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Atropine in Ameliorating the Progression of Myopia in Children with Mild to Moderate Myopia: A Meta-Analysis of Controlled Clinical Trials

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Abstract

Objectives: Myopia is the most common ocular disorder associated with increasing risk for chorioretinal degeneration, retinal detachment, and other vision-threatening abnormalities worldwide. Recently, atropine has been becoming a focus of attention due to its role in ameliorating the myopia progression in children. This meta-analysis was conducted to address the efficacy and safety of atropine on myopia in children and the dose–response relationship between atropine and annual rate of myopia progression.
Methods: Controlled clinical trials were retrospectively analyzed to compare atropine and placebo for the treatment of myopia. The primary outcome measure was annual rate of myopia progression after daily atropine application over 1 year. Data were extracted from 6 randomized clinical trials and analyzed using standard meta-analysis and meta-regression methods.
Results: Comparing with placebo, the effect size of atropine for retarding myopia progression was 0.773 diopters (D)/year [95% confidence interval (CI): 0.699–0.848]. Regression model, $-0.728+1.281\log(\text{dose}+1)$, revealed the dose–response relationship between atropine and myopia progression. The estimate of effect for 0.05%, 0.1%, and 0.25% atropine was −0.665 (95% CI: −1.070 to −0.260), −0.606 (95% CI: −0.967 to −0.245), and −0.442 (95% CI: −0.701 to −0.183) D/year respectively, whereas that for 0.5% and 1% was −0.208 (95% CI: −0.435–0.018) and 0.160 (95% CI: −0.293–0.613), respectively, suggesting that myopia might deteriorate at low dose of atropine but not at 0.5% atropine and 1% atropine within the duration of 6–24 months. No serious adverse event was reported during the period of treatment. The major adverse reactions associated with 0.5% and 1% atropine were photophobia, glare, and recurrent allergic blepharitis. Photochromatic lenses or sunglasses with ultraviolet protection could be used to minimize the glare and photophobia.
Conclusion: In summary, 0.5% and 1% atropine was demonstrated to be effective and safe to ameliorate myopia progression in childhood with low-to-moderate myopia.

Introduction

Myopia is the most common ocular disorder worldwide affecting both children and adults. In the United States, the prevalence of myopia has been estimated at 20%. Nearly 1 in 10 (9.2%) American children have myopia between the ages of 5 and 17.[1–3] In southern China, Singapore, Hong Kong, and Taiwan, the prevalence of myopia ranges from 15% to 81% in Chinese children.[4–7] The myopia rates in East Asians, particularly the Chinese populations, are much higher than that in the European-derived population. Ethnic Chinese children living in Canada developed myopia and it was comparable in prevalence and magnitude to those living in East Asian countries.[8]

National myopia surveys conducted in Taiwan have found that prevalence of myopia was progressively increased over time. From 1983 to 2000, the prevalence of myopia for 7-year-old children was increased from 5.8% to 61% and that for 12-year-old children was increased from 36.7% to 61%, and the prevalence of high myopia [over −6.0 diopters (D)] for children between the age of 16 and 18 was increased from 10.9% to 21%. In addition, the age of onset

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became younger and younger, 11 years old in 1983, 10 years old in 1990, 9 years old in 1995, and 8 years old in 2000, with more rapid myopia progression rates in recent years.[8] Myopia was proposed to increase rapidly at an epidemic rate among adolescents of Chinese descent, particularly in East Asia.[9–11]

Myopia occurring at younger age will lead to greater risk of high myopia.[12,13] Patients with high myopia are more susceptible to develop ocular abnormalities, such as macular degeneration, retinal detachment, and glaucoma, which may lead to substantial visual loss.[14–16] Currently, myopia has become a severe worldwide public health problem, and it is urgent and critical to seek effective treatment to ameliorate the progression of myopia and reduce final refractive error among young children.

