

# Efficacy, feasibility, and patient acceptance of using low-dose atropine in retarding myopia progression: A general ophthalmologist's perspective

## ABSTRACT

**Purpose:** Assessing efficacy of atropine 0.01% eye drops in retarding myopia progression in children, the feasibility of its use, and patient acceptance outside institutional practice. **Design:** Prospective observational hospital-based study was conducted in children who were prescribed atropine 0.01% eye drops to retard the progression of myopia. **Methods:** Fifty-seven children who showed a documented progression of 0.5 diopters (D) of myopia were prescribed atropine 0.01% eyedrops. In those patients who followed up, the mean change in spherical equivalent was assessed using a paired *t*-test and a pairwise correlation test. Data of those who were lost to follow-up were evaluated. **Results:** Out of the 57 children 10 opted out of the study and of the remaining 47 children 20 (42.55%) were lost to follow-up. The mean age of the remaining 27 children was  $9.04 \pm 3.05$  years and 48.1% ( $n = 13$ ) were female. The mean age of dropouts was significantly higher than those who were followed up ( $P = 0.003$ ). The mean duration of follow-up was  $10.8 \pm 5.1$  months (range 3–23 months). The mean spherical equivalent from baseline to last follow-up was 0.329 by the paired sample *t*-test ( $P < 0.001$ ). Twelve (44.4%) of the 27 children showed a progression of myopia despite treatment. **Conclusion:** Mean change in spherical equivalent in our study is comparable to previous studies with hardly any adverse effects suggesting efficacy of atropine 0.01%; practical hurdles in follow-up and adherence need to be improved with better patient education.

**Keywords:** Atropine, Myopia, Acceptance

## INTRODUCTION

Myopia is a major public health problem with a higher risk for several ocular complications that may lead to irreversible blindness. High myopia that is defined by the World Health Organization as  $-5$  diopters (D) or greater is associated with degenerative changes in the macula, optic nerve, and peripheral retina and potentially blinding complications such as retinal detachments, myopic choroidal neovascularization, myopic macular degeneration, foveoschisis, glaucoma, and cataract.<sup>[1–3]</sup> An estimated 2%–5% of Caucasian populations and 5%–10% of Asian populations have high myopia and an estimated 1% of Caucasian populations and 1%–3% of Asian populations have pathologic myopia.<sup>[4–6]</sup> The estimate of high myopia is expected to increase from 2.7% in 2000 to 9.8% in 2050 while the overall prevalence of myopia will increase

from 22.9% in 2000 to 49.7% in 2050.<sup>[6]</sup> The prevalence of myopia in school-going children in India was reported as 13.1% with a mean myopic spherical error of  $-1.86 \pm 1.4$  diopters which shows that myopia is a significant health problem in our country.<sup>[7]</sup>

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It is not considered a major problem despite these staggering numbers as it is viewed as a refractive error that can be managed with spectacles, contact lenses, or refractive surgery. Myopia progresses at about  $-1$  D per year in East Asians and around  $-0.5$  D per year in Caucasians.<sup>[8,9]</sup> Atropine is the only medication that has shown consistent effectiveness to reduce the progression of myopia.<sup>[10,11]</sup> Higher concentrations of atropine such as 1% or 0.5% are effective in retarding myopia progression but have rates of photophobia as high as 100% and dropout rates ranging from 16% to 58%.<sup>[12,13]</sup> The efficacy of atropine eye drops in varying concentrations from 0.5% to 0.01% has been demonstrated in the atropine for the treatment of myopia (ATOM) 1 and ATOM 2 studies.<sup>[14]</sup> Lower concentrations of atropine (0.05%, 0.01%, and 0.025%) have also been found to be effective in arresting the progression of myopia in the LAMP study.<sup>[15]</sup> A multicentric trial from India has shown promising results in reducing myopia progression in mild-to-moderate myopia.<sup>[16]</sup> However, the systemic and ocular side effects of atropine can affect long-term use and lead to a high dropout rate, especially with higher concentrations. Thirty-four (17%) of participants who withdrew from the ATOM 1 study stated hypersensitivity, glare, and poor near-visual acuity as the reasons for withdrawal, and 4.1% of children in 0.1% and 0.5% atropine group reported allergic conjunctivitis in the ATOM 2 study.<sup>[14]</sup> We designed a prospective observational study of a group of children with myopia who were prescribed 0.01% atropine at a private eye hospital in north Kerala with a specific aim to understand the uptake and compliance with the prescribed dose of atropine for myopia.

## METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and informed consent was obtained from the parents of children enrolled in the study and an ethics committee approval was sought. Children with a documented progression of myopia of  $\geq 0.5$  diopters, with a minimum follow-up of 3 months, aged between 2 and 15 years were recruited consecutively for 2 years from June 2018. Children with congenital high myopia, pathological myopia, who had undergone ocular surgery, who were using other drugs or contact lenses, and whose parents did not provide informed consent for participation were excluded from the study. Each child underwent a detailed ophthalmic examination that included assessment of the best-corrected visual acuity, anterior segment assessment using slit-lamp biomicroscopy, and posterior segment assessments after pupillary dilatation. Every child underwent cycloplegic refraction before starting the drops and the change in refraction was confirmed. Parents of eligible children were counseled in the native language regarding the use of atropine 0.01% eye drops

to retard the progression of myopia. They were briefed about the current available studies and the benefits and an informed decision involving the parents were made before starting the medication. Parents were advised to administer one drop of the drug once daily in both eyes at bedtime. The method of administration (child in supine position with the creation of a lower lid pouch) was also explained and anticipated common side effects like photophobia, blurring, flu-like symptoms, or rashes, etc.). Parents and children were asked to self-report at any stage if they perceived any side effects. It was planned to use the drops for a minimum of 2 years before stopping the drug.

Enrolled children were followed up at 1 month after the start of the drug and thereafter at 4-month intervals for 2 years till August 2020. Each child was assessed for the best corrected distant and near vision at each visit and parents were enquired regarding adverse effects and difficulty in near work on using the drug.

## Statistical analysis

Data were entered into a Micro Soft Excel Spreadsheet and then exported to the STATA statistical software version 14.0 (College station, Texas, USA) for further analysis. Continuous variables were expressed as mean (standard deviation) and categorical variables as proportions. The change in mean spherical equivalent was assessed using a paired *t*-test and a pairwise correlation test. A  $P < 0.05$  was considered significant.

## RESULTS

Parental counseling was provided to 57 children that were considered eligible for enrolment in the study. Ten parents opted out of the study and the remaining 47 (82.46%) children were enrolled in the study. Twenty (42.55%) children were lost to follow-up after the initial dose and were excluded from further study. Of the patients who were lost to follow-up, 7 were male (35%) and 13 were female (65%) and the mean age was  $11.7 \pm 2.5$  years (range 5–15 years). Three participants were lost to follow-up after the initial 2 months of usage and the rest of them did not follow-up after prescribing the drops. The mean age of the remaining 27 children was  $9.04 \pm 3.05$  years (range 2–14 years) and most ( $n = 13$ , 48.1%) were aged 5–10 years and were female ( $n = 17$ , 62.96%). The mean age of dropouts was significantly higher than the children who continued in the study ( $P = 0.003$ ). The mean duration of follow-up of the study participants was  $10.8 \pm 5.1$  months with a minimum follow-up of 3 months and maximum of 23 months.

The mean change spherical equivalent at the last follow-up of 54 eyes of 27 children is shown in Table 1. The overall

**Table 1: Change in spherical equivalent from baseline to last follow-up in the study population**

Mean spherical equivalent	Paired samples statistics			P	Paired differences		
	n	SD	Correlation		Mean±SD	t	Significance (two-tailed)
Mean spherical equivalent right eye							
At start of atropine 0.01%	27	3.32644	0.991	<0.001	0.344±0.464	3.852	0.001
At the end of last follow-up	27	3.38573					
Mean spherical equivalent left eye							
At start of atropine 0.01%	27	3.057	0.985	<0.001	0.314±0.539	3.031	0.005
At the end of last follow-up	27	3.124					

SD - Standard deviation

change in the mean spherical equivalent from baseline to last follow-up was 0.329 by the paired sample *t*-test ( $P < 0.001$ ). Twenty-two of the children had more than 6 months of follow-up and 15 eyes (34.09%) showed an increase of spherical equivalent change of  $\geq 0.5$  diopters and 4 eyes (9.09%) showed an increase of  $\geq 1$  dioptre. Overall, twelve (44.44%) of the 27 children progression of myopia despite atropine 0.01% use.

None of the patients including those who stopped the drug after 2 months reported any of the above-mentioned adverse effects. A treatment-related event was reported in one patient who procured atropine 1% drops instead of 0.01%, despite having a correct prescription which resulted in difficulty in reading for 2 weeks.

## DISCUSSION

Antimuscarinic topical medications have been shown to be effective in slowing myopia progression in children and multifocal lenses may confer a minimal benefit. Orthokeratology contact lenses do not modify refractive error but may be effective in slowing axial elongation. The review found very low certainty evidence regarding rigid gas permeable contact lenses and spherical aberration contact lenses to slow the progression of myopia.<sup>[10]</sup>

Donders introduced the concept of atropine in the treatment of myopia as he hypothesized that spasms of accommodation in myopic patients are the reason for progression.<sup>[17]</sup> Pollock was the first to use atropine in the treatment of myopia.<sup>[18]</sup> The exact mechanism of action of atropine in retarding myopia progression is not clear though several postulates have been put forward. One theory is that atropine acts on the retina or sclera regulating the growth by preventing the thinning or stretching.<sup>[19-21]</sup> Several studies have attributed myopia to reading and doing near work uninterruptedly.<sup>[22-27]</sup> The Singapore Cohort Study of the Risk Factors for Myopia and the Orinda Longitudinal Study of Myopia reported that reading, playing video games, and watching television was not a significant risk factor for myopia and showed that

parental history was an important association and increased outdoor activity had a beneficial effect on myopia.<sup>[22,28]</sup> Two additional factors that have incidentally happened for our study are an increased time of online teaching and increased use of gadgets ( $> 2$  h in most children) due to the pandemic during the latter half of follow-up that has also reduced outdoor activity. These factors were not included as a parameter as they occurred midway through the follow-up period.

