Review Article

Taiwan J Ophthalmol 2024;14:179-189

Access this article online

Quick Response Code:

Website: http://journals.lww.com/TJOP

DOI: 10.4103/tjo.TJO-D-24-00026

# Impact of atropine use for myopia control on intraocular pressure in children: A comprehensive review including postpupil dilation intraocular pressure changes

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**Abstract:**

Topical atropine has been widely used for controlling myopia progression in children, yet its long-term efficacy and safety, including potential intraocular pressure (IOP) elevation, are still being studied. The mydriasis and cyclopegia induced by atropine may reduce traction on the trabecular meshwork, together with pigment released into anterior chamber due to the friction between the iris and lens during pupil dilation, may obstruct and reduce the trabecular outflow. This review first explores postdilation IOP changes across different groups – healthy individuals, glaucoma patients, and children. The response to pupil dilation varies widely, with IOP potentially increasing or decreasing. Glaucoma patients, whether with open or closed-angle glaucoma, may experience more significant IOP rises postdilation. The second section examines IOP effects in children using topical atropine for myopia, where most of the 25 reviewed studies showed nonsignificant IOP changes, although slight increases were observed in a few. In addition, no alterations in the retinal nerve fiber layer thickness were found. However, the research on children's IOP under topical atropine is constrained by small sample sizes, cross-sectional studies, brief follow-ups, and often lacks control groups or pretreatment IOP measurements. Given the extended atropine use for myopia and the significant individual variation in IOP response, we recommend routine IOP monitoring for children receiving topical atropine.

**Keywords:**

Atropine, intraocular pressure, myopia

## Introduction

The global prevalence of myopia has surged dramatically in recent decades, with noticeable increases in East Asia, the United States, and Europe.[1,2] Besides, the decreased uncorrected visual acuity, individuals with elongated eyeballs, especially those with high myopia, were more susceptible to vision-threatening complications, such as chorioretinal atrophy, choroidal neovascularization, myopic tractional maculopathy, glaucoma, retinal detachment, and cataract. While some of these complications could be addressed through standard care, others present challenges with limited available treatments, resulting in a guarded visual prognosis.[3] Therefore, the importance of myopia control in school-age children cannot be overstated. Currently, strategies including optical, pharmaceutical, and lifestyle adjustments are employed to control myopia.[4] Research has highlighted

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Submission: 28-02-2024
Accepted: 02-04-2024
Published: 21-06-2024



**How to cite this article:** Chen PJ, Hsia Y, Tsai TH, Su CC, Huang JY, Wang TH. Impact of atropine use for myopia control on intraocular pressure in children: A comprehensive review including postpupil dilation intraocular pressure changes. Taiwan J Ophthalmol 2024;14:179-89.

the protective role of increased outdoor activities in mitigating myopia progression.[5,6] In addition, several optical designs aiming to induce peripheral myopic defocus were introduced, including multifocal or peripheral defocus soft contact lenses, specially-designed spectacles, and orthokeratology.[7-9]

In recent decades, the use of topical atropine, a muscarinic receptor antagonist, has been applied widely to control myopia progression in children, mostly in Asian countries.[10,11] The efficacy and safety of atropine have been established by randomized controlled trials, observational studies, systemic reviews, and meta-analyses, with recent studies focusing on low-concentration atropine.[12-19] However, some dose-dependent side effects have been documented, including photophobia, allergic conjunctivitis and blepharitis, decreased amplitude of accommodation, and difficulties in near work. Another noteworthy concern is the potential increase in the amount of ultraviolet light reaching the retina owing to excessive pupil dilatation.[4,20] While this might theoretically elevate the risk of cataracts and retinal degeneration, existing literature lacks conclusive evidence. Notably, the results of the multifocal electroretinogram from a subset of patients in the atropine in the treatment of myopia (ATOM) 1 trial, who received 1% atropine for 2 years, demonstrated no significant impact on retinal function.[21] Similarly, a gradual decline in cone function was observed in a subset of patients from the ATOM 2 trial who underwent a full-field electroretinogram before atropine use, 2 years after atropine use, and 8 months after discontinuation of atropine, attributed to myopia progression rather than the effects of atropine.[22] A recent long-term safety report on ATOM1 and ATOM2 participants found no lens opacity, and the incidence of glaucoma suspect was comparable to that of the control group, remaining below 5% across all the concentrations of atropine.[23]

Elevated intraocular pressure (IOP) has been identified as a concern associated with topical atropine use.[11,24] However, the literature on this topic is limited. Therefore, this review aimed to focus on IOP in children undergoing topical atropine treatment for myopia control. In addition, it also summarized the current understanding of IOP changes following cycloplegia and mydriasis in various populations. Our objective was to present a comprehensive summary of the current research findings in this area.

