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Combined Orthokeratology with Atropine for children with Myopia: A Meta-analysis

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Short Title: Orthokeratology with Atropine for Myopia in children

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Abstract

Background: Myopia has become a worldwide public health issue, which is occurring at a younger age, leading to an increased risk of high myopia. Ocular complications associated with high myopia can lead to irreversible vision loss. It is urgent and critical to explore effective treatment to slow or even stop the progression of myopia in young children. **Objective**: To evaluate the additive effects of orthokeratology (OK) and 0.01% atropine ophthalmic solution for myopia in children. **Methods**: We searched PubMed, Cochrane Library, EMBASE, MEDLINE, Web of science, Ovid, EBSCO host, CNKI, CBM to collect eligible studies. Efficacy and safety were evaluated in terms of the axial length, uncorrected distant visual acuity, corneal endothelial cell density, and intraocular pressure. We calculated the weighted mean difference (WMD) and the 95% confidence intervals (CIs) of all outcomes, and plotted on forest plots. **Results**: Four studies were ultimately included, involving a total of 267 subjects. This meta-analysis revealed that the mean axial length of the subjects in the experimental group was 0.09 mm less than that of subjects in the control group [WMD=-0.09, 95%CI (-0.15, -0.03), P=0.003]. There was no significant difference in uncorrected distant visual acuity, corneal endothelial cell density, and intraocular pressure between the two groups [WMD was -0.01 (95% CI: -0.03, 0.01), 11.75 (95% CI: -4.09, 27.58), 0.12 (95% CI: -0.40, 0.63), respectively]. None of the studies reported severe adverse events. **Conclusion**: Our study suggests that the combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia in a relatively short duration of treatment. In addition, the combination therapy has no negative influence on uncorrected distant visual acuity, corneal endothelial cell density, and intraocular pressure.

Introduction

Myopia has become a worldwide public health issue, particularly in some eastern Asian areas, where the prevalence in children is as high as 90% [1]. It is estimated that the global prevalence of myopia and high myopia will show a significant increase, affecting nearly 5 billion people and 1 billion people, respectively, by 2050 [2]. In addition to a huge socioeconomic burden, ocular complications associated with high myopia such as cataract, glaucoma, retinal detachment, and myopic maculopathy, can lead to irreversible vision loss, which seriously affects the quality of patients' life [3]. Myopia is occurring at a younger age, leading to an increased risk of high myopia [4]. Therefore, it is urgent and critical to explore effective treatment to slow or even stop the progression of myopia in young children.

The progression of myopia in children is mainly caused by axial elongation, so controlling axial elongation is important to prevent high myopia [5]. Current popular methods for controlling the progression of myopia include optical, pharmaceutical and behavioral interventions [6]. It is possible that an additive effect could exist if the treatments with different mechanisms of action are combined. Orthokeratology (OK) is custom-designed rigid contact lens, which can reshape the cornea to reduce refractive error and allow clear unaided vision during the day [7]. A number of prospective clinical trials and meta-analyses have demonstrated that OK could inhibit axial eye growth and myopia progression [8-13]. Atropine has also been shown to ameliorate the myopia progression in children.
The mechanism of action may a direct effect of atropine on the eyeball to stop eyeball elongation or an indirect effect by relaxing the focusing muscles of eyes [4]. Efficacy and adverse effects of atropine in myopia with children have been becoming a focus of attention. A 2011 meta-analysis [4] showed better efficacy at higher doses, but included only 6 studies, and evaluated only the moderate and high doses of atropine, without the low dose. In 2017, a meta-analysis of 3137 children younger than 18 years with myopia found no difference in the efficacy of atropine at different concentrations (low dose, 0.01%; moderate dose, >0.01% to <0.5%; and high dose, 0.5% to 1.0%), whereas the adverse effects were dose dependent, which supported the use of low dose atropine (0.01%) to reduce the progression of myopia in children [14]. However, several randomized control trials have demonstrated that atropine

