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# A STROBE-compliant case–control study

## Effects of cumulative doses of topical atropine on intraocular pressure and myopia progression

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**Abstract**

Topical atropine has become a mainstream treatment of myopia throughout East and Southeast Asia, but it is uncertain whether long-term topical atropine therapy induces intraocular pressure (IOP) elevation and subsequent development of glaucoma. We then prospectively examined the effects of long-term atropine treatment on IOP.

Our case series collected 186 myopic children who were younger than 16 years of age. Complete ocular examination data, IOP and refractive status measurements beginning in 2008 were collected for all participants. Participants were divided into two groups: 121 children who received atropine therapy at various concentrations were classified as the treated group, whereas 65 children who did not receive atropine therapy were classified as the untreated (reference) group. In the treated group, clinicians prescribed different concentrations of atropine eye drops according to their discretion with regard to the severity of myopia on each visit of the patient. We then calculated the cumulative dose of atropine therapy from 2008 to the patients' last follow-up in 2009. Furthermore, the treated group was then further divided into low- and high-refractive-error groups of nearly equal size for further analysis.

There were no significant differences for the baseline refractive errors and IOPs between the treated and untreated groups. Both the low- and high-cumulative atropine dosage subgroups showed significantly lower myopic progression than the untreated group, but there was no significant difference between the two subgroups in terms of different cumulative dosages. All groups, including the untreated group, showed an increase of mean IOP at the last follow-up, but both low- and high-cumulative atropine dosage subgroups experienced a smaller increase of IOP. The mean IOP of all atropine-treated groups showed no significant increase in either low- or high-refractive-error eyes.

This study revealed that topical atropine eye drops do not induce ocular hypertension and are effective for slowing the progression of myopia. The treatment effects are not correlated with the cumulative atropine dosages.

**Abbreviations:** ANOVA = analysis of variance, D = diopters, IOP = intraocular pressure, OCT = optical coherence tomography, SE = spherical equivalent.

**Keywords:** atropine, intraocular pressure, myopia

## 1. Introduction

Myopia is one of the most common ocular disorders, and its rapidly increasing prevalence is becoming an important public health problem worldwide. The prevalence of myopia in young adults in several Asian countries such as Taiwan, Hong Kong, and Singapore is 60% to 80%, higher than that in the United States and Europe (20%–60%).[1–5] Myopia-related complications include macular degeneration, retinal detachment, glaucoma, and cataracts.[4,6–8] Due to these potentially blinding complications, the World Health Organization proposed the Strategic Plan for Vision 2020 to eliminate avoidable blindness with refractive error, including myopia.[9]

Atropine, a non-selective muscarinic receptor antagonist, has been successfully used to prevent the progression of myopia in Asian children[10–16]; in fact, topical atropine has become a mainstream treatment of myopia throughout East and Southeast Asia.[11,17–20] After conducting an evidence-based review, Saw et al[17] recommended that the evidence rating of atropine therapy be set at B-I, where "B" means a moderately important recommendation for clinical outcome and "I" means that there is strong evidence supporting the recommendation. However, the routine use of atropine in all myopic children is not recommended due to the lack of long-term studies and the possible side

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*All data generated or analyzed during this study are included in this published article (and its supplementary information files).*

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effects.[17] One of the potential complications of this treatment is an increase in intraocular pressure (IOP).

The antimuscarinic effects of atropine can paralyze the ciliary muscle and thus may increase the drainage resistance of aqueous humor through the trabecular meshwork. Systemic atropine was found to increase IOP by more than 6 mm Hg in 8% of normal adults.[21] Atropine and other anticholinergic agents are, therefore, contraindicated for glaucoma patients.[22] The risk factors of glaucoma with atropine are short hyperopic eyes, narrow angles, and occlusion of aqueous outflow.[22] In myopic children, it is unclear whether topical atropine therapy induces IOP elevation and subsequent development of glaucoma.[21,22] The safety of long-term atropine treatment has also been largely overlooked. In 2012, we conducted the first cross-sectional study to evaluate IOP after 3 years of treatment with varying cumulative dosages of atropine in school-aged myopic children, and found neither the cumulative dose nor the duration of atropine therapy was statistically associated with the risk of IOP elevation.[23] Considering that there might be some potential bias due to the cross-sectional and retrospective nature of the study, we decided to conduct this prospective case series study to further evaluate the safety of varying cumulative dosages of atropine.

