ORIGINAL ARTICLE

Safety and efficacy of atropine treatment for slowing myopia progression in children: a 5-year review

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Abstract

Aim: To report the efficacy and safety of atropine treatment (0.01% and 0.125%) in slowing myopia progression in children.

Methods: This is a retrospective non-interventional case series. All patients aged <18 years who received topical atropine for myopia control from 2011 to 2016 in the Hong Kong Sanatorium & Hospital were included for analysis. Myopia progression, atropine treatment, and other factors affecting treatment outcomes were analyzed. We also reported any adverse effects associated with atropine use.

Results: A total of 346 patients were recruited, with mean a follow-up period of 2.26±0.82 years. The patients had a mean reduction of myopia progression of 68.4% after atropine treatment (p<0.001). The mean myopia progression rate (in spherical equivalent) was -0.38±0.36 D/year, and the mean axial length elongation rate was 0.23±0.19 mm/year. More reduction of myopia progression was associated with baseline myopia progression of <-1 D/year (p<0.001) and initial atropine dosage of 0.125% (p<0.001). Reduction of myopia progression was associated with starting age (p=0.041) and baseline myopia progression (p=0.004). Patients aged <6 years who received atropine treatment (n=17) showed reduction of myopia progression by 71.1%. Only mild adverse effects such as photophobia were reported.

Conclusion: Topical atropine is an efficacious and safe treatment for slowing myopia progression.

Key words: Atropine; Axial length, eye; Myopia; Refractive errors

Background

Myopia is the most common refractive error and a major public health problem worldwide.[1-4] A study conducted in Hong Kong showed 36.71% of children aged 5 to 16 years (n=7560) had myopia.[3] In a prospective cohort study in Singapore,[2] the 3-year cumulative incidence rates of myopia were 47.7%, 38.4%, and 32.4% for children aged 7, 8, and 9 years, respectively, and Chinese had the highest 3-year cumulative incidence rate of myopia, compared with Malays and Indians.

Various methods are effective in slowing myopia progression, including pharmacological treatments (atropine and pirenzepine), optical interventions (peripheral defocus modifying contact lenses, progressive addition spectacle lenses), and orthokeratology. A meta-analysis in 2016 reported that topical use of atropine is the most effective.[4]

Atropine is a nonspecific muscarinic antagonist. Two randomized control trials have shown that topical application of atropine significantly reduces myopia progression, in terms of spherical equivalent (SE) progression and axial length (AL) elongation.[1,5] A daily dose of 1% atropine reduced myopia progression to -0.28 D over 2 years, compared with -1.20 D in the placebo group (p<0.001).[5] Atropine in 0.5%, 0.1%, and 0.01% concentrations reduced myopia progression to -0.30 D, -0.38 D, and -0.49 D, respectively.[1] Nevertheless, the exact mechanism of how atropine inhibits myopia progression remains unclear.[1,4]

In clinical practice, dosage of atropine may be titrated according to the clinical response. A step-down approach (rather than immediate discontinuation) may be used to reduce the effect of rebound of myopia progression after discontinuation of the medication. However, there were different opinions regarding the dose-dependent effect of

atropine treatment. Yam et al[6] showed the dose-dependent effect in low-dose atropine treatment, whereas Gong et al[7] showed that only adverse effects, rather than efficacy, of atropine, are dose-dependent.

In the present study, we aim to evaluate the efficacy and safety of topical atropine (with or without dosage titration) in myopia control in a large cohort of pediatric patients.

Methods

This study is a retrospective non-interventional case series. Patients aged <18 years who received topical atropine of any concentration for myopia control from 2011 to 2016 in the Hong Kong Sanatorium & Hospital, Hong Kong and were followed up for ≥1 year were included for analysis. Data were extracted from the electronic system of the hospital. Approval was obtained from the institutional review board (Reference number: RC-2018-28), and the study was conducted in accordance with the principles of Declaration of Helsinki.

