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Low-Concentration Atropine Differential Effects on Ocular Biometrics (Clinical Pilot Study)

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Abstract

Atropine low concentration is an evolving treatment for myopia progression, but its effectiveness and optimum concentration remain unclear. The current study was conducted to assess the effectiveness and protection of low-concentration atropine for one year with different doses, and a placebo was used as a control. For this purpose, a double-blind single-centered clinical trial consisting of 132 children (subjects), aged (5-13) years with myopic refraction of at least −1.0 D in both eyes, astigmatism of less than −2.5 D and confirmed myopic development of at least 0.5 D for 1 year were performed. The participants in this trial were allocated randomly with a 1:1 ratio in 6 levels identified by genders and age groups, and categorized into 5 to 7 years, 8 to 10 years, and 11 to 13 years, so that gender and age could be equilibrated between 4 atropine levels, i.e., 0.05%, 0.025 %, or 0.01 and placebo. The demographic factors like baseline near work, outdoor time, basic refractive error, lodging, pupil diameter, and best corrected visual acuity (BCVA) were recorded. Furthermore, the best corrected visual acuity was determined after two weeks, 4, 8, and 12 months. A concentration-dependent myopia control response was observed at all atropine levels. During the first year, 69.6%, 51.6%, and 0.05%, 0.025%, and 0.01%, respectively, of subjects with atropine groups increased by less than 0.5%, compared to 24.2% in the placebo group;15.2%, 12.6% and 27.8%, respectively. In all classes, both near and distant BCVA were not significantly affected. Every group's visual acuity and vision-related quality of life were

unaffected. The study showed that atropine eye drops of 0.05 (%), 0.025 (%), and 0.01 (%) decreased myopia progression in a concentration-dependent manner. Both concentrations were well tolerated and had no negative impact on visual quality of life.

Keywords: Myopia, atropine, placebo

Introduction

Myopia is the world's most common eye disorder, particularly in Eastern Asia(Morgan, 2005). The prevalence of myopia and high myopia, as more than 6 diopter (D) refractive errors, has increased and by 2025 is estimated to affect approximately 50% and 10% of the world population, respectively(Holden, 2016). High myopia is particularly associated with excessive axial elongation, which can cause complications of sight including macular hemorrhage, retinal detachment, cataract, and glaucoma(Celorio, 1991; Mitchell, 1999)**.** Given the increasing prevalence of myopia, a significant health burden is placed on affected people and society with the visual dysfunction and cost of handling complications related to myopia. Atropine eye drops are an emerging therapy to reduce the progression of myopia.

Atropine 2, 0.01 (%) atropine for Myopia Treatment (ATOM) has given a 59 percent reduced progression of spherical equivalent (SE) compared to an ATOM (Morgan, 2005) historical control, with no axial length elongation (AL) effects have been observed(Bullimore, 2018). ALMP has demonstrated the best efficacy of 0.05 percent atropine between 0.05%, 0.025%, and 0.01 percent atropine. The study of the Low Concentration of atropine for Myopia Progression showed 0.05% (Yam, 2020). The growth of 0.27 ± 0.61 D, –0.46 ± 0.45 D, —0.59 ± 0.61 D and –0.81 ± 0,50 D, while the reduced AL elongation values of 0.20 ± 0.25 mm, 0.26 ± 0.29 mm, and 0.41± 0.22 mm, were at 0,05 (%) atropine, and 0,01 (%) atropine and placebo. Note that the difference in AL elongation was statistically significant between 0.01 percent atropine and placebo group(Saw, 2005).

(Gong, 2018) submitted that the difference between SE and AL might be due to interactions between atropine effects and certain changes in corneal power in the development of the cornea. An animal study of infant marmosets found that 1% and 0.1% of topical atropine could lead the lens to thicken and move forward, suggesting its effect on the anterior segment. The question remained whether axial elongation and other related biometric changes mediate the anti-myopic effect of low-contents atropine. Excessive axial elongation causes the retinal, choroid and sclera

to be mechanically stretched and thinner; this leads to degenerative problems and following myopic complications, including myopic choroid neovascularization. In the study, we evaluated changes in ocular biometrics in SE progression by 0.05%, atropine by 0.025%, and placebo over one year compared to the LAMP study by 0.01%.