## 2. Patients and methods

### 2.1. Patients

In 2008, we conducted this prospective, interventional, longitudinal, and non-randomized study of 190 children at Shin-Kong Wu Ho-Su Memorial (SK) Hospital's Department of Ophthalmology in Taipei, Taiwan, R.O.C. This study was primarily designed to evaluate whether topical atropine can increase IOP in myopic children with a refractive error of myopic spherical equivalent (SE) $> -0.25$ diopters (D) in at least one eye. All patients were recruited and followed at the clinic of Dr Tzu-En Wu. The research adhered to the tenets of the Declaration of Helsinki. Informed consent and Institutional Review Board approval at the SK Hospital (98E-005) were both obtained. The study (treated) group consisted of 122 myopic children (60 boys and 62 girls) younger than 16 years old who were treated with topical atropine. The exclusion criteria included:

1. having a congenital eye disorder;
2. any disease influencing the cornea, lens, retina, or optic nerve; and
3. the current use of other cycloplegic agents, steroids, or antiglaucoma medications.

On each visit, clinicians prescribed different concentrations of atropine eye drops, such as 1%, 0.5%, 0.25%, and 0.1% (Oasis Chemical Industries, Dombivli, India) according to their discretion with regard to the severity of myopia in the patient.

The control (untreated) group consisted of 68 myopic children (40 boys and 28 girls) who did not receive atropine to control myopia. The primary outcome measures were to evaluate the effects on IOP and refractive status under various cumulative dosages of atropine in myopic children. The secondary aim was to assess the above outcome measures in different refractive statuses. The data regarding SE, IOP, and concentrations of atropine treatment were collected for the period between January 1, 2008 and December 31, 2009. We had excluded one child without final refractive error measurements, and three children without final IOP measurements. Figure 1 shows the algorithm of case identification and a total of 186 children (372 eyes) were eligible for final analysis.

### 2.2. Ocular examinations

The standard ocular examinations for myopic children at the SK Hospital were

1. a slit lamp biomicroscopy for anterior segment and lens,
2. assessment of refractive errors; and
3. fundoscopic examinations.

All examination results revealed normal status except for the refractive errors before the study. We first assessed refractive errors by using a Canon RK5 autorefractor/autokeratometer (Canon, Ōtawara, Japan). When the results revealed the probable presence of myopia, a cycloplegic procedure was used with three drops of 1% Cyclogyl (cyclopentolate) (Alcon-Couvreur, Puurs, Belgium) given at 10-min intervals. Cycloplegic autorefraction was taken at least 30 min after instillation of the third drop of cyclopentolate, and converted to SE refraction for analysis. Cycloplegic visual acuity with correction was measured using a projected Snellen chart at a distance of 6 m.

All IOP measurements were obtained before cyclopentolate instillation. We used an Xpert NCT plus (Reichert Technologies, Buffalo, NY) to perform pneumatic tonometry without topical anesthesia on both eyes in conscious children, with the right eye first. Every child was in seated position with eyes in the primary position during IOP measurement. No lid speculum was used. Before measurement, the alignment spot was centered and not obscured by the eyelashes or eyelids. Each patient received three measurements and the average of those measurements was the

