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Low-Concentration Atropine Eye Drops for Myopia Progression

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Purpose: Atropine eye drops is an emerging therapy for myopia control. This article reviews the recent clinical trials to provide a better understanding of the use of atropine eye drops on myopia progression.

Methods: All randomized clinical trials of atropine eye drops for myopia progression in the literatures were reviewed.

Results: Atropine eye drops 1% conferred the strongest efficacy on myopia control. However, its use was limited by the side effects of blurred near vision and photophobia. ATOM 2 study evaluated 0.5%, 0.1%, and 0.01% atropine on 400 myopic children, and suggested that 0.01% is the optimal concentration with good efficacy and minimal side effects. Since then, the use of atropine eye drops has been transitioned from high-concentration to low-concentration worldwide. Recent Low-concentration Atropine for Myopia Progression (LAMP) study evaluated 0.05%, 0.025%, 0.01% atropine eye drops and placebo group in 438 myopic children. The study firstly provided placebo-compared evidence of low-concentration atropine eye drops in myopia control. Furthermore, both efficacy and side effects followed a concentration-dependent response within 0.01% to 0.05% atropine. Among them, 0.05% atropine was the optimal concentration to achieve best efficacy and safety profile.

Conclusions: Low concentration atropine is effective in myopia control. The widespread use of low-concentration atropine, especially in East Asia, may help prevent the myopia progression for the high-risk children. Further investigations on the rebound phenomenon following drops cessation, and longer-term individualized treatment approach should be warranted.

Key Words: atropine, low concentration, myopia

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EPIDEMIOLOGY OF MYOPIA IN ASIA

Myopia is the most common ocular disorder, predominantly in East Asia. [1–4] It is estimated that around 2.5 billion people will have myopia by 2020,[1] and approximately half of the world population will become myopic, with 10% of them highly myopic by 2050.[5] In mainland China, the 3-year incidence of myopia (SE ≤ -0.5 D) in school-aged children aged 6 to 7 years was 39.5%.[6] In urban areas, such as Guangzhou, the prevalence was 5.7% in 5-year olds, 30.1% in 10-year olds, and up to 78.4% in 15-year olds, respectively.[7] In rural areas, such as Yangxi and Shunyi, the prevalence was zero in 5-year olds, 36.8% in 13-year olds, 43.0% in 15-year olds, and 53.9% in 17-year olds, respectively.[8,9] Prevalence of myopic kindergarten children was 0.8% in 4-year old, 1.3% in 5-year old, and 3.7% in 6-year old.[10] In Taiwan, the 1-year incidence rate of myopia was 17.7% from age 7 to 11.[11] From the year 1983 to 2000, there was significant increase in prevalence of myopia in Taiwan. It increased from 5.8% to 21.0% at 7-year olds, from 36.7% to 61.0% at 12-year olds, from 64.2% to 81.0% at 15-year olds, and from 74% to 84% among 16 to 18-year olds.[12] There was a high prevalence of myopia in Hong Kong school-age children: 17.0% in children younger than 7-year olds, which increased to 37.5% in 8-year olds, and 53.1% in children older than 11 years.[2] In Singapore, its prevalence was 11.0% in Chinese children younger than 6 years, 29.0%, 34.7%, and 53.1% in 7-, 8-, and 9-year olds, respectively.[13,14] In Korean children aged 5 to 18 years, the prevalence of myopia was 64.6%, and high myopia (SE ≤ -6.0 D) 5.4%.[15] Another Korean cohort reported the prevalence of myopia was 50% in 5- to 11-year olds, 78% in 12- to 18-year olds, and 45.7% in high school students respectively.[16] In India, its prevalence was found to be 21.1% in children aged 5 to 15 years.[17] In Nepal, prevalence in the urban was 10.9% in aged 10, 16.5% in aged 12, and 27.3% in aged 15, respectively.[18]

Different interventions have been attempted to reduce myopic progression, including increasing outdoor time,[6,19,20] optical methods such as bifocal/progressive spectacles,[21–24] orthokeratology,[25,26] defocus spectacles and contact lens,[27,28] and pharmacological methods including atropine eye drops.[29–33] Previous review and meta-analyses suggested that atropine eye drops conferred the best efficacy among all myopia prevention methods,[34,35] and this was further supported by the evidence in recent clinical trials.[30,31,33] This article reviewed the recent clinical trials to provide a better understanding of the use of atropine eye drops on myopia progression.

