• Clinical Research •

The diluted atropine for inhibition of myopia progression in Korean children

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Received: 2018-07-02 Accepted: 2018-08-21

Abstract

• AIM: To evaluate the efficacy and safety of three different concentrations of diluted atropine for the control of myopia in Korean children, and to assess the risk factors associated with rapid myopia progression.

• METHODS: A total of 285 children, with refractive errors within the range of -6 diopters (D) between 5 and 14 years of age were included. After using 0.01%, or 0.025%, or 0.05% atropine, for about 1y, changes in refraction, axial lengths and frequency of adverse events were analyzed. Logistic regression analyses were performed to evaluate the risk factors associated with rapid myopia progression.

• RESULTS: The changes in the mean spherical equivalent values were -0.134 D/mo in the before atropine group, -0.070 D/mo in the 0.01% atropine group, -0.047 D/mo in the 0.025% atropine group, and -0.019 D/mo in the 0.05% atropine group, with significant differences between the groups (*P*<0.001). The axial elongation was 0.046 mm/mo, 0.037 mm/mo, 0.025 mm/mo, and 0.019 mm/mo respectively, with significant differences between the groups (*P*=0.003). The incidence of photophobia and near vision difficulty was not different among the three atropine groups (*P*=0.425 and *P*=0.356, respectively). Multivariate logistic regression analyses showed that only highly myopic parents were a significant predictive factor of rapid myopia progression in Korean children (odds ratio, 8.155; 95% confidence interval, 3.626-18.342; *P*<0.001).

• CONCLUSION: Treatment with 0.01%, 0.025% and 0.05% atropine solution inhibits myopia progression in Korean children in a dose-dependent manner. Children with highly myopic parents preferentially shows a rapid myopia progression rate.

• **KEYWORDS:** atropine; Korean children; myopia; progression
DOI:10.18240/ijo.2018.10.13

Citation: Moon JS, Shin SY. The diluted atropine for inhibition of myopia progression in Korean children. *Int J Ophthalmol* 2018; 11(10):1657-1662

INTRODUCTION

Myopia is a considerable ophthalmic concern. Because pathologic myopia may result in complications such as choroidal neovascularization, retinal detachment, and glaucoma[1-3]. Due to increases in near-distance work and urban lifestyles, the prevalence of myopia has increased in both Asia and Western countries for the last several decades. The prevalence of myopia in some East Asian countries, including the Republic of Korea, has increased up to 90% in young adults[4-6]. Pathologic myopia is estimated to have a global prevalence of 0.9%-3.1%, and it is the cause of low vision in 5.8%-7.8% of Europeans and 12.2%-31.3% of East Asians[7]. Myopia is, therefore, a significant public health problem due to its increasing prevalence, associated visual morbidities, increased social disability, consequential reduction in the quality of life, and its considerable costs for correction.

Interventional approaches such as bifocal glasses, progressive lenses, orthokeratology, and anticholinergic eye drops are current methods to suppress the progression of myopia[8-11]. In the latest network Meta-analysis to determine the effectiveness of different interventions in slowing the progression of myopia in children, Huang *et al*[12] reported that the most effective intervention that showed a significant reduction in myopia progression involved pharmacological agents such as atropine and pirenzepine. Orthokeratology and peripheral defocus modifying contact lenses showed moderate effects, and progressive addition spectacle lenses showed minimal effects[12]. Atropine eye drops are therefore considered the most effective treatment for inhibiting myopia progression. Atropine is a nonselective muscarinic antagonist. The mechanisms in retarding the progression of myopia were based on the inhibition of excessive accommodation and the alternative actions at the retina or the sclera[11,13].

Several studies have reported the effects of atropine on the control of myopia[11-15]. However, there have been no reports on the effects of different concentrations of atropine on Korean

children. It is important to determine the atropine effects in different countries and racial groups to confirm whether similar or unique atropine effects exist. It is also important to identify the risk factors associated with myopia progression in children. This study was conducted to evaluate the effect of diluted atropine solution on myopia progression, and to identify the risk factors of rapid progression in Korean children.

SUBJECTS AND METHODS

A total of 285 children with myopia were treated with diluted atropine eye drops, and their medical records were reviewed. This retrospective study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Catholic University of Korea, College of Medicine. The Institutional Review Board waived the need to obtain informed consent.

