Analysis of Changes in Refraction and Biometry of Atropine- and Placebo-Treated Eyes

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PURPOSE. To analyze changes in refraction and associated biometric changes in atropine- and placebo-treated eyes in the Atropine for Treatment of Myopia study (ATOM1).

METHODS. A total of 400 myopic children, aged 6 to 12 years, were assigned randomly to receive 1% atropine or a placebo agent in one eye daily for 2 years, after which drops were stopped and children monitored for another year. Cycloplegic autorefraction, A-scan biometry, and automated keratometry were performed at the initial visit, 2 weeks (baseline), and at 4, 8, 12, 16, 20, 24, 30, and 36 months.

RESULTS. A total of 315 children (78.3%) completed the study. In placebo-treated eyes, there was myopic progression of −1.55 diopters (D), between baseline and 36 months, associated with reductions in corneal curvature (K; −0.13 D) and anterior chamber depth (ACD; −0.17 mm) and increases in lens thickness (LT; 0.05 mm), vitreous chamber depth (VCD; 0.65 mm), and axial length (AL; 0.53 mm). Multivariate analysis of change in spherical equivalent demonstrated that the hyperopic shift (0.20 D) noted in atropine-treated eyes between baseline and 4 months, and the myopic rebound (−0.74 D) noted between 24 to 30 months when atropine was stopped, were associated with a reduction and increase in VCD and AL, respectively, after adjusting for age and sex. Changes in K, ACD, and LT were less relevant. Between 4 and 24 months, atropine-treated eyes demonstrated gradual myopic progression (−0.40 D), accompanied by reduction in K (−0.06 D) and ACD (−0.07 mm) and increase in VCD (0.13 mm) and AL (0.06 mm).

CONCLUSIONS. Atropine appeared to slow myopia progression mainly by reducing or slowing the growth in VCD, and thereby AL. (ClinicalTrials.gov number, NCT00371124.)

Keywords: atropine, myopia, biometry

Myopia is prevalent among Singaporean children at 6.4% in 5- to 6-year-olds and 43.9% in 9-year-olds, and atropine has shown efficacy in slowing myopic progression. In the Atropine for Treatment of Myopia (ATOM1) study, 1% atropine eye drops slowed progression by 80% compared with placebo at 36 months. Specifically, in atropine-treated eyes, there was a hyperopic shift on commencement from baseline to 4 months, gradual myopic progression between 4 and 24 months, a myopic rebound after atropine was stopped, between 24 and 30 months, and myopic progression from 30 to 36 months. In the ATOM2 study, eyes were randomized to lower doses of atropine (0.5%, 0.1%, and 0.01%) and a hyperopic shift was not observed on starting treatment. However, there was still reduced myopic progression and a myopic rebound, which were less pronounced with lower doses.

Refractive error is dependent on biometric parameters, including corneal curvature (K), anterior chamber depth (ACD), lens thickness (LT), vitreous chamber depth (VCD), and axial length (AL). This study investigated associations between changes in biometry and refraction in both atropine- and placebo-treated eyes in ATOM1, which would allow for a better understanding of how atropine influences ocular growth in children.

MATERIALS AND METHODS

The ATOM1 was a randomized, double-masked, placebo-controlled trial designed primarily to investigate the efficacy of topical atropine 1% eye drops in preventing progression of childhood myopia. The study conformed to the tenets of the Declaration of Helsinki and was approved by the Singapore Eye Research Institutional Review Board. A total of 400 children aged 6 to 12 years with myopia of spherical equivalent −1.00 to −6.00 diopters (D) were recruited in the study. Children were randomized to receive either 1% atropine or placebo drops in one eye daily for 24 months. Treatment was then stopped and children monitored for a further year.

Refractive error was measured by cycloplegic autorefracation and cycloplegia was achieved with 1 drop of proparacaine hydrochloride (Alcaine; Alcon-Couvreur, Puurs, Belgium) followed by 3 drops of 1% cyclopentolate hydrochloride (Cyclogyl; Alcon-Couvreur), administered approximately 5 minutes apart. Measurements were taken at least 30 minutes later, using a Canon RK5 autorefractor (Canon, Inc., Ltd., Tochigiken, Japan). Five recordings were taken (all within 0.25
D in both sphere and cylinder components) and averaged. Spherical equivalent was calculated as sphere plus half cylindrical power. Corneal curvature (K) was also measured using the Canon RK5 autokeratometer (Canon, Inc., Ltd.). Five recordings were taken along the maximum and minimum axis (all within 0.5 D) and averaged.

