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Efficacy of atropine eyedrops in reducing myopia progression and axial elongation in myopic children: a meta-analysis

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Abstract

Purpose: *To determine the efficacy of various concentrations of atropine eyedrops on retarding myopia progression and axial elongation in Asian children.*

Study design: *Meta-analysis.*

Methods: *Randomized clinical trials and prospective interventional non-randomized studies which enrolled children aged 4 to 14 years old who received atropine treatment for myopia were included in the study. The Cochrane Collaboration 6 aspects of bias was used to assess the risk of bias for all included studies. Outcome measures were myopia progression and axial elongation. Meta-analysis was conducted using the random-effects model.*

Results: *Eight randomized clinical trials and two prospective interventional non-randomized studies which included a total of 1,229 Asian children were included in the analysis. The pooled mean difference between control and atropine for myopia progression was 0.77 diopters (D) per year [CI 0.64, 0.89]. Subgroup analysis by concentration showed a decreasing trend with decreasing concentration. The pooled mean difference of myopia progression for 1%, 0.5%, 0.25%, and 0.1–0.125% atropine was 0.97 D/year [CI 0.72, 1.21], 0.88 D/year [CI 0.74, 1.02], 0.79 D/year [CI 0.37, 1.21], and 0.80 D/year [CI 0.62, 0.97], respectively; whereas that for 0.01% atropine was 0.46 D/year [CI -0.02, 0.94] indicating that this intervention may or may not be favorable for slowing myopia progression. The pooled mean difference between control and atropine for axial elongation was -0.22 mm [CI -0.29, -0.14] favoring atropine. Subgroup analysis by concentration also showed decreasing trend with decreasing concentration. The pooled mean difference of axial elongation for 1%, 0.5%, 0.1%, 0.05%, and 0.025% atropine was -0.44 mm [CI -0.57, -0.32], -0.19 mm [CI -0.35, -0.04], -0.10 mm [CI -0.17, -0.03], -0.21 mm [CI -0.28, -0.14], and -0.12 mm [CI -0.16, -0.08], respectively; whereas that for 0.01% atropine was -0.01 mm [CI -0.09, 0.06] indicating that this intervention may or may not be favorable in reducing axial elongation.*

Conclusion: *This meta-analysis shows that the effects of atropine for both myopia progression and axial elongation are dose-dependent for the concentration 0.025% to 1%. Results for 0.01% atropine are still equivocal.*

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Keywords: *atropine, Asian children, axial elongation, meta-analysis, myopia progression*

Introduction

Myopia is the most common ocular condition and has been increasing in prevalence, particularly in East Asia. In certain countries such as Singapore, Hong Kong, and Taiwan, the prevalence of myopia has reached 80% or even higher in the young adult population.[1] Likewise in the United States, the prevalence rose from 25% to 42% between 1971 and 1999.[2] Studies have also shown that myopia has been increasing in younger age groups from 5.8% in 1983 to 61% in 2000 in 7-year-old children in Taiwan.[3] Prevention of myopia progression is critical due to the risks and complications associated with it such as retinal detachment, cataract, glaucoma, choroidal neovascularization, and myopic degenerative changes.[4] Epidemiological studies done in Asian areas found that retinopathy secondary to high myopia has become the second most frequent cause of low vision and blindness among adults.[5]

Several treatment methods have been studied with the aim of retarding myopia progression in children. These treatment methods include eyeglasses that undercorrect, multifocal eyeglasses, novel lens eyeglasses design, various contact lens therapies such as bifocal or multifocal contact lenses or orthokeratology, topical timolol, and topical antimuscarinic agents including pirenzepine and atropine.[2] A Cochrane database review done by Walline *et al.* concluded that antimuscarinic agents are the most likely effective treatment to slow myopia progression.[6] This review compared various antimuscarinic agents to placebo, with a subgroup analysis of atropine that included only two studies that were available at the time.

Atropine is a nonselective muscarinic antagonist which has been used in myopia control for the past few decades. However, there is still no ideal approach as to the concentration and duration of atropine treatment for the control of myopia progression.[1] Several clinical trials have already been conducted to determine the most effective and safest dosing in reducing myopia progression while minimizing adverse effects inherent to atropine, such as photophobia and blurred near vision.[5] The exact mechanism by which atropine reduces myopia progression is still not clearly understood. Previously, it was thought that accommodation has a role in retarding myopia progression, but studies have demonstrated that atropine was able to inhibit myopia in animals that have no capacity for accommodation. Another theory states that atropine may have a role in remodeling of the sclera.[7] However, current theories suggest that pupillary dilation may result in increased ultraviolet A exposure, which limits axial elongation, or that myopia may be associated with increased chronic inflammation in the eye, which may be downregulated by atropine.[2]

A meta-analysis by Song *et al.*[3] in 2011 showed that the effect of atropine increased with higher doses, suggesting a dose-dependent effect. However, a more recent meta-analysis by Gong *et al.*[1] in 2017 found no significant difference between various doses of atropine, with 0.01% dose as its lowest concentration. The first meta-analysis[3] in 2011 reviewed only six studies, with 0.1% dose as its lowest concentration. More recent clinical trials with lower concentrations have since been conducted to determine the lowest effective concentration with the least adverse effects, such as photophobia, blurred near vision, and allergic reactions. The 2017 meta-analysis by Gong *et al.*[1] combined different types of studies (randomized clinical trials and cohort studies) due to lack of availability of studies examining each atropine concentration. Furthermore, axial length was also not evaluated across various doses of atropine because results were only available in higher doses.

