Efficacy and Safety of Atropine to Control Myopia Progression: A Systematic Review and Meta-analysis

Congling Zhao  
Aier eye hospital of Wuhan university

Chunyan Cai  
Aier eye hospital of Wuhan university

Qiang Ding  
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Hongbin Dai  
Aier eye hospital of Wuhan university  
https://orcid.org/0000-0002-2390-1640

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Abstract

Background: The effect and safety of atropine on delaying the progression of myopia has been extensively studied, but its optimal effect dose is still unclear. Therefore, the purpose of this meta-analysis is to systematically evaluate the safety and effectiveness of atropine in controlling the progression of myopia, and to explore the relationship between the dose of atropine and the effect of controlling the progression of myopia.

Methods: This work was done through the data search from PubMed, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The Cochrane Handbook was also used to evaluate the quality of these included studies. In addition, a meta-analysis was performed using Revman5.3 software.

Results: A total of 10 randomized controlled trials (RCTs) were included. Myopia progression was mitigated greater in the atropine treatment group than the control group, with MD = -0.80, 95% CI (-0.94, -0.66) during the whole observation period. There was a statistical difference between 0.05%, 0.5%, and 1.0% atropine (P = 0.004). In addition, less axial elongation was showed, with MD = -0.26, 95% CI (-0.33, -0.18) during the whole observation period.

Conclusion: The effect of atropine in controlling the progression of myopia was dose related. A 0.05% atropine was likely to be the optimal dose.

Background

Myopia is a multifactorial disease caused by the uncoordinated development of various parts of the eyeball during the process of emmetropization, which is affected by the environment and genes. It is a mismatch between the optical power and length of the eye, causing the incoming light focusing in front of the retina. It was the most common eye disease in children and adolescents, and has grown rapidly worldwide over the past few decades, especially in East Asian regions where the prevalence of myopia in young adults was around 80-90% [1]. It had been predicted that 4.8 billion people in the world would be myopic by the year 2050, which meant that 50% of children would become myopic 30 years later [2].

Myopia reduced children's academic performance, affected children's physical activity, psychological development and people's employment choices. Children with an early onset of myopia accompanying with high progression rates had a higher incidence of high myopia, and had a great risk of having glaucoma, cataract, myopic maculopathy, retinal detachment and choroidal neovascularization [3]. Myopia is the leading cause of preventable blindness in children and adolescents [4]. It is urgent to manage this public health issue.

Currently, there are several approaches to slow down myopia progression. First, an increase in outdoor activities, and a reduction in near work or study could delay the progress of myopia [5], but because of the high educational pressure, the outdoor time was limited. Second, people with myopia displayed relative peripheral hyperopia, compared to emmetropic and hyperopic counterparts who demonstrated relative peripheral myopia. Orthokeratology lens shifted the relative peripheral refraction in the myopic direction [6],
slowed the axial elongation and thus helped to delay the myopia progression [7]. However, orthokeratology lens is not appropriate for all the patients and such lens are also very expensive. Third, atropine, an anticholinergic blocking agent, could interplay with different ocular tissues, slowing the rate of axial elongation of the eye and the myopia progression [8].

Although many studies have demonstrated the effectiveness of atropine in controlling myopia, its optimal dose is still under study, and it has not been approved by the FDA to control myopia [9]. Therefore, a meta-analysis was conducted in this work to systematically evaluate the safety and effectiveness of atropine in controlling the progression of myopia, and to explore the relationship between the dose of atropine and the effect of controlling the progression of myopia.

**Methods**

This meta-analysis of prospective randomized controlled trials (RCTs) was performed according to the PRISMA statement. The PRISMA Checklist were shown in the Supplementary Dataset. No protocol existed for this meta-analysis.

**Information source and search strategy**

A purposive literature search was conducted in PubMed, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials to yield relevant studies, using Medical Subject Headings (MeSH) and free words combined with myopia and atropine. (((((((Atropine)) OR (Atropinol)) OR (Atropine Sulfate)) OR (Sulfate, Atropine)) OR (Atropine Sulfate Anhydrous)) OR (Anhydrous, Atropine Sulfate)) OR (Sulfate Anhydrous, Atropine)) OR (AtroPen)) OR (Atropin Augenöl)) OR (Augenöl, Atropin))) AND (((((Nearsightednesses)) OR (Nearsightedness)) OR (Myopias)) OR (Myopia)) was used in searching the Pubmed. We also searched clinicaltrials.gov and the reference lists of published reviews to find additional relevant studies. The last search date was January 20, 2020. It is noted that only studies published in English were used.

**Eligibility criteria**

The included studies must meet the following criteria:

(1) A randomized placebo-controlled clinical trials.

(2) Spherical equivalent refraction more than -0.25D measured by cycloplegic autorefration was diagnosed with myopia.

(3) All patients were under 18 years old.

