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Strategy of Suppressing Myopia Progression in Children With Atropine: A Systematic Review

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KEYWORDS
Myopia, Atropine, Progression

ABSTRACT
Introduction: The prevalence of myopia in children has been a global issue in recent decades. Atropine is becoming more popular in suppressing myopia progression. Still, there is no clear guidance regarding the timing of commencement and cessation, as well as the duration of treatment. Objectives: To assess the timing and regimen of atropine therapy in myopia progression, response towards therapy, and rebound phenomenon. Method: A comprehensive literature search (Cochrane®, Pubmed®, and ProQuest®) was performed using relevant search terms. Inclusion criteria included randomized controlled trials and cohorts of myopic children undergoing atropine therapy. Conference abstracts, case reports, and duplicate publications were excluded. The primary outcome is identifying the optimal treatment regimen. The secondary outcome is the evaluation of the rebound effect. Results: Some studies revealed that atropine can be administered once myopia progression is diagnosed, as early as 4 years old. Yet younger age would apt to rebound. The administration suggestion is the 2-year period with 6 monthly follow-ups, with increasing concentration if myopia continues to progress. Tapering off recommendations differs by population. Higher concentrations were prone to rebound, hence lower concentrations (0.01%) maintain better clinical efficacy with minimal side effects. However, another study revealed that a higher myopia baseline requires a slightly higher dose (0.05%) for its axial elongation suppression, with tolerable pupil size and accommodation. Although atropine showed more progression after cessation compared to placebo (-1.14±0.80D vs. -0.38±0.39D), absolute progression significantly lowered after 3 years (-4.29±1.67D vs. -5.22±1.38D). Conclusion: Atropine is widely used and appears to be effective in controlling myopia in children with appropriate doses and proper duration of treatment to minimize rebound.

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INTRODUCTION

Myopia prevalence and progression in children become a serious health problem in the world recently, particularly in Asia (Wong & Saw, 2016). Nowadays, near-work activities are inevitable for children, while time for outdoor activities is scarce. This situation has a close relation to the progression of myopia in childhood. Studies have shown that early onset of myopia increases the risk of high myopia in the future, thus accountable for macular degeneration and retinal detachment risk factors, that

potentially cause blindness. By early detection and proper treatment, the incident of permanent vision loss hereafter could be preventable (Nahid et al., 2019).

Low-dose atropine eyedrop is widely known as a good option for controlling myopia progression in children with an effective outcome (Khanal & Phillips, 2020a). However, some children have a poor response to therapy. Factors associated with the poor respondent need to be clarified. Some studies revealed that younger children tend to respond worse.

Myopia is commonly diagnosed in childhood and becomes stabilized after it stops progressing (Medina, 2022). Hence, early intervention such as atropine would reduce the "final myopia" by controlling myopia progression

This study aimed to systematically compile and evaluate current findings from relevant peer-reviewed publications to assess the timing and regimen of atropine eyedrop in suppressing myopia progression in children—additionally, the response towards therapy and rebound phenomenon.

This study aims to systematically compile and evaluate current findings from relevant peer-reviewed publications to assess the timing and regimen of atropine eye drops in suppressing myopia progression in children. Additionally, it seeks to investigate factors influencing treatment response and the phenomenon of rebound in myopia control therapy.

METHOD

Types of Studies

The review included data from all types of relevant randomized controlled trials and cohort studies. The focus of this review was on the timing and regimen of atropine therapy in myopia progression, response towards therapy, and rebound phenomenon.

Search Strategy for Identification of Studies

A literature search was done on selected articles restricted to cohort and randomized controlled trial studies. The study included certain inclusion criteria such as children with myopia under 18 years old and 2 year atropine administration minimum. Then we exclude duplicate publications, conference abstracts, and case reports. Afterward, titles were then assessed and summarized to obtain full copies of all potentially relevant studies to determine whether the studies met the inclusion and exclusion criteria for this review (Hiebl, 2023). References to all included publications were also checked.

In between groups on different articles, this review will find out the optimal timing and regimen of atropine eyedrop. While the secondary outcome would be the response and rebound phenomenon.

Validity Assessment

Based on a Jadad scale score of 3 out of 5, three prospective studies have proven to be high-quality evidence-based trials. All studies are randomized control trials that included 1229 subjects, each study consists of 400, 345, and 484 patients.

