LITERATURE REVIEW

EFFICACY OF ATROPINE SULPHATE EYE DROPS IN CONTROLLING MYOPIA PROGRESSION: A REVIEW

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ABSTRACT

Introduction: *Myopia is major public health concern that has become increasingly common. Severe myopia has become one of the main causes of untreatable vision loss throughout the world, often due to its irreversible complications. Studies shows atropine can reduce myopia progression in children. Currently, there are no guidelines for the use of atropine specifically to control myopia progression. This study was made to review the efficacy of various atropine doses in controlling myopia progression.*

Methods: *Literature searching was conducted in four online databases (PubMed, EBSCOhost, ScienceDirect, and Scopus. Search terms included were "Atropine" and "Myopia". Validity was assessed using assessment tool from Cochrane. Efficacy was evaluated using myopia progression in spherical equivalent per year and axial lengthening per year.*

Results: *Sixteen randomized controlled trial studies fulfilled our inclusion criteria and eligibility screening. Overall, atropine shows favorable results in spherical equivalent progression (D/year) compared to control, with SMD = -1.13, 95% CI (-0.58, -1.68). Less axial elongation (mm/year) was observed in atropine group, with SMD = -1.28, 95% CI (-0.18, -2.37). Atropine 0.01% concentration shows overall significantly better myopia progression and axial lengthening compared to control, with SMD = -0.76, 95% CI (-0.08, -1.44) and SMD = -0.63, 95% CI (-0.14, -1.12), respectively. Higher atropine doses showed larger effect sizes with higher occurrence of adverse effects.*

Conclusion: *Atropine eye drops in various doses shows overall effective myopia control in spherical equivalent and axial lengthening. Atropine 0.01% has significant myopia progression inhibition with less adverse effects than higher doses.*

Keywords: *myopia, near-sightedness, atropine, myopic progression*

INTRODUCTION

It is estimated that over 285 million people in the world have vision impairment and that 42% of this is due to uncorrected refractive errors. Epidemiological studies estimates that myopia affects 1.4 billion people worldwide in year 2000 and 4.9 billion people is projected to be myopic in year 2050. Studies shows east Asian countries such as China, Japan, the Republic of Korea, and Singapore have a higher prevalence of myopia, approximately 50%, than western countries such as Australia, Europe, and North America.[1–3] This mirrors the trend with children in many countries spending considerable amounts of time engaged in reading, studying, or – more recently – using computer and smartphones which probably explain the myopia epidemic.[4]

Various approaches to control myopia progression have been evaluated over the past few decades which was based on different hypotheses of myopia progression such as accomodative lag asssociated with myopia and peripheral defocus. Some optical approaches such as undercorrection and bifocal lens theoretically should reduce myopia progression, but studies showed either increase in myopia progression or not statistically significant improvement. Standard rigid gas permeable lenses do not reduce myopia progression, but bifocal contact lens and orthokeratology shows some results in reducing myopia progression. A number of pharmacologic interventions also have been investigated, in which Atropine is the most common treatment used in a number of Asian countries.[1]

Atropine, an antimuscarinic receptor blocker, works by inhibiting stimulation of neurotransmitter acetylcholine. The evidence showed Atropine can reduce myopia progression in children in a dose related manners but side effects and rebound phenomenon are observed in higher doses. Lower doses such as 0.01% (contrary to usual clinical dose of 1%) showed reduce common side effects with some reduction to myopia progression. Atropine eye drops were recently approved by Food and Drug Administration for long term-amblyopia therapy in children, but currently there are no regulatory approval for the use of atropine to slow myopia progression.[1] This literature review aims to evaluate the efficacy of atropine eye drop in various doses in reducing myopia progression.

METHODS

Literature searching was conducted in four online databases (PubMed, EBSCOhost, ScienceDirect, and Scopus). Search terms included were “Atropine” and “Myopia”. There was no limitation in the publication year, but we only include article written in English. Articles were considered eligible to be reviewed if met following criteria: (1) studies have to include atropine eye drop as the sole main therapy or combined with other therapy; (2) control group have to not be given atropine eye drop; (3) have myopia progression data as main or secondary outcome, either in spherical equivalent mean difference or myopic progression rate OR have axial length data as main or secondary outcome, either in axial length mean difference or progression rate; (4) minimal follow up of 12 month; (5) randomized controlled trial as study design. The final search date was October 5th 2022. Data then extracted from each study, including: author, year published, basic characteristics, follow up period, treatment arms, myopia progression (spherical equivalent per year), and axial length progression per year. Adverse effects was recorded if the study presented the data.

