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Website: www.e-tjo.org
DOI: 10.4103/tjo.tjo_110_18

Short-term refractive and ocular parameter changes after topical atropine

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Abstract:

PURPOSE: The purpose of this study is to explore short-term refractive and ocular parameter changes and their correlations after cycloplegia with atropine.

MATERIALS AND METHODS: This is a prospective clinical trial that enrolled 96 eyes of 96 participants (mean age, 8.5 ± 2.1 years). Spherical equivalent refractive error (SER), axial length (AL), mean keratometric value (mean-K), anterior chamber depth (ACD), and intraocular pressure (IOP) were measured at baseline and 1 week after topical use of 0.125% atropine. Postcycloplegic changes of refractive error and ocular parameters were evaluated, and their correlations were analyzed with multiple linear regression models.

RESULTS: After topical atropine use, the mean AL decreased by 0.016 mm ($P = 0.008$), and the mean ACD increased by 0.58 mm ($P < 0.0001$). There was no significant change in the Mean-K or IOP. Eighty-two eyes (85%) had an emmetropic or hyperopic shift, and 14 (15%) had a myopic shift. Those with an emmetropic or hyperopic shift had their mean AL shortened by 0.023 mm, whereas the eyes with myopic shifts had their mean AL lengthened by 0.026 mm ($P = 0.003$). Change in SER was negatively correlated with change in AL (-2.57 D for an increase of 1 mm in AL, $P < 0.001$) and positively correlated with change in ACD ($+0.96$ D for an increase of 1 mm in ACD, $P = 0.013$).

CONCLUSION: Most eyes had emmetropic or hyperopic changes after short-term topical atropine use, and AL shortening and anterior chamber deepening both contributed to the hyperopic changes. Meanwhile, myopic change may be observed in some eyes (15%), which were related to transient AL elongation but not invalid myopic control. This encouraged clinicians to sustain the atropine treatment for a longer period before switching to other modalities for myopic control in clinical practice.

The clinical trial registration number NCT03839888 (clinicaltrials.gov).

Keywords:

Anterior chamber depth, atropine, axial length, cycloplegia, refraction

Introduction

Myopia is a significant public health issue due to its high prevalence worldwide; the condition affects about 25% of adults in the United States and Europe and up to 80% of schoolchildren in Asia regions such as Taiwan, Hong Kong, and Singapore.^[1-4] In Taiwan, from 1983 to 2000, the prevalence

of myopia in schoolchildren and adolescents increased with the mean spherical equivalent refractive (SER) deteriorating from -0.48 to -1.45 D in 12-year-old.^[2] Moreover, the proportion of high myopia (over -6.0 D) among 18-year-old also increased from 10.9% in 1983 to 21% in 2000.^[2] Given the swift increase in prevalence and severity of myopia, various interventions have been used to slow myopic progression.^[5] Atropine, a powerful cycloplegic drug, is widely used in Asian countries for myopic control. It has been shown to reduce myopic progression

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How to cite this article: Ho MC, Hsieh YT, Shen EP, Hsu WC, Cheng HC. Short-term refractive and ocular parameter changes after topical atropine. Taiwan J Ophthalmol 2020;10:111-5.

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Submission: 13-09-2018

Accepted: 08-12-2018

Published: 20-02-2019

by 77% compared with a placebo.^[6-8] According to a report by Lin *et al.*, atropine use significantly decreased myopic progression in Taiwan in recent years with the prescription rate of atropine increasing from 36.9% in 2000 to 49.5% in 2007.^[9,10] Many studies had shown its efficacy in preventing myopic progression in children.^[11-13]

Pharmacologic mechanism of atropine involves blocking the muscarinic action of acetylcholine and inhibiting cholinergic stimulation of the ciliary muscle and iris sphincter, which results in cycloplegia and mydriasis.^[14] Besides backward lens movement and decreased lens thickness (LT), additional elastic deformation of the globe, and other ocular parameter changes may occur because of paralysis of the ciliary muscle after cycloplegia. Since corneal curvature (CC), anterior chamber depth (ACD), lens curvature, and axial length (AL) all contribute to the refractive status, it would be interesting to determine if the cycloplegic refractive change is due to changes in ocular parameters other than lens curvature. Ourselves and other studies had previously studied the short-term effect of tropicamide on the refractive status and ocular parameters of children.^[15-17] However, the correlations between the changes of refractive status and these ocular parameters after short-term use of atropine have not been well documented.

