Title

Efficacy and Safety of 0.01%, 0.03%, and 0.05% Atropine Eye Drops in Reducing Myopia Progression: A Randomized Controlled Trial

Introduction

Myopia is an increasingly prevalent refractive error worldwide, particularly among children, and is now considered a major public health concern. Its rising incidence has been attributed to a combination of genetic predisposition and environmental factors such as increased near work and reduced outdoor activity[1].

Progressive myopia is associated with serious ocular complications, including myopic maculopathy, retinal detachment, glaucoma, and cataract[2]. Notably, even a 1-diopter increase in myopia is associated with a higher risk of these vision-threatening conditions, emphasizing the importance of early intervention to slow disease progression[3].

Atropine eye drops have been widely studied for myopia control. While high concentrations (e.g., 1%) are effective, their use is limited by side effects such as photophobia and near vision impairment[1]. Recent evidence from major trials, including ATOM and LAMP studies, has demonstrated that low-dose atropine (0.01%–0.05%) can effectively slow myopia progression with a significantly improved safety profile[4,5].

Rationale

There remains uncertainty regarding the optimal concentration that provides the best balance between efficacy and tolerability, particularly in different populations[6]. Most existing data are derived from East Asian populations, and there is limited evidence from South Asian settings, including Pakistan.

Therefore, this randomized controlled trial aims to compare the efficacy and safety of 0.01%, 0.03%, and 0.05% atropine eye drops in reducing myopia progression among children, to identify the most appropriate concentration for clinical use in our population.

Research Question

Among myopic children aged 6–18 years, does atropine 0.01%, 0.03%, or 0.05% differ in efficacy in reducing myopia progression, as measured by change in spherical equivalent refraction (SER) and axial length (AL) over the study period?

Objective of the Study

To evaluate and compare the effectiveness of 0.01%, 0.03%, and 0.05% atropine eye drops in slowing the progression of myopia among children aged 6-18 years and assess their safety profiles.

Variables of Interest

Independent variable: Concentration of atropine eye drops (0.01%, 0.03%, and 0.05%).

- **Dependent variables**: Change in SER of myopia taken with autorefractometer & keratometry (K) readings and AL taken with Zeiss IOL Master over 18 months.

- **Safety outcomes**: Frequency and severity of reported ocular side effects such as photophobia or irritation, near blur, dilated pupils and systemic side effects such as dry mouth, facial flushing, tachycardia.

Operational Definitions

- **Myopia progression**: Increase in SER of > -0.50D/year and/ or increase in AL by >0.5mm/year.
- **Efficacy**: ≤ -0.50D/year increase in SER and/ or ≤ 0.5mm/year increase in AL.
- **Safety**: Fewer than 10% of participants reporting ocular and systemic side effects.

Methodology

Settings, Duration, Ethical Concerns

- This study will be conducted at the Department of Ophthalmology, Khyber Teaching Hospital, Peshawar, after obtaining approval from the Ethical Review Board of Khyber Medical College (KMC) from June 2024 to Dec 2026. Written consent will be obtained from parents/guardians.

Study Type/Design

This study will follow a **Prospective Randomized Open-label Blinded Endpoint (PROBE) design**. Due to the nature of the intervention, both the participants and treating clinicians will be aware of the allocated concentration of atropine (open-label design).

However, to minimize assessment and analytical bias:

- **Outcome assessors** measuring SER, and AL will be **blinded to treatment allocation**.
- **Data analysts/statisticians** will also be **blinded to group allocation**, with treatment groups coded (e.g., Group A, B, C) until completion of the primary analysis.

Enrollment:

Pediatric participants aged 6–18 years with SER of myopia ≥ −0.50 diopters (D) will be recruited through the pediatric ophthalmology and optometry outpatient services. Eligible participants will be enrolled after meeting the inclusion criteria.

Baseline Assessment

All participants will undergo a comprehensive ophthalmic evaluation. Cycloplegia will be induced using Cyclopentolate 1% (Cyclopen 1%). The following baseline measurements will be recorded:

- Cycloplegic autorefraction, which will be converted into SER for analysis
- AL measured using IOL Master
- Keratometric reading (K-readings) measured using IOL Master
- Best-corrected visual acuity (BCVA)
- Anterior and posterior segment examination, performed by a consultant ophthalmologist

Demographic data, including age and gender, will also be documented.