The following data were collected: demographics (sex, age, date of birth), ophthalmic history, past health, parent with history of high myopia (defined as myopia of ≥-6 D), baseline ophthalmic data (visual acuity, cycloplegic refraction, AL (measured by IOL Master, Carl Zeiss), atropine regimen (frequency and concentration), subsequent titration of treatment regimen, adverse effects, and ophthalmic parameters (AL and SE) of first 3 years and most recent follow-up.

SE progression and AL elongation after treatment were calculated as the difference in measurements between the beginning and end of treatment divided by the treatment period (in years). Baseline SE progression was defined as the mean change in SE by cycloplegic refraction over 1 or 2 years before atropine treatment.

Statistical analysis was performed using SPSS (Windows version 22.0; IBM Corp., Armonk [NY], United States). Only one eye from each patient was selected at random for analysis. Normality of data distribution was assessed with Kolmogorov-Smirnov statistic. Changes in SE and AL were analyzed with paired *t* test. Factors that may affect reduction of myopia progression was determined with Student's *t* test or Mann-Whitney *U* test according to normality of data distribution. Correlations between reduction of myopia progression and various factors were analyzed with Pearson correlation and analysis of covariance. Level of significance was defined as $p<0.05$.

Results

A total of 346 eyes from 346 children (161 male and 185 female) were included for analysis (**Table 1**). Of them, 254 children were initially prescribed a daily dose (n=244) or twice daily dose (n=10) of 0.01% atropine eye drops (Aseptic Innovative Medicine, Taiwan), 90 children were initially prescribed a daily dose (n=88) or 2 doses per week (n=2) of 0.125% atropine eye drops, and the remaining two children were initially prescribed 0.02% and 0.5% atropine (after dilution of 0.125% and 1% atropine with lubricant eye drops, respectively). The mean baseline SE was -3.72±2.5 D and AL was 24.73±1.13 mm. The mean follow-up period was 2.26±0.82 years.

The mean SE at the latest follow-up visit was -4.54±2.51 D, and the mean SE progression reduced to -0.38±0.36 D/year during atropine treatment from -1.20±0.70 D/year at baseline (68.4%; $p<0.001$). The AL elongation during atropine treatment was 0.23±0.19 mm/year. The distribution of the rate of SE progression changed after atropine treatment, with most

Table 1. Demographic data and baseline parameters of patients receiving atropine for myopia control (n=346)

Baseline parameter	Value*
Sex	
Male	161 (46.5)
Female	185 (53.5)
Laterality†	
Right eye	184 (53.2)
Left eye	162 (46.8)
Parent with high myopia	119 (34.4)
Age of starting atropine, y	8.64±2.19
Visual acuity, logMAR	0±0.07
Axial length, mm	24.73±1.13
Spherical equivalent, D	-3.72±2.5
Baseline spherical equivalent progression, D/y	-1.2±0.7
Follow-up, y	2.26±0.82
Ophthalmic health	
Intermittent exotropia	10 (2.9)
Amblyopia	2 (0.6)
Retinal break	2 (0.6)
Ptosis + superior oblique palsy	1 (0.3)
Cataract	1 (0.3)
Epiblepharon	1 (0.3)

* *Data are presented as mean±standard deviation or No. (%) of patients*
† *Only one eye from each patient was selected at random for analysis*

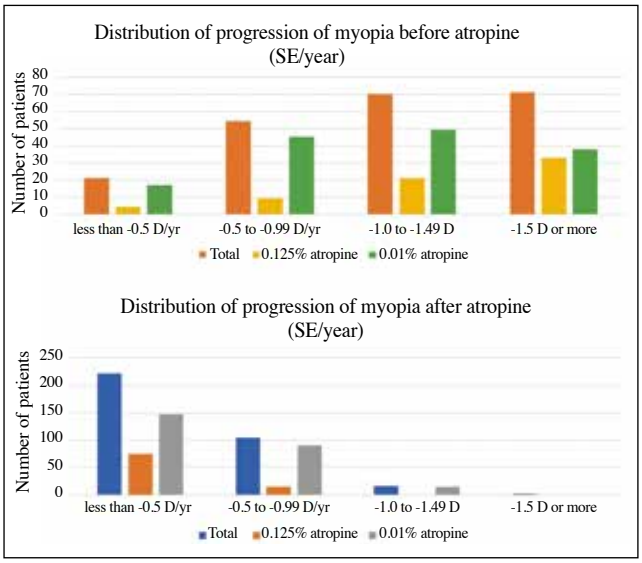

Figure. Patient distribution of myopia progression (in spherical equivalent [SE]/year) before and after atropine treatment

children had less than -0.5 D/year SE progression (**Figure**).