(4) Atropine was used for at least one year.

(5) The study reported at least the annual rate of myopia progression.
Congling Zhao and Chunyan Cai independently reviewed titles, abstracts, and full-length articles to identify potentially eligible articles using the criteria listed above. Disagreements regarding eligibility were resolved through a discussion with Qiang Ding. When a study was reported more than once, only the latest study was included to avoid double inclusion of data. When a study contained different doses of atropine, only the dose recommended by the study was included. The exclusion studies list and exclusion reason were shown in the Supplementary Dataset.

**Data Extraction**

Two reviewers (Congling Zhao and Qiang Ding) independently extracted information using the pre-established data extraction tables, including the following: (1) Basic characteristics of the study, including the name of the first author, year of publication, and follow-up time (2) Basic characteristics of the patients, including the age of the patients, equivalent spherical power before treatment, changes in cycloplegic spherical equivalent, changes in axial elongation, adverse reactions, etc.

**Qualitative Assessment**

The quality of the included studies was assessed by the Cochrane Handbook, including 6 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other biases. Two reviewers determined the risk of bias which had three options (low, high, and unclear). When necessary, we contacted the authors of the study to obtain the full text or related information for an accurate assessment.

**Statistical Analysis**

Review Manager (version 5.3; Cochrane Collaboration) was used for data analysis. The statistical heterogeneity of included studies was tested by the Cochrane $I^2$ test. If $I^2$ was 50% or less, indicating a low-to-moderate heterogeneity, a fixed-effect model was used. If $I^2$ was higher than 50%, indicating a high degree of heterogeneity, a random effects model was applied. MD with a 95% confidence interval (CI) was used to estimate the effect. A sensitivity analysis was performed by excluding the included studies one by one.

**Results**

**Search Results**

A total of 642 studies were retrieved. Finally, 10 studies were included in this meta-analysis. The basic characteristics of the 10 studies are shown in the Table 1. There were 809 patients in the atropine group and 814 patients in the control group. One study was using 0.05% atropine, five studies were using 0.5% atropine, and four studies were using 1.0% atropine. The literature screening process is shown in Fig 1.

**Methodological Quality Evaluation**
The results of the methodological evaluation according to the Cochran Handbook are shown in Fig 2. Only two studies reported the generation of random sequences, one study was conducted [10] through a computer-generated randomization list and the other [5] through a computer SAS package.

**Efficacy Analysis**

**Spherical equivalent refraction**

All the ten studies reported changes in equivalent spherical power. The overall heterogeneity $I^2$ was 95%, so a subgroup analysis was performed using a random effects model. The less myopia progression were in 0.05% atropine group (MD, -0.54; 95% CI, -0.69 to -0.39; $p<0.05$), 0.5% atropine group (MD, -0.89; 95% CI, -1.04 to -0.75; $p<0.05$), 1% Atropine group (MD, -0.75; 95% CI, -1.20 to -0.30; $p<0.05$) than that of the control group during the whole observation period. The overall MD was -0.80 (95% CI -0.94 to -0.66). There were statistical differences between different subgroups ($P=0.004$) (See Fig 3).

**Axial length**

Seven studies reported changes in the axis of the eyes. The date showed an less axial elongation in 0.05% atropine group (MD, -0.21; 95% CI -0.27 to -0.15), 0.5% group (MD, -0.20; 95% CI -0.48 to 0.08) and 1% atropine group (MD, -0.34; 95% CI -0.40 to -0.28) than that of the control group during the whole observation period. The overall MD was -0.26 (95% CI -0.33 to -0.18; $p<0.05$) (See Fig 4).

**Adverse effects**

A total of five studies showed the adverse effects (Table 2). Among them, the most common adverse effects were photophobia, and the others included allergies, headaches, blushing, and gastrointestinal reactions. No serious complications were found at any dose of atropine.

**Sensitivity analysis and publication bias**

We performed a sensitivity analysis on the spherical equivalent refraction and the changes in the axis of the eyes. When Wang’s study [11] were excluded individually from this study, the random-effect pooled estimate for the subgroup differences was the smallest ($P=0.02, I^2=75.1\%$). The myopia progression was -0.79D, 95% CI: (-0.89, -0.61), similar to that of all the included studies. Therefore, the original result was robust. There were no signicant differences between the atropine group and the control group. Funnel plots suggest no significant publication bias(See Supplementary Dataset).

**Discussion**

Myopia is widespread in the world. Every year, a large amount of money is spent to treat myopia-related complications, which causes a huge burden to the social and economic life. Currently, the best treatment strategy is to control the progression of myopia.
In this meta-analysis, less myopia progression was showed in the atropine treatment group than the control group during the whole observation period, with $MD = -0.80$, 95% CI (-0.94, -0.66). There was a statistical difference among 0.05%, 0.5%, and 1.0% atropine ($P = 0.004$). Less axial elongation was $MD = -0.26$, 95% CI (-0.33, -0.18). This confirmed that the effect of atropine was related to its dose [12]. 0.05% atropine could effectively control the progression of myopia [13].

