• Meta-Analysis •

The optimal atropine concentration for myopia control in Chinese children: a systematic review and network Meta-analysis

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Received: 2023-10-30 Accepted: 2024-03-19

Abstract

● **AIM:** To figure out whether various atropine dosages may slow the progression of myopia in Chinese kids and teenagers and to determine the optimal atropine concentration for effectively slowing the progression of myopia.

● **METHODS:** A systematic search was conducted across the Cochrane Library, PubMed, Web of Science, EMBASE, CNKI, CBM, VIP, and Wanfang database, encompassing literature on slowing progression of myopia with varying atropine concentrations from database inception to January 17, 2024. Data extraction and quality assessment were performed, and a network Meta-analysis was executed using Stata version 14.0 Software. Results were visually represented through graphs.

● **RESULTS:** Fourteen papers comprising 2475 cases were included; five different concentrations of atropine solution were used. The network Meta-analysis, along with the surface under the cumulative ranking curve (SUCRA), showed that 1% atropine (100%)>0.05% atropine (74.9%)>0.025% atropine (51.6%)>0.02% atropine (47.9%)>0.01% atropine (25.6%)>control in refraction change and 1% atropine (98.7%)>0.05% atropine (70.4%)>0.02% atropine (61.4%)>0.025% atropine (42%)>0.01% atropine (27.4%)>control in axial length (AL) change.

● **CONCLUSION:** In Chinese children and teenagers, the five various concentrations of atropine can reduce the progression of myopia. Although the network Meta-analysis showed that 1% atropine is the best one for controlling refraction and AL change, there is a high incidence of adverse effects with the use of 1% atropine. Therefore, we suggest that 0.05% atropine is optimal for Chinese children to slow myopia progression.

● **KEYWORDS:** atropine; China; children and adolescents; myopia; network Meta-analysis

DOI:10.18240/ijo.2024.06.19

Citation: Wang XY, Deng HW, Yang J, Zhu XM, Xiang FL, Tu J, Huang MX, Wang Y, Gan JH, Yang WH. The optimal atropine concentration for myopia control in Chinese children: a systematic review and network Meta-analysis. *Int J Ophthalmol* 2024;17(6):1128-1137

INTRODUCTION

The most prevalent refractive error in children and teenagers is myopia. The disorder typically starts in childhood and lasts into adulthood[1], and it is now a significant global public health issue. According to the 2019 report, about 2.6 billion people worldwide suffer from myopia[2]. Global myopia patients are predicted to number 4.7 billion by 2050, while the number of people with high myopia will rise to 900 million[3]. Relevant data indicates that 4.7% of African kids and teenagers have myopia[4], while 52.7% of Chinese children and adolescents are myopic overall[5]. In Taiwan, China, up to 76% of kids and teenagers between the ages of 6 and 16 have myopia.

The possibility of vision impairment and ocular pathologies is greatly increased by myopia, particularly high myopia, which can lead to physiological illnesses like glaucoma, retinal degeneration, retinal detachment, macular degeneration,

and optic neuropathy[6-7]. Anxiety and sadness are strongly correlated with visual impairment, particularly uncorrected refractive error, and have an impact on the mental health of children and adolescents[8]. As a result, it is critical to slow down the evolution of myopia in young people and adolescents since adolescent myopia is a serious issue.

There are numerous ways to treat myopia in kids and teenagers. Increasing the amount of time spent outside, altering close work habits, using topical drugs, having eye surgery, donning corrective eyewear, and repeatedly receiving low red light therapy are among treatments that delay the progression[9-11]. Among these, it has been demonstrated that atropine eye drops and vision correction glasses are more productive than other approaches at slowing development[12], and it has been demonstrated that atropine is the most efficient[13].

While atropine's effectiveness has been shown, side effects and the rebound phenomena following treatment are still problems. Atropine eye drops have dose-dependent side effects, although its effectiveness is not[14]. In the network Meta-analysis published in 2022, Ha *et al*[15] investigated the impact of eight distinct atropine concentrations on the onset of myopia in youngsters throughout the world, and ranked the effects of the eight atropine concentrations on axial length (AL) and refraction, which showed that the three concentrations of atropine (1%, 0.5%, and 0.05%) were the most efficient way to control myopia. However, variations in iris color in different races might have various effects on atropine's effectiveness, and the results may not be suitable for the Chinese population[16]. A Meta-analysis by Wei *et al*[17] showed that atropine concentrations less than 1% were effective in slowing the progression of myopia in Asian children, but the optimal atropine concentration was not studied. In order to create the basis to figure out the optimum atropine concentration to lower the progression of myopia in various nations and racial groups, this study was set out to investigate the concentration of atropine that is most effective in China for delaying the progression of myopia in children.

MATERIALS AND METHODS

Ethical Approval This systematic review protocol (Identifier: INPLASY202380025) was prospectively registered at the International Platform of Registered Systematic Review and Meta-analysis Protocols. Ethical approval is not necessary for this study because it does not entail the collection of subjects' personal information. Adolescent research participants will also sign informed consent forms during the study, as will their families.

