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Evaluation of Accommodation and Pupillary Reaction in Children with Myopia Treated by Highly Diluted Atropine in the M.A.R.S. Trial

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ABSTRACT

Background: Myopia is a growing challenge in paediatric ophthalmology. Despite the benefits of novel therapeutic approaches, it is essential to assess their side effects. The aim of this study was to determine the impact of twelve months of local application of 0.02% and 0.04% atropine and placebo on the static and dynamic features of accommodation and pupil diameter, representing prominent side effects of myopia progression treatment.

Methods: This study involved 127 subjects aged 6-11 years who were randomized to the M.A.R.S. trial, a randomized, double-masked, placebo-controlled multicentre study investigating the efficacy, safety, and side effects of highly diluted atropine collyrium (0.02% and 0.04%) in slowing the progression of myopia. Photopic and mesopic light-adapted horizontal pupillary diameters (PD; mm) were measured. Static accommodation capability was assessed monocularly and binocularly as the amplitude of accommodation (AoA; dioptres) calculated as the inverted value of the measured near point of accommodation in meters. The dynamic properties of accommodation were represented by the near accommodation facility (NAF, ±1.25 D flipper; monocularly/binocularly; number of cycles in a 60-second interval).

Results: The effects of atropine on static PD were treatment-related (P<0.001) and dose-unrelated. Under photopic and mesopic light conditions, changes from baseline after twelve months of treatment were observed: in the 0.02% atropine group: from 3.48 ±1.23 to 4.65 ±1.52 (P<0.001); from 5.59 ±1.34 to 6.33 ±1.14 (P<0.001), respectively; in the 0.04% group: from 3.41±1.27 to 4.86±1.64 (P<0.001); and from 5.64±1.13 to 6.55±0.82 (P<0.001), respectively. The effects of the study medication on AoA were not treatment-related in the break point and were marginally treatment-related in the recovery point (P=0.049) in monocular tests. The results of the binocular tests were treatment-unrelated in the break point or at the recovery point. There were no statistically significant differences in NAF among the groups after the 12-month treatment period in monocular and binocular conditions.

Conclusions: Local 0.02% and 0.04% atropine treatment for twelve months resulted in treatment-related increases in photopic and mesopic PD, respectively. Accommodation capability, assessed by AoA, was diminished by atropine treatment only at extreme limits (due to enlarged NPA distances) but remained unchanged at standard near working distances (as indicated by unaltered NAF test results) according to the M.A.R.S. trial data.

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Abbreviations

ANOVA	Analysis of Variance
AoA	Amplitude of Accommodation
D	Dioptre
M.A.R.S	Myopia & Atropine Restriction Study
mm	Millimetre
MOSAIC	Myopia outcome Study of Atropine in Children
NAF	Near Accommodation Facility
NPA	Near Point of Accommodation
PD	Pupillary Diameter
RAF	Royal Air Force