Children with ages between 5-14y with myopia and a spherical equivalent (SE) refractive error below -6.0 diopters (D) myopia were included in the study. Children with anisometropia of SE > 2.0 D; astigmatism more than -1.5 D; other combined ocular diseases such as strabismus, congenital cataract, glaucoma, corneal scar, optic neuropathy, or traumatic ocular injury, and a history of any ocular surgery were excluded.

Before using atropine, children were regularly followed-up and risk factors for rapid myopia progression were evaluated at the first visit. To confirm the family history, the refractive errors of the parents were also measured. A family history of high myopia was defined when any one of the parents showed more than -6.0 D myopia. After that, we prescribed diluted atropine as a routine clinical treatment with dose selection and follow-up for about 1y according to the protocol of our institution. The 0.01%, 0.025% and 0.05% atropine solutions were prepared by diluting a 1% atropine eye drop solution (Isopto®Atropine, 10 mg/mL; Alcon, Fort Worth, TX, USA) with 0.9% normal saline. The eye drops were used daily before bedtime. The 0.05% atropine was prescribed when the calculated myopia progression rate exceeded -1.50 D/y, the 0.025% atropine was prescribed when the calculated myopia progression rate exceeded -1.00 D/y but less than -1.50 D/y, and 0.01% atropine was prescribed when the calculated myopia progression was below -1.00 D/y.

The refraction was measured in SE of cycloplegic autorefraction. The cycloplegic regimen consisted of three drops of 10 mg/mL cyclopentolate hydrochloride (OcuCyclo®, Samil, Republic of Korea), administered approximately 5min apart. Cycloplegic autorefraction measurements were performed at least 30min after instillation of the third drop of cyclopentolate. A Huvitz HRK-7000A® auto ref-keratometer (Coburn Technologies, South Windsor, CT, USA) was used to take five reliable readings. The results selected for analyses showed the same measurement values at least three times. The main outcome, the rate of refractive growth for all groups was calculated by the formula of McClatchey and Hofmeister to reflect the logarithmic nature of refractive growth[16].

$$\text{Rate of refractive growth}=(\text{Refraction}_2-\text{Refraction}_1)/\log(\text{Age}_2+0.6\text{y})/(\text{Age}_1+0.6\text{y})$$

The secondary parameter involved the axial length, which was measured using an IOLMaster® 500 (Carl Zeiss, Jena, Germany). Five measurements were obtained for each eye, and the axial length was calculated using an automated system included with the equipment.

The adverse event was monitored by changes in the near point of accommodation (NPA) and pupil size. The NPA was defined as the closest point at which an object could be seen clearly and measured with the Royal Air Force Rule. The pupil size was measured using a VIP™-200 pupillometer (Neuroptics, Berkeley, CA, USA) in a photopic environment. All measurements of cycloplegic autorefraction, axial length, NPA, and pupil size were performed by investigators who were trained and certified at every visit.

Other examinations included the best-corrected visual acuity using the Snellen eye chart, slit-lamp biomicroscopy and a fundus examination.

Statistical Analysis All measured variables were calculated as the average of both eyes. Data are expressed as the mean±standard deviation or number (percentage) as appropriate. The clinical baseline measurements and demographic characteristics of all groups were evaluated by one-way analysis of variance (ANOVA) for continuous variables and the Chi-square test for categorical variables. The analyses of outcomes were based on an evaluation of the magnitude of change in SE, the rate of refractive growth, and the axial lengths between the follow-up and baseline among all groups using one-way ANOVA with Bonferroni post hoc analyses. Rapid myopia progression was defined as a progression rate of more than -1.0 D/y. The most relevant risk factors associated with rapid myopia progression were selected using univariate logistic regression analyses. Variables with a value of $P<0.2$ using univariate logistic regression were included in the final multivariate logistic regression analyses. In all other analyses, except for univariate logistic regression analyses, a value of $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS statistical software for Windows, version 21 (SPSS, Chicago, IL, USA).