Inclusion and Exclusion Criteria The inclusion criteria were as follows: 1) age ≤18y with a confirmed diagnosis of myopic refractive error as study subjects; 2) application of atropine eye drops to the intervention group; 3) usage of a blank placebo or atropine eye drops at varying dosages in the control group as opposed to the intervention group; 4) change in refraction and AL of the eye as outcome observables; and 5) randomized clinical trial research (RCT) or observational study; 6) study conducted in China; 7) studies need to be reviewed by an ethics committee. The exclusion criteria were as follows: 1) literature whose full text was unavailable; 2) duplicate publications; 3) literature with poorly formulated and low-quality research protocols; 4) studies examining the combination treatment of atropine with other myopia prevention and control measures.

Search Strategy Web of Science, PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Biological Medicine (CBM), Chinese Scientific Journals Database (VIP), and Wanfang database were searched. The database construction date was set to January 17, 2024, for the duration of the search, and the search terms used were free words and medical subject headings (MeSH). The corresponding Boolean logic operators "AND", "NOT", "OR" were used to establish the search formula, and the English search terms mainly included "myopia", "myopias", "nearsightedness", "children", "teens", "adolescents", "male adolescents", "female adolescents", "juvenile", "youths", "teenagers", "atropine", "atropine sulfate anhydrous", "atropine sulfate", "sulfate anhydrous, atropine", *etc*. The language used was limited to English. To find other pertinent papers, we also skimmed the published reviews' references.

Selecting Studies and Extracting Data After the search results were imported into EndNoteX9 to remove duplicates, two qualified researchers (Wang XY and Zhu XM) independently reviewed the articles for initial screening by reading the titles and abstracts, followed by rescreening through reading the full text of the articles based on the criteria for inclusion and exclusion. Disagreements were settled through discussion with a third investigator (Gan JH). After study screening, the first authors' names, publication year, location, age, follow-up length, treatment arm, sample size, baseline for refraction and AL, mean change in refraction and AL were all included in the data extraction. Two investigators (Wang XY and Zhu XM) divergences were settled by the third investigator (Gan JH) after they had separately obtained the data and assessed its risk and quality of bias.

Risk of Bias Assessment Six elements were assessed using the risk of bias assessment technique from the Cochrane Handbook for Systematic Evaluation: allocation concealment, sequence generation, blinding, incomplete outcome information, sequence generation, sequence generation, and other sources of bias[18]. Each aspect's bias risk was ranked as "low", "high", or "unclear".

Statistical Analyses

Network Meta-analysis and statistical model selection A reticulation plot was made using Review Manager (version 5.3) and STATA (version 14.0) to compare the outcomes of various atropine solution concentrations directly and indirectly. The consistency of the data was analyzed using a node-split model. The consistency model was utilized for analysis if there was a statistically insignificant difference (P>0.05) between the findings of the direct and indirect comparisons; otherwise, the inconsistent model was chosen. If the consistency model is used, the inconsistency model verifies the stability of the results: when the inconsistency standard deviation is greater than one and the inconsistency factors (IF) include zero, the inconsistency model's output is more dependable and stable. Subsequently, two-way comparisons were conducted between distinct atropine solutions, and a P-value of less than 0.05 indicated statistically significant variations. STATA software was used to design the surface under the cumulative ranking curve (SUCRA). A more advanced ranking was indicated by a bigger proportion of the area under the cumulative ranked probability curve, which in turn suggested a better intervention impact. As indicators for categorical variable analysis, odds ratio (OR) and the 95% confidence interval (CI) were used. The construction of funnel plots was done to assess publication bias.

Subgroup analysis and sensitivity analysis Sensitivity analysis will be employed if required to evaluate how the studies affect the random effects model. The data analysis was repeated to assess the stability of the findings after every study was eliminated one at a time. The results are steady if there is no discernible change in the cumulative effect that is displayed in the data. We will perform a subgroup analysis based on the patient's age, the severity of their myopia, the length of their treatment, or the caliber of the study if there is clinical and methodological heterogeneity.

Publication bias With STATA software, a comparison-adjusted funnel plot is produced to assess the presence of publication bias or small sample effects in the intervention network if ten or more studies are included in the network Meta-analysis. Publication bias may be present if the plot is asymmetric and the funnel shape is not inverted. The short sample size, allocation concealment, and inadequate blind method implementation could be the causes.

RESULTS

A total of 2497 articles were retrieved from PubMed, Web of Science, Cochrane Library, EMBASE, CNKI, CBM, VIP, and Wanfang database. And 748 of these duplicate articles were eliminated. After evaluating the complete texts of 135 articles, 2360 studies were disqualified for various reasons (Figure 1). Finally, 14 eligible articles were obtained. Of these studies, 11 were RCTs, and three were retrospective cohort studies. The study selection process flow is summarized in a PRISMA flow diagram (Figure 1).

Basic Literature Characteristics A total of 2475 cases were included in 14 studies, 743 and 1732 cases in the control and experimental groups, respectively. These studies included children and adolescents aged 4-2y with mild to moderate myopia, treated with five different concentrations of atropine solution: 0.01%, 0.05%, 0.025%, 0.02%, and 1%. Of these studies, 12 studies had outcomes of change in refraction and AL, whereas two studies measured refraction change alone. The eligible trials were published between 2006 and 2023. Every trial was carried out in China. The follow-up time reported for participants was between 5 and 24mo. The specific characteristics are presented in Table 1[19-32].

Risk of Bias Eight studies mentioned the use of a table of random numbers to generate a randomized sequence, 8 studies mentioned the use of blinding of researchers during intervention implementation and outcome measurement, 10 studies described in detail the rate and reason behind loss of sample, and 14 studies had essentially balanced baseline information between the experimental and observation groups before intervention. Five studies showed a high risk of bias. There were some bias risk concerns with eight studies. Additionally, one study showed a low risk of bias. The risk of bias diagrams are shown in Figures 2 and 3.