Subgroup analysis was performed to identify factors that affected reduction of SE progression with atropine (ie, difference between SE progression before and after atropine treatment). More reduction of SE progression after atropine was associated with the starting age of ≤8 years, the baseline SE progression of <-1 D/year, and initial atropine dosage of 0.125% (**Table 2**). Further analysis with analysis of covariance showed that only the baseline SE progression of <-1 D/year (p<0.001) and initial atropine dosage of 0.125% (p<0.001) remained significant after controlling for other independent variables.

Regarding AL elongation and SE progression during atropine treatment, those with starting age of >8 years (n=160) had slower SE progression (-0.34 D/year vs -0.41 D/year, p=0.031) and AL elongation (0.18 mm/year vs 0.25 mm/year, p=0.038) than did those with starting age of ≤8 years (n=186). Children who initially received 0.125% atropine (n=90) had slower SE progression (-0.25 D/year vs -0.42 D/year, p<0.001) and slower AL elongation (0.19 mm/year vs 0.26 mm/year, p=0.031), compared with children who initially received 0.01% atropine (n=254). Children with baseline high myopia (n=43) had slower SE progression (-0.18 D/year vs -0.33 D/year, p=0.046) but not slower AL elongation (p=0.117), compared with children without baseline high myopia (n=303). Further analysis with analysis of covariance showed that starting age (p=0.012) and initial dosage of atropine (p<0.001) remained significant factors for SE progression. No significant differences were identified in other parameters including sex, children with high myopia parents, or children with baseline SE progression more than -1 D/year. Reduction of SE progression was correlated with the starting age (r= –0.227, p=0.041) and baseline SE (r= –0.319, p=0.004).

Table 2. Factors that affect reduction of myopia progression (in spherical equivalent [SE]/year) after atropine treatment

Factor	No. (%) of patients (n=346)	Mean±SD reduction of myopia progression, SE/year	p Value
Age, y			0.031
≤8	186 (53.8)	0.98±0.78	
>8	160 (46.2)	0.71±0.63	
Sex			0.850
Male	161 (46.5)	0.85±0.72	
Female	185 (53.5)	0.87±0.73	
Baseline high myopia			0.550
Yes	43 (12.4)	0.95±0.64	
No	303 (87.6)	0.82±0.80	
Baseline myopia progression (n=216)			<0.001
>-1 D/y	101 (29.2)	1.37±0.59	
≤-1 D/y	115 (33.2)	0.42±0.50	
Parent with high myopia (n=175)			0.720
Yes	119 (34.4)	0.99±0.81	
No	56 (16.2)	0.94±0.61	
Atropine preparation at start (n=344)			<0.001
0.125%	90 (26.0)	1.23±0.66	
0.01%	254 (73.4)	0.8±0.67	

Of 346 patients, 186 had change in frequency or concentration of atropine during the study period, and dosage of atropine were titrated according to the rate of myopia progression or adverse effects experienced by patients. 95 of the 186 patients required up-titration of atropine (36 had increase in concentration, 50 had increased frequency, and 9 had both), and their mean SE progression reduced from -1.01 D/year during initial regimen of atropine to -0.5 D/year after up-titration of atropine (p<0.001). 61 of 186 patients had atropine down-titrated (6 had decrease in concentration, 49 had decreased frequency, and 6 had both), their mean SE progression was -0.16 D/year before down-titration and -0.22 D/year after down-titration (p=0.09). The remaining 30 patients received both up- and down- titration during the study period.

Adverse effects were reported in 14 (4.05%) patients; 10 of them were using 0.125% atropine daily. Photophobia was the most commonly reported adverse effects (n=8) despite usage of photochromatic spectacles. Other adverse effects included dizziness, eye irritation, allergic conjunctivitis, and blurred near vision.

