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Atropine for the Treatment of Childhood Myopia in India: Multicentric Randomized Trial

This multicentric, double-blinded, placebo-controlled, randomized clinical trial reports 1-year data proving efficacy of 0.01% atropine drops in reducing myopia progression (spherical equivalent [SE]) in Indian children having mild to moderate myopia without any significant effect on axial length (AL) elongation.

Myopia is rapidly emerging as a major public health problem worldwide. A recent meta-analysis documents an increasing trend of myopia in the last 4 decades in India with a prevalence of approximately 7.5%.[1] Atropine for the Treatment of Childhood Myopia in India (I-ATOM) was a multicentric, double-masked, placebo-controlled, randomized clinical trial conducted at 3 tertiary centers to evaluate the 1-year efficacy of 0.01% atropine in myopic children of Indian ethnicity. This trial was registered in the Clinical Trial Registry − India (CTRI/2016/11/007450) and followed the tenets of the Declaration of Helsinki. Institutional ethics committee approval was obtained by all participating centers, and informed consent was obtained from parents and guardians. A total of 100 children aged 6 to 14 years with −0.5 diopters (D) to −6 D of myopia on cycloplegic refraction, astigmatism $\leq$ 1.5 D, anisometropia $\leq$ 1 D, distance best-corrected visual acuity of $\geq$ 20/40, and documented myopia progression of $>$ 0.5 D in the preceding year were enrolled. Our primary outcome measure was change in SE and AL at 1 year in cases compared with controls. Secondary measures were change in anterior chamber depth, lens thickness, vitreous chamber depth, pupil size, accommodation amplitude (D), and any side effects related to therapy.

The participants were randomized in 1:1 ratio to the atropine or placebo group using computer-generated random numbers. Baseline evaluation included assessment of best-corrected visual acuity using the Early Treatment Diabetic Retinopathy Study chart at 4 m (converted to the logarithm of the minimum angle of resolution scale), distance-corrected near vision using Snellen's near vision chart at 33 cm, near point of accommodation using Royal Air Force ruler, photopic and mesopic pupil size using PLR-200 monocular infrared pupillometer (NeurOptics), and ocular biometry using IOLMaster 700 (Carl Zeiss, Meditec AG). The refractive error was noted as SE. Accommodation amplitude was calculated as inverse of near point of accommodation (in meters).

Commercially available 0.01% atropine sulfate eye drops with stabilized oxychloro complex as a preservative (Myopin, Appasamy Ocular Devices [P] Ltd.) were used. The vehicle, preservative, and pH were the same in atropine and placebo eye drops. Bottles, similarly labeled with the subject identification number and date of expiration, were distributed to all participating centers. The investigators and participants were masked to the type of intervention. After the parents were told about the dose (single drop), time (before bedtime at night), method of administration (in supine position after pulling the lower eyelid), and expected side effects (e.g., photophobia, blurring, flu-like symptoms, rashes), bottles were dispensed on every visit. An optometrist who was masked to the group allocation reassessed the parameters on follow-up at 2 weeks, 2 months, 4 months, 8 months, and 12 months. Parents were asked to self-report any side effects with topical therapy and subsequently directly asked about the symptoms. Compliance was monitored by collection of used bottles on every visit. After 1 year, all the participants were administered 0.01% atropine eye drops.

Age (atropine = 10.6 ± 2.2 years; placebo = 10.8 ± 2.2 years), mean SE (atropine: −3.5 ± 1.3 D; placebo: −3.7 ± 1.3 D), and other baseline parameters between the 2 groups were comparable (Table S1, available at www.aaojournal.org). Of 100 recruited children, 8 were lost to follow-up (3 in the atropine-treatment group and 5 in the placebo-control group).

Mean increase in myopia (SE at 1 year minus baseline values) was −0.16 ± 0.4 D ($P = 0.005$) in the atropine group and −0.35 ± 0.4 D ($P < 0.001$) in the placebo group (Table 1, Fig S1, available at www.aaojournal.org). The difference of mean SE between the 2 groups was 0.19 D ($P = 0.021$) with significantly greater myopia progression in the placebo group compared with the atropine group (Table 1). Mean AL elongation in the atropine-treatment and placebo-control groups was 0.22 ± 0.2 mm ($P < 0.001$) and 0.28 ± 0.28 mm ($P < 0.001$), respectively, at 1 year (Table 1, Fig S1). Although the difference in AL change between the groups (0.06 mm $P = 0.19$) did not reach statistical significance, there was a greater elongation in the placebo group (Table 1). Likewise, the mean change in other ocular biometric parameters, such as anterior chamber depth, lens thickness, and vitreous chamber depth, was not significantly different in the 2 groups (Table 1, Table S2, available at www.aaojournal.org). These findings corroborate with the results of ATOM 2[2] and Low concentration Atropine for Myopia Progression study,[3] in which favorable effects of 0.01% atropine in inhibiting myopic SE progression have been observed with minimal effect on AL elongation.

