion criteria, provide written informed consent from both themselves and their guardians, be willing to wear glasses, and be available for the required follow-up visits during the study period. Each participant was tentatively selected on the basis of the inclusion/exclusion criteria at the baseline visit. During the baseline visit, ocular measurements were taken and compliance with the placebo medication was examined. Patients who met these requirements were enrolled in the study. Follow-up visits occurred every three months and eyedrops were distributed at the same time. A total of 227 myopic children, without tropia or amblyopia, were recruited from the vision care center of National Taiwan University Hospital. Seventy-six of these children were assigned to the atropine with multi-focal lenses group, 75 children were to the multi-focal lenses with eyedrop placebo group, and 76 children were to wear traditional single vision lenses with eyedrop placebo. The 227 children recruited included 122 girls and 105 boys. About 124 children were younger than 9.5 years old and 103 children were older. Thirty-nine cases were excluded from the study.

A complete ocular exam and interview were performed at baseline visits and semi-annual visits. The examination included before- and after-cycloplegic auto refraction, intra-ocular pressure, slit lamp exam, and biometric axial length measurements. The corneal radius and refractive status was measured with autorefractor (Topcon RK-3000). The cycloplegic refraction, with 3 successive drops of 1% tropicamide at 5-min intervals, was measured 30 min after the last instillation. All values of refractive status were rechecked with retinoscope by either one of two

senior ophthalmologists. The mean values of spherical equivalents of refractive errors and corneal radii from the autorefractometer were used for calculation. Intra-ocular pressure was measured with a tonopen (Biomed). For the refractive status and intra-ocular pressure, three measurements were recorded for each procedure. The mean value was calculated from three separate measurements. The biometric axial length [including anterior chamber depth, lens thickness, and total axial length] was measured by A-scan ultrasonography (Sonomed A-1500). Five measurements were recorded for each procedure. The mean value was also calculated from the five separate measurements.

The average baseline refractive errors for the three treatments groups were  $-3.28$  D ( $\pm 0.13$ ),  $-3.34$  D ( $\pm 0.14$ ), and  $-3.20$  D ( $\pm 0.14$ ), respectively. The average of axial length in three treatment groups was  $24.62$  mm ( $\pm 0.10$ ),  $24.80$  mm ( $\pm 0.09$ ), and  $24.75$  mm ( $\pm 0.10$ ), respectively. Any subject who developed an increase in refractive error of more than  $0.75$  D during the study period was given a new pair of spectacles with corrected lenses. Any subject with a cumulative progression of more than  $2$  D in any eye was terminated from the study treatment and followed at an assigned outpatient department. The right eye was used for data analysis to evaluate the differences between the different groups. The interview contained a questionnaire about the time spent in near-work, far-sight seeing

and the compliance of wearing the prescribed glasses and instillation of eyedrops.

## Results

After 18 months' follow-up, 17.2% of children had dropped out of the study. A total of 39 cases were excluded, 10 cases from the atropine with multi-focal lenses group, 14 cases from the multi-focal lenses group, 15 cases from the regular lenses group. Most reasons for dropping out were: 1) cannot attend follow-up at regular intervals, 2) try to use another treatment such as contact lenses, or traditional treatments, 3) show poor compliance in wearing glasses or instilling the eyedrops, 4) have fast progression (two cases showed more than  $-2.0$  D/year, one is from multi-focal group and the other is from regular group, 5) loss to follow-up without any reason.

The mean myopic progression over 18 months was  $0.42 \pm 0.07$  D in 0.5% atropine with multi-focal lenses group. It was significantly less than the multi-focal lenses group ( $1.19 \pm 0.07$  D) and regular single vision lenses group ( $1.40 \pm 0.09$  D) ( $p < 0.0001$ ) using analysis of variance (ANOVA) and multiple comparison. However, no significant difference was found between the multi-focal and regular lenses group ( $p = 0.44$ ) by multiple comparison. There was an obvious flattening effect on the myopic progression slope during 0.5% atropine with the mul-

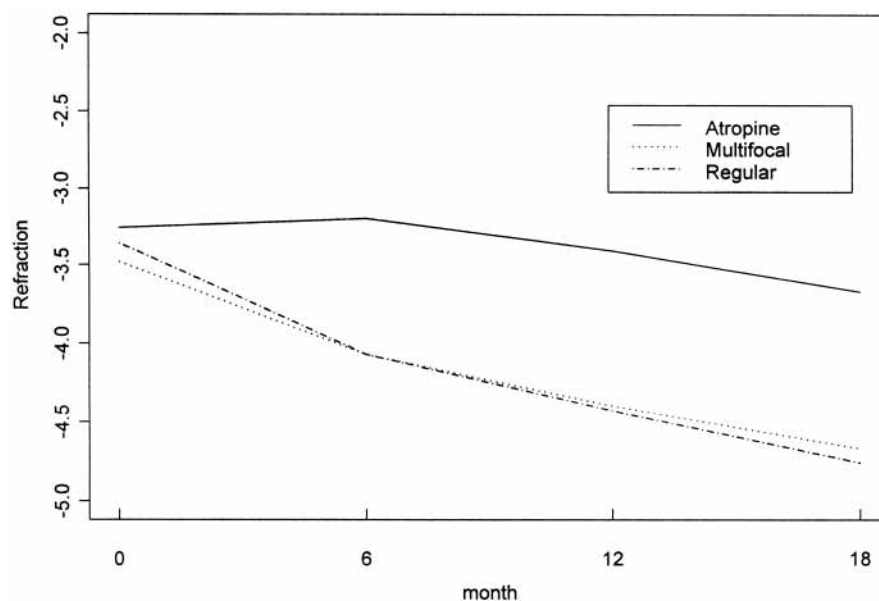


Fig. 1. The long-term effect of myopic progression (D) for three treatment groups.

