The Effect of Atropine Alone or Combined with Orthokeratology for Children with Myopia: A Meta-Analysis

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Abstract

Objective: To evaluate the effect of atropine alone or combined with orthokeratology on myopia control by meta-analysis system.

Methods: The current study searched PubMed, Cochrane Library, EMBASE, MEDLINE, Web of science, Ovid to collect eligible studies. The Weighted mean difference (WMD) of mean changes in axial elongation between the atropine alone or combined with orthokeratology group and the orthokeratology (ortho-k) group was used as evaluation index.

Results: Twelve studies were eventually included, involving 671 children in the atropine alone and 547 children in the atropine combined with orthokeratology（AOK） group. This meta-analysis showed that the mean axial elongation of atropine alone was faster than that of ortho-k alone. [WMD=0.06mm, 95％CI(0.02~0.10), p＝0.007]. The function of AOK for slowing axial elongation was affected by the baseline diopter of children. The WMD in -1~-3D subgroup was -0.10 mm(95％CI,-0.14~-0.05,P＜0.00001),which mens that the AOK was more effective than OK alone in retarding axial elongation. In -3~-6D, WMD is -0.04mm (95% CI, -0.11~0.03), and there is not statistically significant between two groups (P<0.30).

Conclusion: This study suggested that ortho-k monotherapy is better in slowing axial elongation than atropine monotherapy in children with myopia. For children with low degree of myopia, the combination of ortho-k and 0.01% atropine is more effective than ortho-k monotherapy in slowing axial elongation in children. But there is no significant difference between two treatments in children with moderate degree of myopia.

Objective

Myopia is an important public health problem and one of the main causes of visual impairment among adolescents[1] The prevalence of myopia in Asian populations, especially in China, is 40 to 70 percent.[2]. A meta-analysis estimates that the prevalence rate of children under 18 years old will reach 80%. [3] The development of high myopia will lead to excessive axial growth and lead to severe and irreversible vision loss such as retinal detachment [4], macular dystrophy and glaucoma[5]. Therefore, it is particularly important to take effective measures to slow the growth of axial length for inhibitingthe progress of myopia.

Huang et al took axial elongation as the evaluation standard and conducted a meta-analysis of 16 myopia control methods, and found that the top five myopia control effects were: high concentration of atropine, medium concentration of atropine, low concentration of atropine, orthokeratology lens, peripheral defocus control soft lens. [6] At present, the mechanism of atropine controlling the growth of myopia is not clear. Studies suggested that atropine can delay the development of myopia through a non-regulatory mechanism. It may act on M1 and M4 subtypes of muscarinic receptors on retina and sclera, inhibit the growth of ocular axis, and may also promote the release of dopamine and other neurotransmitters, thus affecting the signal transduction of retina and controlling the growth of ocular axis. [7]

Many previous studies reported the clinical efficacy and adverse reactions of different concentrations of atropine for myopia control. Qianwen gong 2017 founded that the efficacy of different concentrations of atropine (low dose, 0.01%; medium dose, > 0.01% to < 0.5%; high dose, 0.5% to 1.0%) was not dose-dependent, while the adverse reactions were dose-dependent.[8]Low dose of atropine can reduce the adverse reactions and rebound effects. Chia's et al founded that the efficacy and adverse reactions of 0.5%, 0.1% and 0.01% atropine were concentration dependent, but was not significant different in efficacy . Compared with 0.5% and 0.1% atropine, The lowest concentration of 0.01% atropine thus seems to retain efficacy and is a viable concentration for reducing myopia progression in children, while less side effects and rebound[9]A recent study showed that 0.05%, 0.025% and 0.01% atropine responded in a concentration-dependent manner, with 0.05% being the optimal concentration for myopia control. [10]Therefore, the optimal concentration of atropine is still controversial. At present, 0.01% of atropine is the most commonly used drug for myopia control in East Asia, especially in Taiwan and Singapore.[11]

ortho-k is a special type of rigid contact lens with anti-geometric design. Wearing at night can change the corneal curvature of patients, thus reversibly reduce the degree of myopia and make patients obtain better daytime vision.[12] Most studies have confirmed that ortho-k can reduce axial elongation by 43-63% in two years. [13][14]That corneal epithelial remodeling (thinning of the central cornea and thickening of the peripheral cornea) causes myopia defocusing in the peripheral retina, thus controlling the progression of myopia was considered the mechanism by ortho-k.[15] Many reports have shown that ortho-k are more effective in slowing axial lengthening in children with moderate and high myopia than in children with low myopia. [16][17]