## Cycloplegics and Intraocular Pressure Changes

Atropine-induced change of IOP is postulated to occur through various mechanisms. Atropine induces mydriasis and cycloplegia, by blocking parasympathetic innervation to the ciliary muscle, potentially reducing traction on the trabecular meshwork and impeding outflow, consequently leading to increased IOP.[25-28] Furthermore, during pupil dilation, friction between the iris and lens might release pigments into the anterior chamber. If these pigments obstruct the trabecular meshwork, it could contribute to a subsequent rise in IOP.[29,30] Valle also observed increased aqueous inflow in patients with elevated IOP after the instillation of cyclopentolate.[31]

IOP changes following pupil dilation exhibit significant variability among the general population. Although postdilation IOP elevation is not a common phenomenon,[32-37] it can be detected in certain individuals. Kim *et al*. reported an approximately 2 mmHg increase in IOP during mydriasis, with this effect diminishing 4 h postdilation and gradually returning to predilation levels.[38] Conversely, a decrease in postdilation IOP is also observed in healthy participants.[30,33,39,40] In a cohort without glaucoma, Qian *et al*. found that 31% participants experienced IOP elevation, while 69% had decreased postdilation IOP. Notably, marked IOP fluctuations exceeding 2 mmHg were observed in 35% of patients after pupil dilation.[39] The mechanism behind postdilation IOP reduction involves changes in the tone of the ciliary body, leading to increased uveoscleral outflow.[33] Consequently, the balance between inflow and outflow facilities determines postdilation IOP,[31] with the changes often following a normal distribution.[35]

In individuals with open-angle but compromised outflow facilities or a narrow angle, the variations in IOP after pupil dilation may be more significant.[20,26,27,36,41] Harris *et al*. conducted a study to demonstrate the positive results of cycloplegic provocative testing after the topical administration of steroids in a group of participants without glaucoma. Before using topical steroids, none of the participants experienced a cycloplegic-induced IOP elevation of more than 6 mmHg. The same group of participants was subsequently challenged with topical steroids. In the subgroup of steroid responders, 41% of individuals had postcycloplegic IOP elevation >6 mmHg, while only 6% nonsteroid responders had postcycloplegic IOP elevation.[27]

In patients with primary open-angle glaucoma, postdilation IOP elevation was observed in 16%–32% of the population.[26,27,36,42,43] The amount of increase in postdilation IOP was even associated with risk of future glaucoma progression.[44] Harris noted that cyclopentolate and atropine were more likely to induce IOP elevation,[26] although IOP elevation after using tropicamide was also reported.[36,42,43] Shaw and Lewis reported that 32% of eyes with open-angle glaucoma had an IOP elevation

over 5 mmHg after receiving topical 2.5% phenylephrine and 1% tropicamide, with 12% experiencing an elevation over 10 mmHg.[42] Currently, there are no predictive factors for postdilation IOP elevation, except for mitotic use.[35,43] The IOP may start to rise 0.5–1 h after instillation of cycloplegics, peak at 1.5–2 h, last up to 4–6 h, and diminish afterward.[26,38] While this IOP change may be negligible in healthy eyes, it could have detrimental effects on the damaged optic nerve of glaucoma patients. Therefore, rechecking postdilation IOP and the use of topical glaucoma medication to reverse IOP elevation in patients with glaucoma have been suggested.[34,35,42,45]

While the risk of acute angle-closure attack may be low in eyes with narrow angles under pharmacological dilatation,[41,46-48] postdilation IOP elevation has been observed in this population.[33,41,49] Apart from the proposed mechanism for postdilation IOP elevation in eyes with open angle, mydriasis could induce IOP elevation in angle-closure eyes through a relative pupillary block and increased iridotrabecular contact related to iris crowding.[48,50] Conversely, cycloplegics lead to the relaxation of the ciliary muscle and posterior displacement of the lens diagram, which deepens the depth of the anterior chamber.[47] Therefore, postdilation IOP changes are determined by these complex changes in the anterior segment structures. In a group of patients with primary angle-closure suspect, a significant rise in postdilation IOP was noted in laser iridotomy-treated and nontreated eyes, with 10% of eyes experiencing an IOP increment of more than 5 mmHg. Eyes with a narrower angle, detected by anterior segment optical coherence tomography (AS-OCT) or gonioscopy, were prone to greater IOP elevation.[41,47] Angle-closure detection using AS-OCT could also worsen 1 h after pharmacological pupil dilation.[51] In another community-based cohort, hyperopia was identified as a risk factor for postdilation IOP elevation.[34] Ko *et al*. demonstrated that 3.5% of participants in a community-based cohort with prevalent angle-closure disease experienced postdilation IOP elevation >6 mmHg, and in those with IOP spikes, 75% had angle-closure disease. Crowded angles and a shallow anterior chamber were the predictive factors for higher postdilation IOP.[49]

In the pediatric population, limited studies have explored IOP changes after pupil dilation. Hung *et al*. investigated 91 children with an average age of 7.3 years, revealing a significant IOP increase of 1.1 mmHg following the administration of cyclopentolate and 1% tropicamide in hyperopic children. Conversely, myopic children did not exhibit a significant IOP change. Notably, three children experienced postdilation IOP elevation exceeding 5 mmHg, with two being hyperopic and one myopic, underscoring that myopic children are not exempt from the risk of IOP elevation after pupil dilation.[52] Tsai *et al*. assessed IOP changes following pupil dilatation with tropicamide in a cohort of 163 children, finding no significant overall IOP change. While the majority experienced IOP changes within 2 mmHg, a wide distribution was observed, with 34 children displaying an increase of more than 4 mmHg and 18 children having a decrease of more than 4 mmHg. The spherical equivalent did not significantly differ between those with and without an IOP increase of more than 2 mmHg.[53] Given the considerable individual variation in postdilation IOP changes, IOP monitoring is recommended in the pediatric population, particularly in those requiring frequent pupil dilation for refraction or undergoing long-term atropine use for myopia control. The studies covered in this section are summarized in Table 1. In the subsequent sections, we shift our focus to the literature reporting IOP in children using topical atropine to control myopia progression.