eyedrops are effective in the control of myopia in a dose-dependent manner. Chia et al [15] showed that a dose-related response on myopia was found among the three treatment arms (0.5%, 0.1%, and 0.01% atropine treatment arms), although differences between treatment arms were clinically small. Their five-year clinical trial [16] found that 0.01% atropine eyedrops were more effective in slowing myopia progression with less visual side effects compared with higher doses of atropine. In addition, they found that a myopic rebound was greater in eyes that had received 0.5% and 0.1% atropine after atropine was stopped. In contrast, the 0.01% atropine had less myopic rebound, and the effect was more modulated and sustained [17]. A randomized, placebo-controlled, double-masked trial [18] also showed the 0.05%, 0.025%, and 0.01% atropine reduced myopia progression along a concentration-dependent response. Similarly, some studies clearly confirmed the dose-dependency on axial length growth and spherical equivalent refractive error (SER) [6,19]. It can be seen that the relationship between atropine effect and dose in controlling myopia progression is still disputable. However, considering the adverse effects and rebound effects of atropine in different doses, 0.01% atropine combined with OK could be an optimal treatment option.

In recent years, several prospective randomized clinical trials [20-22] have been conducted to investigate the additive effects of OK and 0.01% atropine ophthalmic solution in slowing the progression of myopia. The results of these studies were similar, suggesting that combined treatment with atropine and OK was more effective in slowing axial elongation than OK monotherapy in children with myopia. We conducted this meta-analysis to better evaluate whether the combination of OK and 0.01% atropine has an additive effect in slowing the progression of myopia in children.

Methods

Search Strategy

We searched PubMed, Cochrane Library, EMBASE, MEDLINE, Web of science, Ovid, EBSCO host, CNKI, CBM to obtain relevant studies from their inception to March 2020 in all languages, using Medical Subject Headings and free words combined with myopia, refractive errors, orthokeratology, and atropine. We also carefully screened the reference lists of

published reviews to identify applicable studies.

Eligibility Criteria

We selected the studies according to the following criteria: (1) the type of study included was randomized controlled trial (RCT), (2) the participants were younger than 18 years and definitely diagnosed as myopia, (3) the experimental group was treated with OK and 0.01% atropine, while the control group was treated with OK or 0.01% atropine alone, (4) at least one outcome that we were interested in was reported in the studies, including the changes in axial length (AL), uncorrected distant visual acuity (UCVA), corneal endothelial cell density (CECD), and intraocular pressure (IOP) and so on. The followings were excluded: conference abstracts, case reports, duplicate publications, letters, and reviews, studies without complete data or with inconsistent or erroneous data, incorrect random methods or intervention methods.

Data Extraction and Quality Assessment

Two researchers (SZW, JW) independently screened titles and abstracts of the retrieved literatures, and then they read the full text carefully to determine which studies were eventually included. Disagreements were resolved by discussion. Two researchers independently extracted the required data from each eligible study, including first author, publication year, country or area, sample size, age, intervention and control, duration of treatment, and outcomes.

We assessed the qualities of the included literature for the following 7 aspects according to the Cochrane Collaboration's tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each entry was evaluated at "low risk of bias", "high risk of bias" or "unclear risk of bias". Discrepancies were resolved by discussion.

Statistical Analysis

The Review Manager (version 5.3; Cochrane Collaboration) was used for data analysis. We used the weighted mean difference (WMD) with 95% confidence intervals (CIs) in AL,

UCVA, CECD, and IOP to assess myopia progression as well as adverse effects. Heterogeneity was assessed by means of I^2 statistics. If $I^2 \geqslant 50\%$, the random effect model was used for meta-analysis, otherwise the fixed effect model was chosen. A sensitivity analysis was performed to investigate the sources of heterogeneity. There were not sufficient studies ($n < 10$) to analyze publication bias.

Results

Literature Search and Characteristics of Included Studies

A total of 643 records were initially identified through database searching. 453 records were screened after duplicates removal. Among them, 430 records were excluded due to irrelevance, and then, 23 of full-text articles were assessed for eligibility. Ultimately, 4 studies were included in meta-analysis after reading the full text. The screening process of eligible studies is shown in the flow diagram in Figure 1.

Table 1 shows the characteristics of 4 eligible studies. A total of 267 children were enrolled in this meta-analysis (age range from 6 to 16 years old). One study (Qi Tan 2019 [21]) was performed in Hong Kong, China, one (Nozomi Kinoshita 2018 [22]) in Japan and the remaining two (Shi Menghai 2018 [23], Shi Yinghui 2017 [24]) in mainland China. The time to intervention ranged from 1 to 12 months. All studies concentrated on children with low to moderate myopia (less than -6.00D). The 0.01% atropine was self-prepared in all studies. In Nozomi Kinoshita 2018 study, the atropine 0.01% ophthalmic solution was specially prepared by diluting Nitten ATROPINE Ophthalmic Solution 1% with physiological saline at a ratio of 1: 99 in a sterile manner. The 0.01% atropine used in Qi Tan 2019 study was single-dose and preservative-free. The other two studies did not describe the preparation methods in detail.