Background

Myopia is considered a significant public health problem globally [1, 2]. The increasing prevalence of myopia, especially among Asian ethnicities, has led to a higher incidence of sight-threatening complications [3]. Early manifestations with accelerated axial length progression include exacerbated myopia progression even in non-Asian regions [4, 5]. Innovative treatment modalities aimed at decelerating myopia progression are under intensive study in experimental trials and have been clinically implemented in some European regions [2, 6]. Evaluating the complex effectiveness of treatment strategies requires prolonged investigation. The rapidly increasing body of evidence is mainly based on shorter trials with one-year or two-year follow-up intervention periods [2]. However, there are insufficient data related to the sustainability of the observed effects. Critical outcomes primarily include differences in spherical equivalent refraction (SE, dioptres (D)) measured in cycloplegia and/or axial length (mm) in the intervention and control groups. Short-term effectiveness varies considerably among environmental, optical, and pharmacological interventions, with results often heterogeneous and associated with a significant degree of uncertainty. According to the latest Cochrane meta-analysis, orthokeratology provides the greatest potential for treatment effectiveness [2]. Although high doses of atropine may decelerate myopia progression, the effect of highly diluted atropine, the most commonly used clinical treatment modality worldwide, remains unclear. The therapeutic efficacy of atropine is related to its concentration, as the majority of its unwanted effects are [7-12]. The prominent subjective side effects of local atropine application intended for myopia progression treatment include glare (related to pupil dilation) and blurred near vision (i.e., iatrogenic presbyopia due to cycloparesis or cycloplegia) [8-11, 13-16]. The severity of subjective unwanted effects is generally mild and usually does not lead to subject dropout from the trial [15]. The individual impact of subjective inconvenience is modulated by interindividual differences in motivation for treatment and muscarinic receptor sensitivity and habituation [13]. Compensatory measures, if rarely needed, involve photochromic and/or progressive spectacle lenses. The published incidence of subjective side effects generally remains low, but this depends on the methodology, primarily the sensitivity of monitoring (occasionally, considerably higher levels are reported, for example, 69%, associated even with a high dropout ratio in a small Australian study [14-17]. The frequency of dropout due to side events in trials in non-Asian regions ranged from 0% to 22% [16]. Contrary to its importance for individual compliance, the extent and severity of prominent side effects related to locally applied atropine intervention are only fragmentally addressed in published reports. Safety data were specified in only 8 of 15 selected publications, with authors focusing preferably on subjective unwanted effects (glare, photophobia, and blurred vision) [2]. Even less information is available about objective measures related to prevalent subjective complaints: changes in pupillary diameter and accommodation amplitude (the alternative expression, the reciprocal value of the near point of accommodation) consequent to pharmacological intervention are infrequently referred to [9-11, 13, 14, 18-29]. To the best of our knowledge, sporadic relevant data related to near accommodation facility in eyes treated with highly diluted atropine have been published [11]. The main aim of our study was to address the lack of sound evidence regarding the potential unwanted effects of the local application of lower-middle-diluted atropine in children with myopia. We describe the impact of twelve months of local application of 0.02% and 0.04% atropine and placebo on the parameters of accommodation (near point of accommodation, NPA (cm), and near accommodation facility, NAF (number of cycles in a 60-second interval)) and pupillary reaction (photopic and mesopic diameter in mm).

Methods

Subjects

A total of 229 patients with progressive myopia (> -0.5 dioptres spherical and < -4.57 dioptres spherical, < 2.5 dioptres cylindrical) were enrolled in the randomized controlled trial (RCT) M.A.R.S. The age of the children at the time of randomization ranged from 6 to 11 years. The first subject was randomized on June 29, 2022. Two patients were excluded due to exclusion criteria, while 2 patients used D.I.M.S. glasses during the first twelve months of the study. Additionally, 35 patients discontinued the study, and 63 patients had not yet reached the 12-month visit as of the reference date of January 4, 2024. A total of 127 patients were included in the analysis of accommodation and pupillary reaction parameters. The group of subjects comprised 64% females and 36% males. The age distribution of the sample is depicted in Table 1. According to the study protocol, these parameters are classified as secondary outcomes related to the safety and tolerability of treatment [30].

Table 1: Age at the Time of Randomization and Gender Structure of the Subject Sample (n=127 children)

Age	Placebo		atropine 0.02%		atropine 0.04%	
	male [n,%]	female [n,%]	male [n,%]	female [n,%]	male [n,%]	female [n,%]
6-7	1 (7.7%)	2 (9.1%)	1 (4.3%)	3 (7.9%)	1 (10.0%)	4 (19.0%)
8-9	5 (38.5%)	5 (22.7%)	11 (47.8%)	8 (21.1%)	3 (30.0%)	5 (23.8%)
10-11	7 (53.8%)	15 (68.2%)	11 (47.8%)	27 (71.1%)	6 (60.0%)	12 (57.1%)
Total	13 (100.0%)	22 (100.0%)	23 (100.0%)	38 (100.0%)	10 (100.0%)	21 (100.0%)

Age at randomization (years)

Study Design

M.A.R.S. is a randomized, double-masked, placebo-controlled multicentric study investigating the efficacy, safety, and side effects of highly diluted atropine collyrium (0.02% and 0.04%, respectively) in slowing the progression of shortsightedness (EudraCT No: 2020-002046-16). Subjects who met all the inclusion criteria, including accelerated prerandomization axial elongation greater than 0.1 mm in the 6 months before enrolment, were randomized into three parallel arms according to the type of pharmacological intervention evaluated (0.02% atropine, 0.04% atropine, and placebo) at a ratio of 2:1:1. All the study collyria were individually prepared and manufactured according to a technological procedure validated by the State Institute for Drug Control of the Czech Republic at the University Hospital Pharmacy in Prague.