RESULTS

Between January 2015 and May 2018, totally 285 children were enrolled and followed-up. Among the 285 children, 89, 63 and 133 children were included in the 0.01%, 0.025% and 0.05% atropine groups, respectively. There was no significant difference in age, sex, family history of high myopia, previous refractive error and an axial length between the three atropine treated groups (Table 1).

Table 1 Patient characteristics *n* (%)

Characteristics	Before atropine (*n*=285)	0.01% atropine (*n*=89)	0.025% atropine (*n*=63)	0.05% atropine (*n*=133)	*P*
Sex					
F	153 (53.7)	45 (50.6)	35 (55.6)	73 (54.9)	0.436
M	132 (46.3)	44 (49.4)	28 (44.4)	60 (45.1)	
Age (y)	7.0±2.1	8.0±2.2	8.4±2.1	8.1±2.1	0.516
Family history of high myopia	84 (29.5)	27 (30.3)	21 (33.3)	36 (27.1)	0.823
Follow-up duration (mo)	9.0±2.4	13.7±1.7	10.5±1.8	14.0±1.8	0.714
Pre-refraction (diopters)	-2.76±2.38	-3.84±2.47	-3.97±1.65	-3.94±2.76	0.058
Pre-axial length (mm)	24.39±1.36	24.86±1.22	24.66±0.93	24.91±1.43	0.561
NPA (cm)	7.4±3.2	7.7±3.8	7.5±2.2	7.1±2.6	0.447
Pupil size (mm)	5.2±0.8	5.1±0.4	5.2±0.7	5.3±1.1	0.126

NPA: Near point of accommodation. Data are expressed as the mean±standard deviation or number (percentage), as appropriate.

Table 2 Changes in refraction and axial length

Variables	Before atropine	0.01% atropine	0.025% atropine	0.05% atropine	*P*
Refraction change (D/mo)	-0.134±0.160	-0.070±0.072	-0.047±0.072	-0.019±0.056	<0.001[a,b,c,d,e,f]
Rate of refractive growth (D)	-4.498±5.957	-2.664±2.955	-1.636±2.194	-0.725±1.574	<0.001[a,b,c,d,e,f]
Axial elongation (mm/mo)	0.046±0.020	0.037±0.027	0.025±0.020	0.019±0.021	0.003[a,b,c,d,e,f]

D: Diopters. Data are expressed as the mean±standard deviation. Pairwise comparison *P* values are represented by [a]significant ($P<0.05$) difference between before atropine and 0.01%; [b]Significant difference between before atropine and 0.025%; [c]Significant difference between before atropine and 0.05%; [d]Significant difference between 0.01% and 0.025%; [e]Significant difference between 0.01% and 0.05%; [f]Significant difference between 0.025% and 0.05%.

The changes in the refraction of the before atropine group, 0.01% atropine group, 0.025% atropine group, and 0.05% atropine group were -0.134±0.160 D/mo, -0.070±0.072 D/mo, -0.047±0.072 D/mo and -0.019±0.056 D/mo, respectively. There was a statistically significant difference between the four groups according to the concentration of eye drops ($P<0.001$; Table 2).

Table 2 also shows the rate of refractive growth of the before atropine group, 0.01% atropine group, 0.025% atropine group and 0.05% atropine group. There was also a statistically significant difference between the four groups according to the concentration of eye drops ($P<0.001$). As the secondary outcome, the changes in axial length were 0.046±0.020, 0.037±0.027, 0.025±0.020 and 0.019±0.021 mm/mo, respectively, in each group. There was also a statistically significant difference between the four groups according to the concentration of eye drops ($P=0.003$; Table 2).

We graded the rate of myopia progression as follows: the slowest rate was a change of the calculated refraction less than 0.25 D/y, the moderate rate was between 0.25 and 0.5 D/y, and the fast rate was between 0.5 and 1 D/y. The fastest rate was a calculated change of more than 1 D/y. The fastest myopia progression rates occurred in 66.3% of the before atropine group, 38.2% in the 0.01% atropine group, 34.9% in the 0.025% atropine group, and 6.8% in the 0.05% atropine group. The lowest progression rates of myopia were 8.5%, 24.7%, 30.2% and 58.6%, respectively (Table 3).

