Assessing Low-Concentration Atropine in Myopia Progression: A Systematic Review

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ABSTRACT

Objective: Low-concentration atropine (LCA) eye drop is used as a promising treatment for the management of myopia but its effectiveness has not been widely evaluated. Therefore, this study aimed to analyze the efficacy of LCA eye drop for myopia progression.

Materials and Methods: This review was conducted following the PRISMA guidelines and a comprehensive literature search was performed on 3 online databases including PubMed, Cochrane, and ProQuest. The keywords used included 'Low-concentration atropine eye drop', 'Atropine', 'Eye Drop', 'Myopia', and their Mesh. All studies included were available in English and full-text format. Myopia progression rates were analyzed from all studies, and Rayyan, an online-based tool was used in the screening process.

Results: The results showed that 3 randomized control trials (RCT), 2 cohort studies, and 3 case reports with a total of 1389 participants were analyzed. The majority studies were conducted in Asia, while one RCT was performed in Australia. The participants ranged from 4-12 years old, while atropine eye drop concentrations used were 0.01%, 0.025%, 0.05%, 0.1%, 0.125%, and 0.2%. All studies showed a slower progression rate of myopia in the atropine group compared to the control (-0.31 D vs. -0.90 D; -0.05 D vs. -1.05 D; -0.27 D vs. -0.81 D; -0.28 D vs. -0.54 D; -0.36 D vs. -0.90 D;−0.31 D vs. −0.76 D; -0.31 vs. -0.53 D; -0.38 D vs. -0.55 D) with $P < 0.05$.

Conclusion: LCA eye drop showed promising effects in slowing myopia progression. However, further investigation is needed, particularly in non-Asian countries.

Keywords: Low-concentration atropine eye drop; myopia; children (Siriraj Med J 2023; 75: 902-908)

INTRODUCTION

Myopia is one of the most frequent refractive disorders and is expected to become increasingly prevalent globally, affecting nearly 5 billion people with 1 billion having high-severity cases.[1] The prevalence among 6-7-year-old children in Taiwan and Singapore ranges from 20% to 30%, reaching levels of 84% among high school students in Taiwan.[2] This growing incidence indicates a rising epidemic in developed regions of East and Southeast Asia,[3] making it a significant public health issue that should not be underestimated.

Myopia is characterized by abnormal elongation of the eyeball, even with the use of refractive lenses or surgical interventions. The severity can ultimately lead to blindness and significantly affect children's quality of life.[2] Several methods have been implemented to manage the progression of myopia, including progressive bifocal glasses, peripheral defocus and contact lenses, orthokeratology, multifocal contact lenses, and pharmacological agents.[4] Atropine, a nonselective muscarinic antagonist, has shown efficacy in inhibiting myopia progression, with several studies examining different concentrations, from the lowest (0.01%), to moderate (0.01%-0.5%), and high (1%).[5,6]

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Previous studies reported that the use of high-concentration atropine may result in adverse effects such as blurred vision, reduced accommodation, and glare. Optimal concentrations of low-concentration atropine (LCA) were proposed for inhibiting myopia progression, but the efficacy has not been widely evaluated. Therefore, this study aimed to analyze the efficacy of LCA eye drop in inhibiting myopia progression.

MATERIALS AND METHODS

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.[7] A comprehensive literature search was performed on 3 online databases namely PubMed, Cochrane, and ProQuest. The inclusion criteria for studies included (1) the population focused on children with myopia, and (2) used LCA eye drop. Meanwhile, the exclusion criteria were: (1) studies not conducted written English language, (2) full publication was unavailable, and (3) reviews. Three independent reviewers conducted the search, and the keywords used were 'Low concentration atropine eye drop', 'Atropine', 'Eye Drop', 'Myopia', and their corresponding Mesh terms. The search, conducted up to March 17th, 2023, used terms adapted to fit the requirements of each database, without any publication year filter. The screening process was carried out with Rayyan, an online-based tool.[8] Blinding was maintained until each reviewer completed the screening process, and any disagreements were resolved by discussion.

The myopia progression in children was analyzed across all included studies. This condition was defined as spherical equivalent (SE) change after 12 months of treatments. The following data were extracted from each study: authors, year of publication, design, country, number of samples, patient demographics, intervention given, comparison, myopia progression rate, and side effects.

The risk of bias assessment was conducted by three reviewers using version 2 of the Cochrane risk of bias tool (RoB 2) for randomized controlled trial (RCT) included in this review.[9] The quality of the case-control and cohort studies was assessed using the Newcastle-Ottawa Scale.[10] All reviewers independently conducted the assessment and extracted the data.