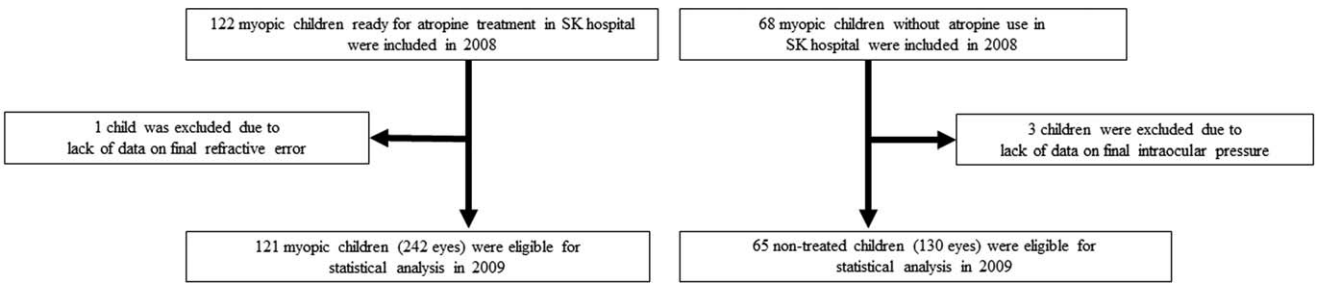


**Figure 1.** The algorithm of case identification. Initially, data were collected for 190 children <16 years old and who had refractive error of myopic spherical equivalent $>-0.25$ diopters in at least one eye. We excluded one myopic child without final refractive error, and three children without final intraocular pressure. A total of 186 children (372 eyes) were eligible for final analysis and their medical records were reviewed for the period between January 1, 2008 and December 31, 2009.

final IOP. The IOP was measured between 9 AM and 1 PM. If patients underwent all the above procedures, IOP was recorded and the day of IOP measurement in 2008 was defined as the recruitment date.

### 2.3. Measurement of atropine exposure and other characteristics

The medical records from a total of 186 myopic children (98 boys and 88 girls, aged 9.0±2.3 years) who were eligible for final analysis (Fig. 1) were collected for refractive status, medical history, ocular disease, and the duration and dose of atropine treatment. One hundred twenty-one children who were scheduled for atropine therapy on the recruitment date were classified as the treated group, while the other 65 children who were not recommended atropine therapy were classified as the untreated group. The duration of atropine exposure was calculated from the first date of atropine prescription in 2008 to the date of the last follow-up in 2009. On each visit, clinicians prescribed different concentrations of atropine eye drop, such as 1%, 0.5%, 0.25%, and 0.1% (Oasis Chemical Industries) according to their discretion with regard to the severity of myopia in the children. The exact dosage of each bottle for atropine was 50, 25, 12.5, and 5 mg, respectively. The dosage of atropine prescribed at each visit was assessed by multiplying the number of prescribed bottles and the dosage of atropine in each bottle; we used this method to calculate the prescribed dosage of atropine for each outpatient visit. The concentration we used was the original concentration from the pharmacological corporation. No dilution or condensation occurred at any point during the study and no patient shared the same bottle of atropine. Data collection was halted if a patient experienced a severe allergic reaction and proper management was subsequently arranged by medical professionals. No patients in the untreated group received any placebo eye drops in this study.

### 2.4. Statistical analyses

All statistical analyses were conducted using SPSS software version 25 (IBM, Armonk, NY). Two sample independent *t* tests were used to compare the subject characteristics, including age, SE, and IOP, between the atropine-treated and untreated groups. The gender among groups was evaluated using the Chi-square test. An analysis of variance (ANOVA) was conducted to evaluate the effects of cumulative atropine dosages, which were divided into tertiles. In comparing the IOP and refractive errors among the three groups, we analyzed variance first. If the variances among the three groups were homogenous, we used ANOVA for analysis and added Fisher's Least Significant Difference test for post hoc analysis of equally sized groups. The Scheffe test was used for post hoc analysis of unequally sized groups. If the variances among the three groups were heterogenous, we used Welch's test for analysis and added the Games-Howell test for post hoc analysis. Confidence intervals of 95% were regarded as a comparison for mean values and $P < .05$ was considered statistically significant for the paired-t, Chi-square, ANOVA, and Welch's tests.