## Literature Review for Studies Investigating Intraocular Pressure in Children Using Atropine to Control Myopia Progression

A comprehensive literature review was conducted in the PubMed database, covering studies published in the English language published from January 1, 1970, to January 7, 2024, utilizing the search terms "Atropine" AND "IOP" AND "Myopia." The inclusion criteria comprised clinical trials, cohort studies, observational studies, case reports, case series, reviews, editorials, and comments that presented the significant findings on IOP in children using atropine for myopia control. Articles lacking pertinent information were excluded.

Out of 51 initially identified articles, seven focused predominantly on the IOP during topical atropine use. For these articles, we summarized the following information: IOP levels before and during the use of atropine, study design, case number, methods and schedule of IOP measurement, atropine concentrations, methods of statistical analysis, and key findings. Other studies evaluating the efficacy of topical atropine and adjunctly reporting IOP were also included. In addition, we cross-referenced the studies included in the most recent network meta-analysis to verify the monitoring of IOP in these randomized controlled trials.[17,18] Trials or studies with available IOP records were also reviewed and summarized [Figure 1].

## Studies Focused on Investigating Intraocular Pressure under the Treatment of Atropine to Control Myopia

We identified seven published literature and one unpublished data specifically reporting IOP of children

**Table 1: The summary of research on postdilation intraocular pressure variation across different populations**

| Author, year | Number; design; IOP measurement; medications | Average age (years); SE (diopter) | Response to pupil dilation | Pre and postdilation IOP (mmHg) |
|---|---|---|---|---|
| Harris, 1968[26] | Normal (100)/OAG (40); prospective; applanation tonometry; 1% cyclopentolate | Adult; NA | ≧ +6 mmHg: Normal (2%); OAG (23%) | Responder (OAG), 18.5 (4.1)/28.0 (4.0)* at 60 min<br>Nonresponder (OAG), 20.1 (4.6)/20.9 (4.8) at 60 min |
| Harris, 1971[27] | Normal (58); prospective; applanation tonometry; 1% cyclopentolate; treated with topical steroid | Adult; NA | Before steroid, ≧ +6 mmHg: 0%<br>Steroid responder: ≧ +6 mmHg: 41%<br>Steroid nonresponder: ≧ +6 mmHg: 6% | Postdilation IOP<br>Steroid responder: 27.1 (1.1)<br>Steroid nonresponder: 19.4 (0.9) |
| Cabrera, 1998[28] | Normal (36); prospective; NCT; 1% cyclopentolate | 18.3; −0.75~−2 | NA | Significant IOP elevation at 45 min after instillation of cyclopentolate |
| Atalay, 2014[30] | PXS (31)/PXG (37)/subclinical PXS (31)/control (30); prospective; 1% tropicamide+10% phenylephrine, GAT | 67.4~70; NA | NA | PXS: 15.6 (2.6)/17.1 (2.1)*; PXG: 17.4 (3.4)/17.7 (3.8); subclinical PXS: 15.8 (2.9)/15.5 (2.9)<br>Control: 14.5 (2.7)/13.5 (2.5)* |
| Xiong, 2023[32] | Diabetic patients (2287); prospective; 0.5% tropicamide + 0.5% phenylephrine; NCT | 64.4; NA | ≧ +5 mmHg: 2.7%; 37% with decreased postdilation IOP, mean 1.4 mmHg | Right eye: 16.1 (2.7)/16.5 (2.8)*<br>Left eye: 16.5 (2.7)/16.8 (2.8)* |
| Tan, 2009[33] | Diabetic patients (1910); prospective; 1% tropicamide; NCT | 63.6; NA | ≧ +5 mmHg: 3.6%; IOP > 25 mmHg: 1.9% | Right eye: 15.5 (3.8)/15.0 (3.8)*<br>Left eye: 15.9 (3.8)/15.4 (3.8)* |
| Kuang, 2022[34] | General population older than 65 (1265); prospective; 1% tropicamide; NCT | Adult; NA | > 21 mmHg: 1.3%; > 30 mmHg: 0.2%<br>≧ +4 mmHg: 4.1%; ≧ +8 mmHg: 0.2% | 12.9 (3.1)/12.8 (3.4) |
| Hancox, 2002[35] | Patients with eye disease: Glaucoma (100)/cataract (83)/medical retina (87); prospective; 1% cyclopentolate; GAT | 67.8; NA | > +4 mmHg: glaucoma (5%); retina (10%); cataract (6%); increased IOP: glaucoma (39%); retina (50%); cataract (53%) | Mean changes in IOP 0.4* (glaucoma 0.2; cataract 0.4; retina 0.8*) |
| Pukrushpan, 2006[37] | Patients with eye diseases (111), open-angle, nonglaucoma; prospective; 1% tropicamide; NCT | 54.7; NA | NA | 15.8 (3.3)/16.1 (3.6) |
| Kim, 2012[38] | Cataract, with open angles (32); prospective; 1% tropicamide+2.5% phenylephrine; GAT | 61.7; NA | ≧ +10 mmHg: 0%; > 21 mmHg: 3.1%; increased: 69%; decreased 6%; unchanged: 25% | 11.5 (2.9)/12.4 (2.6)* |
| Qian, 2012[39] | Normal (127); prospective; 0.8% tropicamide+5% phenylephrine; GAT | 65.9; NA | ≧ ±2 mmHg: 37.5% (31.1% increased; 68.9% decreased) | Right eye: 16.8 (3.1)/15.7 (3.1)<br>Left eye: 16.1 (2.9)/15.4 (3.1) |
| Atalay, 2015[40] | PXG (46)/POAG (42)/control (37); prospective; 1% tropicamide+10% phenylephrine; GAT | 65.7~67.9; NA | ≧ +2 mmHg: PXG (28.3%); POAG (16.7%); control (2.7%) | PXG: 17.4 (3.9)/17.5 (4.0); POAG: 15.9 (2.4)/16.1 (2.9); control: 14.2 (2.9)/13.5 (2.9)* |
| Lavanya, 2012[41] | Subjects older than 50, with narrow angles (471); prospective; 1% tropicamide; GAT | 63; NA | Acute angle-closure: 0.6%; ≧ +5 mmHg: 4.7%; ≧ +8 mmHg: 1.3%; > 25 mmHg: 0.9% | Right eye: 14.2 (2.4)/14.8 (2.8)*<br>Left eye: 14.3 (2.4)/15.1 (3.6)* |
| Shaw, 1986[42] | POAG (60); retrospective; 1% tropicamide+2.5% phenylephrine; GAT | 67; NA | Increased: 60%; decreased 29%; unchanged: 11%; ≧ +5 mmHg: 32%; ≧ +10 mmHg: 12% | 22.9 (6.1)/25.8 (7.7)* |
| Chen, 2005[43] | OAG (116)/normal (110); retrospective; 0.8% tropicamide + 2.5% phenylephrine; GAT | 63.8; NA | ≧ +6 mmHg: Normal (1%); OAG (19.8%) | IOP changes: Normal 0.1 (2.2); POAG 2 (4.1); NTG 3.2 (3.2) |
| Wang, 2022[47] | PACS (836); prospective; 0.5% tropicamide + 0.5% phenylephrine; GAT | 60.4/1.3~1.6 | With LPI: ≧ +5 mmHg (10.7%)<br>Without LPI: ≧ +5 mmHg (10.8%) | With LPI: 15.0 (2.6)/16.5 (2.8)*<br>Without LPI: 14.8 (2.7)/16.4 (2.7)* |
| Zhao, 2021[48] | PACS, visually significant cataract (78); prospective; 0.5% tropicamide +0.5% phenylephrine; GAT | 70.9/0.7 | Postdilation 1h: ≧ +5 mmHg (5.1%); ≧ +8 mmHg (2.6%) | 14.8 (2.6)/postdilation 1h: 15.5 (3.5)*/postdilation 4h: 14.9 (3.1) |
| Ko, 2021[49] | General population older than 72 (460); prospective; 1% tropicamide; GAT | 77.8; NA | ≧ +6 mmHg: 3.5% | 13.4 (3.l)/13.7 (3.8) |