In this study, we evaluate the changes of refractive status and ocular parameters as well as the correlations between them after 1 week of topical atropine use.

Methods

Study population

All patients aged 3–18 years who visited Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, for a regular visual examination between January 2015 and December 2015 were candidates for this study. Refraction was measured using an automatic refractometer, Topcon KR-8800 (Topcon, Tokyo, Japan). SER error was calculated as follows: SER = sphere + cylinder/2. AL, CC, and ACD were measured with IOLMaster Version 4.0 machine (Carl Zeiss Meditec, Dublin, CA, USA), and keratometric (K) values were obtained by converting the radius of the CC into a diopter value using a corneal conversion refractive index ($n = 1.3375$). A mean-K value (mean-K) was calculated as the mean of the maximum and minimum K values. Intraocular pressure (IOP) was measured with a noncontact tonometer (CT-80; Topcon Corporation, Tokyo, Japan).

For those who had an SER of -0.5 D or less in their eyes, their parents were informed of the nature and possible consequences of the study. Their parents were also informed of the treatment effects of topical atropine for myopic control, as well as potential side effects, including

photophobia, near blurred vision, and retinal damage. Those patients who had already been undergoing cycloplegic treatment for myopia were excluded from this study. A written informed consent was obtained from all the parents of the study participants at the time of study enrollment.

After enrollment, the patients were given 0.125% atropine eye drops (Aseptic Innovative Medicine Co, Ltd) once nightly for their myopic eye. Following the use of topical atropine for 1 week, the patients returned to the clinic for follow-up examinations to obtain their SER, AL, ACD, mean-K, and IOP. If the SER of the eyes increased more than -0.5 D, the topical atropine treatment was discontinued; otherwise, the topical atropine treatment was continued following our clinical principle for myopia control. If both eyes of the same patient were qualified for the study, only the left eye was enrolled for study. However, the right eye would be given the same treatment if it was also myopic. This study followed the tenets of the Declaration of Helsinki, and Institutional Review Board approval was obtained from the IRB of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation (IRB 03-XD17-041).

Statistical analysis

All descriptive statistics are expressed as mean \pm standard deviation. Paired *t*-tests were used to compare the measured parameters before and after topical atropine use. T-tests were used to compare the ocular parameter changes between two groups (emmetropic/hyperopic shift versus myopic shift after topical atropine use). Multiple linear regression models were used to evaluate the effect of ocular parameter changes on refractive changes after cycloplegia with atropine. A value of $P < 0.05$ was considered statistically significant. SAS 9.4 computer software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

A total of 96 eyes from 96 patients were enrolled in this study. The mean age was 8.5 ± 2.1 years (range, 3–14 years), and 56% of the patients were female. Table 1 shows the mean SER and ocular parameter values for the 96 eyes before and after topical atropine use. The mean SER value was -1.810 ± 1.105 D before cycloplegia; after treatment with 0.125% atropine for 1 week, the mean SER had positively shifted to -1.496 ± 1.144 D ($P < 0.001$ by paired *t*-test). Of the 96 eyes, 82 (85%) had an emmetropic or hyperopic shift, and 14 (15%) had a myopic shift after cycloplegia with atropine.

The mean AL decreased from 24.082 ± 0.933 mm to 24.066 ± 0.937 mm ($P = 0.008$ by paired *t*-test), and the mean ACD increased from 3.586 ± 0.199 mm to

3.644 ± 0.185 mm ($P < 0.001$ by paired t -test) after topical atropine use for 1 week. As for the mean-K and IOP, they did not significantly change.

Emmetropic/hyperopic shift versus myopic shift after cycloplegia with atropine

For eyes that had an emmetropic or hyperopic shift in SER after treatment with topical atropine, the change in standard error (SE) was 0.41 ± 0.34 and the mean AL decreased by 0.023 ± 0.056 mm; however, the change in SE was -0.27 ± 0.11 ($P < 0.001$ by t -test) and the mean AL increased by 0.033 ± 0.058 mm ($P = 0.003$ by t -test) for eyes with a myopic shift in SER after using topical atropine. As for the ACD and mean-K, changes after cycloplegia with atropine did not differ significantly between these two groups ($P = 0.16$ and 0.91 , respectively, by t -tests) [Figure 1].