At present, there are some literature reports on the comparative study of atropine and ortho-k single treatment for juvenile myopia, but results are still controversial. [18]-[21] Due to the different mechanism of atropine and ortho-k in controlling myopia, the combination of atropine and ortho-k may produce additive effect. Considering adverse effects and rebound reactions of different doses of atropine, several studies confirmed that the combination of 0.01% atropine and ortho-k is more effective than ortho-k alone in slowing down the axial elongation of myopia children. [22][31] we conducted this meta-analysis to further evaluate the effect of atropine alone or combined with ortho-k on myopia control.

Methods

Search Strategy

We searched PubMed, Cochrane Library, EMBASE, MEDLINE, Web of science, Ovid to obtain relevant studies from their inception to December 2020 ,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 all studies according to the following criteria:(1) Study population: myopic children under 18 years old; The equivalent spherical refraction was < -6D, and the binocular anisometropia was < -1.5D. (2) Intervention measures: Due to the side effects of high concentration of atropine and obvious rebound effect after drug withdrawal, low and medium concentrations of atropine (< 0.5%) were included in this paper. The experimental group was treated with atropine combined with ortho-k, or atropine alone, while the control group only received ortho-k treatment. (3) Study Design: Randomized controlled trial (RCT) and cohort study; (4) Main outcome measure: mean change in axial length (AL). Studies that do not meet inclusion criteria, incorrect data and incomplete data, conference reviews, case reports, and duplicate publications will be excluded.

Data Extraction And Quality Assessment

Two reviewers (WZY and YZP) performed data extraction and quality assessment independently. All extracted data were recorded in a Microsoft Excel form along with study characteristics (first author, year, country and region, research type), research objects (age, sample size, baseline Ser), intervention measures (study group and control group, follow-up time), outcome indicators (axial length, pupil diameter).

The quality of RCTs was evaluated according to Cochrane Collaboration's tool for assessing risk of bias,[32] which included seven domains as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. In each domain, reviewers' judgments were categorized as "Low risk" of bias, "High risk" of bias or "Unclear risk" of bias according to the given criteria. If insufficient detail of the criteria is reported in the study, the judgment will be "Unclear risk" of bias. We used the Newcastle-Ottawa Scale [33] to assess the quality of observational studies. A study awarded seven or more scores was regarded as high quality, four to six scores as moderate quality, and less than three scores as low quality. Disagreements were resolved by discussion with third party experts or focused discussion (at least 3 people) .

Statistical Analysis

Our reviewer performed statistical analyses using Review Manager (version 5.3). We calculated the weighted mean difference (WMD) and 95% confidence intervals (CIs) to investigate the difference in axial elongation between the experimental and control groups, and pupil diameter to evaluate the efficacy of atropine in myopia control. Heterogeneity was assessed by means of I2 statistics. If $I2 \geq 50\%$, the random effect model was used for meta-analysis, otherwise the fixed effect model was chosen. Sensitivity analysis was performed by sequentially eliminating one study in turn .Publication bias was detected using the Funnel plots test.

Results

Literature Search and Characteristics of Included Studies

A total of 238 studies were obtained from online databases according to the search strategy. After eliminating 117 duplicates, we reviewed abstracts of 121 studies, of which 93 studies were irrelevant. The final 28 studies were reviewed in full, and 16 studies were excluded because they did not meet the inclusion criteria. Finally. There are 12 studies included in this meta-analysis, with 9 RCTs and 3 cohort studies respectively. The screening process of eligible studies was shown in the flow diagram in Figure 1.

