A Real-World Study on Myopia Control 6 Months After Withdrawal of 1% Atropine Eye Gel

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Abstract

Purpose: This study aimed to observe the changes in spherical equivalent and ocular axial length 6 months after withdrawal of 1% atropine eye gel.

Methods: Due to COVID-19, the follow-up of patients in our optometric clinic who were undergoing myopia control treatment with a dropwise 1% atropine "5+3" regimen was interrupted. No return visit was made after the 3 months of at-home treatment, and follow-ups resumed 6 months after treatment withdrawal. The contralateral eye was not treated over the 9-month period. A total of 16 patients aged 11.5 years (average) were enrolled from November 2019 to March 2021 during the COVID-19 pandemic. The treated eyes formed a treatment group (16 eyes) and the contralateral eyes formed a control group (16 eyes). The changes in spherical equivalent, ocular axial length, and intraocular pressure (IOP) were compared between groups.

Results: After 9 months, the changes in spherical equivalent were significantly less in the treatment group (0.00 ± 0.20 [D]) compared to the control group (-0.67 ± 0.25 [D]) (P<0.05). The ocular axial length changes were significantly less in the treatment group (0.00 ± 0.06 mm) compared to the control group (0.25 ± 0.11 mm) (P<0.05). There was no significant difference between the two groups for changes in IOP.

Conclusions: Despite treatment withdrawal after 3 months, treatment with 1% atropine eye gel successfully controlled myopia progression in the 6 months after withdrawal, as evidence by no rebound increase in myopic spherical equivalent after the withdrawal.

Keywords: myopia progression, 1% atropine, rebound， spherical equivalent; ocular

axial length

Introduction

Atropine application for clinical treatment of myopia dates back to the 1980s, representing a history of more than 40 years.[1] In current clinical application, low-concentration atropine (mainly 0.01%) has few side effects and is currently recommended as the first choice treatment for myopia,[2] but some studies suggest that its efficacy in myopia control is limited.[3] Although 1% atropine has obvious curative advantages in myopia control, its clinical application is limited because of concerns about its side effects such as withdrawal rebound, photophobia, and blurred near vision.[4-6]

In order to reduce the side effects of 1% atropine and improve patient compliance with treatment, in our institution, treatment is performed on alternating eyes, namely continuous administration of 1% atropine on one eye for 3 months, followed by a return visit to observe the status of myopia control, and then the contralateral eye is administered continuous treatment for 3 months. For some patients, the COVID-19 outbreak occurred during the course of their treatment in 2020. Due to the risk of patients becoming infected with COVID-19 when attending the hospital for treatment, medication with 1% atropine eye gel was suspended after 3 months on the first eye, and patients did not return to the hospital until the pandemic was contained 6 months after withdrawal of the medication. The myopia progression in these patients is reported in the present study.

Methods

General information

Patients who received 3 months of treatment with 1% atropine on one eye, followed by no treatment for 6 months during the period of November 2019 to March 2021 were enrolled. The treated eyes formed a treatment group, and the contralateral eyes formed a control group. The changes in spherical equivalent, ocular axial length, and intraocular pressure (IOP) were observed in both groups. The study was approved by the Medical Ethics Committee of Shanghai Eye Disease Prevention & Treatment Center. The methodology and privacy protection of the present study were introduced to all guardians and children in detail before data collection, and they provided informed consent for participation and publication of their data.

Treatment regimen

In the treatment group, 1% atropine eye gel was administered dropwise for 5 consecutive days in the 1st week of each month, followed by 1 day per week in the 2nd, 3rd, and 4th weeks of the same month, and this treatment pattern was repeated for 3 months, followed by 6 months of no medication and then a return visit. In the control group, no myopia control measures were adopted during the 9 months from the initial visit to the return visit. See Figure 1 for details of the treatment regimen. At the initial and return visits, the following indicators were examined: spherical equivalent (ARK-1; NIDEK, Tokyo, Japan); ocular axial length; anterior chamber depth; lens depth (IOLMaster, version 5.02; Carl Zeiss, Jena, Germany); choroidal thickness (DRI OCT-

1 Atlantis; Topcon Inc., Tokyo, Japan); and IOP (non-contact IOP sensor, NT-510, NIDEK, Japan).

Statistical analysis

For descriptive analysis, normally distributed continuous data were presented as a mean ± standard deviation, non-normally distributed continuous data as a median with quartiles, and categorical data as a constituent ratio. Comparison between the treated and contralateral eyes at baseline and changes in equivalent spherical and ocular axial length were performed using a paired t-test. Differences were assessed in terms of point estimates with 95% confidence intervals (95% CI) using a two-tailed test, with $P<0.05$ indicating a statistically significant difference.