Consistency Test The results of the inconsistency test demonstrated no significant inconsistency in the evidence network under each effect indicator, and the node-splitting analysis indicated that there was no statistically significant difference between the original research' direct and indirect comparisons (P>0.05); thus, the consistency model was used to merge the data.

Results of the Network Meta-analysis

Evidence relationship diagram Network relationship diagrams for the different outcome indicators of the 14 studies are shown in Figures 4 and 5. Interventions are represented by dots; bigger dots represent more patients getting the intervention. Thicker lines denote a higher number of studies that included these direct comparisons, while straight lines provide evidence of a direct comparison of two interventions.

Nodal analysis model One set of closed loops in the included studies was the control: atropine 0.01%, 0.05%, 0.025%, and 0.02%. The results of the nodal analysis showed a consistent model for refraction and axis length (P>0.05; Figures 6, 7).

Result of direct and indirect comparisons To compare various therapies with control and with one another, we combined the direct and indirect evidence in a random effects network Meta-analysis (Figures 8, 9). As shown in Figure 8, in comparison with control, 0.01% atropine (change in refraction:

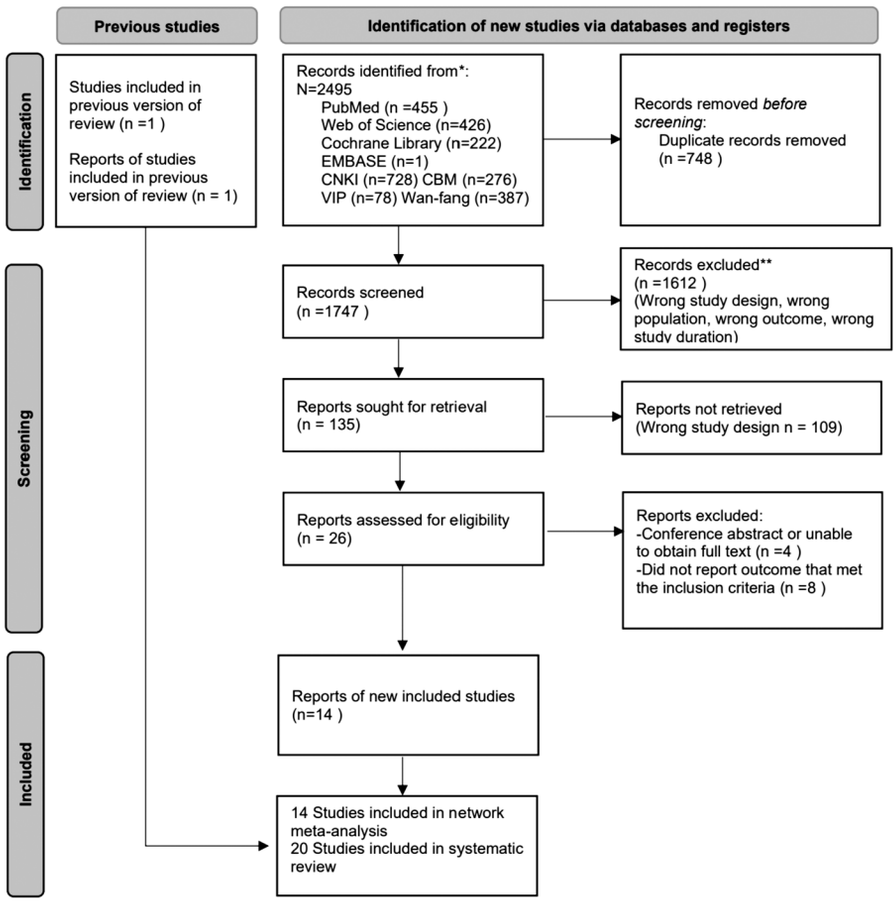

Figure 1 A overview of the research selection process using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

0.35 D, 95%CI, 0.24-0.45; change in AL: -0.13 mm, 95%CI, -0.19 to -0.06), 0.05% atropine (change in refraction: 0.57 D, 95%CI, 0.41-0.73; change in AL: -0.23 mm, 95%CI, -0.34 to -0.13), 0.025% atropine (change in refraction: 0.46 D, 95%CI, 0.30-0.61; change in AL: -0.16 mm, 95%CI, -0.26 to -0.05), 0.02% atropine (change in refraction: 0.44 D, 95%CI, 0.24-0.64; change in AL: -0.21 mm, 95%CI, -0.33 to -0.09) slowed myopia progression moderately, and 1% atropine (change in refraction: 1.18 D, 95%CI, 0.88-1.47; change in AL: -0.41 mm, 95%CI, -0.57 to -0.25) markedly slowed myopia progression. The pairwise comparisons of all interventions demonstrated that 1% atropine was significantly superior to other atropine concentrations in refraction and AL change.

Result of SUCRA Notably, in refraction change, the 1% atropine was the most effective, with a statistically significant improvement relative to other atropine concentrations (P<0.05; Figure 10). The SUCRA results showed 1% atropine (100%)>0.05% atropine (74.9%)>0.025% atropine (51.6%)>0.02% atropine (47.9%)>0.01% atropine (25.6%)>control (Figure 10). In AL change, all five different atropine concentrations were more effective than the control treatment in slowing myopia progression. 1% atropine had the best effect, demonstrating a statistically significant difference (P<0.05; Figure 11). The SUCRA results showed 1% atropine (98.7%)>0.05% atropine (70.4%)>0.02% atropine (61.4%)>0.025% atropine (42%)>0.01% atropine (27.4%)>control (Figure 11).