Atropine, a nonselective muscarinic antagonist, produces dilatation of the pupil (mydriasis) and prevents the eye from accommodating for near vision (cycloplegia). It is often used to aid eye examinations in young children. In recent years, atropine has drawn a focus of attention due to its role in controlling deterioration of myopia in children. The exact mechanism how atropine retards myopia progression is still unclear. It could be a direct effect of atropine on the eyeball to stop the eyeball elongation that occurs when myopia worsens or it could be an indirect effect by relaxing the focusing muscles of the eyes.[17–19]

Several clinical trials have been conducted to evaluate the efficacy and safety of eye drops with atropine in preventing the myopic deterioration in children. However, the results appear contradictory, suggesting both beneficial and detrimental effects. Chua (2006)[20] and Fan's (2007)[21] studies reported that myopic progression and the increase of axial length were significantly slowed down in patients treated with 1% atropine for more than 1 year, with the mean of annual reduction of spherical equivalent refractive errors (SERs) as 0.03 D and 0.06 D respectively. In addition, Fan (2007)[21] has also found that myopic progression was significantly ameliorated in the atropine group (0.06 ± 0.79 D) than that in the control group (-1.19 ± 2.48 D) ($P = 0.005$). The increase of axial length was also significantly smaller in the atropine group (0.09 ± 0.19 mm) than in the control group (0.70 ± 0.63 mm) ($P = 0.004$). However, other studies[22–27] indicated that atropine was hardly beneficial on refractive error with the annual magnitude of enhancement ranging from -0.04 D to -0.47 D.

In 2002, an evidence-based review[28] was designed to evaluate the efficacy of interventions such as eyedrops with atropine, bifocal lenses, or contact lenses in improving myopia in myopic children, but there was no sufficient information to support atropine eyedrops to prevent myopia progression. The conclusion of this review seemed not solid since it was based on the descriptive analysis of 3 relevant small size trials, not meta-analysis, a statistical method with high confidence to achieve scientific result, and the dose–response relationship has not been defined. Thus, it is necessary to evaluate the efficacy of atropine on ameliorating the progression of myopia with a well-conducted evidence-based analysis.

With the aim of precisely assessing whether atropine could slow children myopia progression, a standard meta-analysis with more updated evidence was performed to ascertain the effect size of atropine on controlling myopia and a random-effect meta-regression was conducted to explore the dose–response relationship of atropine in children with mild-to-moderate myopia.

Methods

Identification of clinical trials

Randomized clinical trials on myopia were retrieved from databases, including Cochrane Library, PubMed, the U.S. Food and Drug Administration Web site, European regulatory authorities, clinicaltrials.gov, manufacturers' product information sheets, and Chinese Biomedical Literature Analysis and Retrieval System for Compact Disc (CBMDISC) from 1952 to April 2009, with the key words atropine, treatment, myopia, short-sightedness, and near-sightedness. A total of 27 abstracts were found.

Trial selection

To be included in the meta-analysis, studies had to meet the following criteria:

(1) A randomized double-blind, single-blind, or open-label placebo-controlled clinical trial.
(2) Diagnosis compatible with spherical equivalent refraction (SER) more than -0.50 D as measured by cycloplegic autorefraction, under 16 years old.
(3) Primary measure of drug effect in terms of the annual rate of myopia progression.
(4) Secondary measure of drug effect in terms of the annual change of axial length.
(5) Trial with Jadad quality score ≥ 2.

All retrieved titles and abstracts were reviewed and checked each other by 2 independent reviewers to choose eligible trials in line with the first criterion listed above. After obtaining full reports of potentially relevant trials, the same reviewers independently assessed eligibility of full-text articles according to the criteria. Disagreements regarding eligibility were resolved by discussion with other reviewers through consensus.

Data extraction

Data were extracted from the published reports. For each trial, the following data were documented: design mode (parallel or crossover randomized clinical trial), masking patterns (double, single, or none), country of origin, study population, number of subjects, average age, the ratio of gender, level of myopia at baseline, primary variable, secondary variable, adverse reaction, and treatment regimen. The annual rate of myopia progression is defined as the change in SER relative to baseline after 1 year application of atropine or placebo. The positive value indicated myopia improvement and the negative value indicated myopia progression. The secondary variable is change of axial length during 1-year follow-up relative to baseline measured by A-scan ultrasonography, and the negative value means axial length decreased indicating myopia improvement; otherwise, the positive value means axial length increased hinting myopia progression. If there were multiple reports for a particular study, data from the most recent publication were extracted. When specific aspects of the data required clarification, the authors of the original articles were contacted to be consulted.