Table 1.
Jadad Scale Score

Item	Score	
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1	1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1	0
Was the study described as double blind?	0/1	0
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1	1
Was there a description of withdrawals and dropouts?	0/1	1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/−1	0
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/−1	0
	Total 3/5	

Description of Studies

The original electronic search identified 4604 abstracts through three databases. Subsequently, 199 potentially relevant articles were collected for further evaluation. Furthermore, 152 articles were included based on inclusion and exclusion criteria. A total of three articles were used in the final review.

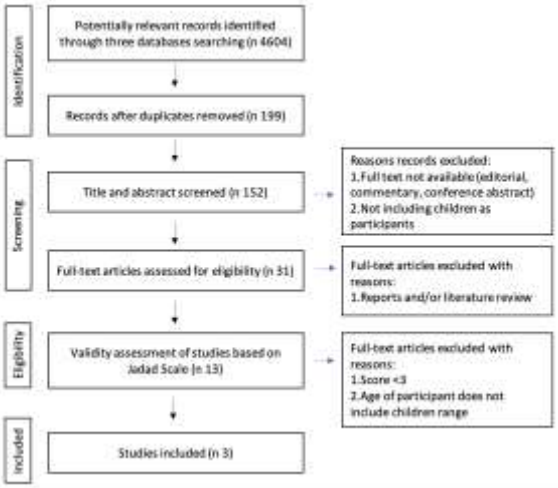

Figure 1. Flowchart of Description of Study

RESULT

Timing and Regimen

All randomized control studies have similar age characteristics consisting of school-age students as the subjects as shown in Table 2. Three studies approached a 2-year initial duration treatment of atropine eyedrop. All patients included in all three studies have a history of myopia progression of at least 0.5D in the previous year. Then et al. and Chia et al. evaluated the myopia progression up to five years after cessation. The spherical equivalent shown in diopters (D) is the common measurement to assess myopia progression.

Response and Rebound

Clearly seen in Table 3, Wang et al. found that atropine eyedrop is superior compared to placebo despite of spherical equivalent difference still being higher in the first two years of treatments and one year after halting the treatment. However, Wang et al. revealed that the absolute progression within three years post-cessation was significantly lowered in the atropine group compared to the placebo, -4.29 ± 1.67D vs. -5.22 ± 1.38D.

Table 3 also showed that a newer study by Chia et al. discovered the regimen of low-dose atropine such as 0.01% and 0.5% is still effective in suppressing childhood myopia progression after a minimum of two years of therapy. The trend of spherical equivalence change was even better in the 0.01% atropine group compared to 0.5% after cessation of 24 months of initial therapy by -0.01 ± 0.36D and -0.05 ± 0.37D respectively.

According to Yam et al. also revealed that the trend of myopia suppression in 0.01% atropine was better compared to 0.05% in the second year. The spherical equivalent change in 0.01% first year was -0.63 ± 0.56D and lowered to -0.48 ± 0.44D in two years period (Tomiyama et al., 2022). However, the 0.05% group was -0.25 ± 0.61D in 12 months, then a slight increase to -0.30 ± 0.44D in the second year.

The dilated pupil was the side effect when receiving atropine. Clearly seen in Table 3, Chia et al. revealed that pupil diameter is greater in 0.5% atropine compared to 0.01% after cessation of initial therapy by 7.28 ± 1.46mm vs 5.02 ± 0.92mm. The pupil size of 0.5% is more than 3mm after a 2-year treatment. Yam et al. also found that pupil size change is greater by 0.05% compared to 0.01% by 1.25 ± 1.13mm and 0.60 ± 0.84mm respectively.

All three studies suspended atropine eyedrop in 24 months without frequency tapering off. Table 3 revealed that after treatment ceased, 1% atropine showed the highest rebound as spherical equivalent

changes in 36 months was leading followed by placebo, 0.5%, and 0.01% groups by 0.76 ± 0.70D, -0.38 ± 0.58D, -0.38 ± 0.34D, and -0.16 ± 0.24D respectively.

According Chia et al. noticed that number of children who needed re-treatment (progression of -0.5D or more in the cessation phase) was less in the 0.01% atropine group compared to 0.1% and 0.5% by 24%, 59%, and 68% respectively.