Measurements

Amplitude of accommodation (AoA; D) and near accommodative facility (NAF; number of cycles in a 60-second interval) are standard parameters used to describe the properties of accommodation. Static accommodation capability is assessed monocularly and binocularly as the amplitude of accommodation. AoA is measured using an accommodation rule (RAF Binocular Gauge, Clement Clarke Ophthalmic, Haag Streit UK Ltd.) with the patient wearing their own optimal myopic correction. The text block optotype of the accommodation rule is slowly moved toward the patient's eyes until the patient reports subjective blurring of the text (break point), and then it is moved back until subjective restoration of focus is reported (recovery point). The inverted value of the measured near point of accommodation in meters (NPA, m) then corresponds to the of the accommodation amplitude, which is expressed in diopters (D) [31].

The subjective dynamic properties of accommodation are represented by the near accommodative facility (NAF). The NAF is measured monocularly and binocularly using an accommodation flipper (Amcon, Centre, St. Louis, U.S.A.) with a value of ±1.25 D while wearing the patient's own optimal myopic correction. A text block (a short fairy story, Times Roman 8, equivalent to Jager 0.5) is placed in front of the patient at a distance of 40 cm [32]. Lenses of the flipper are alternated in front of the patient's eyes until the presented text is subjectively seen clearly for one minute. Accommodative facility is expressed as the number of cycles per minute, where each cycle includes focusing on both sides of the flipper.

The photopic and mesopic pupil diameters are used in the study to describe the size of the pupil depending on the level of illumination. Pupillary horizontal diameters of both eyes were captured after 2 minutes of adaptation to photopic and mesopic static light stimulation and then measured using the Oculus Keratograph M5 (Oculus Optikgeräte GmbH, Wetzlar, Germany).

Statistical Analysis

Standard descriptive statistics were used to describe patient characteristics and parameters measured at baseline and at the 12-month visit. Absolute and relative frequencies were employed for categorical variables, and means with standard deviation were applied for continuous variables (normality was visually assessed by comparing the histogram with the expected normal distribution). To account for within patient variability in monocular analysis, mixed-effect models with a random effect of patient were utilized to test differences between baseline and 12-month values. The mixed-effect model was also employed to assess the treatment effect in monocular analysis. In binocular analyses, comparisons between baseline and 12-month values were conducted using paired t tests. Differences among various treatment types were examined through analysis of variance (ANOVA). Testing within individual treatment types underwent correction for multiple comparisons using Bonferroni correction, while differences between treatment types were tested without correction. For statistically significant differences post-hoc tests with Tukey´s adjustment for multiple comparison were performed. All the statistical tests were performed at a 5% level of significance. All analyses were conducted using R version 4.4.0.

Results

The results of the twelve-month follow-up of subjects enrolled in the RCT M.A.R.S. included measurements of pupillary diameters and basic parameters of accommodation. Table 2 and Figure 1 depict the changes in horizontal pupillary diameter (PD) after twelve months of treatment with highly diluted atropine (0.02% and 0.04%) and placebo, respectively, compared to the baseline values. The treatment effects on static PDs were found to be significant for local highly diluted atropine ($P < 0.001$). Specifically, under both photopic and mesopic light conditions, there were significant changes from baseline after twelve months of treatment in all the active subgroups (0.02% and 0.04%) but not in the placebo subgroup. Dose-related effects were not significant in photopic and mesopic light conditions (Table 2).

Table 2: Pupillary Diameter in the 0.02% and 0.04% Atropine and Placebo Groups

Pupillary diameter (monocular) [mm]											
	placebo [N1=35, N2=64]			**atropine 0.02% [N1=60, N2=107]**			**atropine 0.04% [N1=30, N2=54]**			**Treatment effect**	**Dose effect of atropine 0.02% vs. 0.04%**
	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	P value	P value
Photopic	3.71 (1.313)	3.88 (1.351)	0.141[3]	3.48 (1.229)	4.65 (1.517)	<0.001[3]	3.41 (1.270)	4.86 (1.645)	<0.001[3]	<0.001[3]	0.188[4]
Mesopic	5.97 (1.135)	5.92 (1.208)	>0.999[3]	5.59 (1.341)	6.33 (1.138)	<0.001[3]	5.64 (1.134)	6.55 (0.824)	<0.001[3]	<0.001[3]	0.294[7]

[1]Number of patients with measurements at baseline and at 12 months.
[2]Number of eyes where the placebo or treatment was applied (number of observations used in monocular analysis).