Materials and Methods

The study was conducted in the Pediatric Ophthalmology department. Sheikh Zayed Medical College and Hospital, Rahim Yar Khan, and the government Sadiq College Women University, Bahawalpur from October 2022 to April 2024. This double-blind single-center clinical trial consists of children aged 5 to 13 years with myopic refraction of at least 1.0 D in both eyes, astigmatism of less than 2.5 D, and confirmed myopic development of at least 0.5 D for the past 1 year. The patient was excluded from the study, those who have ocular disease i.e., amblyopia, contract and strabismus, or patients already taken the dose of atropine, the optical procedure for myopia control, and atropine allergy. The participants in this trial were allocated randomly with a 1:1 ratio in 6 levels identified by genders and age groups, and categorized into 5 to 7 years, 8 to 10 years, and 11 to 13 years, so that gender and age could be equilibrated between 4 atropine levels, i.e., 0.05%, 0,025 %, or 0.01 and placebo. Test medicines were pre-packaged with equal numbers, mentioned expiry date, and were described to the research subjects. The concentration of atropine sulfate at 0.05%; 0.025%; or 0.01% was suitable and 0.9% sodium chloride was recommended in placebo. Each batch of eye drops had an expiration period of 2 years. The manufacturer gives analytical certificates with assurances of concentration, stability, and sterility for 0.05% 0.025 %, 0.01 % atropine, and 0.9 percent sodium chloride for placebo. The baseline visit recruited all studied subjects and randomized them to four atropine levels. The following timetables were used for all subjects: two weeks (monitor visit) 4 months, 8 months, and 12 months from baseline visits using 0.05%, 0.025, 0.01%, and placebo following the same procedure. The two-week monitored visit was to decide whether any hyperopic change was observed due to the application of a higher atropine dose in ATOM(Chua, 2006). An optometrist masked for the group allocation of subjects was assessed during each visit with the remote best corrected visual acuity (BCVA) in the logarithm of minimum resolution angle (logMAR). The best correction of the distance for evaluating near visual acuity spectacle with a reduced read graph of logMAR, set under well-lit conditions at 40 cm. Participants were told to move the target toward the inside of the N5 print point and then toward the outside before it only became obvious. The accommodation

amplitude (D) was measured as the opposite of the host point. The OPD-Scan III was used to assess the mesopic and the photopic pupil scale (Nidek, International, USA). Cycloplegic self-fracturing (Nidek, USA), at least 2 periods of eye drops were done after the cycloplegic procedure periodically in the first, second, and third cycles. To ensure that the eyes were properly dilated, additional cycles of cycloplegic eye drops were added. Spherical equivalent (SE), plus half of the cylinder power, was measured as spherical power. Ocular AL was tested based on non-contact partial coherence interferometry on the Zeiss IOL Master (Dublin, CA). Each subject was categorized by the mean number of participants reporting atropine in the first 12 months according to the compliance standard. All of the participants were given the best-corrected spectacles. Outdoor activities including time spent on sport and recreation, cellular telephone, computer, video games, and TV viewing were also considered while recording data. The non-cycloplegic auto refraction (Nidek, USA) and Zeiss IOL Master for both parents of each child were registered in the parental refraction process and AL, respectively. The Visual Function Framework was given to all subjects during a 12-month follow-up visit to assess the effect of various treatment groups on vision-related life. A list of eleven sub-scales was dealt with: general health, overview, eye pain, near vision, view from a distance, social function, weaknesses in position, mental health, dependence, color vision, and peripheral vision. The main result was a 1-year increase in myopia to SE changes. Each eye myopia development was further subdivided into mild (<0.5 D), moderate (0.5-0.99 D), or extreme myopia progressions (≥1.0 D). AL transition at 1 year was part of the secondary results. Parameters for side effects were improvements to the amplitude of accommodations, mesopic and pupil sizes remote BCVA, and near visual acuity. The basic monitoring process was conducted on all ophthalmic parameters, including SE, AL, lodging, pupil size, and visual acuity. Patients and parents were allowed during each visit to disclose any medical issue or adverse effects observed during the study. They were also asked about asthma symptoms, visual blurriness, glare, lack of sight, and any illness reported after the previous visit. All adverse effects were noted regardless of their link with atropine use.