Publication Bias Analysis A funnel plot was drawn for the different outcome concentrations of the studies. As shown in Figures 12 and 13, the scatters of the studies were not on both sides of the funnel plot and roughly symmetrically distributed, suggesting that there is a likelihood of publication bias among the studies included herein.

DISCUSSION

The Optimal Atropine Concentration in Terms of Efficacy and Safety A total of 14 articles[19-32], of which 11 were RCTs, and three were retrospective cohort studies, were included to assess the efficacy of 1%, 0.05%, 0.025%, 0.02%, and 0.01% atropine for the treatment of Chinese children and adolescents using network Meta-analysis as an evaluation tool to select the optimal concentration for clinical provision. The results of this study showed that five different concentrations of atropine solution were superior to the control group in terms of efficacy. 1% atropine was the best among the five atropine concentrations in terms of controlling refraction and AL change. However, many studies have shown that the incidence

Table 1 General information of included studies

mean (SD)

Study	Region	Age (y)	Follow-up (mo)	Arm	Sample size	Baseline refraction (D)	Baseline AL (mm)	Mean change in refraction (D/y)	Mean change in AL (mm/y)
Wang *et al*[19], 2020	Shanghai	6-14	6	Atropine 0.01%	37	-1.94 (1.17)	24.21 (0.90)	-0.30 (0.42)	0.24 (0.16)
			6	Control	24	-1.78 (1.15)	24.33 (0.64)	-0.60 (0.43)	0.35 (0.20)
Zhao and Hao[20], 2021	Liaoning Province	5-14	12	Atropine 0.01%	20	- 1.98 (0.45)	24.17 (0.68)	- 0.34 (0.16)	0.24 (0.12)
			12	Control	20	- 1.93 (0.74)	24.28 (0.83)	- 1.30 (0.44)	0.72 (0.21)
Li *et al*[21], 2020	Hong Kong	4-12	12	Atropine 0.05%	102	-3.95 (1.64)	24.86 (0.9)	-0.27 (0.61)	0.20 (0.25)
			12	Atropine 0.025%	91	-3.83 (1.81)	24.92 (0.89)	-0.46 (0.45)	0.29 (0.20)
			12	Atropine 0.01%	97	-3.95 (1.9)	24.79 (1.02)	-0.59 (0.61)	0.36 (0.29)
			12	Control	93	-4.1 (1.91)	24.9 (0.99)	-0.81 (0.53)	0.41 (0.22)
Yu *et al*[22], 2023	Shanghai	6–13	5	Atropine 0.01%	41	-1.75 (1.36)	24.47 (0.93)	-0.26 (0.37)	0.13 (0.15)
			5	Control	32	-1.45 (1.36)	24.24 (0.83)	-0.46 (0.42)	0.21 (0.17)
Fu *et al*[23], 2020	Henan Province	NA	12	Atropine 0.02%	117	-2.76 (1.47)	24.60 (0.72)	-0.38 (0.35)	0.30 (0.21)
			12	Atropine 0.01%	119	-2.70 (1.64)	24.58 (0.74)	-0.47 (0.45)	0.37 (0.22)
			12	Control	100	-2.68 (1.42)	24.55 (0.71)	-0.70 (0.60)	0.46 (0.35)
Yam *et al*[24], 2019	Hong Kong	4-12	12	Atropine 0.05%	102	-3.98 (1.69)	24.85 (0.90)	-0.27 (0.61)	0.20 (0.25)
			12	Atropine 0.025%	91	-3.71 (1.85)	24.86 (0.95)	-0.46 (0.45)	0.29 (0.20)
			12	Atropine 0.01%	97	-3.77 (1.85)	24.70 (0.99)	-0.59 (0.61)	0.36 (0.29)
			12	Control	93	-3.85 (1.95)	24.82 (0.97)	-0.81 (0.53)	0.41 (0.22)
Fang *et al*[25], 2010	Taiwan	6-12	12	Atropine 0.025%	24	-0.31 (0.45)	NA	-0.14 (0.24)	NA
			12	Control	26	-0.17 (0.50)	NA	-0.58 (0.34)	NA
Lee *et al*[26], 2006	Taiwan	6-12	12	Atropine 0.05%	21	-1.58 (1.37)	19.9 (8.98)	-0.28 (0.26)	NA
			12	Control	36	-1.41 (0.86)	21.5 (10.10)	-0.75 (0.35)	NA
Cui *et al*[27], 2021	Henan Province	NA	24	Atropine 0.02%	105	-2.81 (1.47)	24.61 (0.69)	-0.8 (0.52)	0.62 (0.29)
			24	Atropine 0.01%	106	-2.76 (1.56)	24.60 (0.72)	-0.93 (0.59)	0.72 (0.31)
			24	Control	89	-2.66 (1.39)	24.54 (0.69)	-1.33 (0.72)	0.88 (0.35)
Wei *et al*[28], 2020	Beijing	6-12	12	Atropine 0.01%	76	-2.52 (1.33)	24.50 (0.76)	-0.49 (0.42)	0.32 (0.19)
			12	Control	83	-2.64 (1.46)	24.69 (0.97)	-0.76 (0.50)	0.41 (0.19)
Pan *et al*[29], 2022	Shanghai	6-12	6	Atropine 0.01%	125	-1.64 (0.8)	24.13 (0.76)	-0.27 (0.33)	0.19 (0.14)
			6	Control	60	-1.59 (0.94)	24.06 (0.77)	-0.60 (0.35)	0.26 (0.14)
Yi *et al*[30], 2015	Chongqing	7-12	12	Atropine 1%	68	-1.23 (0.32)	23.75 (0.12)	0.32 (0.22)	-0.03 (0.07)
			12	Control	64	-1.15 (0.30)	23.72 (0.12)	-0.85 (0.31)	0.32 (0.15)
Fan *et al*[31], 2007	Hong Kong	5-10	12	Atropine 1%	23	-5.18 (2.05)	25.06 (1.03)	0.06 (0.79)	0.09 (0.19)
			12	Control	23	-5.12 (2.33)	24.85 (0.78)	-1.19 (2.48)	0.70 (0.63)
Yam *et al*[32], 2020	Hong Kong	4-12	12	Atropine 0.05%	93	-3.93 (1.63)	24.88 (0.91)	-0.30 (0.44)	0.18 (0.16)
			12	Atropine 0.025%	86	-3.88 (1.83)	24.94 (0.90)	-0.39 (0.48)	0.22 (0.18)
			12	Atropine 0.01%	91	-3.99 (1.94)	24.78 (1.02)	-0.48 (0.44)	0.25 (0.18)

