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EFFICACY OF ATROPINE EYE DROPS AS THERAPY OF PROGRESSIVE MYOPIA IN CHILDREN : A SYSTEMATIC REVIEW

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ABSTRACT

Objective: This review was carried out to determine the efficient concentration of atropine eye drops in inhibiting the progression of myopia in children.

Materials & Methods: A literature search was conducted across databases such as PubMed, ScienceDirect, SpringerLink, and ProQuest, using search terms such as "myopia progression", "myopia", and "atropine". The evaluation of efficacy was based on Corrected Visual Acuity, axial length, and adverse effects.

Results: The study included data from 12 Randomized Controlled Trials (RCTs) comprising 3,651 participants exposed to seven atropine concentrations, including 1%, 0.5%, 0.1%, 0.05%, 0.02%, 0.025% and 0.01%. The results showed that higher atropine doses were more effective in slowing myopia progression.

Conclusion: Very Low Dose Atropine eye drops have proven to be sufficiently efficacious in decelerating the progression of myopia in pediatric patients, showing minimal side and rebound effects.

Keywords: Atropine, Childhood myopia, Efficacy, Progressive myopia

INTRODUCTION

Myopia is the most prevalent refractive disorder on a global scale, impacting an estimated 1.44 billion individuals, which is equivalent to 22.6% of the world's population as of 2010.[1] In recent years, the lack of time spent on outdoor activities has been acknowledged as a significant risk factor for the development of myopia.[2,3]Furthermore, the duration and intensity of near-work activities are also associated with this condition.[4]According to Wang J et al (2021), policies advocating for indoor activities during the COVID-19 pandemic significantly correlate with alterations in myopia among children aged 6-8 years.[5]

Interventions aimed at slowing the progression of myopia are recommended when the progression exceeds 0.5 D per year, accompanied by an increase in axial length exceeding 0.20 mm per year. Accurate assessment of progression includes monitoring axial length.[6,7,8] Various therapies contemplated for progressive myopia comprise bifocal spectacles, orthokeratology lenses (Ortho-K), multifocal lenses, augmented time spent outdoors, and the application of topical atropine.[9,10]

Atropine, functioning as a muscarinic antagonist, operates through M1 to M5 receptors located in the sclera and retina. The application of atropine for myopia was initially introduced by Wells in the

19th century. In 1979, Bedrossian conducted a non-randomized trial evaluating the effects of 1% administered once nightly to one eye for a year, with the contralateral eye serving as a control. Meanwhile, the control eye showed a statistically significant improvement[11]and the efficacy correlated with the dosage while considering the associated side effects.[12]

METHODS

A comprehensive literature search was carried out across four online databases, namely PubMed, ScienceDirect, SpringerLink, and ProQuest. The search terms used were "myopia progression," "myopia," and "atropine." Articles were included when written in English and had full-text accessibility. All studies were required to meet the following inclusion criteria, namely (1) randomized clinical trials (RCT), (2) studies conducted within the last 10 years, (3) participants with myopia below 18 years old, (4) studies conducted with atropine at any dosage, at least within one group (1-treatment arm), (5) at least one of the assessed outcome criteria being spherical equivalent, axial length, or side effects. The excluded variables were (1) secondary articles such as reviews, and (2) articles presenting case reports, series, laboratory studies, or animal experiments.

In instances where two reports existed within a single title, the latest report was selected to avoid duplicative data. The studies were assessed according to the Oxford Center of Evidence-Based Medicine 2011 Level of Evidence and selected based on the inclusion criteria, specifically focusing on RCTs (figure 1).

The collected information data were categorized based on authors, year of the study, number of study subjects, age range of subjects, intervention provided, and duration of the intervention. The effectiveness of the given management was assessed based on Spherical Equivalent (SE), Axial Length (AL), and Adverse Events (AE).