*Contd...*

**Table 1: Contd...**

| Author, year | Number; design; IOP measurement; medications | Average age (years); SE (diopter) | Response to pupil dilation | Pre and postdilation IOP (mmHg) |
|---|---|---|---|---|
| Yamada, 2016[50] | PACD (70); prospective; 0.4% tropicamide | 72.7; NA | ≧ +8 mmHg: 10 mmHg | IOP change: 3.4 (6.0) |
| Narayanaswamy, 2020[51] | PACS older than 50 (106); prospective; 1% tropicamide; GAT | 68.0; NA | NA | 15.0 (2.5)/15.6 (2.1)* |
| Hung, 2015[52] | Children (91); retrospective; 1% cyclopentolate+1% tropicamide; NCT | 7.3; −0.7 | ≧ +5 mmHg: 3.3% (2 hyperopic, 1 myopic) | All: 14.5 (2.5)/15.1 (3.1)*<br>Hyperopia: 14.5 (2.5)/15.7 (3.4)*<br>Myopia: 14.4 (2.4)/14.6 (2.8)* |
| Tsai, 2005[53] | Children (163); prospective; 1% tropicamide; NCT | 9.1; −0.8 | Increased: 48%; decreased 50%; unchanged: 2%; ≧ +4 mmHg: 13.5%; ≦ −4 mmHg: 7.4% | All: 15.6 (3.2)/15.7 (3.5)<br>Boy: 16.0 (3.7)/15.8 (3.9)<br>Girl: 15.3 (2.7)/15.6 (3.1) |

*Statistically significant. This table summarizes only the research covered in this review article. GAT=Goldmann applanation tonometer, IOP=Intraocular pressure, LPI=Laser peripheral iridotomy, NA=Not available, NCT=Noncontact tonometry, NTG=Normal tension glaucoma, OAG=Open-angle glaucoma, PACD=Primary angle-closure disease, PACS=Primary angle-closure suspect, POAG=Primary open angle glaucoma, PXG=Pseudoexfoliation glaucoma, PXS=Pseudoexfoliation syndrome, SE=Spherical equivalent