Statistical methods

1. Standard statistical model: fixed-effect model and random-effect model described by Whitehead (2002)[29] employed to pool the effect size and 95% confidence intervals (CIs) were calculated to evaluate whether atropine was effective using the primary variable of the mean of annual rate of myopia progression and the secondary variable of the mean of annual change of axial length. Mean difference was used to scale effect sizes of individual studies by subtracting the mean change in the control group from that in the treatment group. Larger the mean difference for the annual rate of myopia progression, better the treatment effect is. Zero value or negative value indicates that atropine could not slow the myopia progression. Smaller the mean difference for the secondary variable, better the treatment effect is. Zero value or positive value indicates atropine could not improve myopia.
2. Cochrane Q test was employed to test whether heterogeneity existed among the studies or not. The α level was set at 0.2. Between-studies variance was reflected by the value tau-squared. If the Q statistic was significant, a random-effect model was assumed. Funnel plot and Egger's test were used to detect the possibility of publication bias (Egger et al. 1997).[30]
3. A random-effect meta-regression (Berkey et al. 1995)[31] was performed to address dose–response relationships using mixed model. The estimation method was restricted maximum likelihood. For the dose–response analysis, if the control was not placebo in some study, the control group effect was excluded from the regression, but the treatment group was still included in regression.

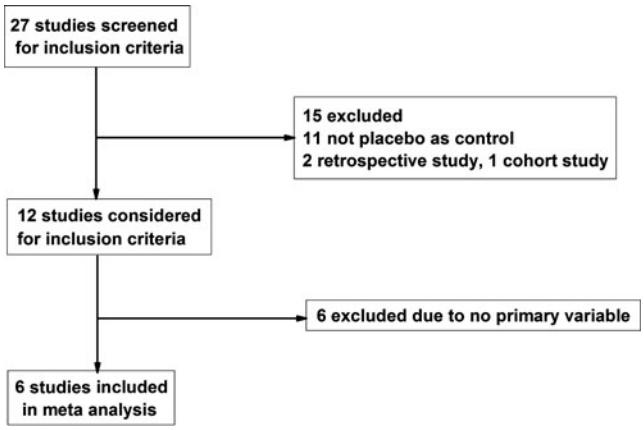

FIG. 1. The screening process of the eligibility of retrieved studies.

Software package SAS 9.13 was used to perform all statistical analyses. The α level was set to 0.05.

Results

Description of trials

Six clinical trials were selected from 27 studies according to inclusion and exclusion criteria. The process of study selection was showed in Fig. 1. Eight hundred twenty three participants were included in the standard meta-analysis. The number of patients in the individual studies ranged from 46 to 400. Study characteristics were listed in Table 1.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Study	*Countries and regions*	*Patient population*	*Randomization*	*Blinding*	*Intervention*	*Usage and treatment course (months)*
Liang (2008)	Taiwan	Mean age: 6–15, SER: > −0.5D	Yes	Single	0.25% Atropine 0.5% Atropine 0.25% Atropine + stimulation of auricular acupoints 1% atropine	Once every night, ≥6
Fan (2007)	Hongkong	Age: 5–10 Initial SER: > −3.0D	No	Single	blank	Once daily, 12
Chua, (2006)	Singapore	Age: 6–10, Initial SER: −1.0 to −6.0D	Yes	Double	1% atropine placebo 0.5% atropine + multifocal glasses	Once nightly, 24
Hsiao (2005)	Taiwan	Age: 6–13, Initial mean SER: −3.37D	Yes	Double	placebo + multifocal glasses placebo + single-vision lenses	Once per day at bedtime, 18
Shih (1999)	Taiwan	Age: 6–13, SER: −0.5 to −6.75D	Yes	Unknown	0.25% atropine 0.5% atropine 0.1% atropine 0.5% tropicamide 1% atropine	Once every night, 24
Yen (1989)	Taiwan	Age: 6–14, SER: −0.5 to −4.0D	Yes	Unknown	saline 1% cyclopentolate	Every other night, 12

SER, spherical equivalent refractive error.
D, diopters.