Table 1 shows the characteristics of 12 eligible studies. Five studies involved atropine monotherapy, including atropine at a low concentration of 0.01% and atropine at a medium concentration of 0.02% and 0.125%.[18][21] 8 articles involved atropine combined with ortho-k treatment, and the concentration of atropine included was 0.01%. [22][31] Zhao 2020 30 involved both atropine monotherapy and atropine combined with ortho-k therapy. Two studies (nozomi Kinoshita 2018 [24], nozomi Kinoshita 2020[27]) were conducted in Japan, and rest of studies were conducted in China. A total of 1218 myopic children were included in this study, with 671 in the atropine monotherapy group and 547 in AOK group. All children in the study had refractive error below -6.00D and were younger than 18 years old. 0.01% atropine was self-prepared in all studies. In the Yong Lyu study[21], the 0.02% atropine eye drops were made by diluting 1% atropine with saline. The 0.125% atropine used in Ren 2017[20]study was the lowest concentration of atropine available on the market.

Bias risk assessment

According to the Cochrane Collaboration's tool for assessing the risk of bias, , the quality of RCTs is high (Fig 2). Three studies [20][24][27]adopted randomization methods, but Only one study reported the allocation concealment[31]. Four Articles mentioned the blind method and explain applyment of the blind method in outcome evaluation[24][27][30][31]. Included studies completely report all outcome data In addition, other biases in six studies were low risk[24][26][27][29][31]. The Newcastle Ottawa scale was used to evaluate the cohort study, and results showed that moderate quality with four, seven and five scores in three cohort studies respectively(Table 2).

Atropine monotherapy group

Change in AL

Five studies[18][21][30] all reported and analyzed the changes in AL in the atropine monotherapy group and the ortho-k monotherapy group. There was statistical heterogeneity between the two groups (I2 =81%)，which may be related to the different concentrations of atropine. Low concentration atropine and moderate concentration atropine were used as the first and second subgroups for analysis .Heterogeneity results showed that P < 0.0009, I2=79% > 50%. So random effect model was employed in this study.

Subgroup 1 (0.01% atropine) included three studies.[19][20][30]. Heterogeneity analysis showed that P = 0.83 , I2 = 0%. .The mean AL of atropine was 0.03 mm longer than that of ortho-k (z = 3.74, P = 0.0002), indicating that ortho-k control axial elongation more effectively than low concentration atropine monotherapy (Fig. 3).

Subgroup 2 (0.01% ~0.5% atropine) included two studies .[18][21] Heterogeneity analysis showed that P = 0.72, I2 = 0%. The mean AL of atropine was 0.09mm longer than that of ortho-k (z = 7.84, P < 0.00001), indicating that ortho-k control axial elongation more effectively than medium concentration atropine monotherapy(Fig. 3).

Atropine combined with ortho-k **therapy group**

Change in AL

There are 8 studies[24][27][29][31] on atropine combined with ortho-k and ortho-k monotherapy in slowing myopia progression. To investigate the effect of baseline diopter on axial elongation, we performed a subgroup analysis. We divided all included studies into two subgroups according to low myopia (- 1 ~ - 3D) and medium myopia (- 3 ~ - 6D).

There were 6 studies with baseline SER ranging from - 1 to - 3D ,146 patients in AOK group and 149 patients in ortho-k group.[24][27][29][31]1The combined results showed that the WMD in the low myopia subgroup was - 0.10 mm (95% CI, – 0.14, - 0.05), which represented that the mean axial elongation of AOK was 0.10 mm shorter than that of ortho-kwithin baseline diopter -3D.There were 3 studies[24][27][29] with baseline SER ranging from - 3 to - 6D,62 patients in AOK group and 62 patients in ortho-k group. The combined results showed that the WMD of the midium myopia subgroup was -0.04mm (95% CI, - 0.11, 0.03). There was no significant difference in the mean axial elongation between the AOK group and the ortho-k group (P = 0.30, I2 = 54%) (Fig. 4). However, due to the limited number of studies in midium myopia subgroup, extra data are needed to confirm the relationship between AOK and ortho-k in midum baseline myopia. It was suggested that the lower the baseline diopter, the better effect of AOK on the suppression of the axial elongation.

