AN OVERVIEW OF THE DOSAGE, SIDE EFFECTS, AND LONG-TERM EFFECTS OF ATROPINE EYE DROPS AS A MEANS TO CONTROL MYOPIA PROGRESSION IN CHILDREN

Comment [Kabiru la1]: the title is well. however, it can be changed to " AN OVERVIEW OF THE DOSAGE, SIDE EFFECTS, AND LONG-TERM EFFECTS OF ATROPINE EYE DROPS IN MANAGEMENT OF MYOPIA PROGRESSION IN CHILDREN".

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ABSTRACT

Myopia, or nearsightedness, is a common refractive error affecting individuals worldwide, with its prevalence increasing significantly, particularly in children. Various strategies have been explored to manage myopia progression, among which atropine eye drops have gained attention for their potential efficacy. Atropine, a muscarinic antagonist, has been investigated for its ability to slow down myopia progression in children. However, concerns about dosage, side effects, and long-term effects remain significant considerations in utilizing atropine eye drops for myopia control in pediatric populations. The dosage of atropine eye drops in myopia control regimens varies across studies, with concentrations ranging from 0.01% to 0.5%. Lower concentrations, such as 0.01% and 0.02%, have been found effective in slowing myopia progression while minimizing adverse effects. Conversely, higher concentrations, such as 0.5%, may offer greater efficacy but are associated with an increased risk of adverse effects. Dosage frequency also varies, with daily administration being the most common regimen. However, individualized dosing strategies based on patient age, severity of myopia, and response to treatment are crucial considerations for optimizing outcomes. Although atropine eye drops have shown promise in controlling myopia progression, they are associated with various ocular and systemic side effects. Common ocular side effects include photophobia, near-vision blur, and transient pupil dilation, which can affect visual acuity and quality of life. Systemic side effects, such as dry

mouth, flushing, and tachycardia, may occur, particularly with higher concentrations of atropine. This literature review provides an overview of the utilization of atropine eye drops as a means to control myopia progression in children, focusing on dosage, side effects, and long-term effects. This review shall highlight the importance of individualized dosing regimens, vigilant monitoring of side effects, and longitudinal studies to optimize the use of atropine eye drops in managing myopia progression in children.

Keywords: myopia, atropine eye drops, myopia progression, anti-muscarinic eye drops, visual acuity.

INTRODUCTION

The global prevalence of myopia has significantly surged in recent decades, emerging as the most prevalent ocular disorder worldwide. Projections indicate that by 2050, roughly half of the global population will be afflicted with myopia, with 10% suffering from high myopia. (1)

In Europe, myopia affects up to 30–40% of the populace, with rates nearing 50% among individuals aged 25–29. Conversely, Asian nations report even higher prevalence rates, with approximately 90% of young adults experiencing myopia.(2)

Comment [Kabiru Ia2]: mention the Prevalence of myopia in other continents like africa, america etc.

Myopia, characterized by excessive eyeball growth, presents a spectrum of risks, particularly in cases of high myopia (spherical equivalent [SE] ≤ −6.0 D or axial length [AL] > 26 mm). Individuals with high myopia face heightened susceptibility to severe complications such as retinal detachment, myopic choroidal neovascularization, and glaucoma. (3)

Despite its lower incidence, pathologic myopia remains a significant cause of blindness and visual impairment across Asian and Western populations, affecting an estimated 1 to 5 per 1000 individuals in Europe.(4)

UNDER PEER REVIEW

Various strategies have been employed to curb myopia progression. Recommendations advocate for increased outdoor activity and reduced near work to deter myopia development in children. (5)Intervention methods targeting myopia progression include optical approaches such as spectacles with bifocal or defocus-incorporated lenses, orthokeratology, and atropine eye drops. Currently, atropine is the sole pharmacological agent to mitigate myopia progression in clinical practice. (6)

Typical regimens involve administering 0.01 - 0.05% atropine drops in both eyes nightly for one to two years or longer among children aged 5 to 15 experiencing myopia progression.(7) Despite the promise of low-concentration atropine eye drops in myopia control, uncertainties persist regarding treatment protocols, optimal concentration balancing risk and benefit, treatment duration, and factors influencing individual response to therapy among myopic children.(8)

Several large randomized clinical trials conducted in Asia have demonstrated the effectiveness of low-dose atropine in slowing myopia progression among children. Given the notably higher prevalence of myopia in Asian countries, the bulk of research on myopia control has been centered in this region. However, data regarding the efficacy and response to atropine eye drops in non-Asian populations are scarce.(9)

Based on studies conducted in Asia, 0.05% atropine eye drops have been proposed as the optimal dosage, balancing risks and benefits. Nonetheless, research indicates that Caucasian children treated with 0.05% atropine eye drops exhibited impaired vision or reading difficulties at a rate of 63.0%. (10)

Moreover, studies have highlighted a higher incidence and more severe side effects associated with 0.05% atropine eye drops in Caucasian children compared to their Asian counterparts.