Table 2. Mean Changes of Myopia Progression in Each Study

Study	Concentration	Atropine group: No. of patients	Atropine group: Mean of change	Atropine group: SD	Control	Control group: No. of patients	Control group: Mean of change	Control group: SD	Difference between groups
Liang (2008)	0.5%	23	−0.150	0.150	Not placebo	—	—	—	—
	0.25%	22	−0380	0.320					
Fan (2007)	1%	23	0.060	0.790	Blank	23	−1.190	2.480	1.250
Chua (2006)	1%	200	0.030	0.500	Placebo	200	−0.760	0.440	0.790
Hsiao (2005)	0.5%	66	−0.160	1.261	Placebo	61	−0.920	1.328	0.760
	0.5%	41	−0.040	0.630	Tropicamide	49	−1.060	0.610	1.020
Shih (1999)	0.25%	47	−0.450	0.550					0.610
	0.1%	49	−0.470	0.910					0.590
Yen (1989)	1%	32	−0219	0.538	Saline	49	−0.914	0.581	0.695

The progression of myopia was defined as the change in SER relative to baseline. For this scale, positive value indicated myopia improvement and negative value indicated myopia progression. If the control was not placebo, then the data of control were not listed.
SD, standard deviation.

Data on annual rate of myopia progression were available from all 6 studies (Table 2). The progression of myopia was defined as the change in SER relative to baseline. For this scale, positive value indicates improvement in myopia and negative value indicates progression in myopia. Because only clinical trials with placebo control were eligible for standard meta-analysis, so 1 randomized, single-blinded, nonplacebo-controlled trial[32] was excluded from standard meta-analysis, but it was included in the analysis of dose–response relation. There were 3 dose groups in trial of Shih's study.[23] Each dose was considered as 1 independent trial, so standard meta-analysis was based on 7 clinical trials.

All included studies were parallel-group trials. Although randomization was not adopted in Fan's study (2007),[21] the goal of randomization was achieved by using restricted rule of matched-pair method during the enrollment period and there was no difference between treatment and control groups in patients' age, sex, and initial SER, which likely affected the final effect. In the clinical trial of Shih (1999),[23] tropicamide, which is an anticholinergic agent that produces short-acting mydriasis and cycloplegia in eye examination, was used as control. Since the effect size of 0.5% tropicamide was −1.06 D/year, similar to that of placebo,[21,23] and it was found to have no effect on myopia progression,[28,33–36] 0.5% tropicamide was considered as placebo in our study and Shih's study was included in the final analysis.

Effect of atropine on annual rate of myopia progression

Fixed-effect model showed the pooled mean difference of atropine versus placebo was 0.773 D/Year (95% CI: 0.699–0.848) (Fig. 2), indicating that atropine could slow the progression of myopia. Heterogeneity test was not significant ($\chi^2 = 8.01$, $P = 0.237$) and tau-squared was 0.005. Random-effect model showed that the corresponding effect size was 0.763 D/Year (95% CI: 0.655–0.872). Due to small between-study variance, the treatment effect size of the random-effect model was similar to that of fixed-effect model.

Egger test displayed that asymmetry was equal to −0.027 ($P = 0.976$), suggesting that publication bias was not confirmed. Funnel plot was drawn and shown in Fig. 3. The plot indicated that it was Fan's study (2007) probably leading to a phenomenon of large effect and small sample size.

Sensitivity analysis

When Fan's study (2007)[21] and Shih's study (1999)[23] were excluded individually from this study, the random-effect pooled estimate of 6 studies and 4 studies was 0.758 D/Year (95% CI: 0.645–0.870) and 0.783 D/Year (95% CI: 0.697–0.868), respectively, similar to that of all 7 studies. Hence, the original result was robust.