Publication Bias

A funnel plot demonstrated that all included studies have a certain degree of asymmetry, indicating that the research results may have potential publication bias. However, the results were as reference only because of the limited number of studies.(Fig. 5).

Sensitivity analysis

Subgroup 1 (low myopia “-1 to - 3D”): We performed sensitivity analysis (removal of a study one by one) to investigate the sources of heterogeneity. By omitting the Qi Tan 2019[26] study, heterogeneity was reduced from 88% to 44% and the overall effect was not inversed (Supplemental Table 3). The results are reliable. It may be related to that the follow-up time of this study is only one month, while other studies are more than one year.

Subgroup 2 (midium myopia“-3~ -6D”) showed that the heterogeneity decreased from 54% to 0% after excluding Tang 2020,[29]but the results remained unchanged. (Table 3). It suggested that Tang2020[29] took the axial length at 1 months after wearing OK as the baseline，Kinoshita2018 and 2020 [24][27]took the axial length at 3 months after wearing OK lensas the baseline. The central corneal thickness tends to stabilize after the first 1-2 months of OK therapy,[37][38] which may affect the experimental results.

Discussions

Our meta-analysis showed that ortho-k monotherapy was superior to low and medium concentrations of atropine monotherapy in slowing axial elongation. The combination of ortho-k and 0.01% atropine is more effective than ortho-k monotherapy in slowing axial elongation, and the effect of

combination was affected by children's initial degree of myopia. To the best of our knowledge, this is the first meta-analysis comparing atropine and ortho-k ortho-k monotherapy in slowing axial elongation of myopic children, and it is also the first analysis the combined effect of atropine and ortho-k depending on low and moderate myopia.

Presently, both atropine and ortho-k are considered effective treatment for myopia control, but which is the better still controversial. Huang [6] et al believed that the ortho-k was worse than high-dose and medium dose atropine, and equal to low-dose atropine for myopia control. Current two studies suggested that ortho-k displayed better effect than that of 0.02% and 0.125% atropine. [18][21]Current meta-analysis showed that low and medium concentrations of atropine monotherapy showed a faster axial elongation than ortho-k monotherapy .

There are many reports that ortho-k is more effective in slowing axial elongation in children with moderate to high myopia than in children with low myopia.[16][17] Kinoshita[24][27] et al study showed the effects of SER and children's age on myopia control, and found that the inhibitory effect of ortho-k monotherapy on axial elongation was affected by SER rather than age. Lin et al [18] study showed that the increase of axial length in patients with high baseline myopia was less than in patients with low myopia for both the ortho-k group and the atropine group,. The linear correlation was more significant in the ortho-k group than in the atropine group (r = 0.259 and r = 0.169).

Our subgroup analysis showed that the combination of ortho-k and 0.01% atropine was more effective than ortho-k monotherapy in slowing axial elongation in myopic children with − 1.00 to − 3.00 D, but no difference with .− 3.00 to − 6.00 D. The reason may be that the more peripheral myopia defocus was induced in high myopia compared with low myopia during Otho-k treatment as described by previous studies[16][17][24]. The effect of OK monotherapy in slowing the progress of high myopia may be strong enough, while in children with low initial myopia, the amount of peripheral myopia defocusing was insufficient. Additionally, the use of low concentration atropine can make up for the control effect of ortho-k in low myopia and play a synergistic role.