RESULTS

The search identified 36 articles from the databases but after removing duplicates and conducting the screening process, this review included 8 studies consisting of 3 RCT, 3 case controls, and 2 cohort studies. A total of 23 irrelevant articles and 1 written in the Russian language were excluded (Fig 1). About 1389 samples of myopic children were included in this review. The studies were conducted in various locations, with the majority coming from Asia, and 1 RCT from Australia.

The characteristics presented in Table 1 showed that each study had a different age range, except for Wu PC et al., and Lee CY et al., which had the same range (6-12 years old). Jeon GS et al., and Lee SS et al., had a 10-year gap between the youngest and oldest patients.

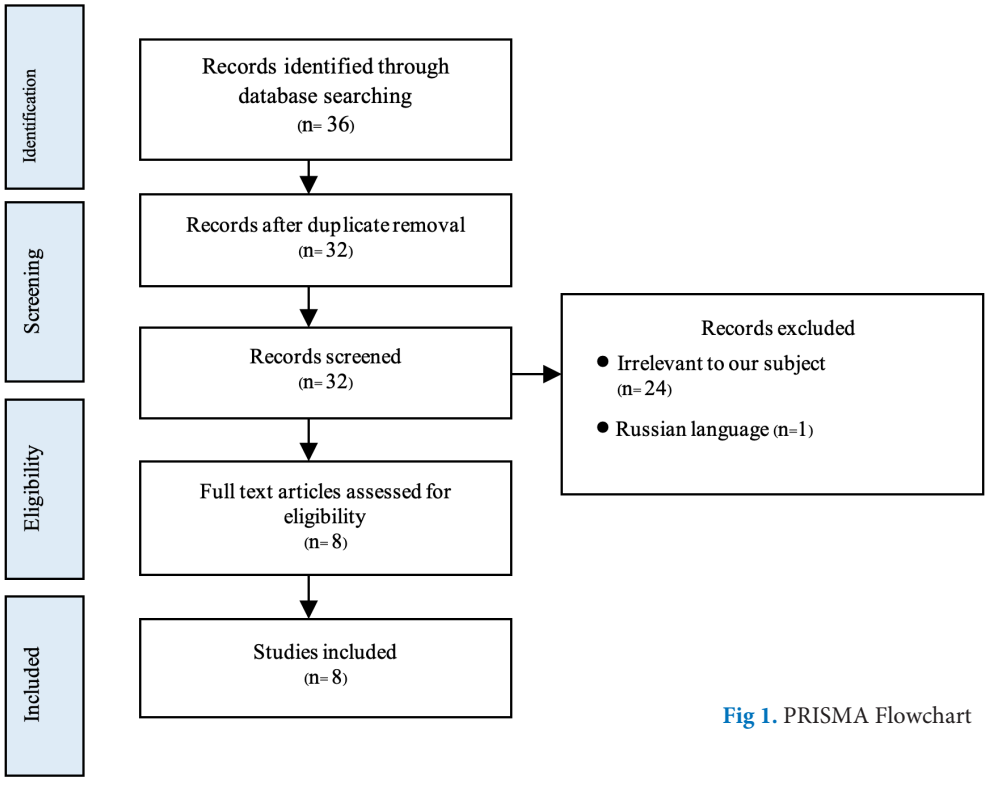

Fig 1. PRISMA Flowchart

TABLE 1. Study result.

Author	Year	Country	Study design	Follow up (yr)	Number of samples	Age	Intervention	Comparison/ Control	Mean Myopia Progression (D)		
									IG	CG	p-value
Wu PC, et al	2011	China	Case-control	≥ 3 years	117 • 97 IG • 20 CG	6-12	AED 0.05 -0.1%[a]	No treatment	-0.31 ± 0.26	-0.90 ± 0.30	*p* <0.001
Lee CY, et al	2016	Taiwan	Case-control	1 year	56 • 32 AED 0,125% • 12 AED 0,25% • 12 CG	6-12	- AED 0.125% - AED 0.25%	Spectacle	-0.05 0	-1.05	*p* >0.025
Yam JC, et al	2018	Hong Kong	RCT	1 year	438 • 109 AED 0,05% • 108 AED 0,025% • 110 AED 0,01% • 111 CG	4-12	- AED 0.01 % - AED 0.025% - AED 0.05%	Placebo ED (0.9% sodium chloride)	- 0.59 ± 0.61 - 0.46 ± 0.45 -0.27 ± 0.61	- 0.81± 0.53	*p* <0.001
Chuang MN, et al	2021	Taiwan	Cohort	10 years	23 • 15 IG • 8 CG	5-9	AED 0.05-0.1%	AED 0,25-0.5%	− 0.28 ± 0.43	-0.54 ± 0.58	*p* <0.001
Jeon GS, et al	2021	South Korea	Cohort	1 year	68 • 37 IG • 31 CG	5-15	AED 0.01%[b]	AED 0.01%[c]	-0.36 ± 0.17	-0.90 ± 0.22	*p* <0.001