The objective of this study is to determine the efficacy of atropine in reducing the rate of myopia progression and increase in axial length among myopic children who were treated with atropine ophthalmic drops ranging from 0.01% to 1% *versus* control based on data from published literature.

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials and prospective interventional controlled trials were considered for inclusion in this review.

Types of participants

Participants of the included studies were pediatric patients aged 4 to 14 years old with myopia on cycloplegic refraction (automated, using either cyclopentolate or tropicamide) regardless of degree.

Types of interventions

Only studies that employed daily topical administration of atropine ophthalmic drops, regardless of concentration, were included. Controls may consist of placebo, alternate treatment, or observation. The study done by Shih *et al.* in 1999[8] used 0.5% tropicamide as control, while in 2001[9] they used multifocal lenses as control. All other studies compared atropine with placebo.

Types of outcome measures

1. Mean difference of rate of myopia progression in diopters per year.
2. Mean difference of increase in axial length in millimeters.

Search methods for identification of studies

Electronic search was done through PubMed, Embase, Google Scholar, Herdin, and Cochrane using free text search and Medical Subject Headings (MeSH) search. Free text search was done through all the above databases up to November 2018. We used the search terms *atropine* and *myopia progression*. Only studies published in English were included in the analysis.

Data collection and analysis

Selection of studies

The studies considered for review were individually screened by two independent reviewers for eligibility. All studies meeting the criteria for eligibility and containing as outcomes either rate of myopia progression or increase in axial length, or both, were included in the analysis. In case of a dispute, this was settled through discussion with a third reviewer.

Data extraction and management

Means and standard deviations for each outcome measure as well as sample sizes for each treatment arm were extracted from each study using a data collection form by a single author. Data was then analyzed using Cochrane's Review Manager 5.3 software. Outcomes were reported as pooled mean difference using the inverse variance method of the random effects model.

Assessment of risk of bias in included studies

The Cochrane Collaboration Risk of Bias Tool for randomized controlled trials was used for the assessment of included studies.[10] Studies were assessed as being "low risk," "high risk," or "unclear" regarding five domains of bias: allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.

Measures of treatment effect

Since both outcome measures were dichotomous data that were measured on the same scale across all trials, pooled mean difference (MD) was used to summarize the treatment effect for both rate of myopia progression and increase in axial length. Level of significance was set at alpha = 0.05. Outcomes were reported using the point estimate of the pooled mean difference, its *p*-value, and 95% confidence interval.

Unit of analysis issues

The unit of analysis of each outcome measure was by number of eyes enrolled instead of number of participants. Data for rate of myopia progression and increase in axial length were measured from baseline compared to final measurements.

Multi-arm studies were treated as separate two-arm studies that compared each intervention with control. The multi-arm studies that were treated as separate studies were labeled accordingly using letters.

Myopia progression was expressed in diopters (D)/year. Because myopic refraction is a negative value, a more negative value of myopia progression indicated a higher rate of progression, while a less negative or more positive value indicated a lower rate of progression, which was the beneficial result. For the increase in axial length, values were expressed in millimeters. A lower or more negative value was considered a beneficial result.

Dealing with missing data

Most studies reported complete data including mean, standard deviation, and number of samples for each treatment arm. Only the study by Lee *et al.*[11] did not report the standard deviation for the 0.25% atropine treatment arm. Missing standard deviations were imputed using the correlation coefficient from another study in the meta-analysis, as recommended in the Cochrane Handbook.[12] Studies with imputed standard deviations were subjected to sensitivity analysis.

Assessment of heterogeneity

For each analysis, statistical heterogeneity was computed on each forest plot. Chi-square (I^2) > 50% or its *p*-value ≤ 0.10 was considered as statistically significant heterogeneity of data.

Assessment of reporting biases

Funnel plots of the included studies were generated for each outcome measure. Symmetry and shape of the funnel plots were assessed for publication bias.

Data synthesis

The random effects model was used based on the assumption of heterogeneity of data due to differences in the study populations and treatment concentrations.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses were done for each concentration of atropine and each study methodology. For each subgroup analysis, Chi-square (I^2) and its corresponding *p*-value were also computed as described above.

Sensitivity analysis

Sensitivity analysis was done by excluding data from the study with missing standard deviations that were imputed from the correlation coefficient of another study. If treatment effects were the same in the sensitivity analysis, the results of the study were considered robust.