In the meta-analysis of atropine monotherapy, heterogeneity was significant (I2 = 81%). After subgroup analysis, result suggested that atropine concentration might be the source of heterogeneity.Some studies suggested that atropine can slow myopia progression along a concentration-dependent response. The higher the concentration of atropine, the stronger the effect in controlling myopia progression.[9][10] Through sensitivity analysis, Qi Tan 2019[26] study was identified as the main source of heterogeneity in the low-concentration AOK group. It may be related to that the follow-up time of this study is only one month, while other studies are more than one year. Yam et al[36] found that the effect of atropine on slowing axial elongation became more obvious with the extension of the intervention period, which indicated that the length of intervention time would affect the experimental results.

There were no serious adverse events in the included studies. The main complications of atropine were photophobia, blurred vision and allergic reaction.40 The main complications of ortho-k were infectious keratitis and allergic conjunctivitis.[40]These adverse reactions were completely recovered after treatment, and the two interventions were relatively safe.

Notably,current meta-analysis has some limitations. First of all, although we tried our best to search all the literatures, the final included articles are still limited and there may be publication bias.Secondly, the duration of treatment was relatively short. Most of the included studies were followed up for one year, and their long-term cumulative effects and adverse reactions have not been fully established. Finally, we did not fully consider the participants' environmental factors, genetic factors, outdoor activities and close work, and most of the articles we included were Asian. In future studies, we should also consider the impact of external factors on the progress of myopia.

Conclusions

For myopic children,ortho-k monotherapy was superior to low and medium concentrations of atropine monotherapy in slowing axial elongation. For low initial myopia with poor response of ortho-k treatment, the combination of ortho-k and 0.01% atropine may be more effective than ortho-k monotherapy in slowing axial elongation, but there was no significant difference in children with moderate initial myopia.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the tenets of the Declaration of Helsinki. Consent to participate was not applicable due to the retrospective design of this study.

Consent for publication

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

Availability of data and materials

The data generated during the present study is available upon request from the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WZZ drafted the manuscript. YZZ critically revised the manuscript, and MFF collected patient information and analyzed and interpreted the patient data. All authors have read and approved the final manuscript.

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Tables

Table 1. Characteristics of included studies

	country	study type	sample （E/C）	age,y	Intervention （E/C）	baseline SER,D(E/C)	Duration	Outcomes
Tiang 2018	china	Cohort	40/40	8~11	0.1%atropine/OK	-2.85±0.54/-2.73±0.52	1y	AL
Ren 2017	china	Cohort	50/50	8~15	0.1%atropine/OK	-3.08±0.11/-3.16±0.28	1y	AL
Lin 2014	china	Cohort	105/105	7~17	0.125%atropine/OK	NA	3y	AL
Yong Lyu 2020	china	Cohort	90/113	7~14	0.02%atropine/OK	-2.69±1.56/-3.55±1.29	2y	AL
Zhao 2020	china	RCT	39/36	10.23/10.33	0.01%atropine or OK+0.01%atropine /OK	-3.12±1.2/-2.74±1.06	1mo	AL
Shl 2017	china	RCT	47/47	9~6	OK+0.01%atropine /OK	-1.5~-6D	6mo	AL
Kinoshita 2018	Japan	RCT	20/20	8~12	OK+0.01% atropine/OK	LM:-1~-3D HM:-3~-6D	1y	AL
Kinoshita 2020	Japan	RCT	38/35	8~12	OK+0.01% atropine/OK	LM:-1~-3D HM:-3~-6D	2y	AL
Chen 2018	china	Cohort	28/29	7.5/8.8	OK+0.01% atropine/OK	-2.65±1.08D/-2.50±0.94D	1y	AL
QiTan 2019	china	RCT	30/34	9	OK+0.01% atropine/OK	-2.71±0.91/-2.88±0.92	1mo	AL
QiTan 2020	china	RCT	29/30	9	OK+0.01% atropine/OK	-2.65±0.43D/-2.84±0.42D	1y	AL
Stehpen 2020	china	RCT	25/28	8.9/9.1	OK+0.01% atropine/OK	-1~-4D	6mo	AL
Tang 2020	china	RCT	66/60	8~14	OK+0.01% atropine/OK	LM:-2.26±1.15/-2.59±1.12 HM:-4.9±1.16/-4.92±1.21	2y	AL