AL: Axial length.

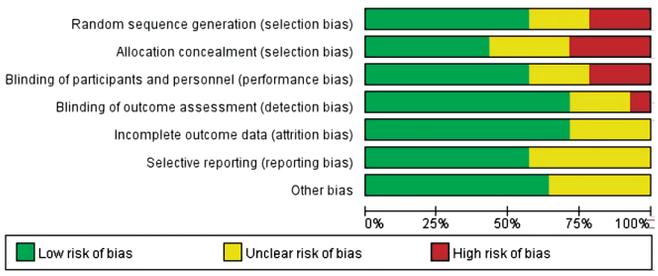

Figure 2 Overall risk of bias diagram.

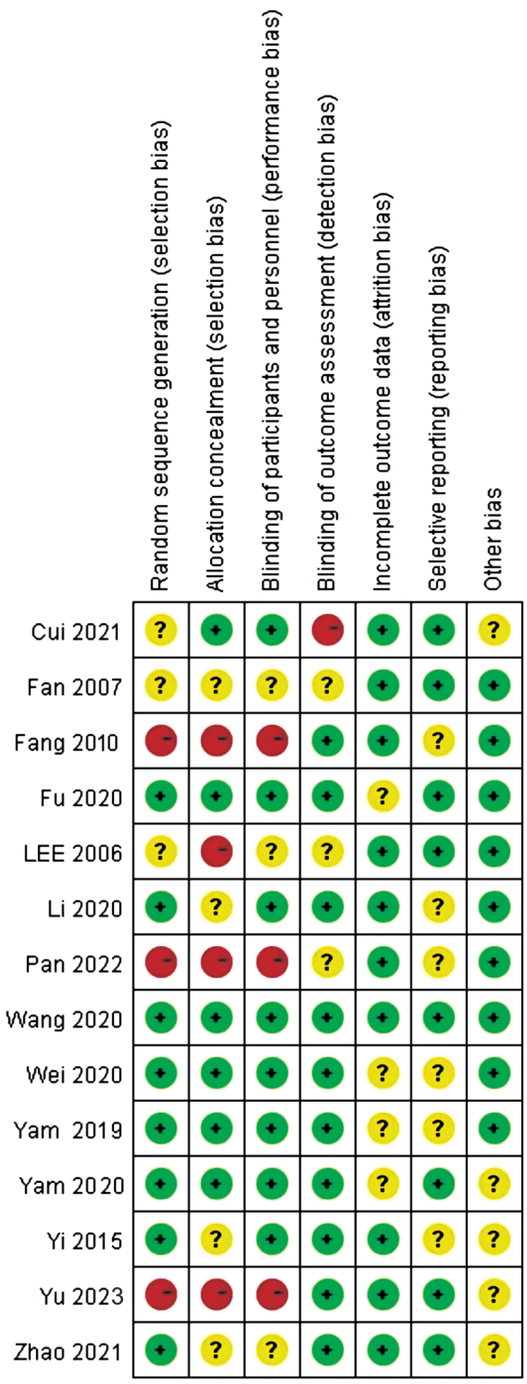

Figure 3 Risk of bias diagram in each included studies.

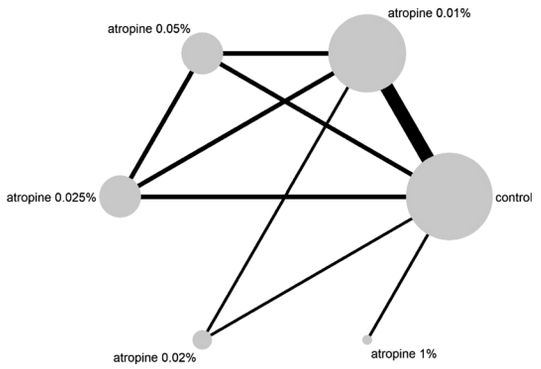

Figure 4 Network plot about refraction change.