**Table 1.** The progression of myopia (D/year) in atropine and multi-focal lenses, multi-focal lenses, and regular lenses groups.

	<=0.25 D/Y	0.25~0.75 D/Y	>=0.75 D/Y	Total
Atropine+ Multi-focal	38 (57.6%)	21 (31.8%)	7 (10.6%)	66 (35.0%)
Multi-focal	6 (9.8%)	19 (31.2%)	36 (59.0%)	61 (32.5%)
Regular	3 (4.9%)	14 (23.00%)	44 (72.1%)	61 (32.5%)
Total	47 (25.0%)	54 (28.7%)	79 (46.3%)	188 (100%)

**Table 2.** The changes of astigmatism (D/year) in atropine and multi-focal lenses, multi-focal lenses, and regular lenses groups.

	<=0.25 D/Y	0.25~0.75 D/Y	>=0.75 D/Y	Total
Atropine+ Multi-focal	49 (74.2%)	14 (21.2%)	3 (4.6%)	66 (35.0%)
Multi-focal	52 (85.2%)	7 (11.5%)	2 (3.3%)	61 (32.5%)
Regular	47 (77.1%)	13 (21.3%)	1 (1.6%)	61 (32.5%)
Total	148 (78.7%)	34 (18.1%)	6 (3.2%)	188 (100%)

**Table 3.** The difference of ocular measurements between baseline and the 18th month visit.

	Atropine+M	Multi-focal	Regular	p-value
Numbers	66	61	61	
Spherical equivalent (D)	-0.42 (0.07)	-1.19 (0.07)	-1.40 (0.09)	0.0001
Astigmatism (D)	-0.34 (0.05)	-0.18 (0.06)	-0.27 (0.06)	>0.05
Anterior chamber depth (mm)	0.005 (0.013)	-0.006 (0.014)	-0.015 (0.017)	>0.05
Lens thickness (mm)	-0.010 (0.012)	0.033 (0.014)	0.042 (0.014)	0.01
Axial length (mm)	0.22 (0.03)	0.49 (0.03)	0.59 (0.04)	0.0001
Intraocular pressure (mmHg)	1.67 (0.39)	1.66 (0.36)	1.27 (0.38)	>0.05

\* p value was derived based on the comparison among three treatment groups.

ti-focal group over those in the multi-focal and regular lenses groups (Fig. 1).

Around half of the children in the 0.5% atropine with multi-focal group showed no progression of myopia (less than 0.25 D/year); only less than 10% of patients in the multi-focal lenses group and the regular lenses group did. 11% of children in the 0.5% atropine with multi-focal group still had fast progression of myopia (more than 0.75 D/year). However, the multi-focal (59%) and regular lenses (72%) groups were significantly higher (Table 1). Also most of the children showed no progression or changes in astigmatism (less than -0.25 D/year) (Table 2).

As to the difference of ocular measurement between baseline and 18th month, we noted that the refraction and axial length of the atropine with multi-focal lenses group showed significantly less progression than the other two groups ( $p < 0.0001$ ). Besides, lens thickness became slightly thinner than the multi-focal and regular lenses groups ( $p < 0.01$ ) (Table 3).

The progression of myopia was highly

correlated with the increases of axial length ( $r = -0.64$ ,  $p = 0.0001$ ). In contrast, it was not correlated with the changes of anterior chamber depth ( $r = -0.023$ ,  $p = 0.75$ ), or lens thickness ( $r = -0.08$ ,  $p = 0.28$ ). Also, it was not correlated with the change of intra-ocular pressure ( $r = -0.008$ ,  $p = 0.91$ ). We chose the cases with less progression of myopia (less than 0.25 D/year) to see whether the axial length increased with age. The results showed axial length increased 0.1 mm/year with age.

### Discussion

There have been various methods to reduce the onset and progression rate of myopia. However, the validity and applicability of most of the results are often limited. The problems could arise from the non-randomization of the treatments, no control group for comparison, large proportion of dropouts, and/or insufficient sample size. In this study we conducted a double blind randomization for

the different treatments: regular lenses, multi-focal lenses, and 0.5% atropine with multi-focal lenses. We found that the ocular refraction and axial length showed less progression in the atropine with multi-focal lens group.

The use of progressive lenses is based on the rationale that bifocals do not control accommodation at all working distances nor do they necessarily allow clear vision at all working distances. Multi-focal progressive lenses allow the possibility of reduced accommodation, securing clear vision at all working distances. However, we could not detect significant difference in arresting the myopia progression between multi-focal lenses and regular lenses treatment. In this study, we found that 0.5% atropine with multi-focal lenses did slow down the myopic progression rate. Because there was no significant difference in arresting the myopia progression between multi-focal lenses and regular lenses, the major effect should be due to the atropine effect. The result was similar to our previous study (Shih et al. 1999). Around half of the schoolchildren receiving 0.5% atropine showed no progression of myopia.

Control of myopia progression by atropine may work by two distinct mechanisms. First, atropine could inhibit the accommodation (Lee et al. 1999). We found that the lens thickness seems to stop increasing in the atropine with multi-focal group. Perhaps, accommodation may exert force on the eye that leads to axial elongation. Second, atropine may inhibit growth factors acting to elongate the eye (Taylor et al. 1985; McBrien et al. 1993; Wang et al. 1998). Further studies are needed, however, to establish whether this is true.

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