We used A-scan ultrasonography (Nidek US-800 EchoScan; Nidek Co., Ltd., Tokyo, Japan) to assess ocular biomechanical parameters after pupillary dilation. Six independent measurements of ACD, LT, VCD, and AL between eyes from each treatment arm at the initial visit and between those lost to follow-up and those remaining in the study. Within-group differences in spherical equivalent, K, ACD, LT, VCD, and AL between baseline and 4 months, 24 and 30 months, and 30 and 36 months were assessed using the Wilcoxon signed ranks test. As there were three within-group comparisons, the threshold for statistical significance was appropriately adjusted according to the Bonferroni method. To assess for possible effects of age on change in biomeometry and refraction, data were stratified into three groups (6.0–7.9, 8.0–9.9, and 10.0–12.0 years) based on age at the initial visit and reviewed.

### Statistical Analysis

We used SPSS Statistics version 21 (IBM Corp., Armonk, NY, USA) for data analysis. Between-group differences and P values were assessed using the Mann-Whitney U test, as the variables did not conform to a normal distribution. This was performed to assess for differences in age, sex, spherical equivalent, K, ACD, LT, VCD, and AL between eyes from each treatment arm at the initial visit and between those lost to follow-up and those remaining in the study. Within-group differences in spherical equivalent, K, ACD, LT, VCD, and AL between baseline and 4 months, 24 and 30 months, and 30 and 36 months were assessed using the Wilcoxon signed ranks test. As there were three within-group comparisons, the threshold for statistical significance was appropriately adjusted according to the Bonferroni method. To assess for possible effects of age on change in biomeometry and refraction, data were stratified into three groups (6.0–7.9, 8.0–9.9, and 10.0–12.0 years) based on age at the initial visit and reviewed.

### Table 1. Within Group and Between Group Analysis of Changes in Refraction and Biometry in Atropine- and Placebo-Treated Eyes Between Baseline and 4 Months, 24 to 30, 24 to 36, and Baseline to 36 Months

<table>
<thead>
<tr>
<th>Change Between</th>
<th>Spherical equivalent, D</th>
<th>P Value</th>
<th>K, D</th>
<th>P Value</th>
<th>ACD, mm</th>
<th>P Value</th>
<th>LT, mm</th>
<th>P Value</th>
<th>VCD, mm</th>
<th>P Value</th>
<th>AL, mm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline and 4 mo</td>
<td>0.20 (0.03, 0.38)</td>
<td>&lt;0.001</td>
<td>0.00 (−0.07, 0.07)</td>
<td>0.132</td>
<td>−0.01 (−0.12, 0.08)</td>
<td>0.224</td>
<td>−0.02 (−0.07, 0.04)</td>
<td>0.013</td>
<td>−0.05 (−0.05, 0.04)</td>
<td>&lt;0.001</td>
<td>−0.10 (−0.23, 0.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4 and 24 mo</td>
<td>−0.40 (−0.74, −0.10)</td>
<td>&lt;0.001</td>
<td>−0.06 (−0.13, 0.00)</td>
<td>&lt;0.001</td>
<td>−0.07 (−0.19, 0.02)</td>
<td>&lt;0.001</td>
<td>0.01 (−0.05, 0.06)</td>
<td>0.504</td>
<td>0.13 (0.00, 0.28)</td>
<td>&lt;0.001</td>
<td>0.06 (−0.11, 0.25)</td>
<td>0.006</td>
</tr>
<tr>
<td>24 and 30 mo</td>
<td>−0.74 (−1.00, −0.43)</td>
<td>&lt;0.001</td>
<td>−0.05 (−0.13, 0.06)</td>
<td>0.002</td>
<td>−0.13 (−0.25, 0.02)</td>
<td>&lt;0.001</td>
<td>0.06 (0.03, 0.15)</td>
<td>&lt;0.001</td>
<td>0.17 (0.05, 0.31)</td>
<td>&lt;0.001</td>
<td>0.16 (−0.02, 0.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30 and 36 mo</td>
<td>−0.35 (−0.60, −0.15)</td>
<td>&lt;0.001</td>
<td>0.00 (−0.07, 0.07)</td>
<td>0.222</td>
<td>0.02 (−0.12, 0.13)</td>
<td>0.443</td>
<td>0.01 (−0.07, 0.08)</td>
<td>0.580</td>
<td>0.15 (0.06, 0.25)</td>
<td>&lt;0.001</td>
<td>0.16 (0.02, 0.35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline and 36 mo</td>
<td>−1.35 (−1.89, −0.75)</td>
<td>&lt;0.001</td>
<td>−0.07 (−1.89, 0.00)</td>
<td>&lt;0.001</td>
<td>−0.20 (−0.32, −0.06)</td>
<td>&lt;0.001</td>
<td>0.08 (−0.08, 0.14)</td>
<td>0.179</td>
<td>0.15 (0.06, 0.25)</td>
<td>&lt;0.001</td>
<td>0.16 (0.02, 0.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values in parentheses are 25th and 75th percentiles.
Linear regression was performed using change in spherical equivalent as the dependent variable, changes in K, ACD, LT, and VCD as independent variables, and adjusted for age and sex. Before conducting the analysis, we checked assumptions for the linear regression: (1) checking outliers-residual analysis was conducted and seven (five atropine and two placebo) outliers removed; (2) checking independence using the Durbin-Watson estimate, all estimates were less than 4; (3) checking normality assumptions of residuals, normality probability plot was satisfactory; and (4) checking constant variance, scatter plot of standardized residuals versus standardized predicted value were satisfactory. Outliers-residual analysis was conducted and seven (five atropine and two placebo) outliers removed. Change in AL was not included as it brought about collinearity. Statistical significance was set at P less than 0.05.