Results

Baseline patient information

A total of 16 patients were enrolled, including seven males (43.8%) and nine females (56.3%). Ages ranged from 8.5 years to 15.9 years with a mean of 11.5 years. There was no significant difference in baseline IOP between the treatment and control groups. Spherical equivalent was significantly less ($P<0.05$) in the treatment group (-1.58 ± 1.02 D) than in the control group (-0.73 ± 1.29 D) at baseline. Mean ocular axial length was significantly longer ($P<0.05$) in the treatment group (24.56 ± 0.95 mm) than in the control group (24.12 ± 0.95 mm) at baseline. See Table 1 for details.

Changes in eye parameters in the treatment and control groups over the 9-month period

The changes in spherical equivalent, ocular axial length, and IOP in the treatment group after 9 months were -0.05 ± 0.19 (6%), 0.00 ± 0.06 (0%), and 1.19 ± 2.17 (9%), respectively, with only the change in IOP being statistically significant (P<0.05). In the control group, the changes after 9 months were -0.71 ± 0.26 (55%), 0.25 ± 0.11 (1%), and 0.19 ± 2.01 (2%), respectively, with the first two being statistically significant (P<0.05) (Table 1, Figure 2). Anterior chamber depth increased (0.12 ± 0.27) in the treatment group and decreased (-0.04 ± 0.05) in the control group, representing a statistically significant change in both groups. Choroidal thickness showed an increasing trend in the treatment group and a decreasing trend in the control group, while the changes were statistically insignificant.

Comparison between the degree of change in eye parameters in the treatment and control groups over the 9-month period

After 9 months, the changes in spherical equivalent were -0.05 ± 0.19 and -0.71 ± 0.26 in the treatment and control groups, respectively. The changes in ocular axial length were 0.00 ± 0.06 and 0.25 ± 0.11, respectively. These spherical equivalent and ocular axial length results indicated a significantly smaller change (better result) in the treatment group compared to the control group (paired t-test; P<0.05) (Table 2 and Figure 3). The degree of change in IOP between the groups was statistically insignificant (1.00 [95% CI: -0.17, 2.17], P>0.05). Relative to the control group, the 9-month changes in anterior chamber depth and lens thickness in the treatment group were significantly better (P<0.05) (0.16 [95% CI: 0.01, 0.31] and -0.07 [95% CI: -0.11,

-0.02], respectively), with an increase in anterior chamber depth and a decrease in lens thickness in the treatment group. The 9-month changes in choroidal thickness did not differ significantly between the two groups, but the difference still suggested an increasing trend towards choroidal thickness in the treatment group relative to the control group (Table 2).

Discussion

Main results

The effect of 1% atropine withdrawal on myopia control has been rarely investigated. The present observation of myopia progression after 1% atropine withdrawal was unplanned. Due to the sudden COVID-19 outbreak, the myopia control clinics suspended routine outpatient follow-ups until the pandemic was contained and then it gradually resumed the outpatient visit service. Among the patients who made a return visit, only 16 had previously received 1% atropine treatment for a single eye for 3 months and then had no treatment for 6 months.

Analysis of the follow-up data of these 16 patients revealed that although 1% atropine was only administered for 3 months, its performance in controlling myopia progression was not compromised. Six months after the withdrawal of treatment, the treated eyes exhibited obvious control of myopia progression. Compared with pre-treatment baseline measurements, the spherical equivalent and ocular axial length of treated eyes were not significantly changed, but the degree of myopia and ocular axial length in control eyes showed an obvious increasing trend.

In the meantime, examination of the biological parameters of the two groups

revealed that the treatment group exhibited lens thinning, anterior chamber deepening, and choroidal thickening. However, the control group exhibited lens thickening, anterior chamber shallowing, and choroidal thinning. These results were consistent with previous findings.[8-10]

Comparison of longitudinal studies

Louis et al.[7] conducted an observational study on patients who had withdrawn from 1% atropine treatment for 1 year after 2 years of treatment, and found that the degree of myopia rebounded in the first 6 months after withdrawal, and it deepened in the last 6 months, but the progression slowed down. Over the 3-year period, the increase in spherical equivalent and ocular axial length was less in patients who withdrew from treatment compared to those who continued treatment. In the present study, as it was an observational study on an unplanned medication withdrawal, we could not measure the spherical equivalent and ocular axial length after 3 months of medication. However, the changes in relevant parameters after 9 months showed that the effects of the first 3 months of treatment with atropine persisted at 6 months after withdrawal.