Song et al. identified that the effect of atropine was related to its dose. A low dose of atropine worsened the progression of myopia. 0.5% and 1.0% of atropine could safely and effectively control the progression of low to moderate myopia [14]. However, the meta-analysis done by Song et al. only included 6 studies conducted in 2011. In addition, the low-dose atropine only included 0.1% and 0.25% and no placebo control was used. Therefore, it is impossible to determine whether the low-dose atropine is ineffective or if it has a worse effect than the higher dose of atropine.

Gong et al. reported that the effect of atropine was independent of its dose, but its side effects were dose-dependent [15]. However, it included the Cohort study which had insufficient evidence.

A recent 2-year follow-up observation [16] in children in the United States found that 0.01% atropine could effectively control the progression of myopia. A meta-analysis [17] published last year verified the effect of 0.01% atropine on myopia, but it did not compare with other doses.

When atropine was discontinued after one year usage in the atropine group, myopia progressed faster than that of the placebo group [18], especially for a high-dose atropine (low-dose atropine cases rebounded less after discontinuation) [19]. Therefore, the effect of rebound was closely related to its dose.

This meta-analysis provides evidence-based medical evidence for the use of atropine in controlling the progression of myopia by including only high-quality RCTs. This meta-analysis verified that the effect of atropine in controlling myopia progression was closely related to the dose. 0.05% atropine might be the optimal atropine dose which could slow the myopia progression and had the least adverse effects and rebound. Although only one study in our meta-analysis confirmed the effectiveness of 0.05% atropine, the study was of good quality after the Methodological Evaluation and was currently the largest placebo-controlled RCT to comprehensively evaluate its safety and effectiveness. In our study, the same conclusion is also got. Therefore, the study is sufficient to indicate that 0.05% may be the best dose of atropine according to all the concentrations of atropine in this meta-analysis. If atropine can be widely used in clinical prevention and control of myopia, it will help prevent high myopia and related complications.

Kinoshita has reported that the combined application of 0.01% atropine eye drops and orthokeratology can significantly slow the axis elongation compared to the use of orthokeratology alone [20]. A retrospective study also reported similar results [21]. But the growth of the eye axis could not predict the progression of myopia. Therefore, the effects of the combined application of atropine and orthokeratology needed to be further studied.

There were several limitations. First, although this meta-analysis had established strict inclusion and exclusion criteria, the heterogeneity was still high after using the subgroup analysis. However, through the
sensitivity analysis, the results of this meta-analysis were stable and consistent. Secondly, there were no studies involving 0.01% atropine in this study. And some of the included studies did not report adverse reactions, and few studies reported the progression of myopia after atropine was discontinued. The further determination and validation of the optimal dose required additional research.

**Conclusions**

The effect of atropine in controlling the progression of myopia was closely related with dose. A 0.05% atropine was likely to be the optimal dose.

**Declarations**

**Ethics approval and consent to participate**

Not Applicable.

**Consent for publication**

Not Applicable.

**Availability of data and materials**

All data are available under request. Congling Zhao should be contacted if someone wants to request the data.

**Abbreviations**

Randomized controlled trials (RCTs)

Confidence interval (CI)

**Author Contributions**

C.L.Z designed this study. C.L.Z and C.Y.C collected and double checked the data. Q.D. analyzed the data. C.L.Z wrote the paper. C.Y.C and H.B.D provided critical revision to the article. All authors participated in revision and approved the final version for submission. All authors read and approved the final manuscript.

**Competing financial interests**

The authors declare that they have no competing financial interests.

**Funding**

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**Acknowledgments**
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References


27. Yam JC, Jiang Y, Tang SM, Law AKP, Chan JJ, Wong E, Ko ST, Young AL, Tham CC, Chen LJ et al: Low-Concentration Atropine for Myopia Progression (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control. *Ophthalmology* 2019, 126(1):113-124.