### Results

A total of 313 children (78.3%) completed the 3-year study, of whom 147 were treated with atropine and 166 with placebo. At the initial visit, there was no difference in age (0.24 vs. 0.15 years, P = 0.495), sex (56.9% vs. 52.4% males, P = 0.538), spherical equivalent (~3.36 vs. ~3.58 D, P = 0.074), K (43.65 vs. 43.82 D, P = 0.170), ACD (3.87 vs. 3.89 mm, P = 0.488), LT (3.41 vs. 3.42 mm, P = 0.751), VCD (17.52 vs. 17.50 mm, P = 0.554), or AL (24.80 vs. 24.80 mm, P = 0.837) between atropine- and placebo-treated eyes. There was no significant difference between children lost to follow-up and those still in the study with regard to age, sex, spherical equivalent, K, ACD, LT, VCD, and AL.

Between baseline and 36 months, myopic progression (~1.55 D) was observed in placebo-treated eyes. This was accompanied by reductions in K (~0.13 D) and ACD (~0.17 mm) and increases in LT (0.05 mm), VCD (0.65 mm), and AL (0.53 mm). (Fig.) Looking at the biometric growth pattern stratified into ages 6.0 to 7.9, 8.0 to 9.9, and 10.0 to 12.0 years, changes of the various parameters over time were unidirectional (with no U-shaped relation noted), although rate of change was greater in younger children.

In the atropine-treated eyes, the hyperopic shift between baseline and 4 months was accompanied by a reduction in LT (P = 0.013), VCD (P < 0.001), and AL (P < 0.001). Between 4 and 24 months, while still on atropine, there was a gradual increase in myopia, which was accompanied by reduction in K (P < 0.001) and ACD (P < 0.001), and increase in VCD (P < 0.001) and AL (P = 0.006). Compared with placebo-treated eyes, atropine-treated eyes showed less myopic progression and less increase in LT (P < 0.034), VCD (P < 0.001), and AL (P < 0.001) between 4 and 24 months. When atropine was stopped (between 24 and 30 months), there was a marked increase in myopia and greater reduction in ACD (P = 0.008), and increase in LT (P < 0.001), VCD (P < 0.001), and AL (P < 0.001) compared with placebo-treated eyes. Atropine-treated eyes continued to demonstrate greater rates of myopic progression compared with placebo-treated eyes between 30 and 36 months, but these were mainly accompanied by an increase in VCD (P < 0.001) and AL (P < 0.001). These results have been summarized in Table 1. Median, 25th percentile, and 75th percentile values have been presented.

