Clinical and Experimental Vision and Eye Research (2022), 5, 17–20

REVIEW ARTICLE

Current Evidence of Atropine for Treatment of Progressive Myopia

Hitisha Mittal, Savleen Kaur, Jaspreet Sukhija

Advanced Eye Centre, Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, Punjab, India

Key words:

Myopia, Atropine, ATOM

Address for correspondence:
Dr Savleen Kaur, Department of Ophthalmology, Post Graduate Institute of Medical Education and Research, Chandigarh, Punjab, India. E-mail: mailsavleen@gmail.com, Phone: +91-9988167746

Received: 04-04-2022;
Accepted: 21-04-2022
doi: 10.15713/ins.clever.83

Abstract

The morbidity of myopia, which includes vision-threatening consequences such myopic maculopathy, extreme myopia, and severe hyperopia, necessitates early intervention in children. Myopia-related conditions such ocular neuropathy, posterior staphyloma, macular degeneration, traction maculopathy, and choroidal neovascular membrane have been linked to myopia. The current COVID-19 pandemic has made myopia more common throughout the world by significantly reducing outdoor time and increasing near work. Over the past few decades, a lot of research has been done on the effectiveness of atropine in slowing the progression of myopia in children. In this paper, we have covered briefly the processes by which atropine serves to control the progression of myopia, the findings of important studies on the subject, and the monitoring and follow-up procedures for myopic patients receiving atropine.

Introduction

The need to intervene early in children with myopia stems from the morbidity associated with it, which includes vision threatening complications such as myopic maculopathy, high myopia associated optic neuropathy, posterior staphyloma, myopic macular degeneration, myopic traction maculopathy, and myopic choroidal neovascular membrane.[1] The recent COVID-19 pandemic, with significant decrease in outdoor time and increased near work, has exacerbated the global prevalence of myopia.[2-5] It is predicted to affect more than half of the world's population by 2050, thereby making early measures of myopia control necessary to decrease the myopia-related economic and public health burden in the society.[6,7]

Atropine has been extensively studied as an effective means of controlling myopic progression in children over the past few decades. Usage of low concentration topical atropine is currently one of the most recognized pharmacological methods of myopia control. However, it is still being used as an off-label treatment modality in most of the countries due to its associated side effects such as blurring of near vision (due to cycloplegia), photophobia due to pupillary dilatation, local and systemic allergic reactions, and rebound effect on cessation of treatment.[8]

In this article, we have reviewed briefly about the mechanisms by which atropine helps in controlling myopia progression, the results of landmark studies on the topic and how to monitor and follow-up myopic patients being treated with atropine.

How Does Myopia Progress?

Vision and refractive state of the eye are the most important local regulators of ocular growth. Neonates are born with axial hyperopia and complete the emmetropization process slowly by 7–8 years of age.[9] The exact mechanism of myopia development is not well understood; however, multiple theories have been hypothesized to explain its development. When the observed accommodative response is less than the stimulus, that is, the rays of light from a near object entering the eye are focused behind the retina, it is known as "Lag of accommodation."[10] This stimulates axial length elongation and scleral remodeling at posterior pole to focus the image on central retina. As the eye grows, it attains a prolate shape,

leading to a central myopic defocus and a peripheral hyperopic defocus. This hyperopic defocus, in turn, stimulates scleral remodeling and axial elongation, thereby worsening the myopia.[11] Environmental factors such as increased near work, decreased outdoor time, and genetic factors such as parental myopia are also known to play an important role in myopia development.[12]

How Does Atropine Act?

Atropine is useful in treating axial myopia. It has minimal to no role in other forms of myopia such as curvatural, lenticular, index, or positional myopia.[13] Multiple studies (including animal myopia models) suggest a multifactorial mechanism of action of atropine in controlling myopic progression. Some suggest that it directly acts on the sclera and alters its remodeling. Others suggest that it binds to muscarinic receptors on retinal amacrine cells, which, then, release dopamine and inhibit the axial growth of eye.[14] Some studies also suggest that myopia is seen in children with chronic ocular inflammation and an anti-inflammatory action of atropine helps in halting myopia progression in such children.[15]

What is Premyopia?