REVIEW OF CLINICAL RANDOMIZED CONTROLLED TRIALS FOR MYOPIA PROGRESSION

Atropine is the most effective medication that has been demonstrated to be consistently effective in slowing myopia progression.[35] A summary of randomized controlled trials (RCTs) in atropine for myopia progression is presented in Table 1. In 1989, Yen et al[36] conducted the first randomized placebo-controlled trial of 1% atropine for myopia control. A total of 96 children aged 6 to 14 years were randomized to 1% atropine, 1% cyclopentolate, and placebo group for 1 year. They proved that 1% atropine conferred the best efficacy in myopia control among

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TABLE 1. Summary of RCTs in Atropine for Myopia Progression

Author(s), y	Study Design	Area	Follow-Up (mo)	Sample Size	Age (y)	Treatment	Baseline SE (D)	Baseline AL (mm)	Change in SE	Change in AL
Yen et al, 1989[36]	RCT	Taiwan	12	96	6–14		−0.5 to -4 D			
				32	10.5	1% Atropine	−1.52 (0.96)	NA	−0.22 (0.54) D/y	NA
				32	10	1% Cyclopentolate	−1.45 (0.85)	NA	−0.58 (0.49) D/y	NA
				32	10.4	Placebo	−1.59 (0.92)	NA	−0.91 (0.58) D/y	NA
Shih et al, 1999[37]	RCT	Taiwan	24	200	6–13		−0.5 to -7 D			
				41	9.8	0.5% atropine	−4.89 (2.06)	NA	−0.04 (0.63) D/y	NA
				47	9.7	0.25% Atropine	−4.24 (1.74)	NA	−0.45 (0.55) D/y	NA
				49	8.9	0.1% Atropine	−4.41 (1.47)	NA	−0.47 (0.91) D/y	NA
				49	8.3	0.5% Tropicamide	−4.5 (1.86)	NA	−1.06 (0.61) D/y	NA
Shih et al, 2001[47]	RCT	Taiwan	18	227	6–13					
				76		0.5% Atropine + multifocal lenses	−3.20 (0.14)	24.75 (0.10)	−0.41 (0.07) D/y	0.22 (0.03) mm/y
				75		Multifocal lenses	−3.34 (0.14)	24.80 (0.09)	−1.19 (0.07) D/y	0.49 (0.03) mm/y
				76		Single-vision spectacles	−3.28 (0.13)	24.62 (0.10)	−1.40 (0.09) D/y	0.59 (0.04) mm/y
Chua et al, 2006 (ATOM1 study)[30]	RCT	Singapore	24	400	6–12		−1 D to -6 D			
				200	9.2	1% Atropine treated	−3.36 (1.38)	24.80 (0.83)	−0.28 (0.92) D/2 y	−0.02 (0.35) D/2 y
						1% Atropine untreated	−3.40 (1.35)	24.81 (0.84)		
				200	9.2	Placebo treated	−3.58 (1.17)	24.80 (0.84)	−1.20 (0.69) D/2 y	0.38 (0.38) D/2 y
						Placebo untreated	−3.55 (1.21)	24.76 (0.86)		
Liang et al, 2008[50]	RCT	Taiwan	8.28 (2.48)	71	6–15		−0.50 D or less			
				23	10.91 (2.43)	0.5% Atropine	−2.17 (1.48)	24.11 (0.89)	−0.15 (0.15) D/y	NA
				22	9.91 (2.11)	0.25% Atropine	−2.09 (1.68)	24.24 (0.53)	−0.38 (0.32) D/y	NA
				26	10.23 (1.66)	0.25% Atropine + acupoints	−1.91 (1.20)	23.95 (0.77)	−0.21 (0.23) D/y	NA
Chia et al, 2012 (ATOM2 study)[31]	RCT	Singapore	24	400	6–12		−2.00 D or less			
				161	9.70 (1.5)	0.5% Atropine	−4.7 (1.8)	25.2 (0.9)	−0.30 (0.60) D/2 y	0.27 (0.25) mm/2 y
				155	9.70 (1.6)	0.1% Atropine	−4.8 (1.5)	25.2 (0.8)	−0.38 (0.60) D/2 y	0.28 (0.27) mm/2 y
				84	9.50 (1.5)	0.01% Atropine	−4.5 (1.5)	25.1 (1.0)	−0.49 (0.63) D/2 y	0.41 (0.32) mm/2 y
Yi et al, 2015[39]	RCT	China	12	132	7–12		−0.5 to -2 D			
				68	9.91 (1.36)	1% Atropine	−1.23 (0.32)	23.75 (0.1)	0.32 (0.22) D/y	−0.03 (0.07) mm/y
				64	9.72 (1.40)	Placebo	−1.15 (0.30)	23.72 (0.12)	−0.85 (0.31) D/y	0.32 (0.15) mm/y
Wang et al 2017[40]	RCT	China	12	126	5–10		−0.5 to -2 D			
				63	9.1 (1.4)	0.5% Atropine	−1.3 (0.4)	24.1 (1.0)	−0.8 D/y	23.0 mm at 1 y
				63	8.7 (1.5)	Placebo	−1.2 (0.3)	23.8 (0.9)	−2.0 D/y	24.3 mm at 1 y
Yam et al, 2018 (LAMP study)[33]	RCT	Hong Kong	12	438	4–12		−1 D or less			
				109	8.45 (1.81)	0.05% Atropine	−3.98 (1.69)	24.85 (0.90)	−0.27 (0.61) D/y	0.20 (0.25) mm/y
				108	8.54 (1.71)	0.025% Atropine	−3.71 (1.85)	24.86 (0.95)	−0.46 (0.45) D/y	0.29 (0.20) mm/y
				110	8.23 (1.83)	0.01% Atropine	−3.77 (1.85)	24.7 (0.99)	−0.59 (0.61) D/y	0.36 (0.29) mm/y
				111	8.42 (1.72)	Placebo	−3.85 (1.95)	24.82 (0.97)	−0.81 (0.53) D/y	0.41 (0.22) mm/y
Tan et al, 2019 (AOK study)[49]	RCT	Hong Kong	1	68	6–11		−1 D to -4 D			
				33	9.09 (1.17)	0.01% Atropineopine with OK	−2.71 (0.91)	24.45 ± 0.62	NA	−0.05 (0.05) mm/mo
				35	9.09 (1.11)	OK	−2.88 (0.92)	24.46 ± 0.79	NA	−0.02 (0.03) mm/mo