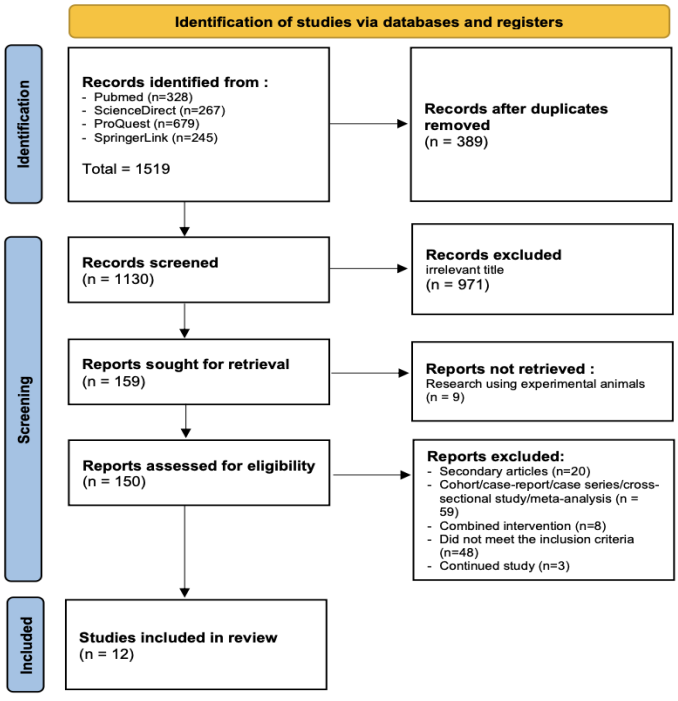

Figure 1. A literature search using the PRISMA flow chart

RESULTS

Characteristics

A total of 12 articles, identified through relevant search terms across diverse databases, have been incorporated into this review, as shown in Table 1. The articles selected are randomized controlled

trials (RCTs), each comprising at least an atropine concentration and a control group. The key features of the eligible studies are presented in Table 1. The cumulative participant count across these studies amounts to 3,651 individuals, with seven different concentrations, namely 1%, 0.5%, 0.1%, 0.05%, 0.025%, 0.02%, and 0.01%. Low-dose atropine (0.01%), moderate-dose atropine (0.02%-0.5%), and high-dose atropine (1%) were featured in nine, six, and three studies, resulting in the formation of 18 intervention groups (Table 1). The investigations were conducted in Asia, with an average follow-up duration of 12 months. The widest age range was observed in Chaurasia et al., where the sample spanned the age group of 6-16 years. Meanwhile, the narrowest age range was documented by Yam et al., with the sample age range falling between 4-12 years.