To determine which factors were most associated with the hyperopic shift and myopic rebound in the atropine-treated eyes, a multivariate linear regression was performed using spherical equivalent as the independent variable, with K, ACD, LT, and VCD as dependent variables, adjusting for age and sex (Table 2). This showed that in atropine-treated eyes, the hyperopic shift between baseline and 4 months and myopic rebound between 24 and 30 months were both associated with a reduction and increase in VCD, respectively. A comparison of atropine- and placebo-treated eyes between 24 and 30 months also showed that there was a small reduction in K, which was similar in the two groups, and a relative increase in LT in atropine-treated eyes. Change in spherical equivalent in

### Table 2. Linear Regression With Dependent Variable Spherical Equivalent and Independent Variables K, ACD, LT, and VCD, Adjusted for Age and Sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>Atropine, n = 142</th>
<th>Placebo, n = 164</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline and 4 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/y</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>K/D</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td>ACD/mm</td>
<td>0.01</td>
<td>—</td>
</tr>
<tr>
<td>LT/mm</td>
<td>—0.03</td>
<td>—</td>
</tr>
<tr>
<td>VCD/mm</td>
<td>—0.06</td>
<td>—</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>0.01 (0.01)</td>
<td>0.05 (0.02)</td>
</tr>
<tr>
<td>B (SE)</td>
<td>0.43</td>
<td>0.00 (0.05)</td>
</tr>
<tr>
<td>P</td>
<td>0.558</td>
<td>0.005</td>
</tr>
<tr>
<td>4 to 24 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/y</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>K/D</td>
<td>—0.07</td>
<td>—</td>
</tr>
<tr>
<td>ACD/mm</td>
<td>—0.09</td>
<td>—</td>
</tr>
<tr>
<td>LT/mm</td>
<td>0.01</td>
<td>—</td>
</tr>
<tr>
<td>VCD/mm</td>
<td>0.14</td>
<td>—</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>—0.05 (0.02)</td>
<td>0.04 (0.02)</td>
</tr>
<tr>
<td>B (SE)</td>
<td>0.510</td>
<td>0.496</td>
</tr>
<tr>
<td>P</td>
<td>0.010</td>
<td>0.081</td>
</tr>
<tr>
<td>24 to 30 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age/y</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sex</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>K/D</td>
<td>—0.03</td>
<td>—</td>
</tr>
<tr>
<td>ACD/mm</td>
<td>0.12</td>
<td>—</td>
</tr>
<tr>
<td>LT/mm</td>
<td>0.04</td>
<td>—</td>
</tr>
<tr>
<td>VCD/mm</td>
<td>0.17</td>
<td>—</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>0.07 (0.02)</td>
<td>0.06 (0.02)</td>
</tr>
<tr>
<td>B (SE)</td>
<td>0.151</td>
<td>0.572</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

—, there is no mean difference for age and sex.
Figure. Refraction and biometry between baseline and 36 months in atropine- (solid line) and placebo-treated (dashed line) eyes (Error bars: 95% confidence interval).
placebo-treated eyes was more complex, being associated with reduction in K and an increase in LT and VCD.