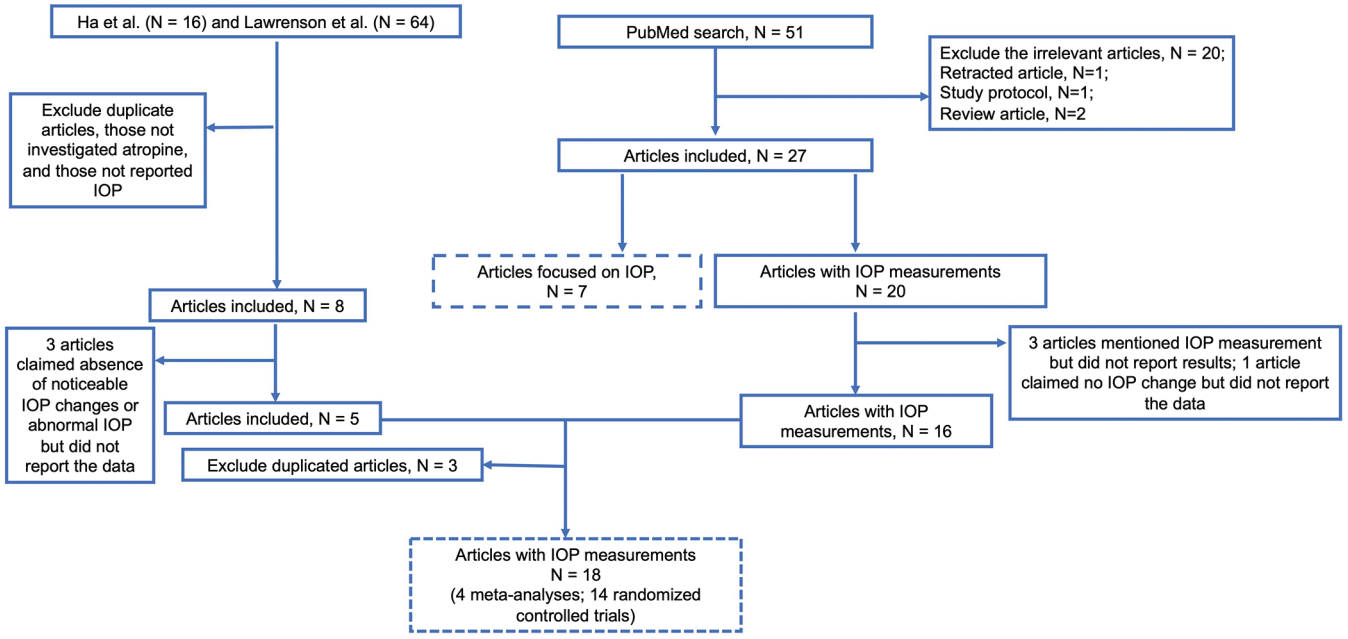


**Figure 1:** Literature review flowchart. Literature pertaining to this topic is identified through a combination of PubMed searches, and a manual review of studies included in recent network meta-analyses. The studies that are outlined within the dotted box are reviewed. IOP=Intraocular pressure

under topical atropine.[54-60] Most of these studies reported no significant difference in IOP between the atropine treated and control groups [Table 2].

One randomized controlled trial conducted by Bukhari *et al*. involving children using 0.01% topical atropine showed a 0.16 mmHg increment in IOP in the atropine group and 0.11 mmHg decrement in IOP in the control group at 12 months ($P$ = 0.525).[60] Lee *et al*. prospectively enrolled a relatively small group of patients using different concentrations of atropine and controls, with IOPs measured at a 3-month interval until 1 year, showing no significant difference between the atropine-treated and control groups.[55] Wu *et al*. retrospectively reviewed a large cohort and elucidated that the single measurement of IOP under atropine treatment was not significantly different between the atropine treated and control groups. IOP was associated with neither the cumulative dosage of atropine nor the duration of atropine treatment.[54] However, the authors acknowledged a limitation in their study: The follow-up involved only a single measurement of IOP, potentially introducing bias due to the natural variability of IOP.[61] Subsequently, these authors enrolled a group of patients with two IOP measurements during a 10.6-month follow-up. Whether the initial IOP was recorded before the commencement of atropine treatment was not specified. The value of IOP was not significantly different between the groups at two time points. A nonsignificant increment in IOP was identified in all the groups of

**Table 2: Summary of studies investigating the intraocular pressure changes in patients using atropine to control myopia progression**