Previous studies have observed ocular axis elongation and myopic drift due to ocular accommodation.[11-13] One 2009 observational study on myopia control after atropine withdrawal[7] was a follow-up of a 2006 study on pediatric patients with myopia who were treated with atropine.[14] In that study, the baseline measurements in the treatment group were the spherical equivalent and ocular axial length after 2 weeks of pupil dilation with atropine. In the placebo group, eyes were subjected to baseline

examination after pupil dilation with dropwise administration of cyclopentolate. After 2 consecutive weeks of dropwise administration of 1% atropine, the paralysis of the ciliary muscles was more complete.[15,16] When paralyzed, the ciliary muscles are relaxed, which leads to the tight pulling of the suspensory ligaments, the thinning of the lens, the shortening of the ocular axis, and a decrease in spherical equivalent.[17] This suggests that the sphere and ocular axial length of the treatment group in that study had already been significantly reduced at baseline. Therefore, as ocular accommodation recovered in the treatment group after atropine withdrawal, the spherical equivalent and ocular axial length returned to original levels as well, which was one of the reasons for withdrawal rebound in the treatment group. In the present study, we observed changes over a 9-month period in spherical equivalent and ocular axial length under small-pupil conditions in both groups, and therefore the measurement data of both groups were subjected to the same level of ocular accommodation.

Limitations

The sample size in the present study was small. Sixteen patients were treated with 1% atropine for only 3 months, and myopia progression after withdrawal of 1% atropine was measured after only 6 months. Although the treatment period was not long, its controlling effect on myopia could be maintained for 6 months after treatment withdrawal, and this has some important implications. In particular, short-term or intermittent treatment with 1% atropine may be feasible, reducing the medication frequency, and thereby reducing side effects and improving patient treatment compliance.

In the 2006 trial, dropwise administration of 1% atropine on single eyes lasted for 2 years. In the first year, spherical equivalent and ocular axial length did not increase, but spherical equivalent began to show an increasing trend in the second year. It is evident that with the extension of treatment course, the controlling effect of 1% atropine on myopia was gradually weakened, leading to a gradual increase in myopic spherical equivalent in the treatment group. The decrease in medication efficacy may be due to the further progression of myopia in adolescents, and also likely due to drug resistance after long-term treatment.[18]

In conclusion, it is necessary to optimize the treatment regimen with 1% atropine for myopia control. Attention should be paid to the problem of drug resistance after a long period of treatment with 1% atropine. The efficacy of a treatment regimen based on intermittent atropine administration for myopia control should be further verified through longer clinical observation and higher-level research designs.

Personal financial interests: **None**

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Table 1 Relevant indicators at baseline and after 9 months, and the degree of change in treated eyes and contralateral (control) eyes

Indicator	Treated eye				Contralateral eye			
	Baseline	**Nine months**	**Change**	**Relative change**	**Baseline**	**Nine months**	**Change**	**Relative change**
Sphere	-1.34±0.96	-1.34±0.96	0.00±0.20	-1.98%	-0.47±1.32	-1.14±1.3	-0.67±0.25 *	-12.81%
Cylinder	-0.37±0.5	-0.47±0.5	-0.10±0.24	-3.49%	-0.36±0.59	-0.59±0.55	-0.23±0.71	-6.25%
Spherical equivalent	-1.53±0.98	-1.58±1.02	-0.05±0.19	-6.00%	-0.73±1.29	-1.44±1.40	-0.71±0.26 *	-55.00%
Ocular axial length	24.56±0.95	24.56±0.95	0.00±0.06	0.01%	24.12±0.95	24.38±0.99	0.25±0.11 *	1.04%
Intraocular pressure	16.13±2.85	17.31±2.39	1.19±2.17 *	9.22%	16.5±1.46	16.69±1.96	0.19±2.01	1.57%
Best-corrected visual acuity	1±0	1±0	0±0	0.00%	1±0	1±0	0±0	0.00%
Corneal thickness	550.75±36.57	549.69±38.17	-1.06±8.44	-0.20%	549.75±38.34	548.69±38.36	-1.06±7.84	-0.18%
Anterior chamber depth	3.75±0.24	3.87±0.32	0.12±0.27 *	3.39%	3.73±0.22	3.69±0.24	-0.04±0.05 *	-1.08%
Lens thickness	3.32±0.14	3.28±0.13	-0.04±0.05	-1.22%	3.32±0.13	3.35±0.16	0.03±0.06	0.82%
Choroid (C)	250.06±41.31	261.73±62.44	13.47±51.98	6.21%	232.44±40.98	226.4±47.79	-6.53±22.93	-2.73%
Choroid (N)	224.06±41.98	222.93±52.62	0.73±48.66	1.89%	196.19±35.21	197.47±46.97	1.47±24.24	-0.40%
Choroid (T)	273.5±44.51	284.67±59.82	14.6±34.91	5.44%	252.13±43.99	246.07±55.46	-4.93±27.61	-2.09%
Choroid (U)	243.56±36.22	237.33±54.79	-1.2±42.51	-0.61%	238.44±38.13	228.73±56.27	-9.27±30.01	-4.56%
Choroid (D)	249.75±36.99	258.8±53.77	11.47±42.17	5.05%	228.25±37.34	213.33±54.54	-13.87±31.43	-6.66%