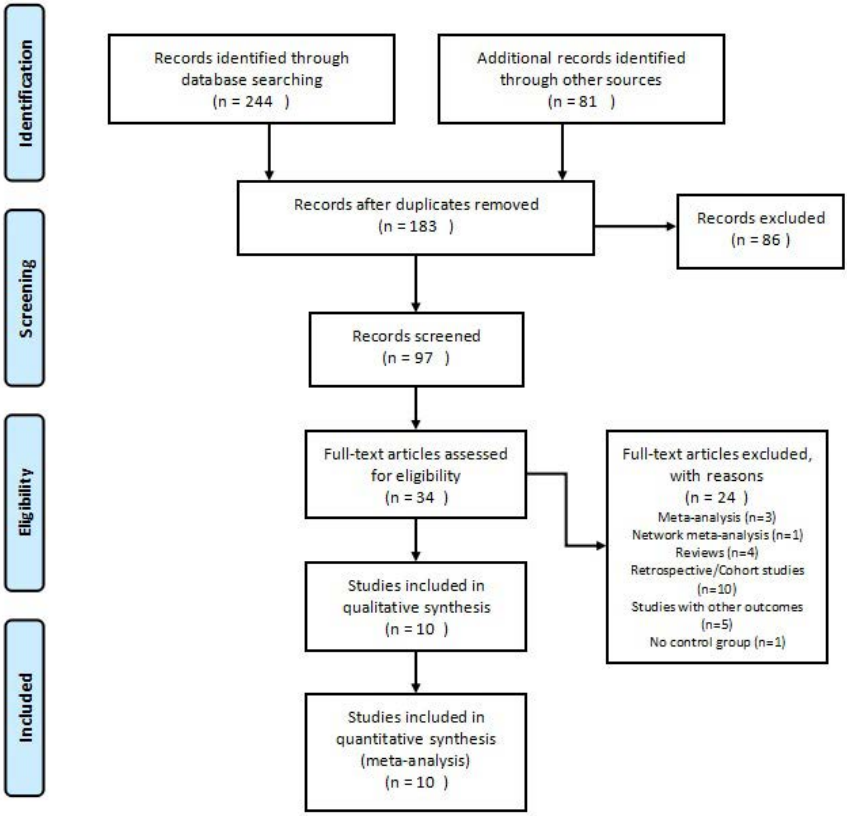

Fig. 1. PRISMA flow diagram of the literature search.

Results

Description of studies

Search results

After a thorough search of the database, 244 studies were retrieved plus an additional 81 studies from other sources. Duplicate reports were removed, resulting in 183 potential relevant studies. Eighty-six reports deemed irrelevant to the objective of this study were excluded. Of the 97 studies screened, 34 full-text articles were assessed for eligibility, of which only ten articles met our inclusion criteria. Eight studies were randomized controlled trials and two were prospective, interventional, non-randomized studies (Fig. 1). Three of the studies had three treatment arms and one had two treatment arms. A total of 1,229 children

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Type of study	Population (age in years)	Degree of myopia	Intervention	Control	Number of eyes (intervention)	Number of eyes (control)	Outcomes assessed	Follow-up period
Yen (1989)[13]	Taiwan	RCT	6–14	-0.5 to -4.0 D	1% atropine every other day	Placebo (saline)	32	32	Myopic progression	1 year
Shih (1999)[8]	Taiwan	RCT	6–13	-0.5 to -6.75 D	0.5% atropine nightly 0.25% atropine nightly 0.1% atropine nightly	0.5% tropicamide nightly	0.5% atropine: 41 0.25% atropine: 47 0.1% atropine: 49	49	Myopic progression	2 years
Shih (2001)[9]	Taiwan	RCT	6–13	mean baseline myopia -3.28 to -3.34 D	0.5% atropine nightly + multifocal lenses	Multifocal lenses	66	61	Myopic progression, axial length	1.5 years
Chua (2006)[14]	Singapore	RCT	6–12	-1.0 to -6.0 D and < 1.5 D astigmatism	1% atropine daily	Placebo (0.5% hydroxypropyl methylcellulose)	166	190	Myopic progression, axial length	2 years
Fan (2007)[15]	Hong Kong	Interventional non-randomized study	5–10	-3.0 D or more	1% atropine daily	No intervention	23	23	Myopic progression, axial length	1 year
Chia (2012)[7]	Singapore	RCT	6–12	at least -2.0 D and < 1.5 D astigmatism	0.5% atropine nightly 0.1% atropine nightly 0.01% atropine nightly	Placebo (0.5% hydroxypropyl methylcellulose)	0.5% atropine: 139 0.1% atropine: 141 0.01% atropine: 75	190	Myopic progression, axial length	2 years
Yi (2015)[16]	China	RCT	7–12	-1.0 and -6.0 D	1% atropine nightly	Hypromellose + dextran + glycerol (Tears Naturale Free)	62	62	Myopic progression, axial length	1 year
Lee (2016)[11]	Taiwan	Interventional non-randomized study	6–12	less than -3.0 D	0.125% atropine 0.25% atropine	No intervention	0.125% atropine: 32 0.25% atropine: 12	12	Myopic progression	1 year
Wang (2017)[17]	China	RCT	mean: 9.1 (intervention); 8.7 (control)	-0.5 to -2.0 D	0.5% atropine	Hypromellose + dextran + glycerol (Tears Naturale Free)	54	55	Myopic progression	1 year
Yam (2018)[4]	Hong Kong	RCT	4–12	at least -1.0 D and ≤ -2.5 D astigmatism	0.05% atropine nightly 0.025% atropine nightly 0.01% atropine nightly	0.9% sodium chloride	0.05% atropine: 102 0.025% atropine: 91 0.01% atropine: 97	93	Myopic progression, axial length	1 year