It is a non-myopic refractive state of eye, in which a combination of risk factors and the observed pattern of eye growth in normal population indicates a high risk of myopia progression. It is defined as a refractive state of eye of ≤ +0.75 D and > −0.50 D in children, where a combination of baseline refraction, age, and other quantifiable risk factors provide a sufficient likelihood of the future development of myopia to merit preventative interventions. It has been defined to target the younger age groups, where the onset of myopia can be prevented or delayed by early intervention with therapies such as low concentration topical atropine.[16]

What is the Ideal Topical Atropine Concentration for Clinical Use?

Various concentrations of topical atropine (ranging from 0.01% to 1%) have been studied in multiple randomized controlled trials all over the world, especially in Asian countries for controlling myopic progression and axial length elongation. An ideal atropine concentration can be described as the one that shows –

1. Maximum efficacy in reducing myopia progression
2. Least associated side effects of photophobia and near vision difficulties
3. Least rate of rebound myopia on cessation of treatment.

Atropine for Treatment of Myopia (ATOM) studies done by Singapore Eye Research Institute have been the landmark studies, where efficacy of atropine in controlling myopic progression was studied.[17,18]

In 2006, ATOM 1 study reported the safety and efficacy of 1% atropine in comparison to a placebo in controlling myopia progression and axial length elongation in 400 Asian children aged 6–12 years with a myopic error between −1 D and −6 D and astigmatism <1.5 D. At the end of 2 years, the mean myopia progression in the placebo group was −1.2 D +/− 0.69 D, whereas it was only −0.25 D +/− 0.92 D in the atropine treated eyes. The axial elongation was +0.38mm +/− 0.38 mm in placebo group, while it was essentially similar to baseline axial length in atropine group. Thus, 1% atropine was found to significantly reduce myopia progression. However, it caused significant side effects and rebound myopia on stopping treatment, thus necessitating the need to study lower concentrations of atropine for control of myopia progression.[17]

ATOM 2 study was a 5-year trial launched in 2012 that was split into three phases (2 years of treatment phase, 1 year of washout phase, and 2 years of re-treatment phase) and compared lower doses of topical atropine (0.5%, 0.1%, and 0.01%) in 400 Asian children aged 6–12 years with myopia of −2 D or worse. It revealed that the efficacy as well as side effects of atropine were dose dependent. The mean myopia progression and axial elongation were lowest with 0.5% atropine in phase 1; however, these differences among the three groups were small and clinically insignificant. It also noted that the efficacy of 0.01% atropine in 2nd year of treatment was better than the 1st year, unlike with 0.5% and 0.1%, where the results in 1st year and 2nd year were comparable. This phenomenon with 0.01% atropine has been attributed to its cumulative effect over time. In phase 2, it revealed that children receiving 0.01% had least myopic progression on stopping the treatment. Rebound myopia was seen in 68%, 59%, and 24% children treated with 0.5%, 0.1%, and 0.01% atropine, respectively. In phase 3, all children who had myopic progression in phase 2 were treated with 0.01% atropine. Fewer children in the initial 0.01% atropine group required retreatment for myopia progression after washout phase as compared to those treated with 0.5% and 0.1% atropine in the treatment phase. Thus, it concluded that 0.01% atropine was the most effective concentration for controlling myopic progression at the end of 5 years with minimal side effects and least rate of rebound myopia.[18]

ATOM 3 is a randomized control trial, launched in 2017 and currently in its phase 3. The aim is to study the role of 0.01% atropine in preventing or delaying the onset of myopia in high-risk children with premyopia or low myopia. Risk factors considered are history of parental myopia and low hyperopia or low myopia in children. The hypothesis that we can delay or prevent the onset of myopia is based on the observation that younger age of onset of myopia is associated with higher degree of myopia progression (in terms of both spherical equivalent and axial length progression). Children aged 5–9 years (lower as compared to ATOM 1 and ATOM 2 studies, where 6–12 year old children were recruited) with cycloplegic refraction between +1 D and −0.5 D and at least one parent with moderate myopia are being recruited in the study. Results of the study shall add to our existing knowledge about role of 0.01% atropine in younger

children to delay or prevent the onset of myopia in high-risk children. The study is aimed to be completed by 2023.