Table 2 .Results of Quality Assessment Using the Newcastle-Ottawa Scale for

Cohort Studies

	Selection				Comparabiliy	Outcome			Score
	Representativeness of the exposed cohort	Seletion of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Chen et al	*	*	*	-	-	*	*	-	5
Yong Lyu et al	*	*	*	-	*	-	*	*	7
Lin 2014 et al	*	*	*	-	-	-	*	-	4
A study can be awarded a maximum of one asterisk for each numbered item within the Selection and Outcome categories. A maximum of two asterisks can be given for Comparability.									

Table 3 . Subgroup sensitivity analysis.

	Total (95%CI)	Heterogeneity	Test for overall effect
-1~-3D			
Removal of Kinishita2018	-0.08 [-0.13, -0.03]	(P = 0.0002); I² = 85%)	P=0.001
Removal of Kinoshita2020	-0.08 [-0.13, -0.04]	(P = 0.0002); I² = 85%)	P=0.001
Removal of Qi Tan2019	-0.12 [-0.16, -0.07]	(P = 0.14); I² = 44%)	P□0.00001
Removal of Qi Tan2020	-0.10 [-0.16, -0.04]	(P □0.0001); I² = 88%)	P=0.006
Removal of Tang2020	-0.11 [-0.19, -0.03]	(P = 0.0006); I² = 83%)	P=0.009
-3~-6D			
Removal of Kinishita2018	-0.05 [-0.14, 0.04]	(P =0.14); I² = 55%)	P=0.25
Removal of Kinoshita2020	-0.05 [-0.13, 0.03]	(P =0.13); I² = 55%)	P=0.18
Removal of Tang2020	0.01 [-0.07, 0.10]	(P =0.91); I² = 0%)	P=0.75

Figures

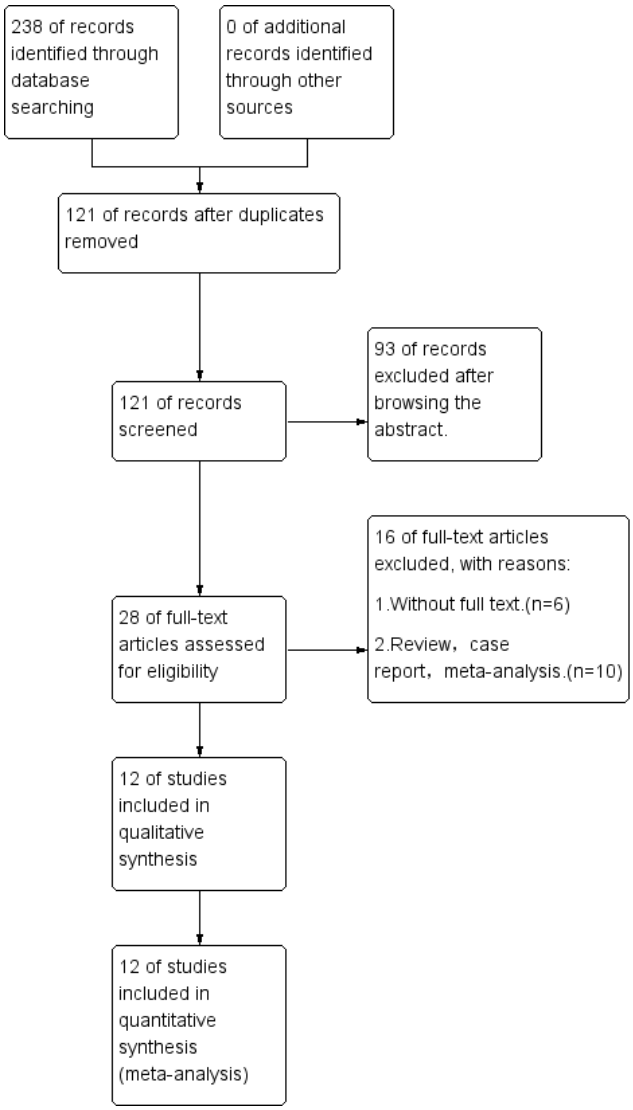

Figure 1

A flow diagram of the included studies eligible for meta-analysis.