D: diopters; RCT: randomized controlled trial

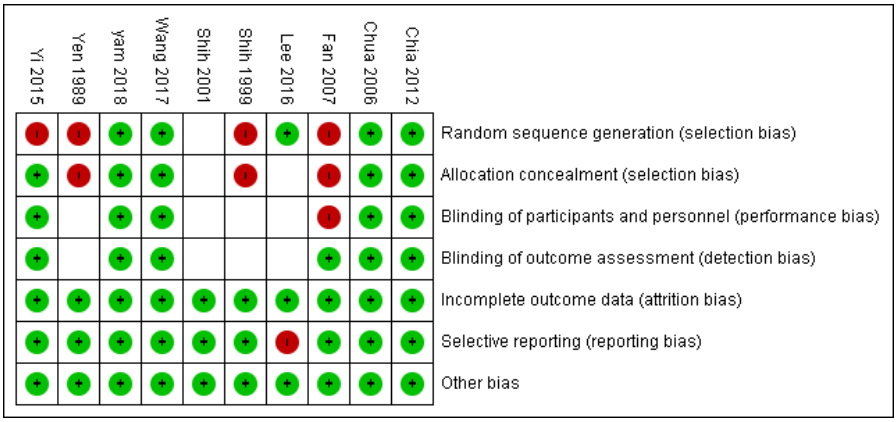

Fig. 2. Summary of risk of bias according to the Cochrane Collaboration Tool.

aged 4 to 14 years were included in this meta-analysis. The baseline cycloplegic refraction (automated, using either cyclopentolate or tropicamide) ranged from -0.5 to -6.75 D and follow-up period was 1 to 2 years. Only six studies had axial length measurement as part of their outcome. The characteristics of studies included are summarized in Table 1.

Risk of bias in included studies

The risk of bias in included studies are summarized in Figure 2. Five[4,7,11,14,17] out of ten included studies described how randomization was done. Methods employed were computer-generated randomization list, draw lots, and stratified random sampling. Studies by Fan *et al.*,[15] Yen *et al.*,[13] and Yi *et al.*,[16] on the other hand, did not elaborate on how the subjects were randomized. Allocation concealment was adequate in most studies and was generally achieved by preparing prepackaged bottles with similar appearance as intervention for different treatment groups or using sequentially numbered opaque sealed envelopes. Approximately 50–60% of the included studies did blinding of participants and outcome assessment as stated in their methodology. Studies by Lee *et al.*,[11] Shih *et al.*,[8,9] and Yen *et al.*[13] did not mention blinding of participants and investigators. Incomplete outcome data were appropriately analyzed. Studies done by Yam *et al.*,[4] Wang *et al.*,[17] Yi *et al.*,[16] Chia *et al.*,[7] and Chua *et al.*[14] used intention-to-treat principle to minimize attrition. All the studies adequately reported the outcomes of interest of the study except for Wang,[17] wherein the results were reported in confidence interval instead of standard deviation.