Table 2.
Study Characteristics

	Tong L[1]	Chia A[2]	Yam JC[3]
Subjects	400 children	345 children	484 children
Age	6-12 y.o	6-12 y.o	4-12 y.o

Table 3.
Outcomes Parameters

PARAMETERS	Tong L[1]			Chia A[2]			Yam JC[3]		
	1%	Placebo	P values	0.01%	0.5%	P values	0.01%	0.05%	P values
12 Mo S.E Change	-1.14 ± 0.80D	-0.38 ± 0.39D	<0.0001	-0.31 ± 0.45D	-0.13 ± 0.44D	0.055	-0.64 ± 0.56D	-0.25 ± 0.61D	<0.001
24 Mo S.E Change	-1.51 ± 1.40D	-0.40 ± 0.65D	<0.0001	-0.01 ± 0.36D	-0.05 ± 0.37D	0.638	-0.48 ± 0.44D	-0.30 ± 0.44D	<0.001
36 Mo S.E Change	-0.76 ± 0.70D	-0.38 ± 0.58D	<0.0001	−0.16 ± 0.24D	-0.38 ± 0.34D	<0.001	N/A	N/A	N/A
60 Mo S.E	-4.29 ± 1.67D	-5.22 ± 1.38D	<0.0001	−6.20 ± 1.59D	-6.77 ± 2.19D	0.428	N/A	N/A	N/A
P.S Screening	N/A	N/A	N/A	3.89 ± 0.58mm	4.02 ± 0.60mm	0.363	3.61 ± 0.59mm	3.82 ± 0.68mm	N/A
P.S 24 Mo Change	N/A	N/A	N/A	N/A	N/A	N/A	0.60 ± 0.84mm	1.25 ± 1.13mm	<0.001
P.S 24 Mo	N/A	N/A	N/A	5.02 ± 0.92mm	7.28 ± 1.46mm	<0.001	N/A	N/A	N/A

Mo = Months; S.E = spherical equivalent; D = diopters; P.S = pupil size

DISCUSSION

Recently, atropine eyedrop is becoming more popular and has proven to be effective in slowing myopia progression in children (Khanal & Phillips, 2020b). The rate of progression in school-age children is approximately around -1D in Asians, and -0.5D in Caucasians. Studies have come across that high doses of atropine such as 1% and 0.5% found to be effective in suppressing myopia progression. However, the photophobia effect is undeniable. This phenomenon could cause drop-out before the treatment is completed in 2 2-year period.

The exact mechanism of atropine topical remains unknown, although some studies discovered the up-down regulation of sclera and retina muscarinic receptors. In consequence, low-dose atropine is

recommended since atropine works on retina receptors M1/M4, not via visual accommodation (Garcia Del Valle & Alvarez-Lorenzo, 2021).

Response and Rebound

Randomized control trial by Wang et al. reported that atropine showed more progression after cessation compared to placebo. However, atropine could reduce final myopia significantly after 3 years of cessation compared to placebo, -4.29±1.67D vs. -5.22±1.38D. This proved that atropine itself is superior in inhibiting myopia progression compared to placebo groups (Fu et al., 2020).

A later experiment by Chia et al. with similar children's age characteristics published that low-dose atropine has a better effect in slowing down myopia progression with minimal side effects with an initial treatment of two years. After cessation, atropine 0.01% shows better spherical equivalent mean changes in 36 months, and a lower absolute progression in 60 months compared to 0.5% (Jawaid et al., 2024).

According to Yam et al. also investigated that 0.01% efficacy is superior in the second year than the first year compared to 0.05%. Due to the lower concentration of 0.01% atropine, it may take time for cumulative effect until it has reached the concentration threshold. Over time, the effect of 0.01% would reach its maximum (Joachimsen et al., 2021). In contrast with 0.05%, the initial period has reached its maximum, then no better efficacy or even lower in the second year.