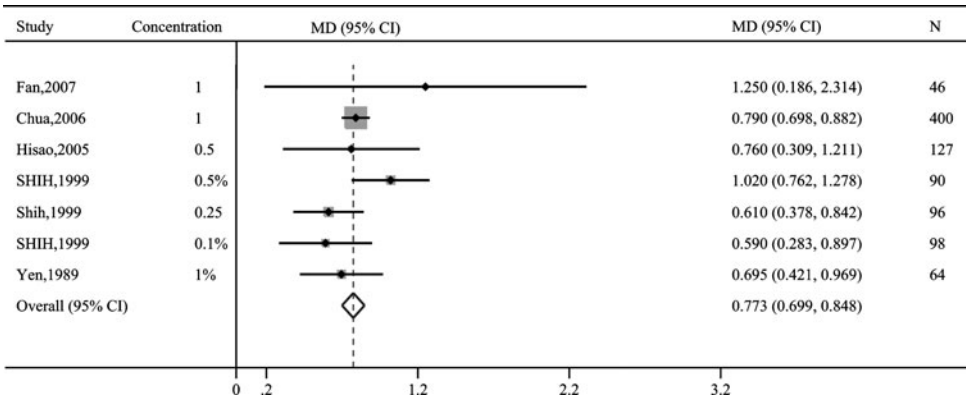

FIG. 2. The forest graph of effect size for atropine in ameliorating the progression of myopia. The horizontal lines denoted the 95% CI. CI, confidence interval. MD, mean difference.

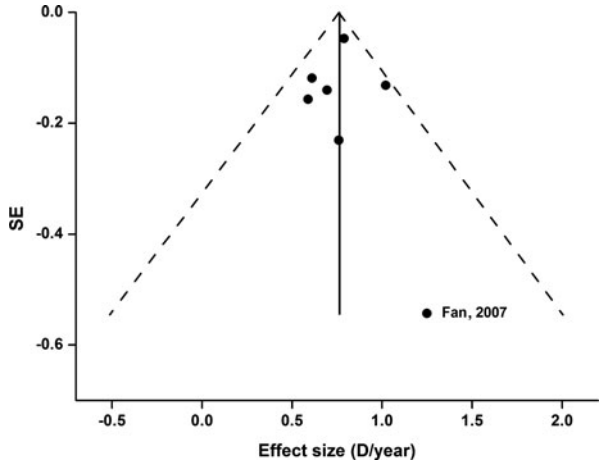

FIG. 3. The funnel plot of all trials included in meta-analysis on ameliorating progression of myopia.

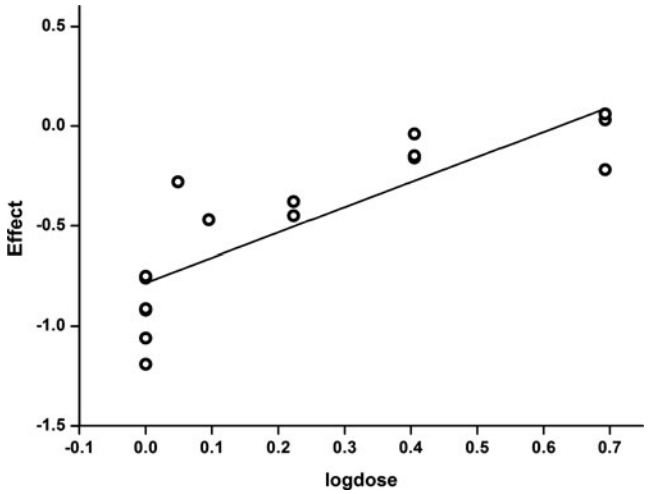

FIG. 4. Dose–response relation of atropine in ameliorating myopia based on random effect regression. Scatter points represented the observed value of effect. The predicted value of effect was on the line.

Dose–response relation for atropine

Dose–response relation between log term of doses (0.05% to 1%) and myopic change per year was established using random-effect regression model (Fig. 4). The regression model was $-0.728+1.281$ log (dose+1). The model was statistically significant with the *P* values of intercept and regression term as 0.025 and 0.029, respectively. The estimate of effect size for placebo was −0.728 D/Year (95% CI: −1.181, −0.274). The coefficient of log term dose was positive, suggesting that the effect of atropine was increased with dose. The predicted values for various concentrations were listed in Table 3.

Meta-analysis of changes in axial length

There were only 2 studies reporting the changes in axial length (shown in Table 4). Changes in axial length was defined as mean baseline value subtracted by mean end point value. Axial elongation-retarding effect size was calculated by subtracting the mean change in the control group from that in the treatment group. Negative value suggested the amelioration in the progression of myopia by using atropine. The higher the absolute value was, the better the improvement in myopia was. Heterogeneity test was significant ($\chi^2=3.71$, $P=0.054$)) and the tau-squared was equal to 0.027. Random-effect model showed that the corresponding effect size was −0.442 mm (95% CI: −0.698, −0.185) (Fig. 5), indicating that the axial length increase was significantly smaller in atropine group than in the control group.