The approximate 0.05%, 0.025%, and 0.01% atropine levels and placebo effect for myopia rate of development were set at -0.28 D; -0.14 D; -0.43 D, and -0.76 D, respectively. All data have been evaluated based on the purpose of treatment. The discrepancy between the baseline and the respective follow-up values has established the changing of parameters. For statistical analysis, the Chi-Square test and Fisher exact test were used. The analysis of variance has been used to

measure the continuous data group discrepancy. A generalized estimate equation with robust standard errors was used to check the correlation among eyes and to include both eyes of a subject in the study. The coefficient of treatment groups in a regression model after the arrangement of treatment groups in an ordinary scale verified the concentration-response effect of atropine on the ophthalmic parameters. The data was analyzed using the SPSS software and means were separated using a 5% significance level.

Results

Eligibility was evaluated for a total of 246 subjects and, at last, 132 subjects with 31, 37, 28, and 36 subjects attributed 0.05% atropine, 0.025% atropine, 0.01% atropine, and placebo respectively, were recruited. The mean and standard deviation values for each group are described in Table 1. The demographics, baseline near work and outdoor time, basic refractive error, lodging, pupil diameter, BCVA, parental SE, and AL showed no significant differences in cases and controls.

Spherical and Axial Length Changes

Concentration-dependent myopia control response was observed in all atropine levels (Table 1). At the 2-week monitor visit in all 4 groups, no first hyperopic change was observed. The change in atropine groups axial length during the 1 year was greater in placebo than other atropine groups of 0.05%, 0.025%, and 0.01%. No AL gap was noted when comparing the 0,01% atropine and the placebo groups. In year 1, 69.6%, 51.6%, and in 0.05%,0.025%, and 0.01%, respectively, of subjects with atropine groups increased by less than 0.5%, compared to 24.2% in the placebo group;15.2%, 12.6% and27.8%, respectively 0.05%, and 0.01%, respectively, of atropine populations increased by 0.01 and 0.05%.

Accommodation, Pupil Diameter, and Visual Accuracy Changes

The changes in the amplitude of accommodation have resulted in concentration reactions. The mean amplitudes of accommodation between all 4 classes were different. A direct comparison between 0.01 percent atropine and placebo groups showed similar variations in the accommodation amplitude, but comparisons between others showed substantial differences. Over time, the changes in accommodation were stable. In all classes, both near and distant BCVA were not significantly affected (Table 2).

The photophobia symptoms of individuals varied but decreased over time within 1 year from the baseline in groups on the 2-week visit (P<0.001; Table 3). The study also reported that the participants receiving low atropine did not need a progressive lens. In both treatment groups, the mean intraocular pressure was similar (15.32.10 mmHg at 0,05%, 15.82.06 mmHg at 0.025%, and 15.42.07 mmHg atropine groups at 15, and 32.09 mmHg at placebo; =0.54). Both groups had a similar allergic conjunctivitis occurrence. Four subjects had serious hospitalization adverse events (Table 3).

The correlation study between the spherical equivalent, axial length (mm), photopic pupil size, mesopic pupil size, accommodation amplitude, distance VA (Log MAR), and Near VA (log MAR) was presented in Table 3. The spherical equivalent (D), axial length (mm), photopic pupil size (mm), mesopic pupil size (mm), and accommodation amplitude (D) recorded significant correlation in all four atropine groups along with placebo. In the case of distance VA (logMAR) and Near VA (logMAR), a non-significant correlation for all atropine levels and placebo was observed. The overall group and individual time effects were also recorded as positive and significantly different for all studied ophthalmic parameters. The study also describes the other diseases diagnosed during the atropine-level treatments (data not mentioned). It includes gastroenteritis, flu, and asthma symptoms recorded at (0.05%) of atropine patients, similarly, pneumonia, gastroenteritis, and influenza signs were also reported during (0.025%) of atropine treatment. However, at 0.01% level, and in placebo patient's influenza and lip damage were recorded. Similar results were reported by (Yam, 2020) suggesting that the application of atropine with high and low concentrations has side effects on the health of the patients.