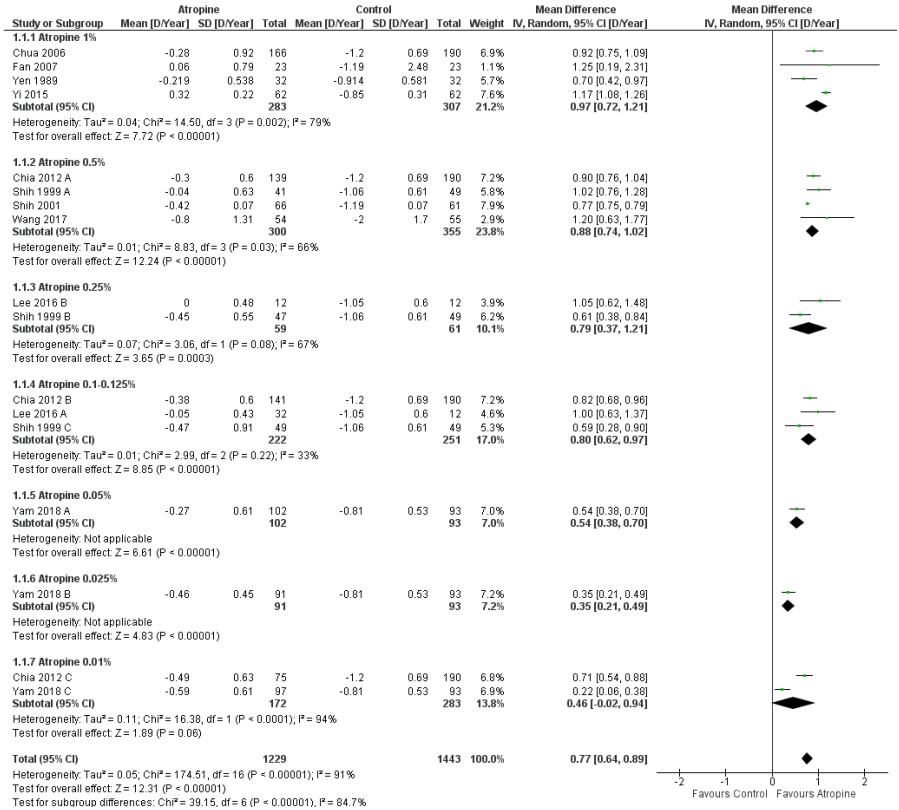

Fig 3. Forest plot of atropine versus control for myopia progression (D/year) with subgroup analysis by concentration.

Effects of interventions

Myopia progression

Meta-analysis of all included studies regardless of atropine concentration using the random effects model yielded a pooled mean difference of 0.77 D/year [CI 0.64, 0.89] between control and atropine for myopia progression (Fig 3). This result shows that, in general, atropine is a favorable intervention for controlling myopia progression in terms of rate of change in refraction. However, heterogeneity was high (I^2 = 91%) across all the studies.

Planned subgroup analysis by concentration showed favorable outcomes for 1%, 0.5%, and 0.1% to 0.125%, 0.05%, and 0.025% concentrations of atropine (Fig 3). The effect showed a decreasing trend with decreasing concentration. The

pooled mean difference of myopia progression from the four studies[13-16] that used 1% atropine was 0.97 D/year [CI 0.72, 1.21], still with significant heterogeneity (I^2 = 79%). For the four studies[7-9,17] that used 0.5% atropine, the pooled mean difference was 0.88 D/year [CI 0.74, 1.02], also with significant heterogeneity (I^2 = 66%). For the two studies[8,11] that used 0.25% atropine, it was 0.79 D/year [0.37, 1.21], with significant heterogeneity (I^2 = 67%). For the three studies[7,8,11] that used 0.1% to 0.125% atropine, the pooled mean difference still favored the intervention at 0.80 D/year [0.62, 0.97], with no significant heterogeneity (I^2 = 33%). There was only one study[4] each for the 0.05% and 0.025% subgroup analyses, precluding meta-analysis of data for those subgroups. Nevertheless, both concentrations of atropine showed favorable outcomes in terms of myopia progression. For the two studies[4,7] in the 0.01% atropine subgroup, the pooled mean difference between atropine and control was 0.46 but the confidence interval [-0.02, 0.94] crossed the midline, indicating that this intervention may or may not be favorable for slowing myopia progression. There was also high heterogeneity within the subgroup (I^2 = 94%) (Fig. 3).

Subgroup analysis by type of study showed that randomized controlled trials favored atropine for decreasing myopia progression, with pooled mean difference of 0.74 D/Year [CI 0.61, 0.86]. This subgroup also had significant heterogeneity (I^2 = 92%). On the other hand, subgroup analysis of nonrandomized controlled trials also favored atropine, with a slightly higher pooled mean difference of 1.04 D/year, a wider confidence interval [CI 0.61, 1.31], and no significant heterogeneity (P = 0.91) (Fig. 4). This subgroup analysis shows that even with nonrandomized

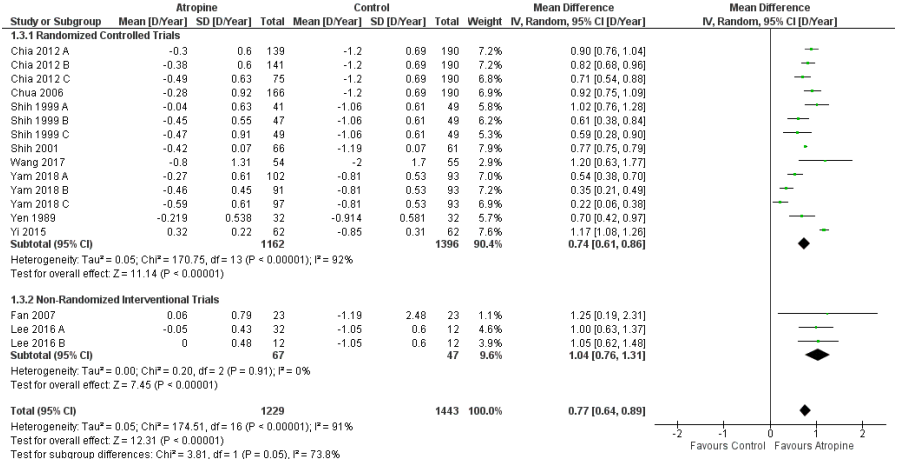

Fig 4. Forest plot of atropine versus control for myopia progression (D/year) with subgroup analysis by study methodology.