RESULTS

Using relevant search terms in previously mentioned databases, a total of 16 articles are included in this study. Every articles is a randomized controlled trial studies with treatment group given solely atropine eye drop in various doses or in combination with orthokeratology. Some articles which reports previous results of the same study was excluded and newest articles is included instead. Literature searching process based on PRISMA Flow Diagram can be seen in **Figure 1**.

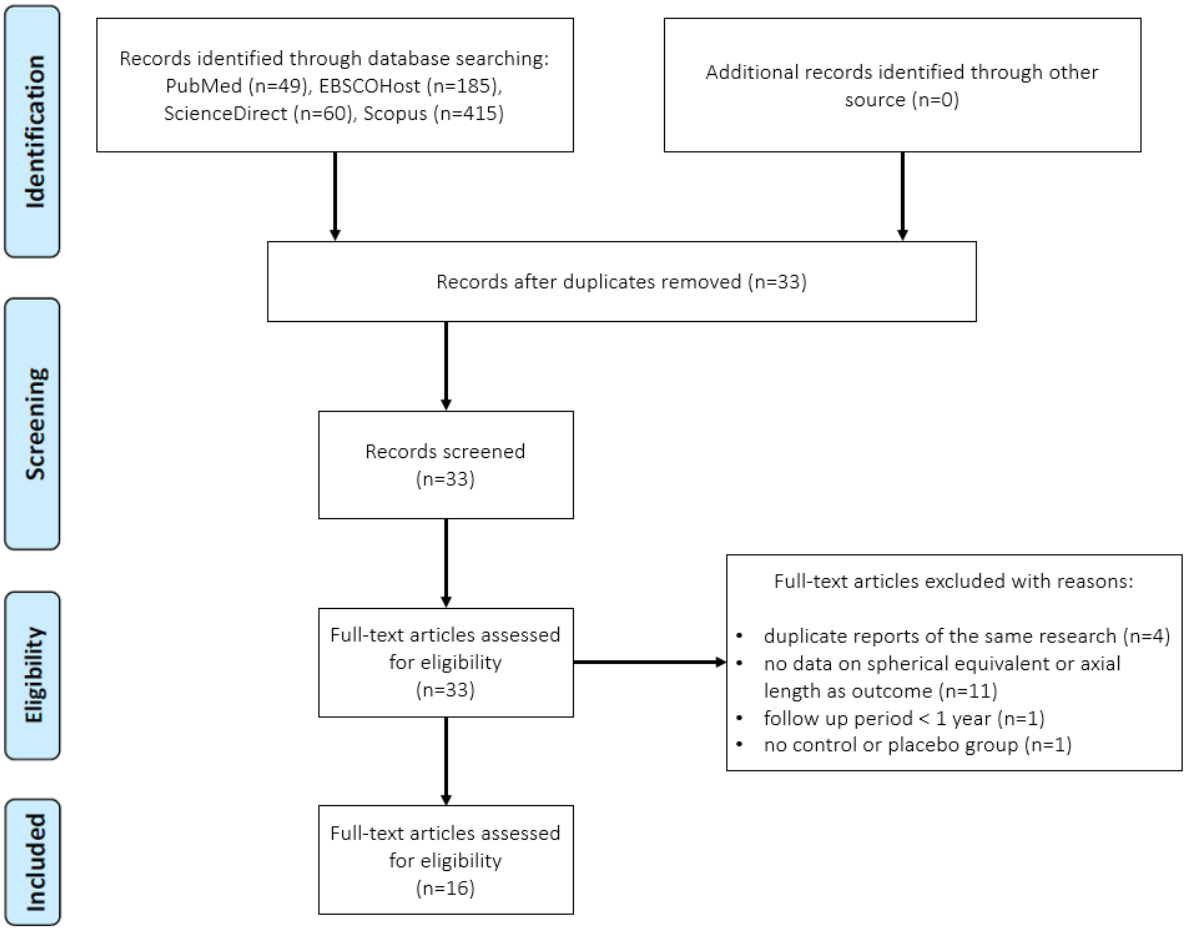

Figure 1. Literature Searching Process (PRISMA Flow Diagram)