Data are represented as mean (SD). AL indicates axial length; OK, orthokeratology; RCT, randomized controlled trial; SE, spherical equivalent.

3 groups, with myopia progression of 1% atropine −0.22 ± 0.54 D/year, 1% cyclopentolate −0.58 ± 0.49 D/year, and placebo −0.91 ± 0.58 D/year.[36] However, axial length (AL) data were not available, and therefore effect of atropine on axial elongation was not certain. Furthermore, all children in 1% atropine group complained photophobia causing a significant drop outs. Because of the significant side effects of 1% atropine, lower concentration was evaluated with the aim to decrease the side effects and to maintain the efficacies. In year 1999, Shih et al[37] conducted a randomized controlled trial on 200 children aged 6 to 13 years, on 0.5%, 0.25%, 0.1% atropine, and 0.5% tropicamide (as control group). After 2 years of follow-up, the mean myopic progression in each group was −0.04 ± 0.63 D/year, −0.45 ± 0.55 D/year, and −0.47 ± 0.91 D/year in the 0.5%, 0.25%, and 0.1% atropine groups, and −1.06 ± 0.61 D/year in 0.5% tropicamide control group, respectively. All atropine treatment groups were effective compared with the control group ($P < 0.01$).[37] Of note, only 22% of children in atropine 0.5% group complained of photophobia during the first 3 months of treatment, supporting that lower concentration atropine would have lower side effects. However, the study was limited by the lack of AL data, and a placebo control group. Therefore, the respective efficacy of 0.5%, 0.25%, and 0.1% needs to be further established.