## 3. Results

### 3.1. Comparison of IOP, refractive status, and atropine therapy

A total of 186 myopic children aged younger than 16 years were enrolled in this study. Table 1 summarizes the details of refractive status for both eyes, IOP measurements, and the cumulative dosages of atropine therapy. Patients in the treated group were significantly younger and made more outpatient visits than the untreated group ($P < .05$ in both parameters). There were no significant differences in refractive errors or IOPs between treated and untreated groups (Table 1). The mean examination follow-up period was 10.6±4.0 months, and the mean cumulative atropine dose was 36.04±49.66 mgs in these 186 children. No atropine-treated patient had experienced a severe allergic reaction or an acute angle-closure glaucoma attack.

### 3.2. Distribution of demographic and clinical characteristics by tertiles of cumulative dose of atropine therapy in 186 myopic children

We further compared the demographic and clinical characteristics between subgroups with different cumulative dosages of atropine therapy stratified by tertiles (Table 2). Both low- and high-cumulative atropine dosage subgroups showed significantly lower myopic progression, but there was no significant difference between the two subgroups with different cumulative dosages. All groups, including the untreated group, showed an increase of mean IOP at the last follow-ups, but both the low- and high-

**Table 1**

**Summary of refractive status, intraocular pressure, and information on atropine therapy for 186 myopic children.**

| Variables | | Atropine-treated group (N = 121) Mean ± SD | Non-treated group (N = 65) Mean ± SD | *P* |
|---|---|---|---|---|
| Age (year) | | 8.6±2.3 | 9.6±2.3 | .008 |
| OD | S (D) | −1.5±1.4 | −1.3±1.4 | .235 |
| | C (D) | −0.6±0.9 | −0.6±0.9 | .810 |
| | SE (D) | −1.8±1.5 | −1.6±1.6 | .267 |
| | IOP (mm Hg) | 14.2±2.8 | 14.5±2.5 | .463 |
| OS | S (D) | −1.5±1.7 | −1.1±1.2 | .107 |
| | C (D) | −0.6±1.0 | −0.6±0.9 | .713 |
| | SE (D) | −1.8±2.0 | −1.4±1.5 | .138 |
| | IOP (mm Hg) | 14.4±2.8 | 14.3±2.8 | .954 |
| Number of outpatient visits | | 6.1±2.6 | 4.6±3.1 | .001 |
| Cumulative dose of atropine (mg) | | 55.4±52.2 | 0.0±0.0 | <.001 |

C = cylinder refraction, D = diopter, IOP = intraocular pressure, OD = oculus dexter, OS = oculus sinister, S = spherical refraction, SE = spherical equivalent.

**Table 2**

**Distribution of demographic and clinical characteristics by tertiles of cumulative atropine doses for 186 myopic children.**

| | | | Cumulative dose of atropine (mg) | | |
|---|---|---|---|---|---|
| Characteristics | | | 0 (Control group) | 1–39 | >40 |
| Number of myopic children | | | 65 | 60 | 61 |
| Age (year) | | | 9.59 ± 2.28 | 8.59 ± 2.46* | 8.69 ± 2.18* |
| Male/female | | | 38/27 | 25/35 | 35/26 |
| Cumulative dose of atropine (mg) | | | 0.00 ± 0.00 | 25.46 ± 8.43* | 84.84 ± 59.94*# |
| Initial | SE (D) | OD | −1.56 ± 1.63 | −1.58 ± 1.34 | −2.07 ± 1.70 |
| | | OS | −1.42 ± 1.46 | −1.52 ± 1.27 | −2.16 ± 2.53* |
| | IOP (mm Hg) | OD | 14.48 ± 2.50 | 14.32 ± 3.18 | 14.03 ± 2.34 |
| | | OS | 14.34 ± 2.82 | 14.37 ± 2.77 | 14.36 ± 2.86 |
| Final | SE (D) | OD | −2.86 ± 2.22 | −1.65 ± 1.41* | −2.20 ± 1.53 |
| | | OS | −2.88 ± 2.08 | −1.63 ± 1.34* | −2.38 ± 2.59# |
| | IOP (mm Hg) | OD | 15.77 ± 2.77 | 14.63 ± 2.76* | 14.74 ± 3.01* |
| | | OS | 15.42 ± 2.36 | 14.92 ± 2.87 | 15.28 ± 2.81 |
| Mean difference | SE (D) | OD | −1.30 ± 1.46 | −0.07 ± 0.80* | −0.13 ± 1.31* |
| | | OS | −1.46 ± 1.71 | −0.10 ± 0.73* | −0.23 ± 1.24* |
| | IOP (mm Hg) | OD | 1.29 ± 2.92 | 0.32 ± 2.47 | 0.71 ± 3.13 |
| | | OS | 1.08 ± 2.59 | 0.55 ± 2.68 | 0.92 ± 2.62 |