All studies are assessed as level 2 evidence according to oxford centre of evidence based medicine criteria. We appraised the risk of bias of each studies using criteria from Cochrane Handbook, including: random sequence generation, allocation concealment, selective reporting, blinding of participant and outcome, incomplete outcome data, and other biases. The results of each articles assessment can be seen in **Figure 2** below.

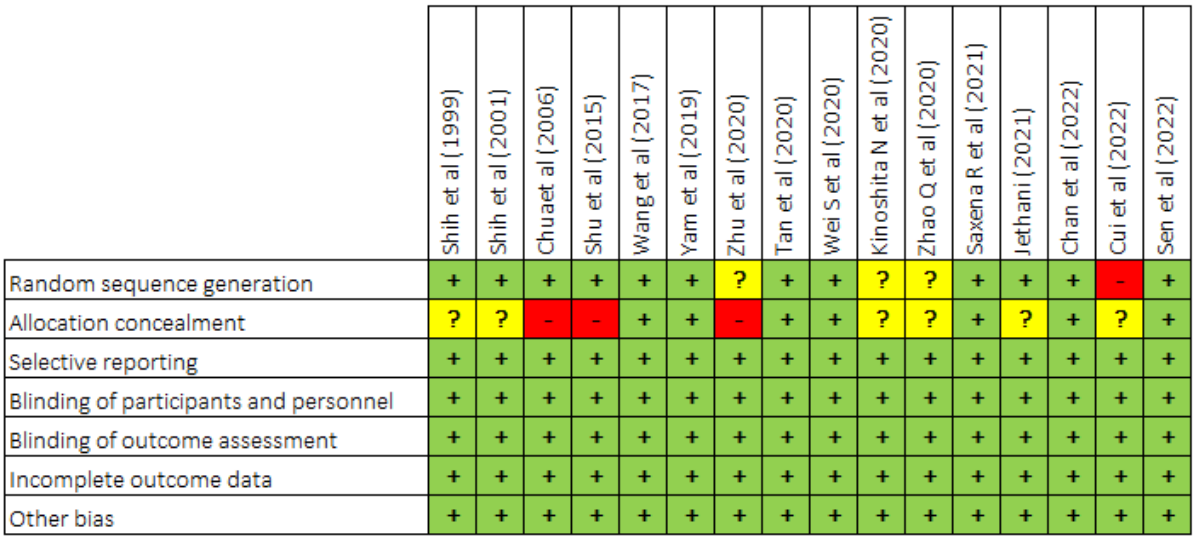

Figure 2. Risk of bias assessment

Eligible articles to be reviewed were published from 1999 to 2022. All studies were conducted in Asia with participant ranges from 8 to 14 years old. All studies reported baseline spherical equivalent ranges from mild to moderate myopia, no studies reported participant with high myopia. Most studies reported baseline axial length, with two studies didn't include the data. Follow up reported ranges from 12 to 48 months. The details of base characteristic of each studies can be seen in **Table 1**.