TABLE 1. Study result. (Continue)

Author	Year	Country	Study design	Follow up (yr)	Number of samples	Age	Intervention	Comparison/ Control	Mean Myopia Progression (D) IG	CG	p-value
Jethani J	2021	India	Case-control	2 years	60 • 30 IG • 30 CG	4-12	AED 0.01%	No treatment	-0.31 ± 0.3	-0.76 ± 0.4	*p* <0.05
Lee SS, et al	2022	Australia	RCT	2 years	153 • 104 IG • 49 CG	6-16	AED 0.01%	Placebo ED	-0.31 (95% CI = -0.39 to -0.22)	-0.53 (95% CI = -0.66 to -0.40)	*p*= 0.004
Yam JC, et al	2023	Hong Kong	RCT	2 years	474 • 160 AED 0,05% • 159 AED 0,01% • 155 CG	4-9	AED 0.01% AED 0.05%	Placebo ED (0.9% sodium chloride)	- 0,38 (-0.46 to -0.30) -0.11 (-0.18 to -0.04)	-0.55 (-0.64 to -0.45)	*p* <0.001

Abbreviations: yr: year, D: diopter, IG: intervention group, CG: control group, AED: atropine eye drop, RCT: Randomized controlled trial

[a]If myopia progression was > -0.5 D at 6 months follow-up, the concentration was increased to 0.1% AED

[b]if SE progression ≤ 0.50 D after 12 months of treatment

[c]if SE progression > 0.50 D after 12 months of treatment

All studies stated there were no significant differences among groups in terms of demographics.[3,11-17] The follow-up period varied from 1 to 10 years and LCA eye drop was used within a range of 0.01% to 0.5%, specifically once daily at night. In the studies conducted by Chuang MN et al., and Jeon GS et al., the control group also received the atropine eye drop, either in a higher concentration or included a subgroup of poor responders (SE progression > 0.50 D after 12 months of treatment). However, others used a placebo eye drop, spectacles, or implemented no treatment at all within the control group.

The mean myopia progression rates presented in Table 1 showed that although some studies had a follow-up period of more than one year, only the first-year report was included, with all showing better outcomes in LCA group. In the case of Chuang MN et al., where both groups received LCA eye drop, the intervention group exhibited a significantly higher rate of myopia progression.

All studies reported minimal side and adverse effects, with Yam et al., (2018) showing photophobia in LCA 0.05%, 0.025%, and 0.01% groups at a rate of 7.8%, 6.6%, and 2.1%, while another study in 2023 found a similar case in LCA 0.05% and 0.01% groups at a rate of 20.6% and 20.9%, respectively. Lee SS et al. reported a total of 9 adverse events in the treatment group (8.7%), but none were classified as severe. Among these, only 3 were related to LCA including two cases of sore or heavy-feeling eyes and one case of blurred near vision.

The critical appraisal results for each study, based on their respective designs, are presented in Tables 2, 3, and 4. Table 2 shows the assessment results for RCT, all of which indicated a 'low risk' of bias, while Table 3 presents the quality assessment outcomes for the case-control. Two studies achieved high scores, with a total of 9 and 8, indicating good quality. However, the study by Jethani J was rated as 'fair quality,' receiving only 2 stars in the selection domain. Table 4 showcases the quality of the cohort studies, all of which received high scores of 9 and 8.

TABLE 2. Risk of bias assessment using RoB 2.0.

No	Study	Domain 1 (Risk of bias arising from the randomization process)	Domain 2 (Risk of bias due to deviations from the intended interventions)	Domain 3 (Missing outcome data)	Domain 4 (Risk of bias in the measurement of the outcome)	Domain 5 (Risk of bias in selection of the reported result)
1	Yam JC, et al	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
2	Lee SS, et al	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
3	Yam JC, et al	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

TABLE 3. Quality assessment using Newcastle-Ottawa Scale for Case-Control Studies.