D = diopter, IOP = intraocular pressure, OD = oculus dexter, OS = oculus sinister, SE = spherical equivalent.
Data are means ± standard deviation. *$P < .05$ compared to the control group. #$P < .05$ compared between the two atropine-treated groups.

cumulative atropine dosage subgroups experienced a smaller IOP increase.

### 3.3. The effects of various cumulative atropine dose in eyes with different myopic SE

To evaluate the effects of various cumulative atropine in eyes with different myopic SEs, all 242 eyes of the 121 atropine-treated children in our study were further divided into low- and high-refractive-error groups with nearly equal size, at a SE cutoff point of −1.50 D. There were 44.4% of the eyes having a myopic SE of −1.5 D or greater (47.3% in the right eyes, and 41.4% in the left eyes). The mean SE of all subgroups in various cumulative atropine doses showed progression in low-refractive-error eyes, although these were significantly less than those of the untreated group (Table 3). As for high-refractive-error eyes, the mean SE of all atropine-treated groups showed a refractive error regression, in contrast with the myopic progression in the untreated group (Table 4). The mean IOP of all atropine-treated groups showed no significant increase in either low- or high-refractive-error eyes (Tables 3 and 4). The effect of slowing the progression of myopia caused almost no significant differences between the low- and high-cumulative atropine dosage subgroups, except that the subgroup of left eyes with low refractive error and low-cumulative atropine dosage displayed significantly lower myopia progression than the subgroup of high-cumulative atropine dosage (Table 3).

## 4. Discussion

Myopia is not only an ocular disease but also a serious public health problem, affecting 33% of individuals over the age of 12 years in the United States[5] and a much higher percentage (60%–80%) in Southeast Asian countries such as Taiwan and Singapore.[2,4] The prevalence of myopia and severe myopia are increasing at an alarming rate globally, with significant increases in the risks for visual impairment from pathologic conditions related

**Table 3**

**Comparison of demographic and clinical characteristics between various cumulative atropine dosages in eyes with myopic spherical equivalent lesser than −1.5 diopter (SE > −1.5D).**