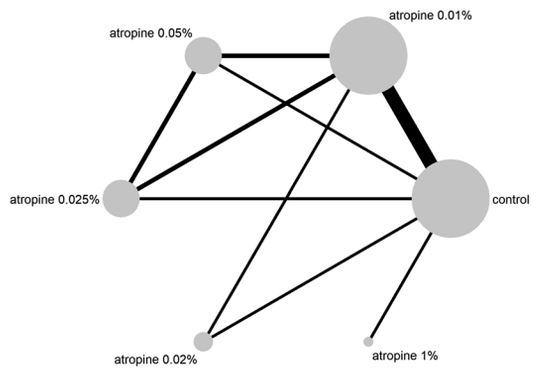

Figure 5 Network plot about axial length change.

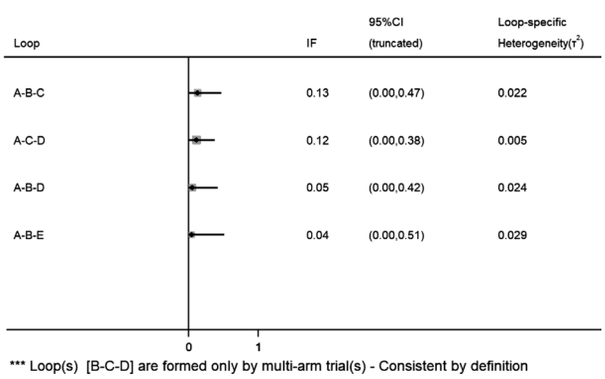

Figure 6 The consistent model for refraction change A: Control; B: Atropine 0.01%; C: Atropine 0.05%; D: Atropine 0.025%; E: Atropine 0.02%. CI: Confidence interval; IF: Inconsistency factor.

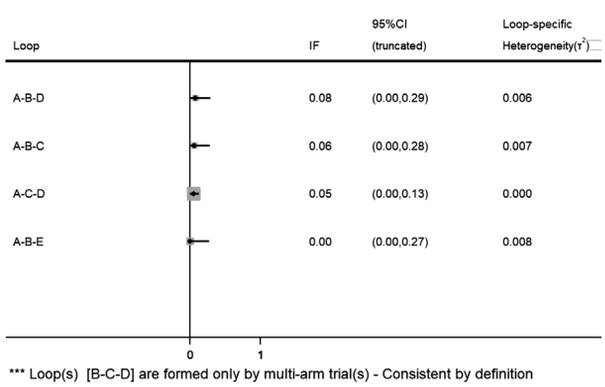

Figure 7 Consistent model for axis length change A: Control; B: Atropine 0.01%; C: Atropine 0.05%; D: Atropine 0.025%; E: Atropine 0.02%. CI: Confidence interval; IF: Inconsistency factor.

of atropine-induced adverse events varied depending on the solution doses, and a higher dose of atropine was associated with a higher incidence of adverse events[14,33]. There is a high incidence of adverse effects with the use of the high-dose atropine, including photophobia, allergy and other adverse

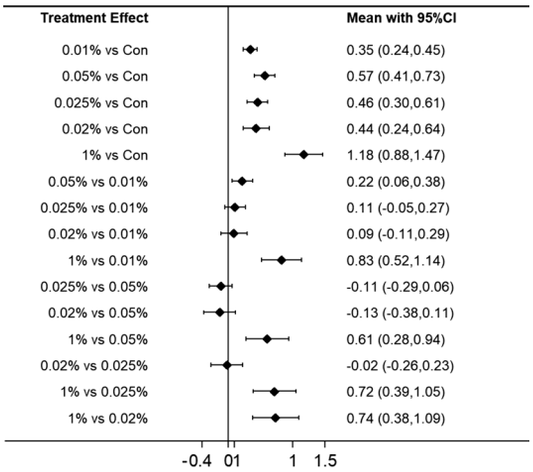

Figure 8 Forest plots contrasting various atropine doses for myopia therapies (change in refraction) CI: Confidence interval; Con: Control.

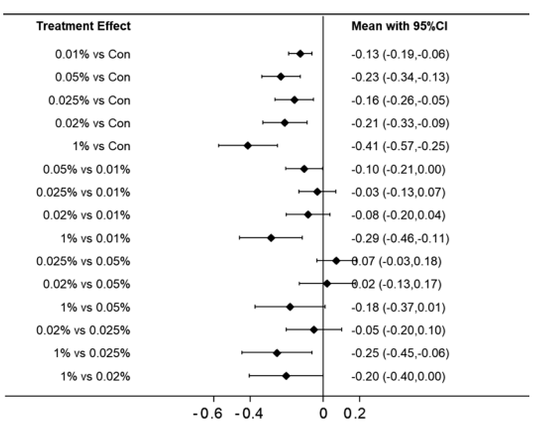

Figure 9 Forest plots contrasting various atropine doses for myopia therapies (change in AL) CI: Confidence interval; Con: Control; AL: Axial length.

