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

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Abstract
Purpose: To systematically evaluate the safety and effectiveness of atropine in 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 in the atropine treatment group, with MD = -0.80, 95% CI (-0.94, -0.66). There was a statistical difference between 0.05%, 0.5%, and 1.0% atropine (P = 0.004). In addition, axial elongation was slowed, with MD = -0.26, 95% CI (-0.33, -0.18).

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

Introduction
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 myopia 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 are 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]. Therefore, a meta-analysis was conducted in this work to systematically evaluate the safety and effectiveness of atropine in controlling the progression of myopia.

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 [9] through a computer-generated randomization list and the other [10] 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 myopia progression 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) were slower than that of the placebo group. 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 data slowed an 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). 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. The results of this meta-analysis were reliable and consistent. There were no significant differences between the two groups. Funnel plots suggest no significant publication bias (See Supplementary Dataset).

**Cession of atropine**

When atropine was discontinued after one year usage, myopia progressed faster in the atropine group than that of the placebo group [11], especially after a high-dose atropine (a low-dose atropine case rebounded less after discontinuation) [12]. Therefore, the effect of rebound was closely related to its dose.

**Combined with orthokeratology**

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 [13]. A retrospective study also reported similar results [14]. But the growth of the eye axis
could not predict the progression of myopia. Therefore, the efficacy of the combined application of atropine and orthokeratology needed to be further studied.

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 the meta-analysis, including only high quality RCT, myopia progression was slowed in the atropine treatment group, 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). Axial elongation was slowed, MD = -0.26, 95% CI (-0.33, -0.18). This confirmed that the effect of atropine was related to its dose [15]. 0.05% atropine could effectively control the progression of myopia [16].

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 [17]. 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 [18]. However, it included the Cohort study which had insufficient evidence.

A recent 2-year follow-up observation [19] in children in the United States found that 0.01% atropine could effectively control the progression of myopia. A meta-analysis [20] published last year verified the effect of 0.01% atropine on myopia, but it did not compare with other doses.

This meta-analysis conducted in this work 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. But it still required a larger sample size and longer-term follow-up observations.

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.

**Methods**

This meta-analysis of prospective 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 RCT.

2. Spherical equivalent refraction more than -0.25D measured by cycloplegic autorefraction 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 analyse. 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.

Declarations

**Competing financial interests**

The authors declare that they have no competing financial interests.

**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.

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Tables

| SCFAAB  | Experimental group | Control group | Total No. of Patients (test group/control group) |
|---------|--------------------|---------------|-----------------------------------------------|
|         |                    |               |                                               |

11
| Study | Atropine | Placebo | Number |
|-------|----------|---------|--------|
| 116   | 1%       |         | 156/190|
| 116   | 0.5%     | Multi-focal lenses | 66/61 |
| 116   | 1%       |         | 147/166|
P<10 -0.5% Atropine placebo 60/17

ST106- 0.5%Atropine+multi-focal multi-focal glasses 66/61

ST106- 0.5,0.25,0.1% Atropine placebo 41/49

W105- 0.5% Atropine placebo 63/63
Table 2. The adverse effects on the different dose of atropine studies
| Source                    | Atropine Dose, % | Adverse effects                                                                 |
|---------------------------|------------------|----------------------------------------------------------------------------------|
| Chua et al, 2005 [9]      | 1                | No serious adverse events. Reasons for withdrawal: allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), blurred near vision (1%), logistical difficulties (3.5%), and others (0.5%). |
| Polling et al, 2016 [23]  | 0.5              | Photophobia (72.4%); reading problems (37.7%); headaches (22.4%); systemic flushes (only in a minority); pain in the eye, irritated eyes, overflow of tears, trouble with depth perception, cosmetically disfiguring pupils, and an unpleasant taste in mouth (all reported only in one patient). |
| Yam et al, 2018 [26]      | 0.05             | Gastroenteritis, influenza, or asthmatic attack [1 case].                         |
| YEN et al, 1989 [27]      | 1                | Photophobia (100%), No systemic or ocular complications                           |
| Yi et al, 2015 [28]       | 1                | No complain                                                                      |

Figures

Figure 1

PRISMA Flow Diagram of the Literature Search Process
Figure 2

the Results of the Methodological Evaluation
Figure 3

Forest Plots of the Effect of Atropine on Refraction
### Figure 4

**Forest Plot of the Effect of Atropine on Axial Length**

#### Supplementary Files

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

**Supplementary Dataset.pdf**