There are some side effects that myopic children with atropine complain about such as photophobia, due to dilated pupils (Polling et al., 2016). Chia et al. discovered that pupil dilation in the atropine 0.01% group was approximately 1mm, while in the 0.5% group was around 3.5mm. Yam et al. also came across that pupil size change in 0.01% was minimal compared to 0.05% groups. The study by Li et al. mentioned that tolerable pupil size towards accommodation for children aged between 4 to 12 years old is a 3mm cutoff. Herewith, atropine 0.01% remains superior towards the photophobia side effect, thus may cause drop out in treatment. Even though pupil accommodation in children was decreasing with age, Li et al. mentioned that pupil sizes were similar in all groups.

Another important thing to note is the age at the start of treatment. A recent study by Li et al. suggests that younger age is associated with poor treatment response and apt to rebound in lower dose atropine (Fudin et al., 2018). The spherical equivalent progression difference of 6-year-old children with 0.05% atropine (-0.90D; 95% CI, -0.99 to -0.82) has a similar effect on 8-year-old children with 0.025% atropine (-0.89D; 95% CI, -0.94 to -0.83), and 10-year-old children with 0.01% atropine (-0.92D; 95% CI, -0.99 to -0.85). Chia et al. discovered that tapering atropine frequency over time would lessen the rebound phenomenon (no acceleration of myopia progression even a year after cessation), especially in higher concentrations of atropine. Contrary to atropine 0.01%, the rebound phenomenon was not significant, and axial length growth seemed slowed naturally (Sander et al., 2019).

Another significant finding by Chia et al. was that the number of children who needed re-treatment was less in the 0.01% atropine group compared to 0.1% and 0.5%. It concludes that a higher dose of atropine may increase rebound after the washout year. Wang et al. supported that high dose atropine has more tendency to rebound, in line with Chia et al. that 0.5% spherical equivalent change spike after discontinuation of atropine in the second year. On the other hand, the 0.01% group, trend was even plateau.

Timing and Regimen

Considering the risks and benefits of different atropine concentrations, the 0.01% dose appeared to be the appropriate first-line therapy for myopia progression >0.5D per year as it has no clinically significant side effects and less rebound after cessation. Nonetheless, concentration adjustment must be evaluated after a 2-year cessation, especially in younger patients, or if myopia continues to progress >0.5D within 6 months of a regular checkup.

According Li et al. found that baseline spherical equivalent also plays a role in myopia progression. Hence, younger age and/or higher baseline myopia may require a higher concentration such as 0.05% to achieve the same effectivity in slowing myopia progression in terms of spherical equivalent, and axial length elongation reduction (Brennan et al., 2021).

Another factor that plays a role in myopia progression is time outdoors. There is strong evidence that lack of time outdoors may induce myopia progression (Xiong et al., 2017). Studies show that time outdoors was related to lessening near-work activities thus effective in delaying myopia onset.

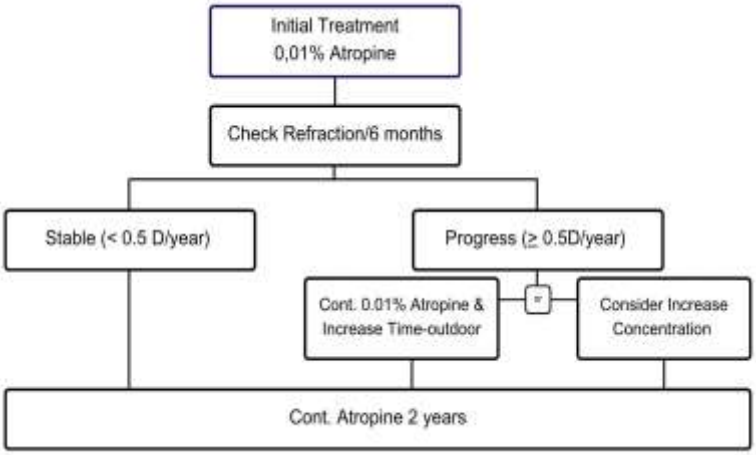

Figure 2. Summary Strategy Atropine Approach

CONCLUSION

Atropine eye drops are effective in both high and low concentrations in controlling myopia progression in children. However, over the years, low-concentration atropine (0.01%) tends to have minimal side effects, rebound, and re-treatment after washout. Yet, increasing atropine concentration may need to be considered in younger patients with poor response to low-dose atropine combined with intensifying time outdoors.

In summary, appropriate doses, proper evaluation, and duration of treatment would impact myopia progression and minimize rebound in the future.

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