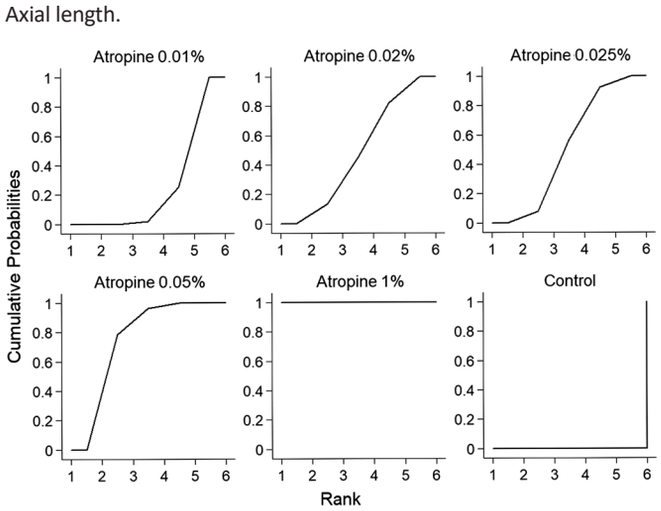

Figure 10 Cumulative probability ranking results for refraction change.

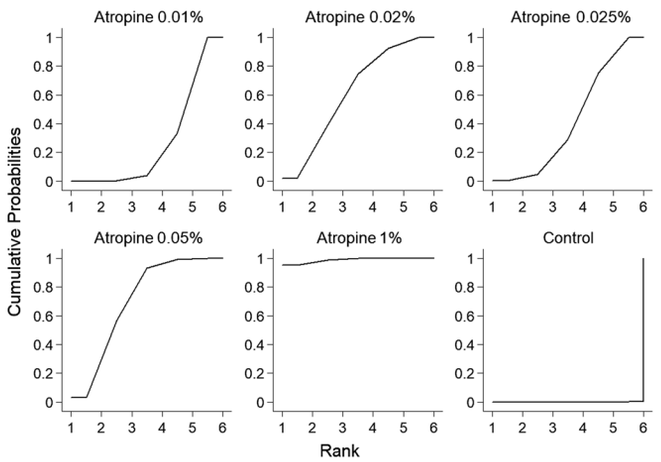

Figure 11 Cumulative probability ranking results for axial length change.

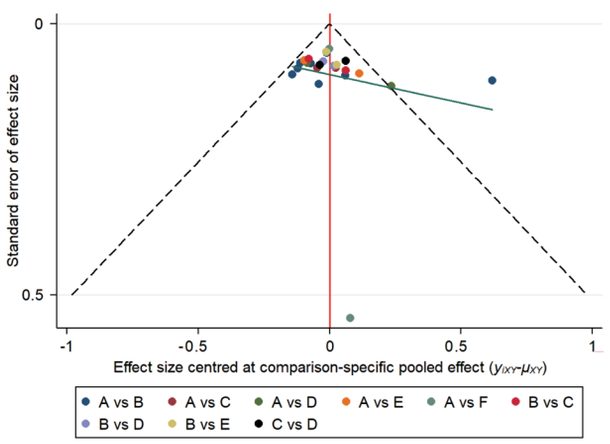

Figure 12 Inverted funnel plot of refraction change A: Control; B: Atropine 0.01%; C: Atropine 0.05%; D: Atropine 0.025%; E: Atropine 0.02%; F: Atropine 1%.

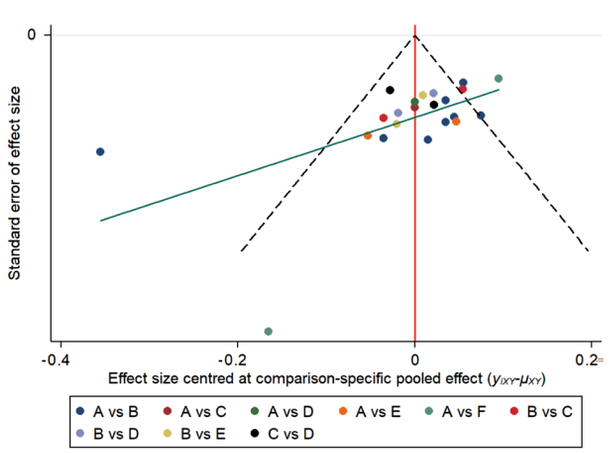

Figure 13 Inverted funnel plot of AL A: Control; B: Atropine 0.01%; C: Atropine 0.05%; D: Atropine 0.025%; E: Atropine 0.02%; F: Atropine 1%. AL: Axial length.

effects[33]. A Meta-analysis by Gong *et al*[14] showed that the incidence of photophobia with high-dose atropine including 1% atropine was 43.1%, and with moderate-dose atropine including 0.05% atropine was 17.8%, which the difference was statistically significant (P<0.05). The 0.05% atropine had a lower incidence of adverse effects and differed little from the 1% atropine in terms of efficacy. Combined efficacy and safety considerations suggest that the use of the 0.05% atropine is recommended to slow myopia progression in children and adolescents.

Explain the Differences in the Results of Relevant Studies

In this study, the network Meta-analysis showed that, for

Chinese children and adolescents, the top three atropine solutions delaying refraction change were 1%, 0.05%, and 0.025%, and the top three delays in the growth of ocular AL were atropine at 1%, 0.05%, and 0.02%, which was in agreement with the findings of Ha *et al*[15], who revealed that 1%, 0.5%, and 0.05% atropine were, in order, the best for delaying refraction change. As for improving ocular axis length, 1% atropine solution was the best, followed by 0.05% and 0.5%. This may be because the efficacy of atropine varies between races. Although the mechanism by which atropine slows myopia progression has not yet been elucidated[34], some studies have shown that atropine mainly acts on melanocytes in the retina to produce novel chemicals that inhibit scleral extension, thereby slowing myopia progression[20]. The amount of melanin in the iris can vary between races and affect the efficacy of atropine[23]. Prior studies have shown that the efficacy of atropine in slowing myopia is greater in Asian children than in Caucasian children[12]. Although most of the RCTs included in Ha *et al*'s[15] study were Chinese, one European study and five studies from other Asian countries were also included, and it is possible that racial differences led to different findings. RCTs with 0.5% atropine were not included in this study, and the study by Ha *et al*[15] did not include RCTs reporting 0.02% atropine solution; therefore, the possibility that these studies had consistent results cannot be excluded.