Discussion

The findings of the present study are consistent with those of the ATOM2 study[1] that myopia progression can be controlled by atropine (both 0.01% and 0.125% preparation). However, the 0.01% group in the ATOM2 study showed better control of myopia progression (-0.49 D progression over 2 years) than did the same group in the present study (-0.38 D/year). The difference could be accounted partially by the difference in treatment regimen and the age of patients. In the ATOM2 study, all patients received daily dose of 0.01% atropine in the treatment arm and the patients recruited were aged 6 to 12 years, whereas in our study, we included patients aged 4 to 16 years and some received 0.01% atropine with lower frequency (eg. 2 to 3 times a week) when there was no significant myopia progression. Moreover, AL elongation results of the two studies are similar (0.41 mm over 2 years in ATOM2 study and 0.23 mm/year in our study). However, in ATOM1 study[5] and ATOM2 study[1] the effect of 0.01% atropine on AL elongation was negligible (0.38 mm in ATOM1study and 0.41 mm over 2 years in ATOM2 study).

In the present study, patients with higher baseline myopia progression (<-1 D/year) benefitted more from atropine treatment in terms of reduction in SE progression (1.37 D/year, reduction of 76.5% from baseline) than patients with baseline myopia progression of >-1 D/year (0.42 D/year, reduction of 55.8% from baseline). Mouse and Syrian hamster models showed that there was upregulation of muscarinic receptors in the myopic sclera.[8,9] This may indicate that eyes with higher myopia progression are more sensitive to atropine, a muscarinic

receptor antagonist; however, this is yet to be elucidated.

Previous observational studies in Hong Kong[2] and Singapore[10] showed that younger children have higher myopia progression than do older children. This was also reflected in the present study that patients aged >8 years experienced slower AL elongation and SE progression after atropine treatment than did patients aged ≤8 years. Owing to the high prevalence of myopia in Hong Kong students and public awareness of the complications related to pathological myopia, parents may prefer earlier treatment for their children, especially those parents who also have high myopia. In our cohort, 17 children received atropine treatment when aged <6 years and their baseline SE was -0.875 D to -9.5 D and mean myopia progression before treatment was -2 D/year. Ten (58.8%) of them had a family history of high myopia. After atropine treatment, the myopia progression was significantly reduced by 71.1% (p=0.007) and no adverse events were reported. Moreover, earlier starting age of atropine treatment was correlated with greater reduction in myopia progression (r= –0.227, p=0.041). This suggests that earlier commencing atropine treatment for myopia control may be recommended in selected patients.

There were modifications in atropine concentration and frequency in some patients during the treatment period, based on patient response to the treatment regimen and the individual ophthalmologist's judgment on the control of myopia progression. Although there was no standard on the timing or magnitude of atropine titration, the principle adopted was to use the minimum atropine dose that still controls myopia progression at a reasonable level.

Our study has a relatively homogenous study population (>90% were Chinese) and a reasonable sample size; however, it is limited by its non-randomized and retrospective nature. Only data on baseline SE progression instead of baseline AL elongation were available for the analysis because AL was not measured routinely in patients who were not receiving atropine treatment. Furthermore, patients were managed by different ophthalmologists in the team, so the choice of atropine regime may not be standardized. Nevertheless, the study reflects the practical use of atropine treatment with titrations according to the patient's clinical response.

Conclusion

Atropine treatment slows myopia progression by 68.4% in pediatric patients. Early treatment is considered safe for selected children aged <6 years with a high rate of myopia progression. With regular monitoring of patient's clinical response, titration of atropine could be applied to optimize its effects on myopia control while minimizing adverse effects.

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Author contributions

Concept or design: CSLL, DSPF.
Acquisition of data: CSLL.
Analysis or interpretation of data: CSLL, DSPF.
Drafting of the article: all authors
Critical revision for important intellectual content: all authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an Advisor of the Journal, DF was not involved in the peer review process for this article. All authors have no conflicts of interest to disclose.

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Ethics approval

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