Table 1. Characteristics of each studies included in this review

	Study (year)	Location	Arms	Size	Age (year)	Baseline Spherical Equivalent (D)	Baseline Axial Length (mm)	Study Period (month)
1	Shih (1999)[5]	Taiwan	Atropine 0.5% Atropine 0.25% Atropine 0.1% Control	41 47 49 49	9.8 9.7 8.9 8.3	-4.89 (2.06) -4.24 (1.74) -4.41 (1.47) -4.5 (1.86)	- - - -	24 24 24 24
2	Shih (2001)[6]	Taiwan	Atropine 0.5% Control	66 61	- -	-3.28 (0.13) -3.34 (0.14)	24.62 (0.10) 24.80 (0.09)	18 18
3	Chua (2006)[7]	Singapore	Atropine 1% Control	200 200	9.2 9.2	-3.58 (1.17) -3.36 (1.38)	24.80 (0.84) 24.80 (0.83)	24 24
4	Shu (2015)[8]	China	Atropine 1% Control	68 64	9.91 (1.36) 9.72 (1.40)	-1.23 (0.32) -1.15 (0.30)	23.75 (0.12) 23.72 (0.12)	12 12
5	Wang (2017)[9]	China	Atropine 0.5% Control	63 63	9.1 (1.4) 8.7 (1.5)	-1.3 (0.4) -1.2 (0.3)	24.1 (1.0) 23.8 (0.9)	12 12
6	Yam (2019)[10]	China	Atropine 0.05% Atropine 0.025% Atropine 0.01% Control	93 86 91 80	8.32 (1.71) 8.48 (1.69) 8.35 (1.8) 8.41 (1.87)	-3.93 (1.63) -3.88 (1.83) -3.99 (1.94) -4.91 (1.96)	24.88 (0.91) 24.94 (0.9) 24.78 (1.02) 24.96 (1.02)	24 24 24 24
7	Zhu (2020)[11]	China	Atropine 1% Control	262 308	9.11 (0.09) 9.19 (0.14)	-3.82 (0.44) -3.74 (0.51)	24.93 (0.21) 24.91 (0.18)	48 48
8	Tan	China	Atropine 0.01%	29	9.0 (1.2)	-2.65 (0.92)	24.43 (0.62)	12

	(2020)[12]		Control	30	9.0 (1.2)	-2.84 (0.96)	24.43 (0.81)	12
9	Wei	China	Atropine 0.01%	76	9.44 (1.80)	-2.52 (1.33)	24.50 (0.76)	12
	(2020)[13]		Control	83	9.84 (1.53)	-2.64 (1.46)	24.69 (0.97)	12
10	Kinoshita	Japan	Atropine 0.01%	38	10.33 (1.59)	-2.60 (0.58)	24.69 (0.58)	48
	(2020)[14]		Control	35	10.37 (1.65)	-2.72 (1.31)	24.86 (0.81)	48
11	Zhao	China	Atropine 0.01%	20	9.65 (1.53)	-1.98 (0.45)	24.17 (0.68)	12
	(2020)[15]		Control	20	9.7 (1.49)	-1.93 (0.74)	24.28 (0.83)	12
12	Saxena	India	Atropine 0.01%	47	10.6 (2.2)	-3.5 (1.3)	-	12
	(2021)[16]		Control	45	10.8 (2.2)	-3.7 (1.3)	-	12
13	Jethani	India	Atropine 0.01%	30	7.7 (2.1)	-0.72 (0.3)	20.8 (0.6)	12
	(2021)[17]		Control	30	7.2 (1.9)	-0.69 (0.4)	21.0 (0.5)	12
14	Chan	China	Atropine 0.01%	34	8.6 (1.0)	-1.88 (1.08)	24.17 (0.79)	18
	(2022)[18]		Control	27	8.4 (0.8)	-1.74 (0.71)	24.09 (0.74)	18
15	Cui	China	Atropine 0.02%	105	9.6 (1.8)	-2.81 (0.47)	24.61 (0.69)	24
	(2022)[19]		Atropine 0.01%	106	9.4 (1.7)	-2.76 (0.26)	24.6 (0.63)	24
			Control	89	9.3 (1.4)	-2.66 (1.39)	24.54 (0.69)	24
16	Sen	India	Atropine 0.01%	73	-	-3.92 (1.00)	24.54 (0.64)	24
	(2022)[20]		Control	72	-	-4.05 (1.25)	24.58 (0.79)	24

Efficacy of Myopia Progression Control

Fifteen studies reported on myopia progression (D/year) data. Eight type of atropine doses was studied, with Atropine 0.01% studied the most in nine studies. The overall heterogeneity I^2 = 97% and subgroup analysis was performed using random effect model. In overall results, better control on myopia progression was shown in groups receiving atropine treatment (SMD = -1.31; 95% CI = -0.58, -1.68). There is overall statistical difference between treatment and control groups ($p<0.001$). More prominent myopia control are shown in higher doses of atropine, such as atropine 1% (SMD = -1.26; 95% CI = -0.54, -1.97) and atropine 0.5% (SMD = -3.10; 95% CI = -1.14, -5.06) compared to lower doses such as atropine 0.01% (SMD = -0.76; 95% CI = -0.08, -1.44). Forest plot of the studies can be seen in **Figure 3**.