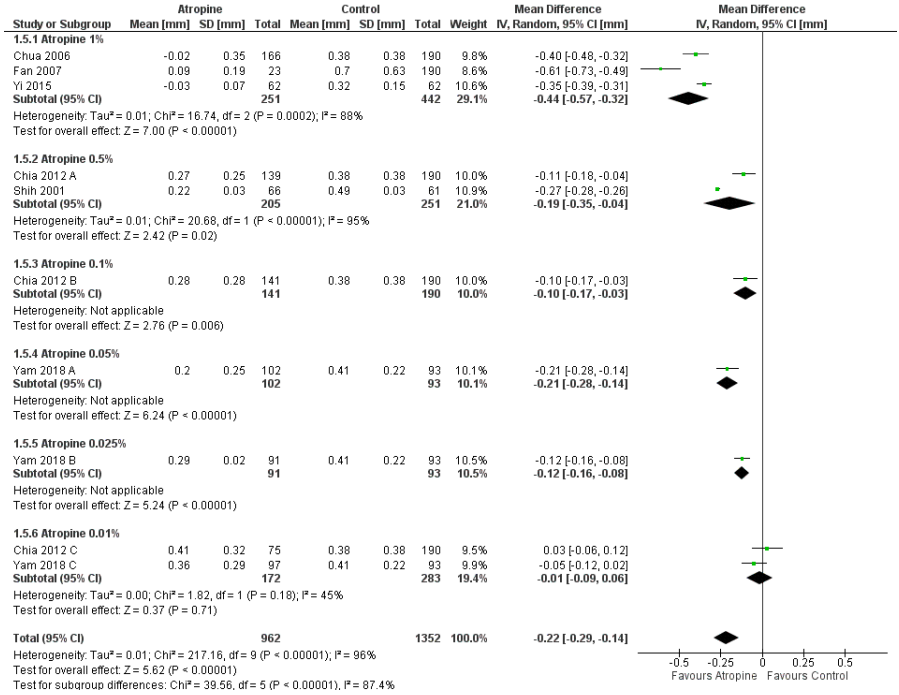

Fig 5. Forest plot of atropine versus control for increase in axial length (mm) with subgroup analysis by concentration.

trials included in the analysis, the results were still robust for retarding myopia progression.

Increase in axial length

For increase in axial length, the overall pooled mean difference between the atropine and control groups was -0.22 mm [CI -0.29, -0.14], which favored atropine. The studies included for this outcome also had high heterogeneity (I^2 = 96%). Subgroup analysis by concentration showed that atropine 1%, 0.5%, 0.1%, 0.05%, and 0.025% had favorable results compared to control for reducing axial elongation, while atropine 0.01% had equivocal results. There was high heterogeneity within the 1% and 0.5% subgroups, while the 0.1%, 0.05%, and 0.025% subgroups only had one study for each analysis. Only the 0.01% subgroup had low heterogeneity (I^2 = 45%). The effects show a decreasing trend with decreasing concentration from 1%, 0.5%, to 0.1%, with pooled mean differences of -0.44 mm [CI -0.57, -0.32], -0.19 mm [CI -0.35, -0.04], and -0.10 mm [CI -0.17, -0.03], respectively. Effects were similar among the 0.5%, 0.1%, 0.05%, and 0.025% subgroups, with pooled mean differences of -0.19 mm [CI -0.35, -0.04], -0.10 mm [CI -0.17, -0.03],

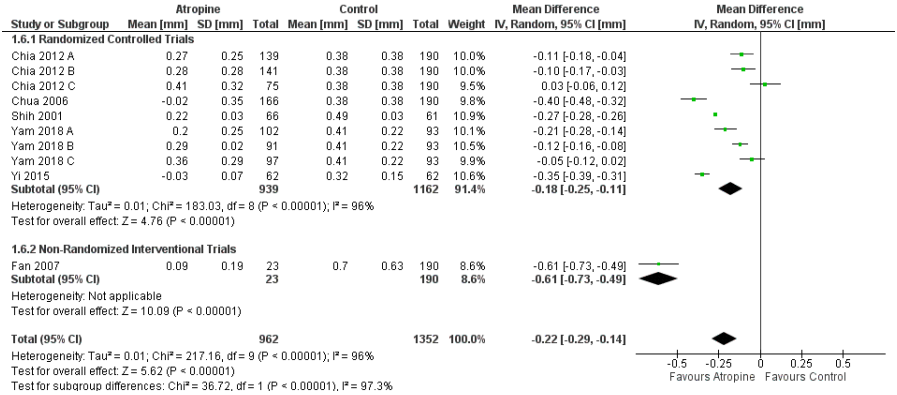

Fig 6. Forest plot of atropine versus control for myopia progression (D/year) with subgroup analysis by study methodology.