In 2006, Chua et al[30] conducted the Atropine for the Treatment of Childhood Myopia (ATOM 1) Study, which provides the strongest evidence for 1% atropine on myopia control. A total of 400 children aged 6 to 12 years with myopia (spherical equivalent −1.00 to −6.00 D) were randomized to 2 groups. In the treatment group, children received 1% atropine once per night in 1 eye and no treatment in the fellow eye. In the control group, placebo drop was used in 1 eye and no treatment was administered to the fellow eye. At 2 years, the mean progression of myopia was significantly lower in the 1% atropine group (−0.28 ± 0.92 D/2 years), compared with the control group (−1.20 ± 0.69 D/2 years). The mean increase in AL measured by A-scan ultrasonography in ATOM 1 study remained unchanged (−02 ± 0.35 mm/2 years) in the 1% atropine group compared with significant elongation of AL (0.38 ± 0.38 mm/2 years, $P < 0.001$) in placebo eyes.[30] Over 2 years, atropine treatment achieved approximately a 77% reduction in mean progression of myopia compared with placebo treatment. Moreover, ATOM 1 study has detailed documentation showing that only 18% participants complained photophobia. However, the safety profile of atropine, such as pupil size and accommodation, also needs to be a concern and deterred many children and parents from using this medication. The primary ocular side effects of topical atropine include mydriasis leading to photophobia, loss of accommodation resulting in blurred near vision, and local allergic responses.

In addition to the side effects, high concentration atropine leads to a significant rebound following cessation of eye drops.[38] In ATOM1, myopic progression during the 1-year washout was −1.14 ± 0.8 D/year in the atropine 1% group and −0.38 ± 0.39 D/year in the control group ($P < 0.001$).[38] Altogether during the

entire 3-year study, the myopic progression was -0.46 ± 0.26 D/year and -0.52 ± 0.30 D/year for the atropine 1% and placebo groups, respectively ($P = 0.043$). The AL change was 0.29 ± 0.37 mm in 1% atropine-treated eyes, and 0.52 ± 0.45 mm in the placebo-treated eyes ($P < 0.001$).

The antimyogenic effect of 1% atropine and 0.5% atropine for myopia progression was also evident in other subsequent RCTs.[39,40] However, they did not evaluate the side effects in details. By far, high concentration atropine remained the most efficacious treatment for myopia progression, but the side effects profile and the rebound following drops cessation limited its widespread use. Thus, in 2012, the ATOM2 study evaluated lower-concentration for myopia progression to determine the lower optimal concentration. They evaluated 0.5%, 0.1%, and 0.01% concentration on 400 children with myopia of at least −2.0 D and randomized allocation in a 2:2:1 ratio. The authors initially planned to use 0.01% as the control group, and therefore no placebo control group was allocated. Over 2 years, the myopia progression was -0.30 ± 0.60 D, -0.38 ± 0.60 D, and -0.49 ± 0.63 D, respectively, and axial elongation was 0.27 ± 0.25 mm, 0.28 ± 0.28 mm, and 0.41 ± 0.32 mm in the 0.5%, 0.1%, and 0.01% atropine groups, respectively.[31] Interestingly, the children in the atropine 0.01% progressed by −0.43 D in the first year, and then significantly slowed down during the second year (only 0.06 D progression). Whereas the axial elongation was 0.24 mm during the first year and 0.17 mm during the second year, with a total of 0.41 mm increased over the 2 years.[31] The efficacy of 0.01% atropine in ATOM2 was mainly based on the second year with a significantly less SE progression better than AL elongation. 0.01% atropine also had minimal side effects. The photopic pupil size was increased by 3.11 mm, 2.42 mm, 0.91 mm in 0.5%, 0.1%, and 0.01% atropine groups, respectively.[31] Accommodation amplitude was 3.6 D in atropine 0.5%, 6.0 D in atropine 0.1%, and 11.7 D in atropine 0.01% respectively.[31] By using a ≥3-mm increase in photopic pupil size and 5 D accommodation amplitude as the cut-off beyond which there will be significant discomfort for a number of users, the data suggest that atropine concentration less than 0.1% is acceptable.[41,42] Interestingly, a similar rebound was seen in 0.5% and 0.1% atropine group, but much less with 0.01%. Myopic progression in 1-year washout was -0.87 ± 0.52 D, -0.68 ± 0.45 D, and -0.28 ± 0.33 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively ($P < 0.001$). During the entire 3-year study period, the SE became more myopic by -1.15 ± 0.81 D, -1.04 ± 0.83 D, and -0.72 ± 072 D in the atropine 0.5%, 0.1%, and 0.01% groups, respectively ($P < 0.001$).[43] An increase in AL continued to be observed in the 0.01% atropine group during the third year of the study (0.19 ± 0.18 mm), compared with atropine 0.1% (0.24 ± 0.21 mm; $P = 0.042$) and atropine 0.5% (0.26 ± 0.23 mm; $P = 0.013$) groups.[43] The overall progression of myopia over the 36 months was the slowest in the 0.01% atropine group (-0.72 ± 0.72 D), followed by the 0.1% atropine group (-1.04 ± 0.83 D), and then 0.5% atropine group (-1.15 ± 0.81 D) ($P < 0.001$).[43] At phase 3 of ATOM2, 192 children who had rapid progression of myopia (defined as >−0.5 D/year) within the washout year (third year) went on to resume the atropine 0.01% for another 2 years. At the end of this 5-year trial, the overall myopia progression among the 0.5%, 0.1%, and 0.01% atropine group was similar, with -2.32 ± 1.04 D, -2.34 ± 1.07 D, and -2.25 ± 1.11 D, respectively ($P = 0.95$).[32] With fewer side effects and rebound following atropine cessation, the authors suggested that the 0.01% atropine was better in treatment-to-side effect balance.