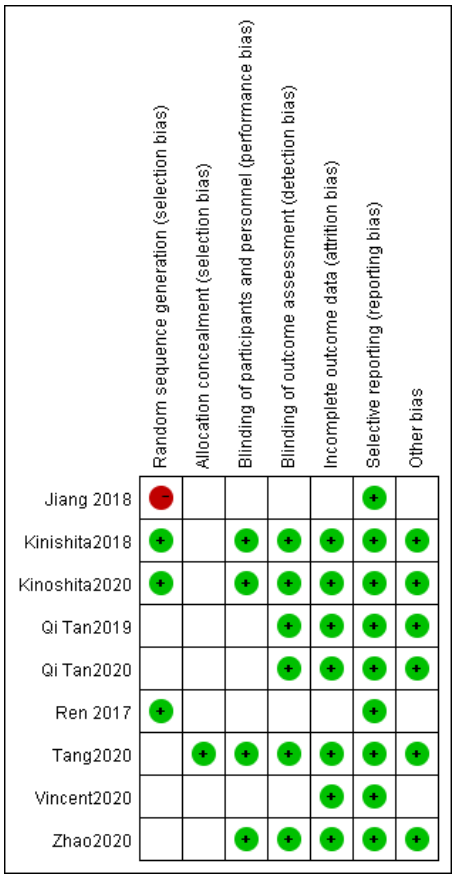

Figure 2

Risk of bias for RCT

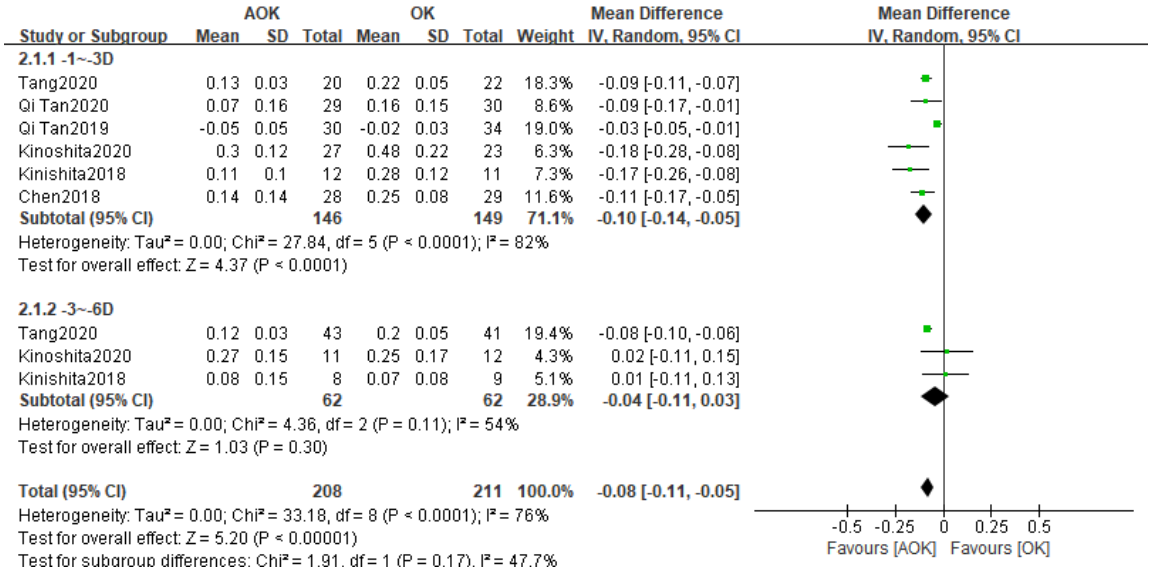

Figure 3

Forest plot of WMD of axial elongation in the atropine monotherapy group and the ortho-k monotherapy group and subgroup analysis by atropine concentration . WMD, weighted mean difference.