Discussion

Our meta-analysis of 1-dimensional results indicated that the daily use of atropine over 1 year could ameliorate the progression of myopia in children. The pooled effect size was 0.773 D/Year (95% CI: 0.699–0.848). Dose–response relation was found between atropine and annual rate of myopia progression in regression model. The higher the dosage was, the slower the rate of myopia progression was. The results of dose–response model showed that the 95% CIs of predicted values of 0.05%, 0.1% and 0.25% atropine were −1.070 to −0.260, −0.967 to −0.245, and −0.701 to −0.183, respectively, suggesting that myopia degree was still keeping worsening upon these dosages. The predicted values (95% CIs) of 0.5% and 1% atropine were −0.208 (−0.435, 0.018) and 0.160 (−0.293, 0.613), respectively, and their 95% CIs contained 0, which indicated that these 2 doses could keep the myopia from getting worse.

No serious adverse event was reported during the period of treatment. The major adverse reactions associated with 0.5% and 1% atropine were photophobia, glare, blurred near vision, and recurrent allergic blepharitis,[4,20,23] with the rates ranging from 0.048% to 4.5%. These adverse reactions, which were associated with the cycloplegia induced by atropine, were temporary and reversible after cession of treatment.[36] No long-term adverse effects, including permanent paralysis of accommodation, retinal toxicity, and cataract, occurred after long-time treatment, with the median duration ranged from 18 weeks to 11.5 years.[37] In earlier studies, photophobia occurred in every child after the administration of 1% atropine, and most of them did not want to go outdoors and do physical training.[25] In recent studies, photochromatic lenses or sunglasses with ultraviolet protection were used to minimize the photophobia, glare, and potential toxicity to the retina and lens due to long-term dilation and exposure to ultraviolet light.[20,21] Thus, using atropine to ameliorate myopia progression for children was feasible in clinical setting.

The treatment duration is the major issue concerning the clinical application of atropine for myopia in children. Until now, the course of treatment has been 1 year in most of the studies, and the annual rate of myopia progression has been actually the change of myopia level at the end of 1-year

Table 3. The Estimates of Pooled Effect of Different Concentrations of Atropine on Myopia Progression Based on the Random-Effect Regression Model

Concentration	*Effect size (95% CI)*	P *value*
0.00%	−0.728 (−1.181, −0.274)	0.002
0.05%	−0.665 (−1.070, −0.260)	0.001
0.1%	−0.606 (−0.967, −0.245)	0.001
0.25%	−0.442 (−0.701, −0.183)	<0.001
0.5%	−0.208 (−0.435, 0.018)	0.071
1%	0.160 (−0.293, 0.613)	0.488

CI, confidence interval.

Table 4. Mean Changes of Axial Length in Each Study

Study	Atropine group			Control group			Difference between groups
	No. of patients	Mean of change	SD	No. of patients	Mean of change	SD	
Fan (2007)	23	0.090	0.190	23	0.700	0.630	−0.610
Chua (2006)	200	−0.140	0.280	200	0.200	0.300	−0.340

Changes in axial length was defined as mean baseline value subtracted by mean end point value. For this scale, negative value indicated myopia improvement and positive value indicated myopia progression.