Correlations between refractive changes and ocular parameter changes after cycloplegia with atropine

Multiple regression models were used to evaluate correlations between refractive and other ocular parameter changes after cycloplegia with atropine. As shown in Table 2, change in SER was negatively correlated with change in AL (-2.57 D for an increase of 1 mm in AL, $P < 0.001$) and positively correlated with change in ACD ($+0.96$ D for an increase of 1 mm in ACD, $P = 0.013$). Refractive change was not significantly correlated with change in CC.

Discussion

In this study, we found an increase in mean SER and mean ACD with a decrease in the mean AL after

1 week of topical atropine use. AL is the distance from the anterior cornea to the retina; specifically, it is the summation of the central corneal thickness, ACD, LT, and vitreous cavity depth (VCD). However, distinct changes in AL after cycloplegia differed among various studies. Huang *et al.* reported an increase in ACD but not the AL 1 h after instillation of 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P) in adults.^[18] Another comparable study by Chang *et al.* showed ACD deepening and angle-to-angle widening without AL changes after 1% tropicamide use in adult participants.^[19] In contrast to the adult group in which the AL does not change after tropicamide use, the

Table 1: Spherical equivalent of refractive error and ocular parameters after 1 week use of topical 0.125% atropine

	Before cycloplegia	After 0.125% atropine	P
SER (D)	-1.810±1.105	-1.496±1.144	<0.0001
AL (mm)	24.082±0.933	24.066±0.937	0.008
ACD (mm)	3.586±0.199	3.644±0.185	<0.0001
Mean-K (S)	43.456±1.345	43.472±1.362	0.22
IOP (mmHg)	16.05±2.68	16.17±2.98	0.80

ACD = Anterior chamber depth, AL = Axial length, IOP = Intraocular pressure, Mean-K = Mean keratometric value, SER = Spherical equivalent of refractive error

Table 2: Multiple linear regression analysis for factors correlating with refractive changes after one week use of topical 0.125% atropine

	SER change (D)	
	Coefficient	P
AL change (mm)	-2.57±0.73	0.0007
ACD change (mm)	0.96±0.38	0.013
Mean-K change (D)	0.59±0.31	0.061

ACD = Anterior chamber depth, AL = Axial length, Mean-K = Mean keratometric value, SER = Spherical equivalent of refractive error

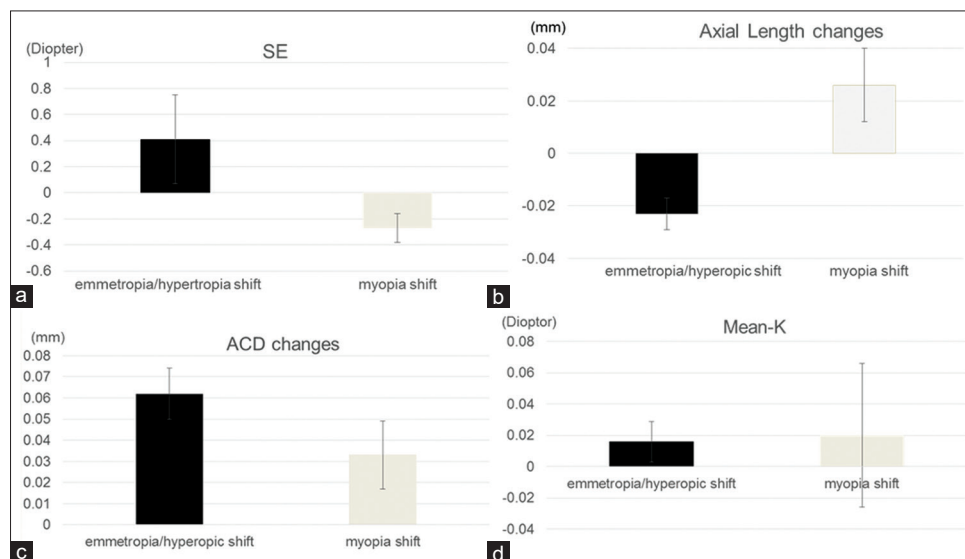


Figure 1: Comparisons of changes of (a) spherical equivalent, (b) axial length, (c) anterior chamber depth, and (d) mean keratometric value between eyes with emmetropic/hyperopic shift and eyes with myopic shift after one week use of topical 0.125% atropine. Standard errors were shown as the error bars

globes of schoolchildren seem more susceptible to the influence of cycloplegia. Our previous study showed a 0.06-mm decrease of AL after tropicamide use,^[15] which is supported by others also demonstrating varying degrees of decrease in AL after cycloplegia in schoolchildren^[8,20] About the possible mechanism for the decrease of the AL, there might be real reversal of the eyeball growth due to change in choroidal or scleral thickness. Further studies are required to clarify the true cause of the AL shortening. According to the study by Coudrillier *et al.*,^[21] older age was associated with greater stiffness of the matrix within eyeballs. The globe may, therefore, be less likely to change in AL especially in adults after cycloplegic treatment. Therefore, our study is aimed at understanding the changes in ocular parameters after short-term atropine use in myopic children.