Table 1:

	0.05% (N=55)		**0.01% (N=65)**		**0.025% (N=60)**		**Placebo (N=66)**		
Parameters	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P value**
Gender (Male %)	31	0.56	37	0.57	28	0.47	36	0.55	0.37
Age (yrs)	9.01	1.22	8.97	1.3	9.28	1.17	9.47	1.15	0.57
BMI (kg/m2)	15.18	2.37	15.15	2.12	15.3	2.21	14.75	2.45	0.16
Paternal Axial Length (mm)	23.38	1.10	23.62	1.20	23.45	1.08	23.56	1.07	0.58
Maternal Axial Length (mm)	23.05	1.20	22.85	1.27	23.06	1.54	23.00	1.38	0.48
Central Corneal Thickness (μm)	527.94	28.45	536.80	30.00	524.20	25.31	525.34	31.75	0.22
IOP (mmHg)	14.58	2.27	14.78	1.92	14.02	1.92	2.52	0.22	0.42
Paternal Spherical Equivalent (D)	-4.02	2.49	-4.38	2.59	-4.01	2.34	-4.30	2.54	0.71
Maternal Spherical Equivalent (D)	-0.40	0.26	-0.42	0.30	-0.38	0.26	-0.41	0.30	0.37
History of Myopic Progression (D)	-0.9	-0.41	-0.85	0.31	-0.81	0.32	-0.88	0.36	0.66

Outdoor Activity (hours/day)	2.05	0.80	1.84	0.73	1.98	0.83	2.07	0.94	0.28
Near work (dioptic hours/day)	14.24	3.59	13.85	3.95	14.68	5.41	13.61	4.50	0.15
Spherical Equivalent (D)	-3.70	1.57	-3.45	1.72	-3.51	1.72	-3.58	0.67	0.52
Near VA (log MAR)	0.02	0.12	0.01	0.1	0.03	0.1	0.01	0.10	0.14
Axial Length (mm)	22.61	0.82	22.62	0.86	22.48	0.90	22.59	0.88	0.40
Distance VA (logMAR)	0.01	0.07	0.01	0.07	0.01	0.07	0.00	0.05	0.73
Anterior Chamber depth (mm)	3.43	0.18	3.45	0.24	3.42	0.21	3.40	0.22	0.16
Photopic Pupil Size (mm)	3.51	0.66	3.49	0.67	3.40	0.59	3.48	0.76	0.42
Accommodation Amplitude (D)	11.24	2.45	10.94	2.07	10.78	2.56	10.77	2.21	0.70
Mesopic Pupil Size (mm)	6.06	0.71	6.10	0.68	5.99	0.62	5.99	0.62	0.40

Table 2:

	0.05% (55)		**0.01% (65)**		**0.025% (60)**		**Placebo (66)**		
Characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P value**
General Health	59.79	19.08	62.38	17.67	63.75	19.10	62.35	19.73	0.43
VFQ-25 Composite	78.97	4.16	77.46	7.08	79.06	4.08	78.02	5.77	0.10
General Vision	71.33	13.54	67.63	16.05	70.55	12.17	69.68	12.68	0.23
Peripheral Vision	83.54	6.17	80.84	10.57	83.51	5.45	82.66	8.82	0.06
Ocular Pain	78.96	8.91	77.57	12.41	79.05	8.98	78.58	10.12	0.63
Color Vision	84.57	3.01	82.40	11.41	83.90	7.11	82.14	11.64	0.15
Near Activities	82.29	6.15	80.20	8.56	81.32	6.08	80.10	7.74	0.09
Dependency	82.99	6.01	82.48	7.21	83.23	5.46	81.81	8.19	0.41
Distance Activities	81.04	8.18	79.75	10.46	81.07	7.34	79.98	9.42	0.53
Role Difficulties	81.25	8.42	79.52	12.59	80.86	8.12	79.98	11.46	0.54
Social Functioning	84.03	4.82	83.23	4.85	84.46	2.36	84.29	3.12	0.14
Mental Health	79.17	6.54	77.00	7.70	78.46	6.91	77.08	8.38	0.09