Risk of Bias Assessment

Figure 2 shows the risk of bias of the included studies. Two of the included studies [22,23] explicitly pointed out the randomization methods, while the remaining two studies only referred to randomization, but did not describe it in detail. All studies did not clearly report allocation concealment. Only one study [22] mentioned blind method. Two studies [21,22] did not completely report all outcome data, but the generation of missing data was

unlikely to be related to the real outcomes. Furthermore, other bias in 2 studies [21,22] were low risk.

Change in AL

Four studies all reported and analyzed the changes in AL in the OK and 0.01% atropine combination group and the OK monotherapy group. We extracted the data from these four studies for a meta-analysis. The combined results showed that the mean AL of the 128 subjects in the experimental group was 0.09 mm (95% CI: -0.15, -0.03) less than that of 134 subjects in the control group, as shown in Figure 3. There was statistical heterogeneity between the two groups (P＜0.00001, I^2 =89%). We performed sensitivity analysis (removal of a study one by one) to investigate the sources of heterogeneity. By omitting the Qi Tan 2019 study, heterogeneity was reduced from 89% to 9% and the overall effect was not inversed (Table 2). The WMD in the change of AL was 0.12 mm (95% CI: 0.09, 0.14; P = 0.33, I^2 = 9%).

Change in UCVA

Three studies involved the changes in UCVA. We combined the data from these three studies to obtain the results. There were 81 participants in the experimental group and 87 participants in the control group. The pooled results indicated that there was no significant difference in UCVA between the two groups (95% CI: -0.03, 0.01), as shown in Figure 4. There was no statistical heterogeneity between the two groups (P = 0.99, I^2 = 0%).

Change in CECD

Two studies reported the changes in CECD between the combination group and monotherapy group. The combined results indicated that there was no statistical difference in CECD between the two groups (95% CI: -4.09, 27.58), as shown in Figure 5. There was no significant between-study heterogeneity (P = 0.49, I^2 = 0%). It should be noted, the high variability of CECD in the Kinoshita study led to a disputable conclusion. The value of meta-analysis for CECD is limited.

Change in IOP

The changes in IOP between the two groups were reported by two studies. The combined results revealed a WMD of 0.12, 95%CI (-0.40, 0.63), which suggested there was no significant difference in IOP between the two groups, as shown in Figure 6. There was no statistical heterogeneity between the two groups (P = 0.51, I^2 = 0%).

Adverse Event

No severe adverse events were reported in our included studies. The most common ocular health issues were corneal stains and conjunctivitis. The incidence of central corneal staining reported by one study [21] was less than 10% in either group, which was consistent with previous studies. The authors analyzed that the corneal staining was mainly related to OK lens wearing rather than 0.01% atropine eye drops. One case of brief episodes of conjunctivitis occurred in each group, which may be associated with contamination of the lens during insertion and increased eye rubbing. In another study [22], there was one case of corneal infiltration in the monotherapy group and one case of mild superficial punctate keratopathy in the combination therapy group, which were resolved after topical therapy. Shi Menghai [23] reported that at follow-up a total of 47 (36.7%) of the patients in both groups had mild corneal staining, which were cured after treatment, and 4 cases (12.9%) presented mild outdoor photophobia in the combined treatment group, which did not affect normal study and life.

Discussion

Our meta-analysis confirms that the combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia. Moreover, no significant difference was found in UCVA, CECD, and IOP between the combination group and monotherapy group, indicating that the combination therapy for children with myopia has no negative influence on clinical results. No severe adverse events were reported in our included studies. To our knowledge, this is the first overview of systematic reviews and meta-analysis on efficacy of the combined treatment of OK and 0.01% atropine for children with myopia.