TRANSITIONS FROM HIGH-CONCENTRATION TO LOW-CONCENTRATION ATROPINE

The results from ATOM 2 studies bring paradigm shift of management of myopia control in using low-concentration atropine eye drops, which are well-tolerated, and with less rebound following cessation of treatment. A subsequent meta-analysis by Gong et al[44], which included 19 studies of high, moderate, and low concentration atropine for myopia progression, suggested that the efficacy of atropine is concentration-independent from 0.01% to 1% atropine, whereas the adverse effects are concentration-dependent.[44] Of note, 0.01% atropine for myopia control was also recommended by the American Academy of Ophthalmology.[45] Such data lead to a surge in the popularity in using low-concentration atropine, in particular, 0.01% for myopia control. In a worldwide survey of pediatric ophthalmologists, 0.01% atropine is the most popular measure for myopia control.[46]

Unresolved Questions From Previous Studies

Although ATOM 2 provided important data to suggest the efficacy of low-concentration atropine, it was unfortunately limited by the lack of placebo control group. Of note, comparing with the historical placebo group in ATOM1, the 0.01% atropine has no effect on axial elongation (0.41 vs 0.38 mm/2 years), despite its significant effect on refractive error (−0.49 D/2 years vs −1.20 D/2 years).[31] Important questions on low-concentration atropine for myopia control remained to be answered: Does low-concentration atropine prevent myopia progression compared with the placebo group? Does the effect act along with a concentration-dependent response in low-concentration atropine? What is the optimal concentration with the best efficacy and safety? Thus, we have conducted the Low-concentration Atropine of Myopia Progression (LAMP) study, which is a double-blinded, randomized, placebo-controlled trial to evaluate the efficacy and safety of low concentration atropine 0.05%, 0.025%, and 0.01%.

LOW-CONCENTRATION ATROPINE FOR MYOPIA PROGRESSION (LAMP) STUDY

The LAMP study reported 438 children aged 4 to 12 years with myopia of at least −1.0 D were randomized in a 1:1:1:1 ratio to receive atropine 0.05%, 0.025%, 0.01%, and placebo eye drops daily. After 1 year, the mean SE change was -0.27 ± 0.61 D, -0.46 ± 0.45 D, -0.59 ± 0.61 D, and -0.81 ± 0.53 D, respectively ($P < 0.001$) (Fig. 1). Meanwhile, the mean AL change after 1 year was 0.20 ± 0.25 mm, 0.29 ± 0.20 mm, 0.36 ± 0.29 mm, and 0.41 ± 0.22 mm, respectively ($P < 0.001$) (Fig. 2).[33] There was a clear concentration-dependent response.[33] Among them, 0.05% atropine was most effective for controlling myopia progression and axial elongation during the study period.[33] Of note, 0.01% reduced AL elongation at 12%, compared with the placebo group, and that the difference did not reach statistical significance. Nevertheless, it achieved a 27% reduction in SE progression.