Efficacy of Axial Lengthening Control

Thirteen studies reported on axial length progression (mm/year) data. Six type of atropine doses was included. The overall heterogeneity is 99.3% and subgroup analysis was performed using random effect model. Overall, there were less axial lengthening in atropine group than in control group (SMD = -1.28; 95% CI = -0.18, -2.37). Similar with myopia progression results, there are trend of bigger effect size in higher atropine concentration such as atropine 1% (SMD = -1.95; 95% CI = -0.92, -2.99) with lesser effect size on atropine 0.01% (SMD = -0.63; 95% CI = -0.14, -1.12). Forest plot of axial lengthening can be seen in **Figure 4**.

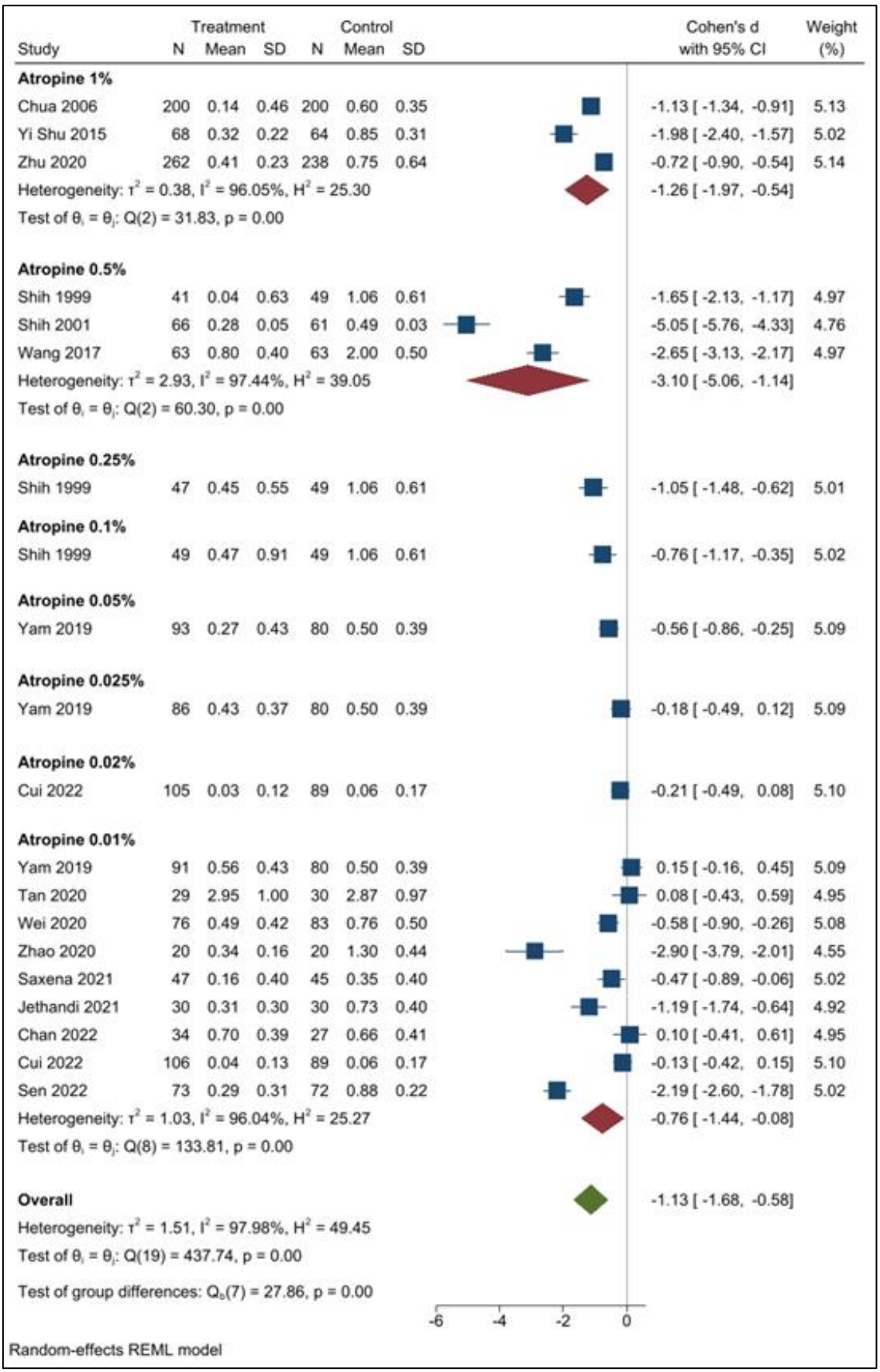

Figure 3. Various atropine doses effect on myopia progression. Negative value indicate better myopia control (less spherical equivalent progression)

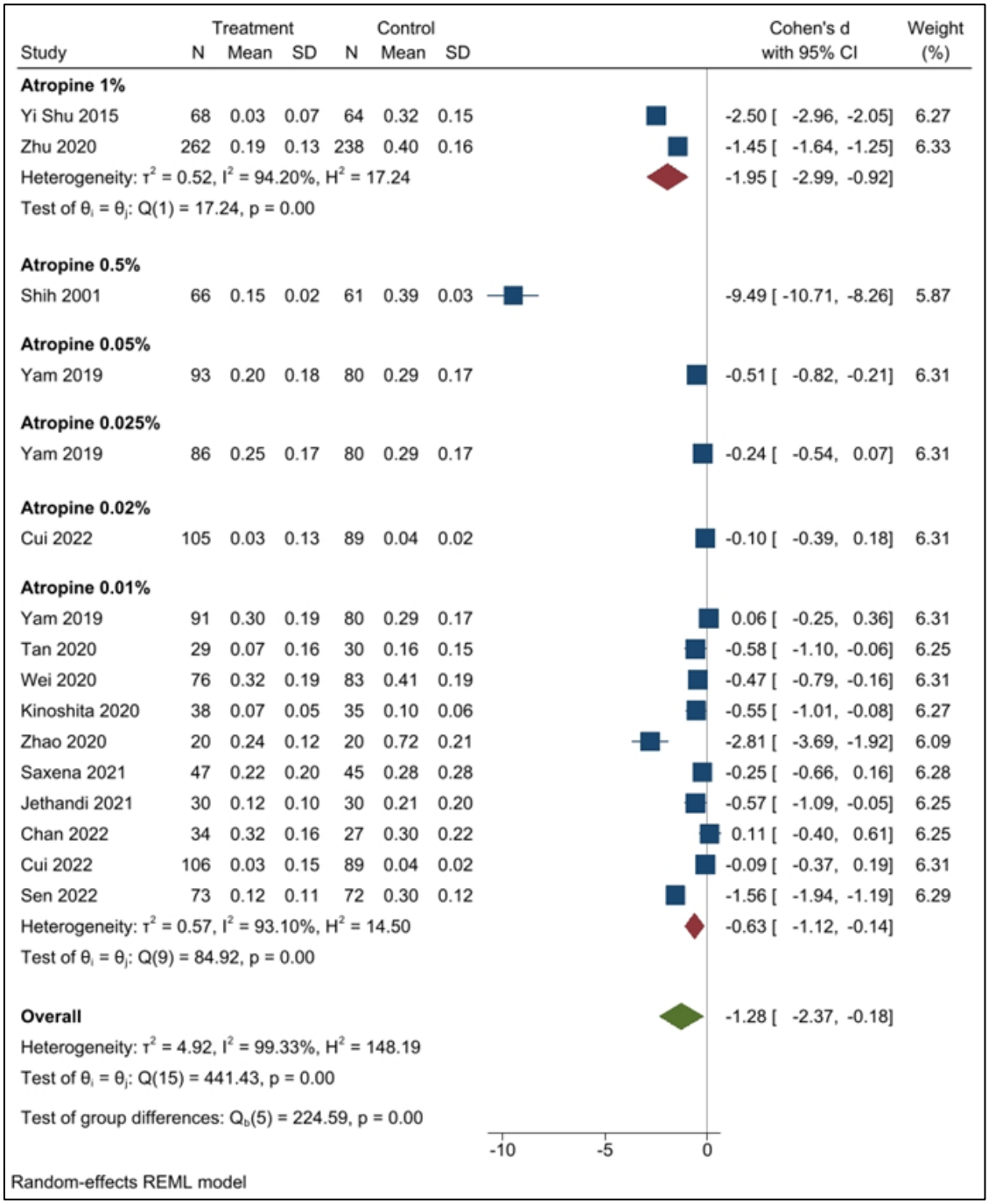

Figure 4. Various atropine doses effect on ocular axial length progression. Negative value indicate less axial lengthening