[3]Tested using a mixed-effect model with random effect of patient.
[4]Tested using post-hoc tests with Tukey´s adjustment for multiple comparison.
Tests of change within individual treatment groups were corrected for multiple comparisons (Bonferroni correction); mo, month; and SD, standard deviation.

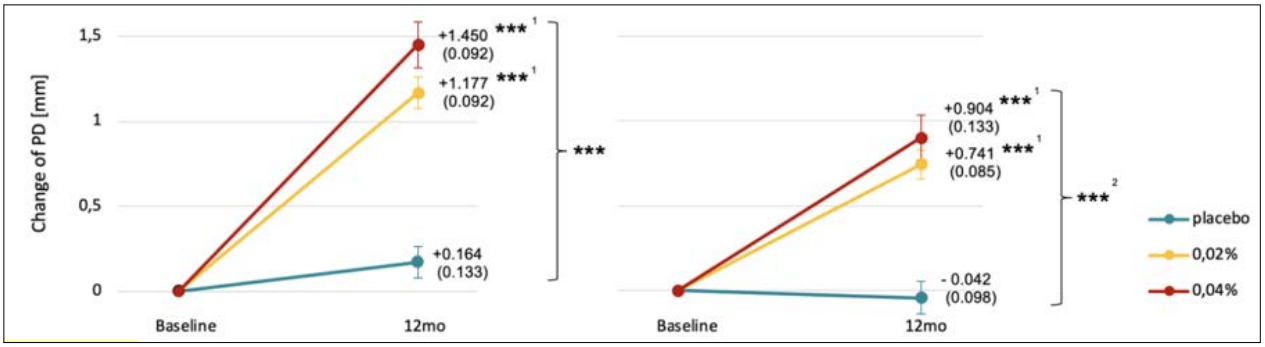

Figure 1: Changes in Pupillary Diameter in Photopic (left) and Mesopic (right) Light Conditions

Legend: Changes in the pupillary diameter in photopic (left) and mesopic (right) light conditions after a 12-month application period in the placebo group and active groups: daily evening local application of 0.02% and 0.04% atropine, respectively. Error bars show the standard error (SE). Abbreviations: PD, pupillary diameter; mm, millimetre; mo, month. *P < 0,05; **P < 0,01; ***P < 0,001; 1P value of difference tested using mixed-effect model with random effect of patient, 2P value of treatment effect tested using mixed-effect model with random effect of patient,

Despite highly significant changes in the static characteristics of accommodation, as assessed by the measurement of the near point of accommodation (NPA), the treatment effects of highly diluted atropine were documented only in the recovery point under monocular measurement conditions (P=0.049). The results of the binocular tests nearly closely paralleled those of the monocular tests. No dose-related effect on AoA was detected in the present study (Table 3, Figure 2).

Table 3: Amplitude of Accommodation (AoA) at Baseline and after a 12-Month Application Period in the Placebo and Active Groups

	placebo [N1=35, N2=64, N3=29]			**atropine 0.02% [N1=61, N2=109, N3=48]**			**atropine 0.04% [N1=31, N2=56, N3=25]**			**Treatment effect**	**Dose effect of atropine 0.02% vs. 0.04%**
	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	P value	P value
Monocular	18.37 (7.042)	16.52 (6.403)	0.020[4]	16.67 (5.349)	13.31 (4.004)	<0.001[4]	16.26 (3.821)	12.73 (3.323)	<0.0014	0.2814	NA
Binocular	18.26 (5.297)	16.99 (6.097)	0.4095	17.16 (4.715)	14.17 (4.249)	0.0045	17.55 (2.670)	13.57 (3.437)	<0.0015	0.1536	NA
Amplitude of accommodation: recovery point [D]											
	placebo [N1=35, N2=64, N3=29]			atropine 0.02% [N1=61, N2=109, N3=47]			atropine 0.04% [N1=31, N2=56, N3=25]			Treatment effect	Dose effect of atropine 0.02% vs. 0.04%
	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	P value	P value
Monocular	15.54 (5.621)	14.21 (5.146)	0.015[4]	14.42 (4.756)	11.64 (3.500)	<0.0014	14.55 (3.386)	11.10 (3.072)	<0.0014	0.0494	0.3557
Binocular	15.48 (4.297)	15.00 (5.841)	>0.9995	14.69 (4.128)	12.16 (3.448)	0.0015	15.15 (2.629)	11.77 (2.832)	<0.0015	0.0586	NA