treatment period, so it is not clear whether or not the progression of myopia would be further slowed down with the continuing treatment. There were few studies with the treatment duration >1 year or results from long-term follow-up. Chua[20] reported the mean change of myopia level at the end of first and second year of treatment: the mean rate of myopia progression was higher in the second year than that in the first year (−0.28 D/year vs. 0.03 D/year), but it was still significantly lower than that in the placebo group (−1.20 D/year). In 2009, this team reported the results of 1-year follow-up of the same study.[35] After cessation of treatment, the mean rate of myopia progression was faster in the first 6 months than that in the second half of the year (−1.51 D/Year vs. −0.76 D/year). Contrasting to the mean rate during the treatment period (0.03 D/Year, −0.28 D/Year), rebound phenomenon occurred after the cessation of atropine. Interestingly, in the placebo group, the mean rate of myopia progression after cessation was slower than that in placebo treatment period (−0.40 D/Year and −0.38 D/Year after cessation vs. −0.76 D/Year and −1.20 D/Year for the first and second year of the placebo treatment), proving the double exponential growth function of myopia progression, which was composed of 4 stages, including the onset stage of myopization, rapid acceleration, deceleration, and stabilization.[12] Contrast to the placebo group, the process of rapid development of myopia was effectively blocked in atropine group although rebound phenomenon was observed after atropine cessation; subsequently, the mean rate of progression became slower and the mean refractive error was lower than that in placebo-treated eyes at the end of the third year. If 1 more year follow-up could be carried out, it would be interesting to learn whether or not the myopia would enter into deceleration phase. If the deceleration occurred, it was likely that the mean of final refractive error in atropine group was lower than that in placebo group. In another long-term study, Kennedy[37] reported that the final refractive error standardized to the age of 20 years was significantly lower in the atropine group (−2.79 D) than that in the control group (−3.78 D) and the beneficial effects of atropine maintained after treatment had been discontinued. This hypothesis should be confirmed by further long-term follow-up data of well-conducted, large-scale, randomized controlled trials.

Fan's study[21] was not a randomized clinical trial. It was defined as an interventional case-control study by authors themselves. In fact, it was known as "quasi-experimental" cohort study.[38] This study used matching method to balance the potential factors that may influence the result. The funnel plot showed that this study was the reason resulting in a phenomenon of large effect and small sample size, but this phenomenon did not magnify the effect size according to the result of sensitivity analysis. Recent study[39] highlighted that the results from well-conducted cohort studies often yield similar results to randomized controlled trials (RCT) and have better external validity. Our study also validated this conclusion.

The results of meta-analysis of the change of axial length, which was based on only 2 studies, indicated that the increase in axial length was smaller in atropine group than that in control group. It could not be confirmed whether or not atropine slowed myopia progression down by ameliorating axial length elongation based on so few studies. Much more studies would be warranted.

In conclusion, this meta-analysis, which was performed with 6 studies (5 randomized controlled trials and 1 "quasi-

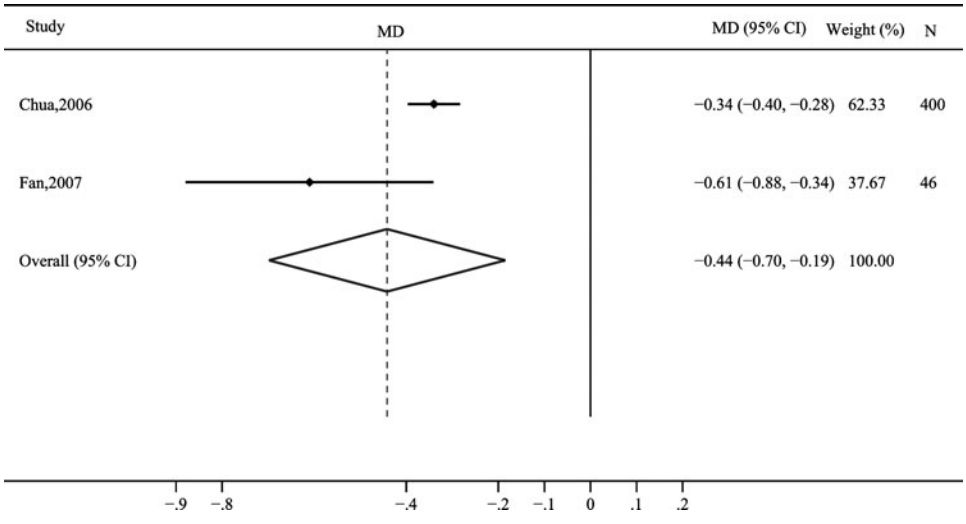

FIG. 5. The forest graph of effect size for atropine showing the axial elongation.

experimental" cohort study), suggested that administration of atropine for >6 months was effective to ameliorate myopia progression in children with low and moderate myopia, and the higher the dosage was, the slower the rate of myopia progression was. Most observed adverse reactions were caused by cycloplegia induced by atropine, which were mild, temporary, and reversible after cession of treatment. More convincing evidence could be expected from the phase II and phase III trial in Singapore, which has not yet been published.

Acknowledgments

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Author Disclosure Statement

No competing financial interests exist.

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