Table 1. Characteristics of the studies

Authors, year	Country	Age (years old)	Follow-up (months)	groups	Sample size	SER Baseline	AL baseline (mm)	SER changes (D/year)	AL changes (mm/year)
Chia et al., 2012[13]	Singapore	6-12	24	0.5%; 0.1%; 0.01%;	139 141 75	-4.30 (1.80) -4.50 (1.40) -4.50 (1.50)	25.10 (0.90) 25.10 (0.80) 25.20 (1.00)	-0.15 (0.30) -0.19 (0.30) -0.25 (0.32)	0.14 (0.13) 0.14 (0.14) 0.21 (0.16)
Yi et al., 2015[14]	China	7-12	12	1%; Placebo	68 64	-1.23 (0.32) -1.15 (0.30)	23.75 (0.12) 23.72 (0.12)	0.32 (0.22) -0.85 (0.31)	0.03 (0.07) 0.32 (0.15)
Wang et al., 2017[15]	China	5-10	12	0.5%; placebo	63 63	-1.3 (0.4) -1.2 (0.3)	24.1 (1.0) 23.8 (0.9)	+0.50 (baseline change from -1.30 to -0.80) -0.8	-1.1 0.5
Yam et al., 2018[16]	China	4-12	12	0.05%; 0.025 %; 0.01%; Placebo	102 81 97 93	-3.98 (1.69) -3.71 (1.85) -3.77 (1.85) -3.85 (1.95)	24.85 (0.90) 24.86 (0.95) 24.70 (0.99) 24.82 (0.97)	-0.27 (0.61) -0.46 (0.45) -0.59 (0.61) -0.81 (0.53)	0.20 (0.25) 0.29 (0.20) 0.36 (0.29) 0.41 (0.22)
Zhu et al., 2020[17]	China	6-12	24	1% Placebo	262 308	-3.82 (0.44) -3.74 (0.51)	24.93 (0.21) 24.91 (0.18)	-0.21 (0.22) -0.89 (0.23)	0.12 (0.10) 0.39 (0.19)
Wei et al., 2020[18]	China	6-12	12	0.01%; placebo	76 83	-2.52 (1.33) -2.64 (1.46)	24.50 (0.76) 24.69 (0.97)	-0.49 (0.42) -0.76 (0.50)	0.32 (0.19) 0.41 (0.19)
Hieda et al., 2021[19]	Japan	6-12	24	0.01%; placebo	77 81	-2.91 (1.30) -2.98 (1.59)	24.43 (0.74) 24.51 (0.78)	-0.63 (0.20) -0.74 (0.21)	0.32 (0.09) 0.39 (0.09)
Saxena et al., 2021[20]	India	6-14	12	0.01%; placebo	47 45	-3.38 (1.32) -3.71 (1.37)	24.60 (1.02) 24.70 (0.80)	-0.16 (0.38) -0.35 (0.40)	0.22 (0.20) 0.28 (0.28)
Zhao et al., 2021[21]	China	5-14	12	0.01%; placebo	20 20	-1.98 (0.45) -1.93 (0.74)	24.17 (0.68) 24.28 (0.83)	-0.34 (0.16) -1.30 (0.44)	0.24 (0.12) 0.72 (0.21)
Cui et al., 2021[22]	China	6-14	24	0.02%; 0.01%;	105 106	-2.76 (1.47)	24.60 (0.72)	-0.80 (0.52) -0.93 (0.59)	0.62 (0.29) 0.72 (0.31)

				placebo	89	-2.70 (1.64) -2.68 (1.42)	24.58 (0.74) 24.55 (0.71)	-1.33 (0.72)	0.88 (0.35)
Chaurasia et al., 2022[23]	India	6-16	12	0.01%; placebo	43 43	-3.04 (1.36) -3.07 (1.32)	24.52 24.56	-0.26 (0.23) -0.72 (0.29)	0.20 (0.21) 0.36 (0.24)
Ye et al., 2022[24]	China	6-12	12	1%; 0.01%;	104 103	-2.11 (1.10) -2.13 (1.10)	24.32 (0.81) 24.25 (0.72)	-0.53 (0.49) -0.74 (0.52)	0.26 (0.17) 0.36 (0.21)

Notes: SER: spherical equivalent refraction; AL: Axial length

Efficacy

a. Change in Spherical Equivalent Refraction

Studies investigating the treatment group with a high dose of atropine, specifically 1%, and a placebo, conducted by Yi et al.[14] and Zhu et al.[17] showed significant results. In the atropine, 1% group, changes of 0.32±0.22 and -0.21±0.22 were recorded, compared to the placebo with-0.85±0.31 and -0.89±0.23 (P<0.0001 and P<0.05, respectively). Similar significant outcomes were observed in studies comparing moderate concentration (0.5%) with control (placebo), as shown by Wang et al.[15]
Other studies comparing more than one atropine concentration include Chia et al.[13]In the ATOM 2 study, the 0.5% concentration showed a greater decrease compared to 0.1% (P=0.02) for changes in spherical equivalent. Cui et al.[22] compared atropine 0.02%, 0.01%, and control, showing that the 0.02% concentration resulted in more significant changes than 0.01% (P=0.03). Additionally, Ye et al.[24] reported that atropine 1%, when compared to 0.01%, led to meaningful changes (P=0.01). Studies focusing on low concentrations by Wei et al.[18], Zhao et al.[21,] and Hieda et al.[19], conducted in China and Japan, indicated statistically significant changes in refractive error in the atropine 0.01% group compared to the control (P<0.001). Similar research with a comparable intervention group by Saxena et al.[20] and Chaurasia et al.[23] in India also showed lower myopia progression in the 0.01% group, with statistical significance (P<0.021 and P=0.0001, respectively)