[1]Number of patients with AoA measurements at baseline and at 12 months.
[2]Number of eyes where the placebo or treatment was applied (number of observations used in monocular analysis).
[3]Number of patients with both eyes treated (number of observations used in binocular analysis).
[4]Tested using a mixed-effect model with random effect of patient.
[5]Tested using paired t-test.
[6]Tested using ANOVA.
[7]Tested using post-hoc tests with Tukey´s adjustment for multiple comparison.
Tests of change within individual treatment groups were corrected for multiple comparisons (Bonferroni correction); mo, month, SD, standard deviation., NA, not applicable.

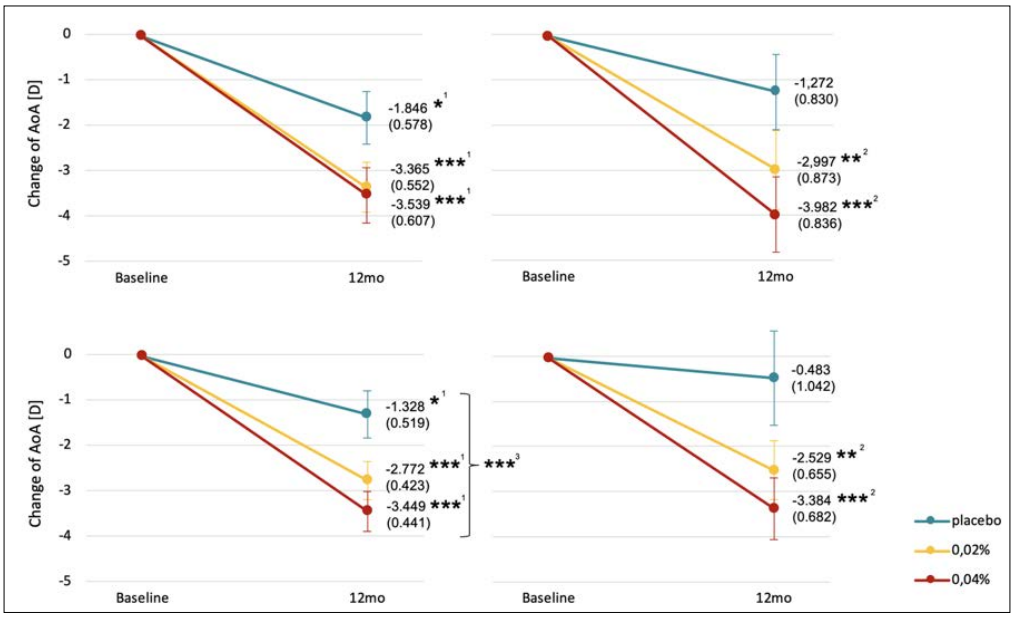

Figure 2: Changes in the Monocular (left) and Binocular (right) Amplitudes of Accommodation as Break Point (up) and Recovery Point (down).

Legend: Changes in the monocular (left) and binocular (right) amplitudes of accommodation measured as the break point (up) and recovery point (down) of the near point of accommodation after a 12-month application period in the placebo group and active group: daily evening local application of 0.02% and 0.04% atropine, respectively. Error bars show the standard error (SE). Abbreviations: AoA, amplitude of accommodation; D, dioptre; mo, month. *P < 0,05; **P < 0,01; ***P < 0,001; 1P value of difference tested using mixed-effect model with random effect of patient, 2P value of difference tested using paired t test, 3P value of treatment effect tested using mixed-effect model with random effect of patient.