Table 3: Pearson correlation between spherical equivalent, axial length (mm), photopic pupil size, mesopic pupil size, accommodation amplitude, distance VA (logMAR) and Near VA (logMAR)

	0.05%		0.03%		0.01%		Placebo							
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	0.05/0.02	0.05/0.01	0.05/placebo	0.025/0.01	0.025/placebo	0.01/placebo
Spherical Equivalent (D)														
Change at 4 mo s	-0.03	0.36	-0.18	0.28	-0.23	0.31	-0.3	0.28	**	**	**	**	**	**
Change at 8 mo s	-0.12	0.45	-0.33	0.34	-0.38	0.5	-0.54	0.46	**	**	**	**	**	**
Change at 12 mo s	-0.24	0.54	-0.41	0.4	-0.53	0.54	-0.72	0.47	**	**	**	**	**	**
Axial Length (mm)									**	**	**	**	**	**
Change at 4 mo s	0.05	0.18	0.11	0.1	0.12	0.14	0.14	0.12	**	**	**	**	**	**
Change at 8 mo s	0.14	0.25	0.2	0.23	0.24	0.18	0.27	0.15	**	**	**	**	**	**
Change at 12 mo s	0.18	0.23	0.26	0.18	0.33	0.26	0.37	0.2	**	**	**	**	**	**
Photopic pupil size (mm)									**	**	**	**	**	**
Change at 4 mo s	0.95	0.96	0.71	0.93	0.23	0.74	-0.02	0.96	**	**	**	**	**	**
Change at 8 mo s	1.07	0.94	0.65	0.84	0.37	0.72	0.08	0.94	**	**	**	**	**	**
Change at 12 mo s	0.92	0.91	0.68	0.81	0.44	0.72	0.12	0.96	**	**	**	**	**	**
Mesopic pupil size (mm)									**	**	**	**	**	**
Change at 4 mo s	0.47	0.57	0.29	0.62	0.16	0.42	0.05	0.46	**	**	**	**	**	**
Change at 8 mo s	0.57	0.55	0.34	0.57	0.15	0.42	0.05	0.67	**	**	**	**	**	**
Change at 12 mo s	0.53	0.57	0.39	0.56	0.21	0.42	0.02	0.5	**	**	**	**	**	**
Accommodation amplitude (D)									**	**	**	**	**	**
Change at 4 mo s	-2.17	2.46	-1.22	2.27	-0.46	2.52	-0.32	2.26	**	**	**	**	**	**
Change at 8 mo s	-1.8	2.66	-1.11	2.48	-0.47	2.63	-0.6	2.41	**	**	**	**	**	**
Change at 12 mo s	-1.8	2.57	-1.47	2.38	-0.24	2.77	-0.29	2.65	**	**	**	**	**	**
Distance V A (log M A R)									**	**	**	**	**	**
Change at 4 mo s	-0.02	0.06	-0.02	0.06	-0.02	0.07	-0.01	0.05	**	**	**	**	**	**
Change at 8 mo s	-0.02	0.05	-0.02	0.07	-0.02	0.07	-0.01	0.05	**	**	**	**	**	**
Change at 12 mo s	-0.02	0.05	-0.02	0.06	-0.03	0.07	-0.01	0.05	**	**	**	**	**	**
Near VA (log M A R)									**	**	**	**	**	**
Change at 4 mo s	0	0.12	0	0.13	-0.02	0.11	-0.02	0.11	**	**	**	**	**	**
Change at 8 mo s	-0.02	0.12	0	0.12	-0.03	0.1	-0.03	0.11	**	**	**	**	**	**
Change at 12 mo s	-0.01	0.12	0	0.12	-0.03	0.12	-0.02	0.11	**	**	**	**	**	**