OK is a clinical technique that uses specially designed rigid contact lenses to reshape the

cornea to temporarily reduce or eliminate refractive error [25]. In recent years, a large number of studies have proved that OK can effectively delay the development of myopia in children, although the mechanism is still unclear [26-29]. A lot of scholars hold that wearing OK improves the defocus on the peripheral retina with increases in the higher-order aberration through corneal epithelial redistribution in which the central cornea is thinned, and the mid-periphery is thickened [22]. Atropine is a nonselective muscarinic antagonist and has been widely studied in recent years to prevent the progression of myopia in children [30]. In addition to relaxing the focusing muscles of eyes, atropine may also block the muscarinic receptors in the retina and sclera that mediate axial elongation [31,32]. 0.01% Atropine ophthalmic solution for children with myopia has been proved to be a safe and effective concentration with few vision-related adverse effects [16,18]. Based on the different mechanisms of optics and pharmacy, combined OK with 0.01% atropine for children with myopia can produce better treatment effects, which our meta-analysis also proves.

A meta-analysis [33] reported that OK slowed the axial elongation more effectively for children with higher myopia than with lower myopia. In our meta-analysis, One [22] of the included studies also researched the effect of SER and age of children on the therapeutic outcomes, and found that the suppressive effect of OK monotherapy on axial elongation was affected by the SER rather than the age of children. The additive effect of the combination group in slowing axial elongation was greater in children with lower myopia, whereas the monotherapy group was as effective as the combination group in children with higher myopia. The authors' point is that when OK therapy is for children with higher myopia, the amount of myopia correction becomes larger, and the defocus on the peripheral retina is further improved with change from hyperopic toward myopic defocus. On the contrary, if the amount of myopia correction becomes smaller, the defocus on the peripheral retina is not sufficiently improved by OK monotherapy for children with lower myopia, and then adding 0.01% atropine seems to be more effective. However, none of the included studies in our meta-analysis reported the peripheral refraction and higher-order aberration, which is not convenient for us to further study the mechanism of combination therapy.

In our meta-analysis, heterogeneity arose between the two groups when the changes of

AL were compared. Using of a random effect model does not deal with heterogeneity. We identified the Qi Tan 2019 study as the primary source of heterogeneity through sensitivity analysis. The study observed significant reductions in AL between the two groups of subjects after one-month of treatment. AL was initially observed to be shortened after commencement of OK lens wear, which was consistent with previous studies [10,34]. It has been suggested that the axial shortening may be due to choroidal thickening in response to myopic defocus or corneal thinning after OK lens wear [35-37]. Since subjects of both groups wore OK lenses in the study, the difference in the amount of axial shortening may have been due to atropine (0.01%). However, in the other three studies (⩾6 months of treatment), axial shortening was not observed in either the experimental group or the control group, suggesting that the length of intervention time would affect the experimental results. In addition, the SER of subjects may also be a factor. In Qi Tan 2019 study, the SER of subjects were − 1.00 to − 4.00 diopters (D), while these in the remaining studies were − 1.00 to − 6.00 diopters (D). Nozomi Kinoshita 2018 study found that the additive effects of OK and 0.01% atropine in slowing axial elongation was greater in children with lower myopia, while OK monotherapy was as effective as combining combination therapy in children with higher myopia. In order to better evaluate the effect of combination therapy, subgroups of the subjects' SER should also be made.

Our study has some limitations. We clearly realized that the small numbers of available studies and their short follow up time are responsible for the limited validity of this early meta-analysis. First, only four RCTs meeting the requirements were found, and high-quality RCTs were relatively lacking, although we conducted an extensive and comprehensive search of the database. If more high-quality, large-sample RCTs were done, we could draw more reliable conclusions. Second, the duration of treatment was relatively short. Controlling myopia treatment requires a long-term assessment. However, the duration of treatment in the studies we included ranged from 1 month to 12 months. Long-term additive effects of OK and 0.01% atropine to slow axial elongation in children with myopia is not yet fully established. Our study only confirms that the combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia in a

relatively short duration of treatment. Larger sample size and longer study duration are warranted to confirm the real effectiveness of this combination treatment for children with myopia. Meanwhile it is also warranted to investigate long-term side effects and rebound phenomenon of OK and 0.01% atropine [38]. Third, all of included studies were conducted only in Asia. In order to obtain more scientific evidence, more large-scale, multi-ethnic, blinded, randomized controlled trials should be carried out in the future. Fourth, none of the included studies took into consideration the external factors such as outdoor activity time and near work time. Some studies have shown that outdoor light exposure is related to myopia incidence, and some evidence suggests outdoor light exposure slows myopic progression in individuals with myopia [39-43]. The influence of external factors on the progression of myopia should also be considered in future studies.