b. Change in Axial Length

The 12 articles collectively addressed changes in axial length and the atropine groups consistently showed less increase compared to the control. In the high-dose atropine group (atropine 1%), studies by Yi et al.[14] and Zhu et al.[17] indicated significant differences in axial length increase compared to controls (P<0.0001 and P<0.001, respectively).
In the moderate-dose atropine group, Chia et al.[13]reported P<0.01 between 0.01% and 0.1% as well as P<0.01 between 0.01% and 0.5%. Yam et al.[16]showed similar results after 2 years of use, with the sequential increase in axial length for the 0.05%, 0.025%, and 0.01% groups being 0.18±0.16 mm, 0.22±0.18 mm, and 0.25±0.18 mm, respectively (p=0.04). Cui et al.[22] stated that the higher the atropine dosage, the slower the increase in axial length of the eyeball (P<0.01 between 0.01% and 0.1% and P<0.01 between 0.01% and 0.5%). Other studies comparing high-dose atropine with low-dose also reported similar findings.[24]

c. Adverse Effect

Adverse effects of atropine administration from the 12 collated studies are detailed in Table 2. A total of six studies reported side effects of atropine at various doses, with photophobia being the most common. Other side effects included changes in pupil size, decreased distance and near vision, changes in accommodation amplitude, allergic conjunctivitis, headache, and irritation. Each study indicated that the occurrence of side effects was dose-dependent but no serious complications were found at any atropine dosage. A rebound effect was reported in the study by Yam et al.[16], where the 0.01% dose showed the lowest rebound effect compared to continued therapy. However, no significant differences were found when comparing the low doses used in the study.

Table2. Adverse Effects in the studies

Authors, year	Groups	Adverse effect						Others
		Photopic pupil size	Mesopic pupil size	Decreased in distance vision	Decreased in near vision	Accommodation amplitude changes	photophobia (%)	
Chia et al., 2012[13]	0.5% 0.1% 0.01%	3.11 (1.10) 2.25 (1.01) 0.74 (0.75)	3.56 (1.14) 2.71 (1.12) 1.15 (0.71)	-0.01 (0.06) 0.01 (0.06) -0.02 (0.06)	0.25 (0.19) 0.06 (0.13) -0.02 (0.08)	-11.80 (4.40) -10.10 (4.30) -4.60 (4.20)	N/A	Allergic conjunctivitis (4.1%) (each group; 0.5% and 0.1%)
Yi et al., 2015[14]	1% Placebo	N/A	N/A	N/A	N/A	N/A	N/A	No adverse effect
Wang et al., 2017[15]	0.5% Placebo	N/A	N/A	N/A	N/A	N/A	N/A	No adverse effect
Yam et al., 2018[16]	0.05% 0.025% 0.01% Placebo	1.03 (1.02) 0.76 (0.90) 0.49 (0.80) 0.13 (1.07)	0.58 (0.63) 0.43 (0.61) 0.23 (0.46) 0.02 (0.55)	-0.02 (0.06) -0.02 (0.07) -0.03 (0.08) -0.02 (0.06)	-0.01 (0.13) 0.00 (0.13) -0.03 (0.13) -0.02 (0.11)	-1.98 (2.82) -1.61 (2.61) -0.26 (3.04) -0.32 (2.91)	7.8 6.6 2.1 4.3	-
Zhu et al., 2020[17]	1% Placebo	N/A	N/A	N/A	N/A	N/A	62.1	headache (12.8%), irritation (22.52%), infection (6.87%)
Wei et al., 2020[18]	0.01% Placebo	N/A	N/A	N/A	N/A	N/A	4.5 0.9	
Hieda et al., 2021[19]	0.01% Placebo	0.26 (0.83) 0.13 (0.85)	0.09 (0.71) 0.14 (0.72)	N/A	N/A	N/A	1.2 0	
Saxena et al., 2021[20]	0.01% Placebo	1.20 (0..47) -0.06 (0.58)	0.05 (0.43) -0.12 (0.64)	0.002 (0.08) 0.002 (0.03)	N/A	-0.98 (1.86) -1.25 (2.01)	-	
Zhao et al., 2021[21]	0.01% Placebo	N/A	N/A	N/A	N/A	N/A	N/A	TBUT changes are not statistically significant
Cui et al., 2021[22]	0.02% 0.01% Placebo	N/A	N/A	N/A	N/A	-0.11 -0.09 N/A	23% 24% N/A	
Chaurasia et al., 2022[23]	0.01% Placebo	N/A	N/A	N/A	N/A	N/A	N/A	
Ye et al., 2022[24]	1% 0.01%	N/A	N/A	-0.01 (0.03) -0.03 (0.04)	0.00 (0.02) 0.00 (0.01)	-1.54 (2.94) -1.55 (3.11)	1.1% 2.5%	