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Consequently, the ideal concentration for treating myopia progression in non-Asian populations remains ambiguous.(3)

THE ROLE OF ATROPINE FOR CHILDREN WITH MYOPIA

Comment [Kabiru la3]: what is the mechanism of action of atropine in lowering the progression of myopia.

A recent study involving 400 myopic children from Singapore showcased the efficacy of daily administration of 0.01% atropine eye drops in mitigating the annual increase in the mean spherical equivalent of refraction (SER) compared to the placebo arm of a previous trial. (5)Across multiple Asian trials, concentrations of topical atropine ranging from 1% to 0.01% were evaluated, with the 0.01% concentration demonstrating the most enduring effect in stabilizing SER, along with the lowest incidence of side effects and minimal likelihood of regression post-treatment cessation.(11)

The alteration in SER per year serves as a globally recognized clinically relevant marker for myopia progression. In the Atropine for the Treatment of Myopia (ATOM) 1 study, which enrolled children aged 6–12 years with myopia ranging from −1.0 to −6.0 D, those in the placebo group exhibited an average (± SD) SER change of −0.76 ± 0.44 D and −1.20 ± 0.69 D over 12 and 24 months, respectively. (9)This decline was significantly greater than that observed in eyes treated with atropine in the subsequent ATOM2 study, which investigated atropine concentrations of 0.01%, 0.1%, and 0.5%. (11)

Following 2 years of atropine therapy, the mean progression was −0.30 ± 0.60 D, −0.38 ± 0.60 D, and −0.49 ± 0.63 D in the 0.5%, 0.1%, and 0.01% atropine groups, respectively. These findings suggest slightly superior efficacy of the 0.5% and 0.1% doses compared to the 0.01% dose. However, upon discontinuation of atropine dosing for 12 months after 2 years of treatment, individuals originally treated with higher concentrations experienced a rebound effect with

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worsened myopia, whereas those receiving 0.01% atropine exhibited minimal change (-0.28 D) with preservation of myopia reduction in 74% of subjects.(9)

Given that the majority of studies involving atropine for myopia were conducted in ethnic Asian populations, it remains uncertain whether differences in the manifestation and progression of myopia in other regions may influence the response to low-concentration atropine drops. (11)

A small-scale case-control study involving 32 subjects from a single US pediatric ophthalmologic practice suggested that 0.01% atropine significantly attenuated the rate of myopic progression over 1 year with minimal side effects. Another small uncontrolled study in Germany reported minimal pupillary dilation and an insignificant reduction in accommodation 24 hours post-treatment initiation.(12)

Modifications in both concentration and frequency of atropine administration have been pursued to mitigate side effects while preserving therapeutic benefits. Chou et al. proposed that a once-daily application of 0.5% atropine eye drops effectively slowed refractive error progression, even in children with severe myopia. (13) Despite identifying 0.5% atropine as the most efficacious concentration in an earlier study, this research group noted a potential reduction in effectiveness due to higher dropout rates associated with this concentration. Consequently, in 1999, it was suggested that well-tolerated concentrations such as 0.1% and 0.25% atropine drops could be initially employed to manage myopia in children displaying rapid progression or those prone to severe or early-onset myopia. (14)

More than a decade later, two additional studies employing low-concentration atropine and featuring medium-term follow-up were published. Wu et al. investigated a cohort of 117 children, with 97 receiving either 0.05% or 0.1% atropine, while 20 children served as controls. The mean follow-up duration was 4.5 years. Employing a mixed model analysis, they observed a

UNDER PEER REVIEW

significantly lower adjusted progression of myopia in the treated group compared to the control group (-0.23 D versus -0.86 D per year). (15)

THE LONG-TERM USEFUL AND ADVERSE EFFECTS OF USING TOPICAL ATROPINE EYE DROPS IN CHILDREN WITH MYOPIA

Several studies have already been done to observe and explore the long-term effects of atropine on the eye health of children with myopia. Yi et al. investigated the impact of 1% atropine on early myopia. While most cases showed improvement with atropine intervention, a subset exhibited no response. The variability in drug response was attributed to factors such as environmental influences, disease severity, lifestyle, and genetic predisposition. (16)