| Eye laterality | | OD | | | OS | | |
|---|---|---|---|---|---|---|---|
| Cumulative atropine dose | | Control group (cumulative dose = 0) | Low-dose atropine group (cumulative dose < 40) | High-dose atropine group (cumulative dose ≥ 40) | Control group (cumulative dose = 0) | Low-dose atropine group (cumulative dose <40) | High-dose atropine group (cumulative dose ≥ 40) |
| Number of eyes | | 40 | 33 | 25 | 42 | 36 | 31 |
| Age (year) | | 9.44 ± 2.45 | 8.18 ± 1.68* | 8.26 ± 1.83 | 9.12 ± 2.30 | 8.38 ± 1.89 | 8.37 ± 2.27 |
| Male/female | | 22/18 | 13/20 | 14/11 | 23/19 | 14/22 | 18/13 |
| Cumulative dose of atropine (mg) | | 0.00 ± 0.00 | 26.06 ± 7.55* | 68.00 ± 41.33*# | 0.00 ± 0.00 | 26.04 ± 8.00* | 70.73 ± 47.51*# |
| Initial | SE (D) | −0.70 ± 0.45 | −0.79 ± 0.44 | −0.97 ± 0.32* | −0.66 ± 0.69 | −0.76 ± 0.41 | −0.89 ± 0.23 |
| | IOP (mm Hg) | 14.68 ± 2.84 | 13.48 ± 3.00 | 13.16 ± 2.04 | 14.52 ± 2.93 | 13.89 ± 2.86 | 13.71 ± 2.65 |
| Final | SE (D) | −2.00 ± 1.41 | −1.01 ± 0.61* | −1.42 ± 0.72 | −2.24 ± 1.67 | −0.97 ± 0.66* | −1.46 ± 0.72*# |
| | IOP (mm Hg) | 15.78 ± 2.52 | 13.97 ± 2.89* | 14.24 ± 2.71 | 15.69 ± 2.15 | 14.92 ± 3.19 | 14.74 ± 3.11 |
| Mean difference | SE (D) | −1.30 ± 1.35 | −0.22 ± 0.68* | −0.45 ± 0.71* | −1.58 ± 1.73 | −0.20 ± 0.48* | −0.57 ± 0.67*# |
| | IOP (mm Hg) | 1.10 ± 2.92 | 0.49 ± 2.43 | 1.08 ± 2.90 | 1.17 ± 2.23 | 1.03 ± 2.46 | 1.03 ± 2.39 |

D = diopter, IOP = intraocular pressure, OD = oculus dexter, OS = oculus sinister, SE = spherical equivalent.
Data are means ± standard deviation. *$P < .05$ compared with control group. #$P < .05$ compared between atropine-treated groups.

**Table 4**

**Comparison of demographic and clinical characteristics between various cumulative atropine dosages in eyes with −1.5 Diopter or greater of myopic spherical equivalent (SE ≤ −1.5D).**

| Eye laterality | | OD | | | OS | | |
|---|---|---|---|---|---|---|---|
| Cumulative atropine dose | | Control group (cumulative dose = 0) | Low-dose atropine group (cumulative dose < 40) | High-dose atropine group (cumulative dose ≥ 40) | Control group (cumulative dose = 0) | Low-dose atropine group (cumulative dose < 40) | High-dose atropine group (cumulative dose ≥ 40) |
| Number of eyes | | 25 | 27 | 36 | 23 | 24 | 30 |
| Age (year) | | 9.83 ± 2.02 | 9.10 ± 3.13 | 8.98 ± 2.37 | 10.46 ± 2.03 | 8.91 ± 3.16 | 9.01 ± 2.07* |
| Male/female | | 16/9 | 12/15 | 21/15 | 15/8 | 11/13 | 17/13 |
| Cumulative dose of atropine (mg) | | 0.00 ± 0.00 | 24.72 ± 9.49* | 96.53 ± 68.15*# | 0.00 ± 0.00 | 24.58 ± 9.14* | 99.42 ± 68.30*# |
| Initial | SE (D) | −2.93 ± 1.89 | −2.54 ± 1.45 | −2.84 ± 1.84 | −2.81 ± 1.49 | −2.66 ± 1.28 | −3.46 ± 3.11 |
| | IOP (mm Hg) | 14.16 ± 1.84 | 15.33 ± 3.14 | 14.64 ± 2.37 | 14.00 ± 2.63 | 15.08 ± 2.54 | 15.03 ± 2.95 |
| Final | SE (D) | −4.23 ± 2.59 | −2.43 ± 1.71* | −2.74 ± 1.71* | −4.05 ± 2.26 | −2.61 ± 1.51 | −3.34 ± 3.38 |
| | IOP (mm Hg) | 15.76 ± 3.18 | 15.44 ± 2.41 | 15.08 ± 3.19 | 14.91 ± 2.70 | 14.92 ± 2.36 | 15.83 ± 2.38 |
| Mean difference | SE (D) | −1.30 ± 1.65 | 0.11 ± 0.91* | 0.10 ± 1.58* | −1.24 ± 1.68 | 0.05 ± 0.98* | 0.13 ± 1.57* |
| | IOP (mm Hg) | 1.60 ± 2.97 | 0.11 ± 2.56 | 0.44 ± 3.29 | 0.91 ± 3.20 | −0.17 ± 2.90 | 0.80 ± 2.88 |