Since the net refraction status is the combined effect of several biometric parameters, including CC, ACD, lens curvature, and VCD, analysis of how changes in each ocular parameter contribute to the net refraction status after atropine use may be helpful in understanding the mechanism of atropine in myopic control. In previous studies, an increased ACD ranging from 0.05 mm to 0.08 mm resulted from backward lens movement and decreased LT during cycloplegia.^[11,18-20] In a study by Gao *et al.*,^[22] the ACD increased to 0.12 mm after a twice-daily atropine ointment application for 5 days. The study is in agreement with these studies and demonstrated a mean ACD increase of 0.058 mm after atropine use. We also demonstrated that the change in SER after atropine use was positively correlated with the change in ACD, which is reasonable due to the posterior shift of the lens.

In this study, we found that the changes in AL after atropine use in cycloplegia are significantly correlated with the changes in SER by multiple regression analysis. Change in SER was negatively correlated with change in AL (-2.57 D for an increase of 1 mm in AL, $P < 0.001$) and positively correlated with change in ACD (+0.96 D for an increase of 1 mm in ACD, $P = 0.013$). The AL elongation 1 week after cycloplegia by atropine resulted in a myopic shift in some patients, even as the lens curvature flattens. However, analysis between the emmetropic or hyperopic group and myopic shift group did not find a significant difference in the change of ACD. Although most children showed a decrease in AL after 1 week of topical atropine, a small percentage (15%) of the eyes had short-term myopic shift with an increase in AL. A postcycloplegic myopic shift (2.6%) after tropicamide use had been observed in our previous study.^[15] A possible explanation for this phenomenon may be a posterior shift of lens-ciliary body diaphragm that caused a compressive force pushing toward the vitreous cavity to result in a temporary AL elongation 30 min after

installation of tropicamide. Other mechanisms for this temporary myopic shift are still required.

Because the long-term effect of atropine in preventing AL elongation and myopic progression has been well documented, atropine for myopic control in children is a routine clinical practice in Asian countries.^[10,23-27] Several studies showed its safety in the follow-ups of IOP and other ocular parameters by OCT.^[28,29] However, there has not been a set guideline or consensus for follow-up schedules after initiating atropine eye drops. With this study, we found that 15% of the children may actually show an increase in AL and myopic shift during the 1-week follow-up visit. This should not deter clinicians from continuing to use topical atropine as its long-term efficacy has been shown. Future long-term follow-ups are particularly advised for these children to determine their myopic control.

There were some limitations in this study. We had only followed the patients immediately after 1 week of atropine instillation; the exact durations of the temporary myopic shift in some patients could not be determined. A further longitudinal study of these children with myopic shift should be conducted to find out how long the myopic shift will persist or when it will revert. In addition, our study lacks a control group, which is very difficult to obtain IRB approval as atropine treatment is the mainstay routine clinical treatment for myopia in Taiwan.

Conclusions

Most eyes had emmetropic or hyperopic changes with a significant decrease in AL and increased in ACD after 1 week of topical atropine use. AL shortening and anterior chamber deepening both contribute to the hyperopic change. For those eyes with myopic shift 1 week after atropine use, transient AL elongation is found. Such myopic shift may be a temporary phenomenon, and continual atropine use may be suggested in these children with close observation of their myopic control. Longer follow-up period should be done before switching to other myopic treatment modalities.

Acknowledgment

This study was supported by a grant from Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan (TCRD-TPE-104-63). The sponsor had no role in the design or conduct of this research. The authors have no potential conflicts of interest to disclose.

Financial support and sponsorship

This study was supported by a grant from Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation,

New Taipei, Taiwan (TCRD-TPE-104-63). The sponsor had no role in the design or conduct of this research. The authors have no potential conflicts of interest to disclose.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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