Sampling Procedure (Randomization and Intervention)

Participants will be recruited through consecutive non-probability sampling. They will be randomly allocated in 1:1:1 into three groups using block randomization to ensure equal distribution. Multiple blocks of size 6 will be randomly selected from 12 permutations made in excel sheet using lottery method to ensure allocation concealment and prevent predictability.

- Group A: 0.01% atropine eye drops once daily at bedtime
- Group B: 0.03% atropine eye drops once daily at bedtime
- Group C: 0.05% atropine eye drops once daily at bedtime

The intervention will continue for the entire study duration.

Follow-up and Outcome Assessment

Participants will be followed at baseline, 4 months, 8 months, 12 months, and 18 months.

At each follow-up visit:

- SER, AL, K-readings, and BCVA will be reassessed

- Treatment adherence will be evaluated
- Ocular and systemic adverse events will be documented

Outcome Measures

- Primary Outcomes:
    - Change in spherical equivalent refraction (SER)
    - Change in axial length (AL) over 18 months
- Secondary Outcomes:
    - Frequency and type of ocular and systemic adverse effects associated with each atropine concentration

Inclusion Criteria

1. Children aged 6–18 years.
2. SER between -1.00 and -6.00 diopters.

Exclusion Criteria

1. History of ocular surgery or trauma.
2. Use of other myopia control interventions in the last 6 months.
3. Allergies to atropine.

Sample Size Calculation

The sample size is calculated using OpenEpi based on an expected reduction of 69% in myopia progression with the highest dose (0.05%), with 80% power and a 5% significance level. Calculate sample size is 95. The number of participants in groups will be 32,32 and 31.

Statistical Methods

- **Efficacy analysis**: The mean change in SER and AL over time will be compared between groups using a **linear mixed-effects model**, accounting for repeated measurements within subjects. Post hoc pairwise comparisons with appropriate adjustment (e.g., Bonferroni correction) will be performed if overall group differences are significant.
- If model assumptions are substantially violated, appropriate data transformation or non-parametric alternatives (e.g., Friedman test) will be considered.
- **Safety analysis**: The frequency of ocular or systemic adverse events will be compared between groups using the **chi-square test** or **Fisher's exact test**, as appropriate.
- **Adjustment for confounders**: like age, baseline refraction (SER) and axial length and parental myopia, multivariate regression analysis will be performed.

Conflict of Interest

None.

References

1. Repka, M., Weise, K., Chandler, D., Wu, R., Melia, B., Manny, R., et al (2023). Low-Dose 0.01% Atropine Eye Drops vs Placebo for Myopia Control: A Randomized Clinical Trial.. *JAMA ophthalmology*. https://doi.org/10.1001/jamaophthalmol.2023.2855.
2. Shah, R., Vlasak, N., & Evans, B. (2024). High myopia: Reviews of myopia control strategies and myopia complications. *Ophthalmic and Physiological Optics, 44*, 1248 - 1260. https://doi.org/10.1111/opo.13366.
3. Yam, J., Jiang, Y., Tang, S., Law, A., Chan, J., Wong, E., Ko, S., Young, A., Tham, C., Chen, L., & Pang, C. (2019). Low-Concentration Atropine for Myopia Progression (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control.. *Ophthalmology, 126 1*, 113-124 . https://doi.org/10.1016/j.ophtha.2018.05.029.
4. Wei, S., Li, S., An, W., Du, J., Liang, X., Sun, Y., Zhang, D., Tian, J., & Wang, N. (2020). Safety and Efficacy of Low-Dose Atropine Eyedrops for the Treatment of Myopia Progression in Chinese Children: A Randomized Clinical Trial.. *JAMA ophthalmology*. https://doi.org/10.1001/jamaophthalmol.2020.3820.
5. Ha, A., Kim, S., Shim, S., Kim, Y., & Jung, J. (2021). Efficacy and Safety of 8 Atropine Concentrations for Myopia Control in Children: A Network Meta-Analysis.. *Ophthalmology*. https://doi.org/10.1016/j.ophtha.2021.10.016.
6. Lee, S., Tseng, B., Wang, J., & Chiu, C. (2024). Efficacy and Safety of Low-Dose Atropine on Myopia Prevention in Premyopic Children: Systematic Review and Meta-Analysis. *Journal of Clinical Medicine, 13*. https://doi.org/10.3390/jcm13051506.