D = diopter, IOP = intraocular pressure, OD = oculus dexter, OS = oculus sinister, SE = spherical equivalent.
Data are means ± standard deviation. *$P < .05$ compared with control group. #$P < .05$ compared between atropine-treated groups.

to severe myopia, including macular degeneration, retinal detachment, cataracts, and glaucoma.[4,6–9] The high prevalence of myopia and associated vision-threatening problems emphasize the importance of finding effective treatments to slow the progression of myopia and axial elongation. Atropine is the most studied pharmacological agent for the topical intervention of progressive myopia[10–17] and has become a main strategy for slowing the progression of myopia throughout East and Southeast Asia.[10,17–20] As a non-selective muscarinic antagonist, atropine causes pupil dilation and may predispose sufferers to glaucoma.[22,23] Besides, previous large population-based studies had supported an association between glaucoma and myopia. Myopic subjects had a 2 to 14 times higher risk of glaucoma compared with that of non-myopic subjects.[7,24–29] However, it is unclear whether topical atropine therapy causes further development of glaucoma in myopic children.[21,22] We, therefore, conducted a retrospective study in 2012 and found that neither the cumulative dose nor the duration of atropine therapy caused significant IOP elevation.[23] Another prospective study also suggested that topical use of low-concentration atropine for 1 year did not induce ocular hypertension.[30] After considering whether various cumulative dosages of atropine led to different results, we decided to conduct this study to gather a more complete picture of the issue.

In our study, the mean age of the atropine-treated group was significantly younger than the untreated group ($P < .001$). We assume that this result may be due to previous atropine treatment at a younger age in the myopic patients we treated. Previous randomized control trials have suggested that children who develop myopia at a younger age experience a faster progression of the condition.[31,32] In order to avoid irreversible myopic change and complications, timely atropine treatment may be beneficial. Our results showed significantly lesser myopic progression in the atropine-treated group than the untreated group at the end of their 1-year follow-up ($P < .01$), whether in spherical power, cylinder power, or SE. The outcome was comparable to those of previous studies that found that atropine treatment may prevent the progression of myopia.[10–13,15–20]

Subgroup analysis by tertiles of cumulative atropine dose showed that the effect of slowing the progression of myopia was irrelevant to the cumulative atropine dose. The post hoc analysis revealed no significant difference of mean SE between the subgroup of the highest cumulative atropine dose and the untreated group, although previous studies suggested that a higher concentration of atropine use results in better myopia control.[11,13,17,20] The probable explanations for this discrepancy are the different study design used in our research, the limited number of cases covered, and the relatively shorter follow-up period. This study focused on the effect of cumulative atropine dose, which was affected by the atropine concentration and the duration of therapy. A high cumulative dose might not necessarily mean a high concentration of the drug was administered at each treatment, and this difference in our study design might cause conflicting results.

The final IOP results revealed an inconsistency in our study. There was no significant difference between the atropine-treated group and the untreated group at recruitment, but different results were found between patients' left and right eyes after 1 year. With regard to the left eyes, there was no significant IOP difference between two groups, but in the right eyes the mean IOPs of all atropine-treated subgroups stratified by tertiles of cumulative dose were lower than those in the untreated group ($P = .048$). This inconsistency in our IOP results might be the result of the method of IOP measurements used. The Goldmann applanation tonometer is thought to be the gold standard for measuring IOP, but the non-contact tonometer is clinically more tolerable for children.[33] We, therefore, used the pneumotonometer for IOP measurement in this study. Sihota et al suggested that the success rate of measuring IOP was 95% in children aged ~6 years and was near 100% in those older than 7 years.[34] The myopic children included in this study were aged between 3 and 17 years, and the mean age of all children was 9.2 years old. If there is a bias in IOP measurements, it should thus be relatively low.[33,35] Our study showed the mean IOP was not correlated with the cumulative atropine dose and did not increase in all atropine-treated subgroups of various cumulative dose.