The dynamic capabilities of accommodation, evaluated by means of a near accommodation facility (NAF), did not show any effect related to atropine treatment in monocular or binocular conditions. The results of the measurements are summarized in Table 4 and Figure 3, and they revealed no significant difference between overall accommodation dynamics at baseline and after twelve months of highly diluted atropine treatment.

Table 4: Near Accommodation Facility (NAF) at Baseline and after 12-Month Application Period in the Placebo and Active Groups

Near accommodation facility (+1,25 D) [number of cycles in 60 seconds interval]											
	placebo [N1=35, N2=64, N3=29]			**atropine 0.02% [N1=59, N2=105, N3=46]**			**atropine 0.04% [N1=30, N2=54, N3=24]**			**Treatment effect**	**Dose effect of atropine 0.02% vs. 0.04%**
	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	baseline mean (SD)	12mo mean (SD)	P value of difference	P value	P value
monocular	12.1 (5.32)	11.9 (4.44)	>0.999[4]	11.2 (4.48)	11.7 (4.90)	0.343[4]	11.5 (5.18)	12.1 (5.07)	0.493[4]	0.613[4]	NA
binocular	11.5 (5.06)	11.5 (4.23)	>0.999[5]	10.3 (3.68)	11.0 (4.06)	0.311[5]	11.1 (4.20)	12.3 (5.50)	0.280[5]	0.429[6]	NA[7]

/daily evening local application of 0.02% and 0.04% atropine.
[1]Number of patients with NPA measurements at baseline and at 12 months.
[2]Number of eyes where the placebo or treatment was applied (number of observations used in monocular analysis).
[3]Number of patients with both eyes treated (number of observations used in binocular analysis).
[4]Tested using a mixed-effect model with random effect of patient.
[5]Tested using paired t tests. 6 Tested using ANOVA.
Tests of change within individual treatment groups were corrected for multiple comparisons (Bonferroni correction); mo, month, SD, standard deviation., NA, not applicable.

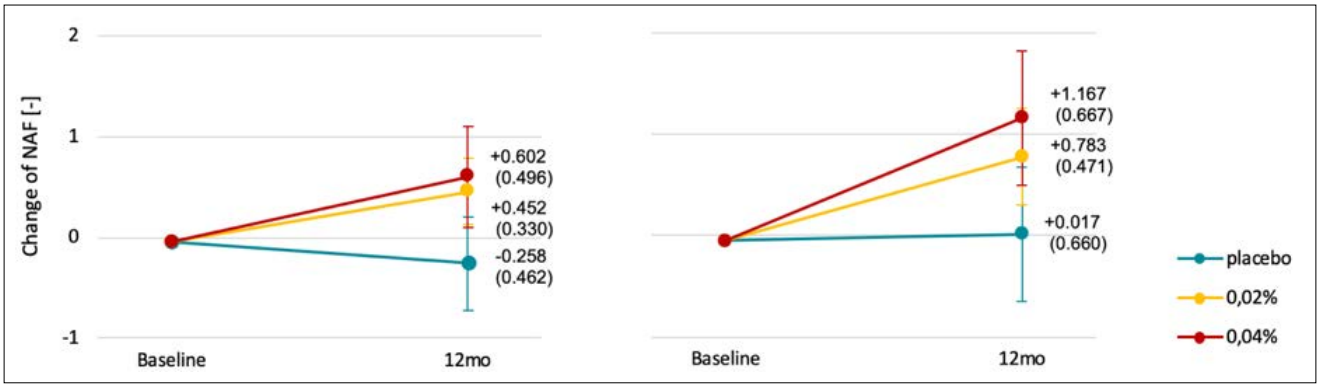

Figure 3: Changes in Monocular (left) and Binocular (right) Near Accommodation Facility

Legend: Changes in monocular (left) and binocular (right) near accommodation facility after a 12-month application period in the placebo group and active groups: daily evening local application of 0.02% and 0.04% atropine, respectively. Error bars show the standard error (SE). Abbreviations: NAF, near accommodation facility; mo, month. *P < 0,05; **P < 0,01; ***P < 0,001

Discussion

Our study describes statistically significant differences in the static and dynamic aspects of pupillary (PD) and accommodative (AoA and NAF) reactions to prolonged local application of diluted atropine in children with progressive myopia. A sound body of experimental evidence has confirmed the efficacy and safety of low- and middle-concentration atropine. However, some studies have focused primarily on the efficacy of atropine in reducing refractive error and/or ocular axial length, while safety has been evaluated based mainly on a very low number of adverse events or subjective complaints [14]. Our results complement the lack of experimental data illustrating potential unwanted side effects of the local application of lower-middle-concentrated atropine in children with myopia published in recent studies [9-11, 32].