*Paired t-test, $P<0.05$

Table 2 Comparison of 9-month degree of change in treated eyes and contralateral (control) eyes

Indicator	Baseline difference between treated eyes and contralateral eyes (95% CI)	Degree of change between treated eyes and contralateral eyes over 9 months (95% CI)
Sphere	-0.88 (-1.28, -0.47)*	0.67 (0.48, 0.86)*
Cylinder	0.14 (-0.02, 0.30)	0.14 (-0.28, 0.55)
Spherical equivalent	-0.80 (-1.17, -0.44)*	0.66 (0.48, 0.85)*
Ocular axial length	-0.25 (-0.33, -0.17)*	-0.25 (-0.33, -0.17)*
Intraocular pressure	-0.38 (-1.36, 0.67)	1.00 (-0.17, 2.17)
Best-corrected visual acuity	0	0
Corneal thickness	1.00 (-4.29, 6.29)	0.00 (-3.87, 3.87)
Anterior chamber depth	0.02 (-0.01, 0.05)	0.16 (0.01, 0.31)*
Lens thickness	-0.00 (-0.03, 0.02)	-0.07 (-0.11, -0.02)*
Choroid (C)	17.63 (-10.65, 45.90)	20.00 (-12.98, 52.98)
Choroid (N)	27.88 (-3.75, 59.50)	-0.73 (-31.30, 29.83)
Choroid (T)	21.38 (-5.45, 48.20)	19.53 (-9.18, 48.24)
Choroid (U)	5.13 (-17.49, 27.74)	8.07 (-21.76, 37.89)
Choroid (D)	21.50 (-3.37, 46.37)	25.33 (-4.40, 55.07)