## Efficacy of the drug

The use of low concentration atropine (0.01%) has become widely accepted<sup>[14]</sup> after the ATOM 2 study showed a progression rate of  $-0.49 \pm 0.63$  D in 2 years. A case-control study among Caucasians in the United States found a rate of myopic progression of  $-0.1 \pm 0.6$  D/year in the atropine 0.01% group. Several studies currently provide evidence on the efficacy of low-dose atropine.<sup>[11,29,30]</sup> Our study also shows a mean change in the spherical equivalent of  $0.329 \pm 0.49$  D between the last and the first follow-up which is comparable to previous studies. Previous studies have recommended that retreatment with atropine 0.01% can be equally effective as the primary treatment and clinicians must titrate treatment by stopping and restarting treatment according to individual progression rates.<sup>[14]</sup>

A study by Sacchi, *et al.*,<sup>[31]</sup> reported that 21% of patients progressed despite the usage of the drug while 24% of participants in the ATOM 2 study<sup>[32]</sup> showed progression of myopia. The rate of progression in our series (44%) is significantly higher than in those studies. There are reports that some children are nonresponders to lower doses of atropine suggesting higher doses to be considered after weighing dosage-related adverse effects.<sup>[9,32]</sup>

## Limitations of the study

The increased progression rates in our study may be due to small sample size, varied periods of follow-up or because of an ethnic difference and needs more detailed evaluation. It is also possible that the increased use of digital devices for longer times and restricted outdoor activity during

the pandemic have influenced the rates and degree of progression. However, we are not able to comment on that as part of this study.

#### Adherence to treatment, safety, and follow-up

In our study, the children were included in accordance with the ATOM 2 study<sup>[32]</sup> criteria and we have included the spherical equivalent at the start and end of the follow-up period with a minimum of 3 months follow-up. In the study conducted by Diaz-Llopis *et al.* in 2018, the dropout rate from the treatment group was 53.5%.<sup>[33]</sup> In our study, 42.55% of children dropped out of the study, and part of the follow-up period coincided with the COVID 19 pandemic. Even though the dropout rates are comparable, the fact that the rest of the patients have continued the treatment despite the pandemic and with good adherence (not more than 2 missed doses/month) is a welcome sign.

None of the patients in our study who were followed up had any adverse effects, except for one patient who used 1%. Atropine drops instead of the prescribed 0.01%. Sacchi *et al.* reported side effects like photophobia, in 9.2% of the patients who were followed up.<sup>[31]</sup> Two patients reported nonavailability of the drug during the pandemic, but they were able to procure it and did not affect the adherence.

#### Patient acceptance of a new treatment

Ten (17.5%) of the 57 children who were advised to start atropine treatment did not start the treatment. The reasons included practical difficulty and apprehension of using the drug for a long time, personal views on various treatment methods, and the availability of various nonevidence-based alternative treatments prevalent in the community. Many parents and children were more concerned about the cosmetic aspect of wearing glasses than the progression of myopia. These are cultural differences which have to be included in charting treatment plans. For a treatment option to be acceptable, it has to be consistent with lifestyle, appropriate for managing the problem, easy to apply, and effective.<sup>[34]</sup> Hence to make a treatment preference and acceptance valid, the caretakers have to be presented with information on each treatment enhancing their understanding, assessing their perceptions, and discussing their treatment choices.<sup>[35]</sup> The hurdles faced in our study during parental counseling were the ambiguous areas regarding treatment like the optimal time to start and stop and duration of any retreatment if needed.

#### CONCLUSION

The studies till date on the efficacy of atropine have shown consistent and comparable results on retardation of progression of myopia and that low-dose atropine is as

effective as the higher concentration,<sup>[29,30]</sup> but there are many facets untouched which remain to be clarified like optimal age, duration of treatment, management of nonresponders including criteria to define nonresponders, whether 0.01% is suitable for all ages or higher concentrations are needed and whether there is a racial or ethnic difference in the response.

#### Recommendations

Patient treatment preference must be modified by parental education and assessing parental preference before starting treatment which will help in further evaluating this promising treatment and provide further clarity to the protocols. Future studies that bring out the role of environmental factors which modify the effect of low-dose atropine may also be worthwhile.

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#### Conflicts of interest

There are no conflicts of interest.

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