Low concentration atropine for myopia progression (LAMP) study was done in 2017 in two phases on 383 children aged 4–12 years with myopia of at least −1 D and astigmatism of up to 2.5D and a documented progression in myopia by at least 0.5 D in past year. It evaluated the efficacy of 0.05%, 0.025% and 0.01% atropine in slowing myopia progression. It concluded that 0.05% atropine is the best concentration among the studied low concentrations of atropine for myopia progression control at the end of 2 years. All three doses were well tolerated by children in terms of side effects of atropine. However, a major drawback of this study was lack of data on rebound myopia after stopping treatment with 0.05% atropine.[19]

A secondary analysis of the LAMP study was done by Li *et al.* in 2021, where they investigated the effect of age at treatment and other factors on the treatment response to the atropine in LAMP study. Factors studied included age at treatment, gender, baseline spherical equivalent, parental myopia level, baseline outdoor hours, baseline near work time, and treatment compliance. They concluded that age at treatment is the main factor responsible for the variable response to treatment with low-dose atropine and this finding was found to be consistent with similar observations made in ATOM 1 study. There was an age-dependent response within each treatment group and a concentration-dependent response in each age group.

I-ATOM study, published in 2021, was done in 100 Indian children aged 6–14 years with myopic error between −0.5 D and −6 D, astigmatism up to 1.5 D, and anisometropia up to 1 D and documented progression in cycloplegic refraction of at least 0.5 D in preceding year. The aim of the study was to evaluate the role of 0.01% atropine in slowing myopic progression and axial length elongation at the end of 1 year. It reported a 54% reduction in spherical equivalent progression and 21% reduction in axial elongation at 1 year with 0.01% atropine. However, it has limitations such as lacunae of data on rebound myopia and lack of comparison groups with other low doses of atropine.[20]

To summarize, atropine has been found to be efficacious in controlling myopic progression. Most of the evidence indicates that its side effects and rate of rebound myopia are dose dependent. Hence, among all the tested doses, 1% atropine is the most effective concentration in halting myopia progression but has intolerable side effects and high rate of rebound myopia. Moderate concentrations such as 0.5% and 0.1% atropine are effective concentrations in slowing myopia progression but causes significant rebound myopia and bothersome side effects. 0.05% atropine is the most effective low concentration of atropine with tolerable side effects, but data on rebound myopia are not available, hence limiting its clinical use. The current evidence indicates that 0.01% atropine is the ideal concentration for clinical use, being most effective in controlling myopic progression at 5 years, with the least rate of rebound myopia and tolerable side effects. Some countries have thus atropine 0.01% available for commercial use.

How to Treat and when to Review?

There is no standard treatment protocol for the treatment with atropine in controlling myopic progression in children. The commonly followed consensus worldwide is to treat children aged 6–12 years with myopia of −0.5 D or worse and documented progression of 0.5 D in last 6 months with 0.01% topical atropine once a day. Baseline cycloplegic refraction and axial length documentation are done before initiating the treatment. First, follow-up after initiating treatment is usually after 3 months. Patient's drug compliance and atropine related side effects should be documented. Re-assessment of cycloplegic refraction and axial length measurement is done to look for response to treatment. Henceforth, the patient is followed up at 6 monthly intervals with cycloplegic refraction and axial length monitoring at each visit. The treatment is usually given for 2 years, because that is the current evidence and the minimum time period for this concentration to be effective.

After discontinuing treatment, reassessment of cycloplegic refraction and axial length is done at 6 monthly intervals for at least 1 year to look for rebound myopia. In case of progression in refractive error (0.5 D progression or more/year) or axial length (0.3 mm/year), 0.01% topical atropine can be restarted and reassessed at 6 months. Children older than 12 years usually do not show progression in myopia due to the natural slowing down in axial length elongation.

Conclusion

Early recognition of premyopia and myopia in children is important for timely management of refractive errors. Increasing outdoor activities and reducing near work duration are modifiable risk factors for controlling myopic progression. In children with documented myopic axial progression, 0.01% atropine once a day along with appropriate refractive error correction is an effective therapy of choice among ophthalmologists.

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How to cite this article: Mittal H, Kaur S, Sukhija J. Current Evidence of Atropine for Treatment of Progressive Myopia. Cli Exp Vis Eye Res J 2022;5(1):17-20.