| Author, year | Number; design; IOP measurement | Age (years); SE (days) | Follow-up (months) | Baseline[b]; follow-up IOP (mmHg) | Statistical analysis | Results |
|---|---|---|---|---|---|---|
| Wu, 2012[54] | A[a] (489)/C (132); retrospective; NCT | A: 10.7 (2.2); −2.6 (1.3)<br>C: 9.7 (2.2); −2.1 (1.0) | 16.1 (14.8) | A: NA; 14.7 (2.7)<br>C: NA; 14.9 (3.0) | *t*-test to compare IOP between groups, single measurement under atropine | No difference of IOP; IOP was not associated with cumulative dosage and duration of atropine |
| Lee, 2016[55] | A 0.125% (32)/A 0.25% (12)/C (12); prospective; NCT | 0.125%: 9.0; −1.2 (0.6)<br>0.25%: 8.2; −1.5 (0.7)<br>C: 8.3; −1.5 (1.0) | 12 | 0.125%: 13.9 (3.3); 14.4 (2.5)<br>0.25%: 14.9 (3.1); 13.6 (2.6)<br>C: 14.5 (2.4); 14.2 (2.9) | One-way ANOVA to compare IOP at 0, 3, 6, 9, and 12 months between the groups | No difference of IOP between different groups |
| Weng, 2017[56] | A 0.15/0.3/0.5% (42); prospective; rebound and applanation tonometers | A: 10 (5–16); −1–−3 (57%) | NA | NA; rebound 17.5 (3.3)<br>applanation 17.1 (2.7) | *t*-test to compare IOP between tonometers | No difference of IOP between tonometers |
| Chan, 2017[57] | A 0.25 (35); retrospective; NCT | A: 10.3 (2.4); −2.6 (1.6) | 15.2 (2.4) | 15.3 (2.9)[c]; NA | Linear mixed model to analyze IOP changes over time | No significant IOP change during follow-up |
| Yu, 2020[58] | A[a] (121)/C (65); prospective; NCT | A: 8.6 (2.3); −1.8 (1.5)<br>C: 9.6 (2.3); −1.3 (1.4) | 10.6 (4.0) | Baseline not specified[d]: A 14.2 (2.8); C 14.5 (2.5)<br>Follow-up: A (high/low dose), 14.7 (3.0)/14.6 (2.8); C 15.8 (2.8) | ANOVA to compare IOP between groups (at two time points with atropine use) | Nonsignificant IOP increase at last follow-up of patients in both groups |
| Wu, 2020[59] | A[a] (1545); retrospective; NCT | 10.5 (2.5); −2.5 (1.6) | 20.0 (12.0) | 14.5 (2.7); 15.1 (2.9) | LR, MARS, CART, RF, XGBoost | Baseline IOP is the most important predictor of final IOP (unspecified direction of correlation) |
| Bukhari, 2022[60] | A 0.01 (76)/C (83); RCT; NCT | A: 9.7 (1.6); −2.6 (1.3)<br>C: 9.9 (1.6); −2.7 (1.4) | 12 | A: 15.8 (2.8); 0.16[e]<br>C: 15.6 (2.6); −0.11[e] | *t*-test to compare the IOP at 6 months and 12 months between the groups | Changes in IOP from baseline is not different between the groups |
| Chen, unpublished | A (166)/C (61); retrospective; NCT | A: 8.0 (2.1); −1.1 (1.3)<br>C: 7.0 (2.6); 0.6 (1.8) | A: 19.5 (11.0)<br>C: 17.4 (9.1) | A: 17.6 (3.0); 18.2 (3.1)<br>C: 17.4 (3.6); 17.0 (3.3) | Multilevel model to analyze IOP changes over time | Atropine use is associated with a 0.3 mmHg increase in IOP per year |

[a]Atropine concentration: 0.1%, 0.25%, 0.5%, and 1%, cumulative dosage of atropine is calculated, [b]IOP measured before atropine use, [c]IOP measured at enrollment, but some patients were under atropine treatment, [d]IOP measurement in 2009 is defined as the final IOP and the day of IOP measurement in 2008 is defined as the recruitment data (initial IOP). However, whether this IOP is obtained with the use of atropine is not specified, [e]IOP change from baseline at 12 months. Mean/median (SD or range). A=Atropine, ANOVA=Analysis of variance, C=Control, CART=Classification and regression tree, IOP=Intraocular pressure, LR=Linear regression, MARS=Multivariate adaptive regression spline, NA=Not available, NCT=Noncontact tonometer, RF=Random forest, RCT=Randomized controlled trial, SE=Spherical equivalent, SD=Standard deviation, XGBoost=eXtreme gradient boosting

patients. The IOP change was not associated with cumulative atropine dosage.[58] Chan *et al*. applied a linear mixed model to analyze the longitudinal changes in IOP over a 12- to 18-month period in 35 children undergoing topical atropine treatment. Their findings indicated no significant alteration in IOP during the specified follow-up duration. However, at the start of the study, 77% of the participants had been receiving atropine treatment for an average of 12.7 months, yet baseline measurements of IOP before the commencement of atropine were unavailable. Therefore, for these individuals, any comparison of IOP was limited to detecting fluctuations during atropine treatment and might not reflect true elevations from the initial baseline IOP accurately.[57] While the above-mentioned studies had great contributions to understanding IOP under topical atropine, they were hindered by different limitations: Small participant numbers, cross-sectional designs, single IOP measurement, short follow-up periods, lack of a control group, and/or the absence of IOP data preatropine initiation.

Hence, we recently conducted a retrospective study enrolling 166 children in the atropine-treated group and 61 children in the control group (unpublished data by Chen *et al*., under peer review). Our inclusion criteria ensured the enrollment of patients with multiple IOP measurements and documented IOP records before treatment initiation. Multilevel model was employed to assess the longitudinal IOP change by incorporating the results of repeated measurement and to adjust for potential confounders, such as age, sex, baseline IOP, central corneal thickness, and spherical equivalent. We observed a statistically significant increase in IOP by

0.3 mmHg per year in the atropine-treated group, while there was no discernible change in IOP over time in the control group. Although the magnitude of the IOP change might be considered clinically insignificant, the extended duration of atropine use in children, spanning several years until late adolescence or adulthood, underscores the continued importance of long-term IOP monitoring in this population.