Table 4: Side effects of atropine during the study

	0.05% (31)		0.025% (37)		0.01% (28)		Placebo(36)		
Variables	**Mean**	**%**	**Mean**	**%**	**Mean**	**%**	**Mean**	**%**	**P value**
Photochromatic glasses needed	8	26	9	24	9	32	12	33	0.28
Hospitalization	1	3	1	3	1	4	1	3	0.55
Progressive glasses needed	1	3	1	3	1	4	1	3	0.75
Allergic conjunctivitis	1	3	2	5	2	7	3	8	0.34
Photophobia at 2 wks	9	29	5	14	2	7	4	11	0.001
Photophobia at 1 yrs	3	10	1	3	0	0	1	3	0.3

Discussion

Although the effects of low-concentration atropine were contributed by further ocular biometrics (Gong, 2018; Kumaran, 2015) this study showed that AL elongation decreases were largely responsible. In the 0.05% atropine group, followed by 0.025% and 0.01% atropine groups compared with the placebo in concentration-dependent response, the greatest reduction in AL elongation was seen. There were no differences in K and lens performance in comparison to placebo over 1 year due to atropine concentrations. In particular, the contribution of AL and corneal and lens power SE progression in each atropine and placebo concentration was similar. Most SE progression has been supported by axial length elongation**.** Thus, mainly axial elongation delayed was the anti-myopic effect of low-concentration atropine. First, our study showed that AL alone contributed 72 to 81 percent of the SE variance. This could be explained by the observation in this LAMP study that 27% SE reduction and 12% axial elongation in the atropine group were achieved in comparison with placebo, 43% SE decrease and 29% AL elongation in the atropine group, and 67% SE decreases and 51% AL elongation in the atropine group were attained in 0.025% and 0.001% and 0, 05% AL elongations (Saw, 2005). Lens and corneal factors accounted for the remaining SE variances in all concentrations. Notably, our studies showed no significant impact of low-placebo atropine K and lens power and similar contributions to SE progression between all atropine and placebo concentrations from AL, K, and lens power. The anti-myopic effect of atropine was further confirmed by delaying axial elongation. Second, the AL prolongation for children comprises both normal, although small, age-related growth and further growth related to myopia. Thus, the SE changes are correlated with the AL elongation only in part. This can partly explain why atropine effects would be lower than that of SE progression in overall AL elongation.

In the LAMP study, statistical importance was achieved only by the effect on SE progression, not AL elongation, in the 0.01% atropine group. While the sample size was sufficient in the LAMP study, it is mainly driven by SE changes. To detect the difference between the 0.01% atropine and placebo groups, a larger sample dimension is required. But compared 0.01% ATOM 2 atropine to historical ATOM 1 placebo (effect 8%) ATOM 1(Rudnicka, 2016), the IOL Master (partial coherence interferometry without contact) was used in the ATOM 2 system, and the A-scan ultrasound was applied in ATOM1. It was possible to influence mainly various methods in biometric measurement (Chia, 2012; Qu, 2006). Due to differences in cohorts and preparations

for the eye drops, direct comparisons between the ATOM 2 and LAMP studies should be carried out carefully. Notably, in the ATOM 2 study, 0.01% atropine was affected by students and accommodation, although they were used with the same measuring methods in both studies, not with the LAMP study. This may indicate that the dropouts between these two studies may be potentially biological and therefore different.