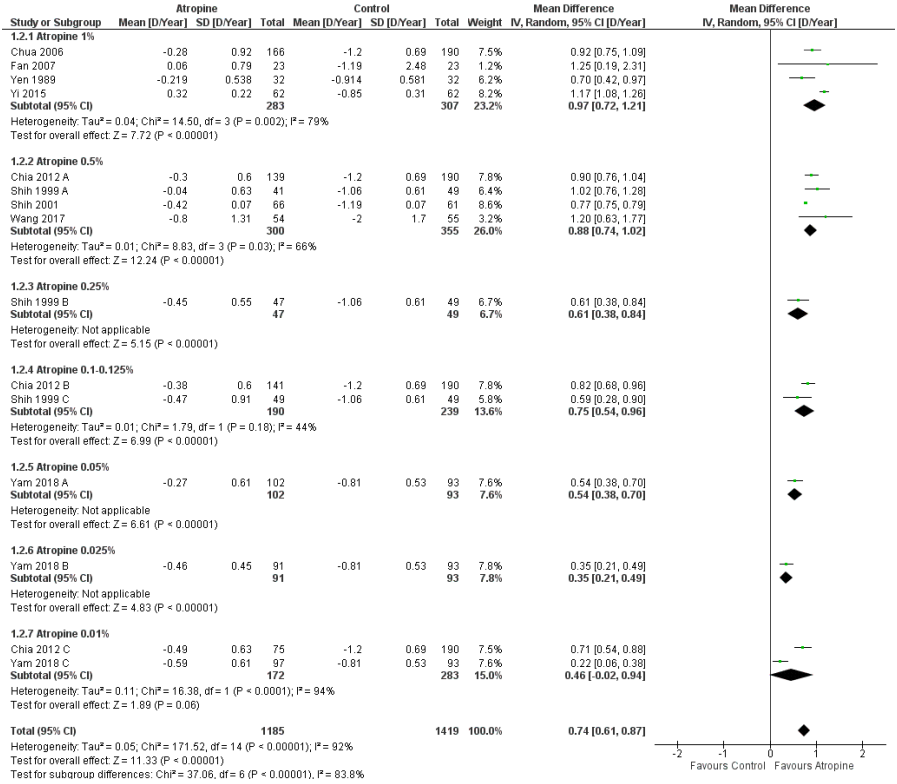

Fig 7. Forest plot of sensitivity analysis for atropine versus control for myopia progression (D/year) with subgroup analysis by concentration.

-0.21 mm [CI -0.28, -0.14], and -0.12 mm [CI -0.16, -0.08], respectively (Fig. 5).

Subgroup analysis by type of study showed that randomized controlled trials favored atropine for decreasing axial elongation, with pooled mean difference of -0.18 mm [C-0.25, -0.11]. This subgroup also had significant heterogeneity (I^2 = 96%). Subgroup analysis of nonrandomized controlled trials only had one remaining study for analysis, which also favored atropine (Fig. 6). This subgroup analysis shows that even with nonrandomized trials included in the analysis, the results were still robust for axial elongation.

Sensitivity analysis

Sensitivity analysis was conducted by excluding data with incomplete and imputed standard deviations from Lee *et al.*[11] for the 0.25% and 0.1–0.125% subgroups. The overall pooled mean difference of 0.74 D/year [CI 0.61, 0.87] on sensitivity analysis was still similar with the original value. The same was true for the sensitivity analysis of the 0.1–0.125% subgroup, with pooled mean difference of 0.75 D/year [CI 0.54, 0.96]. For the 0.25% subgroup, only one study was available for the analysis, which favored atropine (Fig. 7).

Sensitivity analysis of the subgroup analysis by study methodology affected only the subgroup of nonrandomized interventional trials, which had only one remaining study for analysis. The results of the study in this subgroup also favored atropine (Fig. 8).

For the outcome measure increase in axial length, all studies included had complete data and imputation of standard deviation was not done. Hence, sensitivity analysis was not necessary for this outcome.

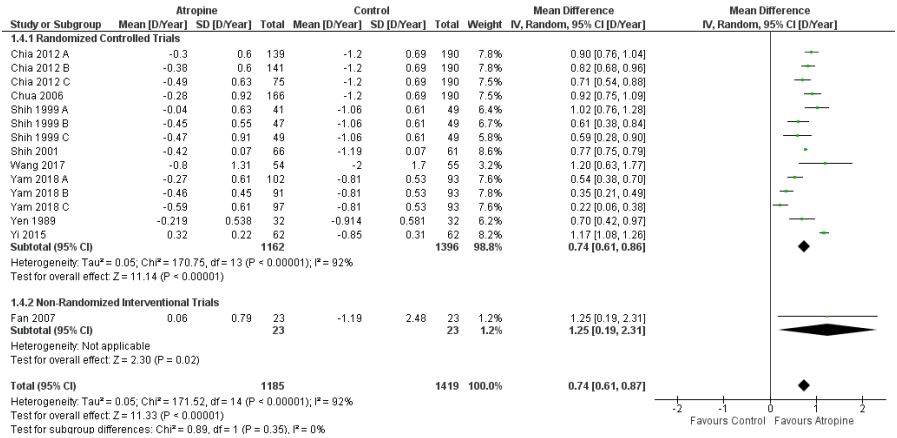

Fig 8. Forest plot of sensitivity analysis for atropine vs control for myopia progression (D/year) with subgroup analysis by study methodology.