Conclusions

The combination of OK and 0.01% atropine is more effective in slowing axial elongation than OK monotherapy in children with myopia, and has no negative influence on uncorrected distant visual acuity, corneal endothelial cell density, and intraocular pressure in a relatively short duration of treatment. The long-term efficacy and safety of the combination therapy of OK and 0.01% atropine in children with myopia will need to be further confirmed by more studies.

Statement of Ethics

All analyses were based on published studies, and thus, no ethical approval and informed consent are required. Nonetheless, the study adhered fully to the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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No funds were used in the conduct and completion of this study.

Author Contributions

S.W. and J.W. extracted data from published studies, analyzed the results, and drafted the manuscript. They contributed equally to the study. N.W. provided oversight for the extraction and analysis, and identified the accuracy of results and discussion presented in the manuscript.

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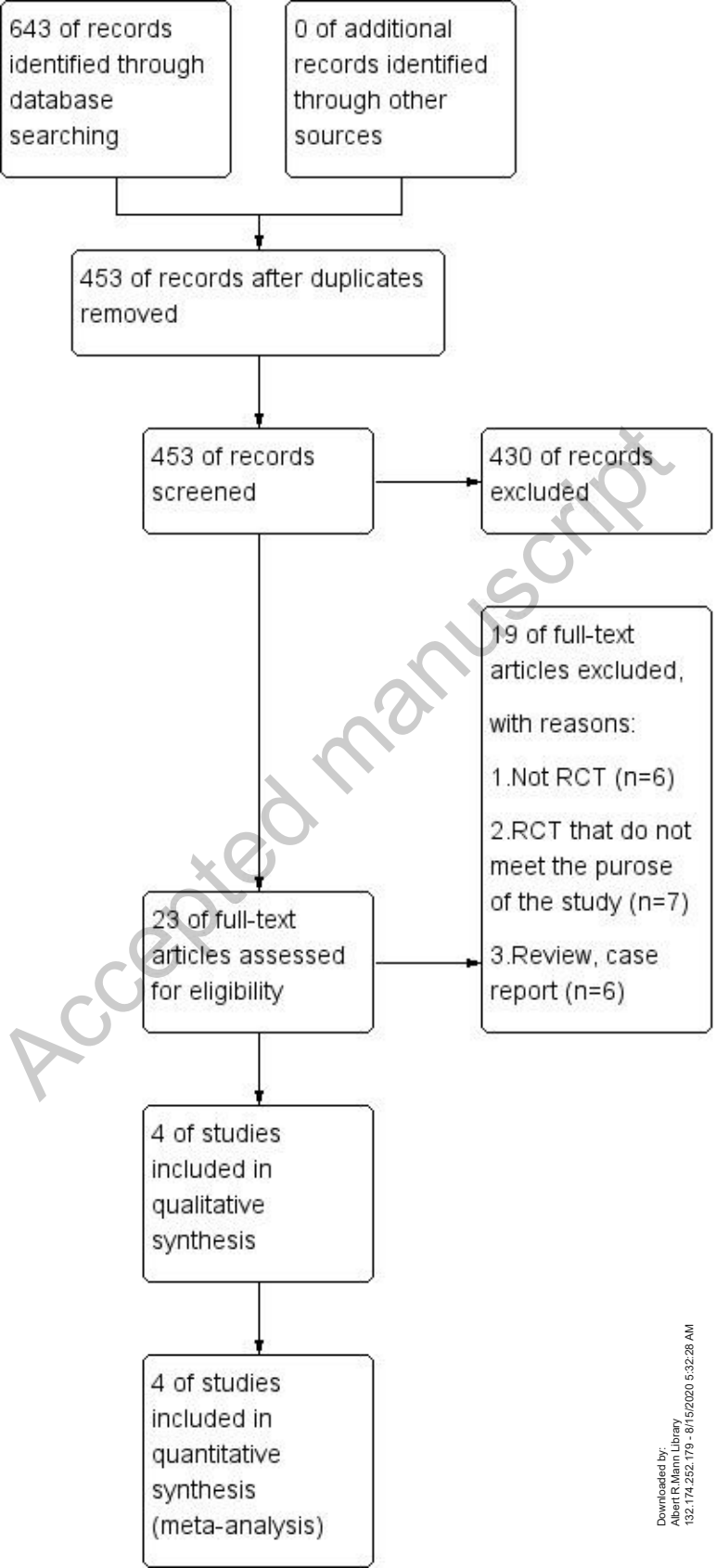
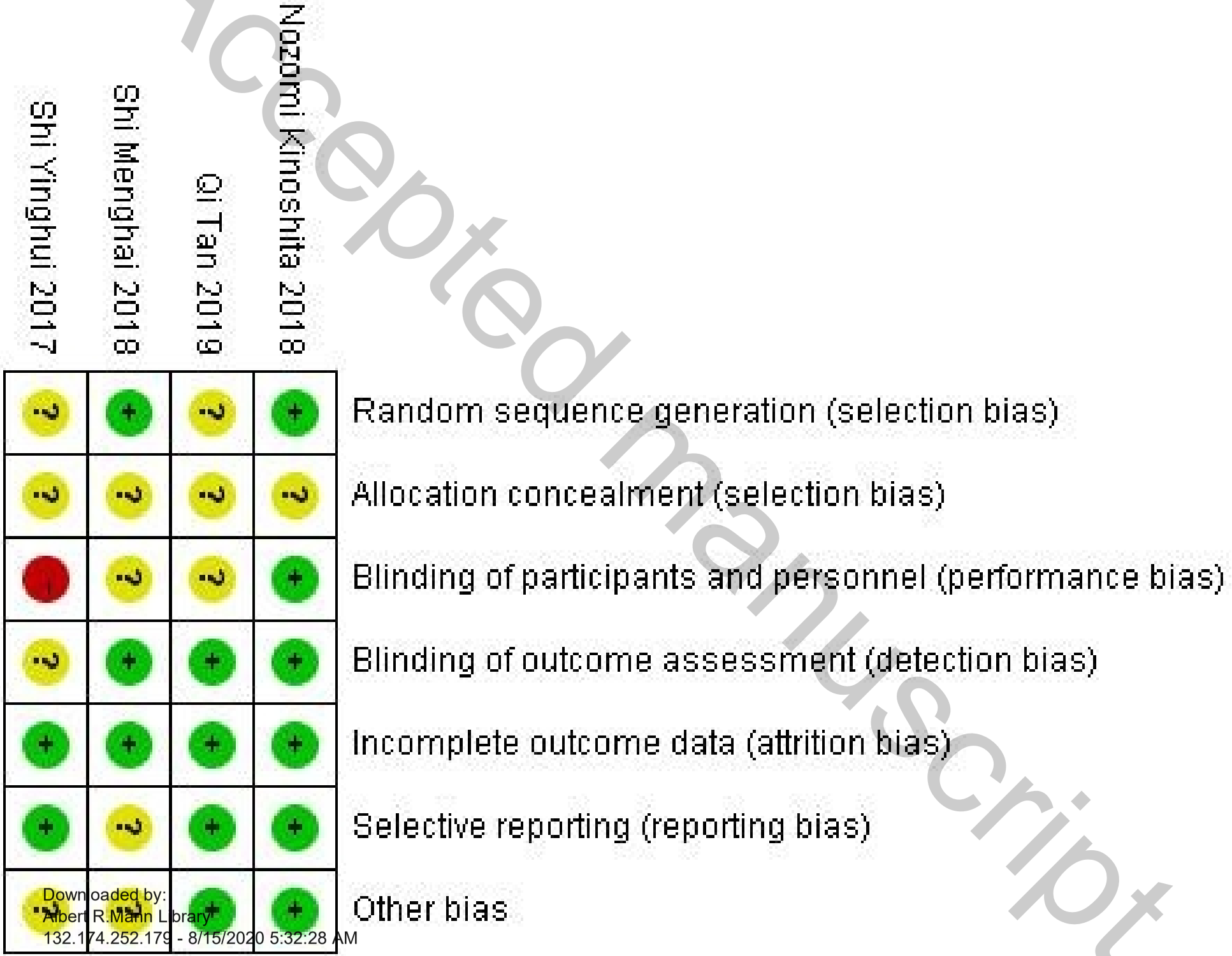
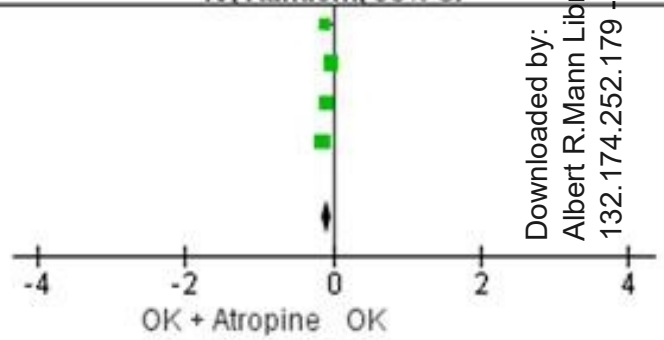




Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nozomi Kinoshita 2018	0.09	0.12	20	0.19	0.15	20	18.5%	-0.10 [-0.18, -0.02]
Qi Tan 2019	-0.05	0.05	30	-0.02	0.03	34	28.7%	-0.03 [-0.05, -0.01]
Shi Menghai 2018	0.12	0.07	31	0.22	0.08	33	26.7%	-0.10 [-0.14, -0.06]
Shi Yinghui 2017	0.11	0.09	47	0.25	0.11	47	26.1%	-0.14 [-0.18, -0.10]
Total (95% CI)			**128**			**134**	**100.0%**	**-0.09 [-0.15, -0.03]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 28.34$, df = 3 ($P < 0.00001$); $I^2 = 89\%$

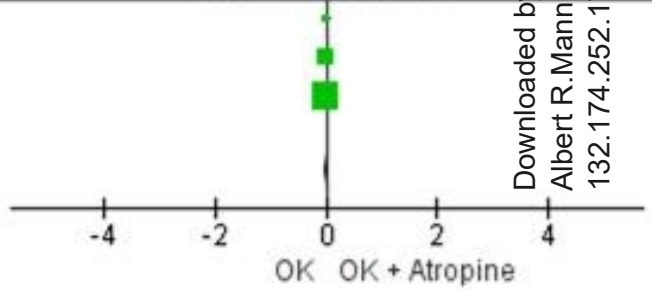
Test for overall effect: $Z = 3.00$ ($P = 0.003$)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nozomi Kinoshita 2018	0.045	0.103	20	0.058	0.097	20	9.0%	-0.01 [-0.08, 0.05]
Qi Tan 2019	-0.04	0.07	30	-0.03	0.07	34	29.4%	-0.01 [-0.04, 0.02]
Shi Menghai 2018	0.032	0.047	31	0.041	0.05	33	61.5%	-0.01 [-0.03, 0.01]
Total (95% CI)			**81**			**87**	**100.0%**	**-0.01 [-0.03, 0.01]**

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%

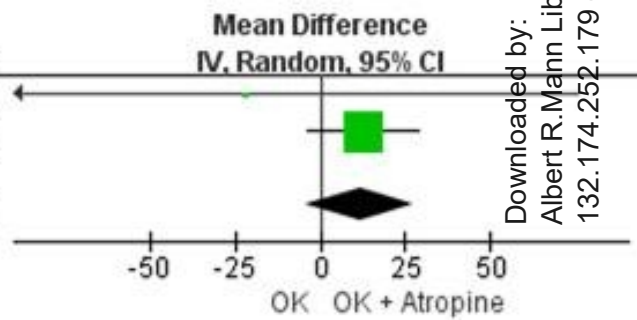
Test for overall effect: Z = 1.02 (P = 0.31)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nozomi Kinoshita 2018	-73	151	20	-51	165	20	2.6%	-22.00 [-120.02, 76.02]
Shi Menghai 2018	-26.17	32.86	31	-38.82	32.61	33	97.4%	12.65 [-3.40, 28.70]
Total (95% CI)			**51**			**53**	**100.0%**	**11.75 [-4.09, 27.58]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.47$, $df = 1$ ($P = 0.49$); $I^2 = 0\%$

Test for overall effect: $Z = 1.45$ ($P = 0.15$)



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nozomi Kinoshita 2018	-0.74	2.38	20	-0.45	1.88	20	15.0%	-0.29 [-1.62, 1.04]
Shi Menghai 2018	-0.45	1.27	31	-0.64	0.98	33	85.0%	0.19 [-0.37, 0.75]
Total (95% CI)			**51**			**53**	**100.0%**	**0.12 [-0.40, 0.63]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0\%$