On the aspect of side effect profiles, all groups of low-concentration atropine in our study (0.05%, 0.025%, and 0.01%) were well tolerated. First, accommodation amplitude reductions in all groups were clinically small, with 1.98 D,

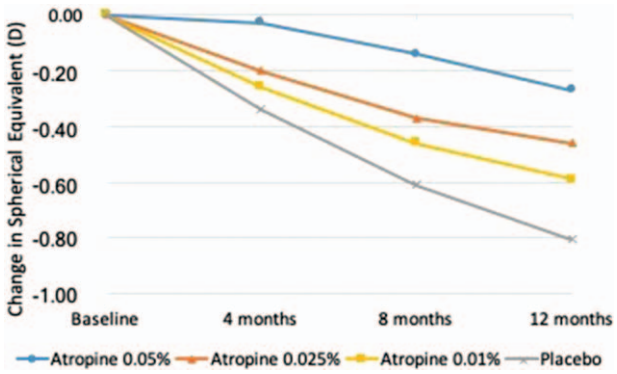

FIGURE 1. Change in spherical equivalent (SE) over one year. (Data from Yam JC, Ophthalmology. 2019).

1.61 D, 0.26 D, and 0.32 D in 0.05%, 0.025%, 0.01% atropine groups, and placebo group, respectively.[31] In a practical term, a reduction of within 2 D accommodation amplitude (eg, from a 12 D accommodation amplitude reduce to 10 D) corresponds to an increase of the near-point distance from 8.3 to 10 cm, which is not a major issue clinically. Second, pupil size increased by 1.03 mm, 0.76 mm, 0.49 mm, and 0.13 mm in 0.05%, 0.025%, 0.01%, and placebo group, respectively. By using a ≥3-mm increase in photopic pupil size as the cutoff beyond which there will be significant discomfort for a number of users, the data suggest that all low-concentration atropine are well tolerated, with increased 3.11 mm, 2.42 mm, 0.91 mm in 0.5%, 0.1%, and 0.01% atropine groups, respectively.[41,42] Third, the near vision and distance vision in all groups were not affected in atropine concentration < 0.05%.[31,33] In addition, a locally validated Chinese version of National Eye Institute Visual Function Questionnaire was administered to evaluate the vision-related quality of life. LAMP study suggested that the vision and quality of life in 0.05%, 0.025%, and 0.01% atropine were similar to those of subjects receiving the placebo.[33] Lastly, symptoms of photophobia were reported similar among all groups, as 7.8% in 0.05% atropine, 6.6% in 0.025% atropine, and 2.1% in 0.01% atropine of participants in LAMP study.[33] In consideration of both efficacy and side effect profiles, LAMP study suggested that 0.05% atropine was the most effective in controlling SE progression and axial elongation during 1 year.

LAMP study contributed to the understanding of low concentration atropine for myopia control in several aspects. First, it is the first double-blinded, randomized, placebo-controlled trial

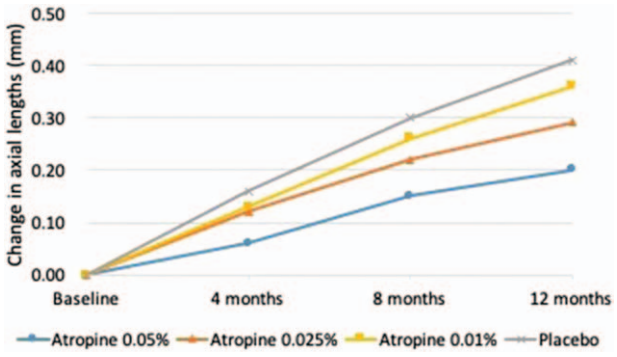

FIGURE 2. Change in axial length (AL) over one year. (Data from Yam JC, Ophthalmology. 2019).

on low concentration atropine drops, which provides the strongest evidence to support its role in myopia control. Second, it has resolved the previous controversy, and delineated a concentration-dependent response in both the efficacy and side effect profile in the low-atropine concentration range from 0.05% to 0.01%. Third, the study has further suggested that a higher concentration of low-concentration atropine 0.05% is most efficacious among the 3 concentrations, and remained well tolerated.