Results of the sensitivity analysis showed that the results of the meta-analysis are robust despite inclusion of studies with imputed standard deviations for myopia progression.

Discussion

The results of this meta-analysis show that atropine is effective in reducing myopia progression and decreasing axial elongation. The pooled mean difference is 0.77 D/year for myopia progression, which is similar to previous studies by Song *et al.*[3] and Walline *et al.*[6] Subgroup analysis showed that the effect size decreases as the concentration of atropine decreases, with the 0.01% subgroup having equivocal results. This is consistent with the results of meta-analysis done by Song *et al.*,[3] which showed a dose-response relationship between atropine and myopia progression. However, this study did not have a 0.01% subgroup since low dose atropine was not yet being studied at the time.[3]

Contrary to our results, meta-analyses done by Li *et al.*,[5] Huang *et al.*,[18] and Gong *et al.*[1] all showed no significant difference in slowing myopia progression among various doses of atropine. Li *et al.*[5] analyzed the overall effects only because there were not enough studies for subgroup analysis, and the lowest dose included was 0.025%. Gong *et al.*[1] categorized the different concentrations of atropine as low dose (0.01%), moderate dose (greater than 0.01% to less than 0.5%), and high dose (0.5% to 1.0%). A network meta-analysis by Huang *et al.*[18] also divided the concentration of atropine into low (0.01%), moderate (0.1%), and high dose (0.5% and 1%). The differences in the effects of the value of the lower doses of atropine may not have been delineated because they were arbitrarily clustered together into subgroups.

Results for the increase in axial length also showed that atropine is effective with an overall pooled mean difference of -0.22 mm. However, the 0.01% subgroup likewise showed equivocal results similar to the outcome in myopia progression. The lowest concentration showing efficacy for axial elongation is the 0.025% subgroup. Although our analysis showed positive results, there are still few studies which included axial elongation as their outcome; therefore, more studies are needed to confirm this finding.

Quality of the evidence

Subgroup analysis of studies by methodology showed that conclusions were consistent even when nonrandomized interventional studies were excluded. Further sensitivity analysis showed that the body of evidence was robust in spite of imputed standard deviations from one study. The eight randomized controlled trials and two interventional studies provided adequate evidence to make robust conclusions regarding the objectives.

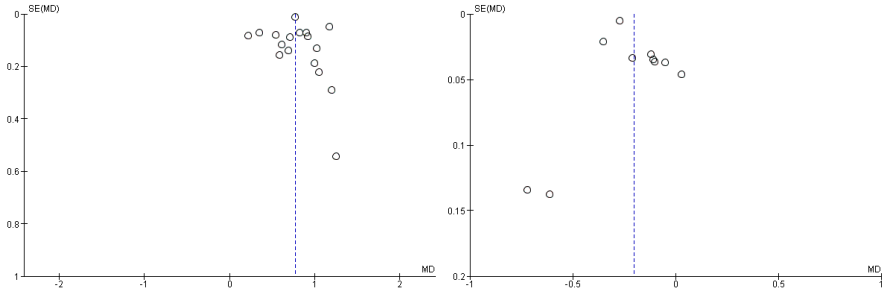

Fig 9. Funnel plots for myopia progression (left) and increase in axial length (right).

Potential biases in the review process

Only articles in English from electronic sources were included in the study. Manual search from offline databases was not done. Only published data from available full-text articles were used. Raw data from authors were not sought in the data collection. Funnel plots for both outcomes (Fig. 9) were asymmetrical with a paucity of small studies, which may indicate publication bias. This asymmetry may also be due to the high heterogeneity of the included studies.

Conclusion

Implications for practice

The use of atropine eyedrops is generally effective for myopic Asian children aged 4 to 14 years old with spherical equivalents of -0.5 D to -6.75 D. Based on current available evidence, the lowest effective dose of atropine in reducing myopic progression and axial elongation is 0.025% atropine daily, but this is based on a single study. The lowest effective concentration for reducing both myopic progression and axial elongation based on more than one study was 0.1–0.125% atropine daily. Pooled results of this meta-analysis showed that 0.01% atropine daily compared to placebo had equivocal results for both outcomes.

Implications for research

More randomized controlled trials are needed to assess the efficacy of low-dose atropine, specifically 0.01%, 0.025% and 0.05%. Only one randomized controlled trial was done for the 0.025% and 0.05% subgroups, while the effect size of the 0.01% subgroup had equivocal results due to lack of statistical difference compared to placebo. Axial elongation should also be included as an outcome measure in all future studies.

Declarations

Ethics approval and consent to participate

This research was submitted to the Institutional Ethics Review Committee of St. Luke's Medical Center Quezon City and was exempted from Ethics Review.

Consent for publication

Not required.

Competing interests

The authors have no proprietary or commercial interest in any materials discussed in this research.

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None to disclose.

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