Letter to Editor

Is 0.01% Atropine Eye Drop Safe and Effective in Slowing Myopia Progression in Nepalese Children?

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Dear Editor,

Adhikari et al. (2023) recently reported the results from Phase I of their five-year non-randomized study "Safety and Efficacy of Low Dose Atropine in Nepalese Children with Progressive Myopia." Two hundred myopic children aged 6 to 16 years with baseline spherical equivalent refractive error (SER) from -1.50D to -8.00 D and myopia progression > 0.5 D in the last six months (based on electronic medical records) received 0.01% atropine eye drops in both eyes once daily at bedtime. At six months, one year, and two years follow-up, axial elongation was 0.18 ± 0.02 D, 0.17 ± 0.02 D, and 0.19 ± 0.04 D, and myopia progression was 0.20 ± 0.01 mm, 0.30 ± 0.02 mm, and 0.30 ± 0.02 mm, respectively. The attrition rate was significant as 30% of children were lost to follow-up after 6 months, 33% after one year, and 50% after two years. The study concluded that "Topical low-dose atropine appears to be safe and efficacious in halting the progression of myopia in a cohort of Nepalese children".

The authors are to be congratulated for attempting to address a topical issue of clinical relevance in a population in which low-dose atropine has yet to be systematically studied. However, several issues with the paper significantly undermine the reported conclusions of both safety and efficacy. It is unfortunate that such a large-scale study only included an intervention group which significantly limits the ability to derive meaningful inferences. Most notably, without comparison of axial elongation and myopia progression to a control group, it is difficult to ascertain whether 0.01% atropine eye drops had any effect on axial elongation and myopia progression or whether the observed slowing of axial elongation and myopia progression in the intervention group was due to natural history.

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As children grow older, there is a natural decline in axial elongation and myopia progression. (Hyman et al., 2005; Jones-Jordan et al., 2021; Shamp et al., 2022) While the authors state that there was a statistically significant slowing of axial elongation and myopia progression, statistically valid comparisons between post-treatment and pre-treatment within-subject outcomes would require a matched-sample (paired) t-test instead of an independent t-test used in the study.(Xu et al., 2017)

Notwithstanding the statistical issues, a case could be made that the enrolled children were progressing at greater than -0.50D in the past six months before the start of the study, so the observed magnitude of myopia progression after 6 months of initiation of the treatment (0.20±0.01) was significantly reduced. This may not necessarily reflect a beneficial effect but rather could be due to non-systematic variation in observations around a true mean on repeat measures, a common statistical phenomenon known as the regression to the mean.(Morton and Torgerson, 2005) After 6 months, axial length increased by 0.18 mm, which appears to be a typical axial eye growth expected of myopic children aged 12 years (the average age of children enrolled at the start of the study). (Donovan et al., 2012; Shamp et al., 2022) Another issue is the apparent inconsistency between the observed axial elongation and myopia progression. After 6 months of treatment, myopia increased by 0.20 D, which indicates a much slower myopia progression than that predicted by a 0.18 mm increase in axial length (assuming 1 mm = 2.5D). (Donovan et al., 2012; Shamp et al., 2022) On subgroup comparisons, it was stated that myopia progression was greater in the Aryan race than in the Mongolian race, but this statement seems unsupported by the data since the average 2-year myopia progression was approximately similar between the two cohorts (Aryan: 0.86D; Mongolian: 0.88D). In addition, the high rate of attrition in the study after two years poses a significant challenge in interpreting the findings as results are subject to sample bias in that the drop-out proportion may consist of children who were not responding to the treatment.

While the authors state that atropine eye drops were safe in the population studied without any ocular and systemic side effects, including no effects on near vision and near point of accommodation, no data on these outcomes have been presented in the paper. Moreover, the lack of effects on near vision and near point of accommodation raises questions about the quality checks (e.g., method of preparation and compounding) of the experimental drug by the pharmaceutical company, since atropine, even in its most diluted form, is known to have a small effect on pupil size and accommodation. (Richdale et al., 2023; Yam et al., 2019)

The authors conclude with the hope that “the results from this study will contribute to the wide use of atropine therapy in progressive myopia in Nepalese children by eye-care professionals in Nepal” and recommend that “the concerned authorities make the drug easily available across the country”. However, considering the limitations of the study design and presented data, these statements appear to be the authors' opinions rather than those supported by the evidence presented in the paper. The study is planned to continue to Phase II where children

will be taken off treatment and Phase III where those who progress by more than 0.50 D will be restarted on atropine eye drops. However, because of the study limitations, it would be difficult to derive any meaningful conclusions on efficacy from these planned phases. As the authors rightly point out, a well-designed randomized controlled trial is necessary to inform the efficacy and safety of low-dose atropine eye drops in this population. Perhaps a multicenter collaborative effort would facilitate optimal designs and reporting of future trials in this population.

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