Pupillary Diameter

In our study, photopic and scotopic horizontal pupil diameter is measured with the Oculus Keratograph M5. Other options for measuring pupil size include manual measurement using a ruler or pupil gauge and automatic pupillometers. Some recent studies use digital pupillometers to measure pupil size [9, 10]. Measurement using the Oculus keratograph is considered a manual method, as the horizontal diameter is evaluated by software after manually marking the edges of the pupil. This can be a source of inaccuracies. As it is an objective method, the errors caused by the examinee are reduced. The measurement took place in the morning when the mydriatic effect from the previous night's application was accentuated [18]. It would be valuable to compare these results to evening measurements.

In our study, we observed a definite effect of the studied drug on pupil size. Static pupillary diameter increased at the 12-month visit in both atropine groups (0.04% and 0.02%) under photopic and mesopic conditions, respectively. The treatment-related increase in pupillary diameter was statistically significant in the atropine groups but not in the placebo group. This result is consistent with the findings of several previous studies; however, usually lower concentrations of atropine were used (0.005%, 0.01%) [8-11, 13, 19-25, 27-29]. For example, Fu et al. used 0.02% and 0.01% atropine concentrations and a placebo in Chinese children [18]. They observed a treatment effect but no dose-related effect on pupil size. In the group treated with 0.02% atropine, a change in the photopic pupil diameter of 0.79±0.08 mm after twelve months of drug administration (baseline diameter of 6.34±0.68 mm) was detected. In our group treated with 0.02% atropine, both the baseline and 12-month pupil diameter values were lower: 3.48 ± 1.229 mm and 4.65±1.517 mm, respectively. This can be explained by differences in the ethnic characteristics of the two groups or differences in the methods (i.e., light intensity) used for pupil size measurements. Treatment-related but not dose-related effects were also observed in other recent studies [8, 11]. Sharma et al. reported no change in the scotopic or mesopic pupil size when using 0.01% atropine. However, light conditions were not specifically monitored during the visits in this study [33]. The ample clinical evidence embodied in the meta-analysis supports our results but indicates that the relationships between changes in pupil diameter and the analysed atropine concentration (0.01%, 0.02%, 0.03%, 0.05%, 0.10%, 0.50%) are not linear [26]. The exponential regression curve has a nearly linear slope at low doses and plateaus at high concentrations. Noticeably wider pupils of subjects in the active trial arms did not involve compliance with prolonged atropine medication. Irrespective of certain mydriasis and potentially related glare, no photochromic lenses were requested, and the trial's dropout ratio was not influenced at the 12-month visits. Children complaining of glare discontinued the study early during the first 2-4 weeks after randomization. Ongoing subjects generally do not complain about glare, and we consider the influence of the robust adaptation process to excessive light stimulation, localized mainly in retinal processing (photoreceptors, horizontal and ganglion cells, and macular pigment) and cortical levels [34-37]. Other studies support this premise (Fu et al., 2020), and no photochromic lenses were needed during the MOSAIC study [11]. Pupil diameter is a static measurement. The measurement of dynamic changes in pupillary reaction could also be beneficial for assessing atropine side effects.

Amplitude of Accommodation

AoA was measured using the accommodation rule (RAF rule) with optimal distance correction. Other methodological options for AoA measurement include the use of minus lenses or dynamic retinoscopy [38]. Recent studies have also used a near point rule for measurement [9, 10]. The advantage of the push-up/push-down method using the RAF rule is the ease and speed of the examination and the possibility of both monocular and binocular examination. Sources of measurement errors can be attributed to depth of focus, reaction time, correction of refractive error, luminance of the visual task, instrument design error, examiner bias, or feedback from the participant [38]. Particularly, the measurement is affected by the depth of focus, which changes with pupillary dilation or increasing the angular size of the text when approaching the test