Previous studies suggested that IOP is lower in children than in adults[34,36–41] and showed an increasing trend with age (correlation coefficient = 0.49–0.71), reaching adult levels by 12 years of age.[34,36,39] Therefore, IOP evaluation in children should take physiologic age levels as a reference. In our study, the

mean age of the atropine-treated group was 8.6 years and the normal pediatric IOP cutoff level was estimated to be ~16 mm Hg.[36] Although there was no significant increase in the final mean IOP after 1 year of atropine therapy, we should keep in mind that the mean value cannot be representative of the total population. Out of 242 eyes receiving atropine therapy, 74 eyes (30.6%) had final IOPs of more than 16 mm Hg, but further exams such as optical coherence tomography (OCT) and visual field tests were still needed to determine whether any related glaucomatous change had occurred. Chan et al[42] performed OCT on 67 eyes of 35 myopic children receiving 0.25% atropine treatment, and found no significant change in IOP, optic nerve parameters, or retinal nerve fiber layer thickness over a mean of 15.2 ± 2.4 months of treatment and follow-up.

In our study, the mean differences of IOPs in the atropine-treated groups were all lower than the untreated group, although these findings were not statistically significant Herring et al[43] also found a significant mean IOP decrease (11.2%) in ocular normotensive horse eyes after 1% topical atropine use, which was thought to be related to uveoscleral outflow increase caused by atropine. However, using the same medication, Mughannamet al[44] found no significant changes in IOP, and Stadtbaumeret al[45] observed elevated IOP in feline eyes. These inconsistent results were also noted in human studies. Harris et al found that atropine may lead to 23% IOP elevations in eyes with open-angle glaucoma, but only 2% in apparently normal eyes.[46] Hadjikoutis et al suggested that the careful use of atropine in neurological operations might prevent IOP elevation and angle closure glaucoma in susceptible patients.[47] Along with this study, several studies on school-aged children[17,23,30] did not find IOP elevation after atropine use in normal eyes.

There are some limitations in this study. First, it is not a double-blind randomized design, and second it used a relatively small sample size and short follow-up period. Third, we used a non-contact pneumotonometer to evaluate IOP with only single measurement. The Goldmann applanation tonometer is considered the gold standard for measuring IOP, but the non-contact tonometer is clinically more tolerable for children.[33] We, therefore, used the latter method for measuring IOP in this study. Jaafar and Kazi[39] reported that the IOP measurements obtained using a pneumotonometer significantly higher than those obtained compared with the Perkins tonometer, which uses the same principle as the Goldmann tonometer. Therefore, it is possible that the prevalence of high IOP may be overestimated, especially in younger children.[41] Repeated measurements of IOP may be performed to reduce potential bias. Furthermore, we did not have any data on corneal thickness that might be associated with IOP, nor on exam results other than IOP to diagnose glaucoma, such as gonioscopy, OCT, or visual field. As for detecting myopic progression, we did not measure axial length elongation for a more comprehensive evaluation.

To the best of our knowledge, this is the first prospective study to evaluate the effects of varying cumulative atropine dosages and shows no physiologically high IOPs in myopic children following the application of atropine for one year. Similar to other studies, topical atropine eye drops are effective in slowing the progression of myopia. However, the treatment effects are not correlated with cumulative atropine dosages. Further studies with a longer follow-up period and a larger sample size are still needed to confirm our results.

## Author contributions

**Investigation:** Teng-Chieh Yu, Tzu-En Wu.
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