Current State of Myopia Control in Children There are many studies that show a variety of ways to slow the progression of myopia. In a study in China[35], changing high-concentration atropine eye drops to medium-concentration drops not only effectively delayed the progression of myopia in children and adolescents but also greatly reduced the incidence of myopic rebound and side effects. The latter eye drops were also well tolerated by patients. The Meta-analyses have shown that small doses of atropine solution (<0.5%) combined with orthokeratology are more effective than atropine eye drops or orthokeratology alone in slowing myopia progression, suggesting that the dosage of atropine as well as the method of application affect its effectiveness[36-37], and suggests that atropine solution can be combined with other methods to control myopia progression[38]. A Meta-analysis by Yu *et al*[39] showed that different add power soft contact lenses can slow the progression of myopia in children, with high add power soft multifocal contact lenses are more effective and stable to control myopia progression. A Meta-analysis of 13 studies by Tang *et al*[11] found that repeated low-level red-light therapy is also effective in slowing myopia progression, but the certainty of the evidence is low. Huang *et al*[12] conducted a network Meta-analysis of 30 randomized controlled studies, which analyzed the effectiveness of 16 interventions such as different concentrations of atropine, soft multifocal contact lenses, and orthokeratology lenses in controlling myopia in children, and found that different concentrations of atropine solution is the most effective. Currently, studies have begun to examine the effects of traditional Chinese medicine decoction in slowing the progression of myopia[40]. In addition, there are many surgeries that are effective in correcting high myopia[41]. Although the present study demonstrated that 0.05% atropine solution is the best choice at present for combined effectiveness and safety considerations, more in-depth discussion on its use is warranted, and there needs to be a consensus regarding the time of initiation, time of tapering or discontinuation, frequency of use, and whether it can be used in combination.

Precautions for Atropine Prior studies have shown that atropine concentration or frequency of use can be appropriately increased in patients who are poorly controlled with low concentrations of atropine[29], patients with high myopia, or patients with a family history of high myopia to more effectively prevent progression[42]. Common adverse effects of atropine include blurred vision, photophobia and allergic reactions, which occur in a dose-dependent manner. It is important to monitor the patients for adverse effects while increasing the dose and to monitor for rebound after discontinuation of the drug. High-risk groups of myopia can be screened out through prediction models[2], and atropine can be used prophylactically for high-risk groups.

Limitations First, it should be noted that significant heterogeneity is present in this study. The mode of atropine administration, elemental solution in which atropine was prepared, dosage form of atropine, whether the control group wore eyeglasses or some other placebo solution, instrumentation used to measure visual acuity, method of measurement, and duration of follow-up were all sources of heterogeneity. Age and baseline myopia of the study subjects also contributed to heterogeneity. Prior studies have shown that atropine solution is more effective in children who are older and have higher baseline myopia[42]. Second, the number and quality of RCTs included in this study must be improved, and only 14 studies were included. The 0.01% atropine solution with a control group had the most studies controlling myopia, and there were fewer studies of other concentrations of atropine solution; the few study that are included and the unevenness in the number of studies of individual concentrations of atropine solution may have had an impact on the results. The inclusion of only five atropine concentrations may result in a bias between the study results and the actual results. Third, this study only assessed changes in refraction change and AL change, and did not analyze other metrics associated with myopia, such as vitreous chamber depth and choroidal thickness. And there was no quantitative

study of the adverse effects of atropine solution. Although the results of this study showed that 0.05% atropine was the optimal atropine concentration, there are relatively few studies on 0.05% atropine eye drops for myopia in China. Therefore, multicenter studies with larger sample sizes are needed for further exploration and validation, and caution should be exercised when drawing conclusions.

Although the network Meta-analysis showed that 1% atropine was the best concentration among the five atropine concentrations in terms of controlling refraction and AL change, there is a high incidence of adverse effects with the use of 1% atropine. Therefore, in terms of efficacy and safety, this study suggests that 0.05% atropine is the optimal concentration among the five atropine concentrations for Chinese children to slow myopia progression. More high-quality studies of other races and atropine concentrations are needed to explore the relationship between race and atropine doses. In addition, the effect of the administration method of atropine on the drug efficacy should be studied.

ACKNOWLEDGEMENTS

Foundations: Supported by the National Key R&D Plan "Intergovernmental International Scientific and Technological Innovation Cooperation" (No.2022YFE0132600); Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (No.SZGSP014); Sanming Project of Medicine in Shenzhen (No.SZSM202311012); Shenzhen Science and Technology Program (No.KCXFZ20211020163814021).

Conflicts of Interest: Wang XY, None; **Deng HW,** None; **Yang J,** None; **Zhu XM,** None; **Xiang FL,** None; **Tu J,** None; **Huang MX,** None; **Wang Y,** None; **Gan JH,** None; **Yang WH,** None.

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