The strength of this study is its randomization design of a relatively wide range of participants, which has been doubly blind and position-controlled for 1 year. The potential bias would be minimized by using generalized estimation equations, including data from either eye, to evaluate changes over time in repeated biometry measurements. Measuring the IOL Master following complete cycloplegia has been carried out, which has avoided the effect of lodging. In our study, we were able to directly compare atropine levels with placebos to determine the effect of atropine surface biometrics. There are certain limitations to this study. First, only the first year of atropine treatment was reported compared to placebo during the present study. In subsequent phases of the LAMP study, further assessment will be required of longer-term biometrical ocular changes, including after cessation of treatment. Secondly, lens power was calculated based on the Bennett and Rabbett formula instead of measured directly. This calculation, however, is considered an acceptable estimate of in vivo lens performance from childhood to adulthood (Chia, 2014).

Low-Concentration Atropine Mechanisms

Our analysis demonstrated the simultaneous reduction of both the SE progression and the AL extension in low-concentration atropine eye drops. The hyperopic change in the ATOMs study suggested that the subjects receiving high concentrations of atropine 1%, 0.5%, and 0.1% atropine did not occur with low 0.05%, 0.025%, and 0.0 1% atropine concentrations in our study with low concentration(Chua, 2006). This hyperopic change in the use of higher atropine concentrations can be partly explained by the subsequent shift of the lens-iris procedure to the back chamber which reduces the glass chamber depth (Kumaran, 2015). The mechanisms of atropine for anti-myopia are not fully understood. Accommodation inhibition was also considered to be involved. However, subsequent studies have shown that atropine may also be an inhibitor of myopia in chicks that do not have accommodating facilities. As a result, the biochemical effects of atropine on the retina or sclera could affect the remodeling of the sclera. Firstly, atropine can be operated on a relatively low dose through a neurochemical cascade, probably in amacrine cells, starting with M1/4

receptors. Furthermore, it was also suggested that the non-muscarinic system, atropine can inhibit glycosaminoglycan synthesis in scleral bubbles (Qu, 2006; Tan, 2016). However, it was also claimed that pupil dilation can contribute to increased sensitivity to ultraviolet, reducing axial elongation(Prepas, 2008). Myopia may be associated with increased chronic inflammation in the eye, which atropine may reduce.

Future Concerns

The current study verified the effectiveness of low-concentration atropine relative to placebo. The former ATOM study also suggested that the low-concentration atropine had better effectiveness than for the first year (second year data going-on), particularly the 0.01%, indicating a time progression stabilization effect and at the end of the second year the efficacy of different low-concentration atropine was reduced to 0.1 % with minor clinical differences between 0.01 % and 0.2 % (Chia, 2012). Some other concerns also exist about whether atropine can be further used until the development of myopia is regulated. There is a need to resolve these issues. Long-term studies would also be conducted to determine the refraction of myopia and improve the AL during the washout cycle. As a result, we can infer the long-term effectiveness of low-concentration atropine.

Strengths and Limitations

The strengths of this research were the double-blind selection of the patients and the inclusion criteria are very strong with various low-concentration atropine doses with large samples and small drop-off rates in placebo. The authors try to cover the maximum ophthalmic characteristics such as distant and near visual acuity of cycloplegic refraction, ocular biometry, pupil size, accommodation amplitude, and logMAR. The study also concentrated on systematic and semi-quantitative evaluation of the visual function in individuals; who received different atropine eye drop doses included in the locally validated visual questionnaires. In all atropine trials along with a placebo, the potential for exposure of the subjects associated with atropine photophobia and cycloplegia is also inevitable. However, our findings essentially identified the photophobia, vision disturbances, and vision-related life quality characteristics which may lower the chance of exposure. It should be noted during the research trial, that the placebo treatment period has been set at 1 year because it is inappropriate for children to proceed with a placebo as atropine is successful after 1 year. There is one limitation in our study at the first stage of research, we did not

calculate the number of corneal endothelial cells. Previous laboratory research suggested that atropine can be corneal endothelial toxic, but there is no clinical evidence.

In summary, low atropine eye drops do not have an important impact on K and lens power. Its effects are mediated via axial elongation reduction, but no further parameters of ocular biometrics, which could thus decrease the risk of further myopia. Additional studies are essential to show the low-concentration atropine myopia mechanism.

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