Adverse Effects

There were eleven studies which specifically reported their adverse effects findings. The most common adverse effects are photophobia which were found more in higher atropine concentration, as much as 62% occurence in atropine 1%. In lesser doses, photophobia is still the most common complaint but found less often. Most studies reported photophobia complaint receding after 3 months or 1 year use of atropine. The details of adverse effects found can be seen in **Table 2** below.

Adverse effect of Atropine 0.01% in combination with Ortho-K was reported in three studies. Tan, et al[12] reported one incidence of bacterial conjunctivitis in both treament and control arm. Kinoshita, et al[14] reported 1 incidence of infiltrate keratitis in control arm. Zhao, et al[15] reported decreasing values of tear break up time (TBUT) in the first three months in treatment arm with Ortho-K and Ortho-K + Atropine 0.01% group although the TBUT values is back to original level in 6 month follow up.

Table 2. Adverse effects and complication observed in various atropine doses

Study	Number of Subjects	Side Effect Reported
Atropine 1%		
Chua (2006)	200	Allergic reactions (4.5%). Glare (1.5%). Blurred near visions (1%)
Zhu (2020)	262	Photophobia 62.12% Blurred near vision 19.70% Headache 11.82% Allergic reaction 0.9% Eye irritation 18.5% Conjunctivitis or Blepharitis 5.45%
Atropine 0.5%		
Shih (1999)	41	Photophobia complaint at the beginning, but 78% had no complaint of light sensitivity after 3 months. One child had recurrent allergic blepharitis
Atropine 0.25%		
Shih (1999)	47	All subjects had no complaint of photophobia or near work problems after 4 weeks
Atropine 0.1%		
Shih (1999)	49	All subjects had no complaint of photophobia or near work problems after 4 weeks
Atropine 0.05%		
Yam (2019)	93	Photochromic glasses needed 31.2%. Progressive glasses needed 1.1%. Photophobia with photochromic glasses 4.3%. Photophobia without photochromic glasses 4.3%
Atropine 0.025%		
Yam (2019)	86	Photochromic glasses needed 44.2%. Progressive glasses needed 1.2%. Photophobia with photochromic glasses 1.2%. Photophobia without photochromic glasses 3.5%
Atropine 0.02%		
Cui (2022)	105	Photophobia (23%), disappeared in 2nd year
Atropine 0.01%		
Yam (2019)	91	Photochromic glasses needed 34.1%. Progressive glasses needed 2.2%. Photophobia with photochromic glasses 1.0%. Photophobia without photochromic glasses 5.5%
Wei (2020)	76	5 children reported photophobia, 3 children developed allergic conjunctivitis
Zhao (2020)	20	No side effects reported
Jethani (2021)	30	Allergic reactions (3.33%)
Cui (2022)	106	Photophobia (24%), disappeared in 2nd year
Sen (2022)	71	No side effects reported
Atropine 0.01% + Ortho K		
Tan (2020)	29	1 subject developed bacterial conjunctivitis. 2 subject complained sensitivity to light after waking up for less than half an hour.
Kinoshita (2020)	38	No side effects reported
Zhao (2020)	20	Decreased mean TBUT values in the first 3 months

DISCUSSION

Myopia has become a significant global public health and socioeconomic problem. According to studies, there are approximately 2 billion people with myopia worldwide and this number is predicted to increase to 5 billion people by 2050. Furthermore, the prevalence of childhood myopia is more prevalent in East Asian countries (49.7-62.0%) compared with other countries (6.0-20.0%).[4,21] These people are subjected with higher risk of debilitating pathologic condition such as retinal detachment, cataract, and glaucoma. World Health Organization predicted that by reducing the rate of myopia progression by 50% could reduce the prevalence of high myopia by up to 90%.[1,21]