Chan *et al*. further conducted an analysis of longitudinal changes in the thickness of the retinal nerve fiber layer and other optic disc parameters using OCT. Their findings indicated no significant alterations in these parameters over time under the treatment of topical atropine.[57] Chen *et al*. conducted a retrospective study, currently under peer review, examining the long-term IOP changes in a cohort of 227 children. This cohort included both subjects treated with atropine and a control group. On average, subjects were followed up for a duration of 19 months. Cross-sectional OCT scans were available for 27% of the subjects. There were no significant differences in the thickness of the retinal nerve fiber layer and the ganglion cell complex when comparing the treated and the control groups. This absence of evidence supports the notion that there is no apparent optic nerve damage in children treated with topical atropine. However, to validate this observation, a longitudinal follow-up study with a larger cohort and an extended follow-up period could be considered. OCT remains valuable in patients at risk of glaucoma, such as those with higher IOP, enlarged cupping, or a family history of glaucoma.

The other two studies, while not specifically concentrating on IOP changes under topical atropine, offer pertinent information on this subject. Wu *et al*. conducted a retrospective analysis using various machine learning models, aiming to identify the predictive factors for IOP under atropine treatment. They determined that baseline IOP is the most predictive factor for the endpoint IOP. However, their model could not specify the positive or negative correlation between baseline and end IOP.[59] Weng *et al*. utilized two different tonometers, applanation tonometry (Tono-Pen-XL, Reichert), and rebound tonometry (ICARE Finland Oy, Vantaa, Finland), to measure IOP in children using atropine. They found a good correlation between these two types of tonometers and concluded that rebound tonometry had the advantage of not requiring topical anesthesia.[56]

## Clinical Trials and Studies Investigating the Efficacy and Safety of Topical Atropine

In this section, our objective was to provide a comprehensive summary of IOP changes reported in clinical trials assessing the efficacy and safety of topical atropine. Returning to the PubMed search results mentioned in the previous section, 51 articles were initially identified. Seven of these specifically focused on IOP in children under topical atropine for myopia control, as discussed previously.[54-60] Among the 24 excluded studies, 20 were disregarded owing to their lack of relevance to the topic, one was a retracted article, one was a study protocol, and two were review articles. The remaining 20 articles were studies or meta-analyses concerning the efficacy and safety of topical atropine. Three studies mentioned IOP measurement in their methods, but did not report IOP in their results;[62-64] while another study stated no IOP change, but did not provide the relevant data.[65]

Furthermore, we manually searched the studies included in the recent network meta-analyses to check whether these studies reported IOP data and related outcomes.[17,18] Ha *et al*. enrolled 16 randomized controlled trials comparing the efficacy and safety of eight different concentrations of atropine in myopia control.[17] Recently, Lawrenson *et al*. included 64 randomized controlled trials in a network meta-analysis to compare the efficacy of various myopia interventions.[18] After reviewing the studies by Ha *et al*. and Lawrenson *et al*., 23 randomized controlled trials had investigated the efficacy of atropine, with eight of them reporting IOP during the follow-up.[13,16,66-71] Among the eight studies, three explicitly mentioned the absence of noticeable IOP changes or abnormal IOP during the follow-up period, without providing the summarized data.[66,69,70] The remaining five studies reported detailed outcomes.[13,16,67,68,71] Combining the results from the PubMed and manual searches, three duplicate articles were removed. Finally, 18 articles, comprising 14 randomized controlled trials and four meta-analyses, were included and summarized.

The ATOM1 study, investigating 1% topical atropine, monitored IOP at 4-month intervals and reported changes within 5.5 mmHg with no absolute value exceeding 21 mmHg.[13] Hieda *et al*. compared 0.01% topical atropine and placebo group, monitoring IOP at baseline, the first and second years. They observed a slight but nonsignificant increase in IOP over the 24-month period compared to the baseline.[67] Kinoshita *et al*. compared the combination of 0.01% topical atropine and orthokeratology with orthokeratology monotherapy. At the end of the second year, the IOP in the combination and orthokeratology groups decreased by 1.1 mmHg and 0.6 mmHg, respectively ($P = 0.28$).[68] In the low-concentration atropine for myopia progression study, which compared three different concentrations of topical atropine (0.05%, 0.025%, and 0.01%) with a placebo, IOP measured at baseline and 1 year showed no significant differences between the groups.[16] Shih