**DISCUSSION**

Over the 3-year study period, there was myopic progression in placebo-treated eyes of ~1.57 D, which was associated with a reduction in K and increase in LT, VCD, and AL. The association between increasing VCD and AL with increasing myopia is well described.8,9 The changes in ACD and LT also have been explored in several studies.10–12 In the cross-sectional population-based Singapore Cohort of Risk Myopia study in which young myopic children were followed for 5 years, the ACD and LT demonstrate a U-shaped change, with ACD deepening until approximately age 10 years before shallowing, and with LT thickening until age 9 to 10 years before thickening.9 A Taiwanese study reported a similar decrease in LT from age 7 to 11 years and subsequent thickening with reciprocal changes in ACD.10 A similar U-shaped change in LT was noted by Twelker et al.11 in the Orinda Longitudinal Study of Myopia study, but change in LT was slower and change in ACD showed a slow and unidirectional increase over time. Van Alphen12 and Mutti and colleagues13 hypothesized that before 10 years, the rapid increase in VCD outpaces lens growth and this stretching of the eye results in a progressively thinner lens, which may in turn result in a deeper anterior chamber. In our study, however, the changes in biomey were unidirectional, even after children were stratified into three different age groups (6.0–7.9, 8.0–9.9, and 10.0–12.0 years). The only difference was that the rate of change in younger children was greater than that in older children. It is interesting to speculate why the U-shaped change noted in other studies was not seen in the younger children in our study, and one possible reason was because our children had much higher myopia and ALs, and behaved more like older children in other studies. To ensure that age and sex were accounted for, these factors were included in our multivariate linear regression to adjust for a possible effect on refraction and biomey. In atropine-treated eyes, changes in ocular parameters varied from placebo-treated eyes (Table 1). Most obvious was the slowing of myopia progression while children were on atropine and then a greater increase when atropine was stopped. These were accompanied by a decrease and then increase in VCD and AL, respectively. Initially when atropine was started between baseline and 4 months, there was also a reduction in LT, which appeared to be pharmacological as LT increased to levels similar to placebo children when atropine was stopped. One effect of atropine is the paralysis of the ciliary or accommodating muscles of the eye. This could cause the ciliary process to pull outward, increasing the tension on the lens, resulting in thinning of LT.14,15 It also could result in a shift of the lens-iris apparatus posteriorly, resulting in a transient deepening in ACD and concurrent flattening of the corneal curvature.15,16 Changes in ACD and K were not apparent in this study, except for a transient increase in ACD between 24 and 30 months when atropine was stopped.

The hyperopic shift seen in atropine-treated eyes was associated with a reduction in VCD and AL (Table 2). The reduction in VCD could partly be explained by the posterior shift of the lens-iris apparatus into the posterior chamber,16,17 but the overall reduction in AL is less easy to explain. Although difficult to imagine, there could be true reversal in growth of the eyeball with actual shrinkage of the globe. Alternatively, changes in the mechanical forces associated with paralysis of the ciliary muscles could cause the young elastic eyeball to change from a prolate to more oblate shape, or there could be a change in choroidal or scleral thickness. Further studies, including more detailed assessment of peripheral refraction and choroidal thickness, are required to elucidate the true cause of the AL change noted.

Conversely, when atropine was stopped, there was a marked myopic rebound, which was associated with a rapid increase VCD and AL. This suggested that atropine had been actively damping the eyeball growth with a reversed feedback reaction being stimulated when its effect was abruptly withdrawn. Indeed, the exact mechanism of how atropine works to slow myopic progression is yet undetermined, and more work needs to be done to better understand its effects.17 However, this study suggest that atropine slowed myopia progression mainly by reducing or slowing the growth in VCD and AL.

More recently, studies have shown that lower doses of atropine could also slow myopia progression but with much less myopic rebound when medication was stopped.7,8 One of the interesting results with atropine 0.01%, was that there was a gradual increase in AL even as myopia slowed while on treatment, and relatively less increase in AL even as myopia increased when treatment was stopped. It is interesting to speculate if the biometric effect of lower doses was similar to that of higher doses, albeit to a lesser degree, but other biometric parameters, such as the difference in changes in K, ACD, and LT may account for some of the discrepancies seen.

The strengths of this study lie in its randomized allocation of treatment of a large number of children, with a very low loss to follow-up rate. The same team of research technicians who were blinded to the treatment each child was receiving did all measurements. In performing repeated biometry measures, the possible bias resulting from variability in the measurement of individual parameters also should be considered when assessing changes over time.18 Measurements were done with contact A-scan, which may be user dependent and performed after cycloplegia, which may have caused ACD to be deeper, but this allowed for better comparison between atropine- and placebo-treated eyes.19,20

In summary, in the normal myopic eye, there was an increase in LT, VCD, and AL, with gradual reduction in K and ACD. The use of atropine altered these growth patterns. The LT thinned while on atropine but increased to sizes similar to placebo-treated eyes when treatment was stopped, suggesting that atropine had a direct pharmacological effect on LT. The hyperopic shift and myopic rebound noted when atropine was started and stopped were mainly associated with changes in VCD. Further studies would be necessary to determine whether there are also changes in the shape of the eye, or in choroidal or scleral thickness associated with the use of atropine in myopic eyes.

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**References**