*Paired t-test, $P<0.05$

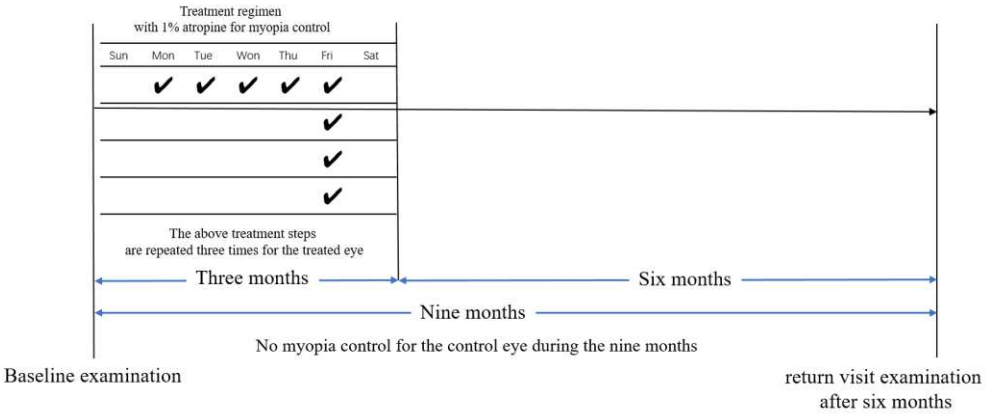

Figure 1 Treatment regimen with 1% atropine

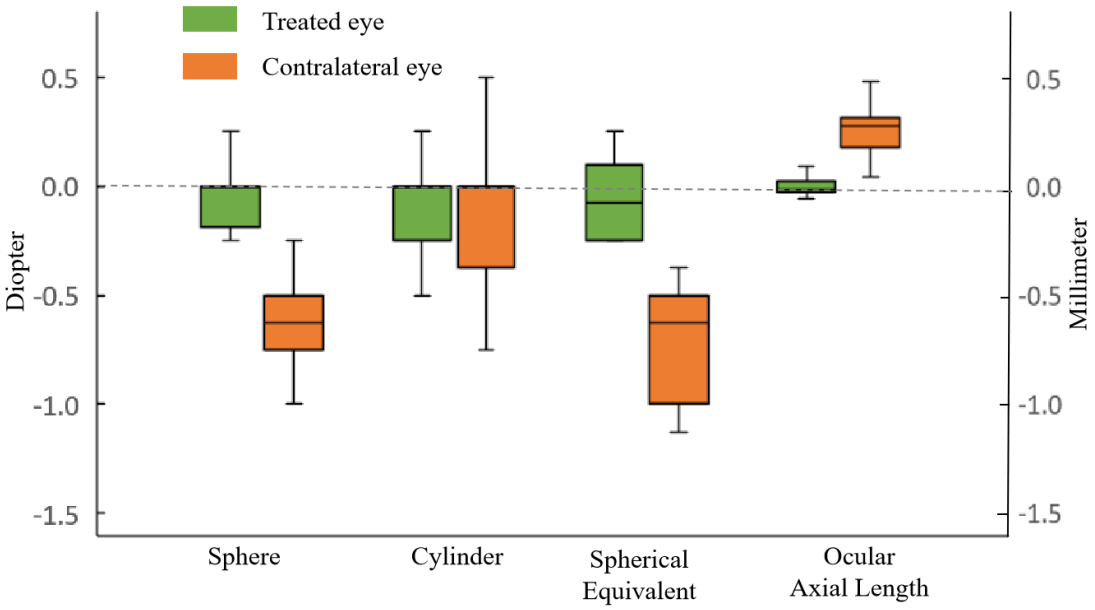

Figure 2 Box plots of the changes in relevant indicators in treated eyes and contralateral (control) eyes. The left axis indicates the for sphere, cylinder, and spherical equivalent in diopters (D), and the right axis indicates the ocular axial length in mm.

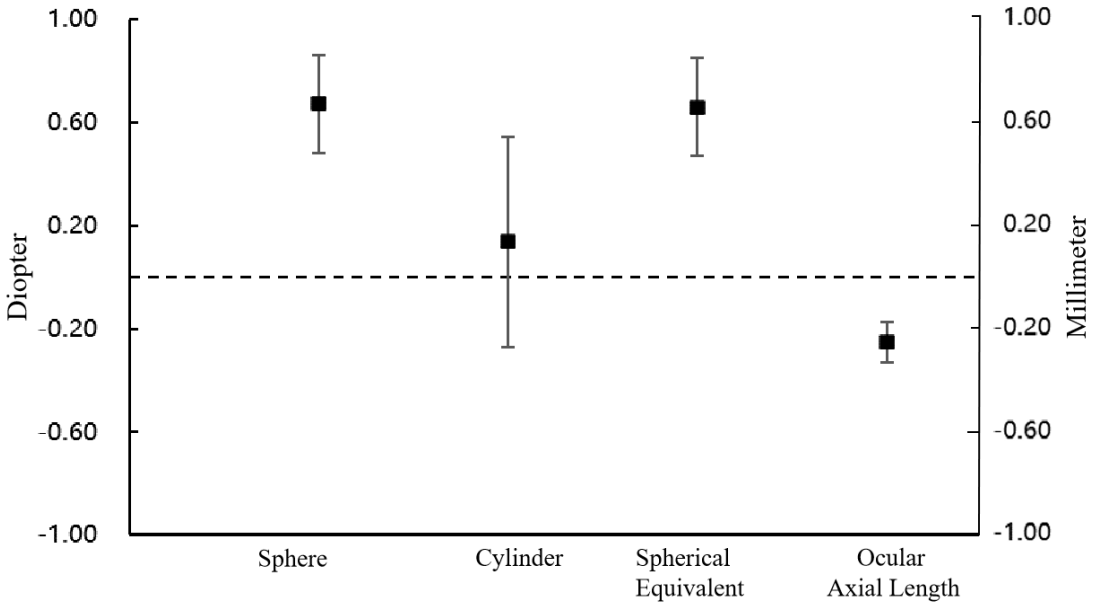

Figure 3 Mean difference (95% CI) between treated eyes and contralateral (control) eyes for 9-month changes in sphere, cylinder, spherical equivalent, and ocular axial length. The left axis indicates the sphere, cylinder, and spherical equivalent in diopters (D), and the right axis indicates the ocular axial length in mm.