target. Another condition that could affect the depth of focus is the illumination of the test task. Measurements were performed under standard lighting conditions in an eye specialist's office. Since this is a subjective test method, reaction time also affects the accuracy of the measurement, including the time taken to decide whether the object is blurred or clear, the time to verbalize the decision, the time for the examiner to register this message, and stop the movement of the text. To achieve the most accurate result, it is necessary to measure the AoA with full spectacle correction for distance. The RAF rule itself can be a source of error. Its construction does not account for anatomical facial differences, and the text is also shifted along the centre line even during monocular examination. Measurements may also be influenced by the examiner's expectations about the result. Verbal feedback from the examiner can encourage the examinee to perform better. Since children are examined in the study, measurement deviations may occur mainly due to misunderstandings, especially during the initial examination.

Regarding the effect of the study medication on accommodation, we observed significant differences in AoA in both the monocular and binocular tests, as well as in both the break and recovery points. Interestingly, there was no significant difference in the treatment relationship except for the border value for the monocular recovery point. This finding aligns with a similar nonlinear relationship documented by a meta-analysis of AoA modification in relation to a wide spectrum of atropine concentrations (0.01%, 0.02%, 0.03%, 0.05%, 0.10%, 0.50%) [26]. However, if we calculate the AoA based on the worst NPA result of our subjects (monocular recovery point in the 0.04% atropine group), we would obtain a mean AoA of 11.10 D. This value is clinically insignificant, as it falls within the comfortable range of accommodation for common life situations. This can also explain the high toleration rate of low-dose atropine observed in relevant studies [9, 14, 21, 32, 33]. Furthermore, it can elucidate our results of accommodation facility, which were tested at reading distance and showed neither a drug nor a dose relationship with the study medication.

Near Accommodation Facility

The dynamics of accommodation are quantified in the M.A.R.S. trial by measuring accommodation facility to a visual target (i.e., a short article of meaningful text) at a standard reading distance of 40 cm using accommodation flippers. The examination is simple to perform but, as a subjective method, requires a significant degree of cooperation and understanding from the subject. Sources of errors in the measurement can include reaction time, the speed of rotation of the flipper by the examiner, failure to maintain the examination distance throughout the measurement, and monotony of the examination. The measured values are influenced by the subjective reaction time of the examinee and the examiner. When testing paediatric patients, it can be challenging to maintain the same examination distance throughout the test. With different test distances, the accommodation requirements and the speed focus change. The examination is performed monocularly (twice) and binocularly for a total of three minutes, which can make it difficult for child subjects to maintain concentration.

Little is known about the modification of accommodative dynamics caused by low concentrations of atropine used in the long term for myopia control in children. There is only a small body of experimental evidence available, limited to the accommodation facility of untreated myopes. Subjective accommodation facility to targets at reading distance is not reduced in younger myopes compared to age-matched emmetropes [39-41]. However, older emmetropes, but not myopes, demonstrate a particular improvement in near accommodation facility (NAF) [42]. Our experimental results, corresponding to observations of the MOSAIC study, revealed no treatment-related effect on the difference in NAF values after twelve months of highly diluted atropine treatment compared to baseline data. Neither binocular nor monocular test conditions yielded these findings [11]. Longstanding subject compliance with study treatment, documented by an acceptable low trial dropout ratio, may particularly parallel the absence of treatment effects on subjective visual outcomes at the standard reading distance. Despite slight, sustained pupil dilation and the consequent increase in light intensity on retinal exposure, near accommodation performance remains unaffected. An increased potential for glare poses no distractive impact on children during NAF measurement procedures. As the assessment of accommodation capability by subjective NAF parallels objective measurements of the dynamics of accommodative reactions, a more detailed description of clinically undetectable changes related to study treatment would require objective measurements of accommodation dynamics, including latency, speed, and accuracy, in a more precise manner [41, 43].

Conclusion

Over twelve months, local treatment with lower-middle concentrations of atropine resulted in the expected treatment-related differences in photopic and mesopic pupillary diameter (PD). Accommodation capability, as measured by the near point of accommodation (NPA) and interpreted by its inverted value of amplitude of accommodation (AoA), showed diminished performance at extreme limits (evidenced by marginally reduced AoA) but remained unaffected at standard near working distance (as indicated by unchanged predominantly subjective NAF tests).

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