No myopia progression ($<$ 0.25 D increase in SE) was noted in 64% (n = 30) of children in the atropine-treatment group compared with only 30% (n = 13) in the placebo-control group; myopia progression $>$ 0.5 D was seen in 13% (n = 6) of cases in the atropine group compared with 38% (n = 17) in the placebo group. Younger age and higher myopia at baseline have been associated with poor response to atropine therapy.[4] In this study, mean age and SE of patients showing myopia progression $>$ 0.5 D was 11 ± 2 years (range, 7−13 years) and −3.12 ± 1.07 D (range, −2 to −5 D), respectively, in the atropine group. A rapid progression ($>$ 1 D) that has been noted in the atropine-treatment group in 18% to 28% of

Table 1. Comparison of Mean Change in Characteristics of Two Study Groups after 1 Year

Variables (Mean ± SD) [95% CI]	Atropine Group [n = 47]	Placebo Group [n = 45]	P Value*
SE (D)	−0.16 ± 0.38 [−0.05 to −0.26]	−0.35 ± 0.4 [−0.23 to −0.48]	0.02
Best-corrected visual acuity (logMAR)	0.002 ± 0.08 [0.025 to −0.02]	0.002 ± 0.03 [−0.006 to 0.01]	0.98
AL (mm)	0.22 ± 0.2 [0.16–0.27]	0.28 ± 0.28 [0.21–0.37]	0.19
Anterior chamber depth (mm)	0.03 ± 0.16 [−0.02 to 0.07]	−0.01 ± 0.15 [−0.06 to 0.03]	0.2
Lens thickness (mm)	1.1 ± 0.14 [−0.03 to 0.05]	0.05 ± 0.21 [−0.01 to 0.11]	0.64
Vitreous chamber depth (mm)	0.17 ± 0.19 [0.11–0.22]	0.24 ± 0.21 [0.18–0.3]	0.11
Amplitude of accommodation (D)	−0.98 ± 1.86 [−0.44 to −1.52]	−1.25 ± 2.01 [−0.67 to −1.82]	0.53
Mesopic pupil size (mm)	0.05 ± 0.43 [−0.07 to 0.17]	−0.12 ± 0.64 [−0.3 to 0.06]	0.15
Photopic pupil size (mm)	1.2 ± 0.47 [−0.11 to 0.16]	−0.06 ± 0.58 [−0.64 to 0.52]	0.45

AL = axial length; CI = confidence interval; D = diopters; logMAR = logarithm of the minimum angle of resolution; SD = standard deviation; SE = spherical equivalent.
*P value evaluated using Wilcoxon signed-rank test.

children with Chinese ethnicity[2,3] was seen in none of our atropine-treatment cohort and remained low in the placebo group (n = 4; 8.9%). This was also seen in the North India Myopia study,[5] which noted a rapid myopic shift of > 1 D in only 7.4% of 1279 children at 1 year. This is due to less rapid myopia progression or low environmental risk factors in Indian children.

Mesopic and photopic pupil size, accommodation amplitude, distance, and near vision remained stable on follow-up and did not change significantly between the groups (Table 1, Table S2). None of the patients reported any blurring of vision or photophobia, or required discontinuation of therapy. In patients who were lost to follow-up, the reason for discontinuation was unrelated to the side effects.

The I-ATOM in India study noted a significant reduction of 54% in mean SE progression with 0.01% atropine at 1 year in myopic children with no side effects. Mean AL elongation was 21% less in the atropine group than in the placebo group, but this was not statistically significant. Limitations of this study include a short follow-up, a relatively small sample size, a lack of comparison of other atropine strengths (0.05% or 0.02%),[3,6,7] and unanswered questions such as optimal duration, rebound effect, and whether 0.01% atropine reduces AL elongation. Nonetheless, the results show a similar efficacy of 0.01% atropine eye drops in Indian children with mild to moderate myopia as seen in other ethnic groups.