DISCUSSION

The complications associated with childhood myopia present a significant socio-economic burden that may lead to complications resulting in blindness. The optimal approach to treatment includes controlling the progression of myopia. Bifocal glasses have not shown significant benefits in slowing the progression. Meanwhile, orthokeratology has reported some advantages, and challenges such as vision-threatening complications, including infections, persist. Atropine has proven effective in the past and has been recently developed as the preferred therapy.[25]

This study, conducted exclusively in Asia due to the high prevalence of cases and the approval of atropine use, showed less myopia progression in the atropine group compared to the control group over the observation period. A reduced increase in axial length was also observed in the atropine group. Among various dosages in different studies, atropine 0.05% indicated superior results, showing dose-dependent effectiveness in addressing myopia.[12]

These findings are consistent with a meta-analysis by Ha et al.[26], where 16 randomized controlled trials (RCTs) identified 1%, 0.5%, and 0.05% atropine as the three most effective doses. Another meta-analysis by Zhao et al.[27], based on 7 RCTs, suggested that atropine 0.01% could strike the best balance between efficacy and safety in preventing and treating myopia. High-dose atropine showed a decrease in accommodation amplitude, suggesting a potential need for bifocal or progressive glasses for reading.[19]

The effects of atropine were not extensively reported but some symptoms, such as photophobia, decreased accommodative amplitude, and pupil size, were more common at higher doses.[28] However, further examination is needed due to varying durations. The side effects of long-term atropine use depend on the administered dosage, with the rebound effect being a crucial consideration. Chia et al. and Yam et al. stated that atropine 0.01% produced a smaller rebound effect but the LAMP study found no statistically significant differences among all low doses. ($p=0.15$)[13,16] In the context of these studies, additional research with extended durations, diverse populations, and low atropine concentrations is essential to substantiate the benefits of atropine in slowing myopia progression in children.

CONCLUSION

In conclusion, the application of atropine eye drops across various studies was reported to show favorable outcomes when juxtaposed with control groups in terms of alterations in refractive status and axial length of the eyeball. The efficacy manifested as a dose-dependent phenomenon, with higher concentrations showing increased effectiveness in impeding changes in refractive status and axial length. However, this increased efficacy was concomitant with corresponding adverse effects.

As evidenced by the present study, the administration of atropine was anticipated to yield a reduction in axial length within the range of 0.1-0.8 mm/year and an increase in spherical equivalent within 0.2 – (-1.3) D/year.The documented side effects included photophobia, alterations in pupil size, diminished distance and near vision, changes in accommodation amplitude, allergic conjunctivitis, headache, and irritation. Furthermore, there were no reported side effects and the occurrence of rebound was minimal, particularly at lower concentrations. Considering the aggregate findings, atropine concentrations of 0.01% and 0.05% consistently yielded positive results in averting the progression of myopia.

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