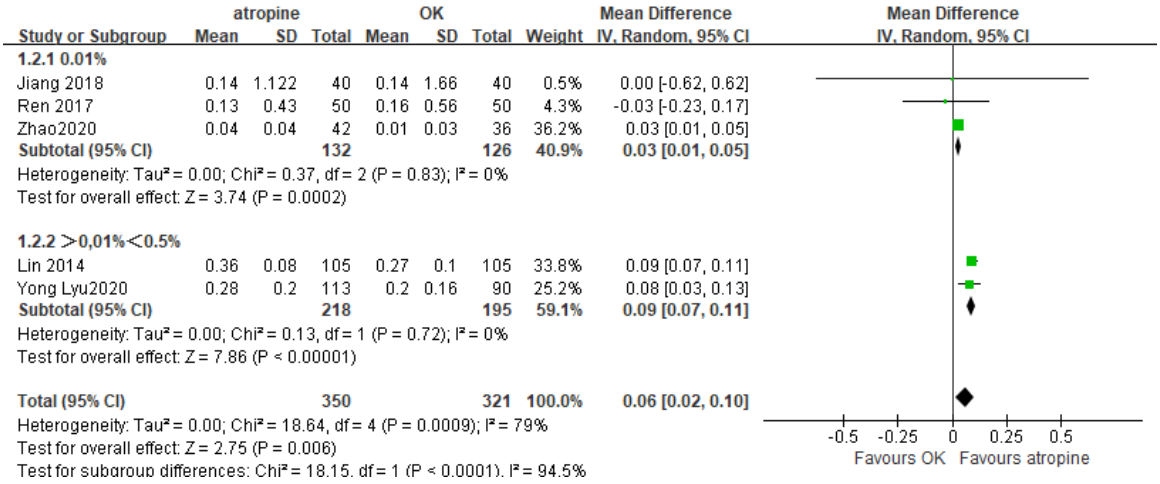

Figure 4

Forest plot of WMD of axial elongation in the AOK group and the OK group and subgroup analysis by baseline SER. WMD,weighted mean difference.

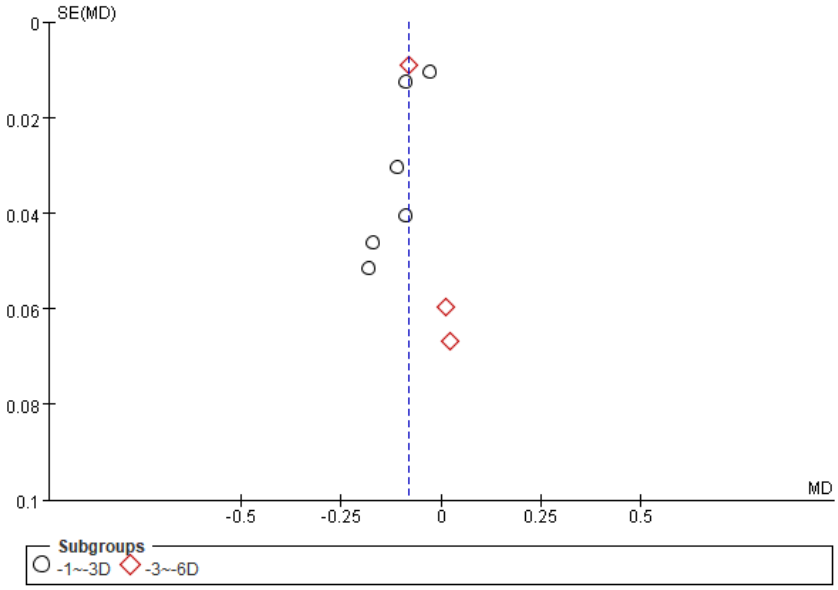

Figure 5

Funnel plot.