Test for overall effect: Z = 0.45 (P = 0.65)

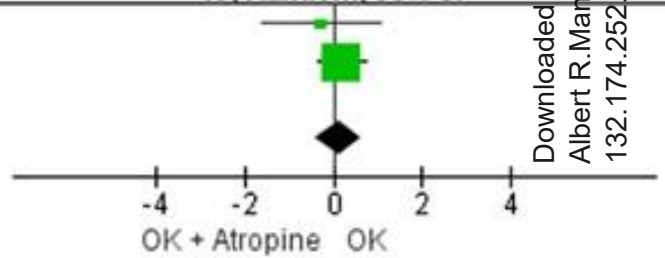


Table 1. Characteristics of included studies

Study	Country /Region	Study type	Sample size(E/C)	Age, y	SER,D(E/C)	Intervention		Duration of treatment, mo	Outcomes
						Experiment group	Control Group		
Nozomi Kinoshita 2018	Japan	RCT	20/21	8-12	-2.81±1.43 /-2.95±1.43	OK +0.01% atropine	OK	12	AL/ IOLMaster; UCVA/ logMAR; CECD/ Noncon, ROBO CA SP-8800; IOP/ TONOREF II
Qi Tan 2019	Hong Kong, China	RCT	33/35	6-11	-2.71±0.91 /-2.88±0.92	OK + 0.01% atropine	OK	1	AL/ IOLMaster; UCVA/ ETDRS chart
Shi Menghai 2018	China	RCT	31/33	9-14	-3.27±0.82 /-3.29±0.89	OK + 0.01% atropine	OK	12	AL/ IOLMaster; UCVA/ TOPCON, Japan; CECD/ TOPCON, Japan; IOP/ Non-contact tonometer (TOPCON, Japan)
Shi Yinghui 2017	China	RCT	47/47	9-16	-1.50~-6.00	OK + 0.01%	OK	6	AL/AL-Scan Eye

	atropine	biometrics
		(TOPCON, Japan)

E/C: experiment group/control group SER: Spherical equivalent refractive error AL: Axial length UCVA: Uncorrected distant visual acuity CECD: Corneal endothelial cell density IOP: Intraocular pressure

Table 2. Sensitivity analysis

	Total (95%CI)	Heterogeneity	Test for overall effect
All studies	- 0.09(-0.15,-0.03)	P＜0.00001, I^2=89%	P=0.003
Removal of Nozomi Kinoshita 2018	- 0.09(-0.16,-0.02)	P＜0.00001, I^2=93%	P=0.01
Removal of Qi Tan 2019	- 0.12(-0.14,-0.09)	P=0.33, I^2=9%	P＜0.00001
Removal of Shi Menghai 2018	- 0.09(-0.17,-0.00)	P＜0.00001, I^2=92%	P=0.04
Removal of Shi Yinghui 2017	- 0.07(-0.13,-0.01)	P=0.002, I^2=83%	P=0.01

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1 (title)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 3 (**Abstract**); Registration number: CRD42020184301
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4,5 (**Introduction)**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4,5 (**Introduction)**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5,6 (**Methods**); Registration number: CRD42020184301
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 6 (**Eligibility Criteria**)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5, 6 (**Search Strategy**)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5, 6 (**Search Strategy**)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 (**Data Extraction**)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6 (**Data Extraction**)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5,6 (**Methods**)

PRISMA 2009 Checklist

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6 (**Quality Assessment**)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6,7 (**Statistical Analysis**)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6,7 (**Statistical Analysis**)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6 (**Quality Assessment**)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 6,7 (**Statistical Analysis**)
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7 (**Literature Search,** Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 7 (**Characteristics of Included Studies,** Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7,8 (**Risk of Bias Assessment,** Figure 2)

PRISMA 2009 Checklist

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 7,8,9 (Table 1, Figure 3, Figure 4, Figure 5, Figure 6)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8,9 (**Change in AL** Figure 3, **Change in UCVA** Figure 4, **Change in CECD** Figure 5, **Change in IOP** Figure 6)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 7,8 (**Risk of Bias Assessment,** Figure 2)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 8 (Table 2)
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 9,10,11 (**Discussion**)
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 11,12 (**Discussion**)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 12 (**Conclusions**)
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 13 (**Funding Sources**)

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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