PERSPECTIVE OF LAMP STUDY

Current randomized controlled trials confirm the efficacy of low-concentration atropine compared with placebo, and 0.05% provides the best efficacy and safety in controlling myopia progression and AL elongation. However, some important questions have yet to be answered: What is optimal concentration of low-concentration atropine eye drops over a longer period? Are the efficacies of low-concentration atropine better in the second year than the first year? The LAMP phase 2 (the second year report) was designed to evaluate the 2-year efficacy and side effect profile of the 3 concentrations 0.05%, 0.025%, and 0.01% atropine. It will also evaluate whether the efficacies of low-concentration atropine will be better in the second year than that in the first year. Another remaining question is the rebound phenomenon following cessation of atropine 1%, 0.5%, 0.1%, and 0.01%, observed in ATOM 1 and ATOM 2 studies. These were based on previous postulations that atropine continuously administered for 2 years may lead to stabilization effect, and therefore could be stopped afterward. However, the subsequent rebound phenomenon observed affects the treatment regimen and wean off strategy. Therefore, we have planned in our phase 3 (third year) study to randomize each of the 3 groups 0.05%, 0.025%, and 0.01% into wash out group and treatment-continued group, to evaluate efficacy of 0.05%, 0.025%, and 0.01% atropine group during 3 years; whether treatment should be stopped after 2 years of atropine; and the rebound phenomenon of 0.05%, 0.025%, and 0.01% atropine following cessation of treatment. Finally, we plan to conduct phase 4 of the study, to resume atropine in children whose myopia refraction and AL progressed during the washout period, to determine the long-term efficacy of low concentration atropine during a 5-year period.

Combination Treatment

Despite the efficacy of atropine therapy, the treatment response remained variable. Shih et al[47] found that 10.6% of children did not respond to atropine 0.5%. In another study, poor response children (defined as myopia progression >1 D/year) account for 4% in the 0.5% atropine group, 17% in the 0.25% atropine group and 33% in the 0.1% atropine group, compared with 44% in the control group.[37] In ATOM 1 study, 12% of children treated with atropine 1% at 1 year continued to progress by >−0.5 D/year.[48] In ATOM 2, children in the 0.5%, 0.1%, and 0.01% group was 4.3%, 6.4%, and 9.3%, respectively, had myopia progression ≥−1.5 D during the initial 2 years of active treatment.[31] In our LAMP study, 30.4%, 48.4%, and 56.2% in the 0.05%, 0.025%, and 0.01% atropine groups, respectively, progressed by ≥-0.50 D, compared with 75.8% in the placebo group.[33]

Updated strategies including increasing the concentration of atropine or combined with more outdoor time, multifocal glasses, or, orthokeratology, are needed to improve the efficacies of

myopia control. [46,47,49] In 2001, 188 school-aged children were treated with 0.5% atropine plus multi-focal spectacles versus multifocal glasses alone, or single-vision glasses alone, in a double-blind, randomized control trial.[47] After being regularly followed up in Taiwan for 18 months, the increase in the AL in the atropine plus multifocal glasses group was significantly less than the other 2 groups ($P = 0.0001$). A small study of 65 children demonstrated that myopia progression of -0.15 ± 0.15 D/year, -0.38 ± 0.32 D/year, and -0.21 ± 0.23 D/year in the 0.5%, 0.25%, and 0.25% atropine plus auricular pressure groups, respectively.[50] Combined Atropine with Orthokeratology (AOK): a 1-month result of AOK, children aged 6 to 11 years, and with -1.00 to -4.00 D myopia were randomly assigned to AOK group or orthokeratology alone (OK) group. Data of 30 AOK and 34 OK subjects who had completed the 1-month visit was analyzed. The mean change in AL was significantly bigger in AOK than OK subjects (AOK: -0.05 ± 0.05 mm; OK: -0.02 ± 0.03 mm, $P = 0.003$).

CONCLUSIONS

In conclusion, results from research have demonstrated that low-concentration of atropine is useful in retarding myopia progression in a particular proportion of myopic schoolchildren. The widespread use of low-concentration atropine, especially in East Asia, may help prevent the myopia progression for the high-risk children. The LAMP study result provides recent evidence in the use of low concentration atropine, in particular, 0.05% atropine, because of its higher efficacy and yet well-tolerated side effect profile. Longer-period efficacy and safety profile are needed. Further investigations on the rebound phenomenon following drops cessation, and longer-term individualized treatment approach should be warranted.

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