Table 4 shows the changes in the NPA and pupil size. There was no statistically significant difference in the frequency of near vision difficulties and photophobia between the three treated groups ($P=0.425$ and $P=0.356$, respectively). No serious adverse event related to atropine was reported. There was no deterioration in the best-corrected visual acuity, and no lenticular, optic disc, or macular change was reported. There were no cases of ocular infections and the contamination of diluted atropine during the study period.

The results of the univariate analyses are summarized in Table 5. Age, family history and axial length were selected for inclusion in the multivariate logistic regression analyses. These analyses indicated that only the family history of high myopia was a significant predictive factor of rapid myopia progression in Korean children [odds ratio (OR), 8.155; 95% confidence interval (CI), 3.626-18.342; $P<0.001$; Table 5].

DISCUSSION

The results of our study indicated that treatment with 0.01%, 0.025% and 0.05% atropine eye drops resulted in both a clinical and statistical reduction in the progression of myopia when compared with before atropine group. The calculated 1-year changes in the refraction of the before atropine, 0.01% atropine, 0.025% atropine, and 0.05% atropine groups were -1.61 D, -0.84 D, -0.56 D and -0.23 D, respectively. In phase 1 of the ATOM 2 study, the myopia progressions were -0.49 D, -0.38 D and -0.30 D in the 0.01%, 0.1%, and 0.5% atropine groups at 24mo, respectively[14]. There was a dose-dependent

Table 3 Distribution of myopia progression rates *n* (%)

Myopia progression rates	Before atropine	0.01% atropine	0.025% atropine	0.05% atropine
Slowest (change of D/y<0.25)	24 (8.5)	22 (24.7)	19 (30.2)	78 (58.6)
Moderate (0.25≤ change of D/y<0.50)	32 (11.2)	12 (13.5)	7 (11.1)	20 (15.0)
Faster (0.50≤ change of D/y<1)	40 (14.0)	21 (23.6)	15 (23.8)	26 (19.6)
Fastest (change of D/y≥1)	189 (66.3)	34 (38.2)	22 (34.9)	9 (6.8)

D: Diopters. Data are expressed as a number (percentage).

Table 4 Changes in accommodation and pupil size

Variables	0.01% atropine	0.025% atropine	0.05% atropine	*P*
Accommodation				
NPA before atropine use (cm)	7.7±3.8	7.5±2.2	7.1±2.6	0.447
NPA after atropine use (cm)	8.7±2.6	9.4±2.8	10.1±4.4	0.142
NPA change (%)	15.2±52.4	23.4±42.8	26.5±59.4	0.113
Near vision difficulty (%)	1 (1.1)	2 (3.2)	10 (7.5)	0.425
Pupil size				
Pupil size before atropine use (mm)	5.1±0.4	5.2±0.7	5.3±1.1	0.126
Pupil size after atropine use (mm)	5.9±0.9	6.2±0.7	6.4±0.8	0.326
Pupil size change (%)	13.7±16.8	13.9±20.2	14.7±21.2	0.189
Photophobia (%)	3 (3.4)	3 (4.8)	14 (10.5)	0.356

NPA: Near point of accommodation. Data are expressed as the mean ± standard deviation or number (percentage), as appropriate.

Table 5 Univariate and multivariate analyses of the risk factors for rapid progression of myopia

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
Sex						
M	1.000					
F	0.865	0.483-1.549	0.625			
Age (y)	0.894	0.771-1.037	0.138	0.868	0.679-1.110	0.259
Family history						
None	1.000			1.000		
Yes	9.635	5.006-18.546	<0.001	8.155	3.626-18.342	<0.001
Refraction basal	1.070	0.929-1.232	0.349			
Axial length basal	0.779	0.561-1.082	0.136	0.911	0.595-1.397	0.670

response to atropine in both studies. The myopia progression rate in 0.01% atropine-treated children was reported as -0.49 D at 2y by Chia *et al*[14], -0.1 D/y by Clark *et al*[15], and -0.84 D/y in our study. Compared with the previous results, the myopia progression rate of Korean children was the fastest. This difference could result from ethnic differences or cultural and/or environmental factors such as more loading near work and less outdoor activity. In this study, the myopia progression rate of 0.05% atropine used children was similar to the rate of children who used 0.01% atropine in the previous study[14]. The calculated rate, -0.84 D/y of 0.01% atropine group in our study was similar to that in control (not treated) group from a previous study by Clark[15]. This implies that higher concentrations rather than 0.01% atropine may be effective for Korean children.