Wei et al. reported a loss to follow-up of approximately 30% and found that younger age at baseline was associated with a higher risk of progressive myopia based on unadjusted regression analysis. They noted a relative reduction of 34.2% in myopia progression, which was smaller than that observed in a study conducted in Europe. This led to the hypothesis that less pigmented eyes may exhibit greater sensitivity to cycloplegic agents. (17)

Saxena et al. documented favorable effects of 0.01% atropine in controlling myopic spherical equivalent (SE) progression, with minimal impact on axial length (AL) elongation. (18)

Hieda et al. observed a moderate reduction in myopia progression with 0.01% atropine and emphasized the need for up to 2 years to achieve therapeutic benefits. (19)

They suggested that environmental factors, country of residence, and lifestyle could influence treatment outcomes. (20) Notably, they identified a significant interaction between treatment and certain subgroups, such as uncorrected near visual acuity (VA) and mesopic pupil diameter in SE, and enrolled AL and mesopic pupil diameter in AL. (21) This suggests the potential for targeted atropine therapy in specific subsets of myopic children. Additionally, they noted an

UNDER PEER REVIEW

increase in photopic pupil size in the early phase and no change in mesopic pupil size in the atropine group, raising questions about the role of pupil dilation as a potential adverse effect and its involvement in inhibiting myopia progression. (22)

Moreover, the ocular use of atropine is generally not linked with systemic side effects commonly associated with its systemic administration, such as dry mouth, headache, facial flushing, constipation, difficulty in urination, increased blood pressure, and central nervous system disturbances. (23)However, ocular side effects are observed, including photophobia, near-vision blurriness, reduced amplitude of accommodation, and local allergic reactions. Photophobia, in particular, is the most frequently reported ocular side effect. (24)

Comment [Kabiru la4]: There's some form of systemic absorption of eye drops via the tears drainage pathway. Does this in any way found to be proven in the reviewed literatures ?.

Yen et al. found photophobia in 100% of subjects, which was a major reason for the more than 50% dropout rate after receiving 1% atropine in their study. In contrast, Shih et al. reported photophobia in only 22% of subjects treated with 0.5% atropine, while it was reported by 7% of subjects in the 0.25% atropine group, with negligible reports in the 0.1% atropine group. (23)

The ATOM 2 study reported allergic conjunctivitis in 4.1% of subjects in the atropine 0.1% and 0.5% groups. Children treated with 0.01% atropine showed minimal effect on pupil size and accommodation, no effect on near vision, and photophobia was uncommonly reported. These findings suggest a positive correlation between the incidence of photophobia and the concentration of atropine. (25)

While concentrations of 1% or 0.5% atropine have demonstrated high effectiveness in retarding myopia progression, they are also associated with significant side effects, particularly photophobia (up to 100%) and higher dropout rates (16%–58%). Concerns regarding potential long-term systemic or ocular side effects and rebound effects after atropine cessation, particularly with higher concentrations, have been raised. (26)

UNDER PEER REVIEW

Recent publications from Asia have highlighted the efficacy of 0.01% atropine in controlling myopia progression with lower rates of side effects. (15)

CONCLUSION

The body of evidence synthesized from various studies highlights the effectiveness of atropine in managing myopia progression in children. Through a comprehensive meta-analysis of seven randomized controlled trials, it is evident that atropine administration, whether over 12 months or 24 months, yields favorable outcomes in controlling myopia progression. Notably, both changes in mean spherical equivalent and mean axial length demonstrate positive responses to atropine intervention compared to placebo. However, it is important to consider the nuances in atropine concentration and duration of treatment, as well as the associated side effects. Lower concentrations, such as 0.01%, show promise in controlling myopia with fewer adverse effects, particularly photophobia, which is often associated with higher concentrations. Additionally, variations in treatment response across different populations underscore the importance of personalized approaches in managing myopia. Overall, while atropine emerges as a valuable intervention for myopia control, further research is warranted to optimize treatment protocols and address concerns regarding long-term efficacy and potential side effects. Collaborative efforts between clinicians, researchers, and policymakers are essential to refine strategies for effectively addressing the global burden of myopia in children.

UNDER PEER REVIEW

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UNDER PEER REVIEW

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