### Tables

Table 1. Basic characteristics of included studies

<table>
<thead>
<tr>
<th>Source, Year</th>
<th>Country/Area</th>
<th>Follow-up, M</th>
<th>Included Atropine Dose, %</th>
<th>Age, Year</th>
<th>Baseline Refraction, Diopter (Mean±SD)</th>
<th>Experimental group</th>
<th>Control group</th>
<th>Total No. of Patients (test group/control group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua et al, 2005 [10]</td>
<td>Singapore</td>
<td>12</td>
<td>1</td>
<td>6-12</td>
<td>-3.58±1.17</td>
<td>1% Atropine</td>
<td>placebo</td>
<td>156/190</td>
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<tr>
<td>Hsiao et al, 2005 [22]</td>
<td>Taiwan</td>
<td>18</td>
<td>0.5</td>
<td>≥18</td>
<td>-3.26±0.15</td>
<td>0.5% Atropine+Multifocal</td>
<td>Multifocal lenses</td>
<td>66/61</td>
</tr>
<tr>
<td>Kumaran et al, 2015 [23]</td>
<td>Singapore</td>
<td>36</td>
<td>1</td>
<td>6-12</td>
<td>-3.36</td>
<td>1% Atropine</td>
<td>placebo</td>
<td>147/166</td>
</tr>
<tr>
<td>Polling et al, 2016 [24]</td>
<td>Europeans</td>
<td>12</td>
<td>0.5</td>
<td>≥18</td>
<td>-6.6±3.3</td>
<td>0.5% Atropine</td>
<td>placebo</td>
<td>60/17</td>
</tr>
<tr>
<td>Shih et al, 2001 [25]</td>
<td>Taiwan</td>
<td>18</td>
<td>0.5</td>
<td>6-13</td>
<td>-3.28±0.13</td>
<td>0.5% Atropine+Multifocal</td>
<td>Multifocal glasses</td>
<td>66/61</td>
</tr>
<tr>
<td>Shin et al, 1999 [26]</td>
<td>Taiwan</td>
<td>12</td>
<td>0.5</td>
<td>6-13</td>
<td>-4.89±2.06</td>
<td>0.5,0.25,0.1% Atropine</td>
<td>placebo</td>
<td>41/49</td>
</tr>
<tr>
<td>Wang et al, 2017 [11]</td>
<td>China</td>
<td>12</td>
<td>0.5</td>
<td>5-10</td>
<td>-1.3±0.4</td>
<td>0.5% Atropine</td>
<td>placebo</td>
<td>63/63</td>
</tr>
<tr>
<td>Yam et al, 2018 [27]</td>
<td>China</td>
<td>12</td>
<td>0.05</td>
<td>4-12</td>
<td>-3.98±1.69</td>
<td>0.05,0.025,0.01% Atropine</td>
<td>placebo</td>
<td>110/111</td>
</tr>
<tr>
<td>YEN et al, 1989 [28]</td>
<td>Taiwan</td>
<td>12</td>
<td>1</td>
<td>6-14</td>
<td>-1.52±0.960</td>
<td>1% Atropine</td>
<td>placebo</td>
<td>32/32</td>
</tr>
<tr>
<td>Yi et al, 2015 [29]</td>
<td>China</td>
<td>12</td>
<td>1</td>
<td>7-12</td>
<td>-1.23±0.32</td>
<td>1% Atropine</td>
<td>placebo</td>
<td>68/64</td>
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<tr>
<td>Source</td>
<td>Atropine Dose, %</td>
<td>Adverse effects</td>
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<tr>
<td>Chua et al, 2005 [10]</td>
<td>1</td>
<td>No serious adverse events. Reasons for withdrawal: allergic or hypersensitivity</td>
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<td></td>
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<td>reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical</td>
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<td></td>
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<td>difficulties (3.5%), and others (0.5%).</td>
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<td>Polling et al, 2016 [24]</td>
<td>0.5</td>
<td>Photophobia (72.4%); reading problems (37.7%); headaches (22.4%); systemic</td>
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<td>flushes (only in a minority); pain in the eye, irritated eyes, overflow of tears,</td>
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<td>trouble with depth perception, cosmetically disfiguring pupils, and an</td>
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<td></td>
<td></td>
<td>unpleasant taste in mouth (all reported only in one patient).</td>
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<tr>
<td>Yam et al, 2018 [27]</td>
<td>0.05</td>
<td>Gastroenteritis, influenza, or asthmatic attack; 1 case</td>
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<tr>
<td>Yi et al, 1989 [28]</td>
<td>1</td>
<td>Photophobia (100%), No systemic or ocular complications</td>
<td></td>
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<tr>
<td>Yi et al, 2015 [29]</td>
<td></td>
<td>No complain</td>
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</tbody>
</table>

**Figures**

![PRISMA Flow Diagram of the Literature Search Process](image)

**Figure 1**

PRISMA Flow Diagram of the Literature Search Process
Figure 2

The Results of the Methodological Evaluation

![Bias Evaluation Table]

- Low risk of bias
- Unclear risk of bias
- High risk of bias
Figure 3

Forest Plots of the Effect of Atropine on Refraction The progression of myopia was defined as the change in spherical equivalent refractive error relative to the end point. For this scale, negative value indicated myopia improvement and positive value indicated myopia progression. SD, standard deviation. CI, confidence interval.
Forest Plot of the Effect of Atropine on Axial Length Changes in axial length was defined as end point value subtracted by baseline value. For this scale, negative value indicated myopia improvement and positive value indicated myopia progression.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryDataset.pdf