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HUMAN SUBJECTS: Human subjects were included in this study. This trial was registered in the Clinical Trial Registry - India (CTRI/2016/11/007450) and followed the tenets of the Declaration of Helsinki. Institutional ethics committee approval was obtained by all participating centers and informed consent was obtained from the parents and/or guardians.

No animal subjects were used in this study.

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Incidence of Retinoblastoma Has Increased: Results from 40 European Countries

Retinoblastoma is the most common intraocular malignancy. Its incidence has been reported to be 1 case in from 15 000 to 18 000 live births, or approximately 12, 6, or 4 cases per 1 million children younger than 5, 10, or 15 years, respectively.[1,2] The aim of this study was to estimate the incidence of retinoblastoma across European countries within a 1-year time frame. Data were collected through an international, multicenter, 1-year cross-sectional analysis that has been described in detail previously.[3] Briefly, retinoblastoma treatment centers reported all new cases of retinoblastoma that were diagnosed between January 2017 and December 2017. The final analysis involved only those countries that described their data as being likely complete. The human ethics committees of the London School of Hygiene and Tropical Medicine as well as the ethics committees of all local hospitals approved the study. All research adhered to the tenets of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective nature of the study.

Two methods were used to estimate the incidence rate of retinoblastoma: the live birth method and the age cohort method. Country population estimates and birth rates were retrieved from the World Bank Population Prospects and the United Nations database for 2017. The formula used to calculate the live-birth incidence rate in each country is:

$$\text{Incidence (live birth)} = \frac{\text{No. of Retinoblastoma Cases in 2017}}{\text{Population in 2017} \times \text{Crude Birth Rate in 2017}}$$

The formula used to calculate the age cohort incidence rate (per 1 million children younger than 5 years) is:

$$\text{Incidence (age cohort)} = \frac{\text{No. of Retinoblastoma Cases in 2017}}{\text{Population Estimate Age} < 5 \textit{ Years in } 2017} \times 1 \text{ Million}$$

Bootstrap sampling was used to estimate the distribution of each incidence rate. Linear regression analysis was conducted to identify factors that may affect the country-level incidence rate, including the following variables: age at diagnosis, proportion of bilateral cases, proportion of familial cases, proportion of male births, and per capita gross domestic product for the year 2017 (World Bank database). Summary data were calculated for each country and European region (north, south, east, west). An α level of 0.05 was used.

From the original 40 countries (with 517 retinoblastoma patients), 24 countries were identified as representing likely-complete national-level data, and all 294 patients from these 24 countries were included in the analysis (Table 1). The number of live births for the year 2017 was calculated for each country and region (Table 1). The combined data resulted in a live birth incidence rate of 1 in 13 915 (confidence interval [CI], 12 315–15 150), or 7.2 per 100 000, live births in Europe. The analysis was repeated with the United Nations population data and similar outcomes were seen for each country and overall (1 in 13 844 live births; CI, 12 309–15 083). The highest live birth incidence was seen in northern Europe (1 in 12 907 live births), whereas the lowest incidence rate was seen in southern Europe (1 in 17 177 live births; Fig S1, available at www.aaojournal.org).

The combined age cohort incidence rate was 14.1 per 1 million children younger than 5 years (CI, 12.9–15.9 per 1 million children younger than 5 years) and 4.6 per 1 million children younger than 15 years (CI, 4.1–5.2 children younger than 15 years; Table 1). The age cohort results were used in a linear regression analysis (Table S2, available at www.aaojournal.org). No significant relationship was found between incidence rate and country gross domestic product. The only variable that resulted in a significant association with incidence rate was the proportion of familial cases ($P = 0.002$), which showed an increasing relationship between the proportion of familial cases and the incidence rate within that country. A similar trend was present for the countries grouped by region (Fig S2, available at www.aaojournal.org).

The incidence rates calculated in this study—1 in 13 844 live births or 14.1 and 4.6 per 1 million children younger than 5 and 15 years, respectively—are higher than those reported previously. Although some studies have suggested stable incidence rates over many years through the early 2000s,[1,2,4] recent national data from Finland document an increase from approximately 1 in 16 700 live births to 1 in 12 500 live births from 1990 to 2014.[5] The increase in Finland was not evident when familial retinoblastoma was excluded. Our study supports the conclusion that the incidence of retinoblastoma has increased in recent decades even more widely in Europe because of an increasing number of familial patients.