In this study, we did not randomly select patients when determining the concentration of atropine. Instead, atropine was administered at a higher concentration in patients with rapidly progressing basal myopia progression. This suggests that the effect to inhibition of myopia progression of 0.025% and 0.05% atropine may be more effective than that shown in this study.

In phase 3 of the ATOM 2 study, it was reported that 0.01% atropine was the most effective inhibitor of myopia progression due to a rebound phenomenon after cessation of higher concentrations of atropine[17]. However, in Korean children, the myopia progression rate was -0.84 D/y even at 0.01% atropine, requiring higher concentrations of atropine to reduce the myopia progression rate. Therefore, it is recommended to administer higher concentration of atropine initially to Korean children with rapid myopia progression and subsequently taper with lower concentrations to minimize the incidence of rebound phenomenon.

The percentage change of the NPA and pupil size showed no

difference between the three treated groups. The poor near visual acuity was 1.1%, 3.2% and 7.5 %, and the photophobia was 3.4%, 4.8% and 10.5%, respectively, in each group. Adverse events were more frequent in the higher concentration group, even though they were not statistically significant. Gong *et al*[18] reported that a meta-analysis of high dose (1.0%) atropine was associated with more adverse effects, such as a 43.1% incidence of photophobia compared with 6.3% for low dose (0.01%) atropine, although the lower dose atropine resulted in fewer side effects and less discomfort in children using eye drops. It may, therefore, be preferable and comfortable to use low dose atropine as much as possible. However, treatment with 0.01%, 0.025% and 0.05% atropine showed no statistical difference in the prevalence of side effects, so percentages as high as 0.05% can be used relatively safely.

Many genetic and environmental parameters/experiences have been shown to be associated with the prevalence of myopia, including higher education, a large amount of near work, socioeconomic status, the level of outdoor activity, and a low birth weight[19-24]. A family history of myopia and ethnicity are also recognized as risk factors for myopia[25-29]. Liang *et al*[30] confirmed that when there was a high myopic parent, the OR of the children developing mild or moderate myopia was 2.5-3.7 (95%CI, 1.1-6.5) and the OR of having high myopia was 5.5 (95%CI, 3.2-12.6). A strong association between parental myopia and the axial length in their children was also found. A 23-year clinical follow-up study confirmed that when parents had high myopia, their children's myopia progression rate was faster and the final adulthood SE was more myopic[31]. In the present study, the factors associated with rapid myopia progression were also analyzed. Age, sex, a degree of basal refraction, and axial length were not associated with the rate of myopia progression. Only a family history of high myopia was associated with rapid myopia progression (OR, 8.155; 95%CI, 3.626-18.342; P<0.001). It is still possible that the association with parental myopia is, at least in part, the result of shared environmental influences. Despite considerable missing data for this parameter, our estimates of the effect of parents and high myopia were consistent with previous studies. Children with high myopic parents were more likely to have rapid myopia progression and were more appropriate candidates for the use of diluted atropine.

There were several limitations in this study. This study was a retrospective study conducted by a single institution. The study population of this study is quite homogeneous, and the sample size of each atropine treated group is different. However, we performed a comparative study using three different concentrations of diluted atropine to reveal the dose-response relationship, which is a strength. To better understand the relationships between different concentrations and their effects, we should conduct a prospective study using atropine at additional concentrations between 0.01%-0.05%.

In summary, this study showed that the use of diluted atropine solutions inhibited myopia progression in a dose-dependent manner in Korean children. Korean children need appropriate strategies involving the appropriate concentration of atropine eye drops and the optimal duration of use for myopia control. Furthermore, patients with a family history of high myopia need to be treated with higher concentrations of atropine to prevent rapid myopia progression.

ACKNOWLEDGEMENTS

Foundation: Supported by the Catholic Medical Center Research Foundation made in the program year of 2018 (No.5-2018-B0001-00006).

Conflicts of Interest: Moon JS, None; **Shin SY,** None.

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