The pathogenesis of myopia in human is still not fully understood.[21,22] Several studies in animal models shed some insight by inducing hyperopic defocus through negative lens that there are choroidal thinning and axial elongation associated with scleral remodelling, particularly at the posterior pole.[23,24] Interestingly, this process is preserved even after the optic nerve is severed, suggesting local control of eye shape.[21,25] The growth of human eye is also believed to be modulated by an active visual feedback from the hyperopic refractive error in neonatal eyes.[21]

Atropine, a non selective muscarinic acetylcholine receptor (mAChR) antagonist, is the only drugs which has been shown to significantly reduce myopia progression in clinical trials.[22,25] Atropine is initially thought to work by blocking accomodation. This theory has since been disproved in animal studies since Atropine also reduces myopia in chick eyes which cilliary muscle contain nicotinic receptors instead of mAChR.[21] Thus Atropine is likely to act at the retina itself and not through the accomodation system. There is also possibility that Atropine did not inhibit myopia through mAChR itself but through other non-muscarinic pathways.[25,26]

From the studies we reviewed, we found all studies consistently reported less spherical equivalent progression in treatment arms with atropine compared to control arms - eventhough some studies showed no statistical test result or statistically insignificant results (**Figure 3**). The same results can be seen in axial length elongation data (**Figure 4**). The effect of myopic inhibition is shown regardless of the subject baseline spherical equivalent as low myopia or high myopia as the effect can be seen in study by Shu, et al[8] and Wei, et al[13]. We can also observed dose dependent responses between the inhibition effect of spherical equivalent and axial length progression in the studies – with subjects given higher concentration dosage of atropine had the larger inhibition effect. However, other studies with follow up more than one year and including washout period such as Chia, et al[27] shows rebounding phenomenon which

must be considered in determining the optimal doses. The changes noted could be explained by the pharmacologic effect of Atropine on actively growing myopic eyes. When Atropine is withdrawn there may be sudden growth spurt as the inhibitory action is released. Higher doses of Atropine effect on biochemical steps in modification and regulating eye growth may be more complex and not fully understood.[27–29]

Orthokeratology, an optical method that employs reverse geometry-designed rigid oxygen-permeable contact lens, is a promising treatment to myopia due to the ability of allowing corneal epithelial redistribution when worn at night. Several studies we reviewed combined the use of Ortho-K with Atropine 0.01% dose.[12,14,15] All of them consistently reported better myopia progresssion inhibition in combination group compared to Ortho-K only group. The use of combination therapy is theoretically promising because of the difference mechanism of Ortho-K and Atropine works to slow down myopia progression – at cornea level and axial length progression inhibition respectively.

The most common adverse effect observed from studies is light sensitivity and near vision disturbances. This is more pronounced in studies using higher concentration of atropine (1% and 0.5%). Lower concentration of atropine gave lower incidence of this adverse effect. Interestingly, Yam et al, the only study that tried to provide photochromic glasses and near vision glasses to the subjects, reported the higher need of photochromic glasses in all spectrum of subjects regardless of atropine concentration received. This report suggested that as light sensitivity is a subjective symptom, it is adviseable to be ready to provide photochromic glasse to patient receiving Atropine treatment regardless of the initial complaint. Other common adverse effect including allergy to atropine medication. Study reported that allergic reactions to atropine eye drops is dose dependent response with higher doses results in more severe reactions. There are reports of reintroducing atropine in lower doses without eliciting allergic reactions.[30]

This review showed that various doses of atropine sulphate eye drop have inhibiting effect in myopia progression, not only in spherical equivalent, but also axial elongation. Higher concentration of atropine have better inhibiting effect sizes but also more adverse effects. Low concentration atropine such as 0.01% have statistically significant effect on myopia progression inhibition and also lesser adverse effects observed which may be the optimal dose in the time of writing of this review.

CONCLUSION

Atropine sulphate eye drops showed significant effect in reducing myopia progression in various doses. Low concentration atropine, such as 0.01% may be the optimal doses considering signiciant effect size and less adverse effect than higher concentration doses.

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