No	Author	Selection				Comparability	Outcome			Total Quality
		Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis controlled for confounders	Ascertainment of exposure	The same method of ascertainment for cases and controls	Non-response rate	
1	Wu PC, et al	★	★	★	★	★★	★	★	★	9
2	Lee CY, et al	★	★	★	★	★★	★	★	-	8
3	Jethani J	★	★	-	-	★★	★	★	★	7

TABLE 4. Quality assessment using Newcastle-Ottawa Scale for Cohort Studies.

No	Author	Selection				Comparability		Outcome		Total Quality
		Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the 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 cohorts	
1	Chuang MN, et al	★	★	★	★	★★	★	★	★	9
2	Jeon GS, et al	★	★	★	-	★★	★	★	★	8

DISCUSSION

A recent healthcare breakthrough for myopia control, known as LCA, has been subjected to extensive investigations to optimize its effectiveness and safety. Despite some studies reporting p values > 0.001, the majority consistently showed promising results in slowing myopia progression. Lee CY et al. found that the use of LCA at 0.25% culminated in no significant myopia progression ($p > 0.025$). According to Wu PC et al., Chuang MN et al., and Yam JC et al., (2018 and 2023), the 0.05% concentration was more effective than 0.1% in myopia control. Chuang MN et al., and Jeon GS et al., also incorporated a control group receiving LCA.

The ATOM studies using the 1% atropine eye drop have shown its efficacy in slowing the progression of myopia in children. However, the use of high concentration was reportedly associated with side effects such as photophobia, glare,[18] and narrow-angle glaucoma resulting from its anticholinergic properties. Photophobia, mydriasis, blurred vision, and systemic side effects such as allergic dermatitis, dry mouth, difficulty swallowing, and warm or red skin have also been reported with high-concentration atropine use.[12,19] However, LCA treatment is both effective in slowing myopia progression and is associated with minimal side effects. The most commonly reported mild symptoms include glare and blurred vision. Compared to higher concentrations of atropine, such as the 0.5% used in the ATOM 2 study, low concentrations exhibit a lower incidence of side effects such as eye discomfort and photophobia.[20] The majority of studies in this review consistently reported that all concentrations of LCA were well-tolerated. The 0.05% and 0.1% concentrations induced only mild to moderate pupil dilation (mydriasis) compared to the full dilation by 1% atropine. LCA may induce less photophobia, thereby making it a more suitable option for long-term use in retarding myopia progression.

All included studies had varying follow-up durations, with some reaching over a period of one year, including Jeon GS et al., Lee CY et al., and Yam JC et al., (2018). Several others extended their evaluation to two years, such as Lee SS et al., and Jethani J, while some continued for more than two years, reaching four and ten years by Wu PC et al., and Chuang MN et al., respectively. Based on the results, the effects of LCA on myopia progression can be assessed early in the first year of medication. In studies with longer time spans, significant effects were observed in the first and fifth years.[14] To standardize the duration, only the mean myopia progression in the first year of treatment was considered. This pattern may also be affected by the mechanism of atropine action.

Atropine functions to slow myopia progression through non-accommodative mechanisms, including the regulation of muscarinic receptors in the retina, choroid, and sclera.[12] It increases choroidal thickness in children by regulating dopamine release, associated with reducing axial eye growth,[19] and may also have biochemical effects on the retina or sclera.[13] However, the anti-myopia mechanisms of atropine are not fully understood, necessitating the need for further studies.

Despite the widespread use of LCA in routine ophthalmological and optometric practices both in the United States and globally, the majority of the included studies were conducted in Asia, while 3 were from other continents. Lee SS et al. (Australia) and McCrann et al. (Ireland) reported significant reductions in myopia

progression with the use of LCA eye drop, while Repka et al. (USA) found that the treatment did not yield a significant result.[16,21,22] The limited representation from Western countries showed the necessity for further investigation to comprehensively evaluate the efficacy of LCA in these regions.

There are several limitations to this study, first, there was a lack of data on LCA from other regions outside Asia. This was attributed to the factors affecting myopia progression, such as sunlight exposure, environmental effects, and ethnicity, according to Lee SS et al. Some studies did not explore the potential effect of demographic differences, sunlight exposure, and activities on the effectiveness of LCA. Further investigation is also needed to understand the correlation between LCA and ethnicity. These factors may introduce bias in assessing the effectiveness of the used atropine concentration. The second limitation was the absence of control groups in some studies, limiting the extent of the evaluations conducted. Finally, half of the studies had a small sample size that did not fully represent the total results.

CONCLUSION

In conclusion, LCA eye drop showed high effectiveness in controlling myopia progression. Healthcare professionals should prioritize patient comfort and safety by minimizing the side effects. However, further investigation was needed, particularly in non-Asian countries.

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