*et al*. compared the efficacy of the combination of 0.5% atropine and multi-focal glasses, multi-focal glasses alone, and single-vision spectacles; the IOP had increased by 1.67 mmHg, 1.66 mmHg, and 1.27 mmHg from baseline to the 18th month, respectively, with no significant between-group difference.[71] Zhu *et al*. compared the efficacy of 0.05% atropine to the placebo, monitoring IOP at a 6-month interval, and reported no significant difference in IOP between the two groups at each time point within 3 years.[72] Du *et al*. compared three methods of myopia control, including single-vision spectacle lenses combined with 0.01% atropine, orthokeratology, and peripheral defocus spectacle lenses. In the atropine group, IOP increased from 16.8 to 16.9 mmHg after the treatment, a nonsignificant change comparable to other groups.[73] Li *et al*.[74] and Guo *et al*.[75] enrolled children using 0.01% atropine and found no significant IOP change at 6 months and 2 weeks, respectively, compared to that at baseline. Using a linear mixed model, Cheng and Hsieh demonstrated the trend of IOP changes as −0.03 mmHg per year in participants using 0.125% topical atropine.[76] Hvid-Hansen *et al*. randomized children into the placebo, 0.01% atropine, and 0.1% atropine loading groups. At 3 months, the changes in IOP from baseline were −0.2, 0.5, and 1.5 mmHg, respectively. Those who received 0.1% atropine had a greater IOP increment than that in the placebo group; however, this change became nonsignificant after adjustment for multiple comparisons ($P$ = 0.03, adjusted $P$ = 0.06). Moreover, this borderline significance was not observed at 6 months.[77] Lu and Chen treated children with myopia using varying concentrations of atropine, ranging from 0.1% to 0.5%, based on the sunlight intensity. They reported comparable IOP between the atropine and control groups at baseline and follow-up. However, the IOP had increased by 0.67 and 0.25 mmHg, respectively, from baseline, with a greater change in the atropine group.[78] Wang *et al*. compared the efficacy of 0.02% and 0.01% atropine with the control group. The IOP in the 0.02% atropine group increased from 15.9 to 16.3 mmHg. Contrarily, the IOP in the 0.01% atropine group decreased from 16.9 mmHg to 16.5 mmHg. Further, the IOP in the control group decreased from 17.0 mmHg to 16.6 mmHg. No significant differences in IOP changes were observed between the groups.[79] Cyphers *et al*. enrolled 31 myopic young adults and administered 0.01% atropine for 1 week. The IOP increased significantly from 15.6 to 16.7 mmHg ($P$ = 0.003). Twenty-six percent of patients had an increment of more than 2 mmHg, with the maximal increment being 5.5 mmHg.[80]

Four meta-analyses were identified. Zhao *et al*. compared the efficacy and safety of 0.01% atropine with the control by enrolling seven randomized controlled trials. The mean difference of the IOP between the groups from two studies was −0.08 mmHg, which was not statistically significant.[81] Wang *et al*. evaluated the efficacy of combined orthokeratology and 0.01% atropine from four studies. Two of these studies reported the change in IOP, and the weighted mean difference was 0.12 mmHg, suggesting no significant difference in IOP changes between the combination treatment and control groups.[82] In addition, Wang *et al*. and Zheng and Tan performed meta-analyses to compare the efficacy of combined orthokeratology and low-dose atropine with orthokeratology alone. While both meta-analyses included four randomized controlled trials with IOP data, three out of four enrolled studies were the same. The weighted mean difference in IOP change was not significantly different between the combined and orthokeratology alone groups in both meta-analyses.[83,84]

To summarize, the majority findings from previous studies demonstrated no significant difference between the control and atropine-treated groups. In some studies, a slight but nonsignificant increase in IOP was observed. Notably, one study by Cyphers *et al*. reported a significant IOP elevation; however, it was conducted in participants aged 21–30 years.[80] Overall, substantial evidence supporting IOP elevation in children under topical atropine treatment is lacking.

This review has certain limitations. First, the studies mentioned primarily employed relatively low concentrations of atropine. Given the dose-dependent nature of atropine side effects, the stability of IOP in children using higher concentrations requires further investigation. For instance, the ATOM1 study, utilizing 1% topical atropine, reported possible IOP changes within 5.5 mmHg, which was a nonnegligible change.[13] Chen *et al*. found a significant trend of IOP elevation in children using 0.125% topical atropine (unpublished data, under peer review). Similarly, Hvid-Hansen *et al*. observed a borderline greater increment in the 0.1% atropine group compared to the 0.01% atropine and the control groups.[77] Lu *et al*., using topical atropine ranging from 0.1 to 0.5%, also reported a greater IOP, and an increase in IOP than in the control group, although statistical significance was not explicitly addressed.[78] Second, the existing evidence is derived from the studies comparing IOP between groups at specific time points or analyzing the changes between groups. Given the inherent fluctuations in IOP and potential challenges in children's cooperation with measurements, longitudinal follow-up with repeated assessments may offer advantages over single measurement-based comparisons (e.g. $t$-test or analysis of variance). Third, a substantial individual variation exists in IOP changes associated with pupil dilation. Specifically, certain individuals may exhibit a noteworthy increase in IOP, whereas others might undergo a reduction in IOP. Hence, relying solely on the average IO*P* value within a cohort

may overlook the possibility of elevated IOP within a specific subgroup of participants. Consequently, while strong evidence supporting IOP elevation is lacking, continued monitoring of IOP is imperative in children using topical atropine, particularly in those exposed to higher concentrations.

## Conclusions

In conclusion, elevated IOP following pupil dilation is more frequently encountered in patients with compromised outflow facilities, stemming from either closed-angle or open-angle with reduced trabecular meshwork outflow. This risk is less prevalent in the general population. Nevertheless, it should be noted that the IOP changes may have significant individual variations. Despite a few studies that observed a slight increase in IOP in children under topical atropine treatment for myopia control, the majority of studies support the absence of significant IOP change in this population. However, regular IOP follow-up should be considered not only to validate the long-term stability of IOP in this population but also to identify certain individuals predisposed to IOP elevation following pupil dilation.

### Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.


### Financial support and sponsorship

This study was partially supported by MS 465, Research fund for Pediatric Ophthalmology, National Taiwan University Hospital.


### Conflicts of interest

The authors declare that there are no conflicts of interest in this paper.

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